CLINICAL AND EXPERIMENTAL
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Horner syndrome

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Horner syndrome is an uncommon but important clinical entity, representing interruption of the sympathetic pathway to the eye and face. Horner syndrome is almost always diagnosed clinically, though pharmacological testing can be used to confirm the diagnosis. Imaging modalities such as PET, CT and MRI are important components of work-up for patients presenting with acquired Horner syndrome. Our patient's presentation with Horner syndrome unmasked the causative superior sulcus squamous cell carcinoma and a coincidental lower lobe adenocarcinoma. Successful radical treatment of these cancers resulted in complete resolution of the syndrome and disease-free survival at 18 months. We review the anatomy and pathophysiology underlying this and other causes of Horner syndrome.

Key words: Horner syndrome, miosis, ptosis, superior pulmonary sulcus tumour, sympathetic nervous system

Horner syndrome is the collection of signs produced by interruption of the sympathetic pathway to the eye and face. It is defined clinically by ipsilateral miosis, partial ptosis, apparent enophthalmos and anhidrosis. The diagnosis of Horner syndrome is based on clinical observation but may be confirmed by pharmacological testing. Its causes range from benign to life threatening. We present a case of Pancoast (superior pulmonary sulcus) tumour, in which acquired Horner syndrome was a feature at presentation and we discuss the pathophysiology and a diagnostic approach for patients with Horner syndrome.

CASE REPORT

JG, a 59-year-old clerical worker, was admitted to the Cardiothoracic Care Centre for investigation in July 2005, following a three-month-history of gradually worsening right arm pain and right hand weakness that were unresponsive to simple

analgesia. During this time, she had also noticed drooping of her right eyelid (Figure 1) and described anorexia and weight loss of approximately five kilograms, as well as worsening shortness of breath on exertion. She had a 15-year history of smoking one packet a day, though she had quit 20 years previously. There were no other remarkable features in the history.

On inspection, the patient appeared well. Visual acuities were 6/6 in both eyes. There was incomplete ptosis of the right upper eyelid. An efferent pupillary defect was observed, with the right pupil one millimetre smaller than the left pupil in room light (Figure 1). In dim light, the disparity was two millimetres greater. There was no afferent pupillary defect and eye movements were normal. The right side of the face appeared flushed and was dry to touch.

A 40 × 30 mm soft tissue mass was felt in the right supra-clavicular fossa. Shooting pain down the right arm was induced by firm palpation of the mass. Finger clubbing was noted and the intrinsic muscles of her right hand were moderately wasted. Right wrist power and right hand grip strength were reduced. Tendon reflexes of both arms were normal. Examination of the head, neck, lower limbs, abdomen and cardio-respiratory system was normal.

CT of the chest demonstrated a 50 × 30 mm right apical lung mass extending beyond the thoracic cavity, encasing the medial portion of the right subclavian vein. This was confirmed with MRI (Figure 2), which also revealed tumour extension into T1 - T2 and T2 - T3 intervertebral foramina. A smaller second lung nodule was found in the apex of the right lower lobe adjacent to the apical mass. Both of these lesions were metabolically active on positron emission tomography (PET) scan (Figure 3A). A single 40 × 40 mm liver lesion was revealed on CT of the abdomen. This was determined to be a benign haemangioma based on the results of liver ultrasound and triple (non-contrast, arterial then venous) phase CT scan. There were no other active lesions seen with PET scan. Fine needle biopsy of the apical lung mass revealed poorly differentiated squamous cell carcinoma.

Figure 1. Horner syndrome with classical features of partial ptosis, apparent enophthalmos and miosis

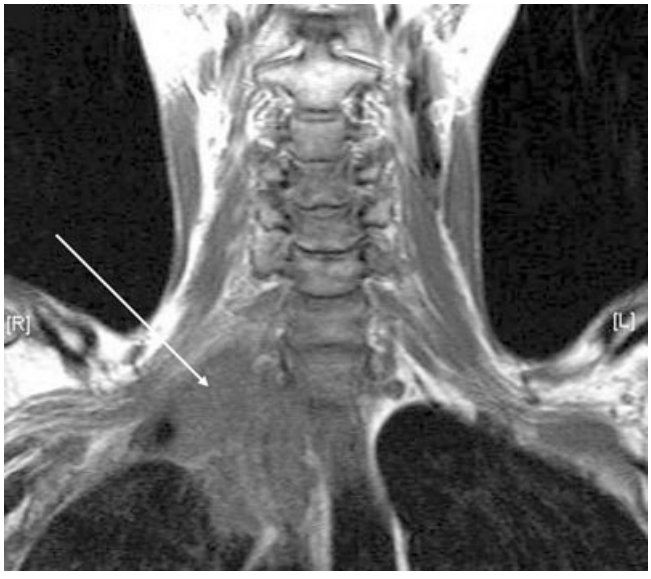

Figure 2. MRI demonstrating right apical lung mass (arrow)

JG was commenced on combined chemo-radio-therapy with curative intent, as current radical multi-modality approaches confer improved survival compared with those reported previously.[1,2] Repeat PET scan was used to monitor the response to treatment. At two months, there had been a significant metabolic response (Figure 3B); at four months, metabolic activity in the apical lung tumour was undetectable on PET, though the nodule in the right lower lobe remained active. Given the difference in response to treatment, it was thought that the lower lobe nodule represented a synchronous primary lung cancer.

The lower lobe tumour was subsequently treated by formal superior segmentectomy and radical lymph node dissection using video-assisted thorascopic surgery. Histology of the resected nodule was that of a poorly differentiated adenocarcinoma. No evidence of tumour was found in the dissected lymph nodes.

JG recovered fully from surgery and has had complete resolution of her neuropathic pain (though incomplete resolution of the Horner syndrome). Twelve months after her surgery, there is no clinical or radiological evidence of relapse of either cancer.

DISCUSSION

Horner syndrome, described by the Swiss ophthalmologist Johann Friedrich Horner,[3] is a constellation of signs that occurs when the sympathetic pathway to the eye

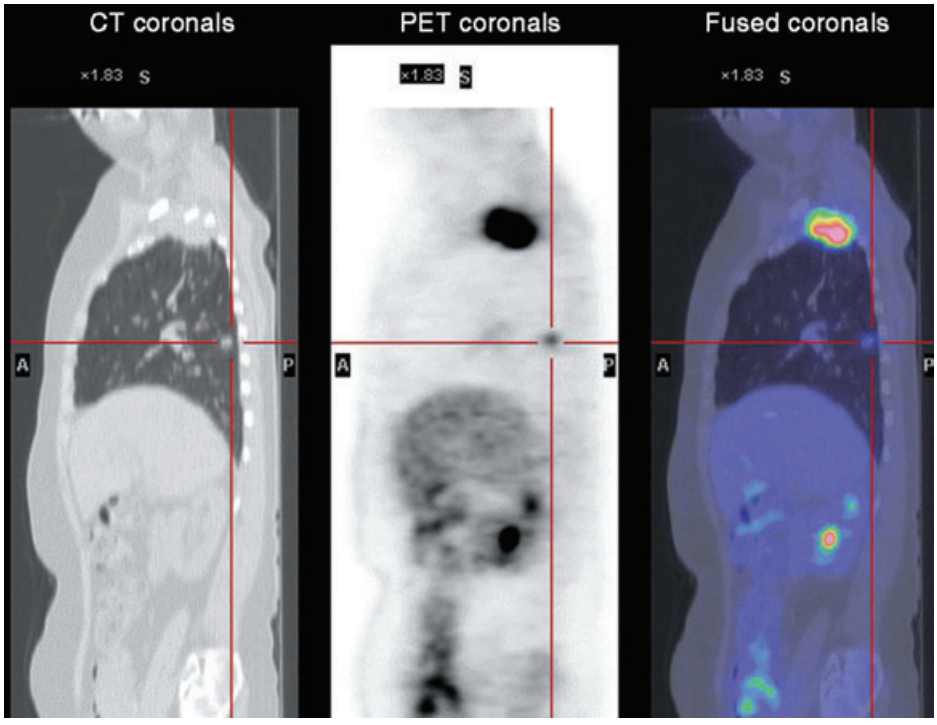

Figure 3A. Coronal CT, PET and fused scan images of upper thoracic region in July 2005, demonstrating intense uptake in the right lung apex and apical segment of right lower lung lobe

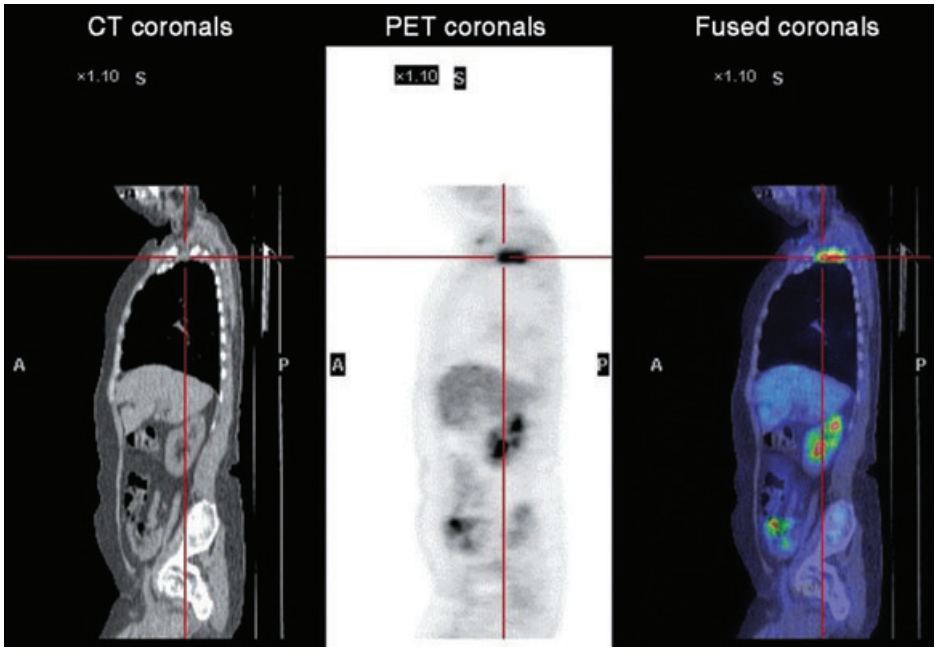

Figure 3B. Coronal CT, PET and fused scan images of upper thoracic region in September 2005 (two months following chemo-radio-therapy) demonstrating marked reduction in the uptake by the right apical lung lesion

is interrupted.[4] Diagnosis of Horner syndrome is primarily clinical, as the prevailing features are readily apparent. They include miosis, partial ptosis, apparent enophthalmos and anhidrosis. Less constant to rare features include (on the affected side): facial flushing, arteriolar or venular dilatation (best seen in the retina), transient lowering of intraocular pressure, hemi-atrophy of the face and iris heterochromia (in congenital Horner syndrome). Visual acuity is rarely affected. Other symptoms and signs can be present due to compression of surrounding structures by the offending lesion. Indeed, as illustrated by our case, Horner syndrome may be the harbinger of serious disease.

Pathophysiology of Horner syndrome

The sympathetic pathway to the eye and its adnexae is a three-neuron pathway, which begins in the central nervous system (Figure 4). The first-order neuronal fibres arise from the postero-lateral hypothalamus. They descend through the brainstem to terminate in the spinal cord at the ciliospinal centre (C8 - T2). The second-order neuronal fibres (pre-ganglionic) exit through T1 root and travel close to the lung apex through the para-vertebral sympathetic chain and the stellate ganglion and terminate in the superior cervical ganglion. Tumours involving the upper lobe of the lung and thoracic outlet can interrupt the pathway at this level because of their proximity to these structures.

The third-order sympathetic fibres (post-ganglionic) exit the ganglion to form a plexus surrounding the internal carotid artery. Dissection of the internal carotid artery is a very important cause that can lead to interruption of the pathway at this level.[5] The plexus then ascends into the cavernous sinus, runs a short course on the sixth cranial nerve and then follows the ophthalmic division of the trigeminal nerve (V1) to the orbit, where they supply the iris dilator muscles and the smooth muscle fibres of upper and lower lid. Vasomotor and sweat gland fibres to the face follow a different course after leaving the ganglion. They follow the

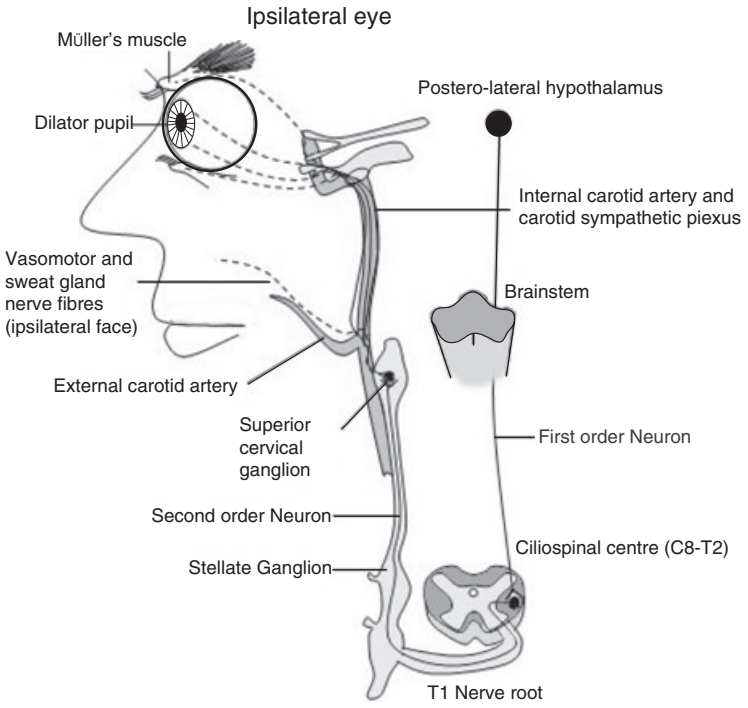

Figure 4. Schematic diagram of the sympathetic nervous system pathway to the eye and face

external carotid artery to supply half of the face on the same side.

Horner syndrome can result from interruption, at any level, of the sympathetic fibres supplying the eye and face. In a case series of 450 patients with Horner syndrome,[6] 270 (60 per cent) had an identifiable cause, of which 34 (13 per cent) had first-order neuronal (central) lesion, 120 (44 per cent) had second-order (preganglionic) lesion and 116 (43 per cent) had third-order (post-ganglionic) lesion. Some of the more common causes of Horner syndrome are listed in Table 1, according to the level of the lesion.

Clinical features of Horner syndrome

MIOSIS

Miosis occurs because the loss of sympathetic drive to the iris dilator muscle results in unopposed (parasympathetic) constriction of the pupil. As miosis in Horner syndrome can appear mild in ambient light, it is important to examine the pupils in both bright and dim light. When the lights of a well-lit room are switched off, a normal pupil will dilate briskly, whereas in Horner syndrome the pupil will dilate slowly (over 15 to 20 seconds) as the active mydriatic action of sympathetic innervation is reduced. This is referred to as 'dilation lag' (Figure 5) and clinches the diagnosis of Horner syndrome (as opposed to other causes of anisocoria).[7] The majority of anisocoria presenting to optometrists and general practitioners is physiologic, in which there is no dilatation lag and the anisocoria is equal in both light and dark.

PARTIAL PTOSIS AND ENOPHTHALMOS

Müller's muscle comprises smooth muscle fibres that aid in the elevation of the upper lid when the eye is open. A similar (unnamed) muscle in the lower lid is also supplied by sympathetic fibres. The loss of sympathetic supply to the eye results in partial ptosis of upper lid and elevation of the lower lid. This causes narrowing of the palpebral fissure, which gives the illusion of enophthalmos,[8] however, actual recession of the eye into the orbit does not occur.[9]

ANHIDROSIS

Anhidrosis, in which the ipsilateral side of the face and neck becomes flushed and dry, is an oft-described sign of Horner syndrome. The flushing is most evident on the ear lobes and can sometimes be associated with redness of conjunctiva and nasal stuffiness. Over time, gradual adjustment of sweat glands and blood vessels can make this sign less obvious.[10] Anhidrosis occurs less often with post-ganglionic lesions because the post-ganglionic sweat gland fibres follow a separate path from the rest of the fibres that travel to the eye. Though clinical tests to assess for anhidrosis have been developed, they are thought to have little diagnostic value.[11]

IRIS HETEROCHROMIA

Differences in iris colour occasionally occur with ocular sympathetic interruption, especially in congenital lesions such as brachial plexus injury during birth.[12] In brown-eyed patients, the lighter iris corresponds to the abnormal pupil (Figure 6), whereas in blue-eyed patients, the affected side is darker. Though rare, depigmentation of the iris can also occur after sympathetic nerve injury in adults.[13] The cause of heterochromia is not well understood though it is thought to result from disruption of neurotrophic development of iris melanocytes.[14]

Pharmacological testing for Horner syndrome

The diagnosis of Horner syndrome is usually made by history and clinical observation alone. In cases in which the diagnosis is unclear, pharmacological testing may be used. We describe four of the pharmacological tests currently in use in specialist practice.

COCAINE TEST

The purpose of the cocaine test is to confirm the presence of Horner syndrome in anisocoria. Cocaine solution instilled

FIRST-ORDER NEURON LESIONS
Arnold-Chiari malformation
Basal Meningitis (for example, syphilis)
Basal skull tumours
Cerebro-vascular accident/lateral medullary syndrome
Demyelinating disease (for example, multiple sclerosis)
Intrapontine haemorrhage
Neck trauma
Pituitary tumour
Syringomyelia
SECOND-ORDER NEURON LESIONS
Pancoast tumour
Birth trauma with injury to lower brachial plexus
Cervical rib
Aneurysm/dissection of aorta, subclavian or common carotid artery
Central venous catheterisation
Trauma/surgical injury (radical neck dissection, thyroidectomy, carotid angiography, coronary artery bypass graft, upper spine chiropractic manipulation)
Chest tube insertion
Lymphadenopathy (for example, Hodgkin's disease, leukaemia, tuberculosis, mediastinal tumours)
Mandibular tooth abscess
Lesions of the middle ear (for example acute otitis media)
Neuroblastoma
Lumbar epidural anaesthesia
THIRD-ORDER NEURON LESIONS
Internal carotid artery dissection
Cluster/migraine headaches
Carotid artery thrombosis
Carotid-cavernous fistula
Herpes zoster
Orbital apex tumour
Idiopathic

Table 1. Differential diagnoses for Horner syndrome

topically inhibits the re-uptake of noradrenaline at the synapse between post-ganglionic nerve endings and the iris dilator muscle, thus increasing sympathetic tone. A normally innervated pupil dilates following instillation of cocaine at a concentration of between four and 10 per cent. In Horner syndrome, sympathetic denervation has occurred and topical cocaine will have little or no effect on the pupil. Anisocoria of one millimetre or more is often considered positive for this test.[15]

The cocaine test does not give information about the site of the lesion in the sympathetic pathway, though it is usual for a third-order neuronal lesion to give a more dramatic result.

Though cocaine has been used for many years in specialist practice, it is a restricted drug in Australia. Therefore, its use is mainly limited to the public hospital setting.

APRACLONIDINE (IOPIDINE) TEST

A promising alternative to cocaine testing is the use of topical apraclonidine 0.5%, a drug sometimes used in the treatment (or post-operative prevention) of ocular hypertension.[16] Apraclonidine is an α-1 adrenergic agonist with good ocular penetration. When applied topically, the affected pupil will dilate more than the normal pupil due to adrenergic supersensitivity (due to post-denervation upregulation of adrenergic receptors of the dilator muscle). Early studies suggest apraclonidine has similar sensitivity and specificity to cocaine in detecting Horner syndrome.[17,18] Apraclonidine has the advantage of being more readily available than cocaine solutions as it is not a controlled substance.[19] It has also been found to be safe and effective in paediatric patients.[20–22] Potentially, it can be used in general practice or optometric settings as a simple test for Horner syndrome. Its disadvantage lies in its dependence on supersensitivity, which can vary between cases.

HYDROXYAMPHETAMINE TEST

Following confirmation of Horner syndrome, topical hydroxyamphetamine can be used to guide differential diagnosis and further imaging studies, as it distinguishes pre-ganglionic from post-ganglionic sympathetic lesions. Hydroxyamphetamine causes pupil dilatation by stimulating the release of noradrenaline from post-ganglionic nerve endings. If the offending lesion is pre-ganglionic, the post-ganglionic nerve fibres will still be functional so pupillary dilatation will occur. Pupillary dilatation will not occur if the lesion affects post-ganglionic fibres.

The hydroxyamphetamine test is not accurate when performed within one to two days of the cocaine test as cocaine inhibits the uptake of hydroxyamphetamine from the nerve terminal.[10] False negative results can occur in acute Horner syndrome, as noradrenaline is yet to be depleted from the post-ganglionic nerve terminals.[23] Therefore, patients with acute Horner syndrome should proceed to imaging of head and neck and upper chest directly.

Hydroxyamphetamine is not currently available in Australia.

PHENYLEPHRINE

Phenylephrine, an α-adrenergic receptor agonist, is a drug readily available to optometrists and general practitioners. For the purpose of confirming Horner syndrome, phenylephrine is used at a concentration of 1% (that is, 10% diluted with normal saline).

Where denervation hypersensitivity occurs as a result of interruption of post-ganglionic fibres (that is, third-order

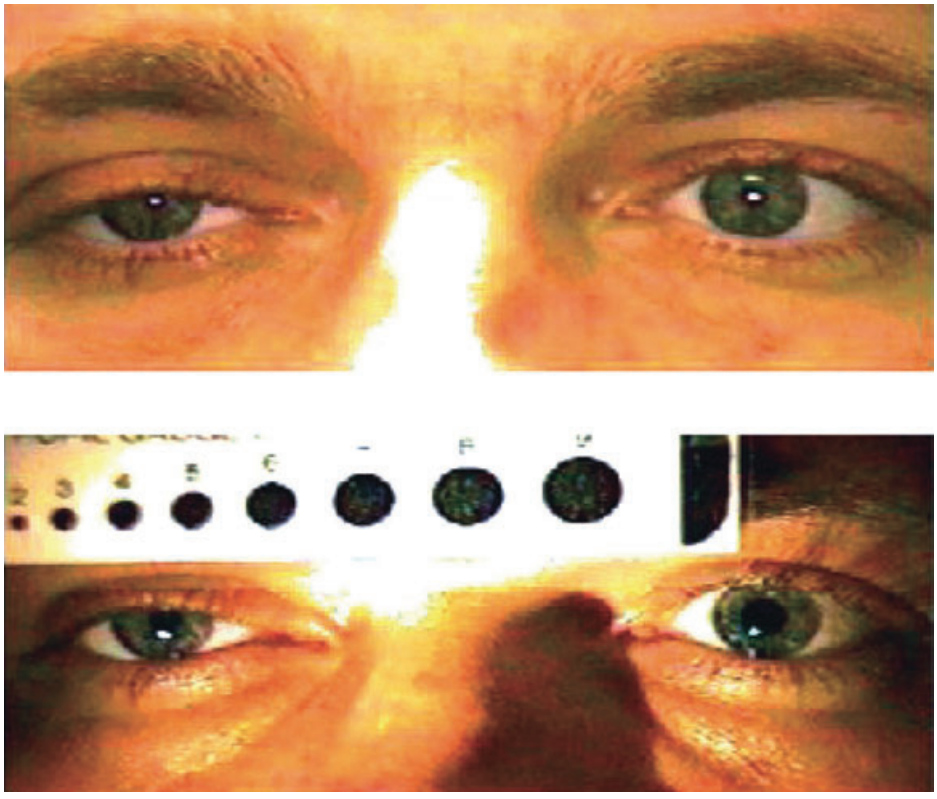

Figure 5. An example of dilation lag in right-sided Horner syndrome. Top panel: in ambient light the difference between the size of pupils is almost unnoticeable. Bottom panel: seconds after room light was switched off, the left pupil has dilated briskly, whereas the right pupil remained small (original contribution from Dr Jade Schiffman and Dr Rosa Tang).

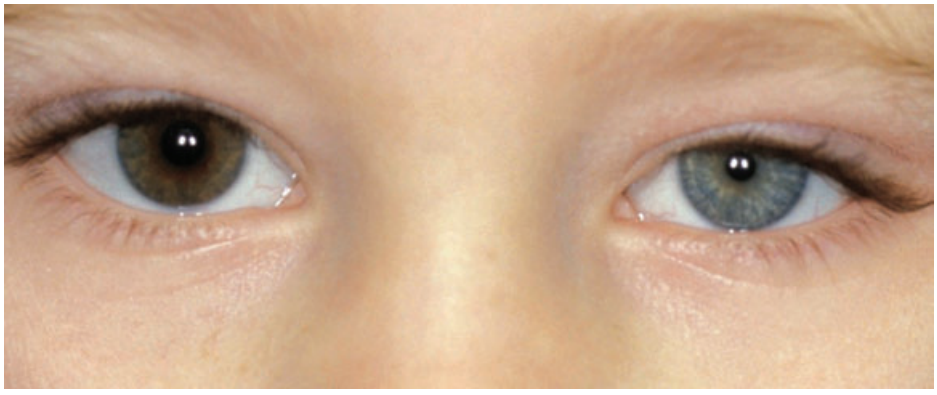

Figure 6. Congenital Horner syndrome with iris heterochromia; the affected side has the blue iris (photograph courtesy of Photographic Case Library, Department of Ophthalmology, Flinders Medical Centre)

lesions), instillation of phenylephrine will result in mydriasis of the affected pupil of the order of two millimetres. The normal pupil typically dilates less than 0.5 mm. As the majority of Horner syndrome cases are the result of a third-order lesion, phenylephrine will often be helpful in confirming the diagnosis. Indeed, phenylephrine has similar efficacy in the detection of third-order lesions in Horner syndrome.[24]

Clinical diagnostic approach and further investigations

A lesion that impinges on the sympathetic pathway is likely to impinge on other nearby structures. Therefore, it is useful to consider the apparent level of lesion when forming the differential diagnosis for Horner syndrome (Table 1).

FIRST-ORDER NEURON ('CENTRAL')

Central causes of Horner syndrome are relatively uncommon, however, given the passage of sympathetic fibres through the brainstem, central lesions are almost always associated with other localising signs and symptoms including dysphagia, dysarthria, ataxia, vertigo, nystagmus and hemisensory loss. The most common cause of central Horner syndrome is posterior inferior cerebellar artery (PICA) occlusion. Three quarters of those with PICA territory stroke have Horner syndrome,[25] in addition to other features of the 'lateral medullary syndrome' (which is characterised by sensory deficits affecting the trunk and extremities on the opposite side of the infarct and sensory and motor deficits affecting the face and cranial nerves on the same side with the infarct. Other common findings are ataxia, facial pain, vertigo, nystagmus, diplopia and dysphagia). Horner syndrome can also result from lesions of cervical spinal cord, such as syringomyelia,[26,27] tumour and trauma.[28] Given that pharmacological tests are relatively unhelpful in first-order lesions, CT or MRI of head and neck is mandatory when a central cause is suspected.

SECOND-ORDER NEURON ('PRE-GANGLIONIC')

Tumour of the lung apex is a common and life-threatening presentation of pre-

ganglionic Horner syndrome. It presents classically with Pancoast syndrome, which includes symptoms and signs of ipsilateral Horner syndrome accompanied by persistent shoulder and arm pain and brachial plexus palsy.[29] Unfortunately, the diagnosis of superior pulmonary sulcus tumour is often delayed as many patients are treated for the more common cervical osteoarthritis or shoulder bursitis before the diagnosis is made.[30] Patients suspected of having superior pulmonary sulcus tumour should be referred urgently for medical management with initial work-up including chest X-ray and CT scan of thorax and abdomen. Further investigations at a tertiary referral centre often include MRI scan of neck and thorax because it has superiority over CT scan in showing the involvement of the brachial plexus and subclavian vessels and in evaluating vertebral bodies and the spinal canal for tumour extension.[31,32] Definitive pathological diagnosis is made with image-guided needle biopsy.[33] CT or MRI of the brain is performed prior to treatment because superior pulmonary sulcus tumours have a predilection for cerebral metastasis.[34] Treatment options depend on the individual case but often involve chemoradiotherapy prior to surgery.[35,36]

Other causes of pre-ganglionic Horner syndrome may be iatrogenic and include brachial plexus trauma, recent thoracic or neck surgery,[37] central venous catheterisation[38] and chest tube insertion.[39]

THIRD-ORDER NEURON ('POST-GANGLIONIC')

Carotid artery dissection is one of the most common and most important causes of post-ganglionic Horner syndrome.[5] Stroke is the major concern with carotid artery dissection, which can occur in more than half of these patients.[40] Horner syndrome is present in about 50 per cent of cases of carotid artery dissection.[41] Other symptoms and signs include acute unilateral face or neck pain, amaurosis fugax and cranial nerve palsies.[42,43] Dissection can occur with minor trauma or spontaneously in people with connective tissue disorders or syphilis.[44] The diagnostic gold standard is carotid angiography, which is being replaced by non-invasive imaging techniques, such as duplex ultrasound, MRI of the carotid vessel (to visualise dissection), MRI angiography or CT angiography.[45] The current recommended medical management of carotid dissection involves anticoagulation or antiplatelet medications for three to six months.[46,47] Surgical intervention is often reserved for cases where medical management has failed or there is absolute contraindication to anticoagulation, as the incidence of post-operative stroke is high.[48] Endovascular stenting for acute dissection is being trialled and is showing some promising results.[49]

Another relatively common presentation of post-ganglionic Horner syndrome is in association with cluster headaches (episodic, excruciating unilateral headache, ipsilateral lacrimation, conjunctival injection, rhinorrhoea, and nasal congestion).[50] This condition is benign and can be managed with abortive and preventive medications. Focal neurological symptoms other than Horner syndrome are rare; if present, a more life-threatening diagnosis such as carotid dissection or lesion in the middle cranial fossa should be suspected.[51,52] Indeed, the diagnosis of cluster headache can be made only following the exclusion of carotid artery dissection.

Other causes of post-ganglionic Horner syndrome include carotid artery thrombosis, lesions in the cavernous sinus[53] or the orbit. Horner syndrome with visual loss should raise the suspicion of a space-occupying lesion in the orbital apex. It has been suggested that in complete clinicopathological isolation, third-order lesions require no further investigation.[54]

Paediatric Horner syndrome

Congenital Horner syndrome is usually idiopathic or associated with birth trauma.[55] Other causes such as agenesis of the internal carotid artery[56] are rare and are often symptomatic. Therefore, extensive medical imaging is not recommended in isolated Horner syndrome in the absence of cervical or abdominal masses or cranial nerve palsies,[55] however, in children, Horner syndrome can be a presentation of serious pathology such as neuroblastoma and other tumours.[57,58] Children presenting with Horner syndrome should have head, neck and thoracic MRI as well as measurement of urinary catecholamine levels,[55,59] as the catecholamine vanillylmandelic acid is raised in up to 95 per cent of cases of neuroblastoma.[60,61] Early detection of primary mediastinal neuroblastoma is critical, as the cure rate is approaches 100 per cent when treated in the first year of life.[62]

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