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Horner's Syndrome Secondary to Neuroblastoma

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ABSTRACT

Horner's syndrome is classically characterized by a triad of miosis, partial ptosis and anhidrosis. The etiology is due to an interruption in the sympathetic innervation to the eye. A prompt diagnosis is crucial, given that Horner's syndrome could be a manifestation of a life-threatening condition. A thorough case history and clinical evaluation must be employed to arrive at the diagnosis. An important means for confirming Horner's syndrome is pharmacological testing, which is also used to localize the level where the sympathetic chain is compromised. Following the diagnosis and localization of the lesion, an algorithm should be followed to determine the testing indicated, in order to ascertain the underlying cause of the condition. There is a known association between mediastinal neuroblastoma and preganglionic Horner's syndrome.

We present a case of a seven-year-old boy with a history of excision of a mediastinal neuroblastoma at age two, who soon after presented with signs and symptoms associated with a residual Horner's syndrome.

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CASE REPORT

A seven-year-old Caucasian male was referred to the Neuro-Ophthalmology Service for evaluation of a suspected left Horner's syndrome. Six days prior to the consult exam, the patient was seen at an optometrist's office with complaints of bilateral, constant, blurred vision and headaches. The child's parents felt the headaches were caused by school related activities and had been occurring on an intermittent basis for approximately one month.

The patient had an unremarkable ocular history except for prior discovery of anisocoria. The patient's medical history included excision of a mediastinal neuroblastoma. The patient initially presented to his pediatrician at age two, with a persistent cough, and was diagnosed with presumptive pneumonia. Given no response to antibiotics, a chest x-ray (CXR) was performed showing a mediastinal shadow. This CXR prompted referral to a local children's hospital, where a computed tomography (CT) of the thorax confirmed a mediastinal mass (Fig. 1A,B). The lesion was excised and histopathology revealed a neuroblastoma. The pediatrician noted a left Horner's syndrome while the patient was hospitalized, which was attributed to the neuroblastoma. The child was compliant with scheduled follow-ups until age five, during which time there were no new symptoms and no recurrences.

The family ocular history revealed macular degeneration in a paternal great-grandmother and the family medical history was unremarkable. The patient was not using any medications, but was allergic to penicillin. The mother reported that he was one of the triplets born at 34 weeks and 4 days gestation.

A review of the patient's prior ophthalmic records disclosed best corrected visual acuities of 6/7.5 (20/25) at distance and 6/9 (20/30) at near in each eye, with a high hyperopic refractive error. Cover tests at distance and near were orthophoric horizontally and vertically. Confrontation fields and ocular motility were normal. Pupil size in the light was 5 mm OD and 3 mm OS; in the dark, the pupils measured 7 mm OD and 4 mm OS. Direct and consensual responses were reactive and no afferent pupillary defect (APD) was detected in either eye. Slit lamp exam was unremarkable and was negative for iris heterochromia. Intraocular pressures (IOPs) were 13 mmHg OD and 11

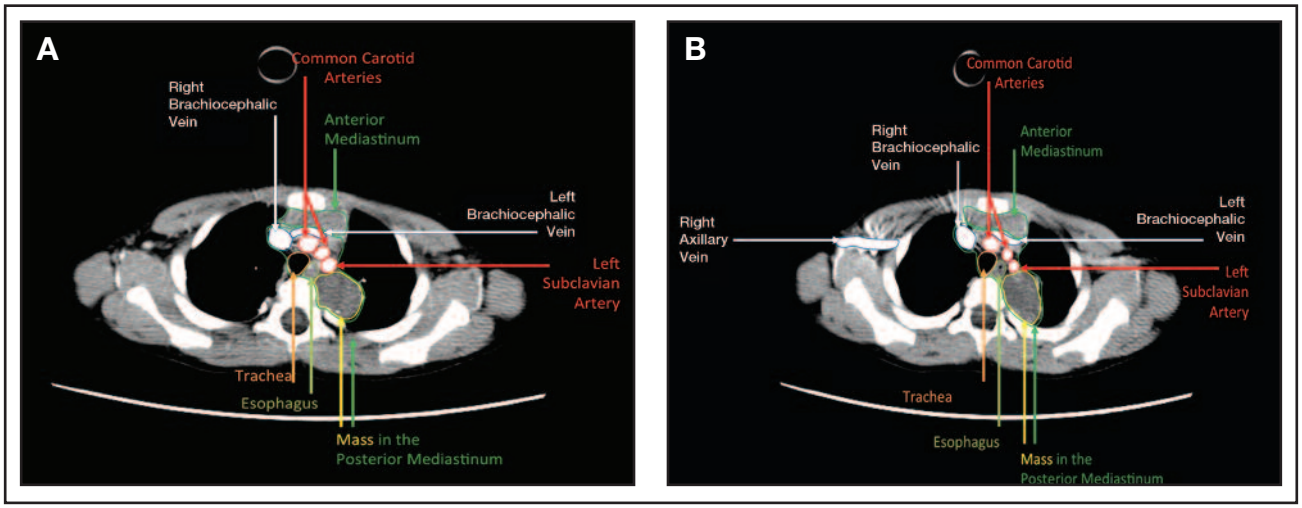

Fig. 1 (A, B) Computed tomography (CT) of the thorax shows the presence of a mediastinal mass. Anatomic relations are indicated in the figures.

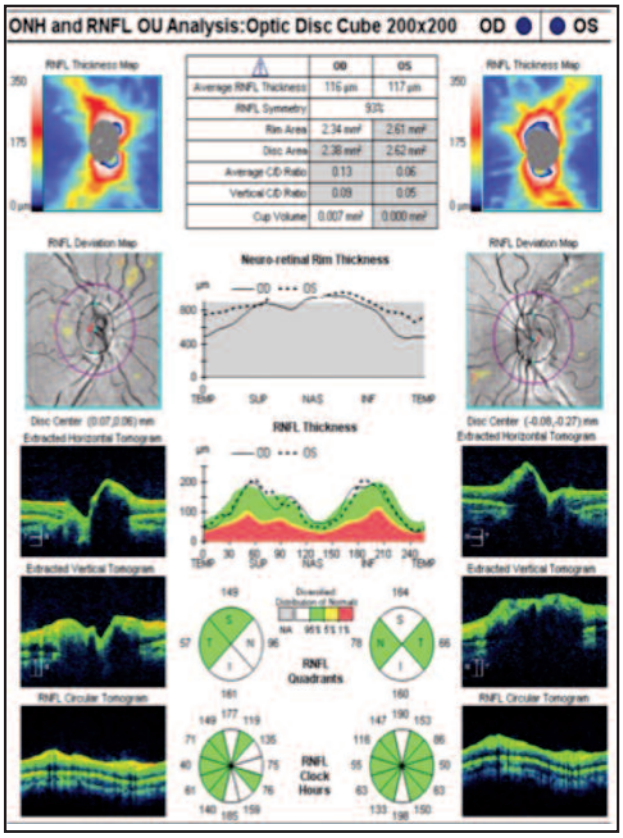

Fig. 2 Optical coherence tomography (OCT) showed slight increased thickness of the nerve fiber layer. There were no nerve fiber bundle defects.

mmHg OS measured with non-contact tonometry. A dilated fundus examination showed a normal vitreous, macula, and no retinopathy. A C/D ratio of 0.20 was estimated in both eyes; however, the optic discs were described as having indistinct borders and appeared to be slightly elevated. The referring doctor's assessment consisted of anisocoria, left Horner's syndrome, and indistinct discs with questionable edema. The plan was to refer to a neuro-ophthalmologist for evaluation of Horner's syndrome and for further investigation of the patients' complaints of headaches.

At the neuro-ophthalmological consult, visual acuities were unchanged, but cover tests showed a comitant esophoria at distant and near. There were no extra ocular movement (EOM) restrictions. The pupil exam confirmed anisocoria, greater in the dark, with no RAPD; a dilation lag was noted for the left pupil. Other pertinent findings included normal IOPs, no cranial nerve abnormalities, and no iris heterochromia. Goldmann visual fields were unremarkable with no hemianopia. Optical coherence tomography (OCT) showed slight increased thickness of the nerve fiber layer (Fig. 2). There were no nerve fiber bundle defects or macular edema in either eye. Fundoscopy revealed no retinopathy or maculopathy and a spontaneous venous pulsation was observed in each eye. Fundus photos documented crowded discs, likely related to hyperopia (Fig. 3).

In this particular case, it was concluded that pharmacological testing was not necessary, as Horner's syndrome had been described since age two and was likely related to the mediastinal neuroblastoma. The patient was sent to a pediatric neurologist for a headache evaluation, given the patient's history of neuroblastoma. A magnetic resonance imaging (MRI) of the brain was unremarkable, as was a chest CT. The patient was given a new prescription for glasses, as well as topiramate for the headaches, which according to the patient's parents, improved both the incidence and severity of his symptoms.

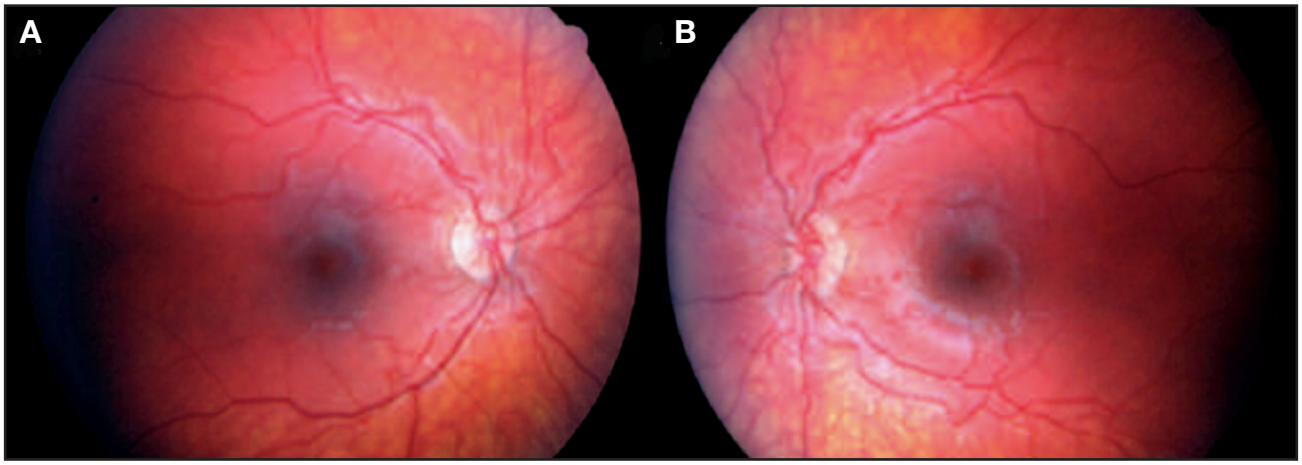

Fig. 3 Fundus photos documented crowded discs likely related to hyperopia in (A) right eye and (B) left eye. Optic nerve head edema was not noted in either eye.

Discussion

Neuroblastoma is a tumor that arises from neuroblasts in the sympathetic nervous system.[1] It is the most common extracranial solid tumor of childhood.[2] The most frequent sites include the adrenal medulla (60%), retroperitoneal cavity (20%) and mediastinum (10%).[1] Peak incidence occurs in children younger than two, with prognosis typically worsening with increasing age.[1,2] The stage of the tumor at diagnosis is equally important to the prognosis, which can have variable courses.[1] Neuroblastomas may regress spontaneously (Stage 4s), may mature to benign ganglioneuromas, or may result in a fatal outcome.[1] Therefore, it is critical to identify symptoms and signs that may lead to diagnosis and appropriate treatment. Non-specific symptoms include weight loss, lethargy, poor feeding and fever, while more specific and local ophthalmic signs may involve proptosis, ecchymosis, and Horner's syndrome.[3] Eye care providers may be the first professional that a patient consults and could play a pivotal role in the diagnosis.

Horner's syndrome results from an interruption in the oculosympathetic pathway, composed of three neurons.[4] The first neuron, termed central, starts at the hypothalamus and descends to the first synapse at the ciliospinal center of Budge (C8-T2).[5] The second neuron, or preganglionic neuron, exits out of the T1 root, courses over the apex of the lung and synapses at the superior cervical ganglion.[5] Finally, the third neuron, postganglionic, leaves the superior cervical ganglion and ascends back via the internal carotid artery to the cavernous sinus.[5] From the cavernous sinus, sympathetic branches travel beside the abducens nerve to the ophthalmic division of the trigeminal nerve prior to stimulating the iris dilator and Muller's muscles[5] (Fig. 4).

Any portion of the sympathetic pathway can be affected and give rise to Horner's syndrome. While congenital Horner's is likely to result from birth trauma, most causes are due to acquired conditions.[6] A lesion within the first neuron will usually result from strokes, demyelinating diseases, and neoplasms.[6,7] Second order neuron lesions are related to a Pancoast tumor at the apex of the lung, as well neuroblastoma or thyroid tumors.[6,7] Lastly, lesions affecting the third neuron are generally associated with dissection of the internal carotid artery and cluster headaches.[6,7]

Thus, Horner's syndrome is a sign of a separate condition and as listed previously, the underlying disorder may be relatively benign or be potentially life threatening. The disorder can be difficult to detect because patients are typically asymptomatic of vision loss. Therefore, it is important to recognize the signs and symptoms associated with the condition. A triad of ipsilateral miosis, partial ptosis, and anhidrosis characterizes Horner's syndrome. Miosis and ptosis are the most common signs, while anhidrosis is seen occasionally.[6] Other signs may include dilation lag, iris heterochromia, enophthalmos, and reverse ptosis.[3,6]

The anisocoria in Horner's syndrome must be differentiated from a physiological anisocoria. Horner's patients will show the greatest amount of anisocoria in the dark.[5] A dilation lag test is the simplest way to distinguish between the two. A normal pupil will fully dilate soon after a light stimulus is extinguished. A Horner's affected pupil, however, will take nearly five seconds to begin dilating.[5]

To validate whether a patient has Horner's syndrome, topical pharmacological agents may be used, which may include 2% to 10% cocaine or 0.5% to 1% apraclonidine.[8]

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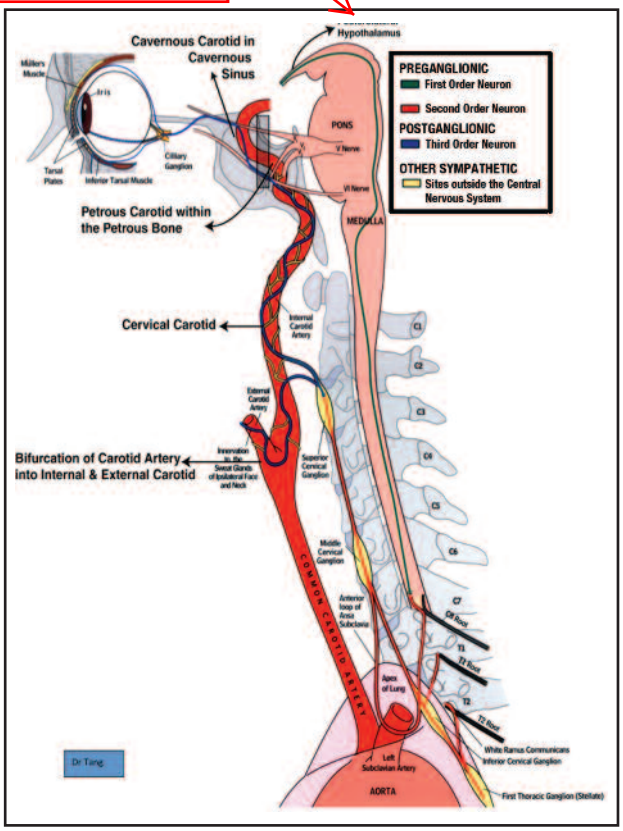

Fig. 4 Diagram of the sympathetic pathway showing the location of first, second and third order neuron. *[Courtesy of: Dr. Tang and Dr. Hayman].*

Cocaine inhibits the re-uptake of norepinephrine and as a result, norepinephrine accumulates in the synaptic cleft and stimulates the dilator muscle in normal pupils.[8] A Horner's syndrome pupil however, will fail to dilate because of lack of norepinephrine in the cleft. Cocaine is highly effective in the diagnostic process, but patient scheduling and availability are major deterrents in its use. Currently, cocaine is primarily used in infants of one year or younger, where apraclonidine is not advised due to the risk of causing dysautonomia.[9] In most patients however, apraclonidine (Iopidine), a weak alpha-1 agonist and strong alpha-2 agonist, can be used and has an opposite effect to cocaine. In Horner's syndrome, there is an up-regulation of alpha-1 receptors in response to sympathetic denervation, leading to super sensitivity for apraclonidine.[8,9] A reversal of miosis and lid elevation of the Horner's affected side with little to no effect on the normal pupil is observed with its instillation.[8,9] A slight drawback to apraclonidine is that up-regulation of alpha-1 receptors takes between 5 to 8 days to develop, which could lead to false negative findings in Horner's before one week of onset.[9]

Once Horner's syndrome has been confirmed, it is critical to localize the lesion causing the condition. One percent hydroxyamphetamine (Paredrine) is used to detect postganglionic Horner's.[8] Hydroxyamphetamine stimulates the release of norepinephrine from presynaptic postganglionic nerve terminals.[8] When instilled, dilation of a Horner's pupil will point to a central or preganglionic lesion because the postganglionic neuron is still intact to release norepinephrine.[8] A postganglionic lesion will result in little to no norepinephrine release and incomplete to absent dilation.[8]

Imaging is crucial, in conjunction with appropriate medical and/or surgical consultation, depending on the localization and suspected etiology. MRI of the brain and spine may be required for central and preganglionic lesions.[10] Contrasted CT or MR scans are sufficient for preganglionic lesions in the lung, mediastinum or neck.[11,12] Finally, MRI/MRA or CTA of the neck is needed if a postganglionic lesion is diagnosed and carotid dissection is suspected, as dissection is a major cause of stroke in young people.[11] ❑

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