ANISOCORIA

October 2004, Hotel Satya Ashoka, Dinner meet. Speaker - Dr Urvashi Sharma

What is it?

Difference in the size of the 2 pupils

- The abnormal pupil may be constricted
- The abnormal pupil may be dilated

The abnormal pupil is constricted...

- Unilateral use of miotic eye drops.
- Iritis (Pain, redness, photophobia, anterior chamber cells, flare, occasionally hypopion).
- Horner's syndrome - mild ptosis on the side of the small pupil; positive cocaine test.
- Argyll Robertson pupil - Tertiary syphilis; the pupil is irregular in shape, reacts poorly or not at all to light, constricts normally during convergence. Although the disease is usually bilateral, a mild degree of anisocoria is often present. Positive syphilis serology (FTA-ABS).
- Long standing Adie's pupil - initially dilated, but constricts over time. Seen to react slowly and irregularly to a bright light. It is supersensitive to pilocarpine 0.125% (one part of pilocarpine 1% with 7 parts BSS).

The abnormal pupil is dilated...

- Traumatized iris sphincter muscle (torn pupillary margin or iris transillumination defects seen on slit-lamp examination).
- Adie's tonic pupil (the pupil is irregular, reacts minimally to light and slowly to convergence, but is supersensitive to weak cholinergic agents like pilocarpine 0.125%).
- III nerve palsy - the pupil does not react to weak cholinergics, but constircts to regular strength miotic drops (e.g. 1% pilocarpine).
- Unilateral use of a mydriatic drop/ointment - if instilled recently the pupil will not react to pilocarpine 1%. If the effect is wearing off (1-2 weeks) the pupil may be semi-dilated and partly reacting to pilocarpine.
- Unilateral optic nerve disease - atrophy (primary and secondary), neuritis, etc. - associated with reduced vision and/or abnormal visual fields, perception of color.

Physiologic anisocoria...

- Pupil size disparity is the same in light and dark.
- The pupils react normally to light.
- The pupils constrict normally on convergence.
- The size difference is usually, but not always 1 mm in diameter.

Workup - History

- When was the anisocoria noted?
- Any associated symptoms or signs?
- History of ocular trauma?
- Use of any ocular/systemic medications?
- History of syphilis?
- History of reduced vision?
- Old photographs?

Ocular examination

- The trickiest part - determining which is the abnormal sized pupil?
- Younger patients tend to have a pupillary size of 4-5 mm. Whereas elderly patients have slightly smaller pupils.
- Compare the pupil sizes in light and dark.
    - Anisocoria greater in light suggests the abnormal pupil is the larger pupil.
    - Anisocoria greater in dark suggests the abnormal pupil is the smaller pupil.
- Check the IOP.
    - Low in Horner's syndrome
- High in Glaucoma
- Test the pupillary reaction to light.
- Test convergence if the reaction to light is normal.
- Look for ptosis.
- Evaluate ocular motility.
- Examine the pupillary margin with a slit lamp.

Inference

- If the abnormal pupil is small, a diagnosis of Horner's syndrome may be confirmed by a cocaine test (10% cocaine eye drops are instilled twice at an interval of one minute. A Horner's pupil dilates less well than the normal pupil in about 15 minutes time).
- In the presence of ptosis and an unequivocal increase in anisocoria in dim illumination, a cocaine test is not needed because the diagnosis can be made clinically.
- If the abnormal pupil is large and there is no sphincter muscle damage or signs of III nerve palsy (extraocular motility defect, ptosis) -
    - The pupils are tested with one drop of pilocarpine 0.125%; If the pupil contricts significantly more than the normal pupil in 10 to 15 minutes an Adie's tonic pupil is diagnosed.
        - If the pupil does not constrict with pilocarpine 0.125% or

pharmacological dilatation is suspected, or both…
Pilocarpine 1% is instilled in both eyes.

- A normal pupil constricts sooner and to a greater extent than the pharmacologically dilated pupil.
  An eye that recently received a strong mydriatic agent such as atropine usually will not constrict at all.

Specific entities

1. Horner's syndrome

 (image taken from the web)

Symptoms

- Unilateral
- Droopy eyelid
- Pupil size disparity
- Often asymptomatic

Signs

- Anisocoria that is greater in dim illumination (especially during the first few seconds the room light is dimmed) because of a small pupil that does not dilates as well as the normal, larger pupil.
- Usually, mild ptosis and lower lid elevation ("reverse ptosis") occur on the same side as the small pupil.
- Lower intraocular pressure.
- Iris heterochromia (lighter iris color in congenital cases).
- Anhidrosis.
- Increased accommodation in the affected eye.
- Light and near reactions are normal.

Etiology… 1

- *First-order neuron disorder*:
  - Stroke
  - Tumor
  - Severe osteoarthritis on the neck with bony spurs.
- *Second-order neuron disorder*:
  - Tumor
  - Lung carcinoma, Pancoast tumor
  - Metastases
  - Thyroid adenoma
  - Neurofibroma
  - In *children* consider
    - Neuroblastoma, lymphoma or metastasis
- *Third-order neuron disorder*:
  - Cluster headaches
  - Raeder's paratrigeminal syndrome
  - Internal carotid dissection
  - Herpes zoster virus
  - Otitis media
  - Tolosa-Hunt syndrome
  - Congenital Horner's syndrome - traumatic delivery at birth.

Workup

If the diagnosis is uncertain - do a cocaine 1% test (as mentioned earlier) (A Horner's pupil dilates less well than a normal pupil)

- Hydroxyamphetamine 1% is used to identify a III order neuron disorder:
- One drop of 1% hydroxyamphetamine into each eye, repeat after one minute.
- Check pupils after 30 minutes.
- The Horner's pupil fails to dilate to an equivalent degree as the fellow eye.
- Hydroxyamphetamine must not be administered within 24 hours of cocaine - they interfere with each others actions
- *Both tests need an intact corneal epithelium and no prior drop administration for accurate results*.

What is the duration of the syndrome?

New onset Horner's syndrome requires a more extensive diagnostic work up.

An old case is more likely benign.

History - Headaches, arm-pain, previous stroke, surgery that may have damaged the sympathetic chain - including cardiac, thoracic, thyroid or neck surgery.

History of head and neck trauma.

Check for supraclavicular nodes, thyroid enlargement or a neck mass.

Investigations

CT Scan of chest to evaluate lung apex for possible mass.

MRI - brain and neck.

TLC, DLC

MRA of head/neck

Carotid doppler ultrasound if carotid artery dissection is suspected

Lymph node biopsy if lymphadenopathy is present

Treatment

Treatment is directed towards the underlying cause, refer to the concerned specialist.

Cosmesis - Ptosis surgery.

Acute Horner's syndrome should be worked up as soon as possible to rule out life-threatening causes.

Chronic Horner's syndrome can be evaluated with less urgency.

With the exception of possible amblyopia in children, which occurs only when the eyelid covers the visual axis, there are no ocular complications that necessitate close follow up.

2. Argyll Robertson Pupils

Symptoms

Asymptomatic

Signs

- Small, irregular pupils that exhibit "light-near" dissociation (react poorly or not at all to light but constrict normally during convergence).
- Vision is normal.
- The pupils do not dilate well.
- May initially be unilateral, but always becomes bilateral, although possibly asymmetric.

Etiology

Tertiary syphilis

Differential Diagnosis

- All causes of anisocoria
- Other causes of "light-near" dissociation:
- Bilateral optic neuropathy or severe retinopathy (visual acuity is reduced, pupil size is normal)
  Adie's tonic pupil (unilateral or bilateral irregularly dilated pupil that constricts slowly and unevenly to light; normal vision)
- Dorsal midbrain (Perinaud's syndrome) - normal to large pupils accompanied by convergence-retraction nystagmus and supranuclear gaze palsy.

Workup

Test the pupillary reaction to light & convergence - for convergence, patients are asked to look first at a distant target and then at their own finger, which the examiner holds in front of them and slowly brings it toward their face.

Look for interstitial keratitis.

Search for chorioretinitis, papillitis and uveitis.

FTA-ABS or MHA-TP, rapid plasma reagin (RPR) or venereal disease research laboratories (VDRL) test.
Consider a lumbar puncture if the diagnosis of syphilis is established.

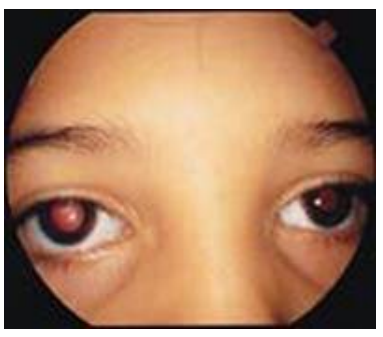
Treatment

The decision to treat is based on whether active disease is present and whether the patient has been treated appropriately in the past.

In case active syphilis is uncovered the patient may be referred to the specialist.

3. Adie's Tonic Pupil

Symptoms

 (image taken from the web)

- Difference in the size of the pupils.
- Blurred vision.
- May be asymptomatic.

Signs

- An irregularly dilated pupil exhibiting minimal or no reaction to light.
- Slow constriction to convergence.
- Slow redilatation.
- Typically unilateral at first.
- Found most often in young women.
- It may develop acutely and may become bilateral.

- Pupil dilates normally to mydriatic agents.
- Deep tendon reflexes (knees and ankles) are often absent (Adie's syndrome).
- The involved pupil may become smaller than the normal pupil over time.
- Super-sensitivity to weak cholinergic agents (0.125% pilocarpine) may not be present in the acute phase but will appear a few weeks later.

Etiology

Idiopathic

Orbital trauma or infection, herpes zoster infection, diabetes, autonomic neuropathies, Gullain-Barre syndrome, others.

Differential diagnosis

Other causes of anisocoria mentioned earlier.
Note: Parinaud's syndrome may produce bilateral mid-dilated pupils that react poorly to light but constrict normally during convergence (that is, not tonic). Eyelid retraction and paralysis of upgaze with retraction nystagmus may additionally be present. A pinealoma or other midbrain anomaly must be ruled out by MRI.

Workup

Observe the suspect pupil on a slit lamp, shining a bright light on it. The Adie's pupil will constrict slowly and irregularly.

Test for a super-sensitive pupil (pilocarpine 0.125%):

Have the patient fixate at a distance and measure the pupil size of each eye, then instill one drop of pilocarpine 0.125% in each eye.

Recheck the pupil size after 10-15 minutes.

The tonic pupil constricts significantly more than the contralateral pupil in Adie's syndrome.

The dilute pilocarpine test may occasionally be positive in an Argyll Robertson pupil and in familial dysautonomia.

If Adie's pupil or super-sensitivity or both are present and the patient is younger than 1 year, refer the patient to a pediatric neurologist to rule out familial dysautonomia (Riley-Day Syndrome).

Treatment

Pilocarpine 0.125% 4 times a day for cosmesis and to aid in accommodation if desired.

4. Isolated III nerve palsy

Symptoms

Double vision that disappears when one eye is closed.

Droopy eyelid.

With or without pain.

Signs

EXTERNAL OPHTHALMOPLEGIA

Complete: Limitation of ocular movement in all fields of gaze except temporal (LR6, SO4, rest 3)
Incomplete: partial limitation of movements.
Superior division palsy: Ptosis and inability to look up.
Inferior division palsy: Inability to look nasally or inferiorly; pupil is involved.

INTERNAL OPHTHALMOPLEGIA

Pupil *involving*: A fixed, dilated or minimally reactive pupil.

Pupil *sparing*: Pupil not dilated and normally reactive to light.

Relative pupil sparing: Pupil partially dilated and sluggishly reactive to light.

Other signs

- Exotropia or hypotropia.
- Aberrant regeneration
- Elevation of the upper eyelid with gaze down or nasally
- Sometimes pupil constricts (segmental) when looking up, down or nasally
- Aberrant regeneration may occur spontaneously (primary regeneration) without a preceding III nerve palsy.
- This is usually caused by a cavernous sinus tumour or aneurysm.

Etiology

PUPIL INVOLVING

Common cause - Aneurysm (particularly a PCA aneurysm)
Less common - DM or HT, tumour, trauma, congenital.
Rare - Uncal herniation, cavernous sinus mass/lesion, pituitary apoplexy, orbital disease, herpes zoster, leukemia and ophthalmoplegic migraine.

PUPIL SPARING

Ischemic microvascular disease (HT, DM), rarely cavernous sinus syndrome,

giant cell arteritis (GCA).

RELATIVE PUPIL SPARING

Ischemic microvascular disease (HT, DM), less likely aneurysm.

ABERRANT REGENRATION PRESENT

Not microvascular (trauma, aneurysm, tumour, congenital).

Differential diagnosis

Myasthenia gravis (and Ocular myasthenia)

- Pupil not involved, increased eyelid droop after sustained upgaze
- Weak orbicularis oculi muscle
- Positive edrophonium test

Thyroid eye disease

- Lid lag, stare, injection over rectus muscles, proptosis, resistance on forced duction testing, abnormal CT orbits, no ptosis.

Chronic progressive external ophthalmoplegia (CPEO)

- Bilateral slowly progressive ptosis, limitation of ocular motility, pupil spared, often no diplopia.

Pseudotumor orbit

- Pain and proptosis are usually present.

Internuclear Ophthalmoplegia

- Unilateral or bilateral adduction deficit with horizontal nystagmus of opposite abducting eye.
- No ptosis.

Lesion in ipsilateral brainstem medial longitudinal fasciculus.

- Skew deviation

Supranuclear brainstem lesion

- Asymmetric mainly vertical ocular deviation not consistent with single cranial nerve defect.

Parinaud's syndrome

Dorsal midbrain lesion

- Inability to look up, pupil reacts slowly to light briskly to convergence, no ptosis, eyelid retraction.

Convergence-retraction nystagmus . BILATERAL

GCA

- Extraocular muscle ischemia causing nonspecific motility defects.
- Pupil not involved.
- Age > 50, associated systemic symptoms.

Workup

Onset and duration of diplopia? Recent trauma? DM, HT? Known cancer or CNS mass? Recent infections?

Ocular examination:

- Pupil reactions
- Eye movements
- Ptosis
- Proptosis
- Visual field defects
- Orbicularis and eyelid fatigue on sustained upgaze
- Look for signs of aberrant regeneration

Full neurological examination - assess all other cranial nerves:

Ipsilateral IV cranial nerve -

- Focus with a slit lamp on a superior conjunctival blood vessel
- Ask the patient to look down and nasally
- The eye should intort, the blood vessel should turn down and toward the nose.

Immediate imaging (MRI brain) to rule out mass/aneurysm:

- In pupil involving III nerve palsies
- In pupil sparing III nerve palsies as under
- Age < 50 (no history of DM, HT)
- Patients with progressing partial III nerve palsies
- III nerve palsy > 3 months in duration, condition not improving
- Additional cranial nerve involvement, or neurological abnormalities

All patients who develop aberrant regeneration, with the exception of regeneration after traumatic III nerve palsies.

Imaging is usually not required in pupil sparing III nerve palsies that do not fit these criteria, especially when patients have known vasculopathic factors such as DM or HT

Cerebral angiography is indicated for all patients older than 10 years with pupil involving III nerve palsies and whose imaging study is normal or shows a mass consistent with aneurysm.

CBC with differential in children (leukemia)

Tensilon (edrophonium) test when myasthenia is suspect (pupil is not

involved)

Blood pressure in suspected ischemic disease

ESR in GCA

Treatment

Directed towards the underlying pathology

In case of symptomatic diplopia an occlusion patch may be placed over the involved eye.

Patching is not done under 9 years of age (amblyopia may develop)

Children must be monitored closely for development of amblyopia in the deviated eye.

FOLLOW UP

Observe daily for 5-7 days from onset for delayed pupil involvement.

Then check every 4-6 weeks.

If III nerve function is not regained by 3 months or develops other neurological signs, or aberrant regeneration, MRI is indicated.