Child Neurology: Horner Syndrome in an Otherwise Well-Appearing Infant

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Abstract

We report an exemplary case of acquired Horner syndrome secondary to neuroblastoma in infancy. The patient presented with ptosis, miosis, and heterochromia. In reviewing the patient's laboratory and imaging workup, we highlight key etiologic differences between the pediatric and adult populations. Other important teaching points included in the discussion are a review of sympathetic neuroanatomy and oculosympathetic paresis, the appropriate and evidence-based diagnostic workup in infants and children, and a review of pharmacologic testing using cocaine and apraclonidine drops.

Case Report

A 5-month-old female with no medical history presented to our hospital for expedited workup of suspected acquired Horner syndrome. She was delivered vaginally at term with no perinatal complications, and there were no developmental concerns by her pediatrician. She developed right upper eyelid ptosis 4 weeks prior to admission, followed 2 weeks later by anisocoria, her right pupil appearing smaller than the left. There was no history of trauma or recent illness.

Upon admission, the infant was afebrile with normal vital signs for age. Her smile was symmetric and she was playful, tracking the examiner in all directions with no misalignment. She was able to sit upright independently and support her weight when her postural reflex was tested. Most pertinently, she displayed right upper eyelid ptosis with reverse lower eyelid ptosis, and anisocoria (right pupil 2 mm, left pupil 4 mm in bright light), which was more prominent in dim light (Figure, A). On close inspection, heterochromia was noted (her right iris appeared lighter than her left). The remainder of her physical examination was unremarkable. A complete blood count and metabolic panel were within normal limits.

Chest X-ray (CXR) demonstrated a well-defined mass abutting the right superior sulcus and right upper mediastinum (Figure, B). Magnetic resonance imaging (MRI) and angiography (MRA) of the neck revealed an enhancing, diffusion-restricted right apical mass encircling portions of the right vertebral artery, in close contact with the right common carotid artery (Figure, C). MRI of
the brain was normal. She underwent thoracoscopic biopsy of the mass 2 days after imaging (Figure, D). At this time, additional labs resulted, significant for a normal urine vanillylmandelic acid-to-creatinine ratio and a slight elevation of homovanillic acid of 35 mg/g creatinine (ref <35). Surgical pathology ultimately confirmed a poorly differentiated neuroblastoma. Iodine 123 (123I) metiodobenzylguanidine (MIBG) uptake occurred at the primary mass, with no other evidence of disease. The tumor was unresectable due to vessel encasement, and it was considered symptomatic in its interruption of the oculosympathetic chain.

The patient began chemotherapy 10 days after presentation (per the Children’s Oncology Group study ANBL0531). Repeat imaging of the tumor after 2 cycles of chemotherapy demonstrated >50% decrease in tumor volume, indicating no need for additional chemotherapy. After chemotherapy completion at 9 months of age, there were no findings of MIBG-avid malignancy.

At the same age, the patient was assessed in neuro-ophthalmology clinic, where she was determined to have normal visual acuity without cranial neuropathy or ocular misalignment. Her right-sided Horner syndrome was unchanged from presentation. Amblyopia risk was considered low given that her pupil was not obstructed by her ptosis.

**Discussion**

Horner syndrome is a neurologic constellation of miosis, ptosis, and hemifacial anhidrosis. It is widely held that this phenomenon was discovered in 1869 by Swiss ophthalmologist Johann Horner, but French ophthalmologist Claude Bernard was first to identify the triad in animal studies in 1852. As a result, the condition is sometimes referred to as Bernard-Horner syndrome in French literature. [1] Regardless of eponymous legacy, the syndrome represents an oculosympathetic paresis, which is perhaps a more apt nomenclature.

Before discussing etiologies, we will highlight a few points on physical exam and neuroanatomy. First, as our patient demonstrated, the degree of anisocoria is more pronounced in scotopic (dim) rather than photopic (light) conditions. Also, the Horner pupil tends to redilate more slowly than the normal pupil. Ptosis is usually minor (<2 mm) due to paralysis from sympathetic denervation of the superior and inferior tarsal muscles (superior tarsal muscle is also known as Müller’s muscle), affecting both the upper and lower eyelid, while the levator palpebrae superioris is unaffected. Weakness of the latter produces a more profound ptosis that can be observed in third nerve palsies. The rudimentary inferior tarsal muscle has no compensatory voluntary muscle as with the upper eyelid. Inferior tarsal paresis leads to a lower lid rise referred to as reverse lower eyelid ptosis, inverse ptosis, or upside-down ptosis. Regarding anhidrosis, the sympathetic fibers responsible for facial sweating and vasodilation branch at the superior cervical ganglion along the external carotid artery, so this sign is only associated with first or second order lesions. Anhidrosis is not always apparent and indeed was not appreciated in our patient. In infants and children, impaired facial flushing (Harlequin sign) is frequently more apparent than anhidrosis. Lastly, a congenital Horner syndrome may be suspected when anisocoria is seen with heterochromia (unequal iris colors where the affected iris is lighter) because the pigmented melanocytes in the superficial stroma of the iris are under sympathetic control in the first months of life. [2,3] Our patient’s heterochromia suggests that her tumor disrupted the oculosympathetic chain in this developmental period.

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The differential diagnosis for Horner syndrome differs between children and adults, but in both populations, the syndrome can result from a lesion anywhere along a three-neuron sympathetic pathway originating in the hypothalamus. To review, the first-order neuron descends from the hypothalamus to synapses at C8-T2, the ciliospinal center of Budge. The second-order neuron exits in the anterior spinal roots to ascend in the sympathetic trunk, traveling through the brachial plexus and over the apex of the lung. Its synaptic destination is the superior cervical ganglion, located near the angle of mandible and the carotid artery bifurcation. The third-order neuron ascends within the internal carotid artery adventitia through the cavernous sinus, where it is in close relation to the abducens nerve. It then joins the ophthalmic division of the trigeminal nerve (V1) to enter the orbit, where it finally innervates the iris dilator as well as the superior and inferior tarsal muscles. The tarsal muscles are small smooth muscles in the eyelid, responsible for a minor portion of upper lid elevation and lower lid retraction. [2,3]

The incidence of childhood Horner syndrome in a 6.5-year period in Northern Ireland was at least 2.54 per 100,000. [4] This estimate contrasts with a population-based study in Minnesota, in which the calculated incidence of pediatric cases was 1.42 per 100,000 over a 40-year period. [5]

Adult etiologies include stroke (e.g., Wallenberg syndrome), dissection, aneurysm, tumor, demyelination, and cluster headache. [3] In contrast, a retrospective study of 73 pediatric patients with oculosympathetic paresis found that 42.5% were congenital (including birth trauma), 42.5% were related to surgery, and 15% were acquired from etiologies such as neuroblastoma, rhabdomyosarcoma, trauma, brainstem vascular malformation, and disseminated demyelinating sclerosis, with some causes undetermined. [6] The rate of neuroblastoma in the aforementioned study from Northern Ireland was 20%, whereas a recent systematic review found a rate of 7.9%. [7]

Given that Horner syndrome can be a heralding sign of malignant and life-threatening conditions, neuroimaging is always warranted in Horner syndrome with unknown etiology in the first year of life and any acquired Horner syndrome thereafter. Accordingly, in the absence of a clear history of birth trauma or perinatal neck surgery, as in our case presentation, an acquired Horner syndrome prompts evaluation for tumor, particularly neuroblastoma. Urgent imaging studies should include MRI of the brain, neck, and chest, as well as MRA of the neck and chest. Measurement of urinary catecholamines should be acquired. Obtaining these catecholamine levels is a non-invasive and low-cost investigation. However, as partly seen in our patient, urinary catecholamine levels may be normal in some neuroblastoma cases and, therefore, should not entirely deter the decision to obtain imaging. [7]

It is important to acknowledge that there are no consensus guidelines for investigating an isolated pediatric Horner syndrome, but clinical judgment and exam should tailor the diagnostic evaluation. [7,8] For example, associated abducens palsy may aid in localizing pathology to the cavernous sinus. Likewise, pain and/or recent trauma might suggest carotid dissection, which necessitates vessel imaging. At our hospital, we include vessel imaging because even minor head trauma, which might go unreported or unnoticed by caregivers, can lead to dissection and possibly ischemic stroke. While precise workup and imaging recommendations remain controversial, most authorities agree that MRI is preferred to computed tomography (CT) and
that the anatomical coverage should at least include the brain, neck and upper chest. Others advocate for extension to visualize the abdomen and/or pelvis as well. [8]

Pharmacologic testing for Horner syndrome diagnosis is warranted in uncertain cases, for example, in patients with unilateral miosis without associated findings like ptosis or heterochromia. Such testing can differentiate a true Horner syndrome from pseudo-Horner syndrome due to benign physiologic anisocoria with mild eyelid asymmetry or aponeurotic ptosis. [9] When available, cocaine or apraclonidine drops are useful (Table). In our patient, a clinical diagnosis of Horner syndrome was made given the presence of the expected ptosis, anisocoria, and heterochromia, substantiating the diagnosis of a true Horner syndrome, and pharmacologic testing was deferred. [3,4,10]

In summary, our patient demonstrates an exemplary case of acquired pediatric Horner syndrome secondary to neuroblastoma. Key teaching points include a review of sympathetic neuroanatomy and oculosympathetic paresis, the different etiologies in children versus adults, and the appropriate diagnostic workup in infants. At 16 months of age, while our patient’s Horner syndrome is unchanged, her neuroblastoma remains in remission.

**Figure. Patient Presentation and Diagnostic Workup.** (A) Right-sided ptosis, miosis, and heterochromia upon hospital admission. (B) CXR. Well-defined 2-cm mass abutting the right superior sulcus and right upper mediastinum that could be either pleural-based, pulmonary, or mediastinal in origin. (C) MRI/MRA neck. Avidly enhancing diffusion restricted right apical mass (approximately 3.2 x 2.1 x 2.9 cm), encircling portions of the right vertebral artery and in close contact with the right common carotid artery with associated regional right lower neck lymphadenopathy. Findings were compatible with a malignant process, most likely neuroblastoma. (D) Thorascopic view of apical mass prior to biopsy. Per operative note documentation, an exophytic mass covered with pleura was identified at the right apex, intimately involved with the sympathetic chain. The lesion was scored to open the pleura. The surgeon then used scissors to obtain a biopsy that was ultimately consistent with neuroblastoma.
Cocaine Apraclonidine

Mechanism of action
Indirect sympathomimetic via NE reuptake inhibition at the NMJ.
Denervation supersensitivity to weak α-1 agonism at postsynaptic membrane; strong α-2 agonism downregulates NE release in the NMJ.

Procedure
Instill one or two drops of 4 or 10% cocaine in each eye and compress medial canthus to avoid systemic delivery via nasal mucosa. Wait 40-60 minutes before exam.
Instill one or two drops of 0.5% apraclonidine in each eye. Apply pressure to lacrimal sac to decrease drainage into nose and throat and minimize possible systemic absorption. Wait 40-60 minutes before exam.

Effect on normal eye
Potentiated NE in NMJ causes pupillary dilation.
α-2 stimulation constricts pupil slightly due to downregulated NE in NMJ.

Effect on Horner eye
No effect due to impaired sympathetic innervation.
α-1 stimulation causes pupil dilation via denervation sensitivity.

Interpretation of a positive test
Increased anisocoria of ≥1 mm after cocaine, whereby normal pupil dilates and Horner pupil remains unchanged.
Reversal of anisocoria, whereby the Horner pupil is larger after drops.

Age recommendation
Preferred for infants 6-24 months. Cocaine has been used <6 months with no side effects, but there is not a large data set on safety.
Preferred for infants >24 months. If used in infants <2 years of age, observe for 2 hours after administration for possible lethargy, bradycardia, or apnea.

Table. Comparison of cocaine and apraclonidine drops for confirming Horner syndrome. [3,4,10]
Hydroxyamphetamine has been historically used to differentiate first- or second-order lesions from third-order postganglionic lesions. The drug releases stored NE from postganglionic adrenergic synapses, so a normal pupil and a first- or second-order Horner pupil dilate an hour after administration. Pediatric providers should be cautioned against hydroxyamphetamine because the normal development of the third-order oculosympathetic neuron and its connections depends on the integrity of the first and second neuron in the chain. Thus, in infants, it is possible that hydroxyamphetamine will fail to dilate the involved pupil due to transsynaptic degeneration of postganglionic fibers, which might falsely implicate a third-order lesion. Additionally, topical hydroxyamphetamine is not readily useful since the drug is no longer a commercial product and requires a specialty pharmacy. [3] NE: norepinephrine; NMJ: neuromuscular junction.
References

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