**Clinical Neuro-Ophthalmology, from Horner’s syndrome to blindness, Should I be worried?**

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Neuro-ophthalmologic disorders can arise from dysfunction of any part of the neuro-ophthalmologic tracts. The clinical signs may be decreased vision, blindness, abnormal pupillary light reflex, anisocoria, abnormal eye movements and strabismus alone or in association with multifocal neurological/systemic signs, depending on the distribution and type of lesion. A firm understanding about the neuroanatomy of the neuro-ophthalmologic pathways is essential to perform a correct neuroanatomic diagnosis. Based on the information obtained from signalment, a detailed history (including disease onset and progression), and physical, ophthalmic and neurological examination, the clinician can formulate a list of differential aetiologic diagnoses and subsequently select and interpret diagnostic investigations. The aetiologic diagnosis enables the initiation of specific treatment and predicting prognosis. Advances in diagnostic imaging have expanded the knowledge of neuro-ophthalmologic conditions. Prompt diagnosis and correct treatment can result in vision recovery in some disorders. During this lecture, we will focus on understanding the neuroanatomy of the visual pathways, parasympathetic and sympathetic innervation to the eyes and the dysfunction of these pathways (vision, dilated and fixed pupil and Horner’s syndrome)

The clinical assessment of the **conscious vision** (in dim and bright light conditions) is mainly performed by observing the animal moving in an unfamiliar environment and negotiating an obstacle course (maze test), tracking of a cotton ball, by visual placing and by assessing the menace response.

The menace response is elicited by making a threatening gesture to the eye involving the extreme visual fields (temporal and nasal, which project to different cortical hemispheres) while the other eye is covered and observing closure of the eyelids. It is important to avoid touching the eye/eyelashes or creating excessive air currents as this can trigger the palpebral and/or corneal reflex and therefore a false positive menace response. The menace response requires an intact sensory pathway (optic nerve, optic chiasm, contralateral optic tract, contralateral LGN, optic radiation and contralateral occipital cortex) and an intact motor pathway to elicit the expected response (closure of the eyelids).

From the visual cortex (occipital cortex) the impulses are transmitted through the internal capsule association fibres to the primary motor cortex (frontal cortex) where the motor pathway of the menace response begins. This pathway has not yet been fully described. The axons from the motor cortex reach the pontine nucleus via projection fibres. The axons from the pontine nucleus decussate and enter the cerebellum via the middle cerebellar peduncle, reaching the cerebellar cortex, which is ipsilateral to the eye where the menace response is elicited. The cerebellum then coordinates this response by efferent cerebellar pathways that activate the facial nuclei in the ventrolateral part of the rostral medulla oblongata. The axons emerge from the medulla oblongata and leave the cranial cavity via the internal acoustic meatus, open into the cavity of the middle ear and emerge from the stylomastoid foramen. The facial nerve (CN VII) innervates the orbicularis oculi muscle eliciting a blink (menace response). If the menace response is decreased or absent, the facial nerve needs to be evaluated by the palpebral reflex because CN VII paralysis or paresis may result in lack of menace response without involving visual perception. Cerebellar lesions can also result in lack of menace response to the ipsilateral side without involving visual perception.

The menace response is a learned response and therefore is usually absent during the first 10 to 12 weeks of age in kittens and puppies. It is important to remember that menace response is a cortically mediated response and therefore animals that are stressed, lethargic or disorientated may not respond appropriately without necessarily being affected by a lesion in the visual pathway.

Ophthalmic examination of the fundus, electroretinogram (ERG) and chromatic PLR are necessary in cases of visual deficits to differentiate lesions affecting the retina such as SARDS, progressive retinal atrophy, or toxicosis from postretinal lesions. Postretinal visual deficits can be caused by lesions affecting the optic nerve (optic neuropathy), optic chiasm, optic tract, LGN, optic radiation and/or visual cortex either unilaterally or bilaterally.

If visual deficits are present, PLR is sometimes useful to differentiate between cortical and subcortical lesions. PLR will be present in both eyes if the lesion is affecting the LGN, the optic radiation or the visual cortex. If there is absent/decreased direct and its indirect PLR with postretinal visual deficits, the lesion is located either in the optic nerve (ipsilateral to the absent direct PLR and visual deficits), optic chiasm (bilaterally absent direct and indirect PLR and visual deficits) or optic tract (contralateral to the absent direct PLR and visual

Lesions affecting the optic nerve/s are mainly divided in inflammatory/infectious, neoplastic, congenital, traumatic and compressive. The most common disorders affecting the optic chiasm are intracranial extension of the orbital disorders (neoplasia or inflammation) and tumours of the pituitary area. . Lesions (inflammatory, infectious, neoplastic and vascular) in the thalamic or visual cortex will also contribute to visual deficits.

The **parasympathetic innervation to the eye** regulates the pupil response to the amount of environmental light, while **the sympathetic innervation to the eye** regulates the pupil response to emotional factors. The afferent pathways that contribute to the parasympathetic innervation to the eye arise from the retina where the impulses originate after light stimulation to the photoreceptors [rods, cones and intrinsically photosensitive retinal ganglion cells (ipRGC)]. These impulses travel within the RGC axons (optic nerve) and reach the optic chiasm. The majority of the RGC axons decussate at the level of the optic chiasm (around 65% in cats and 75% in dogs of the optic nerve axons) and continue as part of the optic tract. Around 10-20% of the optic tract RGC axons bypass the lateral geniculate nucleus and course ventrally to synapse in the pretectal nucleus, particularly the pretectal olivary nucleus (PON). The PON is located rostral to the midbrain tectum and contributes to the pupillary light reflex (PLR) pathway. From the PON, the majority of the axons (around 65% in cats and 75% in dogs) cross over to the contralateral side through the caudal commissure and reaches the parasympathetic nucleus of the oculomotor nerve (Edinger Westphal nucleus), which is located in the rostral part of the midbrain and very closed to the midline. The remaining axons from the PON (around 35% in cats and 25% in dogs) reach the ipsilateral parasympathetic nucleus of the oculomotor nerve.

The efferent parasympathetic fibres (preganglionic fibres) from the oculomotor nucleus travel with the motor fibres of the oculomotor nerve coursing ventrally and emerging on the medial side of the crus cerebri. The parasympathetic fibres are located medially to the motor fibres of the oculomotor nerve at the level of the middle cranial fossa and therefore they are the first to be affected when a structural lesion (such as a pituitary mass) arises and extends laterally from the midline. The parasympathetic fibres leave the skull through the orbital fissure and synapse in the ciliary ganglion caudal to the eye. Postganglionic parasympathetic fibres (short ciliary nerves) innervate the iridal sphincter muscle and gives reciprocal cholinergic inhibition to the iridal dilator muscle, causing iridal sphincter contraction and dilator muscle relaxation (pupillary constriction). There are only two short ciliary nerves (nasal short ciliary nerve and malar short ciliary nerve) in the cat and they are solely parasympathetic while in the dog there are five to eight short ciliary nerves that have both sympathetic and parasympathetic fibres. The cat can also present with abnormal pupil shape (dyscoria) if only one short ciliary nerve is affected. For instance, if the lesion occurs in the nasal short ciliary nerve (medial nerve) of the left eye, this causes a reverse D-shaped pupil, whereas if the lesion occurs in the malar short ciliary nerve (lateral nerve) of the left eye a D-shaped pupil is present.

The sympathetic innervation to the eye is also described as a three-order neuron pathway. The afferent pathways (first order neurons) arise from the caudal nuclei of the hypothalamus, which is activated by emotional factors or noxious stimuli. This first order neurons project caudally and ipsilaterally via the lateral tectotegmental spinal tract (located in the lateral funiculus) to the preganglionic cell bodies (second order neurons), which are located in the lateral grey column at the level of T1-T3 spinal cord segments. The axons from the preganglionic neurons join the ventral roots of the segmental spinal nerves at this level and through the ramus communicans join the thoracic sympathetic trunk. The preganglionic fibres continue cranially as part of the cervical vagosympathetic trunk. At the level of the ventromedial part of the tympanic bulla, the preganglionic fibres terminate in the cranial cervical ganglion (CCG), where they synapse with the postganglionic neurons (third order neurons). The postganglionic fibres leave the CCG and direct cranially through the tympano-occipital fissure. They enter the middle ear cavity together with the internal carotid artery and continue rostrally between the petrosal and basisphenoid bones, coursing ventrally to the trigeminal ganglion and joining the ophthalmic branch of the CN V through the orbital fissure. The postganglionic sympathetic fibres innervate the smooth muscles of the periorbita, Müller's muscle of the upper and lower eyelid and the dilator muscles of the iris. The adrenergic (sympathetic) excitatory input to the dilator muscle causes contraction of this muscle and therefore mydriasis. As previously described in the parasympathetic innervation, the sympathetic innervation also causes a reciprocal adrenergic inhibition of the other antagonist muscle and therefore further relaxation of the iris sphincter muscle.

Anisocoria is a condition characterised by unequal pupil size. The resting pupil size and possible asymmetry should be assessed (by distant direct ophthalmoscopy) in normal light and then in darkened room. The neurological causes of anisocoria with normal vision involve lack of parasympathetic tone to the iris constrictor muscles (mydriatic pupil) or lack of sympathetic tone to the iris dilator muscles (miotic pupil, Horner’s syndrome). The parasympathetic component of the oculomotor nerve can be affected by any lesion located from the midbrain to the periorbita causing a dilated and unresponsive pupil with normal vision (normal menace response, absent direct PLR when the affected pupil is tested and absent indirect PLR when the contralateral eye is tested). In some cases a mydriatic pupil with normal vision could be the first indication of middle cranial fossa syndrome and also presented in conjunction with a ventrolateral neuromuscular strabismus due to an involvement of the motor component of the oculomotor nerve.

The Horner’s syndrome is a clinical disorder caused by a lack of sympathetic innervation to the head. The clinical signs include miotic pupil, ptosis of the upper eyelid, decreased tone of the lower eyelid, protrusion of the nictitating membrane, enophthalmos and conjunctival hyperaemia. The miotic pupil in patients with Horner’s syndrome is most noticeable in the dark because the normal pupil dilates and the affected pupil remains miotic. Horner’s syndrome results from lesions affecting the first, second (preganglionic) or third order (postganglionic) neurons. The presence of other clinical signs in association with Horner’s syndrome can help to localise the lesion and formulate the differential diagnosis list.

Neuro-ophthalmologic signs can be caused by different disease mechanisms including vascular, inflammatory, infectious, trauma, anomalies, metabolic, idiopathic, neoplasia, nutritional and degenerative conditions. It is very important to perform a careful clinical evaluation in order to localise the lesion and select the most appropriate diagnostic investigations and treatment. Early recognition and treatment of certain aetiologies can result in a favourable outcome including recovery of vision.