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CASE REPORT

UNILATERAL MYDRIASIS WITH CHOLINERGIC SUPER SENSITIVITY: A DIAGNOSTIC DILEMMA - A CASE SERIES REPORT

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ABSTRACT: Pupillary abnormalities are a common feature of general ophthalmic practice. It often causes confusion as they can be manifestations of local and/ or systemic diseases. These diseases may range from vision threatening to life endangering to innocuous ones. A keen observational and clinical skill can help the ophthalmologist in diagnosis & timely referral when necessary. We report 3 cases of acquired mydriasis, with cholinergic supersensitivity. The short history poses a diagnostic dilemma as to whether it is Adie's Tonic pupil or a harbinger of a serious neurological problem. 2 of the patients with mydriasis were younger, 32 & 35 years of age, presenting with recent onset of blurring of Vision for distance and difficulty in reading. The 3rd patient was a 45 year old presbyope who presented with sudden drop in near vision in one eye. Our cases raise several important question regarding so-called "benign pupillary dilation of the young" and its relationship with Adie's tonic pupil. Demonstration of probable transient parasympathetic dysfunction suggests that pharmacologic testing with dilute pilocarpine should be considered in patients reporting with near vision problems with isolated unilateral recent onset mydriasis which is probably intermittent. Thorough history and basic clinical neurological examination are mandatory. The importance of timely referral to neurologist must be borne in mind always in such cases.

KEYWORDS: Adie tonic pupil, cholinergic supersensitivity, transient parasympathetic dysfunction, unilateral mydriasis, RAPD.

Case 1: A 32 year old woman complained of disturbed vision in Right eye of vision for distance and near since 1 year with no other specific problems.

Case 2: A 29 year old male patient presented with blurring of Vision in the Left Eye, since 5 months, for both distance and near. He complained of severe intolerance to bright light.

Case 3: A 45 year old male presented with history of blurred vision in Right eye of 2 week's duration.

All the patients were generally healthy without history of any serious disease in past or any treatment with peniciilin. There was no history of ocular trauma. On repeated probing, vague history suggestive of viral infection prior to the onset of ocular symptoms could be elicited, of dubious significance. No history of migraine was present in any of the cases. No history of hearing loss, hair loss, tinnitus or vitiligo present in any case which could be suggestive of VKH.

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On examination

Sl. No.	Age, Sex	Duration	Eye	BCVA distance	Near vision	Pupil size	Accommodation & Direct light response
1	32, female	1 year	Right	6/6	N18	4 mm	Minimal
2	29, male	5 months	Left	6/6	N24	4-5mm	Absent
3	45, male	2 months	Right	6/6	N36	5-6 mm	Absent

Anterior segment examination- pupillary examination

Unilateral anisocoria- 4 -6mm which increased more in bright light than in dark
Direct reaction - not reacting to light/ flicker of reaction, no constriction
Consensual response (constriction on stimulation of opposite pupil) - absent
Accommodation (constriction of pupil when viewing a close object) - absent
No Relative Afferent Pupillary Defect –RAPD

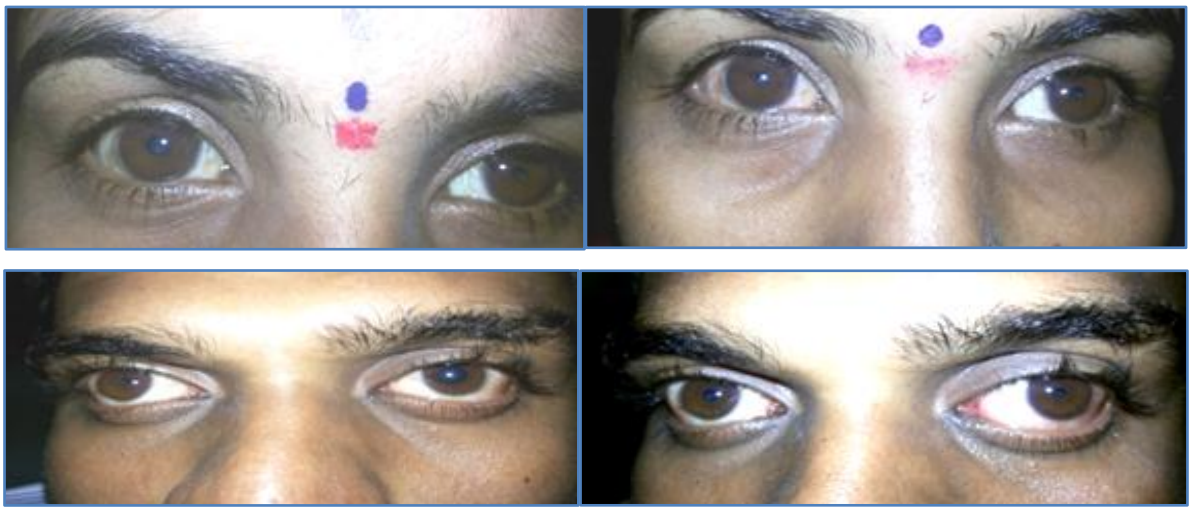
Slit lamp examination showed segmental, vermiform movements of the affected pupil in all the 3 patients, with bunching up of the iris and no typical brisk pupillary constriction. All extra ocular movements were normal.

Intra ocular pressure and ophthalmoscopic examination of the fundus was essentially normal in both eyes.

On instilling dilute pilocarpine – pupil constricted, with significant miosis, showing cholinergic supersensitivity. However the 3rd case showed only slight constriction of pupil.

Neurological Examination: Cranial nerve examination was essentially normal. 3rd & 5th cranial nerve involvement was double checked and were uninvolved. There were no skin lesions suggestive of herpes zoster ophthalmicus or VKH syndrome.

All deep tendon reflexes - especially of lower limbs i.e. knee and ankle jerks were normal. There was no evidence of any other neurological abnormality as confirmed by neurologist, later.



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Photographs demonstrating primary and post dilute pilocarpine pupillary size.
The first 2 patients showed good response confirming denervation supersensitivity,
while the 3rd patient had minimal response.

A clinical diagnosis of Adie's pupil was made.

Neurological reference was advised to all the patients along with routine blood tests, including FBS & PPBS and were within normal limits. MRI of the brain was done to rule out any pathology.

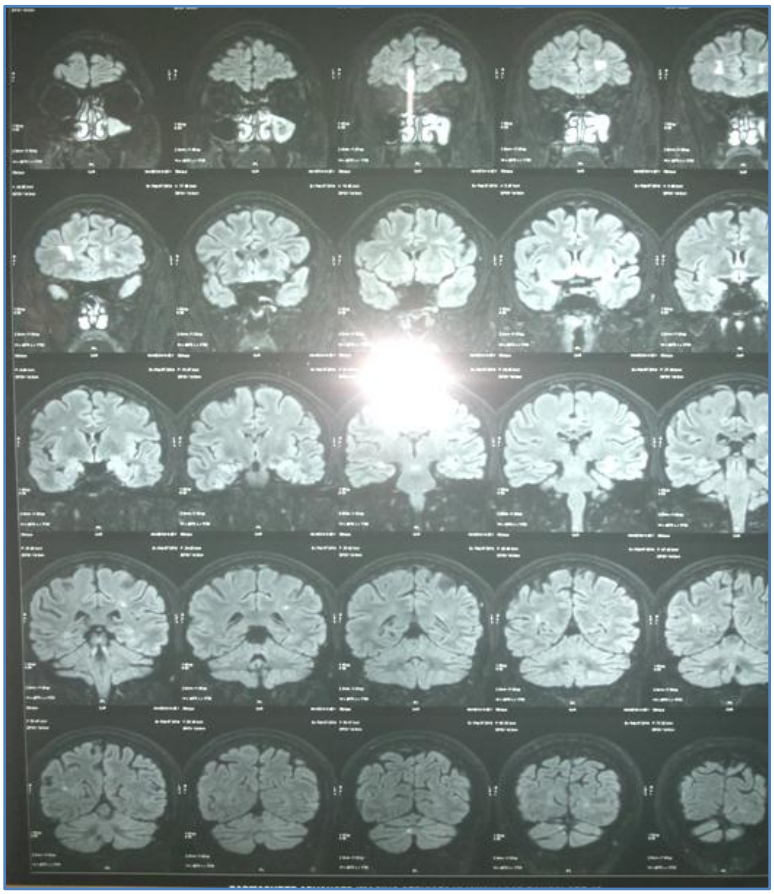

Figure 1

Figure 1: MRI Brain of 3rd patient showing ill-defined areas of T2 hyperintensity scattered in the bilateral frontoparietal white matter- ? Old ischaemic changes, with no evidence of acute infarct, haemorrhage or mass lesion.

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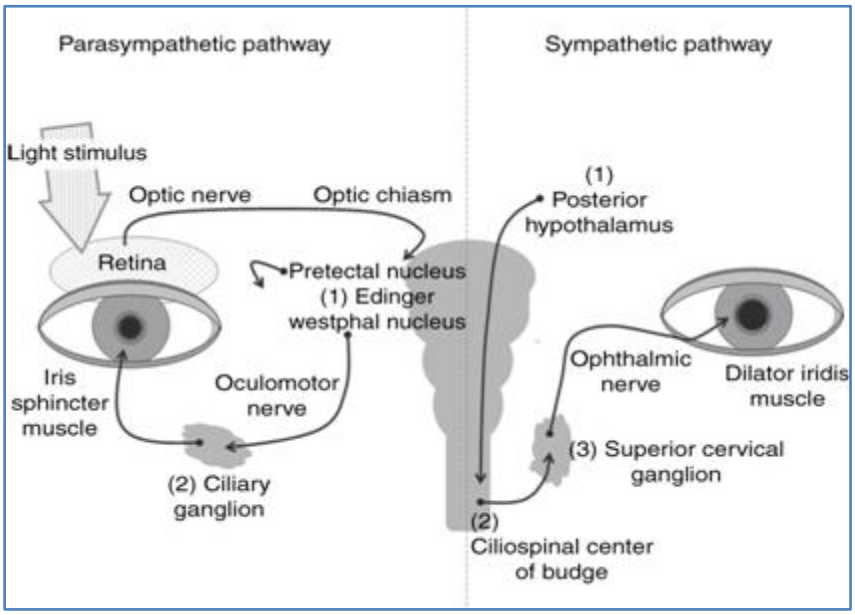
All patients were put on 2% pilocarpine eye drops 4 times a day. At 1 week follow up, they had symptomatic relief, with improved reading comfort. Miosis was well maintained & it was essentially the same as demonstrated at the initial examination with dilute piocarpine. The dose of pilocrpine 2% eye drops was reduced to 2 times a day and the subsequent follow up at 3 weeks showed well maintained miosis and near vision suggesting improved accommodation.

The segmental palsy of the sphincter persisted along with weakness of accommodation on withdrawal of pilocarpine even after 6 weeks. The patients are on regular follow up, continue to be on twice daily dose of 2% pilocarpine for 3 months.

DISCUSSION:

Pupillary pathway - Constriction Dilation



Adie's pupilis thought to be caused from denervation in the postganglionic parasympathetic nerve

ABNORMAL PUPILLARY RESPONSES:

ANISOCORIA: Refers to the asymmetric sizes of pupils. Physiologic anisocoria is very common and a normal variant in up to 20% of the population. The variation should be no more than 1mm and both eyes should react to light normally. A pathological cause of anisocoria must be ruled out as it can be dangerous if due to a manifestation of Horner's syndrome (e.g. carotid dissection) or from damage to the third nerve (e.g. aneurysmal expansion).

Relative Afferent Pupillary Defect (RAPD, Marcus Gunn Pupil): An RAPD is a defect in the direct response. It is due to damage in optic nerve or severe retinal disease**.** If an optic nerve lesion is present, the affected pupil will not constrict to direct light stimulus during the swinging flashlight test. The affected pupil shows normal constriction when light is shown in the other eye (consensual response).

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Swinging Flashlight Test:

- Swing a light back and forth in front of the two pupils and compare the reaction to stimulation in both eyes.
- When light reaches a pupil there should be a normal direct and consensual response.
- An RAPD is diagnosed by observing paradoxical dilatation when light is directly shown in the affected pupil after being shown in the healthy pupil.

This decrease in constriction or widening of the pupil is due to reduced stimulation of the visual pathway by the pupil on the affected side. By not being able to relay the intensity of the light as accurately as the healthy pupil and visual pathway, the diseased side causes the visual pathway to mistakenly respond to the decrease in stimulation as if the flashlight itself were less luminous. This explains the healthy eye is able to undergo both direct and consensual dilatation seen on the swinging flashlight test. Some causes of a RAPD include optic neuritis, ischemic optic disease or retinal disease, severe glaucoma causing trauma to optic nerve, direct optic nerve damage (trauma, radiation, tumor), retinal detachment, very severe macular degeneration, retinal infection (Cytomegalo virus, herpes), etc.

Argyll Robertson Pupil: This lesion is a hallmark of tertiary neurosyphilis. Pupils will NOT constrict to light but they WILL constrict with accommodation. Pupils are small at baseline and usually both involved (although degree may be asymmetrical).

Horner's Syndrome: Loss of sympathetic innervation causing the clinical triad of Ptosis - The superior tarsal muscle requires sympathetic innervation to keep the eyelid retracted, Miosis -A loss of sympathetic input causes unopposed parasympathetic stimulation which leads to pupillary constriction (miosis may be subtle and require a dark room), Anhidrosis or decreased sweating caused by a loss of sympathetic activity. The pattern of anihidrosis may help identify the lesion. Causes of Horner's Syndrome include carotid artery dissection, Pancoast tumors, nasopharyngial tumors, lymphoproliferative disorders, brachial plexus injury, cavernous sinus thrombosis, fibromuscular dysplasia, etc

Light Near Dissociation: Pupils that “accommodate but do not react” are said to show light-near dissociation- i.e., the absence of a miotic reaction to light, both direct and consensual, with the preservation of a miotic reaction to near stimulus (accommodation-convergence). Causes include: Unilateral: Afferent conduction defect, Adie pupil, Herpes zoster ophthalmicus, Abberent regeneration of 3rd nerve; and Bilateral: Neurosyphilis. Type 1 diabetes, Myotonic dystrophy, Parinaud dorsal midbrain syndrome, Familial amylodosis, Encephalitis, Chronic alcoholism.

Adie's (Tonic) Pupil: Some-times known as Holmes – Adie syndrome.[1]

A neurological condition of unknown origin characterized by a tonically dilated pupil, an unusual asymmetric presentation known as Anisocria. It is thought to be caused from denervation in the postganglionic parasympathetic nerve innervating the ciliary body. Alternatively, the problem may be located at the ciliary ganglion. Accommodation is affected, as well as pupillary dilation and contraction in response to ambient light.

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This condition primarily affects women from 20 to 40 yrs of age[1], but also can be present in men. It is considered to be a benign condition with no known cure. Named after the British neurologist William John Adie, who in 1931 described this condition as self – generating.

In 1934, French neurologist Jean-Alexandre Barre named it as Adie's syndrome.[1] When deep tendon reflexes of legs are also affected, accompanied by other symptoms including localized, discrete areas of the skin that do not sweat, postural hypotension and unsteady heart rhythms, the condition is referred to as "Adie's Syndrome".

Adie's pupil is associated with a number of diseases, including celiac disease, autoimmune hepatitis, endometriosis, orbital hamartoma, and migraine.[2,3,4,5,6,7,8,9] Recently, this clinical condition was associated with Ross syndrome.[2] Ross syndrome is characterized by Adie's pupil, hyporeflexia, and anhidrosis. Adie's pupil is thought to be a disease of young adults, and has rarely been reported in childhood.[4,5,6,7]

Holmes-Adie syndrome consists of unilateral or bilateral tonic pupils with near light dissociation and tendon areflexia. It is associated with autonomic disturbances affecting sudomotor and vasomotor function. According to a case report patients had a troublesome chronic dry cough, which was of unknown aetiology and was resistant to a range of treatments. The cough may be related to involvement of afferent or efferent pathways in the Vagus. Chronic cough may be an accompaniment in the Holmes-Adie syndrome, like other forms of autonomic dysfunction.[3]

OTHER NAMES: Tonic pupil syndrome, Holmes-Adie syndrome, Pseudotabes, Pupillotonic pseudotabes, Kehrer-Adie syndrome, Markers syndrome, Weill's syndrome, Weill-Reys-Adie syndrome, Pseudo-Argyll Robertson pupil[1], Saenger's syndrome, Constitutional areflexy-tridoplegia interna, Ross syndrome.[2, 10]

Signs and Symptoms – Presents with 3 Hallmark Symptoms:

1. Unilateral Mydriasis – No Reaction to Light.
2. Loss of deep tendon reflexes.
3. Absence of sweating.

Others – hyperopia, due to accommodative paresis, photophobia and difficulty reading.

DIAGNOSIS: Made on the basis of thorough history and physical examination, followed by tests to rule out other suspected causes according to the history.[11, 12]

Examination using slit lamp reveals undulating, irreversible, worm like movements with a segmented or ratcheted appearance in the iris of the affected eye, uncoupled to the movements in the iris of the unaffected eye.

The tonic pupil may become miotic over time, when it is called as "little old Adie's"

A positive i.e. hypersensitive response to low dose 0.125% pilocarpine drops causes the otherwise slow-to-constrict pupil to constrict intensely, is considered diagnostically additive. (cholinergic denervation supersensitivity)[13, 14]

CT scans and MRI may be useful in the diagnostic testing of focal hypoactive reflexes.

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TREATMENT:

Non specific:

1. Prescription of glasses for correcting refractive error.
2. Pilocarpine drops – trial 2%, BID need based.
3. Thoracic sympathetomy for troublesome diaphoresis, if not treatable by drug therapy.
4. B-complex vitamins, antioxidants including vitamin C/E, alpha-lipoic acid and superoxide dismutase(S.O.D.) and dietary modifications have been found helpful in multiple sclerosis.[11]
5. Lifestyle practices that reduce stress and tone the parasympathetic nervous system such as yoga or massage may be helpful.

Diabetes was ruled out in all our patients because pupillary autonomic denervation with increasing duration of diabetes mellitus has been documented. Denervation hypersensitivity to dilute pilocarpine as a result of damage to the pupillary parasympathetic supply is known to occur in diabetic patients before the sympathetic pathway is affected. It can be detected early in the disease and it may be a possible explanation for the small pupil size seen in diabetic patients.[15, 16, 17]

According to a report, a case of Herpes zoster ophthalmicus complicated with complete ophthalmoplegia showed mydriatic pupil reacting to dilute pilocarpine, which is a sign of Adie's pupil and is not supposed to occur in mydriasis caused due to third nerve palsy.[18]

A case was reported showing presence of Adie's pupil in a paediatric patient presenting with ophthalmoplegic migraine, pupil changes persisted even after the migraine attack resolved. By definition, a diagnosis of ophthalmoplegic migraine with third cranial-nerve involvement and a diagnosis of Adie's pupil are mutually exclusive. In fact, a clinical diagnosis of Adie's pupil requires the absence of an extraocular motility abnormality, whereas for a diagnosis of ophthalmoplegic migraine, there must be a movement disorder.[19]Although no gadolinium enhancement of the cisternal segment of the oculomotor nerve (third or sixth) was detected by magnetic resonance imaging, the patient was diagnosed with ophthalmoplegic migraines, based on her medical history and a clinical picture fitting the international criteria for ophthalmoplegic migraines. The subsequent diagnosis of Adie's pupil after her last ophthalmoplegic-migraine attack was determined by clinical presentation, her response to the pilocarpine test, and the long-lasting dilatation of her pupils, which remained unresolved for 2 years. In fact, even after 24 months, a poor reaction to light was present according to the pilocarpine test, confirming the diagnosis of persistent Adie's pupil.

The persistence of Adie's pupil after remission from ophthalmoplegic migraines in this patient was similar to two reported cases: one patient [20] exhibited transient Adie's pupil associated with migraine with aura, and another manifested a permanent deficit of the third cranial nerve after an ophthalmoplegic-migraine attack.[21]

	Adie's Pupil	**Ophthalmoplegic Migraine**
Associated etiology	Ocular/extraocular diseases (Ross syndrome, celiac disease, amyloidosis, diabetes, autoimmune hepatitis, neurologic malignancies)	Headache with migraine-like features and ocular motor impairment, mainly third and sixth cranial nerves [22].

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	Adie's Pupil	Ophthalmoplegic Migraine
Clinical features	Unilateral dilated pupil, unresponsive to light. May follow long-lasting migraine.	Recurrent attacks of headache with migrainous characteristics associated with paresis of one or more ocular cranial nerves, commonly third nerve. Mainly pupillary mydriasis.
Cranial nerve involvement	Only postganglionic parasympathetic fibers are involved.	Cranial nerves III, IV, and VI, associated with ocular paresis.
Magnetic resonance imaging	Normal.	Gadolinium uptake in cisternal part of affected cranial nerve during acute period, although this is not mandatory [22].
Pilocarpine test	Positive.	No response.
Prognosis	Usually good.	Good; rare permanent deficit of involved cranial nerves.

Characteristics of Adie's pupil compared with ophthalmoplegic migraine

A case was reported where Measles virus vaccine live was given to a boy (9 yr old) who developed Adie's pupil and reversible posterior leukoencephalopathy.[23, 24]

A case of Vogt-Koyanagi-Harada Syndrome has been reported in a female patient who developed bilateral Adie's pupil. After treatment symptoms of VKH resolved but Adie's pupil persisted.[25]

CONCLUSION: Tonic pupil may occur due to local or systemic causes. A neuropathic tonic pupil may be a manifestation of generalized, wide spread autonomic neuropathy, syphilis, alcoholism, diabetes, Guillean Barre syndrome, etc., just to name a few. In a nut shell, mydriasis of 3rd nerve origin is likely to be larger, have other evidences of 3rd nerve involvement; while pharmacological mydriasis which may also show larger pupil will have no response to dilute pilocarpine. Adie's pupil is a diagnosis of exclusion, the confirmatory evidence being largely clinical. Neurological examination is mandatory along with thorough local examination. A thorough knowledge of pupillary masquerades and high index of suspicion can help in management & symptomatic relief.

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