“Practically Pupils” by Dr Kristopher Kowal MD
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Introduction

The pupil is the aperture that allows light to enter the eye and eventually fall onto the retina to start the cascade of visual perception.

Much as the eyes are said to be the window to the soul, much useful information can be gleaned in neurological disease (and others) by carefully assessing the shape, size, symmetry and reactivity of the pupils in conditions of differential light conditions (light and dark) as well as under the influence of accommodation, lack thereof or even during specific activation of related cranial nerves. This will be discussed in detail below.

For the purposes of neuro-ophthalmology, the discussion will omit pupil irregularities due to trauma, old uveitis or post surgical changes although these findings can also be important for uveo-meningeal syndromes that have overlap with retinal diseases. (Sarcoidosis, Susac’s Retino-cochleo-cerebral vasculitis, Behcets, Vogt Koyanagi-Harada syndrome)

As is the case in all other neurology, a discussion of the relevant neuroanatomy is required to establish a solid basis of understanding. Relevant anatomical dissociations and syndromes based on anatomical subtlety will be elaborated upon with clinical examples.

Prior to this however, we should quickly establish how to recognize a third vs a horner, based on pupil size alone.

Exam

Simply dim the room lights and apply the dimmest stimulus you can, and with a Snellen near eye card, measure the pupil size

The, brighten the room lights to maximal intensity and repeat. Document pupil size.

Also useful is starting in a bright room and variably dimming the lights slowly to watch as the pupil dilates.

A third nerve palsy often comes comes with anisocoria, a sluggishly reactive pupil, that is more noticeable in bright light due to failure of constriction.

3rds measure as such, with sluggish or no reaction to light and moderate to severe ptosis

	Dim	Bright
OD	8	7
OS	7	3

Or if a complete CN III palsy (same format)

OD	8-8
OS	7-3

A Horners comes with perfect constriction to light and a subtle ptosis, as well as dilation lag of the affected pupil, which will not dilate as much as the normal pupil, in the dark, or as a bright light source is slowly dimmed and you observe the pupil relax, the relaxation will be slower or delayed and incomplete compared to the fellow eye.

	Dim	Bright
OD	3	2
OS	6	2

Pupillary Light Reflex Arc - Parasympathetic and Sympathetic and relevant clinical syndromes

The pupillary reflexes consist of dilation in response to focus in the distance and constriction (with concomitant convergence) in response to near focus. The well known responses to light and dark with both the direct and consensual response are subserved by similar pathways with some important distinctions to be made. In broad strokes, the parasympathetic nervous system and cranial nerve III are responsible for pupillary constriction and accommodation and the sympathetic nervous system is responsible for pupillary relaxation and focus of vision at distance with the obvious dilation seen of the pupil. Nicotinic acetylcholine receptors are present at the ciliary ganglion to pass information to postganglionic nerves which then release acetylcholine onto muscarinic receptors on the pupillary sphincter/iris muscle.

Sympathetic tone is mediated by a long arc beginning in the hypothalamus descending to the high cervical cord and upper brachial plexus, passing over the lung apex, and then running back up the internal carotid artery, passing into the cavernous sinus briefly with CN VI beside it, before exiting into the orbit and innervating the pupil with both alpha and beta adrenergic receptors that mediate dilation

The pupillary constriction circuit is made up of an afferent and efferent loop subserved largely by cranial nerves II and III.

The pupil allows light onto the retina, this photonic information is then turned into an electrochemical signal that then travels along the optic nerve, cranial nerve II, which is actually a diencephalic white matter tract in its entirety. Because the nasal retina is larger the temporal retina, (the nose interferes with the nasal field making it smaller) 53 percent of the total optic nerve fibers decussate at the optic chiasm) and slightly more light information travels to the contralateral hemisphere from any one eye.

The optic tract courses superiorly and laterally from the chiasm in the medial temporal lobe and terminates in the lateral geniculate nucleus, however, prior to the tract joining the thalamus, an extrageniculate branch leaves the optic tract proper and enters the midbrain in the superior brachium conjunctivum, joining the tectal nuclei and then moving along to the Edinger Westphal nucleus, to join fibers from the remaining subnuclei of the cranial nerve three nucleus in the superior medial midbrain, and sending efferent motor information to both CN III fascicles.

At this point it is reasonable to point out that since 53 percent of all retinal fiber end up decussated an afferent defect can arise due to an optic tract lesion or even potentially a lesion of the extrageniculate tract and finally the brachium or tectal nuclei, as long as the fellow nucleus isn't also involved. Once the EW nucleus is reached however the afferent information can no longer cause an APD as this is where generation of an efferent signal begins. This would

be called the almost mythical “tectal APD” and it will be associated with no vision loss, no optic atrophy as well as normal visual fields.

From clinical knowledge we are aware of the Argyll Robertson pupil, from neurosyphilis, which is manifested in a pupil that accommodates but does not react. This is different from an Adie's pupil as it is a central. This implies that there must be dissociation of the tectal nucleus and Edinger Westphal nucleus loop that subserves pupillary light constriction, versus accommodation, which does not involved the tectal nucleus. The neurosyphilis must selectively involve the tectal nucleus. The Parinauds dorsal midbrain syndrome, which also causes light near dissociation, amongst many other signs, supports this supposition, as compression of the midbrain tectum often by a pineal tumour, is the cause.

Cranial nerve three leaves the EW nucleus, travels anteriorly medially and then anterior laterally enters into the cavernous sinus. As it leaves the midbrain it passes near the posterior communicating artery and this may be the most important part of the pupil talk. (Remember aneurysms; they kill people.)

The efferent response from the light to one pupil results in the consensual response where both pupils constrict.

The anatomy of the CN III at this location has the pupillary fibers travelling superficial, and hence, should a compressive lesion be present, say from a PCOMM aneurysm or other malignant/infectious/inflammatory disease, the pupil will almost certainly be involved. In incredibly infrequent circumstances, at the level of a handful of case reports, a compressive lesion may not involve the pupil very early, but inevitably, it always must.

This leads us to “The Pupil Rule” which states the converse of the situation above.

“In an otherwise complete third nerve palsy, total sparing of the pupil implies there is no compressive lesion (read here aneurysm). This type of lesion is almost exclusively due to a microvascular third nerve palsy.”

Corollary one - A partial cranial nerve three lesion is compressive or intramedullary until proven otherwise

In the circumstance of a diabetic, hyperlipidemic smoker with hypertension the vast majority of these lesions, will still be non compressive/microvascular in nature according to the rules of Bayesian analysis.

The concern is always “how certain can you be that the third nerve lesion is complete?”

If there is any suspicion of a partial lesion, the safest approach is to get a CTA to rule out an aneurysm or follow very very closely to watch for evolution that would necessitate an MRI to look for something more unusual than a microvascular palsy or PCOMM aneurysm.

Realistically, in the absence of the typical thunderclap headache, an expanding aneurysm is exceedingly unlikely and any patient who present with a partial lesion that does not have the clinical history of a subarachnoid hemorrhage should be watched with clinical reassessment at short intervals.

The vast majority of microvascular lesions will heal within months.

Any progression implies compression, necessitating a search for malignant, inflammatory or infectious causes.

The other thing to watch for is “aberrant regeneration.” When a compressive lesion occurs, on occasion it can partially heal before getting worse and you need to watch for the eye closing or lid changing position or **pupil constricting** during activation of the medial rectus.

Once the third enters the cavernous sinus it travels in the wall of the cavernous sinus and can be seen in combination with CN IV, V1, V2 and CN 6 lesions.

The third then leaves the cavernous sinus, pierce the superior orbital fissure and the third breaks off to a superior and inferior division, the pupillary fibers are with the inferior division.

The inferior division innervates the IO, IR, MR and pupil with the superior branch innervates the SR and levator palpebrae.

The inferior division branches into a pure pupillary branch which terminates in the ciliary ganglion, releases ACh onto the postsynaptic fibers, which have nicotinic receptors, the postsynaptic fibers synapse onto the iris muscles and constrict the pupil, both for accommodation and light.

Very rare case reports exist of myasthenia gravis causing ‘tonic pupils” which react neither to light nor accommodation due to skeletal muscle antibodies sharing 60% sequence homology with the ganglionic type acetylcholine receptor. Often these cases come with other autonomic symptoms and signs like presyncope from orthostatic hypotension, palpitations from tachycardia, or constipation from decreased gut motility.

Onabotulinum toxin poisoning causes unreactive pupils and a similar neuromuscular (but progressive and non fluctuating syndrome) systemic weakness and this occurs bases on the inability of the postganglionic neuron to release acetylcholine onto muscarinic receptors in the pupil.

The other half of the pupillary reflex is dilation with anatomy discussed above. A Horners can be told by the company it keeps. A hypothalamic lesion will come with hyperphagia or anorexia, a thalamic lesion sensory changes, a brainstem syndrome (aka Wallenberg's), a cervical myelopathy, neck pain, or a cavernous sinus lesion as the efferent sympathetic fibers leave the carotid, join CN VI briefly in the cavernous sinus before innervating the pupil

Identifying a Horners can be achieved simply by measuring pupil size bilaterally in light and dark, to the half millimeter, confirming normal constriction and a slight ptosis with or without reverse ptosis. (lower lid margin higher in affected eye)

A Horner can be confirmed at any site, through Apraclonidine testing. A normal pupil will not dilate in response to clinically available Apraclonidine/Iopidine (used for glaucoma) as it is a weak alpha agonist. In a horners, the pupil is denervated so the alpha receptors are upregulated and the affected pupil will dilate in response to the apraclonidine whereas the normal pupil will not. The lid will often also lift 1-2 mm.

Cocaine inhibits reuptake of a released neurotransmitter, so it will fail to dilate a pupil with any Horner syndrome, as in order to release neurotransmitter all three neurons in the circuit need be intact.

Hydroxyamphetamine depletes terminals of neurotransmitter, so it will only dilate a 1st or 2nd order horner, because if the third order neuron is affected there is no terminal to deplete. This has historical interest but the drug is not readily available.

A Horners, when localized, and without any obvious clue by history or exam, requires a CT/CTA of chest and neck for a Pancoast tumour at the lung apex, an extrinsic lesion compressing the carotid artery or a carotid artery dissection

A Horner from the hypothalamus, brainstem or cavernous sinus should have sufficient historical or examination clues to target the proper neuroimaging techniques and investigation.

Adie Pupil - A pupil that fails to constrict to light, that accommodates well, and shows segmental denervation on slit lamp exam. It constricts to dilute pilocarpine due to denervation supersensitivity. A pupil that does not receive parasympathetic input increases its expression of receptors so that a diluted agonist constricts it whereas a normal pupil will not constrict to dilute pilocarpine.

Pharmacologically dilated Pupil - will not constrict to light or accommodation and even full strength pilocarpine. Usually due to scopolamine patch for boasts, accidental by ventolin blowing one eye, a medical professional accidentally inoculating the eye with tropicamide or phenylephrine or a medical health professional (vet tech in my last case) with access to drugs and a subconscious desire for medical attention.

Afferent Pupillary defects

A complete and isolated CN II lesion will result in total blindness in that eye and a pupil that does not constrict to a direct response, but does constrict to a consensual light stimulus. A CN III lesion in converse, will also not constrict to a consensual light source in the fellow eye.

In any relative defect, with a unilateral optic neuropathy, severe retinal disorder (CRAO) or optic tract lesion, will show pupils that still constrict, in isolation, bilaterally. However, when one swings a flashlight between them, the resting tone and “ambient light memory” is set by the eye that is able to transmit a bit of extra light to the brain, so that when the flashlight is moved to the fellow affected eye, the brain “receives and believes” that less light is making it to the tectal and EX nuclei, so they dilate in response.

In the case of a simultaneous suspect APD and Adies pupil (or even iris damage for example) or CN III (all in one eye) die to the mechanical or efferent loop problem, you cannot utilize the ipsilateral light reaction to judge an APD; here you can use the patient's report and quote “reduced subjective visual brightness” or even better, you can look at the normal eye as the light is moved to the eye with the suspected optic neuropathy or optic tract lesion. At this point you would be “testing for an APD using the reverse method.”

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