NOSOLOGICAL ENTITIES?

The Tolosa-Hunt syndrome

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Defining the syndrome
The syndrome of painful ophthalmoplegia is one of periorbital or hemicranial pain, combined with ipsilateral ocular motor nerve palsies, oculosympathetic paralysis, and sensory loss in the distribution of the ophthalmic and occasionally the maxillary division of the trigeminal nerve. Various combinations of these cranial nerve palsies may occur, localising the pathological process to the region of the cavernous sinus/superior orbital fissure.

The constellation of findings described may be due to four major causes: trauma, neoplasm, aneurysm, and inflammation. Comprehensive patient evaluation is essential in establishing the correct diagnosis.

Within the last diagnostic category there is a specific subset of patients who develop painful ophthalmoplegia due to a non-specific inflammatory process in the region of the cavernous sinus/superior orbital fissure. Infrequently, they experience involvement of additional cranial nerves ipsilateral to the ophthalmoplegia, including the optic nerve, mandibular branch of the trigeminal nerve, and facial nerve. Having a relapsing and remitting course, they respond promptly to systemic corticosteroids. The authors stated that “The administration of large doses of systemic steroids for 48 hours produces a dramatic response in painful ophthalmoplegia, which allows prompt differentiation of these cases.”

Since these early descriptions of the Tolosa-Hunt syndrome, numerous reports have confirmed these findings. The clinical syndrome has been found in virtually every continent of the world. The non-specific nature of the pathological process has been confirmed, as has the dramatic clinical response to systemic corticosteroids.

However, over the past quarter century there has been no progress in understanding the pathogenesis of Tolosa-Hunt syndrome. In terms of clinical management some new information is available thanks to advances in neuroimaging techniques. Initially, radiological studies of patients with the syndrome yielded normal results, or subtle cerebral angiographic abnormalities. Orbital venography often disclosed abnormalities in filling of the superior ophthalmic vein or cavernous sinus, but these techniques are difficult and therefore

Historical review
Almost 50 years ago Tolosa reported a patient with left orbital pain, ipsilateral progressive visual loss, total left ophthalmoplegia, and reduced sensation over the first division of the trigeminal nerve. Cerebral angiography disclosed narrowing of the intracavernous segment of the left internal carotid artery. Surgical exploration of the left parasellar region was unremarkable, but the patient died 3 days later. At postmortem, granulomatous inflammation of the affected carotid artery and cavernous sinus was found.

Seven years later, Hunt et al defined a clinical entity “of somewhat obscure aetiology” on the basis of six patients. In one patient surgical exploration of the parasellar region showed all structures to be “intact and healthy”. The authors thought that this syndrome of painful ophthalmoplegia was caused by an inflammatory lesion in the cavernous sinus, as described by Tolosa. They characterised it by the following diagnostic criteria:

1. Pain may precede the ophthalmoplegia by several days, or may not appear until some time later. It is not a throbbing hemicrania occurring in paroxysms, but a steady pain behind the eye that is often described as “gnawing” or “boring”.
2. Neurological involvement is not confined to the third cranial nerve, but may include the fourth, sixth, and first division of the fifth cranial nerves. Periarterial sympathetic fibres and the optic nerve may be involved.
3. Symptoms last for days to weeks.
4. Spontaneous remissions occur, sometimes with residual neurological deficit.
5. Attacks recur at intervals of months or years.
6. Exhaustive studies, including angiography and surgical exploration, have produced no evidence of involvement of structures outside of the cavernous sinus. There is no systemic reaction.

In addition, Hunt and coworkers reported the therapeutic efficacy of systemic corticosteroids with prompt, dramatic improvement of signs and symptoms in two patients. In 1966, Smith and Taxdal were the first to apply the eponym “Tolosa-Hunt syndrome” to this entity. They added five additional cases, “because there has been no previous report of this syndrome in the ophthalmology literature and to emphasise the use of steroids as a diagnostic test.”

Within the last diagnostic category there is a specific subset of patients who develop painful ophthalmoplegia due to a non-specific inflammatory process in the region of the cavernous sinus/superior orbital fissure. Infrequently, they experience involvement of additional cranial nerves ipsilateral to the ophthalmoplegia, including the optic nerve, mandibular branch of the trigeminal nerve, and facial nerve. Having a relapsing and remitting course, they respond promptly to systemic corticosteroid therapy. The diagnostic eponym Tolosa-Hunt syndrome has been applied to these patients, and it is this entity which forms the basis of this review.

Defining the syndrome
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Clinical profile of Tolosa-Hunt syndrome

Tolosa-Hunt syndrome can affect people of virtually any age from the 1st to the 8th decades of life, with no sex predilection. Either side may be affected, with case reports of bilateral simultaneous involvement. Uniformly, patients complain of pain, which is a defining symptom. The pain lasts an average of 8 weeks if untreated. Ocular motor cranial nerve palsies may coincide with the onset of pain or follow it within a period of up to 2 weeks. It is usually described as “intense”, “severe”, “boring”, “lancinating”, or “stabbing”. It is periorbital in location, frequently extending into the retro-orbital, frontal, and temporal regions.

All three ocular motor cranial nerves may be involved, in various combinations. Pupillary reactions may be normal, or there may be either parasympathetic (oculomotor nerve) or sympathetic (third order neuron Horner’s syndrome) involvement.

At times, optic nerve dysfunction has been reported with Tolosa-Hunt syndrome, indicating that the pathological process may involve the orbital apex. The optic disc may be normal, swollen, or pale in appearance, and visual decline may be minimal or lead to blindness. Loss of acuity is variable and unpredictable, and, on occasion, may be permanent.

Infrequently, other cranial nerves not located within the cavernous sinus/superior orbital fissure may be affected. These include the maxillary and mandibular branch of the trigeminal nerve, and the facial nerve.

There are no reports of systemic or other neurological involvement in Tolosa-Hunt syndrome, with the exception of nausea and vomiting. These symptoms are probably due to the intense periorbital pain; they promptly resolve with cessation of pain.

Natural history

As Hunt outlined in his diagnostic criteria, Tolosa-Hunt syndrome follows an unpredictable course. Usually acute at onset, the patient’s symptoms typically last from days to weeks. Before the use of systemic corticosteroids there was clear evidence that spontaneous remissions occurred. However, recurrences are common, taking place in about a half of reported patients, usually at an interval of months or years from the initial attack. These recurrences may be ipsilateral, contralateral, or rarely, bilateral.

Although Tolosa-Hunt syndrome is a self limited illness, it does cause considerable morbidity. Infrequently, residual cranial nerve palsies persist. With the institution of corticosteroid therapy, the natural course is altered.

Although there is no conclusive evidence to show that steroids lessen the degree or duration of the ophthalmoplegia, there is dramatic reduction of pain, often within 24 hours.

Diagnostic evaluation

With careful clinical examination, pain associated with typical cranial nerve palsies localises the pathological process to the regions of the cavernous sinus/superior orbital fissure. As noted above, current neuroimaging modalities allow visualisation of the area of suspected pathology. Contrast enhanced MRI with multiple views, particularly coronal sections, should be the initial diagnostic study performed. Numerous reports have demonstrated an area of abnormal soft tissue in the region of the cavernous sinus in most, but not all, patients with Tolosa-Hunt syndrome. Typically, the abnormality is seen as an intermediate signal on T1 and intermediate weighted images, consistent with an inflammatory process. In addition, there is enhancement of the abnormal area after intravenous injection of paramagnetic contrast. With corticosteroid therapy, the abnormal area decreases in volume and signal intensity in most reported cases.

High resolution CT can also demonstrate soft tissue changes in the region of the cavernous sinus/superior orbital fissure, but is less sensitive than MRI. This is due to lack of sensitivity to soft tissue change with superimposed beam hardening and bone streak artifacts. Thus, even if CT is normal, MRI must still be performed to appropriately evaluate the region of the cavernous sinus or superior orbital fissure.

The major limitation of MRI findings in Tolosa-Hunt syndrome is their lack of specificity. Thus, Yousem et al examined 11 patients and reported pathological MRI findings in the cavernous sinus in nine. In six of these nine the affected cavernous sinus was enlarged; in five of nine it had a convex lateral wall. Extension into the orbital apex was seen in eight patients. Yet the signal characteristics (hypointense relative to fat and isointense with muscle on T1 weighted images; isointense with fat on T2 weighted scans) were also consistent with meningioma, lymphoma, and sarcoidosis.

Because of this fundamental limitation of initial imaging studies, some authorities would suggest that resolution of imaging abnormalities after a course of systemic corticosteroids should be considered “diagnostic” of Tolosa-Hunt syndrome. However, caution is advised when assessing the salutary effects of steroids, as improvement both clinically and radiologically may occur with other disease processes. “False positive” steroid responsiveness with a “remitting” course can be seen with both malignant processes (for example, lymphoma) as well as more benign disorders (for example, vasculitis).

Categorically, Tolosa-Hunt syndrome is a diagnosis of exclusion requiring careful patient evaluation (table 1) to rule out tumour, vascular causes, or other forms of inflammation in the region of the cavernous sinus/superior orbit.
The Tolosa-Hunt syndrome

The Tolosa-Hunt syndrome is caused by an inflammatory process. Tolosa-Hunt syndrome is originally described non-specific, chronic inflammation with proliferation of fibroblasts and infiltration of the septa and wall of the cavernous sinus with lymphocytes and plasma cells. Hunt et al corroborated these findings, emphasising the lack of necrosis and pointed out that “...such inflammatory changes, in a tight connective tissue, may exert pressure upon the penetrating nerves.” Subsequent reports have shown granulomatous inflammation, with epithelioid cells and occasional giant cells. Necrosis may also be seen. There have been no reports of an infectious organism associated with Tolosa-Hunt syndrome.

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Aetiology

The aetiology of Tolosa-Hunt syndrome remains unknown. No information is available as to what triggers the inflammatory process in the region of the cavernous sinus/superior orbital fissure. It seems that the syndrome falls within the range of idiopathic orbital inflammation (pseudotumour). Thus, “non-specific” inflammation typically causes an acute orbitopathy. If located more posteriorly, the inflammatory process involves the cavernous sinus/superior orbital fissure, producing the Tolosa-Hunt syndrome. Rarely, the inflammation may spread intracranially.

Differential diagnosis

Because the diagnosis of Tolosa-Hunt syndrome can be made only after other disease processes have been excluded, it behoves the clinician to be familiar with the differential diagnosis of painful ophthalmoplegia. In fact, during the initial patient evaluation there are often no clues in the history or physical examination to distinguish Tolosa-Hunt syndrome from other causes of painful ophthalmoplegia. Therefore, the clinician should be aware of: (1) causes of parasellar syndrome and (2) other entities producing painful ophthalmoplegia.
CAUSES OF PARASELLAR SYNDROME (TABLE 2)

Cranioorbital trauma may produce painful ophthalmoplegia in various ways: basilar skull fracture with ocular motor nerve damage, intracavernous carotid artery injury with subsequent aneurysm formation, or carotid-cavernous fistula.

Various vascular causes may produce painful ophthalmoplegia, the most frequent being an intracavernous carotid artery aneurysm.38 39 Rarely, giant aneurysms of the posterior circulation, including the posterior cerebral artery, may mimic Tolosa-Hunt syndrome.40 Carotid-cavernous fistula, including the posterior cerebral artery, is rarely accompanied by an aneurysm. Carotid-cavernous thrombosis is characterised by orbital congestion, proptosis, eyelid swelling, chemosis, lacrimation, and ophthalmoplegia. Pain around or behind the eye is common. Treatment of cavernous sinus thrombosis usually involves anticoagulant drugs, at times thrombolytic agents, and in septic cases, appropriate antibiotic therapy.

As outlined in table 2, painful ophthalmoplegia may be caused by either contiguous or metastatic spread of a neoplasm. Metastatic involvement of the cavernous sinus/superior orbital fissure is generally due to haematogenous dissemination of neoplastic cells.41 Occasionally, intracranial neoplastic invasion may occur by intraneural or perineural spread, as in the case of squamous cell carcinoma producing painful ophthalmoplegia many months after local excision of a facial skin tumour.42

Two aspects of neoplastic involvement of the cavernous sinus/superior orbital fissure require emphasis. Firstly, it is important to realise that mode of onset and clinical course are not indicative of the type of lesion causing painful ophthalmoplegia. In their review of parasellar syndrome, Thomas and Yoss43 state that “A sudden onset of symptoms does not weigh in favor of aneurysmal or against neoplastic origin, and gradual onset is not necessarily indicative of a neoplasm . . . spontaneous single or multiple remissions of symptoms, even of years duration, are unreliable in predicting the nature of the underlying process.” Secondly, as noted above, high dose corticosteroid therapy may initially improve signs and symptoms due to neoplasm.

Inflammatory causes of painful ophthalmoplegia include those due to a specific infectious agent. It is essential that careful CSF examination be done and that cultures (bacterial, fungal, mycobacterial) be obtained. The potential role of a parasal sinus as a cause of painful ophthalmoplegia requires attention. Sinus disease may lead to cavernous sinus involvement, either via contiguous spread of infection or due to sphenoid sinus mucocoele.

OTHER CAUSES OF PAINFUL OPHTHALMOPLEgia

Table 3 summarises other aetiologies of painful ophthalmoplegia in which there is no involvement of the cavernous sinus/superior orbital fissure.

Various orbital diseases cause painful ophthalmoplegia. Typically, the patient presents with “orbital signs”, including proptosis, conjunctival injection, chemosis, and resistance to retrodisplacement of the globe. In addition, the eye may be displaced within the orbit, and there may be abnormalities of the ocular adnexa (for example, lids, lacrimal gland).

Diabetic ophthalmoplegia typically produces an acute, often painful mononeuropathy in either a known or previously undiagnosed diabetic person. Invariably there is recovery of ocular motor cranial nerve function, usually

### Table 2 Causes of parasellar syndrome producing painful ophthalmoplegia

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|---------------------------|-----------------------------|
| **(1) Trauma:**           |                             |
| (2) Vascular:             |                             |
| Intracavernous carotid artery aneurysm |                 |
| Posterior cerebral artery aneurysm |                 |
| Carotid-cavernous fistula |                             |
| Carotid-cavernous thrombosis |                             |
| **(3) Neoplasm:**     |                             |
| Primary intracranial tumour |                 |
| Pituitary adenoma        |                             |
| Meningioma               |                             |
| Craniopharyngioma        |                             |
| Sarcoma                  |                             |
| Neurofibroma             |                             |
| Gasserian ganglion neurona |                 |
| Epidermoid              |                             |
| Primary cranial tumour   |                             |
| Chordoma                 |                             |
| Chondroma                |                             |
| Giant cell tumour        |                             |
| Local metastases         |                             |
| Nasopharyngeal tumour    |                             |
| Cylindroma               |                             |
| Adamantinoma             |                             |
| Squamous cell carcinoma  |                             |
| Distant metastases       |                             |
| Lymphoma                 |                             |
| Multiple myeloma         |                             |
| Carcinomatous metastases |                             |
| **(4) Inflammation:**    |                             |
| Bacterial                |                             |
| Sinusitis                |                             |
| Mucocele                 |                             |
| Periostitis              |                             |
| Viral                    |                             |
| Herpes zoster            |                             |
| Fungal                   |                             |
| Mucormycosis             |                             |
| Spirochetal              |                             |
| Treponema pallidium      |                             |
| Mycobacterial            |                             |
| Mycobacterium tuberculosis |                             |
| Unknown cause:           |                             |
| Sarcoceiosis             |                             |
| Wegener’s granulomatosis |                             |
| Eosinophilic granuloma   |                             |
| Tolosa-Hunt syndrome     |                             |
within 3 months. In addition, there are reports of diabetic patients with simultaneous paralysis of multiple ocular motor nerves. Frequently, these episodes are painful, often recurrent, and not particularly responsive to corticosteroid therapy.

Posterior fossa aneurysms may produce either acute, painful ophthalmoplegia, or may present in a more subacute or chronic fashion. The acute presentation is most often due to an aneurysm in the anterior circulation, typically at the junction of the internal carotid-posterior communicating arteries, whereas the subacute presentation is caused by basilar artery aneurysms. In both, cerebral angiography is diagnostic.

Giant cell arteritis may also produce painful ophthalmoplegia. The clinical picture may be one of single or multiple ocular motor nerve palsies. In the only pathological study of ophthalmoplegia occurring in giant cell arteritis, ischaemic necrosis of the extraocular muscles was demonstrated. Examination of the oculomotor cranial nerves was unremarkable. Ophthalmoplegic migraine is a poorly understood form of complicated migraine. Typically, this clinical syndrome occurs in a child or young adult with periodic headache, which is primarily unilateral and in the orbital region. Most often involved is the oculomotor nerve, occasionally the abducens nerve, and rarely the trochlear nerve. The paresis lasts for days to weeks after cessation of a headache; recovery is gradual and tends to be less complete after repeated attacks. A family history of migraine is usually obtained. There are reports of enhancement of the extra-axial portion of the oculomotor nerves of patients with ophthalmoplegic migraine when evaluated with contrast-enhanced MRI.

Conclusion
Although the pathogenetic basis of Tolosa-Hunt syndrome remains unknown, from a practical clinical standpoint it can be regarded as a distinct entity which may be simulated by various other disorders. It cannot be emphasized too strongly that patients suspected of having the syndrome require careful evaluation, appropriate treatment, and scrupulous follow up observation.

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Table 3 Additional causes of painful ophthalmoplegia

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<th>Orbital disease:</th>
<th>Idiopathic orbital inflammation (pseudotumour)</th>
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<td>Macromycosis or other fungal infection</td>
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<td>Metastatic tumour</td>
<td>Lymphoma/leukaemia</td>
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<td>Giant cell arteritis:</td>
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2 Tolosa E. Periarterior lesions of the carotid siphon with the clinical features of a carotid infranodular aneurysm. J Neurol Neurosurg Psychiatry 1954;17:300-2.

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