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The pupillary examination

Introduction

Many pupil abnormalities, including irregularities of shape or position, anisocoria (difference in pupil size) and abnormalities of the light and/or near response, may be seen in hospital.

Although many of these pupil abnormalities are asymptomatic, changes to the pupils may be a sign of underlying ophthalmic or neurological disease. A thoughtful and detailed pupillary assessment, alongside a thorough history and neurological examination, will reward the doctor with clues to many diagnoses. The detail with which the pupils are examined varies depending on the clinical scenario.

This article first reviews relevant anatomy and salient aspects of the examination, then divides pupillary findings into practical categories to enable junior doctors to make a confident clinical diagnosis. Emphasis is placed on neurological causes of pupillary abnormalities, although if signs do not fit with a 'neurological' cause, an ophthalmic opinion should be sought.

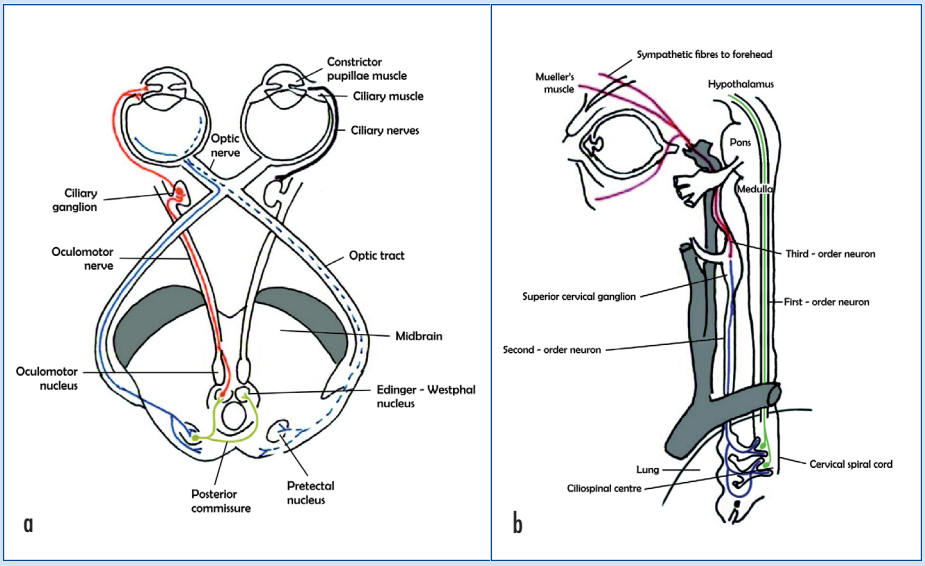
The neuroanatomy

A working knowledge of the anatomy of the light reflex and sympathetic innervation is key to taking the diagnostic leap from a simple description of pupillary findings to meaningful interpretation of these clinical signs. Pupil size is controlled by the interplay between parasympathetic innervated smooth muscle constrictors and sympathetic innervated dilators of the iris. The anatomical separation of these two nerve chains helps in lesion localization.

The pupillary light reflex

The afferent limb of the pupillary light reflex relays information via the optic nerve, chiasm and optic tracts to the dorsal midbrain (*Figure 1a*). From here, both Edinger–Westphal nuclei are innervated. Crossing fibres in the posterior commissure explain the consensual light reflex. The efferent limb of the pupillary response to both light and near stimuli depends on parasympathetic innervation of the iris. This travels from the Edinger–Westphal nucleus to the iris via the oculomotor

Figure 1. Pupil size is controlled by the interplay between (a) parasympathetic innervated smooth muscle constrictors and (b) sympathetic innervated dilators of the iris.



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nerve and ipsilateral ciliary ganglion. The ciliary muscle which also receives parasympathetic fibres serves lens accommodation. Parasympathetic fibres travel superficially in the oculomotor nerve, an important anatomical point when interpreting clinical signs.

The near reflex

Vision is necessary for the near reflex, which enables focus on objects of differing distance from the eye. Signals from the optic nerve reach the occipital cortices from where they are transmitted to the midbrain pretectal nuclei that in turn innervate both Edinger–Westphal nuclei. The pathway is then as described for the light reflex. The anatomical separation of the two pathways is the substrate for the 'light-near dissociation' seen in some diseases.

Pupil dilatation

Sympathetic pupillary innervation consists of a three neuron chain (*Figure 1b*). The first-order neuron descends ipsilaterally from the hypothalamus to the spinal cord (C8–T2) via the lateral brainstem and upper cervical cord. The second-order neuron leaves the spinal cord via the T1 ventral nerve root, traverses the lung apex before passing around the subclavian artery to synapse in the superior cervical ganglion. The third-order post-ganglionic neuron ascends in intimate association with the internal carotid artery into the cavernous sinus, before entering the orbit through the superior orbital fissure, reaching the pupil via the ciliary ganglion through the ciliary nerves. Mueller's muscle, smooth muscle which helps elevate the upper eyelid, also receives sympathetic innervation.

Performing the pupillary examination

Where possible, the patient should be seated with his/her eyes at the examiner's eye level. Before the pupils are examined, a thorough general and ophthalmic inspection should be performed, and visual acuity, colour vision and visual fields examined. Associated signs and symptoms will dictate the detail of examination, and the degree of urgency of investigation needed.

Inspect the pupils in ambient, low and bright light. Is there anisocoria? The pupils are best examined in dim light: Horner's syndrome is often missed when examined in a bright room. Using a bright light and approaching the pupils from the side, examine the direct and consensual light reflex. The examiner should stand to the side, and the patient be asked to gaze into the distance – in order to avoid activation of the near reflex. Note the degree, briskness and symmetry of the response. Perform the 'swinging light test', a sensitive test for examination of the anterior visual pathway: the pen torch is moved repeatedly across the bridge of the nose, from one pupil to the other, pausing each time for ~1 second on each. The normal response sees both pupils constrict in response to light shone in one eye; however, if there is a unilateral or asymmetric lesion of the anterior visual pathway, both pupils will dilate when the light is shone in the affected eye, and there is said to be a relative afferent pupillary defect in that eye.

The near response is tested by asking the patient to look into the distance, then at a finger or pen held ~25 cm from the patient, observing closely for miosis and convergence. If present, light–near dissociation is noted at this point. Complete the cranial nerve and limb examination. Finish with a general medical examination, not forgetting to auscultate the carotid arteries. Take a detailed history focusing on occupation, drugs and medications. It is always useful to ask whether there are any old photos to look at, as in some cases there is a longstanding pupillary abnormality which has only recently come to attention, and may not require detailed investigation.

Interpretation of pupillary findings

Pupillary abnormalities can be divided into abnormalities of the light reflex (including afferent, central and efferent disease), of the eye's sympathetic innervation, diseases of the iris and physiological anisocoria. If anisocoria is present, the critical question is whether it is the big pupil or the small pupil which is abnormal, or neither.

- If there is ptosis or ophthalmoparesis, the abnormal pupil is usually in that same eye
- If the difference in pupil size is more pronounced in bright light, it is the larger pupil which is abnormal (defect of normal parasympathetic constriction)
- If the difference in pupil size is more pronounced in low light, it is the smaller pupil which is abnormal (defect of normal sympathetic dilatation)
- If both pupils respond normally to light, then the smaller pupil is probably abnormal (as the parasympathetic fibres are intact) or the anisocoria is physiological.

Benign 'physiological' anisocoria is common and a difference in pupillary size of up to 1 mm is seen in ~20% of the general population. Vision and the pupillary reactions are normal, and the degree of anisocoria remains equal in both light and dark (*Figure 2d*). There are no associated signs. Pharmacological testing can confirm

Figure 2. Common pupil abnormalities.

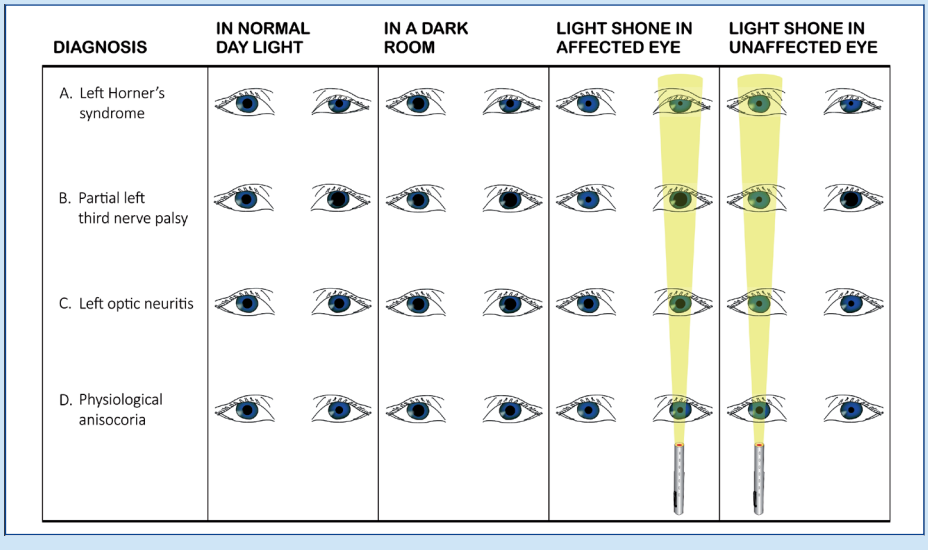


Table 1. Eye drops to differentiate pupil problems

Medication	Indication	Mechanism of action
Tropicamide	To dilate the pupil for examination	Inhibits cholinergic stimulation of the pupillary sphincter, allowing the pupil to dilate
Apraclonidine	For help in diagnosis of Horner's syndrome	Alpha-1 adrenergic receptor agonist. There is upregulation of alpha-1 receptors in the sympathetically denervated pupillary sphincter of Horner's syndrome. This leads to apraclonidine supersensitivity, reversal of ptosis and pupillary dilatation. There is no effect on the normal pupil
Cocaine	To differentiate Horner's syndrome from physiological anisocoria	Blocks noradrenaline reuptake leaving an increased amount available in the synaptic cleft. The normal pupil dilates by ~1 mm or more after ~60 minutes. In Horner's syndrome, there is no dilatation of the pupil as there is no noradrenaline available
Hydroxyamphetamine	To differentiate first or second order from third order Horner's syndrome	By releasing stored noradrenaline from sympathetic nerves, it dilates the normal pupil and the pupil in first and second order Horner's syndrome. The pupil in third order Horner's syndrome is left unaffected
Pilocarpine	0.1% to test for parasympathetic denervation supersensitivity (e.g. Adie pupil), 1% to test for a pharmacologically dilated pupil	Pilocarpine stimulates the cholinergic receptors in the pupillary sphincter muscle causing miosis. At 0.1% it will only constrict the supersensitive pupil. At 1% it will constrict all normal or supersensitive pupils but not a pupil which is pharmacologically dilated

this (*Table 1*) but is rarely needed. The anisocoria can occasionally change size and switch sides.

Now that you have decided which pupil is abnormal, the cause for the pupil abnormality should be sought.

I think that the big pupil is abnormal

Oculomotor nerve palsy (*Figure 2b*) is not an end diagnosis in itself and must be investigated. There is usually a variable degree of ophthalmoparesis and ptosis. The large pupil is caused by disruption of preganglionic parasympathetic fibres. A painful, pupil-involving third nerve palsy is caused by an extrinsic compressive lesion, such as an intracerebral internal carotid or posterior inferior cerebellar artery aneurysm, until proven otherwise. In this case, eye movements may not be severely involved, although are most often abnormal on careful examination.

A dilated pupil without ptosis or extraocular eye movement abnormality is very rarely caused by oculomotor nerve palsy, and other causes should be considered. Oculomotor nerve palsy should never be called 'ischaemic' unless it is complete, without pupillary involvement, and there should be an appropriate past medical history. If the lesion is in the single central third cranial nerve nucleus, both eyes will be involved. Regardless of pupillary involvement, any patient with progressive external ophthalmoplegia requires imaging as the cause is likely to be surgical. In some cases, a formal 4-vessel intracerebral angiogram is performed if there is high clinical suspicion of a compressive lesion yet other imaging techniques are negative.

The tonic pupil is the result of damage to the postganglionic parasympathetic fibres in the ciliary ganglion/nerves. It is often discovered by chance, although the patient may have blurred vision, photophobia or difficulty reading. In the acute phase, the pupil is fixed, dilated and poorly reactive to both light and near. The vast majority of parasympathetic nerve fibres innervate the ciliary muscle, and as these nerve fibres aberrantly reinnervate the iris sphincter, the patient develops a strong, tonic contraction of the pupil during the near response. There is slow pupillary redilatation while the direct light reflex remains poor or even absent. Reinnervation is usually only partial, leading to an irregular pupil with vermiform movements which may only be seen through a slit lamp. There is often cholinergic supersensitivity (*Table 1*), as the denervated iris yearns for cholinergic innervation. With time, the pupil becomes miotic, and the other pupil may become involved. If unilateral, a tonic pupil can be caused by local orbital disorders including trauma, neoplasm and inflammation. If bilateral, a generalized autonomic neuropathy should be considered. In many cases, a cause is not identified and there may be impaired corneal sensation and ipsilateral areflexia in otherwise well young (usually) females: the benign Holmes–Adie syndrome.

Pharmacological mydriasis (*Table 2*) may be either accidental or deliberate, and is either the result of sympathetic stimulation of the pupillary dilator muscle, or of parasympathetic inhibition of the sphincter muscle. When the drug is anticholinergic, the pupil is often largely dilated and does not constrict to light or near. Sympathomimetic drugs, on the other hand, rarely dilate the pupil by more than 1 or 2 mm. Unilateral mydriasis following use of transdermal scopolamine is well described.

Transient unilateral mydriasis has been described during or following a seizure, in patients with migraine and cluster headaches, as well as in normal people.

Pupillary sphincter muscle damage following ocular trauma or surgery may result in a dilated pupil. It is often large and irregular with variable reaction to light and accommodation. Examination in bright light may exacerbate the signs as the damaged sphincter muscle fails to constrict properly. There are no associated neuro-ophthalmic findings. Chronic inflammatory eye disease can lead to the formation of posterior synechiae resulting in a large, eccentric pupil with poor reaction to light or near. A diagnosis of acute angle closure glaucoma should never be missed. If intraocular pressure rises precipitously, the patient may present with decreased visual acuity, headache, ocular pain, and nausea and/or vomiting. The patient may complain of seeing 'halos' around lights. Associated signs may include a red eye, corneal oedema or cloudiness and a mid-dilated poorly reactive pupil. This is an ophthalmic emergency.

I think that the small pupil is abnormal

Horner's syndrome is the result of disruption of sympathetic innervation to the eye and face at any point along the three-neuron chain (*Figure 1b*). The core triad is ipsilateral miosis, ptosis (paresis of Mueller's muscle), and forehead anhidrosis. The latter may not be seen in postganglionic lesions, as the fibres to the face dive off with the external carotid artery. Anisocoria is more obvious in the dark (*Figure 2a*). The pupil reacts normally to light but there is slow redilatation of the pupil compared with the normal side when the light is removed, as a result of poor sympathetic tone.

Horner's syndrome is not an end diagnosis in itself, and further investigation may be needed particularly if it is of acute onset. There may be a history of birth trauma or longstanding idiopathic Horner's syndrome. The development of normal iris pigmentation depends on intact sympathetic innervation, therefore iris heterochromia is seen in congenital cases. An acute isolated Horner's syndrome may be caused by carotid artery dissection, which is not always associated with face or neck pain, and should be actively excluded. There may be associated localizing signs or symptoms such as neck and/or arm pain and/or weakness or numbness (brachial plexus lesion), contralateral limb ataxia, hemiparesis and crossed sensory signs (lateral brainstem syndrome or cervical/thoracic cord lesion), reduced visual acuity (superior orbital apex syndrome or orbital lesion), ipsilateral ophthalmoparesis and/or facial numbness (cavernous sinus lesion), or ipsilateral intrinsic hand muscle wasting (lung apex tumour). Speech and breathing can also be affected if the lesion involves the recurrent laryngeal or phrenic nerve respectively. Horner's syndrome can also occur with primary headache syndromes such as migraine or cluster headache so remember to ask about relevant features including cephalalgic autonomic symptoms.

A targeted approach to investigation is used based on the clinical history and response to eye drops (*Table 1*). Imaging of the brain and brainstem with magnetic resonance imaging, as well the neck vessels with magnetic resonance angiography or computed tomography angiography may be necessary. A chest X-ray +/- chest computed tomography scan may identify an apical lung lesion. In many cases, a definitive cause is not identified.

Other causes of unilateral miosis include the chronic tonic pupil, which tends to become smaller with time, although it maintains the poor light reaction and tonic near response. Pharmacological miosis can be seen after use of certain medications (*Table 2*). Ocular conditions such as anterior uveitis may hinder pupillary dilatation as a result of the intraocular inflammation affecting pupillary sphincter muscle function. There may be associated signs including a red, painful eye, with variable visual loss. Patients with previous ocular surgery may be left with a small or irregular pupil as a result of damage to the pupillary sphincter muscle.

Table 2. Pharmacological causes of pupil abnormalities

Miosis	Opiates – fentanyl, morphine, heroin and methadone (N.B. pethidine does not cause miosis)
	Antipsychotic medication – haloperidol, olanzapine, quetiapine
	Cholinergic agents – acetylcholine
	Mirtazapine
	Monoamine oxidase inhibitors
	Organophosphate poisoning (non-reactive pupil)
	Ecstasy (MDMA)
	Tricyclic antidepressant medication
Mydriasis	Antimuscarinic – atropine, tropicamide, pilocarpine, scopolamine
	Aerosolised anticholinergic – ipratropium bromide (nebuliser-associated mydriasis) may be unilateral
	Sympathomimetic – adrenaline, dopamine, phenylephrine, clonidine, apraclonidine, brimonidine
	N-methyl-D-aspartate receptor blockers – ketamine, dextromethorphan, phencyclidine
	5-hydroxytryptamine-2A blockers – lysergic acid diethylamide (LSD)
	Tetracycline overdose

Most cases of drug-induced pupillary changes are caused by parasympatholytic agents, although topical parasympathomimetic agents can also do this. Eye drops can be used to test for parasympathetic pharmacological blockade (*Table 1*)

The pupils are of equal size but the light reflex is poor in one or both

Lesions of the anterior visual pathway such as optic neuritis result in a pupil which is poorly reactive to light, although there is no anisocoria even if only one eye is involved. The consensual and near responses remain normal as the efferent limb is unaffected. There is a relative afferent pupillary defect (*Figure 2c*) indicating a lesion of the optic nerve or retina. Taking this one step further, if there is complete blindness as a result of a lesion in the anterior visual pathway, the eye will not react to light at all, nor will there be a consensual reflex in the other eye. If there is bilateral symmetric involvement, both pupils will react poorly to light, but there will be no relative afferent pupillary defect, as this is a comparative test. Neurophysiological tests such as visual evoked potentials may help confirm a suspected lesion of the visual pathway.

Pretectal or tectal midbrain lesions can affect the light reflex. The pupils are moderately dilated at rest, although shape and position remain normal (*Figure 3*). There is interruption of the light reflex, but the near response is maintained with brisk constriction of the pupils. This is one of the signs seen in the 'dorsal midbrain syndrome'. Associated findings include voluntary supranuclear vertical gaze palsy, impairment of vergence, convergence-retraction nystagmus and lid retraction on attempted upgaze.

Bilateral Horner's syndrome can be seen in patients with diabetes mellitus and in those with autonomic neuropathies. This is a difficult diagnosis to make, as there is often very little anisocoria and other signs are symmetrical. Eye drop testing is unhelp-

ful as there is no eye to use as a control. In a patient with a tonic pupil, the second eye becomes involved at a rate of ~10%/year. There is often a degree of anisocoria given the difference in timing of involvement. Patients with a long history of diabetes mellitus may have small pupils which react very poorly to light. Very rarely, patients with Guillain–Barré syndrome may become severely paralysed, losing the pupillary reflex as well. Patients with Lambert–Eaton myasthenic syndrome may have sluggish pupillary reflexes related to autonomic involvement.

Drugs including narcotics can be easily overlooked (*Table 2*).

The pupillary shape is abnormal

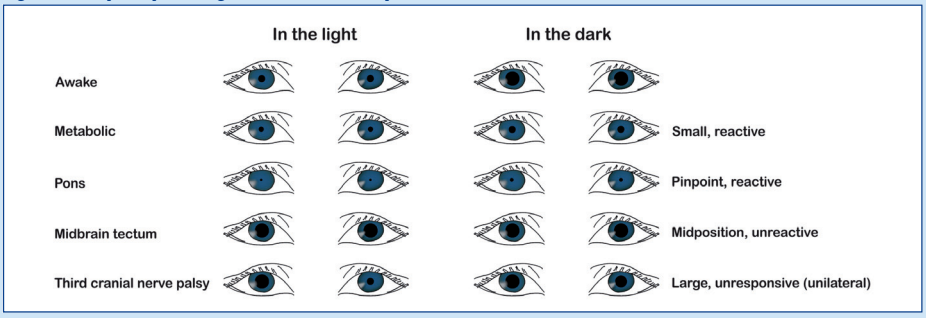
The Argyll Robertson pupil is now rarely seen. It is caused by a lesion to the iridomotor fibres in the rostral midbrain, resulting in small, irregular pupils that do not react, or react very poorly to light, but retain a prompt near response. There may be associated hearing loss. Although characteristically seen in patients with tertiary syphilis, this finding can also be seen in diabetes, sarcoidosis, alcoholic midbrain degeneration, myotonic dystrophy, Wernicke's encephalopathy and in other midbrain lesions. Note that syphilis can also cause bilateral large pupils that are unresponsive to light and near. Other causes of abnormal pupillary shape include ocular trauma, inflammation or surgery. The tadpole-shaped pupil is thought to be caused by spasm of the iris dilator smooth muscle and can be seen as an episodic phenomenon in migraine.

There is a long list of congenital and hereditary conditions that can affect pupillary size, shape and position. These are rare, and beyond the scope of this article.

Pupillary signs in the intensive therapy unit

Pupillary response is an excellent marker of brainstem function in the comatose patient. Perhaps most important is the unilateral dilated pupil, indicating a structural lesion of the midbrain or third cranial nerve. Transtentorial temporal uncus herniation of any cause may result in oculomotor nerve compression with loss of pupillary function often preceding ophthalmoplegia. The pupil is very dilated because of the preserved sympathetic function, and becomes fixed. Eventually the other pupil becomes fixed and dilated. This is a neurosurgical emergency. Other intensive therapy unit pupillary findings are summarized in *Figure 3*.

Figure 3. Pupillary findings in the comatose patient.



KEY POINTS

- Pupillary abnormalities can be divided into those affecting the light reflex (optic nerve and parasympathetic innervation) and those affecting the eye's sympathetic supply.
- If there is anisocoria, ask yourself whether it is the big or small pupil which is abnormal. This will guide your examination.
- Ask for old photos as longstanding pupillary abnormalities may need less urgent investigation.
- Any pupillary abnormality accompanied by loss of visual acuity, eye movement abnormalities, ptosis, new neurological symptoms/signs such as headache or neck pain must be investigated.
- A painful dilated pupil must be urgently investigated, as must a painful Horner's syndrome.
- Remember that ophthalmic disease may also cause pupillary abnormalities.

A note on the use of eye drops

Eye drops can help both in fundus examination and in neurological diagnosis. While rarely used on the wards, it is worth understanding the mechanism of action of the main eye drops used (*Table 1*).

Conclusions

Although many pupillary abnormalities are asymptomatic, a tailored and thoughtful pupillary examination in light of associated signs and symptoms is an invaluable skill, enabling the doctor to distinguish between conditions requiring urgent and less urgent investigation. BJHM

The authors would like to thank Amir V Meshkin for providing the illustrations.
Conflict of interest: none.

Further reading

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