Pupillary Abnormalities

Pupil reactions\cite{1,2}

Pupil size is determined by the interaction of the parasympathetic and the sympathetic nervous system, which constricts or dilates the iris. These are controlled by central nervous system inputs that are influenced by a variety of factors such as light, viewing distance, alertness and cognitive load. The pupil constricts in response to light (the direct light reflex) and, to a lesser extent, to near accommodation. The other pupil constricts consensually.

- **Dilation of the pupil** results from contraction of the smooth cells of the radial muscle, controlled by the sympathetic nervous system. The sympathetic nervous system acts directly on the muscle's cells peripherally and acts centrally by inhibiting the Edinger-Westphal nucleus. Psychosensory reactions are transmitted via the sympathetic system.
- **Constriction of the pupil** in response to light or accommodation occurs when the circular muscle, controlled by the parasympathetic nervous system, contracts.

Pathways of the pupillary reflex

The pathway for pupillary constriction for each eye has an afferent limb taking sensory information to the midbrain, and two efferent limbs (one to each eye).

**The afferent limb** is made up of the retina, the optic nerve and the pretectal nucleus in the midbrain, all on the same side.

**The efferent limb** for pupillary constriction comes from the pretectal nucleus via the Edinger-Westphal nucleus (also in the midbrain) to the ciliary sphincter muscle of the iris. Each pretectal nucleus has two pupillary motor outputs, one to the Edinger-Westphal nucleus on its own side and one to the other side. From each Edinger-Westphal nucleus, preganglionic parasympathetic fibres exit with the oculomotor nerve. They travel in the superficial part of the oculomotor nerve via the cavernous sinus and the superior orbital fissure to synapse in the ciliary ganglia. Short ciliary nerves then innervate the iris sphincter and muscles of accommodation.

**Pupillary dilatation** is controlled by the sympathetic system and is efferent only. The pathway begins in the cortex, which exerts a modulatory effect on constriction which is lost during drowsiness and sleep but increased during intense concentration and arousal. During sleep the pupils are partially constricted but still react to light.

The sympathetic input then comes from the hypothalamus with the first synapse at the ciliospinal centre at C8-T1 level. Postsynaptic neurons travel down all the way through the brain stem on each side and finally exit through the cervical sympathetic chain, travel over the lung apices, and ascend to the superior cervical ganglia with the carotid artery, then onwards as a plexus around the internal carotid artery, passing through the cavernous sinus. The sympathetic fibres then travel with the trigeminal nerve through the superior orbital fissure to the ciliary muscle.

There is a secondary sympathetic effect modulated by adrenergic receptors in the Edinger-Westphal nucleus which are inhibited by the direct action of sympathetic amines.
Examination of the pupils

See also separate Examination of the Eye article.

General examination of the patient
This may provide helpful clues as to the cause of pupillary abnormalities, particularly where there is an underlying neurological cause.

Pupillary observation
Note the shape and size of the pupils in ambient bright light. Size is measured in millimetres and the normal pupil ranges from 1-8 mm. When pupillary function is normal, pupils are isocoric (equally sized) and react equally to light.

Reduce the ambient light and ask the patient to fixate on the far wall. Observe the pupils closely whilst shining a bright light on the patient's face from below (minimise the shadow cast by the nose by placing the light in the midline). If there seems to be size asymmetry, stand back and observe the red reflex of both eyes simultaneously with the ophthalmoscope. A slight difference will become more apparent.

A slit lamp will aid more detailed observation of an abnormally shaped pupil.

Pupillary reflexes
Three reflexes should be tested:

Light reflex
This assesses the integrity of the pupillary light reflex pathway.

- Dim the ambient light and ask the patient to fixate a distant target. Illuminate the right eye from the right side and the left from the left side. Note whether there is a direct pupillary response (the pupil constricts when the light is shone on to it) and a consensual response (the other pupil also constricts).
- A normal result is a brisk, simultaneous, equal response of both pupils in response to light shone in to one or the other eye.

Swinging flashlight test
This compares the direct and consensual pupillary constriction of each eye to look for a difference in the afferent conduction between them, called a relative afferent pupillary defect (RAPD). It relies on a comparison between the two eyes, and is looking for (and can only detect) an asymmetrical abnormality in the afferent pathway.

- Ambient light should be dimmed. Check the light reflex in each eye, then move the beam swiftly and rhythmically from eye to eye, making sure that each eye receives the same light exposure, from the same angle.
- Note the pupillary constriction of both eyes. When the beam is swung from eye to eye, the bilateral pupil constriction should not change and both pupils should hold their degree of constriction.
- If an RAPD is present then when light is shone on to the abnormal pupil, both pupils appear to dilate because the degree of constriction reduces. This means that the afferent signal from this eye is weaker so that both its constriction and also the consensual reflex are reduced. This abnormal response is also known as a Marcus Gunn pupil.
- Note that if the problem lies not with the afferent but with the efferent signal to the pupil then the consensual pupillary response will be unaffected. The affected eye will show poor construction throughout the swinging flashlight test, whereas the normal eye will both constrict normally and show a normal consensual response.
- It can be hard to perform the test accurately. Examiner bias, light position variability, and difficulty observing both eyes, dark irises, pre-existing anisocoria, small pupils and the presence of efferent defects may make it difficult to detect asymmetry.
- In glaucoma an RAPD indicates that there is more optic nerve damage in one eye than in the other, even if the visual acuity in both eyes is equal.

The RAPD is a useful test for determining if visual loss is due to a defect of the optic nerve rather than being due to a cataract, as RAPD will be present in the former but not in the latter.
Near reflex test
This assesses the pupillary component of accommodation. (The other two components of accommodation are increased lens thickness and curvature, and convergence of the eyes.)

- In a normally lit room, instruct the patient to look at a distant target. Bring an object (eg, a finger) to their near point (about an arm’s length away) and observe the pupillary reflex when their fixation shifts to the near target.
- A normal test shows a brisk constriction.
- In near-light dissociation, the patient has a better pupillary near reflex than light reflex.

Pupillary abnormalities[1]
Pupillary disorders may involve the afferent pathways (RAPD) or the efferent pathways. Anisocoria, where not physiological, indicates a problem of the efferent pupillary pathway, either parasympathetic or sympathetic (Horner’s syndrome). Disorders of the parasympathetic system impair the light response and they include third nerve palsy and tonic pupil. Disorders of the iris, including application of cholinergic agents, also need to be considered in impaired pupillary light reaction.

Anisocoria
This refers to unequal pupils. Anisocoria is physiological (and harmless) in about 20% of people. Anisocoria of new onset can suggest serious underlying pathology such as Horner’s syndrome due to carotid dissection, or third nerve palsy due to aneurysm.

It is necessary to ascertain first which pupil is behaving abnormally. Compare the pupils in light and dim conditions:

- If there is a poor (slow, partial or absent) reaction to light in one eye and the anisocoria is more evident in a well-lit room, the affected pupil is abnormally large.
- If there is a good reaction to light in both eyes but a poor, slow or absent dilation in the dark (ie the anisocoria is enhanced), the affected pupil is abnormally small.

The variation between eyes should be no more than 1 mm: both eyes should react to light normally.

Unilateral large pupil
This is a pupil showing poor constriction in a well-lit room. Causes include:

- Traumatic iris damage.
- Third cranial nerve palsy.
- Rubeosis iridis (neovascular eye disease).
- Holmes-Adie syndrome: may also be irregular, unusually unilateral - see below.
- Pharmacological dilation (ie dilating drops).

Unilateral small pupil
This is a pupil showing poor dilatation in low light. Causes include:

- Physiologically small pupil.
- Uveitis with synaechiae.
- Horner's syndrome.
- Argyll Robertson (AR) pupil (may also be irregular, usually bilateral - see below).
- Pharmacological constriction (constricting drops).
Impaired pupillary light reflex

Normally, pupils react (ie constrict) equally. Comparing the direct and consensual reaction to light in both eyes is helpful in locating a lesion, remembering that the retina and optic nerve are needed for the afferent signal and that the oculomotor nerve provides the efferent component of both the direct and consensual reflexes.

- If the optic nerve of the first eye is damaged: the direct light reflex is lost in the first eye, as is the consensual effect in the second eye, as it receives no message. However the oculomotor nerve in the first eye is intact, so its pupil will still constrict when light is shone into the other eye.
- If the optic nerve of the second eye is damaged then when light is shone in the (normal) first eye, the second eye will still show consensual constriction, since its oculomotor nerve is intact.
- If the oculomotor nerve of the first eye is damaged it can produce no direct light reflex as the motor component is lost. However, the optic nerve still conveys the afferent signal, so that the other eye will constrict consensually to light.
- If the oculomotor nerve of the second eye is damaged then when light is shone into the normal first eye there is no consensual constriction of the second.

Relative afferent pupillary defect

An RAPD is a defect in the direct pupillary response and usually suggests optic nerve disease or severe retinal disease. Causes include:

- Unilateral optic neuropathies are common causes of an RAPD. These include arteritic (giant cell arteritis) and non-arteritic causes. Usually there will be a loss of vision or of part of the visual field.
- **Optic neuritis**: even very mild optic neuritis can lead to a very strong RAPD.
- **Severe glaucoma**: while glaucoma normally is a bilateral disease, if one optic nerve has particularly severe damage, an RAPD can be seen.
- **Traumatic optic neuropathy**: this includes direct ocular trauma, orbital trauma, and head injuries which damage the optic nerve as it passes through the optic canal.
- **Optic nerve tumour**: this is a rare cause.
- **Orbital disease**: including compressive damage to the optic nerve from thyroid-related orbitopathy, orbital tumours, or vascular malformations.
- **Optic atrophy**: such as Leber's optic atrophy.
- **Optic nerve infections or inflammations**: cryptococcus can cause severe optic nerve infection in the immunocompromised. Sarcoidosis can cause inflammation of the optic nerve. Lyme disease can affect the optic nerve.
- **Severe ischaemic retinal disease**: eg, ischaemic central retinal vein occlusion, central retinal artery occlusion, sickle-cell retinopathy.
- **Retinal detachment**: an RAPD can often be seen if the macula is detached.
- **Very severe unilateral macular degeneration**.
- **Retinal infection**: cytomegalovirus, herpes simplex and other causes of retinitis can lead to an RAPD if there is extensive disease.
- **Amblyopia**: if very severe, can lead to an RAPD.

Non-reactive pupil

A unilateral fixed dilated pupil suggests injury or compression of the third cranial nerve and the upper brain stem. Fixed and dilated pupils in comatose patients indicate a poor prognosis, especially when present bilaterally.

Causes of a unilateral non-reactive pupil

- Post-traumatic iridocyclitis - eg, direct facial trauma.
- Serious intracranial pathology - eg, extending intracranial mass, intracranial haemorrhage, subarachnoid haemorrhage.
- **Diffuse brain injury**.
- Oculomotor nerve (CN III) palsy (see below).
- A large poorly reactive pupil with diplopia is the most common presentation of an aneurysm of the posterior communicating artery.
- Pharmacological blockade.
- **Ocular prosthesis**: the normal pupil may be relatively constricted.
Causes of bilateral non-reactive pupils

- Extensive intracranial pathology - eg, trauma, haemorrhage.
- Diffuse brain injury.
- Brain stem herniation, brain death.
- Pharmacological blockade.

Third cranial nerve palsy

When the pupil is involved in a oculomotor nerve palsy, it is fixed and dilated (or minimally reactive). A partially dilated pupil which reacts sluggishly to light suggests a relative pupil-sparing CN III palsy. See also separate Cranial Nerve Lesions article.

CN III palsy with involvement of pupil requires urgent investigation. Relative pupil-sparing CN III palsy is usually ischaemic in nature and is less urgent unless there is progression.

The differential diagnosis of a third nerve palsy includes:

- Myasthenia gravis.
- Thyroid eye disease.
- Chronic progressive external ophthalmoplegia.
- Orbital inflammatory pseudotumour.
- Internuclear ophthalmoplegia.
- Pannus's syndrome (vertical gaze palsy caused by a pineal tumour).
- Giant cell arteritis.
- Extradural haematoma, which can cause a progressively dilating pupil, due to gradual compression of the third nerve.
- Multiple cranial nerve palsies: this suggests intracranial or meningeal tumour, polyneuropathy or cavernous sinus lesion.

Horner's syndrome

This is a relatively rare disorder caused by an interruption of the sympathetic nerve supply to the eye. The classic signs are:

- A constricted pupil.
- Ptosis.
- Absence of facial sweating (anhidrosis).
- Enophthalmos.

Horner's syndrome is distinguished from physiological anisocoria by instillation of a drop of 4% cocaine: in physiological anisocoria, this results in dilation, whereas it doesn't where there is a Horner's syndrome. Causes of Horner's syndrome include benign causes (such as migraine, goitre and cluster headache), neurological conditions (such as multiple sclerosis and syringomyelia) but also life-threatening compressive lesions at any point on the long sympathetic pathway, including tumours such as Pancoast's tumour on the lung apex, thyroid carcinoma, cavernous sinus thrombosis and carotid artery dissection.

For much greater detail, see separate Horner's syndrome article.

Near-light dissociation pupils

In the mid-1860s Douglas Argyll Robertson described an abnormal pupil, which reacted poorly to light and briskly to accommodation, in the context of neurosyphilis. In the early 20th century, William John Adie described a second type of pupil that could also accommodate but not react. Adie's tonic pupil is usually associated with a benign peripheral neuropathy, not with syphilis.

AR pupils develop only after decades of untreated syphilitic infection and are now rare in the developed world. A patient whose pupil 'accommodates but does not react' almost always has a Holmes-Adie pupil, not an AR pupil.

It is possible to distinguish between the two types of pupil. The accommodation response in AR pupils is brisk and immediate. The near response in tonic pupils is slow and prolonged.
Holmes-Adie pupil (Adie’s tonic pupil)

- This most commonly affects younger women (3rd/4th decade).
- The condition is benign.
- The pupil is dilated in the early stages and may also be irregular.
- The pupil reacts slowly to light but briskly to accommodation (ie light-near dissociation).
- Once the pupil has constricted it remains small for an abnormally long time (tonic pupil).
- 80% are unilateral.
- Due to damage to the ciliary ganglion or postganglionic parasympathetic fibres, usually by a viral or bacterial infection (eg, *herpes zoster ophthalmicus*).
- Corrective spectacles may be prescribed; no other treatment is usually needed.
- Infants <1 year old should be referred to a paediatric neurologist to rule out familial dystonias (Riley-Day syndrome).
- Over months to years, the pupil diminishes in size, eventually to become miotic.
- Diagnosis is confirmed by the pupil's hypersensitivity to very weak miotic drops which cause the abnormal pupil to contract vigorously and the normal pupil minimally.
- Occasionally associated with diminished deep tendon reflexes (Holmes-Adie syndrome) ± autonomic nerve dysfunction.

Argyll Robertson (AR) pupil

- This is usually bilateral (although it can be asymmetrical).
- A tonically small pupil that reacts poorly or not at all to light but briskly to accommodation (light-near dissociation).
- The pupils are difficult to pharmacologically dilate.
- Believed to be due to bilateral damage to nuclei in the midbrain.
- Considered highly specific for neurosyphilis, the most common cause.
- Other, very rare causes include:
  - Diabetic neuropathy.
  - Alcoholic midbrain degeneration.
  - Parinaud’s dorsal midbrain syndrome: this is caused by a tumour of the pineal gland, which impairs vertical gaze and causes pseudo-AR pupils.
  - Encephalitis.
  - Amyloidosis.
  - Multiple sclerosis.
  - Midbrain tumours.

Midbrain pupils
This refers to the bilateral mid-dilated pupils associated with dorsal midbrain lesions. There is a light-near dissociation but a good response to miotics and mydriatics.

Abnormal pupillary shape
The human pupil should be round. Many other pupillary shapes are seen in nature, including both vertical and horizontal slits, rectangles and crescents. Causes of abnormal pupillary shape include:

- Congenital defects (eg, *coloboma*).
- Iridocyclitis.
- Iris trauma.
- Holmes-Adie pupil (see above).
- AR pupil (see above).
- A fixed oval pupil, in association with severe pain, a red eye, a cloudy cornea and systemic malaise, suggests acute angle-closure glaucoma.
Structural pupillary abnormalities

Congenital abnormalities

- **Aniridia** - this is a bilateral condition arising from the abnormal neuroectodermal development. It is associated with glaucoma and serious, systemic abnormalities.
- **Coloboma** - this is an uncommon, congenital condition characterised by a unilateral or bilateral partial iris defect. See separate Coloboma article.
- **Leukocoria** - this refers to a white pupil. Causes include congenital cataracts, retinoblastoma, persistent fetal vasculature syndrome, Coats' disease and retinopathy of prematurity.

Acquired abnormalities

- **Pseudoexfoliation syndrome** - this is characterised by a grey-white fibrogranular material deposited on the anterior lens. Pupil shape and function are not affected - it is significant due to its association with glaucoma and its potential to make cataract surgery more difficult.
- **Sphincter tear** - iris tear can occur as a result of blunt or penetrating trauma, or during intraocular surgery. Tears may be associated with glaucoma and, if large, visual problems.
- **Synechiae** - these are adhesions between the lens and the iris (posterior synechiae) or the iris and the peripheral cornea (peripheral anterior synechiae). They give rise to an abnormally shaped pupil; treatment depends on the underlying cause. Uveitic posterior synechiae are broken with mydriatics, whereas glaucomatous anterior synechiae may be managed with miotics.

Drugs affecting the pupils

Many drugs can affect pupillary size, both topically applied and generally ingested. The pinpoint pupils caused by opiate use are a barrier to assessment of the head-injured patient. Topical mydriatics are widely used in ophthalmological practice to enable full examination of the eye.

Topical drugs

- **Dilating** - sympathomimetics (eg, phenylephrine, adrenaline (epinephrine)) and antimuscarinics (eg, cyclopentolate, tropicamide, atropine).
- **Constricting** - muscarinic agonists (eg, pilocarpine).

Systemic drugs

- **Dilating** - sympathomimetics (eg, adrenaline (epinephrine)) and antimuscarinics (eg, atropine), tricyclic antidepressants, amfetamines and ecstasy.
- **Constricting** - opiates (eg, morphine and organophosphates).

Further reading & references

- Pupillary abnormalities; Atlas of Ophthalmology
- Clinical Ophthalmology: A Systematic Approach
- Oxford Handbook of Ophthalmology


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