

The Argyll Robertson pupil

Pupillary testing is a critical part of any ocular examination. The visual pathway begins at the retina and terminates in the occipital cortex¹. Pupillary dysfunction can be indicative of neurological disease and can provide insight on the homeostasis of intracranial contents.

In 1869, Douglas Argyll Robertson was the first to describe several patients whose pupils reacted poorly to light with a normal near response². It wasn't until 30 years later that physicians realised the aetiology of this pupillary anomaly was a manifestation of tertiary syphilis²⁻⁶.

ANATOMY

A firm understanding of the pupillary pathway provides the clinician with a neurological 'map' which can help him to detect optic nerve disease. Afferent visual fibres (beginning with the retinal ganglion cells) course backward in the visual system as the optic nerve. They pass through the optic chiasm and travel in the optic tract toward the lateral geniculate body (LGB). Just before reaching the LGB, approximately 1% of optic tract fibres branch off and terminate in the pretectal nuclei at the level of the mid-brain. These nuclei are interconnected through a series of fibres that form the posterior commissure. This interconnection is one of the components responsible for the consensual light response (light in one eye stimulates pupillary constriction in the fellow eye). From the pretectal nuclei, fibres leave and synapse in the Edinger-Westphal nuclei (EWN). The ipsilateral and contralateral innervation to the EWN also contributes to the consensual response.

Parasympathetic preganglionic fibres (efferent pupillary fibres) exit the EWN and travel with the oculomotor nerve. These pupillary fibres branch just before reaching the superior orbital fissure and follow the

inferior division of the third nerve. Within the orbit, pupillary axons follow with oculomotor fibres destined for the inferior oblique muscle, and course to their synapse in the ciliary ganglion. Short ciliary nerves leave the ciliary ganglion as parasympathetic postganglionic fibres and innervate both the ciliary body and iris sphincter muscle. The majority of the fibres (97%) terminate within the ciliary body^{1,2}.

PATHOPHYSIOLOGY

Argyll Robertson pupils are typically small (2mm), irregular in shape and react poorly or not at all to light. The response to both accommodation and convergence remains intact. Visual acuity is usually normal. Dilation with mydriatic agents is typically poor. The dysfunction begins unilaterally and becomes bilateral with time^{2,6}.

The pupillary findings consistent with Argyll Robertson pupils develop over the course of months to years. The abnormality in pupillary function begins with a sluggish response to light and eventually progresses to a complete loss of the light reflex. The iris atrophies with a loss of its radial folds, and crypts have been reported².

The pathophysiologic mechanism which produces an Argyll Robertson pupil is unclear. Studies have failed to demonstrate a focal localising lesion. Research has implicated the rostral mid-brain in the vicinity of the sylvian aqueduct of the third ventricle as the most likely region of damage². A lesion in this area would involve efferent pupillary fibres on the dorsal aspect of the EWN (associated with the response to light) while sparing the fibres associated with the response to near, which lie slightly more ventrally².

DIFFERENTIAL DIAGNOSIS

Certainly not all patients who present with miotic and poorly reactive pupils have syphilitic disease. Other aetiologies include Horner's syndrome, long-standing Adie's tonic pupil, diabetes mellitus, encephalitis, mid-brain tumours, sarcoidosis, Lyme disease, pharmacologic aetiology (miotic administration) and the presence of chronic iritis^{2,4}.

Horner's syndrome involves lesions of the sympathetic innervation to the iris dilator. Sympathetic fibres can be damaged

anywhere along their course, from the hypothalamus, the cilio-spinal centre of Budge (C8-T2), the spinal cord, the superior cervical ganglion, to the final pathway along the internal carotid artery to the dilator muscle. These lesions typically result in ptosis, miosis, and anhidrosis. Cocaine testing can be employed to provide the definitive diagnosis. Paredrine (hydroxyamphetamine) can be used to differentiate a first and second order lesion from third neuron dysfunction^{2,4}.

Long-standing Adie's tonic pupil can present with a miotic appearance. 'Adie's pupils' are initially large in diameter but over time, they can revert and become small. This pupillary dysfunction is an idiopathic form of internal ophthalmoplegia that results from a lesion in the ciliary ganglion or its neurons. Adie's pupils present with an overall sluggish response to both light and near, with vermiform - like movement, iris sector paralysis, iris stromal streaming and iris stromal spread⁴. Deep tendon reflexes may also be decreased^{3,4}. The use of a weak cholinergic agent such as 0.12% pilocarpine, because of denervation hypersensitivity and up-regulation, can help with the diagnosis^{2,4}.

Diabetes mellitus can affect pupillary fibres secondary to vasculopathy. Since light reflex fibres are located along the outside of the oculomotor nerve, the pupils are often spared in this disease. Infarcts or ischemia can damage critical nuclei and axons along the pupillary pathway that may result in dysfunction^{2,4}.

Encephalitis is a severe inflammation of the brain, often caused by a virus. The condition is marked with intense lymphocytic infiltration of the cerebral tissues, with subsequent oedema and degeneration of nerve cells. This process can result in pupillary dysfunction along with fever, headache, vomiting, stiff neck, drowsiness, convulsions and coma.

Sarcoidosis is an inflammatory process that can produce pupillary miosis, mimicking Argyll Robertson pupils. Sarcoid patients demonstrate difficulty in breathing (dyspnea), erythema nodosum, lymphadenopathy, splenomegaly and cardiac arrhythmias. Ocular signs include iritis, keratic precipitates, vitritis and vascular sheathing. Laboratory and

ARGYLL ROBERTSON PUPIL SUMMARY

1. Syphilitic disease must be present
2. There must be zero to trace reaction when stimulated by light
3. The response to near should appear intact
4. The pupil is frequently quite miotic
5. The pupil often has an irregular shape
6. The Argyll Robertson pupil is recalcitrant to pharmacologic dilation

radiological testing can aid in confirming the diagnosis⁸. The pupils in these cases are often completely or partially syneched secondary to chronic, granulomatous inflammation. Here, the pupil may be small, misshapen and sluggish to both light and near.

Lyme disease is an infectious disease caused by a spirochete organism. Since syphilis is also caused by a spirochete, these two disease entities can sometimes present with similar signs and symptoms. The signs and symptoms of lyme disease can include a bull's eye lesion, fever, malaise, arthropathy and central nervous system dysfunction. Ocular sequela can include conjunctivitis, keratitis, iritis, retinopathy and optic neuritis. A lyme titre is helpful in making the diagnosis, although a negative test does not rule out the disease⁶. Pupillary abnormalities may exist secondary to anterior chamber inflammation (uveitis).

Dorsal mid-brain syndrome (DMS) (often secondary to a tumour of the pineal gland) can present with pupils that possess light-near disassociation (poor response to light with an intact near response). DMS patients also present with impaired up-gaze and a convergence retraction nystagmus^{3,4}. These latter signs help make the differential diagnosis.

Iritis can result in small, miotic pupil due to inflammation of the ciliary body as well as synechial paralysis. The patient may present with a history of trauma and complain of photophobia. Typically, cells and flare can be visualised within the anterior chamber⁶. Here, clinicians must investigate potential underlying causes.

SYPHILIS

Venereal diseases are infections that are spread from one individual to another through sexual contact. Sexually transmitted diseases are among the most common of infectious diseases found in the general population. Approximately 400,000 people contract syphilis each year in the United States⁹.

Symptoms of syphilis appear after an average incubation period of about three to four weeks. The organism responsible for the infection is *Treponema pallidum*, the manifestations of which tend to progress in stages^{6,9}. These stages consist of the primary stage, the secondary stage, the latent stage and the tertiary stage.

The primary stage results in a classic painless sore or ulcer known as a chancre which appears on the penis, vulva, vagina, anus, rectum, lips, tongue, throat, cervix or

fingers⁹. The lesion begins as a small, red bump which erupts into an open, raw ulcer. While the sore does not bleed, it does ooze a clear fluid that is inundated with the infectious organism and is highly contagious. The sore typically heals in three to 12 weeks^{6,9}. At this stage, a detailed history should be taken from the patient concerning their sexual habits. Patients should be questioned on the presence of any discharge, pain on urination, or pain on intercourse⁹. Males are frequently more symptomatic than females. Females suspected of infection should undergo laboratory testing and a complete gynecological examination¹⁰. This procedure is important in making the diagnosis and in identifying the offending organism. Often, individuals with syphilis will harbour other sexually transmitted diseases.

In male patients, the genitalia should be examined by the family GP. Any substance extracted from the opening should be immediately swabbed and placed in transport medium for microbiological analysis^{11,12}.

Some patients do not display any telltale lesions of the disease. Those individuals who are in a high risk category or who are suspected of having syphilis, should undergo laboratory analysis via a fluorescent treponemal antibody absorption test (FTA-ABS), treponemal antibody hemagglutination test (MHA-TP), rapid plasma reagin (RPR), and venereal disease research laboratory (VDRL).

The secondary stage occurs anywhere from six weeks to six months after initial infection⁶. The hallmark of this stage is a maculopapular rash, which can involve any part of the body but is most commonly seen on the palms of the hands and the soles of the feet. The patient may complain of malaise, fever, arthritis (10%), periostitis, granulomatous uveitis (4%), optic neuritis, 'salt and pepper' fundus, mouth sores (80%), enlarged and painful lymph nodes (50%)^{6,9}.

The latent stage occurs when the patient has recovered from the secondary bout. The organism seems to go into hiding and manifests no symptoms for years or decades⁹.

The tertiary stage is the last phase of the infection. These people are plagued with cardiovascular and neurological dysfunction, including Argyll Robertson pupils. Cardiovascular complications can include an aortic aneurysm and leakage of the aortic valve. Neurological

LIGHT-NEAR DISSOCIATION SUMMARY

The term light-near dissociation (LND) is a generic term connoting a diminished but not necessarily absent response to light. While syphilis* is the most common cause of LND, other causes exist:

1. Advanced diabetes mellitus
2. Tumours of the pituitary gland
3. Mid-brain lesions
4. Myotonic dystrophy
5. Adie's tonic pupil
6. Familial amyloidosis
7. Aberrant regeneration of cranial nerve III (pseudo - Argyll Robertson pupil)

* The laboratory tests of choice for syphilis include fluorescent treponemal antibody absorption (FTA-ABS), microhemagglutination for antibodies to treponemal pallidum (MHA-TP) and rapid plasma reagin (RPR)

(neurosyphilis) problems can include meningitis, paretic muscles, and tabetic disease (tabes dorsalis: a progressive disease of the spinal cord)⁹.

TREATMENT AND MANAGEMENT

Penicillin by injection is the method of choice for treating all stages of syphilis. The more advanced the disease process, the longer and more potent the doses of penicillin must be to eradicate the infectious organism. A two to four week course of oral doxycycline or tetracycline may be used as alternative therapy. Patients in the latter stages of the disease often experience a reaction called the Jarisch-Herxheimer reaction after administration of treatment. This reaction is a result of millions of infectious organisms succumbing to the antibiotic therapy. These patients develop a fever, headache, sweating and chills⁹. Most patients do well after treatment. Those patients who have suffered permanent cardiac or nerve damage carry the poorest prognosis for a healthy and completely normal life as the manifestations of such advanced disease cannot be reversed⁹.

Once treatment has begun, patients can be followed using the RPR test. Because the RPR measures the level of antibodies to cardiolipin and not antibodies to the treponema organism, the titre will vary based on the effectiveness of the treatment⁶. Once the individual is infected with the organism, both the FTA-ABS or the MHA-TP will always remain positive since it detects the presence of antibodies toward the treponema organism.

CLINICAL PEARLS

Patients who present with miotic pupils should be further assessed for Argyll Robertson pupil. The detection of this pupillary anomaly is significant and requires immediate referral for neurological, physical and laboratory evaluations. The systemic manifestations associated with this condition carry life impacting consequences. The earlier a firm diagnosis can be made, the better the prognosis will be for the patient. Once a diagnosis is established, treatment should be swift and potent in order to eradicate the infectious organism and prevent organ degradation. Practitioners play a critical role in the detection, management and treatment of this disease.

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