# Apraclonidine for the Diagnosis of Horner Syndrome

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When the clinical signs of this syndrome leave some doubt, pharmacologic testing helps confirm the diagnosis. These two cases illustrate the potential for apraclonidine to replace the more traditional, but problematic, topical cocaine in this capacity.

A 51-year-old, male veteran with hypertension and hypothyroidism presented for a neuro-ophthalmic consultation for anisocoria (unequal pupils). His visual acuity was 20/20 in both eyes. Pupil examination revealed slightly less than 1 mm of anisocoria in the light (right pupil, 4 mm; left pupil, slightly greater than 3 mm) and 1 mm of anisocoria in the dark (right pupil, 5.5 mm; left pupil, 4.5 mm) (Figure 1). Both pupils responded normally to light, and the rate of pupil dilation in the dark appeared equal between both eyes. There were no other abnormalities of the pupils. Left upper eyelid ptosis of less than 1 mm was noted.

One drop of apraclonidine 0.5% was instilled in each eye to evaluate for sympathetic hypersensitivity. The patient was examined one hour later. In the light, the right pupil measured 4.5 mm and the left pupil measured 5 mm; in the dark, the right pupil measured 6 mm and the left pupil measured just over 6.5 mm (Figure 2). Thus, the smaller left pupil became the larger pupil after apraclonidine instillation. In addition, the left eyelid ptosis improved.

Results of a chest radiograph, carotid artery ultrasound, and magnetic resonance imaging (MRI) of the brain were normal. Additional questioning of the patient revealed that he had a history of spinal cord injury while serving in the military. He denied paralysis but reported that he had experienced immediate lower extremity numbness after falling down a hill with a heavy pack. He had been placed in traction following the accident and had recovered completely. Based on this history and on the results of his examination, we diagnosed him with likely trauma-induced Horner syndrome localized to the sympathetic chain in the cervical region.

A 49-year-old, female veteran with multiple sclerosis and a history of

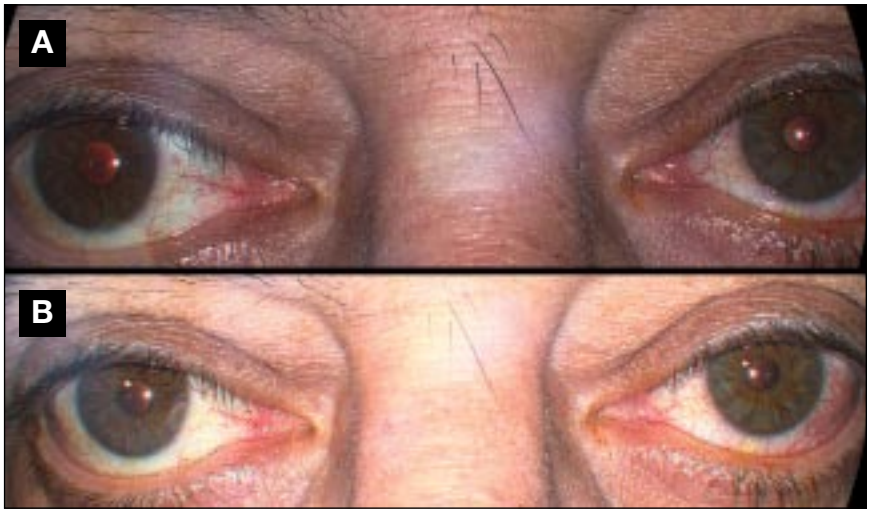


Figure 1. Pupils of the first patient prior to instillation of apraclonidine. In a dark room (A), the left pupil is smaller and the left lid is slightly lower than the right. In a light room (B), there is slightly less anisocoria (as expected with Horner syndrome). Note the conjunctival injection of the left eye due to dilation of capillaries that occurs with decreased sympathetic tone.

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optic neuritis presented for a neuro-ophthalmic consultation regarding optic neuritis, during which she was noted to have anisocoria. Her past medical history also included a bilateral first rib resection performed 10 years prior for a diagnosis of thoracic outlet syndrome. Visual acuity was poor in both eyes (20/400) due to past episodes of optic neuritis. Pupil examination revealed 1 mm of anisocoria in the light (right pupil, 3 mm; left pupil, 4 mm) and in the dark (right pupil, 5 mm; left pupil, 6 mm) (Figure 3). Pupillary constriction to near was slightly greater than to light due to decreased visual acuity. The rate of pupil dilation in the dark appeared equal between both eyes. Palpebral fissures were 7 mm and 9 mm in the right and left eye, respectively, without ptosis.

One hour after one drop of apraclonidine 0.5% was instilled in each eye, the right pupil measured 5 mm and the left pupil measured 4 mm in the light, while the right pupil measured 6 mm and the left pupil measured 5 mm in the dark. Palpebral fissures widened in both eyes by slightly less than 0.5 mm.

Chest radiograph revealed surgical clips along the left medial apical thorax. We diagnosed the patient with bilateral Horner syndrome, greater in the right eye than the left, which was likely due to her prior bilateral thoracic surgery.

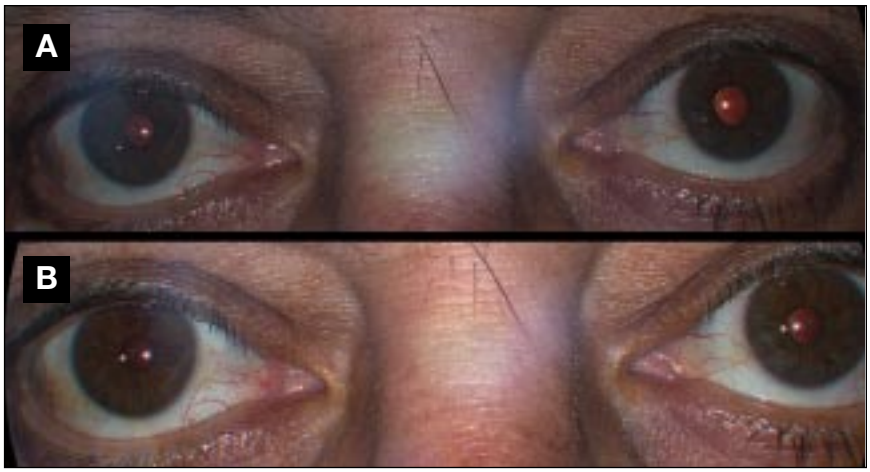


Figure 2. Pupils of the first patient one hour after instillation of apraclonidine. In both a dark room (A) and a light room (B), there is clear reversal of anisocoria (the right pupil is now smaller than the left), elevation of left upper lid, and decreased conjunctival injection.

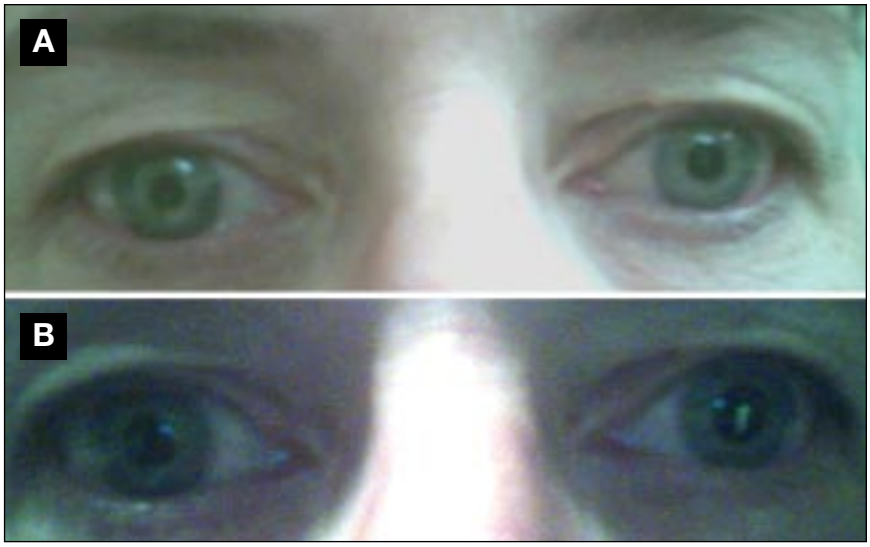


Figure 3. Pupils of the second patient, before (A) and after (B) pharmacologic testing with apraclonidine. Prior to instillation of apraclonidine, the right pupil is smaller than the left. One hour following apraclonidine instillation, both pupils dilate due to bilateral sympathetic dysfunction, but the right pupil is slightly larger than the left. Both lids are elevated.

## ABOUT THE CONDITION

Horner syndrome, or oculosympathoparesis, is caused by interruption of sympathetic input to the eye and ipsilateral face. This interruption may occur at any point along a three-neuron pathway between the hypothalamus and the orbit. The pathway originates in the posterolateral aspect of the hypothalamus, descends the brain stem, and synapses at the ciliospinal center of Budge-Waller located in the cervical spinal cord between C8 and T2. Most second-order neurons exit the spinal cord at T1, ascend with the sympathetic chain, and synapse at the superior cervical ganglion between in the internal jugular and the internal carotid artery. The sympathetic fibers travel with the internal carotid artery and follow a circuitous route intracranially before entering the orbit through the cavernous sinus.[1] Sympathetic fibers in this pathway innervate the iris dilator muscle, Mueller muscles of the upper and lower eyelid, and the sweat glands of the ipsilateral face.

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The classic clinical triad defining Horner syndrome is pupillary miosis (constricted pupil), upper lid ptosis with mild lower lid elevation, and anhidrosis (decreased or absent sweating) of facial skin. The decreased sympathetic tone to the pupillary dilator muscle results in anisocoria that usually is greater in the dark than in the light and slow pupillary dilation (or dilation lag) in the dark.


## ADVANCES IN PHARMACOLOGIC TESTING

In partial or bilateral sympathetic denervation, the greater degree of anisocoria in the dark and the dilation lag may be difficult to observe, as illustrated in the cases presented here. Uncertainty about a diagnosis of Horner syndrome also may exist if other clues to sympathetic dysfunction—such as ptosis—are absent. The differential diagnosis for anisocoria includes physiologic and pharmacologic causes, as well as damage to the iris and various types of parasympathetic dysfunction (such as cranial nerve III palsy, Adie syndrome, and tonic pupil) (Table).

If Horner syndrome is suspected, pharmacologic testing can help confirm the diagnosis. The agent traditionally used for such confirmatory testing has been topical cocaine (4% to 10%). Physiologically, norepinephrine is released from sympathetic terminals to activate α1 receptors in the iris dilator muscle and, as a result, pupil dilation occurs. Cocaine inhibits the reuptake of norepinephrine in the synaptic cleft of the postganglionic fibers and iris dilator muscle, thereby transiently increasing norepinephrine concentration in the synaptic junction. In Horner syndrome, cocaine instillation in the eye results in less dilation of the affected pupil because of the absent or decreased norepinephrine in the synaptic junction. Cocaine also may act directly as a weak dilator, however, and yield equivocal test results.

Recently, apraclonidine has been found to dilate an affected pupil and decrease eyelid ptosis in Horner syndrome.[2–5] Apraclonidine is an α-adrenergic agonist, with strong α2 and weak α1 activity, and it is approved for the treatment of elevated intraocular pressure following argon laser trabeculoplasty for glaucoma. Horner syndrome may result in denervation supersensitivity of α1 receptors due to chronic reduction of norepinephrine in the synaptic junction. Theoretically, when apraclonidine is applied to a pupil affected by Horner syndrome, the upregulated α1 receptors are activated directly and the pupil dilates. Additionally, apraclonidine might improve ptosis because of denervation supersensitivity of α2 receptors in Mueller muscles.[2]

### Advantages of apraclonidine over cocaine

Cocaine is a controlled substance that is expensive and difficult to obtain and store. It has a short half-life and typically is compounded separately for each patient, which is cumber-

**Table. Differential diagnosis of anisocoria**

- Horner syndrome (sympathetic dysfunction)
- Physiologic cause
- Cranial nerve III palsy (parasympathetic dysfunction)
- Pharmacologic cause
- Adie syndrome or tonic pupil (parasympathetic dysfunction at level of ciliary ganglion or short ciliary nerves)
- Iris damage

some and leads to variable potency among preparations. The drop is painful upon instillation, and urine metabolites may be present after administration of ophthalmic solutions.[6]

By contrast, apraclonidine is relatively inexpensive and commercially available. It is used commonly to treat glaucoma with minimal adverse effects.[7] The endpoint of testing with apraclonidine is clear and includes reversal of preexisting anisocoria (in both the dark and light) and decreased ptosis or increased palpebral fissure size.

Authors of one small study compared the efficacy of 4% cocaine to 0.5% apraclonidine in 10 pediatric patients and found them to be equivalent.[8] Another study found apraclonidine to be as sensitive and specific as cocaine.[9] Apraclonidine, like cocaine, cannot localize the lesion within the sympathetic chain, and further testing should be performed if localization is necessary.

Traumatic injury to the carotid artery and spinal cord are common causes of preganglionic Horner syndrome.[10] The first case presented here highlights the potential advantages of apraclonidine after trauma in the confirmation of Horner syndrome, which may be especially useful in prioritizing additional imaging studies. Both cases highlight the importance of pharmacologic testing in instances of partial or unequal, bilateral Horner syndrome, which are often difficult to diagnose without such testing. Although further study of the sensitivity and specificity of apraclonidine for the diagnosis of Horner syndrome is necessary, there is potential for apraclonidine to replace cocaine and ease the burden of pharmacologic testing of this important syndrome. ●

*Author disclosures*

*The authors report no actual or potential conflicts of interest with regard to this article.*

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