Original Article

Tolosa–Hunt Syndrome: Long-Term Outcome and Role of Steroid-Sparing Agents

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Abstract

Background: Tolosa-Hunt Syndrome (THS) is one of the causes of cavernous sinus syndrome causing painful ophthalmoplegia. Literature on long-term outcome of this rare condition is scarce. **Aims and Objectives**: The aim is to study the recurrence and role of steroid-sparing agents in THS. **Methodology:** All cases of THS treated at a tertiary-level teaching hospital during a 10-year period were studied. Clinical and radiological profile, response to treatment and recurrences were noted. **Results:** A total of 44 cases were studied. The mean age was 49.5 years, Males constituted 23/44 (52%). The first symptom was pain in 90%. Ptosis with ophthalmoplegia was the most common deficit 29/44 (66%). Lesions confined to cavernous sinus 27/44 (61%) was the most frequent magnetic resonance imaging finding. All patients received steroids as the initial treatment and 15/44 (34%) received steroid-sparing agents. Follow-up ranged from 6 to 120 months (Mean 39 months). Two patients had alternative diagnosis of leptomeningeal malignancy and hypertrophic pachymeningitis on follow-up. Recurrences occurred in 18/37 (48.6%). Time for recurrence varied from 8 months to 7 years. (Mean 18 months). No clinical or radiological predictors for recurrence were identified. Patients who received steroid-sparing agents had a significantly lower recurrence 3/15 (20%) versus 14/26 (53.8%) $P < 0.034$. **Conclusions**: Around 50% of patients with THS can have recurrence. Steroid-sparing agents appear to prevent recurrence. A prospective multicenter randomized controlled trial may help to evaluate the risk and benefits of steroid-sparing therapy and to identify any possible predictors for recurrence.

Keywords: Cavernous sinus syndrome, painful ophthalmoplegia, Tolosa–Hunt syndrome

Introduction

In 1954, Eduardo Tolosa described granulomatous inflammatory process enveloping the carotid siphon in a patient with clinical features of an anterior intracavernous carotid aneurysm.[1] Hunt in 1961 described six similar cases which responded to steroids.[2] This nonspecific inflammatory process in the cavernous sinus is now called the Tolosa–Hunt syndrome (THS). Biopsy of these lesions had shown granulomatous inflammation, with epithelioid cells and occasional giant cells.[3]

Cavernous sinus syndrome causing painful ophthalmoplegia can be due to a variety of etiologies and THS is one of them. In his analysis of 151 cases seen over a period of 26 years, Keane[4] showed that the most common cause for cavernous sinus syndrome was tumors (30%). THS contributed to 23% of cases of cavernous sinus syndrome in this series.

Similar findings were noted form a series of 73 consecutive patients of cavernous sinus syndrome from India where the most common cause was tumors.[5]

With the advent of magnetic resonance imaging (MRI) and its incorporation into the International Headache Society (IHS) guidelines,[6] the etiologies causing cavernous sinus syndrome with painful ophthalmoplegia were better delineated.

The MRI protocol should include T2 fat-suppressed coronal 2–3 mm slices covering the cavernous sinuses and orbits and also T1 fat-suppressed pre- and postcontrast images.

The classic MRI findings will show a soft-tissue swelling in the region of cavernous sinus and/or superior orbital fissure with contrast enhancement. However, these MRI findings are nonspecific as similar findings can also be seen in sarcoidosis, meningioma, lymphoma, etc. All these differentials need to be ruled out by doing the appropriate investigations.[7]

Since obtaining a tissue biopsy is difficult because of the location of lesion, diagnosis is made by a combination of clinical and radiological findings and also the response to steroid therapy. The IHS diagnostic criterion is currently recommended for the diagnosis of THS. This consists of (1) unilateral headache; (2) granulomatous inflammation of the cavernous sinus, superior orbital fissure or orbit, demonstrated by MRI or biopsy; (3) paresis of one or more of the ipsilateral

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Submitted: 22-Aug-2018 **Revised:** 25-Oct-2018 **Accepted:** 05-Nov-2018
Published: 25-Feb-2020

DOI: 10.4103/aian.AIAN_368_18

third, fourth, and/or sixth cranial nerves; (4) evidence of causation demonstrated by both: headache has preceded oculomotor paresis by <2 weeks or developed with it; headache localized around the ipsilateral brow and eye[5] Symptoms not explained by an alternative diagnosis.[6]

To improve the specificity of this diagnostic criterion, any atypical clinical and radiologic findings should be carefully looked for since they may be pointers for other causes for painful ophthalmoplegia.

Zhang *et al*.[8] validated the 2013 International Classification of Headache Disorder-3 (ICHD-3) beta diagnostic criteria for THS in patients with nontraumatic painful ophthalmoplegia and found that the most common etiology using this criterion was THS.

Pain is the predominant feature in THS. This is because the inflammation occurs in a tight compartment (Cavernous sinus) causing compression of the cranial nerves III and IV, the cerebral bridging vein and the lateral sellar nerve plexus in the lateral wall of the cavernous sinus resulting in pain. Subsequently an ophthalmoplegia can evolve.[9,10]

The most commonly involved cranial nerve is the 3rd followed by cranial nerve 6th and the ophthalmic division of trigeminal nerve.[8] The inflammation can extend beyond the cavernous sinus to the orbital apex to involve the optic nerve and also in rare cases the facial nerve.[11] Pupils can be involved either because of the parasympathetic fibers (oculomotor nerve) or Involvement of sympathetic fibers around the carotid artery in the cavernous sinus. Other than pain-induced nausea, systemic vomiting symptoms can occur rarely.

If left untreated, the inflammation and the symptoms may resolve by itself in 2–3 months. However, this can cause considerable morbidity and also some of the cranial nerve deficits can persist.

Steroids can cause a dramatic reduction of pain[12,13] and hasten radiological resolution of the lesions.[14] Steroids are often used to diagnose as well as treat. However, the ophthalmoplegia may not respond immediately to steroids therapy.[15]

Even though steroids have made a considerable change in the management of this rare syndrome, THS can still follow an unpredictable course with relapses occurring even after years.[15,16] Relapse of disease can occur in 30%–40% of cases after months or years following successful treatment with steroids.[17,18] Zhang *et al*. suggested that younger patients may be more prone for relapses.[15] Relapses can occur in the same or in the contralateral eye or can be bilateral.[19]

When relapse occurs, revaluation may be needed to rule out another steroid responsive conditions causes of a painful ophthalmoplegia such as sarcoid or Wegener's granulomatosis or a more sinister mimics such as lymphoma or carcinoma.[20]

Even though various steroid-sparing agents have been tried in the treatment of THS, their role in preventing relapses is not very clear;[21,22] we studied patients with THS who were treated with steroids alone and those who received steroids and steroid-sparing agents and looked at their response and relapse rate. To the best of our knowledge, this is the largest series of THS patients studied form a single center.

Methodology

This study was conducted in the Department of Neurological Sciences of a tertiary care teaching hospital. Patients with THS over a period of 10 years (2008–2017) were identified from the computerized discharge summaries. The patient data were collected from the inpatient records and the outpatient clinics where the patients were being followed up. Radiological images were reviewed from picture archiving and communication system (PACS, GE).

The diagnosis of THS was based on the guidelines of ICHDs, 3rd edition (beta version).[6] According to this criteria, the patients should have the following:

(a) unilateral headache fulfilling criterion C; (b) both of the following: (1) granulomatous inflammation of the cavernous sinus, superior orbital fissure or orbit, demonstrated by MRI or biopsy and (2) 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: (1) headache has preceded paresis of the IIIrd, IVth, and/or VIth nerves by 2 weeks or developed with it and (2) headache is localized around the ipsilateral brow and eye; and (d) not better accounted for by another ICHD-3 diagnosis.

As per the discretion of the treating team, after the initial treatment with steroids, the patients were given systemic immunosuppressive therapy for varying periods of time.[22]

The clinical and radiological profile, response to treatment and recurrence rates during the follow-up period was noted. Factors influencing the recurrence were noted and analyzed.

Two-tailed Fisher's exact test was used to look for significant associations. Statistical analysis was done using a statistical package (STATA, StataCorp 2015, Statistical Software: Release 14. College Station, TX: StataCorp LP.).

Results

A total of 44 cases of THS were seen over a period of 10 years (2008–2017). The age ranged from 21 years to 73 years (Mean 49.5 years). Males constituted 23/44 (52%).

Even though all the patients were treated by the neurology department, the first consultation was in the ophthalmology department 29/44 (66%) and general medicine department 4/44 (9%). The remaining 11/44 (25%) had seen neurologists directly.

Pain was the first symptom in 40/44 (90%). Four patients did not have pain as the initial symptom (Had drooping of

Table 1: Clinical and examination finding

	Number of patients (out of 44) (%)
First symptom noted by the patient	
Periorbital pain	23 (52)
Unilateral headache	11 (25)
Holocranial headache	6 (14)
Drooping of eyelids	2 (4.5)
Facial numbness	1 (2.3)
Double vision	1 (2.3)
Symptoms during the course of the syndrome	
Pain	
Periorbital pain	30 (68)
Forehead pain (unilateral headache)	15 (34)
Holocranial headache	19 (43)
Diplopia	34 (77)
Ptosis	28 (64)
Facial sensory loss	10 (23)
Vomiting	5 (11)
Fever	2 (4.5)
Decreased vision	2 (4.5)
Photosensitivity	1 (2.3)
Pattern of cranial nerves involvement	
Optic nerve	7 (16)
Oculomotor nerve	44 (100)
Only ptosis	11 (25)
Ptosis with ophthalmoplegia	29 (66)
Only ophthalmoplegia	4 (9)
Pupillary involvement	5 (11)
Trochlear nerve	7 (16)
Trigeminal nerve	22 (50)
Ophthalmic V1	20 (45)
Ophthalmic and maxillary VI and V2	5 (11)
Abducens nerve	7 (16)

Table 2: Investigations

	Number of patients (out of 44) (%)
MRI findings	
Lesion confined to cavernous sinus	27 (61)
Lesion affecting cavernous sinus and orbital apex	12 (27)
Lesion affecting orbital apex alone	1 (2)
Blood investigations	
HB (<10 gm %)	1 (2)
ESR (elevated)	15 (34)
CRP (elevated)	13 (38)
ANA (weak positive)	7 (20.5)
ANCA	0
ACE (elevated>50)	5 (18)
IGg4 levels	0
HBsAg (positive)	1 (4)
HIV	0
VDRL	0
CSF test done in	38 (86)
Cell count (>10)	7 (18)
TB PCR	0
Culture	0

Bone marrow: 9/44 (20%), CT thorax: 18/44 (41%), and whole-body PET scan: 8/44 (18%) were normal. CRP – C-reactive protein; ESR – Erythrocyte sedimentation rate; HB – Hemoglobin; ANA – Antinuclear antibody; ANCA – Antineutrophil cytoplasmic antibodies; ACE – Angiotensin-converting enzyme; HBsAg – Hepatitis B surface antigen; VDRL – Venereal Disease Research Laboratory; CSF – Cerebrospinal fluid; TB – Tuberculosis; PCR – Polymerase chain reaction; CT – Computer tomography: PET – Positron emission tomography

eyelids, facial numbness, and double vision as the initial presentation) [Table 1]. However, all of them had developed pain within the first 48–72 h.

The involvement was on the left side in 27/44 (61%) and on the right in 16/44 (36%). Bilateral involvement was seen only in 1/44 (2%). 18/44 (41%) were diabetic patients.

History of an earlier neurological problem was noted in 4/44 (9%) (ischemic stroke – 2, Bell's palsy – 1, and lumbosacral plexopathy – 1).

Oculomotor nerve involvement was seen in all patients [Table 1]. Ptosis with ophthalmoplegia was the most common pattern seen in 29/44 (66%). Trigeminal nerve involvement was noted in 22/44 (50%) mainly involving the ophthalmic V1 division. An equal proportion of patients 7/44 (16%) had abducens and Trochlear nerve involvement.

MRI was done in all patients and lesions could be demonstrated in all [Table 2]. The most common pattern of involvement was lesions confined to cavernous sinus 27/44 (61%). In those suspected to have sarcoidosis, serum angiotensin-converting enzyme levels and computed tomography thorax were done. Whole-body positron emission tomography scan were done for those patients with a suspension of an underlying malignancy.

Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were found to be elevated in up to 15/44 (34%). Immunoglobulin G4 disease was suspected and ruled out in 8 cases. Cerebrospinal fluid (CSF) test was done in 38/44 (86%) and 7/38 (18%) had a cell count of >10 cell/cumm.

Treatment was with a tapering schedule of steroids (oral 22 and IV 4) in 26/44 (59%). While in 15/44 (34%), steroid therapy was followed– up with steroid-sparing agents [Table 3].

The total duration of oral steroids use ranged from 10 days to 6 weeks. Intravenous tapering schedule of steroid use was from 2 weeks to 8 months. Steroid-sparing agent use ranged from 8 months to 36 months. Three patients received only nonsteroidal anti-inflammatory drugs (NSAIDS). The duration of treatment with NSAID varied (10 days to 20 days).

Improvement in pain as well as the cranial nerve deficits were noted in 30/44 (68%) patients within 2 weeks of therapy. In 12/44 (27%), the improvement in the neurological deficits happened after 2 weeks but within a month.

Table 3: Treatment and follow-up

Treatment and follow-up	Number of patients (%)
Treatment given	
Steroids only (tapering oral steroids 22, tapering pulsed IV steroids 4)	26/44 (59)
Steroids followed by steroid-sparing agents - azathioprine 3, mycophenolate mofetil 10, pulsed IV cyclophosphamide 2	15/44 (34)
Only symptomatic treatment (NSAIDs)	3/447)
Response to therapy	
Immediate improvement (within 48 h)	9/44 (20.5)
Improved over next (1 week)	21/44 (48)
Improved over next (1 month)	12/44 (27)
No improvement after 1 month (one patient was subsequently diagnosed to have leptomeningeal malignancy)	2/44 (4.5)
Initial treatment given to patient who had recurrence on follow-up	
Steroid followed by steroid-sparing agents	3/18 (16)
Steroid only	14/18 (78)
Recurrence following defaulting treatment	1/18 (6)

NSAIDs – Nonsteroidal anti-inflammatory drugs

Follow-up MRI was done in 23 patients (52%) [Figure 1]. Long-term follow-up of at least 6 months was available in 37/44 (84%). Duration of follow-up ranging from 6 to 120 months (mean of 39 months).

Recurrences occurred in 18/37 (48.6%). The time taken to relapse varied from 8 months to 7 years (mean 18 months). 17/18 (94%) or the recurrences occurred on the same side and one patient had bilateral involvement.

14/18 (78%) of recurrences occurred in those treated with only steroids compared to 3/18 (16%) of those who had received steroids which were followed up with steroid-sparing agent therapy. One patient recurred after defaulting on steroid-sparing agent.

Duration of follow-up for steroid-treated patients were similar to those who were initiated on steroid-sparing agents average 38.04 versus 31.0 months.

14/18 (78%) patients who had relapse had multiple cranial nerves involved at the time of diagnosis.

During the follow-up period in 2 patients, alternative diagnosis was made. One patient was diagnosed to have leptomeningeal malignancy and another had features to suggest hypertrophic pachymeningitis.

Other complications noted on long-term follow-up were Cushingoid habitus, steroid-induced cataract, and glaucoma in a patient who had self-medicated by intermittent oral steroids. Mycophenolate-related dysplastic changes in one patient. One patient after 9 years developed motor sensory axonal polyneuropathy which responded to immunotherapy.

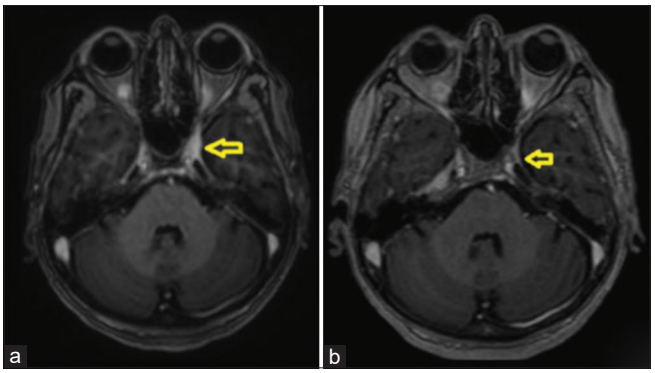

Figure 1: (a) Postcontrast T1 axial scan shows thickening and enhancement of the lateral dural wall of the left cavernous sinus with extension up to the left orbital apex. (b) Follow-up post contrast T1 scan shows resolution of the lesion

Discussion

In this series, we looked at the clinical profile and long-term outcome in patients with THS looking, especially at the recurrence and the role of steroid-sparing agents.

Unlike in other series,[8] we found that the ophthalmic division of the trigeminal nerve was involved (45%) more than the 6th nerve (16%). In a patient presenting with periorbital pain or unilateral headache, a careful sensory examination of the face is important for making an early diagnosis of THS. This is especially important since in 66% of our patients the initial consultation was with an ophthalmologist.

Recurrence occurred in 18/37 (48.5). This was similar to other series in the literature.[4,14,15] We compared the recurrence rate in patients who were treated only with steroids with those who had treatment with steroid followed by steroid-sparing agents. The mean duration of follow-up in both these groups was similar. The recurrence was significantly higher in those who were only treated with steroids 14/26 (53.8%) versus 3/15 (20%) ($P < 0.034$). None of the patients who had recurrences had any markers of systemic autoimmune diseases on reevaluation.

We evaluated possible clinical, radiological, and laboratory parameters which can predict recurrence. More than 2 cranial nerve involvement at presentation ($P < 0.060$), gender ($P < 0.107$); age ($P < 0.457$); early response to steroid therapy ($P < 0.506$;) Diabetes mellitus ($P < 0.359$) elevated ESR ($P < 0.639$) and CSF showing >10 cells ($P < 0.372$).

Systemic inflammatory marker elevation ESR and CRP was seen only in 34%, highlighting the localized nature of the disease. However, an interesting observation in this study was that 3/44 (7%) had other probable autoimmune neurological in other parts of the neuraxis before and during the follow-up phase. Bell's palsy, lumbosacral plexopathy, and motor-sensory axonal polyneuropathy responding to immunomodulation. These may be pointers that THS may be one of the manifestations of an underlying autoimmune phenomenon.

Usually, immunotherapy is given in THS when a recurrence occurs. There are no clear guidelines on the use of immunotherapy for preventing recurrences. This study suggests that immunotherapy may prevent recurrences. Immunotherapy is not without risks and side effects. In this series, we had a patient who had developed mycophenolate-related dysplastic changes.

It is also important to note that even with extensive investigation; causes of sinister THS may be missed. In our series of one patient, a case of leptomeningeal malignancy was initially misdiagnosed. A close follow-up is warranted in all cases of THS even in steroid responsive patients.

One drawback of this study is that it is a retrospective study; however, we had a very good follow-up (mean of 39 months).

Considering the rarity of this disease, we need a prospective multicentric randomized controlled trial to clearly prove the risk and benefits of immunotherapy in THS. Such a study may also help us in identifying any possible predictors of recurrence.

Acknowledgment

The authors would like to acknowledge the contribution of Mr. Kenneth Benjamin, B.Sc., for his help during the data collection.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Tolosa E. Periarteritic lesions of the carotid siphon with the clinical features of a carotid infraclinoidal aneurysm. J Neurol Neurosurg Psychiatry 1954;17:300-2.
2. Hunt WE, Meagher JN, Lefever HE, Zeman W. Painful opthalmoplegia. Its relation to indolent inflammation of the carvernous sinus. Neurology 1961;11:56-62.
3. Goadsby PJ, Lance JW. Clinicopathological correlation in a case of painful ophthalmoplegia: Tolosa-Hunt syndrome. J Neurol Neurosurg Psychiatry 1989;52:1290-3.
4. Keane JR. Cavernous sinus syndrome. Analysis of 151 cases. Arch Neurol 1996;53:967-71.
5. Bhatkar S, Goyal MK, Takkar A, Mukherjee KK, Singh P, Singh R, *et al.* Cavernous sinus syndrome: A prospective study of 73 cases at a tertiary care centre in northern India. Clin Neurol Neurosurg 2017;155:63-9.
6. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition (beta version). Cephalalgia 2013;33:629-808.
7. Cakirer S. MRI findings in the patients with the presumptive clinical diagnosis of Tolosa-Hunt syndrome. Eur Radiol 2003;13:17-28.
8. Zhang X, Zhou Z, Steiner TJ, Zhang W, Liu R, Dong Z, *et al.* Validation of ICHD-3 beta diagnostic criteria for 13.7 Tolosa-Hunt syndrome: Analysis of 77 cases of painful ophthalmoplegia. Cephalalgia 2014;34:624-32.
9. Bleys RL, Janssen LM, Groen GJ. The lateral sellar nerve plexus and its connections in humans. J Neurosurg 2001;95:102-10.
10. Umansky F, Nathan H. The lateral wall of the cavernous sinus. With special reference to the nerves related to it. J Neurosurg 1982;56:228-34.
11. Tessitore E, Tessitore A. Tolosa-Hunt syndrome preceded by facial palsy. Headache 2000;40:393-6.
12. Colnaghi S, Versino M, Marchioni E, Pichiecchio A, Bastianello S, Cosi V, *et al.* ICHD-II diagnostic criteria for Tolosa-Hunt syndrome in idiopathic inflammatory syndromes of the orbit and/or the cavernous sinus. Cephalalgia 2008;28:577-84.
13. Smith JL, Taxdal DS. Painful ophthalmoplegia. The Tolosa-Hunt syndrome. Am J Ophthalmol 1966;61:1466-72.
14. Cakirer S. MRI findings in Tolosa-Hunt syndrome before and after systemic corticosteroid therapy. Eur J Radiol 2003;45:83-90.
15. Zhang X, Zhang W, Liu R, Dong Z, Yu S. Factors that influence Tolosa-Hunt syndrome and the short-term response to steroid pulse treatment. J Neurol Sci 2014;341:13-6.
16. Kline LB. The Tolosa-Hunt syndrome. Surv Ophthalmol 1982;27:79-95.
17. Hannerz J. Recurrent Tolosa-Hunt syndrome: A report of ten new cases. Cephalalgia 1999;19 Suppl 25:33-5.
18. Kline LB, Hoyt WF. The Tolosa-Hunt syndrome. J Neurol Neurosurg Psychiatry 2001;71:577-82.
19. Ohara C, Inoue K, Numaga J. A case of Tolosa-Hunt syndrome developing relapse in the contralateral eye. Folia Ophthalmol Jpn 2000;51:797-800.
20. Esmaeli B, Ginsberg L, Goepfert H, Deavers M. Squamous cell carcinoma with perineural invasion presenting as a tolosa-hunt-like syndrome: A potential pitfall in diagnosis. Ophthalmic Plast Reconstr Surg 2000;16:450-2.
21. Smith JR, Rosenbaum JT. A role for methotrexate in the management of non-infectious orbital inflammatory disease. Br J Ophthalmol 2001;85:1220-4.
22. Hatton MP, Rubin PA, Foster CS. Successful treatment of idiopathic orbital inflammation with mycophenolate mofetil. Am J Ophthalmol 2005;140:916-8.