Pearls & Oy-sters: Idiopathic Orbital Inflammation and Tolosa-Hunt Syndrome With Intracranial Extension

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Editorial
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Page 337

Pearls

- Tolosa-Hunt syndrome (THS) is characterized by steroid-responsive painful ophthalmoplegia from idiopathic granulomatous inflammation of the cavernous sinus, superior orbital fissure, or orbit.
- THS falls under the idiopathic orbital inflammatory (IOI) diseases, which also includes orbital pseudotumor.
- Visual impairment distinguishes lesions of the orbital apex (optic nerve involvement) from the cavernous sinus.

Oy-sters

- THS has diagnostic criteria but is a diagnosis of exclusion; an extensive workup is required for the wide differential diagnosis of painful ophthalmoplegia.
- Steroid-responsiveness is not specific to THS, and patients require long-term monitoring and imaging to ensure remission.
- Intracranial extension is rare but may occur in THS and IOI.

Case Report

A 37-year-old otherwise healthy man developed gradually progressive, nonthrobbing, fairly constant left-sided temporal and orbital pain over 4 weeks. He did not have any photophobia, phonophobia, nausea, or vomiting, and there were no cranial autonomic symptoms such as conjunctival injection, tearing, nasal congestion, rhinorrhea, or aural pressure. He was initially seen at a local community clinic and treated with naproxen, amoxicillin, and clavulinic acid for presumed sinusitis without fever. Despite completing 7 days of antibiotics, he noticed progressive left eye pain and periorbital swelling, followed 2 weeks later by binocular oblique diplopia in all directions of gaze, so he presented to the emergency department. He reported no vision loss or other focal neurologic symptoms. There were no systemic symptoms or fever. He was initially treated empirically with intravenous antibiotics for the possibility of orbital cellulitis at a community hospital and transferred to our center for further investigation.

On examination, he was afebrile with normal vital signs and no nuchal rigidity. He was alert and oriented, and mental status was unremarkable. There was 4 mm of left-sided proptosis (measured using Hertel lenses, right eye [OD] 21 mm vs left eye [OS] 25 mm on a base of 100 mm), which was nonpulsatile with no conjunctival injection or ocular bruit. Visual acuity was 20/20 OD and 20/30 OS. Color vision was equal in both eyes with no subjective red desaturation. Confrontational visual fields were full. Fundoscopy revealed normal appearing optic discs. Left eye was hypertropic with near-complete left ophthalmoplegia in all directions of gaze and normal right eye ductions (Figure 1). Pupils showed anisocoria, measuring 3 mm OD and 5 mm OS in the light, dilating to 6 mm OD and 8 mm OS in the dark (likely physiologic anisocoria, given no parasympathetic failure), with a subtle left afferent pupillary defect. On

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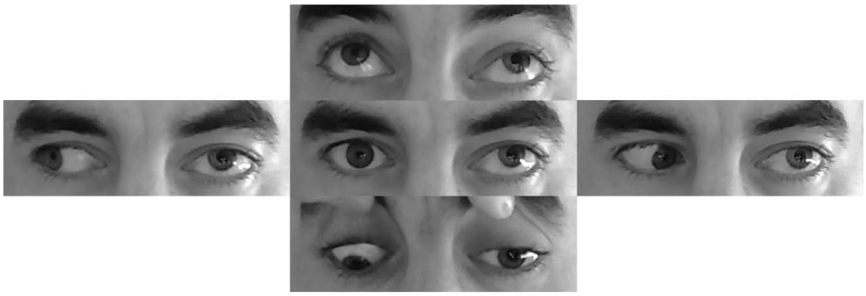
Figure 1 Examination of Eye Movements



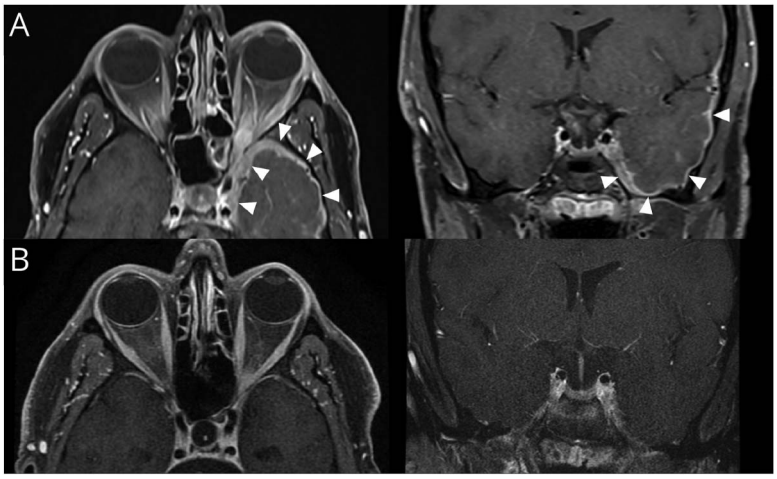
Examination of eye movements shows left proptosis, hypertropia, and mild exotropia and near complete left ophthalmoplegia with normal right eye movements.

facial sensory testing, he reported reduction to pinprick over the left forehead in a V_1 distribution, otherwise normal. Corneal reflexes were present bilaterally. Facial strength was full. Tongue and uvula were midline. The remainder of the examination was noncontributory—he had normal strength, reflexes, sensation, and coordination in the extremities. Collectively, his examination was consistent with a left orbital apex syndrome based on the presence of unilateral optic neuropathy along with cranial nerve III, IV, V1, and VI involvement and proptosis.

MRI showed enhancement of the extraocular muscles, orbital apex, cavernous sinus, and left temporal leptomeninges (Figure 2A). Initial blood work showed no systemic infectious, inflammatory, or malignant disease. Blood cell count and C-reactive protein were within normal range. TSH receptor antibody and antithyroperoxidase antibody showed negative results. Angiotensin-converting enzyme, autoimmune antibodies (antinuclear antibody, proteinase 3 antineutrophil cytoplasmic antibody, and myeloperoxidase-antineutrophil cytoplasmic antibody), and serum complement levels showed negative results. He had a normal serum electrophoresis panel with no monoclonal bands and normal immunoglobulin and immunoglobulin (Ig) G subclass panels (including IgG4 level). HIV and syphilis serologies showed negative results. CSF analysis showed 11 white blood cells/μL (91% lymphocytic, no malignant cells, normal flow cytometry; ref 0–5), protein 0.82 g/L (ref 0.15–0.45), glucose 3.0 mmol/L (ref 2.3–4.1), and angiotensin-converting enzyme 3 U/L (ref 0–3.1). CT chest, abdomen, and pelvis showed negative results for malignancy, fibrosis, or lymphadenopathy, and Gallium scan did not show scintigraphic evidence of sarcoidosis.

Neurosurgical exploration was believed to be too invasive, and instead, a left lateral rectus and orbital fat pad biopsy was pursued, which revealed nonspecific inflammatory changes and moderate chronic inflammation, showing negative results for malignancy, vasculitis, or IgG4-related disease. While in hospital, his visual acuity declined to 20/200 OS, so he was treated empirically with 1 g of IV pulse methylprednisolone

Figure 2 MRI Orbits



(A) Contrast MRI showing enhancement of the left lateral rectus muscle and orbital apex tracking posteriorly to the cavernous sinus with intracranial dural extension to the left middle cranial fossa (arrowheads). (B) Contrast MRI 6 months later, following high-dose corticosteroids with slow taper, shows a complete resolution of enhancement and left lateral rectus enlargement.

Table Diagnostic Criteria for Tolosa-Hunt Syndrome (THS)

IHS criteria (2004) Section 13.16[2]	IHS classification ICHD-3 13.8[3]
A. One or more episodes of unilateral orbital pain persisting for weeks if untreated B. Paresis of one or more of the third, fourth, and/or sixth cranial nerves and/or demonstration of granuloma by MRI or biopsy C. Paresis coincides with the onset of pain or follows it within 2 wk D. Pain and paresis resolve within 72 h when treated adequately with corticosteroids E. Other causes have been excluded by appropriate investigations	A. Unilateral orbital or periorbital headache fulfilling criterion C B. Both of the following: a. granulomatous inflammation of the cavernous sinus, superior orbital fissure, or orbit, demonstrated by MRI or biopsy b. paresis of one or more of the ipsilateral IIIrd, IVth, and/or VIth cranial nerves C. Evidence of causation demonstrated by both of the following: a. headache is ipsilateral to the granulomatous inflammation b. headache has preceded paresis of the IIIrd, IVth, and/or VIth nerves by ≤2 wk or developed with it D. Not better accounted for by another ICHD-3 diagnosis

Abbreviations: *ICHD-3 = International Classification of Headache Disorders, Third Edition*; IHS = International Headache Society.

daily for 5 days, followed by 60 mg of oral prednisone daily. His pain resolved, and he had gradual improvement clinically and radiologically (Figure 2B). At 1 month, proptosis and relative afferent pupillary defect had resolved with persistent anisocoria. Visual acuity was 20/20 OD and 20/60 OS, and his extraocular movements were full in the vertical range, slightly limited by 5% in abduction and adduction. Prednisone was slowly tapered over 2 months. At 24 months, he remained symptom-free with 20/20 vision in both eyes and mild residual exodeviation measuring 2 prism diopters in right gaze.

Discussion

THS is characterized by steroid-responsive painful ophthalmoplegia from idiopathic granulomatous inflammation of the cavernous sinus, superior orbital fissure, or orbit, with accompanying cranial nerve palsies.[1-3] The ocular motor cranial nerves (III, IV, and VI), optic nerve (II), and infrequently other cranial nerves (V, VII) or sympathetic innervation of the pupil may be involved.[1-3] While THS has distinct diagnostic criteria[2,3] (Table), it remains a syndromic diagnosis and, along with orbital pseudotumor, exists on a larger spectrum of IOI diseases. There have been significant advances in diagnostic evaluation (e.g., MRI) and discovery of previously unrecognized etiologies (e.g., IgG4-related disease) since the initial description of THS.[4] The differential diagnosis of painful ophthalmoplegia is broad and can be classified into 4 major categories of trauma, neoplasm, vascular, or inflammatory. An extensive workup is required to exclude other etiologies before diagnosing THS,[1-3] and long-term clinical monitoring is required to ensure remission and exclude alternative diagnosis.

Intracranial extension in IOI is rare, 8.8% in a CT series,[5] and even more uncommon in THS. Inflammation extends through the superior orbital fissure, optic canal, or inferior orbital fissure. In the CT series, the majority presented with cranial nerve palsies of III, IV, and VI, in addition to pain, proptosis, and vision loss, with a mean duration of symptoms for 25 months before CT. Four of the 6 studied patients with intracranial extension had poor response to steroids. Although dural enhancement is seen infrequently on neuroimaging, leptomeningeal enhancement on imaging is exceedingly rare in THS and raises suspicion for other processes including metastases, lymphoma, sarcoidosis, and infection.

The major limitation of MRI in IOI and THS is the nonspecificity and variability of findings.[6] Systemic disease such as IgG4-related disease, granulomatosis with polyangiitis, polyarteritis nodosa, and sarcoidosis may present with a similar clinical picture of noninfectious orbital inflammation.[4,7] Neurosurgical biopsy may be necessary for confirmation of disease, although in some cases, ophthalmology and/or oculoplastic surgery may also be helpful in obtaining tissue diagnosis. However, histopathologic findings may show granulomatous inflammation that can be nonspecific.[1-3] In our case, ophthalmology and oculoplastic surgery were involved for less invasive tissue sampling. Raised protein and white cell count have been reported on CSF examination, but analysis should be generally unremarkable.[1-3] If CSF abnormalities persist, further diagnostic evaluations are required to exclude other diagnoses.

High doses of corticosteroids are effective in treating IOI and THS, but recurrence and chronicity may develop,[8] so long-term monitoring is needed to ensure remission. Although pain improves rapidly with steroids, the course of THS is generally considered to be self-limited, and there is no conclusive evidence that treatment alters the extent or duration of ophthalmoplegia.[9] There are currently no evidence-based recommendations on the dose or duration of steroid therapy,[7,10] so treatment is largely guided by the clinical evaluation of response. Given significant morbidity associated with vision loss, optic nerve involvement often warrants more urgent treatment with high-dose corticosteroids. In refractory cases, radiotherapy or immunosuppressants may be considered.[10]

As a diagnosis of exclusion, THS may become less common as more specific etiologies are defined. However, diagnostic

criteria remain helpful to otherwise characterize those without definitive diagnosis. While atypical features should raise suspicion for alternative diagnoses and further investigation, intracranial extension may occur as a part of THS.

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Tychicus Chen, MD, FRCPC	Division of Neurology, Faculty of Medicine, University of British Columbia, Vancouver, Canada	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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