Chapter 53

The Case of the Man with the Painful Eye…!

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Case History:

A 34-year-old man presented to the emergency room (ER) with a right periorbital and frontal headache associated with diplopia. He had been working as a taxi driver and had emigrated from Pakistan 5 years ago.

Five weeks prior to presentation to the ER, symptoms began with the gradual onset of a moderately severe right periorbital and frontal headache. There were no apparent precipitants and he had been active and in good health. There was photophobia, but no nausea, vomiting, or phonophobia. Headaches were not precipitated or aggravated by postural changes, coughing, straining, or Valsalva.

He saw his family physician 5 days after headache onset, physical examination was unremarkable, and he was given a prescription for oral sumatriptan and was referred to a neurologist. He obtained moderate but incomplete and short-lasting relief from sumatriptan. The headache persisted continuously, and he went to the ER on two occasions. In the ER, he had a normal noncontrast head computed tomography (CT) scan, and after meperidine provided moderate relief, he was discharged. Two to 3 weeks after symptom onset, he saw a neurologist. By this time, he had developed a mild right ptosis. There were no accompanying autonomic features —no tearing, conjunctival injection, rhinnorhea, nasal stuffiness, or eyelid edema. He was diagnosed with "cluster migraine" and was started on prophylaxis with methysergide. His prescription for sumatriptan was renewed.

During the following 2 weeks, the headache persisted, the ptosis worsened, and he developed horizontal and vertical diplopia. His life was now in disarray. He was unable to sleep because of the pain. He was enduring financial hardship as he could no longer work as a taxi driver due to the headache and double vision. He had spent in excess of $1,000 (CDN) on medications. He sought advice from a chiropractor and a naturopath. On the day of presentation to the hospital, he was seen by an ophthalmologist who sent him directly to the ER.

Past medical history was remarkable for two previous periods of significant headache. Seven years ago in Pakistan, he experienced a 10- to 14-day period of continuous moderately severe right periorbital and frontal headache. This headache was similar in character to his current headache, but was less intense, and there were no associated neurologic symptoms. He was diagnosed with migraine and given "antimigraine" medications. His symptoms did not recur until 4 years later. By this time, he had completed a master's in mathematics, moved to Canada, and was working in computers. Again, he gradually developed a moderately severe right-sided pain. His pain was refractory to over-the-counter analgesics. He had difficulty concentrating and sleeping. His family physician diagnosed migraine, started amitriptyline, and referred him to a neurologist. He saw the neurologist 2 to 3 weeks into the headache period. By this time, he had mild ptosis, and a diagnosis of "cluster migraine" was given. Nadolol was added and sumatriptan prescribed. His symptoms worsened, he developed more ptosis as well as diplopia, and was unable to work. By 5 to 6 weeks, his headache had improved, and by 2 months, his vision was normal. A noncontrast CT scan, performed 2 months after headache onset, was normal. He had attributed his daily headaches to job-related stress and eyestrain, and consequently, he quit his computer job.

Family history was noncontributory except for migraine in his mother. He was a nonsmoker, and did not consume alcohol or illicit drugs.

On examination, he appeared uncomfortable and was photophobic. He was afebrile, and heart rate and blood

pressure were normal. Cervical spine was normal and there was no lymphadenopathy. There were no vascular bruits about the head, neck, or orbits, and no proptosis or chemosis. Mental status was normal. On cranial nerve examination, visual acuity was 20/25 bilaterally and visual fields were full to confrontation. The right pupil was 4 mm, left pupil 5 mm, and both were reactive to light. There was no relative afferent pupillary defect. Fundoscopic examination was normal. There was a near-complete right ptosis and right ophthalmoplegia with ductions restricted to less than 30% in all directions. There was mild decrease to light touch and pin prick, and temperature sensation in the ophthalmic division of the right trigeminal nerve. The remainder of the standard neurologic examination was unremarkable.

The patient was admitted to hospital for investigation and treatment.

Questions on the Case

Please read the questions, try to answer them, and reflect on your answers before reading the authors' discussion.

- What is the differential diagnosis of painful ophthalmoplegia?
- What laboratory tests should be ordered?
- What imaging investigations should be ordered?
- What is the most appropriate treatment strategy and follow-up plan?

Case Discussion

Painful ophthalmoplegia typically refers to periorbital or hemicranial pain plus any combination of ipsilateral ocular motor nerve palsies, oculosympathetic paralysis (Horner's syndrome), or sensory loss in the distribution of the ophthalmic and occasionally the maxillary divisions of the trigeminal nerve. The cavernous sinus and superior orbital fissure are the only anatomic locations where the ocular motor nerves, first division of the trigeminal nerve, and internal carotid artery coexist. Pain and impairment in ocular motility can also arise from orbital lesions. The etiologic differential diagnosis of painful ophthalmoplegia is extensive and includes numerous sinister etiologies (Table 53-1). The major categories are vascular (eg, aneurysm, carotid dissection, carotid-cavernous fistula), neoplasms (eg, primary intracranial tumors, local or distant metastases), inflammatory conditions (eg, orbital pseudotumor, sarcoidosis, and Tolosa-Hunt syndrome), trauma and infectious etiologies (eg, fungal, mycobacterial, bacterial), and other conditions (eg, microvascular infarcts secondary to diabetes, ophthalmoplegic migraine).

Table 53-1. Differential Diagnosis of Painful Ophthalmoplegia

Vascular
Intracavernous-carotid artery aneurysm
Carotid-cavernous fistula
Carotid dissection
Carotid-cavernous thrombosis
Cavernous angioma
Large posterior cerebral, posterior communicating, or basilar artery aneurysms
Neoplastic
Primary intracranial/cranial tumors
Pituitary adenomas
Meningiomas
Craniopharyngioma
Epidermoid
Chordoma
Chondrosarcoma
Local or distant metastases
Lymphoma
Squamous cell carcinoma
Nasopharyngeal tumors
Carcinomatous metastases
Inflammatory
Giant cell arteritis
Sarcoidosis
Tolosa-Hunt syndrome
Orbital pseudotumor
Thyroid ophthalmopathy
Wegener's granulomatosis
Idiopathic hypertrophic pachymeningitis
Infectious
Fungal (mucormycosis, actinomycosis)
Mycobacterial (tuberculosis)
Bacterial (extension from sinusitis, cellulitis, otitis, mastoiditis, dental abscess)
Other
Trauma
Diabetic mononeuropathy or multiple cranial neuropathies
Ophthalmoplegic migraine

Clues on history and examination allow the clinician to focus the differential diagnosis and guide investigations. In the present case, the patient's previous headache episodes could be related or unrelated to his current presentation. The benign outcome of his previous episodes suggest the possibility of a relapsing disorder such as Tolosa-Hunt syndrome, but may be falsely reassuring, and this presentation of painful ophthalmoplegia warrants investigation to rule out sinister etiologies.

Aneurysms are the most common vascular cause and typically involve intracavernous carotid aneurysms and posterior communicating-artery aneurysms. Presentation is typically slowly progressive, but aneurysms may present acutely with rupture or with rapid expansion secondary to aneurysm thromboses. The pain arises from pressing on the trigeminal nerve, stretching of the vessel wall, and/or by leaking into the adjacent subarachnoid space; ocular symp-

toms are due to direct compression of the oculomotor nerves. Importantly, neuro-ophthalmologic symptoms and/or retro-orbital pain may be the only indication(s) of an aneurysm prior to rupture.

Pain occurs in up to 90% of patients with internal carotid artery dissections, and may occur maximally in the neck, face, or head. Ophthalmologic symptoms or signs are present in up to two-thirds of patients with extracranial internal carotid artery dissection. A painful Horner's syndrome is the most common presentation, but ophthalmoplegia can develop secondary to ischemia.

Carotid-cavernous fistulas are due to abnormal communication between the carotid artery and the venous plexus of the cavernous sinus. There are two types of carotid-cavernous fistulas: high-flow and low-flow. The more dramatic high-flow fistulas are typically secondary to trauma, or are iatrogenic and present acutely with pain, proptosis chemosis, and ophthalmoplegia due to venous congestion. The more subtle low-flow fistulas develop spontaneously in older women, during pregnancy, or in those with hyperelastic tissues, and typically present slowly with less pronounced symptoms. Magnetic resonance angiography (MRA) or conventional angiography are the diagnostic procedures of choice and neurovascular interventional procedures can be curative.

Cavernous sinus thrombosis is a rare condition that is typically associated with preceding or coexisting sinusitis, otitis, mastoiditis, orbital cellulitis, or dental infections. It is usually septic in origin, but may be aseptic. Aseptic causes include hypercoagulable or hyperviscosity states, pregnancy, dehydration, trauma, and intracranial surgery. Symptoms are often dramatic, and clinical clues include fever, localized infectious symptomatology, proptosis, chemosis, eyelid edema, and orbital congestion. Cavernous sinus thrombosis can be lethal, and a high index of suspicion is necessary because immediate antibiotic and/or anticoagulant therapy may be life saving.

Neoplastic disease can result in painful ophthalmoplegia via direct compression, perineural, or hematogenous spread. History and physical examination should look meticulously for evidence of previous or current head and neck malignancies; the possibility of distant metastases from melanoma, breast, prostate, or lung cancer should also be considered. Importantly, painful ophthalmoplegia can be the presenting symptom of a systemic malignancy. Visual impairment suggests a parasellar lesion such as a pituitary adenoma, craniopharyngioma, or meningioma. A prolactin level can be a useful screen for a pituitary adenoma, especially if there is any evidence of neuroendocrine dysfunction. The presentation of neoplastic disease may be diagnostically challenging for several reasons: 1) while malignancies typically present in a subacute or chronic manner, the presentation can be acute; 2) while a progressive course is the norm, spontaneous remissions may occur (eg, with lymphoma); and 3) while steroid responsiveness is suggestive of inflammatory conditions, neoplastic-associated symptoms may be steroid responsive due to perilesional edema or specific lesion characteristics (eg, lymphoma).

Sarcoidosis is most prevalent in African Americans and occurs most often in individuals aged 20 to 40 years. While sarcoidosis may be asymptomatic, it is suggested by a history of constitutional and/or respiratory symptoms (dyspnea, cough), skin changes (lupus pernio, erythema nodosum), lymphadenopathy, ocular symptoms (uveitis), and/or other neurologic symptoms (facial palsy, optic neuropathy, diabetes insipidus). Wegener's granulomatosis is most common in the fifth decade, in men, and in whites. Constitutional, upper respiratory tract (sinusitis, ulceration, epistaxis), and lower respiratory tract (cough, hemoptysis) symptoms are common. Giant cell arteritis occasionally presents with painful ophthalmoplegia (up to 6%); however, visual loss or amaurosis fugax are far more common accompanying symptoms.

Tolosa-Hunt syndrome, orbital pseudotumor, and idiopathic hypertrophic pachymeningitis are idiopathic inflammatory disorders without associated systemic or constitutional symptoms and are considered diagnoses of exclusion. Patients with orbital pseudotumor often have proptosis, eyelid edema, conjunctival injection, chemosis, and increased pain with eye movement.

Patients with Grave's ophthalmopathy can develop limitation of eye movement with or without proptosis; however, pain typically is not a prominent feature.

Fungal infections (eg, mucormycosis) should be considered in diabetic, immunosuppressed, or immunocompromised patients. Tuberculosis should be considered in patients who have emigrated from or traveled to endemic areas.

Ophthalmoplegic migraine is an uncommon disorder that typically occurs in childhood or adolescence. Attacks of ophthalmoplegic migraine begin with a severe migraine, followed hours to days later by ophthalmoplegia, lasting days to weeks (long after resolution of the headache). Diabetic ophthalmoplegia typically presents as an acute painful oculomotor mononeuropathy; however, there are rare case reports of simultaneous paralysis of more than one oculomotor nerve in diabetics.

Management Strategies

- The patient had normal bloodwork, including complete blood count, glucose, electrolytes, liver and renal function, hemoglobin (Hb)A_{1c}, antinuclear antibodies (ANA), angiotensin-converting enzyme (ACE), c-antineutrophil cytoplasmic antibody (c-ANCA),

serum protein electrophoresis, C-reactive protein, and erythrocyte sedimentation rate (ESR).
- Tests showed normal cerebrospinal fluid (CSF): acellular, normal protein and glucose; negative bacterial, fungal, and mycobacterial cultures; and negative cytology.
- Magnetic resonance imaging (MRI) with orbital and cavernous sinus views demonstrated a soft tissue abnormality in the right cavernous sinus, with the outer dural margin being convex and bulging laterally. The abnormal soft tissue lesion was isointense to gray matter on T1-weighted sequences, and isointense to mildly hypointense to gray matter on T2-weighted sequences. The abnormality enhanced intensely following gadolinium administration. The intracavernous potion of the internal carotid artery was mildly narrowed in caliber; MRA did not disclose an aneurysm or other vascular etiology.
- The neuroimaging differential diagnosis included lymphoma, meningioma, sarcoidosis, and Tolosa-Hunt syndrome.
- CT scan of the pelvis, abdomen, and thorax was normal (no evidence of lymphoma or sarcoidosis).
- The clinical history combined with the neuroimaging features favoured a diagnosis of Tolosa-Hunt syndrome.
- Treatment with prednisone was initiated at 80 mg daily. There was significant improvement in the headache within 48 hours and moderate improvement in ptosis and extraocular motility by 1 week.
- At 10 days, a repeat MRI demonstrated moderate decrease in the soft tissue lesion. Steroids were tapered by 10 mg every 10 days. At 4 weeks, his headache had resolved, ptosis was minimal, and diplopia was significantly improved. At 8 weeks, he was asymptomatic with a normal examination. Repeat MRI at 3 months was normal.

Case Summary

- This patient has Tolosa-Hunt syndrome.
- He experienced attacks of painful ophthalmoplegia separated by 4 years without systemic or constitutional symptoms.
- Failure to diagnose his symptoms early in the course of the illness resulted in significant morbidity, and financial and occupational consequences.
- MRI with gadolinium demonstrated characteristic changes seen in Tolosa-Hunt syndrome, but it could also be compatible with other conditions (lymphoma, meningioma, sarcoidosis).
- Treatment with corticosteroids resulted in dramatic improvement.
- Careful follow-up clinically and with serial MRI was critical to ensure correct diagnosis.

Overview of Tolosa-Hunt Syndrome

In 1954, Tolosa described a patient with unilateral orbital pain, ophthalmoplegia, reduced sensation in the first division of the trigeminal nerve, and ipsilateral visual change. Surgical exploration was unremarkable, but the patient died postoperatively. At postmortem, granulomatous inflammation of the affected cavernous sinus and carotid artery were noted. In 1961, Hunt described six similar patients. Hunt proposed that this syndrome of painful ophthalmoplegia was caused by inflammation within the cavernous sinus and he proposed the following diagnostic criteria:

- Pain typically precedes the ophthalmoplegia by several days, or may not appear until some time later. It is a steady pain behind the eye that is often described as "gnawing" or "boring."
- Neurologic impairment can occur in the IIIrd, IVth, VIth, and ophthalmic division of the Vth cranial nerves. Periarterial sympathetic fibers and the optic nerve may be involved.
- Symptoms last for days to weeks.
- Spontaneous remissions occur, but may leave residual neurologic deficit.
- Attacks may recur at intervals of months or years.
- Exhaustive studies, including angiography and surgery, reveal no involvement outside the cavernous sinus.

Hunt and colleagues also underscored the efficacy of corticosteroids. In 1966, Smith and Taxdal coined the term "Tolosa-Hunt syndrome." The 2004 International Headache Society diagnostic criteria for Tolosa-Hunt syndrome are relatively unchanged from the original descriptions (Table 53-2).

Tolosa-Hunt syndrome can present at any age in any ethnic group, and there is no sex predilection. Affected individuals are usually otherwise healthy without systemic or constitutional symptoms. The pain is typically periorbital, but may be retro-orbital, frontal, or temporal. It is typically intense and may be described as "boring" or "stabbing." Untreated, it usually lasts 8 weeks. Neurologic involvement either occurs concurrently or begins within 2 weeks of headache onset. All three ocular motor nerves and the ophthalmic division of the trigeminal nerve may be involved, in various combinations. A Horner's syndrome may be present. Optic nerve dysfunction is uncommon, but has been reported when the pathologic process extends out of the cavernous sinus and into the orbital apex. Case reports document involvement of the maxillary and mandibular divisions of the trigeminal nerve as well as the facial and auditory nerves.

Table 53-2 2004 International Headache Society Diagnostic Criteria for Tolosa-Hunt Syndrome (13.16)

Description:
Episodic orbital pain associated with paralysis of one or more of the IIIrd, IVth, or VIth cranial nerves, which usually resolves spontaneously but tends to relapse and remit.

Diagnostic criteria:
A. Episode or episodes of unilateral orbital pain persisting for some weeks if untreated
B. Paresis of one or more of the IIIrd, IVth, or VIth cranial nerves and/or demonstration of granuloma by magnetic resonance imaging or biopsy
C. Paresis coincides with the onset of the pain or follows it within 2 weeks
D. Resolves within 72 hours when treated adequately with corticosteroids
E. Other causative lesions have been excluded by appropriate investigations

Comment:
Some reported cases of Tolosa-Hunt syndrome had additional involvement of the trigeminal nerve (commonly the first division) or optic, facial, or acoustic nerves. Sympathetic innervation of the pupil is occasionally affected. The syndrome has been caused by granulomatous material in the cavernous sinus, superior orbital fissure, or orbit in some biopsied cases. Careful follow-up is required to exclude other causes of painful ophthalmoplegia such as tumors, vasculitis, basal meningitis, sarcoidosis, diabetes mellitus, or ophthalmoplegic "migraine."

Adapted from Headache Classification Subcommittee of the International Headache Society, 2004.

Tolosa-Hunt syndrome is caused by an inflammatory process. Tolosa described "nonspecific, chronic inflammation" of the cavernous sinus, and subsequent reports have shown granulomatous inflammation. The etiology of Tolosa-Hunt syndrome is very poorly understood and many questions exist: what is the etiology of Tolosa-Hunt syndrome, what triggers individual attacks and recurrences, and why the predilection for the cavernous sinus? Some argue that Tolosa-Hunt syndrome and orbital pseudotumor represent different anatomic locations of the same disease process.

Tolosa-Hunt syndrome is the correct diagnosis in a small minority of patients with painful ophthalmoplegia. It remains a diagnosis of exclusion, and the clinician must eliminate trauma, vascular, primary and metastatic neoplasms, inflammatory and infectious diseases, diabetes, and ophthalmoplegic migraine as potential etiologies (see Table 53-1). Work-up includes detailed history and careful physical examination (paying attention to lymphadenopathy and skin changes of sarcoidosis or tuberculosis). Routine bloodwork is typically normal. Inflammatory markers such as ESR and C-reactive protein are often normal, but may be elevated. Secondary causes should be sought with specific serologic tests: ACE (sarcoidosis), c-ANCA (Wegener's granulomatosis), ANA, anti-dsDNA (lupus), fasting blood sugar or HbA_{1c} (diabetes). CSF in Tolosa-Hunt syndrome is typically normal, but should be sent to screen for infectious (fungal, mycobacterial, bacterial) or neoplastic (lymphoma or metastases) causes.

Unenhanced CT often is normal in Tolosa-Hunt syndrome, although a high-resolution, contrast-enhanced scan may demonstrate characteristic changes. A gadolinium-enhanced MRI is the imaging modality of choice and should be performed in all patients with painful ophthalmoplegia. In Tolosa-Hunt syndrome, MRI typically reveals an abnormality of the affected cavernous sinus, with the dural margin being convex and the abnormal tissue isointense with gray matter on T1-weighted images, and isointense to slightly hypointense on T2-weighted sequences. The abnormal tissue markedly enhances with contrast administration. The MRI may show focal narrowing of the intracavernous portion of the internal carotid artery. The abnormality may extend into the ipsilateral orbital apex, sphenoid sinus, and middle cranial fossa. It is important to remember that meningiomas, lymphoma, and sarcoidosis may display similar MRI characteristics to those seen in Tolosa-Hunt syndrome.

Consultation with a neuroradiologist is advisable. MRA or conventional angiography may be required to exclude an aneurysm or other vascular anomaly. Cakirer evaluated 23 clinically suspected cases of Tolosa-Hunt syndrome with MRI and found alternative pathologies in 15 of these patients (4 meningiomas, 3 pituitary macroadenomas, 3 leptomeningeal metastases, 2 idiopathic hypertrophic pachymeningitis, 1 aneurysm, 1 epidermoid, 1 neurinoma). Serial neuroimaging follow-up documenting resolution of the lesion is critical for the accurate diagnosis of Tolosa-Hunt syndrome.

Biopsy is not indicated in most cases, but should be considered (by experienced neurosurgeons) in patients with rapidly progressive neurologic impairment, high risk for malignant diseases, lack of steroid responsiveness, or unusual or persistent changes on MRI.

Corticosteroids are the treatment of choice. The pain in Tolosa-Hunt syndrome is exquisitely responsive to steroids. It is unknown whether corticosteroids hasten the recovery of cranial nerve impairment or improve their ultimate recovery. No studies have defined the optimal dose or duration of treatment. Most headache experts utilize high-dose steroids (1 mg/kg) and taper slowly over 3 to 4 months. Longer tapers may be required. As a positive response to steroids is occasionally seen with parasellar/cavernous sinus neoplastic lesions, serial MRI is important to document resolution of the lesion.

Selected Readings

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Editorial Comments

Eponymic neurologic disorders can be specific diseases or anatomic lesions. However, Tolosa-Hunt syndrome is a syndrome in the true sense of the word, in that it is a collection of symptoms and signs that could be due to many etiologies; however, ultimately, it is felt to be an inflammatory process. What challenges the headache doctor is the spectrum of causes for painful ophthalmoplegias, and the need to consider all etiologies in assessing any particular patient. The authors recommend the help of a neuroradiologist in such cases; however, the help of an experienced neurophthalmologist or ophthalmologist is also vital. Once diagnosed, treatment is usually successful in most patients, but recurrence does occur and patients must be monitored and followed. Enjoy this chapter, as it is superbly written and the best of clinical neurology!

Final diagnosis:

Painful ophthalmoplegia or Tolosa-Hunt syndrome