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

Author(s):
Sabrina Yu, MD¹; Tychicus Chen, MD, FRCPC²

Corresponding Author:
Tychicus Chen, tychicus@mail.ubc.ca

Affiliation Information for All Authors: 1. Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, Canada; 2. Division of Neurology, Faculty of Medicine, University of British Columbia, Vancouver, Canada

Equal Author Contribution:

Contributions:
Sabrina Yu: Drafting/revision of the manuscript for content, including medical writing for content
Tychicus Chen: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Figure Count: 2

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

Copyright © 2023 American Academy of Neurology. Unauthorized reproduction of this article is prohibited
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

Oysters
● THS has diagnostic criteria but is a diagnosis of exclusion; extensive work-up 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, non-throbbing, 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 clavulanic 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 and so he presented to the emergency department. He reported no vision loss or other focal neurological 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, oriented, and mental status was unremarkable. There was 4 mm of left-sided proptosis (measured using Hertel lenses, OD 21mm vs OS 25mm on a base of 100mm) which was non-pulsatile 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 3mm OD and 5mm OS in the light, dilating to 6mm OD and 8mm OS in the dark, with a subtle left afferent pupillary defect (likely physiologic anisocoria given no parasympathetic failure). On facial sensory testing he reported reduction to pin prick over the left forehead in a V1 distribution, otherwise normal. Corneal reflexes were present bilaterally. Facial strength was full. Tongue and uvula were midline. The remainder of the examination was non-contributory – 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 bloodwork showed no systemic infectious, inflammatory, or malignant disease. Blood cell count and C-reactive protein were within normal range. TSH receptor antibody and anti-thyroperoxidase antibody were negative. Angiotensin-converting enzyme (ACE), autoimmune antibodies (ANA, pr-3 ANCA, MPO-ANCA), and serum complement levels were negative. He had a normal serum electrophoresis panel with no monoclonal bands, and normal immunoglobulin and IgG subclass panels (including IgG4 level). HIV and syphilis serologies were negative. Cerebrospinal fluid (CSF) analysis showed 11 WBC/uL (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 was negative for malignancy, fibrosis or lymphadenopathy, and Gallium scan did not show scintigraphic evidence of sarcoidosis.

Neurosurgical exploration was felt to be too invasive and instead a left lateral rectus and orbital fat pad biopsy was pursued which revealed non-specific inflammatory changes, moderate chronic inflammation, negative for malignancy, vasculitis, or IgG4-related disease. While in hospital his visual acuity declined to 20/200 OS and so he was treated empirically with IV pulse methylprednisolone 1 gm daily for 5 days, followed by oral prednisone 60 mg 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

Tolosa-Hunt syndrome (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. The ocular motor cranial nerves (III, IV, VI), optic nerve (II), and...
infrequently other cranial nerves (V, VII) or sympathetic innervation of the pupil may be involved\(^1\). 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 idiopathic orbital inflammatory (IOI) diseases. There have been significant advances in diagnostic evaluation (eg. MRI) and discovery of previously unrecognized etiologies (eg. IgG4-related disease) since the initial description of THS\(^4\). The differential diagnosis of painful ophthalmoplegia is broad and can be classified into four major categories of trauma, neoplasm, vascular, or inflammatory. An extensive workup is required to exclude other etiologies before diagnosing THS\(^1\-3\), as well as long-term clinical monitoring 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, VI, in addition to pain, proptosis, and vision loss, with a mean duration of symptoms for 25 months prior to CT. Four of the six 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 non-specificity and variability of findings\(^6\). Systemic disease like 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 histopathological findings may show granulomatous inflammation that can be non-specific\(^1\-3\). 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\(^8\), and 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. There are currently no evidence-based recommendations on dose or duration of steroid therapy, so treatment is largely guided by 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.

As a diagnosis of exclusion, THS may become less common as more specific etiologies are characterized. However, diagnostic criteria remain helpful in order to otherwise characterize those without definitive diagnosis. While atypical features should raise suspicion for alternative diagnoses and further investigation, intracranial extension may occur as part of THS.

FIGURE CAPTIONS

Figure 1. Examination of eye movements showing left proptosis, hypertropia and mild exotropia, and near complete left ophthalmoplegia with normal right eye movements.

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 complete resolution of enhancement and left lateral rectus enlargement.
REFERENCES


### Table. Diagnostic Criteria for Tolosa-Hunt Syndrome (THS)

<table>
<thead>
<tr>
<th>IHS criteria (2004) Section 13.16²</th>
<th>IHS Classification ICHD-3 13.8³</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. One or more episodes of unilateral orbital pain persisting for weeks if untreated</td>
<td>A. Unilateral orbital or periorbital headache fulfilling criterion C</td>
</tr>
<tr>
<td>B. Paresis of one or more of the third, fourth and/or sixth cranial nerves and/or demonstration of granuloma by MRI or biopsy</td>
<td>B. Both of the following:</td>
</tr>
<tr>
<td>C. Paresis coincides with the onset of pain or follows it within 2 weeks</td>
<td>a. granulomatous inflammation of the cavernous sinus, superior orbital fissure or orbit, demonstrated by MRI or biopsy</td>
</tr>
<tr>
<td>D. Pain and paresis resolve within 72 h when treated adequately with corticosteroids</td>
<td>b. paresis of one or more of the ipsilateral IIIrd, IVth and/or VIth cranial nerves</td>
</tr>
<tr>
<td>E. Other causes have been excluded by appropriate investigations</td>
<td>C. Evidence of causation demonstrated by both of the following:</td>
</tr>
<tr>
<td></td>
<td>a. headache is ipsilateral to the granulomatous inflammation</td>
</tr>
<tr>
<td></td>
<td>b. headache has preceded paresis of the IIIrd, IVth and/or VIth nerves by ≤2 weeks, or developed with it</td>
</tr>
<tr>
<td></td>
<td>D. Not better accounted for by another ICHD-3 diagnosis</td>
</tr>
</tbody>
</table>

IHS=International Headache Society, ICHD-3=International Classification of Headache Disorders, 3rd Edition
Pearls & Oy-sters: Idiopathic Orbital Inflammation and Tolosa-Hunt Syndrome With Intracranial Extension
Sabrina Yu and Tychicus Chen

Neurology published online April 25, 2023
DOI 10.1212/WNL.0000000000207368

This information is current as of April 25, 2023

Updated Information & Services
including high resolution figures, can be found at:
http://n.neurology.org/content/early/2023/04/25/WNL.0000000000207368.citation.full

Citations
This article has been cited by 1 HighWire-hosted articles:
http://n.neurology.org/content/early/2023/04/25/WNL.0000000000207368.citation.full##otherarticles

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
All Neuro-ophthalmology
http://n.neurology.org/cgi/collection/all_neuroophthalmology
Orbit
http://n.neurology.org/cgi/collection/orbit

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints
Information about ordering reprints can be found online:
http://n.neurology.org/subscribers/advertise