Pupillary abnormalities
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Introduction

Overview

Does the patient have an aneurysm or physiologic anisocoria? The pupil exam is to the eye what the deep tendon reflexes are to the neurologic exam: objective, helpful, and difficult to fake. The author discusses causes of anisocoria and abnormal pupillary activity. Her “low tech” algorithm leads the clinician through the evaluation process to know whether the patient can be reassured or needs additional testing.

Key points

- The “no fail” pupil examination includes: measurement of the pupil size in the light and in the dark, assessment of the pupillary light reaction in each eye, and the swinging flashlight test to determine the presence of a relative afferent pupillary defect. If 1 or both pupils do not react well to light, check the near response.
- Parasympathetic pupils (Adie tonic pupil, oculomotor palsy pupil) look the same but may be distinguished by the company they keep. Consider diplopia, ptosis (oculomotor palsy), light-near dissociation, and vermiform movements of the iris sphincter (Adie pupil).
- Apraclonidine is useful for pharmacologic testing of a suspected Horner syndrome and, unlike cocaine drops, is commercially available.

Historical note and terminology

Around 200 AD, Galen likened the iris to an elastic circular ring that was passively inflated or deflated by vital spirits sent from the brain to enhance vision. It was not until the first half of the 18th century that it became widely accepted that iris movement and pupil size were due to active interaction of 2 iris muscles: a longitudinal radial dilator and a circular sphincter muscle.

Many contributions to our understanding of pupillary physiology and pathology were made in the 20th century, including the description of the swinging flashlight test for assessing a relative afferent pupillary defect (Thompson 2003).

Clinical manifestations

Presentation and course

There several major types of pupil abnormalities:

Unilateral. (A) unequal pupil size (anisocoria), (B) irregular pupil shape, (C) pupillary displacement (corectopia), (D) asymmetrical pupillary reaction (relative afferent pupillary defect), and (E) episodic abnormalities.

Bilateral. (A) poorly reactive to light with a good near response (light-near dissociation), (B) abnormal shape or position (corectopia), and (C) change in size and reactivity.

The abnormality may be transient or constant. Often pupillary abnormalities are asymptomatic or noticed by an observer. Occasionally, patients complain of photophobia in an eye with a large (mydriatic) pupil because increased light reaches the retina through the wider aperture. Because the parasympathetic system innervates the pupilloconstrictor and the ciliary muscle for accommodation, patients with oculomotor nerve palsy or short ciliary
nerve damage may report blurred near vision (eg, while reading) in addition to the larger pupil size.

**Prognosis and complications**

Prognosis and complications are individually assessed for the specific pupillary abnormality and its etiology.

**Clinical vignette**

A 46-year-old woman experienced episodes of left temporal pain daily for 2 weeks. The pain, described as throbbing and stabbing with pressure behind the left eye, lasted 30 minutes and occurred 4 times daily. At times, the pain radiated to the left ear. Initially, there was no conjunctival injection, lacrimation, pupillary asymmetry, or blurred vision. One week prior to evaluation, she noticed that her left pupil was smaller than her right pupil. There was preexisting right eyelid ptosis, and the left eyelid also appeared ptotic. She also related a 2-month history of intermittent left ear pain of undetermined etiology.

She had a history of migraines since her 20s, but the migraine pain was distinctly different from her current pain. Her typical migraine pain was bi-occipital and throbbing with photophobia, phonophobia, and nausea. There was no history of trauma.

Examination revealed best corrected visual acuity of 20/20 in both eyes. The pupil size in the light was 3 mm in the right eye and 2 mm in the left eye. In darkness, the pupil size was 5 mm in the right eye and 4 mm in the left eye. The pupillary reactions were normal with no afferent pupillary defect. There was bilateral mild ptosis, a bit more prominent on the left. Ocular motility, external examination, fundi, and the neurologic examinations were normal. Instillation of 10% cocaine drops produced dilation of the right pupil and no change in the size of the left pupil.

Computed tomography angiography showed a left internal carotid artery dissection with pseudoaneurysm formation. The patient was anticoagulated for 6 months. Her headaches resolved, but there was no change in her left Horner syndrome at her 6-month follow-up visit.

**Biological basis**

**Etiology and pathogenesis**

There are many causes of pupillary abnormalities. Any process that affects the autonomic innervation of the iris muscles or damages the iris muscles themselves will cause a pupil abnormality. For example, a dorsolateral brainstem stroke may injure the central neuron of the oculosympathetic pathway to cause ipsilateral miosis and poor pupillary dilation (Horner syndrome). Miosis can also result from local trauma to the iris causing mechanical restriction of pupillary movement. Systemic autonomic neuropathies such as diabetes mellitus can denervate the iris sphincter muscle causing a poor pupillary light reaction. A tonic pupil can also result from local inflammation of the ciliary ganglion.

Clarifying the pupil abnormality (sympathetic versus parasympathetic versus iris muscle defect) and then localizing the most probable site of injury (central versus peripheral) will better assist the clinician in identifying the etiology of a pupillary abnormality than will the memorization of a list of diseases.

The pupil is a hole formed by the iris. Two iris muscles control its diameter: the pupillconstrictor and the pupillodilator. The pupilloconstrictor is a sphincter muscle that is innervated by the parasympathetic autonomic nervous system. The pupillodilator is a radial muscle that is innervated by the sympathetic autonomic nervous system (Thompson 1992).

The parasympathetic pathway to the pupil originates in the Edinger-Westphal subnucleus of the oculomotor (third) nuclear complex. The parasympathetic impulse travels through the oculomotor (third) nerve and synapses in the ciliary ganglion. The postganglionic short ciliary nerves transmit the final parasympathetic impulse to the iris sphincter muscle, which constricts the pupil. The sphincter muscle bundles are made up of 5 to 8 muscle cells oriented parallel to the pupillary margin, and each muscle bundle functions as a unit. The parasympathetic pupillomotor system is a 2-neuron pathway.

The sympathetic pathway to the pupil originates in the posterolateral hypothalamus. This is a 3-neuron ipsilateral pathway. The first (central) neuron travels through the lateral brainstem to synapse in the spinal cord at C8-T2, the
The second (preganglionic) neuron skirts across the lung apex and ascends the neck to synapse in the superior cervical ganglion. The third (postganglionic) neuron accompanies the internal carotid artery into the skull base in close proximity to the trigeminal ganglion. After briefly joining with fibers of the abducens nerve, it passes through the inferior orbital fissure with the ophthalmic division of the trigeminal (fifth) nerve. The sympathetic pathway continues in the nasociliary branch of the trigeminal nerve to reach the radial iris muscle that dilates the pupil (Maloney et al 1980; Thompson and Miller 1998).

The pupillary light reflex pathway is composed of afferent and efferent limbs. The afferent limb begins in the retinal photoreceptors that receive the light impulse (input signal) and transmit it to the optic nerves. Similar to the fibers mediating vision, the fibers from the nasal retina (temporal visual field) decussate at the optic chiasm so that the ipsilateral optic tract carries impulses from the ipsilateral temporal retina and the contralateral nasal retina. The pupillary input signal travels in the optic tract, but diverges from the visual fibers to enter the midbrain synapse in the pretectal nucleus. Axons from the pretectal nucleus stimulate both the ipsilateral and contralateral Edinger-Westphal nucleus. Thus, under normal conditions, both Edinger-Westphal nuclei receive identical afferent input. The Edinger-Westphal nucleus begins the efferent limb of the pupillary light reflex and provides the output signal that ultimately directs pupilloconstriction. Only about 4% of the efferent output of the Edinger-Westphal nucleus mediates the pupillary light reflex, whereas 96% is concerned with accommodation. Axons from the Edinger-Westphal nucleus travel through the oculomotor (third) nerves and synapse in the ciliary ganglion. The postganglionic short ciliary nerves transmit the final impulse to the pupilloconstrictor muscle (Thompson 1992).

Because both Edinger-Westphal nuclei receive the same afferent input, a lesion in 1 afferent limb of the pupillary light reflex (eg, optic nerve) decreases the amplitude of pupilloconstriction in both eyes (direct and consensual response) when that eye is stimulated compared to when the eye with the normal afferent limb is stimulated. This can be detected clinically during the swinging flashlight test as a relative afferent pupillary defect. Pupil sizes are equal as long as output signals (efferent limb) are equal. Anisocoria is never due to a relative afferent pupillary defect (Corbett and Thompson 1992).

**Epidemiology**

An ophthalmic population study of 3046 adults ages 50 to 93 years found that pupillary diameter was associated with lower age, female sex, lower body mass index, taller body height, and lower systolic blood pressure (Wang et al 2013). Ocular parameters influencing pupil diameter included longer axial length of the globe, deep anterior chamber, flatter cornea, and higher intraocular pressure.

Pupillary abnormalities are common. The prevalence of simple (physiologic, essential) anisocoria alone is 20% of the general population (Lam et al 1987). Patients with a history of cataract or other ocular surgery may have had iris manipulation with subsequent dysfunction or distortion of the iris muscles.

**Prevention**

Prevention of pupillary abnormalities is directed at prevention of any disease that may affect the eye or the autonomic nervous system (eg, diabetes mellitus).

**Differential diagnosis**

**Unilateral abnormalities**

**Anisocoria.** Anisocoria, or unequal pupil size, can be evaluated by first determining the size of the pupils in light and in darkness. This maneuver reveals whether the anisocoria is greater in darkness or if it is greater in light. Then the light reaction is assessed. If the abnormal pupil does not react to light, check for the presence of near constriction. Sometimes it is difficult to determine whether the abnormal pupil is the smaller one or the larger one.

**Anisocoria with a normal light reaction**

**Physiologic anisocoria.** Physiologic anisocoria is present in about 20% of the general population. It is characterized by an equal amount of anisocoria in light and in darkness. The anisocoria is usually less than 1.0 mm. Although reported to be more common in persons with light colored irides, it may just be more noticeable in that population. It may seem to "come and go" and may even change sides. The pupils are round, react briskly to light, and dilate equally when the
revealed degeneration of the fasciculus gracilis and fasciculus cuneatus, with mild loss of neuronal cell bodies in dorsal Adie syndrome. The pathogenesis of the hyporeflexia is uncertain; autopsy studies in a small number of patients initial evaluation or develop years later. The combination of Adie pupil and hyporeflexia or areflexia is termed Holmes-hyporeflexia or areflexia is also associated with Adie pupil; the deep tendon reflex changes may be present at the Loewenfeld 1981). About 4% of patients per year develop involvement of the pupil of the second eye. Generalized near response with slow redilation, and cholinergic supersensitivity continue to be evident (Loewenfeld 1967; Thompson 1977; Grimson 1979). Ipsilateral anhidrosis may be present if the lesion is preganglionic but is often difficult to discern.

Horner syndrome that is congenital or acquired in childhood may be associated with iris heterochromia. The ipsilateral iris is usually lighter in color from failure of pigmentation (congenital) or depigmentation after denervation (acquired). Horner syndrome may result from injury at any point along the 3-neuron oculosympathetic pathway. A central (first order) Horner syndrome is accompanied by other clinical symptoms and signs of brainstem or spinal cord dysfunction. A preganglionic (second order) Horner syndrome may occur in isolation or with symptoms and signs of a lower cervical/upper thoracic radiculopathy. A postganglionic Horner syndrome is usually an isolated finding but is sometimes associated with neck pain or headache, ipsilateral cerebral hemispheric dysfunction (from thromboembolic disease related to cervical carotid dissection), or ipsilateral trigeminal or abducens palsy. Distinguishing a preganglionic from a postganglionic Horner syndrome can be challenging. In the absence of other localizing signs and symptoms, hydroxyamphetamine 1% instilled in each eye results in pupillary dilation if the Horner syndrome involves the first or second order neuron, but no dilation if the lesion is postganglionic (see Diagnostic workup section for description of testing procedure). A second-order neuron Horner syndrome requires careful imaging of the chest and neck to exclude a tumor. A post-ganglionic Horner syndrome is evaluated with imaging of the neck and the base of the brain.

**Anisocoria with a poor light reaction.** If the pupil does not react well to light, the next step in evaluation is to assess the near response. The differential diagnosis includes oculomotor nerve palsy, pharmacologic pupil, and iris damage. Oculomotor nerve palsy is distinguished from this group by presence of diplopia, ptosis, or motility problems.

**Tonic pupil.** A tonic pupil responds poorly to light, but constricts to a near stimulus. Adie tonic pupil is the most common type of unilateral tonic pupil and was initially described by Ware in 1812 (Kelly-Sell and Liu 2011). It is a benign condition that may occur at any age, although it is most common in adult women. Its cause is uncertain; a viral etiology is suspected but has never been demonstrated. The mechanism of a tonic pupil is hypothesized as follows. Injury to the ciliary ganglion or short ciliary nerves results in postganglionic parasympathetic denervation of the iris sphincter and ciliary muscle. The iris sphincter constricts the pupil and the ciliary muscle regulates accommodation (near vision). When these structures are acutely denervated, the affected pupil is large and reacts poorly, if at all, to light and near stimulation and the patient may notice difficulty reading and doing near work.

After several days, the sphincter develops cholinergic denervation supersensitivity. After several weeks, the injured postganglionic parasympathetic fibers (short ciliary nerves) begin to sprout collaterals and regenerate. Consistent with the output received from the Edinger-Westphal nuclei, there are far more regenerating fibers that serve accommodation than pupilloconstriction, at a ratio of about 30 to 1. Some of these accommodative fibers take an aberrant pathway and reinnervate the iris sphincter in an irregular fashion. This combination of denervation with subsequent aberrant regeneration of the postganglionic parasympathetic fibers leads to segmental areas of palsy. Hippus (nonevoked, spontaneous, nonregular, small amplitude contractions of the iris that occur in normal subjects) in a segmentally denervated iris results in irregular contraction of the iris sphincter and vermiform movements and a slow (tonic) contraction of the sphincter whenever the patient attempts to accommodate. The iris remains poorly responsive to light stimulation due to damage to the less numerous pupilloconstrictor fibers, resulting in light-near dissociation (the pupils react poorly to light and much better to a near stimulus). Over months to years, the resting size of a tonic pupil becomes smaller but the characteristics of segmental sphincter palsy, poor light reaction, tonic near response with slow redilation, and cholinergic supersensitivity continue to be evident (Loewenfeld 1967; Loewenfeld 1981). About 4% of patients per year develop involvement of the pupil of the second eye. Generalized hyporeflexia or areflexia is also associated with Adie pupil; the deep tendon reflex changes may be present at the initial evaluation or develop years later. The combination of Adie pupil and hyporeflexia or areflexia is termed Holmes-Adie syndrome. The pathogenesis of the hyporeflexia is uncertain; autopsy studies in a small number of patients revealed degeneration of the fasciculus gracilis and fasciculus cuneatus, with mild loss of neuronal cell bodies in dorsal
root ganglia (Miyasaki 1988). It is not unusual to evaluate a patient for an acute Adie pupil and find evidence of a chronic Adie pupil in the contralateral eye.

Dilute pilocarpine (0.1%) instilled into both eyes will produce marked constriction of the Adie pupil regardless of its duration, often causing the mydriatic pupil to become the smaller pupil owing to denervation supersensitivity.

Oculomotor (third) nerve palsy. The oculomotor nerve is the preganglionic parasympathetic neuron to the iris sphincter and ciliary muscle and carries motor fibers to the levator palpebrae, superior rectus, inferior rectus, medial rectus, and inferior oblique muscles. The clinical features of oculomotor nerve palsy are ptosis, mydriasis, and ophthalmoplegia. The upper lid ptosis can be mild or complete. The pupil is larger (mydriasis) than the normal pupil and reacts poorly to light and near stimulation. Preganglionic parasympathetic denervation of the pupil (oculomotor nerve palsy) can sometimes lead to cholinergic supersensitivity of the iris sphincter, much like postganglionic denervation of the pupil (tonic pupil). In the comatose patient whose assessment of lid and eye movement function is difficult, pupillary enlargement may be the most important sign of transtentorial herniation.

A diagnostic dilemma often occurs in the awake patient with acute ipsilateral headache, pupillary dilation, and poor pupillary reactivity. This may be the initial sign of oculomotor nerve palsy due to aneurysmal compression but may also represent a benign microvascular cranial mononeuropathy. Pupillary involvement in aneurysmal oculomotor nerve palsy occurs in 85% to 95% of cases. If aneurysm is the cause, ptosis or ophthalmoplegia will usually develop within a week. A microvascular (“ischemic”) oculomotor palsy generally occurs in patients over the age of 50, especially in those with small vessel arteriosclerosis (hypertension, diabetes), and is usually pupil sparing, but pupillary involvement can be as high as 38%. When anisocoria is present in a microvascular third nerve palsy, it is generally less than 1 mm (Jacobson 1998). Anisocoria in such patients may develop up to 2 weeks after the onset of symptoms (Dhume 2013). A fixed dilated pupil that remains an isolated abnormality for more than 1 week in an alert and neurologically intact patient is probably not an acute oculomotor nerve palsy but more likely an Adie pupil (Chen et al 1994; Wilhelm 1995). However, when the distinction between an aneurysmal and microvascular oculomotor palsy is not apparent by history and examination, a magnetic resonance angiogram or catheter angiogram may be needed.

When the oculomotor nerve suffers a nonischemic injury (trauma, compression) that disrupts the Schwann cell tube, the regenerating axons may grow along an aberrant course. For example, axons originally destined to the inferior rectus muscle might instead sprout to the iris sphincter. Therefore, whenever the patient attempts to look down, the pupil constricts due to synkinesis. Each of the oculomotor nerve branches that innervate extraocular muscles have been reported to aberrantly innervate the iris sphincter, leading to a variety of synkinetic eye and eyelid movements involving the pupil (Czarnecki 1978; Loewenfeld 1993). Although the anisocoria of aberrant regeneration is greater in darkness, the abnormal pupil is the smaller one in darkness and is the larger one in bright light.

Pharmacologic mydriasis. Topical agents that can pharmacologically dilate the pupil fall into 2 classes: sympathomimetics, which stimulate the pupillodilator, or anticholinergics, which inhibit the pupilloconstrictor. Topical sympathomimetic agents include phenylephrine, cocaine, and hydroxyamphetamine, whereas anticholinergic agents include atropine, scopolamine, homatropine, cyclopentolate, and tropicamide. Inadvertent exposure to mydriatic agents may occur from over-the-counter eyedrops used for red, irritated, "allergy" eyes, scopolamine skin patches used for motion sickness, aerosolized anticholinergic agents used for asthma and respiratory distress, application of phenylephrine-containing topical hemorrhoidal preparations to reduce eyelid puffiness, or outdoor plants like Jimson weed (Goldstein et al 1997; Polomsky and Smereck 2012). The pupils will not react to light or near, or to dilute or regular-strength pilocarpine. A pharmacologically dilated pupil may be unilateral or bilateral, accidental or intentional.

The isolated dilated pupil. This clinical finding deserves special mention as it often prompts an emergent patient evaluation. Confirmation that the dilated pupil is an isolated clinical finding is important: there are truly no other signs of focal neurologic deficit, ipsilateral ptosis, or ophthalmoplegia. If the patient complains of diplopia, one should assume that weakness of 1 or more extraocular muscles exists. If there is difficulty deciding which extraocular muscles are involved, testing for ocular misalignment with red glass, Maddox rod, Hess screen, or alternate covering of the eyes may reveal subtle misalignment consistent with the diagnosis of a third nerve palsy.

Once it is established that no ophthalmoplegia is present, the 2 most common causes of an isolated, dilated pupil are tonic pupil and pharmacologically induced mydriasis. Rare causes include a fascicular or early compressive oculomotor palsy. In this circumstance, it is important to check the dilated pupil for any reaction to light, to look carefully for areas of segmental constriction and palsy, and to observe the pupillary light reaction to near stimulation. An isolated
A mydriatic pupil is a rare manifestation of giant cell arteritis (Prasad et al 2009). If there is a better near reaction than light reaction (light-near dissociation), the diagnosis is likely to be Adie tonic pupil. If the dilated pupil reacts barely or not at all to light or near stimulation, then consider either an acute tonic pupil that has developed within the past 1 to 2 weeks (before light-near dissociation has had time to occur) or pharmacologic mydriasis. A test for cholinergic supersensitivity using dilute (0.1%) pilocarpine will usually constrict a tonic pupil. If the pupil is still dilated and nonreactive, then instill 1% pilocarpine. An oculomotor palsy and a tonic pupil will constrict, but a pharmacologically dilated pupil will not (Thompson et al 1971; Lee et al 1997).

**Abnormal pupil shape.** The most common cause of irregular pupils is iris damage. Adie tonic pupils are frequently irregular in shape.

**Irish damage.** Anisocoria due to a damaged or anomalous iris may be suspected from the patient's history (iritis/uveitis with synechiae, ocular surgery, use of eyedrops, trauma, etc.) or bedside examination (iris atrophy, distorted pupillary margin, heterochromia). The pupil is generally irregular and poorly reactive to light. Referring a patient with this condition to an ophthalmologist will avoid unnecessary testing (Corbett and Thompson 1992).

**Abnormal pupil position.** Corectopia is the displacement of one or both pupils from the center of the iris. It may be congenital or acquired. Acquired corectopia is most frequently caused by asymmetric damage to the pupil sphincter or displacement of the iris by anterior chamber pathology. When it is associated with midbrain lesions, other manifestations of midbrain dysfunction are present, which warrant evaluative neuroimaging studies (Chu and Sadun 2013).

**Relative afferent pupillary defect.** The relative afferent pupillary defect is a sensitive sign of optic nerve dysfunction, although other disorders (widespread retinal disease, optic tract lesion) may sometimes produce a relative afferent pupillary defect.

**Episodic pupillary abnormalities.** Transient pupillary abnormalities include cyclic oculomotor palsy, ophthalmoplegic migraine, benign episodic unilateral mydriasis, and tadpole pupils.

Oculomotor palsy with cyclic spasms is a rare syndrome with onset usually before 2 years of age. The affected child has a chronic unilateral oculomotor palsy with superimposed spasms of hyperfunction of the third nerve. During the spasms the eye can adduct to midline, the ptotic lid rises, and the mydriatic pupil constricts. The spasms last 10 to 30 seconds, then the oculomotor palsy returns, cycling every 1 to 2 minutes. The cycles persist in sleep and throughout adulthood (Friedman et al 1989). The etiology is uncertain.

Recurrent painful ophthalmoplegic neuropathy (previously termed “ophthalmoplegic migraine”) occurs in children and adolescents, with an average age of onset of 10 years. There is a previous history of typical migraine headaches, which are at times followed by a unilateral oculomotor nerve palsy. Ophthalmoplegia is always present. The oculomotor palsy takes 1 to 4 weeks to resolve. The diagnosis is based on a characteristic history and negative evaluation for other possible causes of an oculomotor palsy. Many reports of gadolinium enhancement along the oculomotor nerve fascicle on MRI during the acute phase of ophthalmoplegia suggest that this process may be a syndrome of recurrent local demyelination rather than a true migrainous event (Carlow 2002).

Benign episodic unilateral mydriasis is characterized by paroxysms of unilateral mydriasis, usually without other associated symptoms. It has been noted in young women with migraine, lasts an average of 12 hours, and recurs with a frequency of 2 to 3 per month (Jacobson 1995).

Tadpole-shaped pupils due to intermittent segmental spasm of the dilator muscle last a few minutes and recur several times daily or weekly (Kawasaki 2012). The episodic distortion eventually resolves spontaneously. Conditions associated with tadpole pupils are Horner syndrome, tonic pupil, and migraine (Thompson et al 1983). Pharmacologic testing for Horner syndrome is recommended for patients with a history of episodic pupillary distortion as it accounts for nearly half of reported cases of tadpole pupils (Balaggan et al 2003).

Harlequin syndrome is manifested by the sudden loss of facial flushing on 1 side of the face after exercise, emotional or heat stress, resulting in a sharp demarcation line between the flushed contralateral side of the face and the pale ipsilateral side. There is often an underlying abnormality, such as birth trauma to the brachial plexus, a systemic dysautonomia, or an apical lung tumor, producing damage to the ipsilateral sympathetic fibers. The most common pupillary abnormality is an ipsilateral Horner syndrome; tonic pupils occur infrequently (Bremner and Smith 2008).
Bilateral pupillary abnormalities. Pupillary abnormalities may be helpful in localizing brainstem lesions and determining the anatomic basis of coma. The pupil size and reaction is normal with processes affecting the cerebral hemispheres. Dorsal tectal or pretectal lesions disrupt the pupillary light reflex, sparing accommodation. Nuclear midbrain lesions also cause midposition fixed pupils, but they are often irregular (corectopia) and unequal. Lesions of the pontine tegmentum result in bilaterally small, “pinpoint” pupils, perhaps from disruption of descending sympathetic pathways. Lateral medullary and ventrolateral cervical spinal cord lesions cause ipsilateral Horner syndrome (Plum and Posner 1972). Uncal herniation is accompanied by an ipsilateral or contralateral third nerve palsy. Bilateral fixed dilated pupils are seen in brain death, presumably owing to midbrain damage.

Many drugs affect pupillary size and reactivity. Mydriatics include belladonna alkaloids, atropine, scopolamine, tropicamide, cyclopentolate, intraorbital lidocaine, epinephrine, phenylephrine, ephedrine, cocaine, tricyclic antidepressants, papaverine, and other sympathomimetic agents. Miotics include pilocarpine, carbachol, acetylcholine, physostigmine, topical guanethidine, heroin, morphine, and dapiprazole (“Rev Eyes”).

Intracranial hypertension may influence pupillary reactivity. A study of patients with severe traumatic brain injury, aneurysmal subarachnoid hemorrhage, or intracerebral hemorrhage found an inverse relationship between pupillary reactivity and intracranial pressure using a handheld pupillometer (Chen 2011). Patients with unreactive pupils had the highest peaks of intracranial pressure. Another study found that the pupil may have prognostic value in patients with an oculomotor palsy caused by a pituitary tumor; patients with pupil-sparing palsies recovered more rapidly than those with pupillary involvement (Chaung et al 2011).

Light-near dissociation may be bilateral. Douglas Mooray Cooper Lamb Argyll Robertson, describing the pupillary sign in 1869 that still bears his name, stated, “I could not observe any contraction of either pupil under the influence of light, but, on accommodating the eyes for a near target, both pupils contracted” (Pearce 2004). Argyll Robertson pupils are small (1 to 2 mm) and irregular and display light-near dissociation; they are specific to CNS syphilis (Loewenfeld 1969). Iris atrophy may be visible on the slit lamp examination. Bilateral tonic pupils have also been reported following botulism, and with Lyme disease, rabies, Sjögren syndrome, systemic lupus erythematosus, and thiamine deficiency. They may be associated with an autonomic neuropathy, as in diabetes, alcoholism, Charcot-Mari-Tooth disease, multisystem atrophy, and other neurodegenerative disorders (Toth 2005). The distinction between bilateral Adie pupils and pupillotonia from a generalized neuropathy may be subtle. The amount of anisocoria (greater than 1 mm) and degree of light-near dissociation tend to be more pronounced in bilateral Adie pupils. However, sectoral palsy of the iris sphincter, larger-than-expected pupillary diameter in bright light, and anisocoria may be present in either condition (Bremner and Smith 2007).

Diagnostic workup

Examination. A complete pupillary examination consists of 5 parts: inspection, measurement of pupillary size in the light and in the dark, reaction to light, the swinging flashlight test, and the near response.

First, the pupils are inspected for evidence of irregularity or iris damage. The pupil size is measured in light and darkness using a pupil gauge as the patient fixates in the distance. The pupil size in darkness is obtained by dimly illuminating the eyes from below in order to visualize the pupils. Asymmetry of pupil size of 0.4 mm or more is clinically visible (Lam et al 1987). The reaction of each pupil to a bright, well-focused light source is assessed.

The presence or absence of a relative afferent pupillary defect is determined by holding the light source on the pupil for 1 to 2 seconds, then rapidly moving the light source to the contralateral eye (swinging flashlight test). Normal pupils will constrict slightly each time the light is shined into the eye. If there is dilation of the pupil to a light stimulus, a relative afferent pupillary defect is present and designated by the side of pupillary dilation. Of note, a relative afferent pupillary defect may be confused with hippus, the normal intermittent bilateral synchronous pupillary dilation and constriction (Yoss 1970). Slowing the speed of the swinging flashlight test will generally differentiate hippus from a relative afferent pupillary defect. In some circumstances, anisocoria may affect the estimation of a relative afferent pupillary defect. Unilateral mydriasis may occasionally induce a relative afferent pupillary defect in the contralateral eye. Pharmacological miosis in normal subjects produced an ipsilateral relative afferent pupillary defect in patients with darkly pigmented irides (Kardon 2013).

The pupillary reaction to a near stimulus is part of the near triad of convergence, lens accommodation, and miosis. It is clinically relevant when there is a poor light reaction as it tests the efferent limb of the reflex arc. It is best performed
in a dimly lit room. The patient is asked to look at a distant target as the pupils are illuminated from below. When the patient converges on a near target, such as the examiner's finger, the pupils will constrict and the smaller pupil size achieved is recorded (Thompson 1992). It is normal for the near response to be somewhat better than the light response, especially in patients who converge well.

This paradigm does not rely on the extent or “briskness” of the pupillary response or measurements of pupil size “before and after” light stimulation. The briskness of the pupillary response is subject to interpretation in clinical practice, depending on whether the examiner emphasizes the extent or the speed of constriction. The amplitude and velocity of pupillary reaction to a fixed light stimulus may vary by 3- to 4-fold in healthy subjects, although these 2 variables are linearly related within subjects, ie, the pupil will constrict more slowly if the amplitude of the response is small (Bremner 2012). Additionally, the amplitude of the pupillary response to light is reduced in older subjects. Thus, the briskness of the response is not to be used in isolation as an indicator of pupillary pathology and adds unnecessary steps in the examination. Some clinicians measure the size of the pupils before and after illumination as part of the pupillary assessment. However, the mechanics of the iris limit the amount of pupillary contraction, depending on the initial “resting” size of the pupil (Chen and Kardon 2013). Unless the pupillary diameter after light stimulation is calculated as a percentage of constriction relative to the baseline diameter, these measurements are likewise unhelpful.

**Pharmacologic testing.** All pharmacologic pupillary testing is performed in a standard fashion. It is important that the corneas not be manipulated (eg, applanation tonometry, testing of corneal sensitivity) prior to the test to ensure proper absorption of the drops. One drop of solution is instilled in each eye, and repeated in 5 to 10 minutes. The response can generally be observed in 30 to 45 minutes.

**Cocaine test.** The topical cocaine test is used to diagnose a Horner syndrome (oculopsymathetic defect). Cocaine inhibits the presynaptic reuptake of released norepinephrine at the neuromuscular junction. When the oculopsymathetic pathway is intact, cocaine will dilate the pupil. If there is any interruption within the oculopsymathetic pathway, then there will be no release of norepinephrine at the neuromuscular junction on which cocaine may act. The normal pupil will dilate and a Horner pupil will fail to dilate. A post-cocaine anisocoria of 1.0 mm or more is considered diagnostic of Horner syndrome (Kardon et al 1990). After the cocaine test is completed, the examiner should verify that the Horner pupil is capable of full dilation by instilling 1% phenylephrine into both conjunctival sacs. As phenylephrine is a direct sympathomimetic agonist on the pupillodilator muscle, both pupils should now dilate well. This step is important to make sure that the miotic pupil that fails to dilate to cocaine is not due to a “sticky” iris or pupillodilator muscle problem. Cocaine solution is not manufactured for ophthalmic instillation. It may be compounded by the pharmacy from powdered cocaine or buffered from the 4% solution that is commercially available for otolaryngologic use, although a 10% solution is preferable.

**Apraclonidine test.** Apraclonidine is an alpha-receptor agonist that down regulates the production and release of norepinephrine. In contrast to cocaine, it is commercially available (Iopidine™). In normal eyes, the alpha 2 activity down-regulates the production and normal release of norepinephrine. However, with chronic denervation and supersensitivity of the alpha 1 receptors, apraclonidine dilates the pupil in Horner syndrome. Instillation of 1 drop of 0.5% apraclonidine into each eye results in reversal of the anisocoria after 30 minutes (sensitivity 0.91). It has no effect on a normal pupil (Freedman 2005).

**Hydroxyamphetamine test.** If it is apparent from the clinical examination that a Horner syndrome is present, or if the cocaine test is positive, the next step in the diagnostic workup of a Horner syndrome is localization of the oculopsymathetic defect using the hydroxyamphetamine test. Hydroxyamphetamine releases stored catecholamines from the terminal bouton of the postganglionic neuron. If the lesion involves this neuron, the storage of neurotransmitter is already depleted and the pupil will not dilate to hydroxyamphetamine. If the lesion causing Horner syndrome involves the central or preganglionic neuron, then the postganglionic neuron is anatomically intact (transynaptic degeneration does not occur in this pathway) and hydroxyamphetamine will dilate the Horner pupil as much as the normal pupil (Cremer et al 1990). There will be no dilation with a postganglionic (third order) Horner syndrome. It is important to remember that the cocaine and hydroxyamphetamine tests cannot be performed on the same day. One should wait to perform the hydroxyamphetamine test until at least 24 hours have elapsed after cocaine testing. Hydroxyamphetamine is not commercially available but may be obtained through a compounding pharmacy.

**Limitations of pharmacologic testing for Horner syndrome.** False negative hydroxyamphetamine testing may occur within the first week of onset of a Horner syndrome, and has been described with acute internal carotid dissection.
positive hydroxyamphetamine test (failure of the pupil to dilate) may persist even after the other ocular manifestations of Horner syndrome have resolved (Moster 2003). The apraclonidine test relies on upregulation of the alpha-1 agonist receptors in the pupillary dilator muscle. The amount of time required to develop receptor suprasensitivity is uncertain and likely varies among individuals. The apraclonidine test was abnormal 36 hours after a dorsolateral photomedullary stroke, indicating that the test may be positive within a short period of time in some cases (Lebas et al 2010). Although there is fairly good correspondence between apraclonidine and cocaine testing for Horner syndrome, false-negative apraclonidine tests may occur, even weeks after the onset of Horner syndrome (Dewan et al 2009).

Pilocarpine test. Dilute pilocarpine (0.1%) is a pharmacologic test for pupillary cholinergic supersensitivity. A denervated iris constricts to dilute pilocarpine but a normal iris will not. Dilute pilocarpine has traditionally been used as a diagnostic test for a suspected Adie tonic pupil, which usually constricts to dilute pilocarpine. However, the test is neither 100% sensitive nor specific for tonic pupil: only 80% of postganglionic lesions (tonic pupils) demonstrate cholinergic supersensitivity and a significant number of nonischemic preganglionic lesions (oculomotor nerve palsy) will also have some degree of cholinergic supersensitivity (Loewenfeld 1967; Jacobson 1994). The testing solution may be prepared using a commercial preparation of pilocarpine mixed with sterile saline.

Management

Management is aimed at the etiology of each specific pupillary abnormality.

Special considerations

Pregnancy

Pregnancy itself is not associated with any particular pupillary abnormality, but complications of pregnancy may affect the pupils.

Anesthesia

Barbiturate general anesthesia causes progressive constriction of the pupils with loss of responsiveness to light and failure of dilation to sensory stimulation as the coma deepens. When used alone, the pupils can be used to assess the depth of the patient’s barbiturate coma. Opiate analgesics (eg, morphine) cause miosis even when the patient is still alert and awake but do not necessarily block the pupillary light reaction. Combination anesthesia utilizing different anesthetic agents have variable CNS actions and should be reviewed individually for their effect on the pupils. The iris sphincter may also be paralyzed by neuromuscular depolarizing agents used to immobilize patients during surgery and in the intensive care unit (eg, pancuronium bromide).

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**References especially recommended by the author or editor for general reading.

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**ICD and OMIM codes

**ICD codes

ICD-9:
Abnormal pupillary function, unspecified: 379.4
Anisocoria: 379.41
Argyll Robertson (syphilitic) pupil: 094.89
Horner syndrome: 238.1
Light-near dissociation (excludes Argyll Robertson): 379.45
Other pupil disorders (hippus, pupillary paralysis): 379.9
Pupillary abnormalities: 364.75
Persistent miosis (not due to miotics): 379.42
Persistent mydriasis (not due to mydriatics): 379.43
Third nerve palsy, partial: 378.51
Third nerve palsy, complete: 378.52
Tonic (Adie) pupil: 379.46

ICD-10:
Anomalies of pupillary function in disease classified elsewhere: 58.0*
Anomalies of pupillary function: H57.0
Argyll Robertson phenomenon or pupil, syphilitic: A52.1+
Horner syndrome: G90.2
Other congenital malformations of the iris: Q13.2
Other disorders of eye and adnexa: H57
Third [oculomotor] nerve palsy: H49.0

**Profile

**Age range of presentation

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

**Sex preponderance

male=female

**Family history

none

**Heredity
Population groups selectively affected
none

Occupation groups selectively affected
none

Differential diagnosis list
anisocoria
Horner syndrome
aberrant regeneration
old Adie (tonic) pupil
tonic pupil
oculomotor (third) nerve palsy
pharmacologic mydriasis
isolated dilated pupil
light-near dissociation
pharmacologic pupil
iris damage
relative afferent pupillary defect
widespread retinal disease
optic tract lesion
cyclic oculomotor palsy
ophthalmoplegic migraine
benign episodic unilateral mydriasis
tadpole pupils
bilateral pupillary abnormalities
Harlequin syndrome

Associated disorders
Anisocoria
Horner syndrome
Miosis
Mydriasis
Transient pupillary abnormalities (cyclic oculomotor palsy, ophthalmoplegic migraine, tadpole pupils, benign episodic unilateral mydriasis)

Other topics to consider
Horner syndrome
Ischemic optic neuropathy
Neurosphiliis
Ophthalmoplegic migraine
Optic neuritis

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