Abstract: The diagnosis of Horner syndrome (HS) using apraclonidine eye drops is an alternative to the use of topical cocaine drops. A number of reports have described the efficacy of apraclonidine testing, but there is some debate over its sensitivity in the acute setting. We describe a patient with HS secondary to carotid dissection who had a positive response to apraclonidine 3 hours after the onset of symptoms. The case is made for a larger study of apraclonidine use to determine its true sensitivity and specificity, identify confounding factors, and redefine the criteria for positive testing.

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Horner syndrome (HS) is classically described as the triad of miosis, upper lid ptosis with mild elevation of the lower lid and, depending on the site of the lesion, anhidrosis of the ipsilateral side of the face and/or body. HS occurs as a result of disruption to the ipsilateral sympathetic innervation to the eye and face (1). Interruption of the ipsilateral sympathetic innervation distal to the superior cervical ganglion produces oculosympathetic palsy without the anhidrosis due to divergence of the sympathetic supply to the eye and face at the ganglion (2).

Depending on the cause of HS, early recognition and intervention can be lifesaving. However, the combination of physiologic anisocoria and involutional ptosis, particularly in the elderly, is not uncommon, and confirmation of the diagnosis of HS is desirable. This is made by pharmacological eyedrop testing, traditionally with cocaine but increasingly with apraclonidine. Cocaine is an indirect sympathomimetic agent, which works by blocking the re-uptake of noradrenaline from the synaptic space (3). In the normal eye, this should produce an increase in pupil diameter, while in HS, the pupil will fail to dilate. However, testing with cocaine has limitations. First, the normal control pupil (contralateral eye) may not dilate due to the relatively weak dilating effect of cocaine (4). Second, there is the risk of a false-positive result if the affected pupil is incapable of dilating for another reason (2). Third, cocaine is a controlled substance, which is often difficult to obtain.

Apreclonidine is an adrenergic drug with a weak agonist action on α-1 receptors and a strong agonist action on α-2 receptors (5). In HS, there is an upregulation of α-1 receptors in response to the loss of sympathetic innervation, which results in a supersensitivity of the affected pupil such that it dilates in response to apraclonidine (6). In contrast, a normal pupil will either show no change in size or constrict because of α-2 activity (6). The current criterion for the diagnosis of HS is a reversal of the anisocoria after bilateral administration of topical apraclonidine (4).

There are a number of unsettled issues regarding the use of apraclonidine in establishing the diagnosis of HS. It has previously been reported that testing with apraclonidine has a similar sensitivity to cocaine, except in the acute setting before the disruption of the sympathetic supply has produced denervation supersensitivity (4). Another confounding factor in the pharmacological diagnosis of HS is the response of a pupil with incomplete disruption to its sympathetic supply. Any blockade of sympathetic firing will result in supersensitivity and thus a positive response to apraclonidine testing (7). However, it is not known for certain whether and to what degree the response to apraclonidine is attenuated with partial lesions. Similarly, an incomplete lesion may produce partial dilation in testing with cocaine as some but not all of the sympathetic nerve fibers are lost, which may lead to a response that is difficult to interpret (8). Finally, it should be noted that...
apraclonidine testing is relatively contraindicated in infants younger than 6 months as it may result in lethargy, bradycardia, and respiratory depression due to immaturity of the blood-brain barrier (9).

CASE REPORT
Following a road traffic accident 4 days previously, a healthy 43-year-old man presented to the ophthalmology department with a 3-hour history of blurred vision in his right eye associated with neck pain. On examination, he was found to have miosis of the right pupil with no evidence of anhidrosis or ptosis and no other neurological signs. A clinical diagnosis of HS secondary to a suspected traumatic internal carotid artery dissection was made.

1% apraclonidine drops were administered and elicited a positive response: the affected pupil dilated, confirming the diagnosis of HS (Fig. 1). MRI and MRA demonstrated a right internal artery dissection within the carotid canal distal to the carotid bifurcation (Fig. 2).

The patient was entered into the Cervical Artery Dissection in Stroke Study (CADISS) of anticoagulation vs antiplatelet therapy (10) and was randomized to dual antiplatelet therapy. When seen 4 months later, he was noted to still have mild pupil asymmetry. Follow-up imaging revealed that his internal carotid artery had returned to a normal caliber.

DISCUSSION
A number of case series have reported the utility of apraclonidine in the diagnosis of HS (4,11–15). With the exception of one of the cases reported by Brown et al (13), all these series reported a 100% sensitivity of apraclonidine in diagnosis of HS caused by a variety of pathological processes affecting the sympathetic pathway at different sites. A positive test was defined as reversal of anisocoria. The case of Brown et al (13) showed a partial response, that is, relative dilation of the affected pupil but not reversal of anisocoria.

In all the above series, the timing of testing after the onset of symptoms was greater than 1 month. The utility of apraclonidine in the acute setting is debated as, unlike cocaine, a positive test depends on the development of sympathetic supersensitivity at the end organ (4). What is not currently known is the exact time interval required for the development of sufficient supersensitivity to produce a positive apraclonidine test and whether this is different in various causes of HS. Bohnsack and Parker (16) reported a positive apraclonidine test 2 weeks after a carotid artery dissection. Garibaldi et al (17) documented 2 cases of positive apraclonidine tests 1 week and 10 days after the onset of sinusitis and internal carotid artery dissection, respectively. Lebas et al (18) described a positive apraclonidine test 36 hours after a dorsolateral medullary brainstem infarction. However, others have reported false-negative apraclonidine testing in cases of HS confirmed with a positive cocaine test. Dewan et al (19) observed a false-negative apraclonidine test in a patient with HS 4, 9, and 16 days after internal carotid artery dissection. Falzon et al (20) reported denervation supersensitivity in response to 1% phenylephrine in 2 patients with HS resulting from internal carotid artery dissection at 10 days but not 3 days after injury (20).

We observed a response to apraclonidine relatively soon after the onset of a HS due to traumatic internal carotid artery dissection. The exact time of onset of the disruption to the sympathetic innervation is not clear. The onset of ocular symptoms 3 hours prior to presentation is suggestive, but the lesion may have occurred at any time prior to the road traffic accident 4 days previously. In our patient, there was a decrease in anisocoria with apraclonidine indicating sympathetic supersensitivity, but reversal of the anisocoria did not occur.

This has been the case with a number of the reported false-negative responses to apraclonidine including the Brown et al report mentioned previously (13). Kawasaki et al (21) described a case of HS of unknown cause with a false-negative apraclonidine test at 6 months and a case of HS secondary to carotid dissection with a false-negative apraclonidine test at 3 years, but in both cases, the affected pupil did show a partial response. It is apparent that the development of sympathetic supersensitivity sufficient to elicit a response to apraclonidine testing is present relatively soon after the development of HS. Yet, current diagnostic criterion of reversal of anisocoria may preclude recognition of that response. It has been suggested that these partial responses, including our case, may represent incomplete lesions of the sympathetic supply sufficient to produce sympathetic supersensitivity and pupillary dilation but not

FIG. 1. Pupil size before (A) and after (B) 1% apraclonidine eyedrop testing. Note the relative dilation of the right pupil in response to apraclonidine resulting in decreased anisocoria.
reversal of anisocoria (7). The absence of observable ptosis in HS, as in our case, has been described (22) and is also consistent with incomplete interruption of sympathetic innervations.

While the usefulness of apraclonidine in acute and chronic HS has been clearly demonstrated, a larger study would provide more data on the utility of this test. Such a study might lead to modifying criteria for a positive test and allow pharmacological diagnosis of HS due to both complete and incomplete disruption of the oculosympathetic pathway.

REFERENCES

15. Chen PL, Hsiao CH, Chen JT, Lu DW, Chen WY. Efficacy of apraclonidine 0.5% in the diagnosis of Horner syndrome in pediatric patients under low or high illumination. Am J Ophthalmol. 2006;142:469–472.

FIG. 2. Right internal carotid artery dissection. A, T1 axial MRI showing "crescent sign" (arrow). B, MRA reveals area of dissection (arrow) within the carotid canal.