

Case Report

Horner Syndrome Related to Nasopharyngeal Carcinoma

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ABSTRACT

Background: Horner syndrome classically presents with ipsilateral blepharoptosis, pupillary miosis, and facial anhidrosis. The syndrome results from interruption of the sympathetic innervation to the eye and ocular adnexae.

Case Illustration: A 43-year-old male complaining of drop of upper eyelid right eye, anhidrosis right side of face, and numbness on his right face since 7 months previously. He had painless, slowly enlarging, right-sided neck mass that was first noticed approximately 7 months before presentation. The biopsy and CT scan confirmed nasopharyngeal carcinoma (NPC). Best corrected visual acuity of both eyes was 6/6, normal IOP and ocular movement. There was mild ptotic eyelid 2 mm of his right eye. Both anterior segment within normal limit. There was unequal pupils greater in the dark, with pupil size of the right eye 3 mm and left eye 5 mm. The pupils were reactive to light, without afferent pupillary defect. Both posterior segment examination were unremarkable. There was reduced sensibility of the right face at maxilla and mandibular region. The patient was diagnosed with Horner syndrome with involvement of right trigeminal nerve at maxillary and mandibular division, and involvement of sweat glands correlate with preganglionic lesion.

Conclusion: Nasopharyngeal carcinoma that affects oculosympathetic pathway may give clinical signs as Horner syndrome. There was found involved of sweat gland in this case, it is correlated with lesion in preganglionic. But the anhidrosis occurs only in maxilla and mandibular region, therefore post ganglionic involvement can not be ruled out.

Keywords: Horner syndrome, nasopharyngeal carcinoma

Horner syndrome first described by Johann Friedrich Horner in 1929, classically presents with ipsilateral blepharoptosis, pupillary miosis, and facial anhidrosis.¹⁻⁵ The syndrome result from interruption of the sympathetic innervation to the eye and ocular adnexae. In the French literature, this condition is called the Claude Bernard-Horner syndrome to honor the work of Claude Bernard in 1852.²

The causes of Horner syndrome are numerous, because the sympathetic pathway to the eye follows a long and circuitous route. The differential diagnosis can be narrowed if the location of the lesion is known or suspected. The three neuron pathway begins in the central nervous system and concludes at the eye.^{1,6} First-order (central) neuron from the posterolateral hypothalamus, descends in the brainstem and lateral column of the spinal cord to exit at the cervical (C8) and thoracic (T1-T2) levels (ciliospinal center of Budge) of the spinal cord as a second-order neuron. This second-order (intermediate) preganglionic neuron exits the ventral root and arches over the apex of the lung to ascend in the cervical sympathetic chain. The second-order neurons synapse in the superior cervical ganglion, located between the internal jugular vein and the internal carotid artery, and exit as a third-order neuron. The neural fibers for sweating of the face travel with the external carotid artery. The third-order postganglionic neuron travels with the carotid artery into the cavernous sinus. Within the cavernous sinus, the sympathetic fibers join the abducens nerve for a short course and then travel with the ophthalmic division of the trigeminal nerve and join the nasociliary branch of the trigeminal nerve.^{3,6,7}

Vertigo, ataxia, sensory deficits, swallowing difficulty, or upper cervical cord syndrome point to a lesion of the central, or first order, sympathetic neuron. Brainstem infarcts are the most common cause of a central Horner syndrome. Hemifacial anhidrosis, a scar or mass in the anterior neck, hand weakness, or past history of central venous catheterization suggest a lesion of the second order neuron (also called the preganglionic neuron). Tumor or trauma is the most common cause of a preganglionic Horner syndrome. Absence of anhidrosis or a new, ipsilateral headache

suggests damage of the postganglionic, or third order neuron.^{3,4,6}

Because the clinical findings or sympathetic denervation of the head and eye are variably present, a firm diagnosis of Horner syndrome often requires pharmacologic confirmation. Cocaine is an indirect-acting sympathomimetic agent that blocks presynaptic uptake of released norepinephrine at the terminal synapse. In a healthy subject, topical cocaine causes vasoconstriction of conjunctival vessels, lid retraction, and pupillary dilation. Hydroxyamphetamine releases stored norepinephrine from the postganglionic adrenergic nerve endings at the dilator muscle of the pupil. Therefore, a preganglionic Horner syndrome dilates after administration of topical hydroxyamphetamine 1%, whereas a postganglionic Horner syndrome pupil does not dilate (nonnorepinephrine stores).^{6,8,9} Apraclonidine has a different mode of action for detecting oculosympathetic insufficiency. Apraclonidine is a weak, direct-acting α_1 -agonist that does not typically cause observable ocular changes in most healthy eyes. A reversal of anisocoria after apraclonidine use is considered diagnostic for Horner syndrome.^{4,10,11} The management of horner syndrome is directed at treating the underlying disease, but some situations may need surgery intervention.¹

This case presentation will report a patient who consulted to Neuro-ophthalmology Division in Cipto Mangunkusumo Eye Clinic that was diagnosed with nasopharyngeal carcinoma. This case presentation is aimed to demonstrate a case of horner syndrome associated to nasopharyngeal carcinoma and discuss about the location of the lesion.

CASE ILLUSTRATION

A 43-year-old male presented to Ophthalmology department in Cipto Mangunkusumo Hospital on May 28th 2013, complaining of drop of upper eyelid right eye, left facial sweating, and felt numb of his right face since 7 months previously. He had no history of blurred vision, redness, double vision, pain, allergy, diabetes mellitus, hypertension, and trauma.

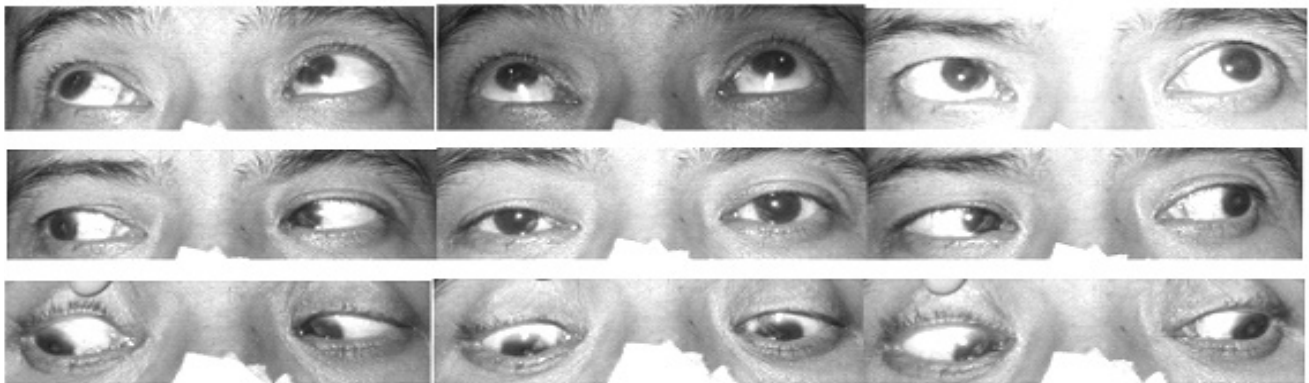


Fig 1. Ocular movement of both eyes within normal limit



Fig 2. There was unequal pupil in the bright light



Fig 3. Unequal pupil in he dark light

He was consulted from Ear-Nose-Throat Department with diagnose of nasopharyngeal carcinoma. He had painless, slowly enlarging, right-sided neck mass that was first noticed approximately 7 months before presentation. Prior to this, he often complain of nasal congestion, nose bleed, and ringing in the ear. The biopsy was taken and result non keratinizing nasopharyngeal carcinoma.

Ophthalmological examination revealed best corrected visual acuity of both eyes was 6/6. He had good of IOP and ocular movement both eyes (Fig. 1). There was mild ptotic eyelid 2 mm of his right eye. Both of bulbi conjunctiva, cornea, anterior chamber within normal limit. There was found unequal pupils that greater in the dim light (Fig 2,3). In the dim light, pupil size of the right eye was 3 mm and left eye 5 mm. The pupils were reactive to light, without an afferent pupillary defect. Both lenses were clear. Both vitreous within normal limit. The fundi examination were unremarkable. There was reduced of sensibility of the right face at maxila and mandibular area. Automatic perimetry (octopus) and fundus photograph was performed and showed normal results (Fig.4,5).

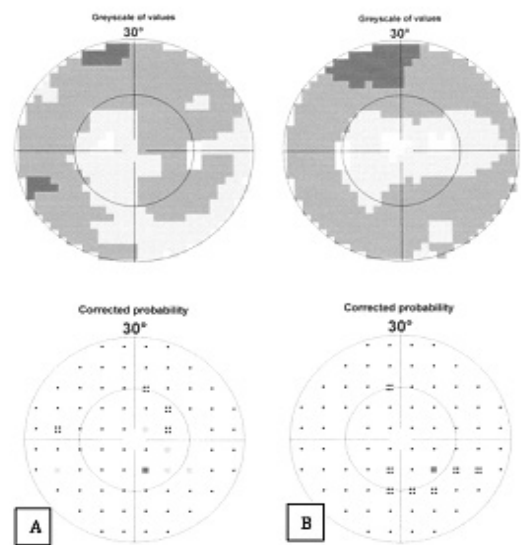


Fig 4. Octopus perimetry within normal limit. A) Right eye, B) Left eye

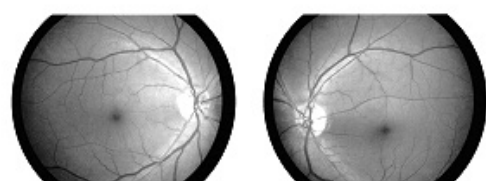


Fig 5. Fundus photograph revealed unremarkable



Fig 6. Nasopharyngeal CT scan revealed the nasopharynx mass obliterate torus tubarius and fossa rosenmuller, infiltrate the right media pterygoid muscle, extended to the right oropharyngeal, right parasellar, and destruct skull base in the right side

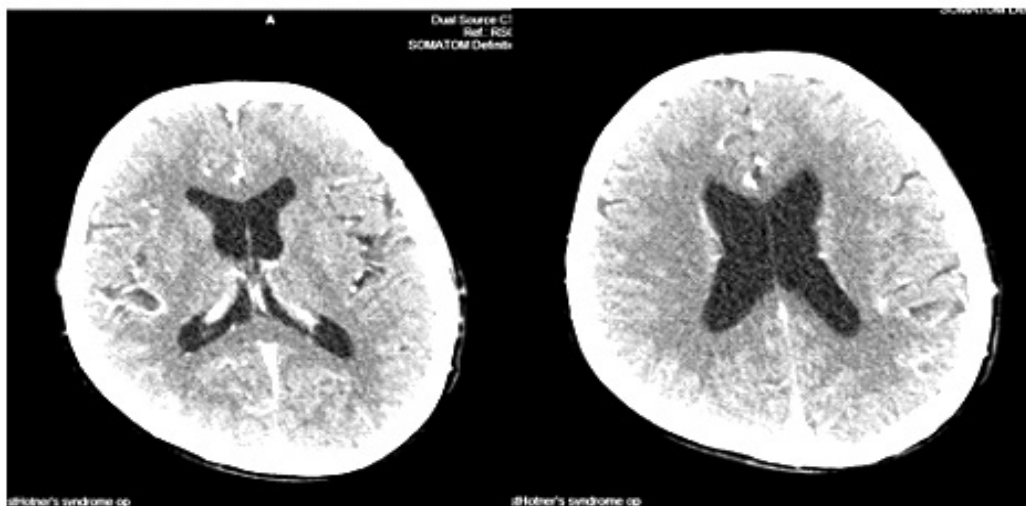


Fig 7. Brain CT showed ventriculomegaly, there was no space occupying lesion

The Computed tomography (CT) scan of nasopharyngeal revealed the nasopharynx mass obliterate torus tubarius and fossa rosenmuller, infiltrate the right medial pterygoid muscle, extended to the right oropharyngeal, right parasellar, and destruct skull base in the right side (Fig.6).

The diagnosis of this patient was Horner syndrome with involvement of right trigeminal nerve at maxillary and mandibular division, and nasopharyngeal carcinoma. The Brain CT revealed ventriculomegaly, there was no space occupying lesion. Nasopharynx mass obliterate torus tubarius and fossa rosenmuller, infiltrate the right medial pterygoid muscle.

DISCUSSION

Horner syndrome, characterized primarily by ipsilateral ptosis, pupillary miosis with anisocoria greater in the dark, facial anhidrosis on the affected side. The upper eyelid ptosis is always mild and rarely ever covers the visual axis.³ Horner syndrome can be divided into three types, depending on where the disruption lies along the oculosympathetic pathway: central, preganglionic, and postganglionic.^{3,12-14} The three-neuron oculosympathetic pathway begins in hypothalamus and ends in the eye.¹⁻⁴

The first-order neurons originates from the posterolateral hypothalamus. There are

probably some synapses in the brainstem at level of the pons, but most of the fibers descend to the sinaps in the ciliospinal center of Budge-Waller, located in the intermediolateral columns of the spinal cord at level of C8 to T2.¹ Lee et al reported that central causes of Horner syndrome are typically recognized based on the accompanying neurologic sign and symptoms that indicate involvement of the hypothalamus, brainstem or cervicothoracic spinal cord. Vertigo, ataxia, sensory deficits, swallowing difficulty, meningeal sign, anhidrosis of the body point to a lesion in the intracranial. Brainstem infarcts are the most common cause of a central Horner syndrome. Other causes include trauma, tumors, demyelinating disease, and arterio-venous malformations.⁶ In this patients, there was no history of head trauma, no neurologic sign and symptom, and there was no found space occupying lesion from brain CT scan. The lesion in the first order was ruled out. In the other hand, the biopsy confirmed non keratinizing nasopharyngeal carcinoma and CT scan showed soft-tissue mass in the nasopharynx with skull base invasion.

Nasopharyngeal carcinomas most often become symptomatic between ages 40–60. Men are affected twice as often as women. Malignant tumors of the nasopharynx frequently escape early recognition. The delay in diagnosis of these tumors can be attributed to their insidious growth, the lack of specificity of initial symptoms, and, until the availability of fiberoptic nasopharyngoscopy as well as CT scanning and MR imaging. Most nasopharyngeal carcinomas arise from the roof of the nasopharynx, its lateral walls (especially in the region of the ostium of the eustachian tube), or both. They most frequently grow within the nasopharynx and may occlude the eustachian tube producing a sense of fullness or plugging of the ear. They may also cause loss of hearing, discharge from the ear, nasal obstruction, nasal bleeding and discharge, or a combination of these. If they become large enough, they can produce a mass in the neck. Otorhinologic symptoms and signs occur in about 50% of patients.¹⁵

Nasopharyngeal carcinomas that affect the cervical lymph nodes may also infiltrate or compress the oculosympathetic pathway in the

neck or within the cavernous sinus and thus produce an ipsilateral Horner's syndrome that may be pre- or postganglionic, depending upon the location of damage. When nasopharyngeal carcinomas spread to adjacent structures, they often infiltrate or compress various branches of the trigeminal nerve.¹⁵ In rare cases, an isolated Horner syndrome is the first sign of the tumor. A nasopharyngeal carcinoma should be suspected in any patient who presents with unilateral facial pain, particularly when the pain is associated with an ipsilateral cranial neuropathy (especially an ocular motor nerve palsy) or a postganglionic Horner syndrome.^{15,16}

The preganglionic (second-order) neuron exits from the ciliospinal center of Budge and passes across the pulmonary apex. It then turns upward, passes through the stellate ganglion, and goes up the carotid sheath to the superior cervical ganglion, near the bifurcation of the common carotid artery. A patient with a preganglionic Horner syndrome and ipsilateral shoulder pain should be investigated thoroughly for neoplastic involvement of the pulmonary apex, the pleural, and the brachial plexus. The preganglionic neuron is the most common site of injury for an iatrogenic Horner syndrome. The varied anesthetic, radiologic, and surgical procedures that can produce the condition include coronary artery bypass surgery, lung or mediastinal surgery, carotid endarterectomy, insertion of a pacemaker, epidural anesthesia, interpleural placement of chest tubes, internal jugular catheterization, and stenting of the internal carotid artery.²

Lee et al stated that anhidrosis involving the face and neck, neck or arm pain suggest the lesion of the preganglionic.⁶ In this patient, there was possibility the lesion in second order neuron because involvement of sweat gland and anhidrosis in entire of right side of face.

The third-order neuron exit the superior cervical ganglion and form a plexus, which surrounds the internal carotid artery. The fibers responsible for the sweat and piloerection of the face follow the external carotid artery. The remainder of the sympathetic plexus and the internal carotid artery enter the skull base through the carotid canal and travel through the

middle cranial fossa into the cavernous sinus. The sympathetic fibers briefly travels with the intracavernous sixth cranial nerve before joining the ophthalmic division of the trigeminal nerve on its course into the orbit. The sympathetic fibers follow the course of the nasociliary nerve through the superior orbital fissure. The fibers pass through but do not synapse in the ciliary ganglion. Distal the ciliary ganglion, the sympathetic fibers divide and innervate various anatomic structures: the middle ear, the orbital vasomotor fibers, the dilator muscle of the pupil, the accessory levator muscle of the upper eyelid (Muller muscle) and its analog in the lower eyelid, and the lacrimal gland.¹ Postganglionic Horner syndrome due to cavernous sinus lesion (e.g. thrombosis, infection, neoplasm) usually is associated with other localizing such as ipsilateral trigeminal and sixth nerve dysfunction.³ Anhidrosis in postganglionic horner syndrome is often absent. The causes of postganglionic neuron include internal carotid artery pathology, cluster headache, tumor, cavernous carotid aneurysm, and inflammation.⁶

In this patient, he had all the classic clinical sign of Horner syndrome such as miosis with anisocoria that greater in the dark, ipsilateral ptosis and facial anhidrosis. The ptosis result from loss of sympathetic innervation of Muller muscle. Because Muller muscle is responsible for only approximately 2 mm of upper eyelid elevation, subtle ptosis occurs.^{4,13} In addition, to an often subtle upper eyelid ptosis with sympathetic denervation, lower eyelid retraction may occur, termed "inversed ptosis". In combination, this can result in narrowing of the interpalpebral fissure, producing an enophthalmos that is more often apparent than real.⁴ In this patient, we have no found the inversed ptosis of the lower eyelid.

There is mild miosis occur in this patient, due to unopposed action of the sphincter pupillae following paralysis of the dilator pathway. Pupillary reactions are normal to light and near. When the lights are turned off the Horner's pupil dilates more slowly than the normal pupil because it lacks the pull of the dilator pupillae. This is called *dilatation lag*. This occurs because the process of pupillary dilation with sympathetic denervation is primarily passive, resulting from relaxation of the iris sphincter alone.^{4,6,17}

Reduced sweating on the ipsilateral face occurs in this patient, termed facial anhidrosis. It results from disruption of the sympathetic fibers traveling with the external carotid artery to innervate the sweat glands of the face. If the disruption is postganglionic, then only the medial part of the upper forehead may be affected, this area being supplied by some third order fibers. In this patient, the anhidrosis occur not only in the upper forehead, but entire of right side of face. It could be the lesion not only in the third order neuron, but occur in the second order also. If a patient with Horner syndrome is placed in an environment or situation that provoked perspiration, the area innervated by the blocked fibers will be dry, and the unaffected side will be moist with sweat.^{11,18-19}

The diagnosis of Horner syndrome is usually a clinical one based upon examination findings. Cocain has been the gold standard test for years. Cocaine eyedrops have been conventionally used to establish a diagnosis of Horner syndrome, with hydroxyamphetamine being used to differentiate between a pre- and postganglionic lesion.^{1,20} The normal pupillary response to topical cocain is dilation. Cocain inhibits the reuptake of norepinephrine at the synaptic junction of the postganglionic fibers and the iris dilator muscle. If the sympathetic innervation has been disrupted, norepinephrine is not released from the nerve terminal and topical cocain does not produce pupillary dilation. Failure of pupillary dilation after instillation of topical cocain confirm the presence of sympathetic denervation.^{1,3,20}

After confirmation with the topical cocain test, topical hydroxyamphetamine can be used to distinguish central and preganglionic sympathetic lesions from postganglionic sympathetic lesions. Topical hydroxyamphetamine produce pupillary mydriasis by releasing norepinephrine from the sympathetic synaptic terminal. Pupillary mydriasis occurs only if the third-order neuron is intact. Pupillary inequality of 1 mm or more after instillation suggest a third-order lesion.^{1,3} Hydroxyamphetamine is becoming more difficult to acquire because of decreasing commercial availability. This, coupled with the high false-negative and positive rate of

the hydroxyamphetamine test, will encourage clinicians in most instances to localize the Horner syndrome and make management decisions clinically, based upon clues in the history or examination. However, in clinical practice pharmacological testing is rarely applied. Therefore, distinguishing between central, pre and postganglionic disease is reliant on recognizing the clinical clues available.^{3,6,10}

The other pharmacological test is apraclonidine. Topical apraclonidine produces a mydriatic result in affected eyes rather than unaffected eye, as is the case with cocaine testing. When testing for horner syndrome with apraclonidine, the reversal of anisocoria is easily detected clinically with the naked eye, even when the reversal is slight. Unlike cocaine, apraclonidine depends on supersensitivity. If supersensitivity develops slowly or incompletely, then theoretically, apraclonidine may have the negligible effect.²¹⁻²³

Imaging of some type typically will be pursued next, and the localization and clinical setting will dictate the modality and region to be evaluated.^{3,4} MRI of the brain should reveal stroke, tumor, or demyelinating causing central Horner syndrome.¹ Chest radiography, computed tomography, magnetic resonance imaging, or angiograms of the thoracic or cervical area may be ordered if additional pathological conditions are observed.¹¹ The management of the horner syndrome is directed at treating the underlying causes.¹

In this patient, the biopsy and CT scan confirmed the nasopharyngeal carcinoma. The pharmacological testing was not performed because the facility was unavailable in our hospital. Although the classic sign of Horner syndrome was found in this patient, such as, ipsilateral ptosis, miosis, and facial anhidrosis. But, we could not distinguish the location of the lesion. If we see the involvement of trigeminal nerve at maxilla and mandibular division, possibility the lesion was in postganglionic or third-order neuron because trigeminal nerve divided itself closed to cavernous sinus. Walton stated that Horner syndrome accompanied by oculomotor, trigeminal, or abducens palsy suggests a lesion in the cavernous sinus, superior

orbital fissure, or orbital apex.^{1,3} If the disruption is postganglionic, then only the medial part of the upper forehead may be affected, this area being supplied by some third order fibers.¹ If we see the type of anhidrosis in this patient, the anhidrosis occur not only in the upper forehead, but entire of right side of face. It could be the lesion not only in the third order neuron, but occur in the second order also.

CONCLUSION

Horner syndrome is denervation of oculosympathetic pathway that characterized by ipsilateral ptosis, miosis, and facial anhidrosis. A thorough evaluation requires a focus history and physical examination as well as a selection of pharmacologic testing and suitable imaging studies to determine the location of lesion. The cause of Horner syndrome generally such as infarction, trauma, tumors, iatrogenic, infection, and inflammation that may occur along the oculosympathetic pathway. One of the most common cause in Neuro-ophthalmology Clinic in Kirana-Cipto Mangunkusumo Hospital is tumors, including nasopharyngeal carcinoma. Nasopharyngeal carcinoma that affects the cervical lymph nodes and infiltrates or compresses the oculosympathetic pathway in the neck, may give clinical signs as Horner syndrome. Regarding of this, we could suspect the presence of nasopharyngeal carcinoma in patient presented with Horner syndrome.

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