

Iatrogenic Horner Syndrome: Etiology, Diagnosis and Outcomes

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ABSTRACT: The identification and prompt diagnosis of Horner syndrome (HS) is essential for preventing permanent damage. HS may arise when a lesion presents anywhere along the three-neuron oculosympathetic pathway that begins at the posterior-lateral nuclei of the hypothalamus all the way through to the orbit. We present four cases and review the literature to familiarize the reader with the identification, diagnosis and treatment of Horner syndrome. The four patients, three adults and one child, were followed for at least 6 months following the initial diagnosis (range 6–18 months). There was partial resolution in three of the four cases, while the fourth resolved completely. There are numerous causes of HS, some of them iatrogenic. While iatrogenic cases of HR are rare in both adults and children, HS is seen more often following surgical procedures. Prompt recognition of the syndrome and correction of the offending agent may prevent permanent damage to the neuronal pathway. It is therefore recommended that practitioners be aware of the risks for development of iatrogenic HS and the signs for early detection.

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KEY WORDS: Horner syndrome (HS), oculosympathetic paresis, iatrogenic cause, obstetric anesthesia, aproclonidine

Horner syndrome (HS) or oculosympathetic paresis consists of the classic triad of unilateral miosis, eyelid ptosis, and facial anhidrosis. Horner syndrome was first described in animals in 1852 by the French physiologist Claude Bernard. In 1869, a Swiss ophthalmologist, Johann Friedrich Horner, was the first to comprehensively describe this syndrome in humans [1]. The oculosympathetic palsy called HS appears when the sympathetic innervation of the eye is interrupted by an injury to the neuronal pathway connecting the hypothalamus through the spinal cord to the eye [Figure 1]. The pathway consists of three neurons. The first-order neuron originates in the posterior-

lateral nuclei of the hypothalamus and ends in the spinal cord at the level of T1 (ciliospinal center of Budge-Waller between C8 and T2). The second-order neuron extends from the spinal cord via the ventral roots of C8-T2, through the stellate ganglion and ascends in the sympathetic chain to the superior cervical sympathetic ganglion. The stellate ganglion lies posterior to the origin of the vertebral artery, and the superior cervical ganglion is located at the level of C2 in the posterior carotid sheath. The third-order neuron exits the superior cervical ganglion and ascends along the common and internal carotid arteries. It courses through the cavernous sinus, accompanying the abducens nerve then branching off the trigeminus nerve, and enters the superior orbital fissure innervating the levator palpebrae superioris muscle and the dilator pupillae muscle [2].

We present four cases of iatrogenic HS that were treated at Soroka Medical Center, Beer Sheva, Israel. The aim of this study is to familiarize the reader with the etiologic factors, diagnosis and outcomes of iatrogenic HS.

PATIENT DESCRIPTIONS

PATIENT 1

A healthy 24 year old man presented to the emergency room (ER) with a one day history of cyanosis, dyspnea and left-side chest pain. Three days prior to presentation in the ER he began treatment with penicillin VK 500 mg twice a day for pharyngitis and cough. The patient denied any additional symptoms as well as a history of trauma or prior cervical thoracic surgery. Clinical examination revealed decreased breath sounds in the left lung. The rest of the physical examination was not contributory. Chest radiography confirmed the presence of a left pneumothorax. A thoracostomy was performed with a 28 French chest tube using the standard approach and the patient was transferred to the cardiothoracic surgery department. Post-thoracostomy chest radiography showed the tip of the chest drain pointing upward and overlapping the posterior part of the space between the left third and fourth ribs [Figure 2A]. On day 5, the chest drain was removed with complete resolution of the pneumothorax. On post-procedure day 3, the patient noticed a slight left upper lid

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Figure 1. Illustration of the sympathetic innervation of the eye, presented here as the three-order neuron system

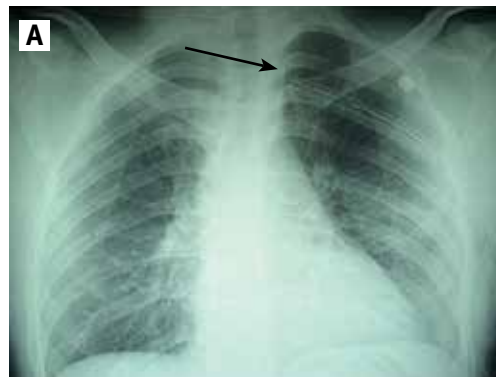
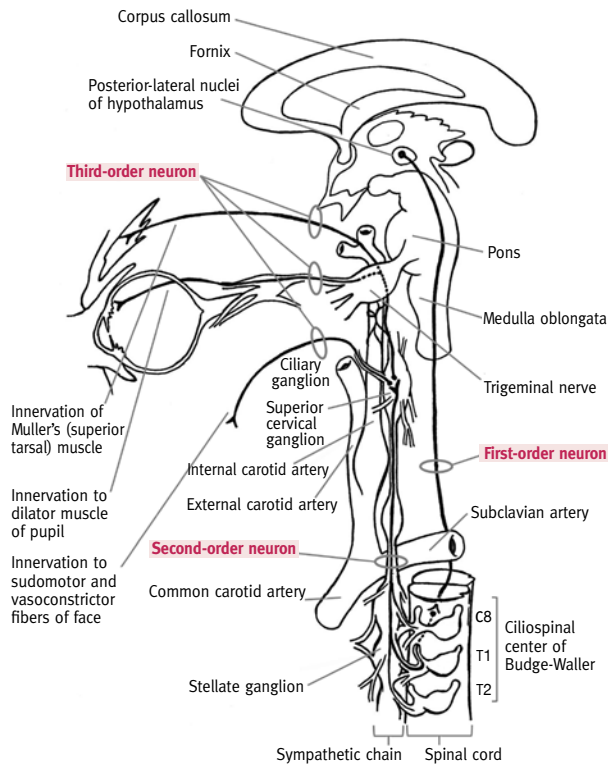


Figure 2.
[A] Post-thoracostomy chest radiography shows the tip (arrow) of chest drain pointing upward and overlapping the posterior part of the space between the left third and fourth ribs



[B] Slight left eye ptosis and miosis after 18 months follow-up

ptosis. The ophthalmic examination revealed left upper eyelid ptosis of 2 mm and anisocoria with a left smaller pupil. Freshly prepared 4% cocaine instillation confirmed the diagnosis. The patient was discharged on day 6 with ophthalmologic follow-up. At the 18 month follow-up, slight left eye ptosis persisted, but the anisocoria resolved [Figure 2B].

PATIENT 2

A 7 month old girl was admitted to our hospital with a diagnosis of pneumonia in her right lung. Chest X-ray revealed a large pleural effusion with pneumothorax and partial lung collapse. The girl underwent a computed tomography (CT)-guided thoracostomy tube insertion and was admitted to the pediatric intensive care unit (PICU) where she developed severe hypoxic respiratory failure and was subsequently mechanically ventilated. During the following 2 days, three additional thoracostomy tubes were inserted due to recurrent tension pneumothoraces. In addition, a percutaneous right internal jugular vein catheter was placed. Cultures from the pleural fluid revealed *Staphylococcus aureus*. On the 5th day of admission mild anisocoria (1–2 mm) was noticed. On the 10th day of admission the chest drains were removed. The child's trachea was extubated with no complications. She was weaned off heavy sedation and was transferred to the pediatric department.

Figure 3. Right-sided Horner syndrome. A positive 4% cocaine test: Ptosis: the right upper and lower eye lids are slightly closed. Anisocoria: the left (intact) pupil is 5 mm and the right pupil 3 mm



Ophthalmic examination revealed a right upper eyelid ptosis with slight elevation of the lower lid and anisocoria. The left pupil was 3 mm in diameter and the right pupil 2 mm. Ocular movements were normal and both pupils were reactive to light. Neurological examination of the cranial nerves and the upper limbs were normal. Instillation of freshly prepared 4% cocaine solution showed the left (normal) pupil dilating to 5 mm and the right pupil to only 3 mm [Figure 3], thus confirming right-sided HS. At the 12 month follow-up visit in the ophthalmology outpatient clinic a slight right eye ptosis could still be noticed. The anisocoria was completely resolved.

PATIENT 3

A 31 year old woman was admitted to the Intensive Care Unit with a moderate asthma attack. During the admission a central line was inserted via the right internal jugular vein. Two days later the patient was noted to have a right-sided ptosis.

Subsequent ophthalmic examination revealed a 2 mm ptosis of the right upper lid and a constricted pupil. The right pupil was 2.5 mm in diameter in bright illumination while the left pupil was 4 mm. In dim light, the right pupil measured 4 mm and the left 6 mm. The diagnosis of right-sided Horner syndrome was confirmed with 4% cocaine eye drops. At the follow-up visit 9 months later the ptosis and anisocoria were both partially resolved.

PATIENT 4

A 78 year old woman presented to our neuro-ophthalmological outpatient clinic with left-side ptosis and miosis (the right normal pupil was 4 mm in diameter and the left pupil 2 mm). A careful clinical history taking revealed that 2 months prior to presentation the patient had undergone a myelomectomy to remove an extramedullary intradural meningioma on level C7-T1. Both pupils were reactive to light. The upper limb, cranial nerve neurological examination and edrophonium test were normal. Instillation of aproclonidine 1% demonstrated dilation of the left pupil but the size of the right pupil remained unchanged. The reversal of anisocoria by aproclonidine confirmed left Horner syndrome. At the 6 month follow-up the ptosis and anisocoria had completely resolved.

DISCUSSION

We performed a systemic review of the relevant literature to investigate the incidence and origin of iatrogenic cases of Horner syndrome, which involved three independent Pubmed Central searches (U.S. National Library of Medicine, Bethesda, MD, USA). All searches were limited to articles published within the last 10 years to limit the number of references to approximately 25. Key words were “iatrogenic Horner syndrome,” “postoperative Horner review,” and “obstetric anesthesia Horner review.” The search yielded 43 articles, of which 15 were excluded because they were written in languages other than English or the studies were not conducted in humans. The total number of cases of iatrogenic Horner syndrome identified was 151.

ETIOLOGY

Horner syndrome consists of miosis, ptosis, enophthalmos, anhidrosis, and vascular dilatation ipsilateral to the lesion. This oculosympathetic palsy is caused by an injury to the sympathetic pathway. Localization of the lesion causing HS is important. First-order neuron lesions are caused by central disorders of the nervous system such as vascular occlusion, particularly in the lateral medulla (Wallenberg syndrome), as well as by tumors, cervical disk disease, and other disorders involving the upper cervical spinal cord. Second-order neuron lesions are caused by apical lung tumors (Pancoast syndrome), metastases, chest surgery, thoracic aortic aneurysms, or trauma to the brachial plexus. Third-order neuron lesions are caused most

commonly by degenerative changes in the wall of the carotid artery or following vasospasm. Other causes include surgery on the carotid artery or structures nearby, internal carotid artery dissection, and extension of tumors such as nasopharyngeal carcinoma into the cavernous sinus [3].

The most common etiologies of HS are neoplasia, representing 35%–60% of the cases. Trauma, including birth injuries, represents 4–13% of cases and iatrogenic injuries are responsible for another 10–18.5% [4]. Second-order neuron injury is most frequently involved in iatrogenic lesions (84%) when comparing the three levels of the sympathetic pathway [3–5].

The literature also suggests that iatrogenic HS can occur in approximately 0.1% of thyroid resections [6], in up to 1.3% of thoracic surgical procedures [7], in 2% of internal jugular vein cannulations [8], and in up to 25% of cervical sympathectomies [9]. A Medline® search using the U.S. National Library of Medicine PubMed® online database showed other rare and sporadic cases. HS was reported secondary to tube thoracostomy for pneumothorax [10–12], carotid angiography [2], post-ablation of the cervical sympathetic chain [13–15], carotid endarterectomy [16], tonsillectomy [17,18] and peridural obstetric anesthesia [19,20].

DIAGNOSIS

The diagnosis of Horner syndrome is usually made clinically together with diagnostic tests, namely, the cocaine test and/or hydroxyamphetamine eye drops. The cocaine test involves the instillation of 4% or 10% liquid cocaine solution into both eyes. Following a 45 minute wait period, the normal pupil dilates to its maximum while the affected pupil dilates poorly. Cocaine blocks the norepinephrine reuptake in the neuromuscular junctions, thereby increasing the available norepinephrine to stimulate the iris dilator muscle. In Horner syndrome the denervated synaptic cleft has little or no norepinephrine. Use of 1% hydroxyamphetamine eye drop solution helps to localize the lesion between the second and third-order neuron lesions [21]. Hydroxyamphetamine stimulates the presynaptic terminal to release norepinephrine. In an intact normal eye, hydroxyamphetamine will cause pupillary dilation. If the third-order neuron is injured, no change in pupil size will be seen. In a second-order neuron injury, the nerve terminal has degenerated and the pupil will therefore dilate poorly. If there is only a first-order neuron injury a hydroxyamphetamine will cause mydriasis [21]. Unfortunately, hydroxyamphetamine is not available commercially in Israel and several other countries.

Use of cocaine eye drops for diagnosis or treatment is associated with some negative implications and risks. Cocaine drops are a controlled drug and therefore difficult to obtain and store. In addition, metabolites of cocaine are excreted in the urine for up to 2 days after topical administration, which can be problematic for those who undergo spontaneous drug screening. For this reason, alternative medications are preferred in some hospitals.

Apraclonidine 0.5% is an alpha-2 adrenergic agonist used to lower intraocular pressure in patients with glaucoma; however, it also has a weak alpha1 adrenergic effect. Apraclonidine minimally constricts a normal pupil and dilates a Horner pupil. This is due to denervation supersensitivity of the alpha1 receptors on its iris dilator muscle, producing a reversal of anisocoria in patients with unilateral HS. In patients with sympathetic denervation of the pupil, it should lead to marked dilation demonstrating denervation supersensitivity. The apraclonidine causes mydriasis of between 1.0 and 4.5 mm in the affected pupil. The test dilates the pupil in pre- and post-ganglionic neuron lesions. Reversal of anisocoria by apraclonidine has therefore been recommended as a new test for Horner syndrome [22].

In cases where iatrogenic HS is suspected, patients should be thoroughly examined and tested, especially with sixth nerve paresis. In the pediatric population, an assay for vanillylmandelic acid in the urine is used to rule out neuroblastoma. Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, neck and chest are also needed to exclude additional causes of HS.

OUTCOMES

Several processes to define the mechanism of the second-order neuron injury that leads to Horner syndrome have been described. Most investigators believe that multifactorial causes lead to neuropraxia of the second neuron pathway. These include, but are not limited to, direct pressure, inflammation, scarification, local hematoma, stretching of the nerve fibers and stellate ganglion, and other underlying conditions [23].

In a series of nine patients who developed iatrogenic Horner syndrome following tube thoracostomy for traumatic pneumothorax or thoracic surgery with insertion of intercostal chest tube, 33% had full resolution, 33% had incomplete resolution, and the remaining 33% had no change in their initial signs and symptoms at the 5 year follow-up [24]. In other studies, the removal or repositioning of a chest tube putting pressure on a sympathetic chain or a tube that is migrating within 1 day of HS onset led to full resolution of Horner signs in up to 66% of cases [25]. Although no association between the time of onset and reversibility has been reported, Kaya et al. [7] noted full recovery after chest tube repositioning in four cases when the diagnosis of Horner syndrome was made within the first 2 days of chest tube insertion. In contrast, other studies report fewer than 57% of cases resolving at follow-up despite removal of the chest drain at 3 months to 1 year follow-up [5]. Despite the conflicting data regarding the prompt diagnosis and reversal of HS, the prevention of iatrogenic HS may be possible through familiarization of the procedures that have potential to cause iatrogenic HS. A systematic Medline® search using the U.S. National Library of Medicine PubMed® online database yielded all possible etiologies and outcomes of iatrogenic HS cases reported, which are presented in Table 1.

Table 1. The causes and outcomes of iatrogenic HS

Cause [ref]	No. of patients (%)	Complete recovery (%)	Incomplete recovery (%)	Recovery not recorded
Insertion of chest tube	29	18	11	0
Carotid endarterectomy	1	0	0	1
Surgery/ablation of the cervical sympathetic chain	32	3	15	14
Thyroidectomy	3	1	1	1
Tonsillectomy	16	9	7	0
Peridural obstetric anesthesia	56	1	2	53
Cardiothoracic surgery	1	1	0	0
Thoracic sympathectomies	3	3	0	0
Laryngectomy	2	0	2	0
Liver cancer/Liver resection	1	0	0	1
Esophageal substitution	1	1	0	0
Temporomandibular joint arthroplasty	1	0	1	0
Total no. of cases	151 (100%)	41 (27.15%)	40 (26.5%)	70 (46.35%)

CONCLUSIONS

Horner syndrome is often overlooked in critically ill patients and can be missed unless suspected by the clinician. The cocaine and apraclonidine tests have become the standard diagnostic method for confirming clinically suspected HS. Although the natural course of HS is not predictable, there has been some evidence suggesting that the longer the injuring process or pressure applied to the neuron the less likely the chance of complete recovery. As such, the prompt diagnosis of HS and immediate removal of the offending agent may prevent irreversible iatrogenic damage.

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