PUPILS: ANISOCORIA

Steven L. Galletta, MD
NYU Langone Medical Center
New York, NY

I. Neuroanatomy

Light directed into either eye usually produces bilateral pupillary constriction. The pupillary light reflex begins with hyperpolarization of the retinal photoreceptors. Ultimately, the retinal ganglion cells are activated. The retinal ganglions cells send their axons through the optic nerve, chiasm, and optic tract to synapse in the pretectal nuclei. Interneurons then connect the pretectal nuclei to the Edinger Westphal nuclei.

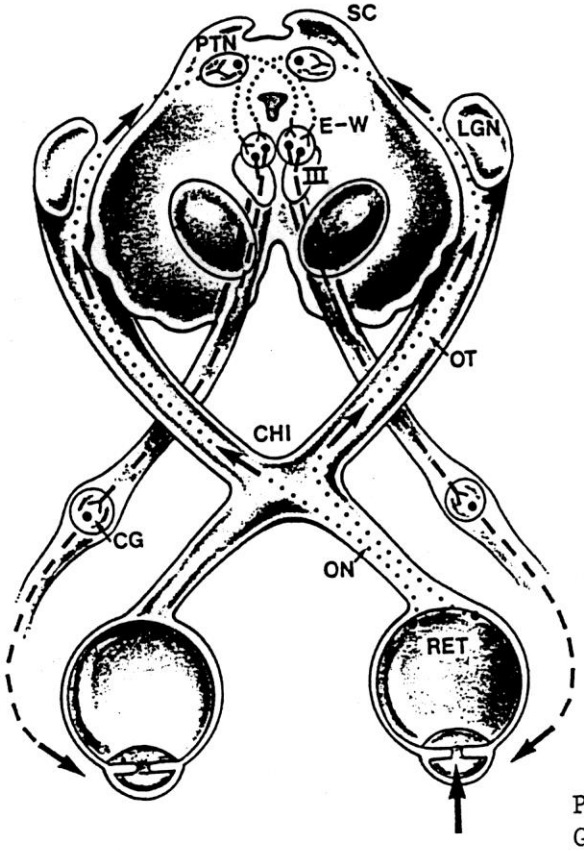


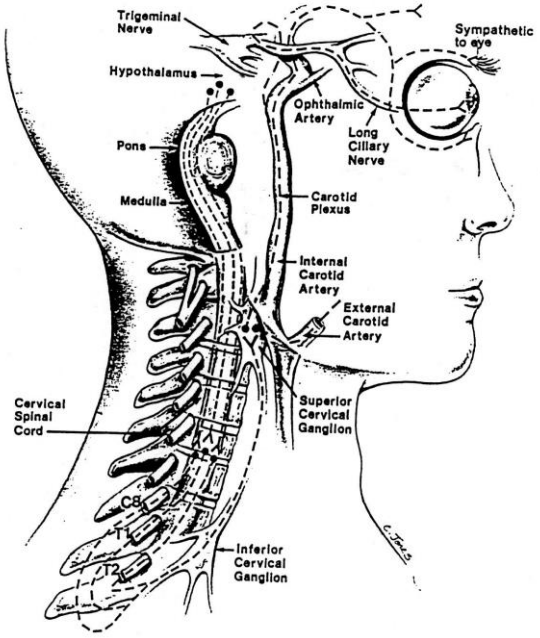
Photo courtesy of
Grant Liu, M.D.

Pupillary light reflex - parasympathetic pathway. Light entering one eye (straight black arrow, bottom right) stimulates the retinal photoreceptors (RET), resulting in excitation ganglion cells, whose axons travel within the optic nerve (ON), partially decussate in the chiasm (CHI), then leave the optic tract (OT) (before the lateral geniculate nucleus [LGN]) and pass through the brachium of the superior colliculucs (SC) before synapsing at the mesencephalic pretectal nucleus (PTN). This structure connects bilaterally within the oculomotor nuclear complex at the Edinger-Westphal (E-W) nuclei, which issue parasympathetic fibers that travel within the third nerve (inferior division) and terminate at the ciliary ganglion (CG) in the orbit. Postsynaptic cells innervate the pupillary sphincter, resulting in miosis. Note that light in one eye causes bilaterally pupillary constriction. (Adapted from Slamovits TL, Glaser JS: The pupils and accommodation. pg. 460. In Glaser JS (ed): *Neuro-ophthalmology*. 2nd Ed. JP Lippincott, Philadelphia, 1990, with permission.

The Edinger Westphal nuclei comprise the rostral portion of the third nerve nucleus. These parasympathetic fibers travel ventrally to exit the midbrain. In the subarachnoid space, the pupillary fibers lie superficially (dorsomedially in the third nerve) making them vulnerable to compression or infiltration at this point. In the anterior cavernous sinus, the third nerve divides into a superior and inferior division. The pupillary fibers run with inferior division . The pupillary fibers run with inferior division and ultimately synapse in the ciliary ganglion. The ciliary ganglion gives rise to the short ciliary nerves which innervate the ciliary body and iris sphincter muscle. Of importance, fibers to the ciliary body outnumber those to the iris sphincter by a ratio of 30:1.

The near response consists of the triad of: 1) pupillary constriction, 2) accommodation (lens becomes spherical), and 3) convergence of the eyes. The cortical region responsible for supranuclear generation of the near response remains uncertain. It probably arises from diffuse cortical projections. Ultimately, supranuclear inputs for the near reflex converge upon the rostral superior colliculus. [1] From here connections are made to the mesencephalic reticular formation, pretectum and Edinger Westphal nucleus to generate the near triad.[1]

Pupillary dilation is the function of the oculosympathetic system. The sympathetic input to the eye is a three neuronal pathway that begins in the posterolateral hypothalamus. From the hypothalamus, the first order neuron projects to the intermedo-lateral cell column at C8-T1 (ciliospinal center of Budge). This second order neuron leaves the spinal cord and travels over the apex of the lung where it lies in proximity to the lower brachial plexus. The second order neuron synapse in the superior cervical ganglion. From here, the third order neuron travels along the internal carotid artery into the cavernous sinus where the sympathetic pathways follow the nasociliary nerve (first trigeminal branch) into the orbit.[2,3] Norepinephrine is the neurotransmitter that activates the iris dilator muscle.



Sympathetic innervation of the pupil and eyelids. First-order hypothalamic (central) neurons descend through the brainstem (midbrain, pons, medulla) and cervical spinal cord. These fibers then synapse with preganglionic neurons, whose cell bodies lie in the intermediolateral gray column and whose axons exit the cord ipsilaterally at C8, T1, and T2. These second-order fibers then travel rostrally via the sympathetic chain and terminate in the superior cervical ganglion. The postganglionic axons ascend within the carotid plexus, which surrounds the internal carotid artery, to reach the cavernous sinus and arrive at the iris via branches of the first division of the trigeminal nerve and then the long ciliary nerve. Sudomotor fibers to the lower face follow the external carotid then facial arteries. Sympathetic fibers to Muller's muscles also travel within the carotid plexus into the cavernous sinus, then may join branches of the third nerve before reaching the upper and lower eyelids.

II. Anisocoria

The normal pupil varies in size, depending on the ambient illumination. Pupil size decreases with age and during sleep. Physiologic anisocoria of 0.4 mm or greater may be seen in approximately 20% of individuals, and, if these patients are followed for a five day period, the number rises to 40%.[4] Distinguishing pathologic anisocoria from a physiologic process requires documentation of pupil reactivity and size in bright and dim illumination.[5] In physiologic anisocoria, the amount of anisocoria does not change with varying illumination. The pupils should respond normally to light and near stimulation. Careful examination of old photographs is often very helpful to document a physiologic anisocoria.

If the anisocoria is not physiologic then one tries to determine if the lesion is in the sympathetic or parasympathetic pathway. Remember, anisocoria does not result from an afferent pathway lesion involving the optic nerve, chiasm or optic tract. If the pupil asymmetry is greater in the light and the pupil is sluggish to direct light stimulation, parasympathetic dysfunction is indicated. A greater difference in the darkness with normal pupillary reactivity suggests oculosympathetic paresis on the side of the smaller pupil.

Hallmark features of a Horner's syndrome include: 1) unilateral miosis, 2) ptosis, and 3) anhidrosis.[6,7] A Horner's syndrome is suggested when anisocoria increases in the dark or when the miotic pupil demonstrates a dilation lag.[8] The normal pupil dilates very quickly when the patient is placed in the dark. For dilation lag, measurements of pupil size are made at 5 and 15 seconds after the patient is placed in the dark. Typically there is more anisocoria present at 5 seconds because the normal pupil should briskly dilate. Pupillary lag is intermittently present in most patients with Horner's syndrome and it may require repeated testing to detect it.[55]

The upper lid ptosis of a Horner's syndrome is usually mild and measures only a few millimeters. The ptosis is never complete with sympathetic interruption. Since the lower lid is also elevated in a Horner's syndrome, it may give the false impression that the eye is sunken into the orbit (pseudo-enophthalmos). The Horner's patient typically has no visual symptoms. Unilateral conjunctival injection and low intraocular pressure are other potential signs of sympathetic interruption.

Lesions of the third sympathetic neuron usually cause a patch of anhidrosis along the medial aspect of the forehead and on the side of the nose. The other sweat fibers have traveled along the external carotid artery and therefore remain uninvolved in third order sympathetic lesions. Lesions involving the first and second order sympathetic neurons would be expected to produce anhidrosis on the entire half of the face.[9] Decreased sweating on one side of the body occurs with first order neuron lesions.

III. Etiology of Horner's Syndrome

The etiology of Horner's syndrome varies with the type of one's practice. In the inpatient setting, first order neuronal dysfunction is most frequently observed and is usually associated with a stroke.10 In other instances, second order neuron cases will predominate, 11,12 while in a headache practice postganglionic dysfunction will be most frequent.13 The presence of clinical signs serve to localize a Horner's syndrome further. Brainstem and spinal cord signs suggest involvement of the first order neuron. Arm pain, hand weakness, or a history of neck surgery or trauma suggest a second order neuron process. Ipsilateral facial pain and a Horner's syndrome imply third order neuron dysfunction.

First order Horner's:

A) Hypothalamic Horner's syndrome is relatively rare because of the rich blood supply to this area. In patient's with persistent fetal circulation, the hypothalamus may be supplied directly by branches of the internal carotid artery. Occlusion of the internal carotid artery in this situation will produce a large infarct and result in contralateral hemiparesis, heminsensory loss or hemianopia.[14,15]

B) Mesencephalic or pontine Horner's: Again, sympathetic interruption is uncommon in this region. A combination of an ipsilateral Horner's and a contralateral superior oblique palsy suggests a lesion in the vicinity of the trochlear nucleus or its fascicle.[16]

Medulla: The most common central cause of Horner's syndrome is a dorsolateral medullary infarction. A Horner's syndrome is seen in at least 75% of cases.17,18 Other eye signs are frequent and include impaired pursuit, ocular dysmetria, lateropulsion and skew deviation.

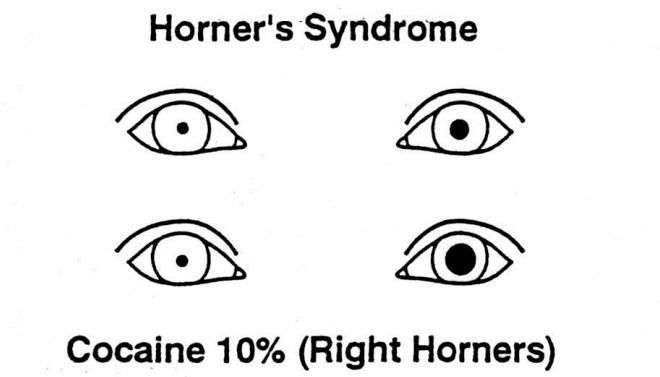
Spinal cord: The most common causes are syringomyelia and trauma to the cord. Other etiologies include tumor, multiple sclerosis, myelitis, and infarction. Occasionally, spinal cord lesions will irritate the fibers producing ipsilateral pupillary dilation and lid retraction.

Second order Horner's:
Lung and neck tumors and traumatic injury are the most common causes of impairment at this level. Many cases are iatrogenic and include neck dissection, mediastinal and lung surgery, chest tube placement, internal jugular catheterization and Swan Ganz catherization.[19-23]

Third order Horner's:
The third order Horner's syndrome usually occurs in isolation. The presence of pain should suggest a differential of carotid dissection, carotid occlusion, vascular headache or cavernous sinus process. In fact, Horner's syndrome is the most common neurologic finding in carotid dissection occurring in approximately 50% of cases.[24-27] Conventional or MRI angiography is essential to help exclude a dissection in the setting of a painful third order Horner's syndrome. T_1 weighted MR images may show the characteristic crescentic high signal abnormality (mural thrombus) in the wall of the affected vessel

HORNER'S IN CHILDHOOD

Birth trauma and occult neuroblastoma are the most important causes of Horner's syndrome to recognize in childhood. Iris heterochromia is a sign that suggests a congenital oculosympathetic paresis.[28] Unfortunately this is not always present and some acquired cases demonstrate this finding as well. Many cases in children, like adults, remain idiopathic.[29]



PHARMACOLOGIC TESTING

Pharmacologic testing is necessary when the diagnosis of a Horner's syndrome remains uncertain. Cocaine and Apraclonidine are the two most commonly used eye drops to determine the presence of a Horner's syndrome. Cocaine is declining as the gold standard eye drop test to determine the presence of Horner's syndrome because of its availability as a controlled substance. Nonetheless, it is important to review its mechanism of action.

Cocaine blocks the reuptake of norepinephrine of the third order neuron. Cocaine fails to dilate the pupil with sympathetic dysfunction while the normal pupil will dilate. Cocaine confirms the presence of a Horner's syndrome but it usually does not further define the localization of the sympathetic paresis. We prefer to use 10% cocaine because it is a weak mydriatic. The pupil sizes should be assessed at baseline and 40-60 minutes later. The most accurate way to interpret the cocaine test is to measure the amount of post cocaine anisocoria. If the anisocoria is 1.0 mm or more the test can be considered positive.[30] The greater the amount of post cocaine anisocoria, the greater likelihood that an oculosympathetic paresis exists. Apraclonidine, an alpha 1 receptor agonist, is emerging as the gold standard eye drop test for the detection of a Horner's syndrome. Since apraclonidine is a weak alpha agonist, it has minimal or no effect on normal pupils. On the other hand, patients with Horner's syndrome show denervation supersensitivity and the pupil should dilate in this setting. Thus, apraclonidine 1% eye drops may reverse the anisocoria observed in a Horner's syndrome.(54) False negative results may occur if the test is used at onset since it takes 3 to 7 days for supersensitivity to occur. [55,56]

HYDROXYAMPHETAMINE

The distinction between a preganglionic and a postganglionic Horner's is important because the former may be a sign of an underlying neoplasm. Hydroxyamphetamine enhances the release of norepinephrine

from the third order terminal. Thus, if the postganglionic neuron is injured the pupil will not dilate or will dilate poorly. Cremer et al found that a 1mm increase in the amount of anisocoria is associated with 85% probability that the lesion is postganglionic.[31] A 2 mm increase is associated with a probability of 99% that postganglionic defect exists. However, the hydroxyamphetamine test is not perfect. Cremer et al found that increase in the anisocoria in 93% of postganglionic cases.[31] The anisocoria did not change in 90% of preganglionic cases. Thus, one has to assume an approximately 10% error rate with Hydroxyamphetamine testing. Because of availability of Hydroxyamphetamine, the test is rarely performed in current clinical practice.

Management decisions for a Horner's largely depend on its localization. In most cases, imaging is directed to the appropriate region.[32] Since pharmacologic localization is imperfect, an isolated unexplained Horner's syndrome requires a chest CT or neck MR to rule out an apical mass lesion. Those patients with a Horner's syndrome and ipsilateral headache should be screened with MRI and MR angiography of the neck to exclude a carotid dissection or thrombosis.[33,34]

MANAGEMENT OF CONGENITAL AND PEDIATRIC HORNER'S

In those patients without trauma, diagnostic testing is directed at considering a neuroblastoma or other mass lesions. MRI of brain, neck, chest, and abdomen along with urinary catecholamine screening is suggested. Imaging protocols appear to be most sensitive to detecting mass lesions than urine testing in children.[35]

THE DILATED PUPIL

One approach to the patient with the dilated pupil is to start in the midbrain and walk the course of the third nerve from its origin to the iris muscle. Therefore, a dilated pupil of midbrain origin usually is associated with other signs of dysfunction referable to this region (convergence retraction nystagmus, eyelid retraction, hemiparesis, and sensory loss). On the other hand, an isolated dilated pupil usually occurs with injury to the: 1) ciliary ganglion, 2) neuromuscular blockage, or 3) iris injury from trauma or inflammation.

1. *Third nerve palsy:* In most cases of third nerve palsy with pupillary involvement, there will be defects in adduction, depression or elevation of the affected eye. In rare instances, a dilated pupil will be the only manifestation of third nerve palsy. In a pupil sparing third nerve palsy, the pupil maintains its normal size and reactivity, but the eye movements and lid function are impaired. Pupil involvement is common in nuclear, fascicular, and especially subarachnoid third nerve palsies. Because the pupillary fibers are located superficially (dorsomedially), they are vulnerable to compressive processes such as uncal herniation and aneurysmal mass effect. If a patient has an isolated pupil involving third nerve palsy, an aneurysm of the posterior communicating artery should be considered until proven otherwise. Those patients with aneurysms without pupil involvement typically have only partial ophthalmoparesis.[36] This subgroup of patients should be followed serially over several weeks for evidence of pupillary involvement.[36]

2. *Cavernous sinus:* Ipsilateral involvement of cranial nerves III, IV, V, and VI indicates a lesion in the cavernous or superior orbital fissure region. Third nerve palsies of cavernous sinus origin often spare the pupil. The pupillary sparing observed in some cavernous sinus lesions may be explained by the slow growth of tumors that originate in this area. One must also consider the possibility of pseudopupillary sparing which results when the pupillary signs of third nerve dysfunction are masked by a Horner's syndrome or aberrant regeneration of the third nerve.

    a. *Aberrant regeneration:* Following acute injury to the third nerve, a mis-wiring phenomenon may occur. Trauma and aneurysms (PCOM and cavernous sinus) are the most common causes of aberrant regeneration. Typically it takes several months for aberrant regeneration to develop. The most characteristic finding is lid elevation in down or medial gaze. Other signs include: 1) pupillary miosis in adduction,[37] 2) globe retraction in attempted upgaze, and 3) adduction in upgaze.

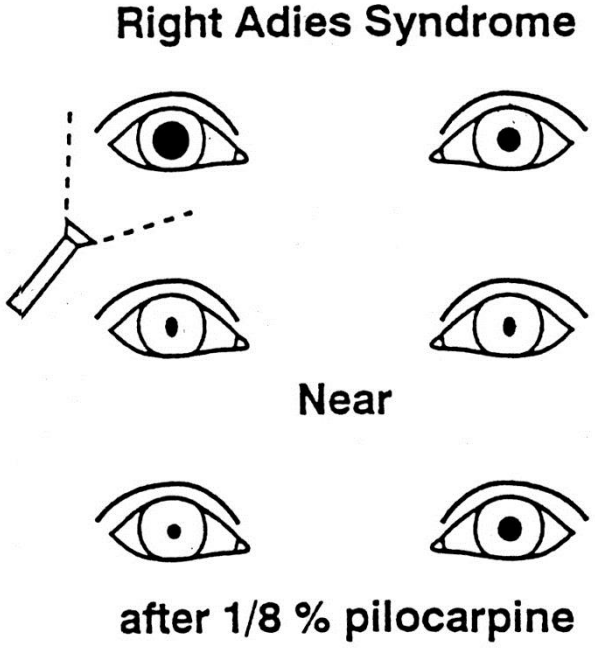
TONIC PUPILS

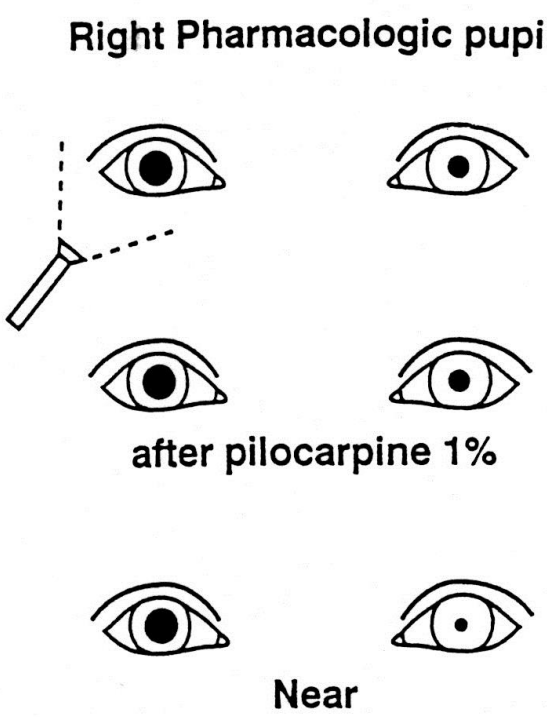
This dilated pupil results from interruption of the parasympathetic supply arising from ciliary ganglion. Partial involvement of the pupil parasympathetic supply results in segmental involvement of the iris. In the acute setting, this is one feature that distinguishes the post-ganglionic dilated pupil from the dilated pupil of a third nerve palsy. The latter has symmetrical involvement of the iris sphincter in the acute setting. One of the other characteristic features of the tonic pupil is the slow contraction of the pupil to a near stimulus.

The better response of the pupil to near contrasts with the poor response of the pupil to direct light stimulation. The light-near dissociation can be explained by a 30:1 ratio of accommodation fibers arising from the ciliary ganglion relative to those responsible for pupillary constriction.[39] Therefore, damage to the ciliary ganglion or short ciliary nerves has a greater chance of disabling pupillary constriction to light than disrupting miosis associated with accommodation. As the nerve cells in the ciliary ganglion sprouts new axons following injury, postganglionic accommodation may mistakenly innervate the iris sphincter. This results in greater pupillary constriction during accommodation. Tonic pupils may occur from a variety of local processes affecting the ciliary ganglion such as trauma, tumor, ischemia, or infection. Other patients have a tonic pupil as a manifestation of a more widespread autonomic process.[39] However most cases of tonic pupil are idiopathic and occur in young women between the ages of 20 and 40. When a tonic pupil is combined with absent deep tendon (extremity) reflexes, it is referred to as Adie's syndrome.[40] The pathophysiology of Adie's syndrome presumably requires injury to both the ciliary and dorsal root ganglion. As the result of iris sphincter dysfunction, these patients have supersensitivity to dilute (1/8%) pilocarpine.[41] This solution can be made by drawing up 0.1 cc of 1% pilocarpine with 0.7 cc of sterile saline in a 1 cc tuberculin syringe. The test is positive when the affected pupil constricts more than the normal pupil. Since some normal patients can occasionally constrict to dilute pilocarpine, the test needs to be interpreted with caution. The tonic pupil is usually unilateral, but may become bilateral in 10% of cases. The pupil usually becomes involved months to years later.[39] Since some patients with neurosyphilis will manifest tonic pupils, it also important to check syphilis serologies in such patients.

PHARMOCOLOGIC BLOCKAGE:

Pupils that are dilated and don't respond to light or near stimulation may be pharmacologically blocked. The lack of response to near stimulation distinguishes the pharmacologic pupil from the tonic pupil. The tonic pupil usually has an intact near response.





This may occur from placement of ophthalmic drugs into the eyes such as Atropine, Tropicamide, or cyclopentolate. Environmental contaminants with an atropine-like affect include jimson weed, blue night shade, and scopolamine patches.[43] One percent pilocarpine drops fail to constrict the pharmacologically dilated pupil.[44] The test needs to be interpreted with caution if performed near the termination of the pharmacologic blockage. Iris causes of a dilated pupil to consider include: 1) trauma, 2) angle closure glaucoma, 3) iritis.

PUPILS IN OTHER DISORDERS

Migraine: Transient isolated mydriasis may occasionally accompany migraine.[45] The dilated pupil may be produced by sympathetic hyperactivity of the iris dilator or parasympathetic dysfunction.[46] In some cases, the pupil may have the features of a tonic pupil[47] or assume a tadpole shape[48] (see below).

Seizures: Many patients with generalized tonic clonic activity will have bilateral mydriasis. However, unilateral ictal mydriasis may also occur ipsilateral or contralateral to cortical focus.[49-51] Ictal miosis also occurs both bilaterally and unilaterally to a seizure focus.[52-53]

Tadpole pupils: Thompson et al described a group of patients with episodic mydriasis and segmental pupillary distortion.[48] The phenomenon occurs over minutes and may be accompanied by an ache or other abnormal sensations in the affected eye. This pupil finding has been observed in patients with Horner's syndrome, tonic pupils, and migraine. This pupil may be due to segmental spasm of the iris dilator muscle.

References

1. Ohtsuka K, Sato A: Descending projections from the cortical accommodation area in the cat. Invest *Ophthalmol Vis Sci* 1996;37:1429-1436.

2. Parkinson D: Further observations on the sympathetic pathways to the pupil. *Anat Rec* 1988;220:108-109.

3. Liu GL, Volpe NJ, Galetta SL. Neuro-ophthalmology: Diagnosis and Management p. 427-463. Philadelphia, WB Saunders, 2001

4. Lam BL, Thompson HS, Corbett JJ: The prevalence of simple anisocoria*. Am J Ophthalmol* 1987;104:69-73

5. Slamovits TL, Glaser JS: The pupils and accommodation. In Glaser JS (eds.*): Neuro-ophthalmology*, p 459-486. Philadelphia, J.B. Lippincott Co., 1990.

6. Wilkins RH, Brody IA: Horner's syndrome. *Arch Neurol* 1968;19:540-542.

7. Thompson HS: Johann Friedrich Horner (1831-1886). *Am J Ophthalmol* 1986;102:792-795.

8. Pilley SF, Thompson HS: Pupillary "dilatation lag" in Horner's syndrome. *Brit J Ophthalmol* 1975;59:731-735.

9. Morris JGL, Lee J, Lim CL: Facial sweating in Horner's syndrome. *Brain* 1984;107:751-758

10. Keane JR: Oculosympathetic paresis. Analysis of 100 hospitalized patients. *Arch Neurol* 1979;36:13-16.

11. Giles CL, Henderson JW: Horner's syndrome: an analysis of 216 cases. *Am J Ophthalmol* 1958;46:289-296.

12. Maloney WF, Younge BR, Moyer NJ: Evaluation of the causes and accuracy of pharmacologic localization in Horner's syndrome. *Am J Ophthalmol* 1980;90:394-402.

13. Grimson BS, Thompson HS: Drug testing in Horner's syndrome. In Glaser JS, Smith JL (eds.): *Neuro-ophthalmology. Symposium of the University of Miami and the Bascom Palmer Eye Institute*. Vol. VIII, p 265-270. St Louis, C.V. Mosby, 1975.

14. Stone WM, de Toledo J, Romanul FCA: Horner's syndrome due to hypothalamic infarction. Clinical, radiologic, and pathologic correlations. *Arch Neurol* 1986;43:199-200.

15. Austin CP, Lessell S: Horner's syndrome from hypothalamic infarction. *Arch Neurol* 1991;48:332-334.

16. Guy J, Day AL, Mickle JP, et al.: Contralateral trochlear nerve paresis and ipsilateral Horner's syndrome. *Am J Ophthalmol* 1989;107:73-76.

17. Sacco RL, Freddo L, Belo JA, et al.: Wallenberg's lateral medullary syndrome. *Arch Neurol* 1993;50:609-614.

18. Kim JS, Lee JH, Suh DC, et al.: Spectrum of lateral medullary syndrome. Correlation between clinical findings and magnetic resonance imaging in 33 subjects. *Stroke* 1994;25:1405-1410.

19. Barbut D, Gold JP, Heinemann MH, et al.: Horner's syndrome after coronary artery bypass surgery. *Neurology* 1996;46:181-184.

20. Bertino RE, Wesbey GE, Johnson RJ: Horner syndrome occurring as a complication of chest tube placement. *Radiology* 1987;164:745.

21. Garcia EG, Wijdicks EFM, Younge BR: Neurologic complications associated with internal jugular vein cannulation in critically ill patients: a prospective study. *Neurology* 1994;44:951-952.

22. Teich SA, Halprin SL, Tay S: Horner's syndrome secondary to Swan-Ganz catheterization. *Am J Med* 1985;78:168-170.

23. Jacobson DM, Olson KA: Influence of pupil size, anisocoria, and ambient light on pilocarpine miosis. Implications for supersensitivity testing. *Ophthalmology* 1993;100:275-280.

24. Kline LB, Vitek JJ, Raymon BC: Painful Horner's syndrome due to spontaneous carotid artery dissection. *Ophthalmology* 1987;94:226-230.

25. Kline LB: The neuro-ophthalmologic manifestations of spontaneous dissection of the internal carotid artery. *Seminars Ophthalmol* 1992;7:30-37.

26. Galetta SL, Leahey A, Nichols CW, et al.: Orbital ischemia, ophthalmoparesis, and carotid dissection. *J Clin Neuro-ophthalmol* 1991;11:284-287.

27. Newman NJ, Kline LB, Leifer D, et al.: Ocular stroke and carotid artery dissection. *Neurology* 1989;39:1462-1464.

28. Jaffe N, Cassady JR, Filler RM et al.: Heterochromia and Horner syndrome. *Brit J Ophthalmol* 1975;59:731-735.

29. Leung A: Congenital Horner's syndrome. *Ala J Med Sci* 1986;23:204-205.

30. Kardon RH, Denison CE, Brown CK, et al.: Critical evaluation of the cocaine test in the diagnosis of Horner's syndrome. *Arch Ophthalmol* 1990;108:384-387.

31. Cremer SA, Thompson HS, Digre KB, et al.: Hydroxyamphetamine mydriasis in normal subjects. *Am J Ophthalmol* 1990;110:66-70.

32. Digre KB, Smoker WR, Johnston P, et al.: Selective MR imaging approach for evaluation of patients with Horner's syndrome. *Am J Neuroradiol* 1992;13:223-227.

33. Stern MJ, Patel M, Davis J, et al.: Painful Horner syndrome associated with occlusion of the extracranial internal carotid artery: MR imaging. *J Comput Assist Tomog* 1995;119:811-813.

34. Brown J, Danielson R, Donahue SP, et al.: Horner's syndrome in subadventitial carotid artery dissection and the role of magnetic resonance angiography. *Am J Ophthalmol* 1995;119:811-813.

35. Mahoney NR, Liu GT, Menacher S et al. Pediatric Horner's syndrome: etiologies and roles of imaging and urine studies to detect neuroblastoma and other responsible mass lesions. Am J Ophthalmol 2006;142: 651-659.

36. Kissel JT, Burde RM, Klingele TG, et al.: Pupil-sparing oculomotor palsies with internal carotid-posterior communicating artery aneurysms. *Ann Neurol* 1983;13:149-154.

37. Czarnecki JSC, Thompson HS: The iris sphincter in aberrant regeneration of the third nerve. *Arch Ophthalmol* 1978;96:1606-1610.

38. Thompson HS: Segmental Palsy of the iris sphincter in Adie's syndrome*. Arch Ophthalmol* 1978;l96:1615-1620.

39. Loewenfeld IE: Lesions in the ciliary ganglion and short ciliary nerves: the tonic pupil ("Adie's" syndrome). In: *The Pupil. Anatomy, Physiology, and Clinical Applications.* Vol. 1., p 1080-1130. Detroit, Wayne State University Press, 1993.

40. Drummond PD, Edis RH: Loss of facial sweating and flushing in Holmes-Adie syndrome. *Neurology* 1990;40:847-849.

41. Bourgon P, Pilley SFJ, Thompson HS: Cholinergic supersensitivity of the iris sphincter in Adie's tonic pupil. *Am J Ophthalmol* 1978;85:373-377.

42. Fletcher WA, Sharpe JA: Tonic pupils in neurosyphilis. *Neurology* 1986;36:188-192.

43. McCrary JA, Webb NR: Anisocoria from scopolamine patches *JAMA* 1982;248:253-354.

44. Thompson HS, Newsome DA, Loewenfield IE: The fixed dilated pupil: Sudden iridoplegia or mydriatic drops? A simple diagnostic test. *Arch Ophthalmol* 1971;86:21-27.

45. Woods D, O'Connor PS, Fleming R: Episodic unilateral mydriasis and migraine. *Am J Ophthalmol* 1984;98:229-234.

46. Jacobson DM: Benign episodic unilateral mydriasis. *Ophthalmology* 1995;102:1623-1627.

47. Purvin VA: Adie's tonic pupil secondary to migraine. *J Neuro-ophthalmol* 1995;15:43-44.

48. Thompson HS, Zackon DH, Czarnecki JSC: Tadpole shaped pupil caused by segmental spasm of the iris dilator muscle. *Am J Ophthalmol* 1983;96:467-477.

49. Pant SS, Benton JN, Dodge PR: Unilateral pupillary dilatation during and immediately following seizures. *Neurology* 1966;16:837-840.

50. Zee DS, Griffen J, Price DL: Unilateral pupillary dilatation during adversive seizures. *Arch Neurol* 1974;30:403-405.

51. Gadoth N, Margalith D. Bechar M: Unilateral pupillary dilatation during focal seizures. *J Neurol* 1981;225:227-230.

52. Afifi AK, Corbett JJ, Thompson HS, et al.: Seizure-induced miosis and ptosis: association with temporal lobe magnetic resonance imaging abnormalities. *J Child Neurol* 1990, 5:142-146.

53. Rosenberg ML, Jabbari B: Miosis and internal ophthalmoplegia as a manifestation of partial seizures. *Neurology* 1991;41:737-739.

54. Freedman KA, Brown S. Topical apraclonidine in the diagnosis of suspected Horner's syndrome. J Neuro-ophthalmol 2005; 25:83-85.

55. Kawasaki A, Borruat FX. False negative apraclonidine test in two patients with Horner syndrome. Klin Monbl Augenheilkd. 2008 May;225(5):520-2.

56. Dewan MA, Harrison AR, Lee MS. False-negative apraclonidine testing in acute Horner syndrome. Can J Ophthalmol. 2009 Feb;44(1):109-10.