PEER REVIEWED

A Clinical Approach to Pupil Testing

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Abstract

Ipsilateral ptosis and miosis are two concurrent findings that can be of concern. These findings are classically associated with Horner's syndrome, but the correct pupil and ancillary testing must be utilized to make an accurate diagnosis. A patient who presents with suspicion for new-onset Horner's syndrome should be evaluated emergently to rule out any underlying life-threatening etiology. This teaching case report explains how detailed case history, diagnostic imaging and clinical testing were utilized to confirm a diagnosis of physiological anisocoria and concurrent ptosis due to trauma.

Key Words: *ptosis, miosis, Horner's syndrome, ocular trauma, pupillary testing, anisocoria*

Background

The following case report discusses the appropriate testing and diagnosis of a patient with ipsilateral ptosis and miosis. It demonstrates the importance of investigating all differential diagnoses, and it provides a guide for teaching third- and fourth-year optometry students and residents to manage cases of ptosis and abnormal pupillary findings. Also provided are an overview of differential diagnoses and additional testing or imaging that may be appropriate in cases of ptosis and abnormal pupils. Anisocoria and ptosis are two findings with varying etiologies that all optometrists encounter. Depending on the etiology, a prompt diagnosis and appropriate treatment may significantly benefit the patient and could be be life-saving.

Case Description

A 60-year-old Black male was referred to the neuro-ophthalmology clinic for further evaluation of right eyelid ptosis and ipsilateral pupil miosis. He reported that these signs had been stable for more than a year. He reported a history of multiple mildly traumatic ocular events that included being poked in the right eye 2 years prior. He did not seek any care at that time and did not notice any changes in vision, eyelid appearance or pupil size following that injury. He also stated that a few months following that injury the eyelid droop may have started after bird waste got into his eye.

In addition, the patient had undergone laser retinopexy to repair a retinal tear in the right eye, and glaucoma was suspected in both eyes. He was not using any ocular medications and reported no drug allergies.

The patient's medical history was positive for hypertension and high cholesterol. His medications included aspirin, atorvastatin and hydrochlorothiazide. He had no significant family medical or ocular history. The patient smoked 10 cigarettes a day and had been doing so for at least 20 years. He was also a social drinker and denied any illicit drug usage. He had an appropriate mood and was oriented to time, space, person and place.

The referring provider had seen him 5 months prior to the neuro-ophthalmology consult. Right eyelid ptosis and ipsilateral pupil miosis were documented at this visit. The referring provider noted that the patient complained of pain in his right shoulder and adjacent to the right side of his neck. The patient had also reported previous right arm weakness and a history of trauma to the right shoulder for which he had undergone rotator cuff surgery. Due to the patient's ipsilateral eyelid ptosis and pupil miosis in the setting of a complicated history and potentially associated ipsilateral systemic symptoms, the referring provider admitted the patient for emergent neuroimaging to rule out Horner's syndrome secondary to a life-threatening etiology. A neurology consult was recommended as well. Pupil testing (using apraclonidine 0.5% ophthalmic solution) for Horner's syndrome was performed with a negative result. Magnetic resonance imaging (MRI) of the brain with and without contrast, magnetic resonance angiography (MRA) of the head and neck, and a chest X-ray were performed. All of the neuroimaging obtained showed no evidence of an acute life-threatening etiology, and the patient was given a follow-up appointment in the neuro-ophthalmology clinic and discharged. Following the in-patient workup, the patient was lost to follow-up for 5 months before presenting to the neuro-ophthalmology clinic.

At the neuro-ophthalmology clinic, the patient's uncorrected distance visual acuity was 20/25-2 in the right and left eye. His confrontation visual fields were full to finger count, and his extraocular motilities were full-range in both eyes with no pain or diplopia in either eye. His intraocular pressure as measured with Goldmann applanation tonometry was 14 mmHg in both eyes.

Table 1. Click to enlarge

At this visit, the right pupil was measured to be 5 mm in the dark and 3 mm in light. The left pupil was measured to be 6 mm in the dark and 4 mm in light. The palpebral fissure was measured to be 8 mm in the right eye and 11 mm in the left eye. Margin to reflex distance (MRD) 1 was measured to be 1 mm in the right eye and 4 mm in the left eye. MRD2 was measured to be 7 mm in the right eye and 7 mm in the left eye **(Table 1)**. Color vision testing with Ishihara color plates was performed with a score of 11/11 in both the right and left eyes. To further assess the ptosis, cranial nerve VII motor testing was performed, and the patient had a normal blink, nasolabial folds and mouth function. The orbicularis oculi strength was normal in both the right and left eyes.

Slit lamp examination showed the patient had nasal and temporal pingueculae in both eyes. He also had multiple subepithelial corneal scars outside of the visual axis in both eyes with no corneal staining or endothelial pigment. No iris transillumination defects were noted. He had grade 1+ nuclear sclerotic cataracts in both eyes.

Table 2. Click to enlarge

On dilated fundus exam, a small retinal tear in the inferior periphery of the right eye that had previously been treated with laser retinopexy was observed. The optic nerves were asymmetric with a cup-to-disc ratio in the right eye of 0.7 round and 0.5 round in the left eye. Diagnostic test results ordered upon initial presentation to the referring provider were reviewed and can be seen in **Table 2**. Due to the incidental finding of hepatic lesions of the liver on the chest X-ray, the patient was directed to follow-up with his primary care physician for additional care.

At this point, differential diagnoses of the ptosis and miosis included idiopathic Horner's syndrome, damage to the sympathetic nerve pathway following rotator cuff surgery, and ptosis secondary to trauma resulting in damage to the levator palpebrae superioris muscle or possible aponeurosis. Physiological anisocoria also remained a consideration but could not be confirmed until further testing was complete.

A computed tomography (CT) scan of the chest with contrast was ordered to further evaluate a differential diagnosis of Horner's syndrome. Blood urea nitrogen and creatinine tests were ordered prior to the CT chest scans to evaluate kidney function. The patient was to return in 1 month after the CT for review of test results and further evaluation.

Follow-up #1

At this visit, clinical findings were stable to previous exams. The chest CT results showed no evidence of a chest mass. Apraclonidine 0.5% pupil testing was repeated to ensure that the first negative result was not a false negative. No dilation was observed in either eye, indicating a repeatable negative test. A CT of the neck was ordered to rule out any possible pathology in this region.

Brief encounter for review of test results

The patient presented for a scheduled follow-up appointment, but he was intoxicated; therefore, an examination was not performed. The neck CT results were reviewed and showed no evidence of a cervical mass or significant cervical lymphadenopathy. The patient was made aware of the findings and rescheduled for a 2-week follow-up.

Follow-up #2

The patient was again lost to follow-up but returned to the neuro-ophthalmology clinic 11 months later.

Table 3. Click to enlarge

At this visit, ptosis and pupil measurements remained stable to previous visits **(Table 3)**. Although it was believed that the right eye was miotic, to rule out any mydriasis of the left eye, pupil testing was performed with pilocarpine 0.125% ophthalmic solution. No constriction was observed, demonstrating no abnormal innervation of the pupil of the left eye.

Upon comprehensive review of all clinical findings, pharmacological testing and neuroimaging, it was determined the patient's ptosis and miosis were not related to a neurological etiology. It was determined the ptosis was likely secondary to trauma. Given that multiple pupil measurements demonstrated equal asymmetry in light and dark conditions, a diagnosis of concurrent physiological anisocoria was made.

At this time, the patient was advised to return immediately to the emergency room for evaluation if an intense headache or sudden vision change occurred.

Education Guidelines

Learning objectives

At the conclusion of this case report, readers should be able to:

1. Understand how to accurately assess pupils
2. Understand the pathophysiology of the pupillary response and eyelid innervation
3. Identify pupil and eyelid abnormalities and their differential diagnoses
4. Understand diagnostic pupil testing of anisocoria
5. Determine which ancillary testing may be warranted in cases of pupil miosis

Key concepts

1. Pupil testing should be performed on all patients at every exam
2. Suspected acute onset of Horner's syndrome should receive emergent evaluation
3. All differential diagnoses for ptosis and miosis should be considered in every patient presenting with these signs
4. Physiological anisocoria is present in up to 20% of the healthy population
5. Trauma can affect all ocular structures including the eyelid and pupil

Discussion questions

1. Measurements

a. What should be assessed when measuring pupils?
b. What is classified as average pupil size?
c. What is the difference between MRD1 and MRD2?
d. What are average MRD1, MRD2 and palpebral fissure measurements?

2. Pathophysiology

a. What controls pupil constriction and dilation?
b. What provides innervation to the eyelid?
c. What causes levator aponeurosis dehiscence?

3. Differential diagnoses

a. What differential diagnoses exist for anisocoria greater in bright light?
b. What differential diagnoses exist for anisocoria greater in the dark?
c. What differential diagnoses exist for eyelid ptosis?
d. What is classified as physiological anisocoria?
e. What is the pathophysiology of the classic triad of Horner's syndrome signs/symptoms?

4. Pharmacological agents utilized for diagnosis

a. What two agents can be utilized to confirm a diagnosis of Horner's syndrome?
b. What result is expected with the use of diagnostic pharmacological agents in a diagnosis of Horner's syndrome?
c. When Horner's syndrome has been diagnosed, what two agents may be used to localize the neuronal order of the lesion?
d. When are 1% pilocarpine and 0.125% pilocarpine utilized in pharmacological pupil testing?

5. Primary care optometrist's role

a. How urgently should a patient be evaluated when new-onset Horner's syndrome is suspected?

Discussion

Teaching instructions

For students: small group discussion. After being taught the pertinent information, the class is divided into small groups. Each small group is given a case chosen by the professor and given time to discuss what testing they would utilize. Case by case, each small group will discuss what methods they have chosen to confirm a diagnosis. Appropriate feedback is given by the professor, and other small groups are given time to ask questions. Following discussion, a quiz may be given to assess the students' understanding of the learning objectives.

For residents: grand rounds. Residents should present cases involving pupil abnormalities. They would outline the case presentation, present the pathophysiology and discuss how they utilized ancillary testing and/or pharmacological agents to confirm a diagnosis. Another option to consider when educating residents is to have the supervisor present an initial case such as the case presented here. The residents would then discuss differential diagnosis, diagnostic testing and pharmacological testing. To assess the residents' knowledge of the learning objectives, the supervisor could ask questions during the discussion. The residents may also be presented with exam findings from a new case involving pupil abnormalities and asked how they would manage the case, applying their new knowledge.

Pupil exam

Pupil testing is an important part of the eye exam and should be performed on all patients at every visit. Components of a thorough pupil exam include measuring pupil size in dark and light, evaluating direct and consensual pupil response, and checking for an afferent pupillary defect (APD). Anisocoria has a wide variety of potential etiologies ranging from physiological anisocoria to life-threatening conditions.[1-3]

The afferent pupillary light reflex begins in the retina and travels through the optic nerve with nasal fibers decussating at the optic chiasm traveling to the opposite optic tract and the temporal fibers continuing to run temporally along the ipsilateral optic tract. Pupillary fibers then pass through the superior colliculus to the pretectal nuclei. At this point, fibers pass ipsilaterally and contralaterally to the Edinger-Westphal nucleus. The decussation of the pupillary fibers at the optic chiasm and then again after the pretectal nuclei ensure that each Edinger-Westphal nucleus receives information about incoming light from both eyes.[3-4] This is why the pupils should be equal in size.[2-4]

When performing a pupil exam, it is important to use a bright light and a pupil gauge. Throughout all pupil testing, it is important that the patient focus on a distance target to prevent any accommodative miosis.[2-3] Pupil size should be measured in both bright light and in the dark. If it is difficult to measure in the dark, a light source may be held below eye level to provide slight illumination.[2] Normal pupil size is 2-4 mm in bright light and 4-8 mm in dark light.[3] Pupil size is controlled by the activity of the iris sphincter muscle and the iris dilator muscle. The iris sphincter muscle is located in a circumferential fashion at the iris margin and is innervated by the parasympathetic nervous system. The iris dilator muscle runs radially from the iris root to the peripheral border of the iris sphincter and contains alpha-adrenergic receptors that respond to the sympathetic nervous system.[3-4]

In addition to measuring pupil size, the provider should evaluate the direct and consensual pupillary responses. In a normal pupil, a light shone in one eye causes pupil constriction in both eyes. The response in the eye in which the light is shone is called the direct response. Constriction in the eye in which the light is not shone is called the consensual response.[1-4]

It is also important to assess for AFD, sometimes referred to as Marcus Gunn pupil, using the swinging flashlight test. In assessing for APD, the provider is essentially measuring the difference in signal strength between the two eyes.[3-4] A light should be shone in one eye for 3-4 seconds and then immediately shone in the fellow eye for 3-4 seconds. This sequence should be repeated several times. A normal finding would be consistent constriction of both pupils due to the consensual response. In a patient with a relative APD, both pupils will dilate when the light is shone in the affected eye and then constrict when the light is shone in the unaffected eye.[2-4]

In patients with only one functioning pupil, the provider can test for a reverse APD. The swinging flashlight test is performed as usual, but only the functioning pupil is observed. If constriction is observed at all times, no APD is present. If the functioning pupil constricts more when the light is shone directly in that eye, an APD is present in the fellow eye with the unreactive pupil. If the functioning pupil constricts more when the light is shone directly in the non-functioning pupil, there is an APD in the eye with the

functioning pupil.[7]

Additional findings about pupil abnormalities may be revealed upon slit lamp exam.[1-2] It is important to evaluate for any signs of inflammation, injury or infection as they may contribute to pupil changes. Iris transillumination and gonioscopy may also prove beneficial to rule out any abnormalities secondary to other causes such as trauma.[2]

In cases of anisocoria, it is important to obtain a thorough case history to assess if the patient has started any new medications or used any illicit substances and to assess for any other neurologic symptoms including ptosis, diplopia, changes in vision and ipsilateral head or neck pain.[1]

Eyelid anatomy

The facial nerve, cranial nerve VII, innervates the orbicularis oculi, which is used to close the upper and lower eyelids. The patient in this case had normal and equal cranial nerve VII function on both sides of his face. The oculomotor nerve, cranial nerve III, innervates the levator palpebrae superioris, which is used to elevate the upper eyelid. The levator palpebrae superioris becomes a tendinous aponeurosis, which fuses with the superior tarsal plate.[5-6] The muscle of Müller elevates the eyelid 1-2 mm and is innervated by the sympathetic nervous system.[7]

Multiple measurements ? of MRD1, MRD2 and palpebral fissure size ? are essential to thoroughly evaluate for the presence and extent of ptosis. These measurements are typically recorded in millimeters.

To measure MRD1, the patient and examiner should be at the same level. The examiner should hold the light source so the patient is looking directly at it in primary gaze. The patient should keep both eyes open naturally, and the examiner should measure the distance between the light reflex on the cornea and the central portion of the upper eyelid margin. This measurement is MRD1. An average MRD1 is 4-5 mm. [5-8]

To measure MRD2, the examiner should measure the distance between the light reflex on the cornea and the central portion of the inferior eyelid margin. This measurement may indicate reverse ptosis if asymmetric between eyes.[8] An average MRD2 is 5-6 mm.[5]

The palpebral fissure measurement is the distance between the central portions of the upper and lower eyelid margins when the patient is looking in primary gaze. The average palpebral fissure is 9-12 mm.[5] The palpebral fissure measurement may also be obtained by the summation of MRD1 and MRD2.

In general, a difference of approximately 2 mm between eyes is classified as mild ptosis. Anything greater than a difference of 4 mm between eyes is considered severe ptosis.[9]

Inter-observer measurement differences

One factor to consider when making a diagnosis based on such small measurements is the presence of inter-observer differences in assessing the same patient. One study utilizing a pupilometer showed that less inter-examiner variability was seen in scotopic conditions than in photopic conditions.[10] The same study also found greater variability in measurements repeated 24 hours apart. This variability seen between examiners utilizing the same piece of equipment indicates that multiple measurements in-office may be necessary. Another study evaluated both intra- and inter-observer measurements of MRD and detected no difference in either factor. These results led to the conclusion that any variability noted was mild and clinically acceptable.[11] The patient in this teaching case report was examined by multiple doctors at a number of visits. It is important to take this potential variability into consideration when evaluating for stability of exam findings.

Anisocoria greater in the dark

With this patient, ipsilateral ptosis and miosis were noted upon clinical exam. When performing the pupil exam, several differentials should be considered in patients with anisocoria greater in the dark, including:

- Horner's syndrome
- Pharmacological miosis
- Argyll Robertson pupil

As this patient had ipsilateral ptosis and miosis, Horner's syndrome had to be considered. In addition, it is important to consider pharmacological miosis and an Argyll Robertson pupil.[3]

The classic presentation of Horner's syndrome is ipsilateral ptosis, miosis and anhidrosis.[14-15] Ptosis occurs due to denervation of the muscle of Müller, which normally provides 1-2 mm of elevation of the upper eyelid. In some cases, the ptosis may be so mild that it goes unnoticed. One study found that in 12% of those with Horner's syndrome, no ptosis was present.[14] A "reverse ptosis" might also be noted, where the lower eyelid appears more elevated than normal. This occurs due to a lack of sympathetic innervation of the muscles of the lower eyelid retractors. Miosis occurs due to a lack of sympathetic innervation to the iris dilator and the resultant uninhibited parasympathetic system acting on the iris sphincter muscle.[14] Anhidrosis occurs when a lesion of the sympathetic pathway is proximal to the external carotid arteryThis proximity causes denervation of the facial sweat glands leading to a dry, warm face.[16]

Another finding that may present in Horner's syndrome is dilation lag of the affected pupil. This is best observed in the first moments after the lights are dimmed. Rather than quickly dilating, the affected eye will take 10-15 seconds to fully dilate. This lag can cause anisocoria to be overlooked.[17]

Horner's syndrome may also be congenital, resulting from birth trauma. Iris heterochromia is common in congenital Horner's syndrome.[14,18,19] This heterochromia occurs because sympathetic innervation is believed to be responsible for the production of iris melanin by melanocytes.[14,18]

A lesion identified as the cause of new-onset Horner's syndrome may be classified as a first-order, second-order or third-order neuron lesion of the sympathetic pathway. First-order (central) neurons originate in the hypothalamus and descend to synapse in the spinal cord. A lesion of the hypothalamus, brainstem or spinal cord resulting from a stroke, neoplasms or demyelination may be classified as a first-order neuron lesion. Central Horner's syndrome is uncommon and typically presents with other neurological signs indicative of where the lesion is located. In these patients, neuroimaging is guided by these neurological signs and symptoms.[14,20]

The second-order (preganglionic) neuron exits the spinal cord and travels through the cervical sympathetic chain, through the brachial plexus and over the lung apex to synapse in the superior cervical ganglion. A lesion of the mediastinum, thoracic region or neck is classified as a second-order lesion. The most common second-order neuron lesion resulting in a preganglionic Horner's syndrome is a Pancoast tumor, a tumor at the apex of the lung. In patients with suspected first- or second-order lesions, multiple types of neuroimaging may be ordered including a CT or MRI of the chest, an MRI of the head and neck with contrast, and potentially an MRA or computed tomography angiography (CTA) of the head, neck and chest.[12,14]

Third-order (postganglionic) neurons exit the superior cervical ganglion and travel along the internal carotid artery into the cavernous sinus where they eventually join the ophthalmic division of the trigeminal nerve and enter the orbit to innervate the iris dilator muscle. A lesion or aneurysm of the internal carotid artery along with tumors, arterial dissection and trauma may be classified as third-order

neuron lesions. If a third-order lesion is suspected, an MRI of the head with contrast and an MRA or CTA of the head and neck may be utilized to visualize the lesion.[12,14]

An acute presentation of Horner's syndrome should be worked up emergently because of the risk of underlying neurological pathology.[3] Imaging both with and without contrast of the spine and chest should be performed to rule out any lesions.[3,14] It is important to note that after a thorough workup, 35-40% of Horner's syndrome cases are determined to be idiopathic.

Pharmacological miosis is uncommon but may occur after contact with pilocarpine ophthalmic solution. In our patient, the pupillary findings were consistent over an extended period of time, and no contact with pilocarpine ophthalmic solution outside of the clinical setting occurred.[3]

Argyll Robertson pupils typically present as bilateral, miotic pupils and are commonly associated with syphilis. These pupils dilate poorly in darkness and with mydriatic agents. "Light-near dissociated" is often used to describe this pupillary response. The pupils will not constrict in response to light but will become more miotic in response to a near target.[3,12,13] Our patient had only unilateral miosis, no history of syphilis, and his pupils dilated in darkness and with the use of mydriatic agents, thereby ruling out this condition.[3,13]

Anisocoria greater in light

In all settings of anisocoria, it is important to evaluate which pupil is the abnormal pupil. It was believed this patient had miosis of the right eye, but he was also evaluated for possible mydriasis of the left eye. In cases of anisocoria that is greatest in bright light, consider the following differentials:

- Adie's tonic pupil
- Oculomotor nerve (CN III) palsy
- Pharmacological dilation

Adie's tonic pupil is a result of postganglionic denervation of the internal ocular muscles including the ciliary body and iris sphincter. Patients are typically asymptomatic and present with one dilated pupil. They may report some mild blur of vision or photophobia due to persistent unilateral dilation. Loss of deep tendon reflexes of the lower extremities is a documented systemic association. With time, the ciliary body and sphincter muscles are reinnervated almost exclusively by the accommodative system, which results in slow constriction in response to a near object or target.[3]

An oculomotor nerve (CN III) palsy can present with complete ptosis, a "down and out" eye and a dilated pupil. The palsy can be either complete or partial. There are many causes of these palsies including vascular pathologies, trauma, aneurysms or other forms of compressive lesions. These patients are typically neuroimaged to identify the underlying etiology.[23]

In addition to the commonly used diagnostic mydriatic agents tropicamide and cyclopentolate, agents that cause pharmacological dilation include scopolamine, marijuana, lysergic acid diethylamide (LSD) and other illicit drugs.[3]

Physiological anisocoria

It was important to consider physiological anisocoria in the differential diagnosis of this patient. Physiological anisocoria is found in approximately 20% of the normal population. In patients with physiological anisocoria, the difference in pupil size is equal in dark and light conditions. Any difference larger than 2 mm is considered abnormal and should warrant a thorough workup. It may be beneficial to examine old photographs to assess for any long-standing presentation of the anomaly.[3] Physiological anisocoria was not diagnosed on initial presentation as other conditions should always be ruled out first.

In this case, after no other underlying etiologies were identified, the patient was ultimately diagnosed with physiological anisocoria.

Ptosis differentials

Important conditions to consider in the setting of ptosis include:

- Trauma
- Levator aponeurosis dehiscence
- Myasthenia gravis
- Horner's syndrome
- Congenital ptosis
- Oculomotor nerve (CN III) palsy

In cases of trauma, damage to the levator palpebrae superioris may occur as a result of cranial nerve damage, muscle damage, neurotoxins or scarring of the skin.[22] Although the patient in this case could not provide significant details regarding his previous episodes of trauma, he did note being poked in the eye, which could have caused subsequent levator palpebrae superioris damage.

Levator aponeurosis dehiscence is the most common cause of acquired ptosis and occurs in the elderly population due to natural changes in the levator muscle. This causes a slowly progressive ptosis that may not be noticed initially. With age, multiple changes, including fatty infiltration of the muscle, levator stretching or dehiscence of the levator from the tarsus, may cause ptosis.[6,22]

Often in cases of myasthenia gravis, patients report varying degrees of ptosis throughout the day as well as difficulties breathing, walking or speakingTo evaluate for myasthenia gravis, a serum assay for acetylcholine receptor antibodies should be ordered. An edrophonium chloride (Tensilon) test may be used to make a definitive diagnosis.[23] The patient in this case report denied any associated symptoms, and he denied any changes in appearance of ptosis throughout the day. Additionally, all measurements were consistent across multiple visits. Given the patient's history, normal orbicularis oculi strength, lack of change in eyelid position throughout the day and the absence of diplopia, a diagnosis of myasthenia gravis was ruled out.

Congenital ptosis is present from the time of birth and may result in varying degrees of ptosis. During development, the levator palpebrae superioris muscle does not form properly, resulting in minimal levator function. Some of these patients find that a chin-up position provides better vision. An additional sign of congenital ptosis is the lack of an upper eyelid crease.[24] In all cases of ptosis, evaluating the patient's driver's license or old photographs may be useful in identifying ptosis onset. A driver's license or photo ID may also serve as a useful tool as most patients present to exams with this on hand. The patient in the case described here reported his ptosis began just a few years prior.

Pharmacological pupil testing

When evaluating for the presence of Horner's syndrome, several diagnostic agents may be used. It is important to always measure pupil size in both eyes prior to instillation of any medication.

To diagnose Horner's syndrome, a cocaine solution or apraclonidine 0.5% or 1% ophthalmic solution may be utilizedIn Horner's syndrome, an interruption to the sympathetic system stops the release of norepinephrine from the presynaptic nerve endingsCocaine ophthalmic solution blocks the re-uptake of norepinephrine at the synaptic cleft, which causes dilation of the normal pupil. A Horner's syndrome pupil will not dilate when cocaine is instilled. As cocaine is a controlled substance and not readily available, apraclonidine ophthalmic solution is typically used in a clinical setting. Apraclonidine is an alpha-2 adrenergic agonist with a weak alpha-1 adrenergic agonist effect. In a Horner's syndrome pupil,

apraclonidine causes dilation due to the heightened sensitivity of the receptors on the iris dilator muscle.[3,14] A negative apraclonidine result occurs when dilation is not observed. Pupil size should be measured carefully in both eyes both prior to, and after, drop instillation. After instillation it is necessary to wait at least 30-45 minutes before evaluating pupillary response.[13,14]

To localize the lesion, hydroxyamphetamine bromide 1% ophthalmic solution or phenylephrine 1% can be utilized. Hydroxyamphetamine bromide causes the release of norepinephrine from the intact adrenergic nerve endings causing dilation in a normal pupil. One-hour after hydroxyamphetamine instillation, the affected eye will dilate if the lesion is a first- or second-order neuron lesion. This is because the postganglionic nerve endings are intact. If the lesion is a third-order neuron, the eye will not dilate as there has been a loss of the stores of norepinephrine. Phenylephrine 1% will cause only a pupil with a postganglionic lesion to dilate due to the heightened adrenergic sensitivity of the iris dilator.[3,14] After phenylephrine instillation the clinician should wait at least 45 minutes before evaluating the pupillary response.[14]

Localizing the lesion utilizing phenylephrine or hydroxamphetamine eye drops cannot be performed the same day as apraclonidine testing. If apraclonidine testing is positive, the patient should return 24-48 hours later to have additional testing performed to localize the lesion.[13,14]

Pilocarpine 1% can be used to differentiate between a pharmacological dilation and Adie's tonic pupil. After instillation, an Adie's pupil rapidly becomes more miotic due to the persistent lack of parasympathetic denervation, whereas a pharmacologically dilated pupil does not change after drop instillation.[3] To confirm an Adie's pupil, 0.125% pilocarpine is instilled. As a result of denervation, the pupil in question is hypersensitive to cholinergic agonists and miosis will be observed in the Adie's pupil. No change is expected in the eye not suspected of Adie's pupil.[27] To create the desired concentration of 0.125% pilocarpine, both 1% pilocarpine ophthalmic solution and saline solution are needed. Using a syringe, seven parts saline solution should be combined with one part pilocarpine 1% in a new vial. The new mixture should be thoroughly mixed before instillation. The new solution should be instilled in both eyes and pupillary response should be observed after 30-60 minutes.

It is important to keep in mind that testing may need to be repeated because false positive or false negative results can occur. In the case of this patient, testing was performed both with apraclonidine to assess for any excess miosis and with pilocarpine to asses for any excess dilation.

Follow-up care

Typically, physiological anisocoria does not need to be treated nor does it require follow-up care. In cases of pharmacological dilation or miosis, Adie's tonic pupil or physiological anisocoria, the patient does not need further intervention.[3] If patients have Argyll Robertson pupils and are found to have syphilis, they would need further care coordinated through their primary care physician or an infectious disease doctor. Horner's syndrome typically resolves on its own after the underlying systemic condition has been treated.[3,14] Both pupil and eyelid abnormalities resulting from cranial nerve III palsies also often resolve with systemic management.[21] In cases of ptosis due to myasthenia gravis, it is necessary to treat the underlying condition and subsequent improvement in ptosis is expected.[22,23] In cases of trauma, levator dehiscence or congenital ptosis, surgical intervention may be warranted as these are not self-limiting conditions.[22]

Conclusion

In patients with ipsilateral ptosis and miosis, pupil testing and neuroimaging play an important role in evaluation. Any patient suspected of having new-onset Horner's syndrome should be thoroughly worked up in an emergent fashion with the appropriate diagnostic imaging to rule out any life-threatening

etiology. In the case of this patient, a detailed case history along with the results of pupil testing and neuroimaging ultimately led to a diagnosis of physiological anisocoria and concurrent ptosis due to trauma.

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