

# The clinical features and outcomes of Tolosa-Hunt syndrome

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## Research Article

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## Abstract

## Background

The objective of this study was to investigate the clinical features and outcomes of Tolosa-Hunt syndrome (THS).

## Methods

A retrospective review of the medical records was performed on patients with THS between March 2016 and January 2020. A total of eleven patients fulfilling the ICHD-3 beta diagnostic criteria for THS were included in this study.

## Results

The average age of the patients with THS was  $57.18 \pm 13.56$  years and the mean duration of recovery was  $26.91 \pm 24.35$  days. All nine patients had orbital or periorbital pain as the first symptom followed by diplopia. Ptosis was found in five patients (45.45%) in the involved eye. Sixth cranial nerve (CN) palsy was most common (eight cases, 72.73%), followed by third and fourth CN palsy (five cases, 45.45%, respectively), optic nerve (two cases, 18.18%), and trigeminal nerve and facial nerve palsy (one case, 9.09%, respectively). One patient with optic nerve (ON) involvement failed to recover visual acuity and the other ten patients completely recovered their ocular motor limitation. All patients were initially treated with steroids. One patient relapsed after five weeks and one patient had a history of THS five years earlier.

## Conclusions

THS responded well to steroid treatment, but if it was accompanied by ON involvement, follow-up with active treatment was important.

## Introduction

Tolosa-Hunt syndrome (THS) is an uncommon idiopathic granulomatous inflammatory disease of the cavernous sinus, superior orbital fissure, or orbit associated with ocular pain and ophthalmoplegia.[1, 2] However, the etiology of THS is still unknown. Thus, the diagnosis of THS should exclude other causes of painful ophthalmoplegia such as tumors, vasculitis, meningitis, sarcoidosis, diabetic ophthalmoplegia, and pseudotumor.[3, 4] THS is described in the International Classification of Headache Disorders (ICHD 3-beta) diagnostic criteria (Table 1).[5] In clinical practice, the disorder is diagnosed based on the above diagnostic criteria and treatment with corticosteroids is generally recommended. There are relatively few reports on the clinical course of THS, so the objective of this retrospective study was to investigate the clinical outcomes of THS.

Table 1  
 ICHD-3 beta diagnostic criteria for 13.7 Tolosa-Hunt syndrome

<b>A. Unilateral headache fulfilling criterion C</b>
<b>B. Both of the following:</b> 1. Granulation inflammation of the cavernous sinus, superior orbital fissure or orbit, demonstrated by MRI or biopsy 2. Paresis of one or more of the ipsilateral third, fourth and/or sixth cranial nerves
<b>C. Evidence of causation demonstrated by both of the following:</b> 1. Headache has preceded paresis of the third, fourth and/or sixth cranial nerves by $\leq 2$ weeks, or developed with it 2. Headache is localized around the ipsilateral brow and eye
<b>D. Not better accounted for by another ICHD-3 diagnosis.</b>
ICHD 3 beta = International Classification of Headache Disorders, third edition.
MRI = magnetic resonance imaging

## Methods

The Institutional Review Board for Human studies at Samsung Changwon Hospital (Changwon, Republic of Korea) reviewed and approved this study protocol (IRB No. 2020-06-014). As this study was a retrospective study, informed consent was obtained from all patients before the imaging examination and all identifiable personal information of patients would be anonymized. All study conduct adhered to the tenets of the Declaration of Helsinki for the use of human participants in biomedical research. The medical records of patients diagnosed with THS from March 2016 to January 2020 at Samsung Changwon Hospital were retrospectively reviewed. The diagnosis of THS was defined by 1) unilateral headache or orbital pain; 2) headache preceded with paresis of the third cranial nerve (CN), fourth CN, and/or sixth CN for two weeks, or developed with it; and 3) headache localized around the ipsilateral brow and eye based on ICHD-3 beta criteria.[5] All patients underwent brain or orbit magnetic resonance imaging (MRI) and enhancing lesions of the cavernous sinus, superior orbital fissure, and/or orbital apex were identified. Furthermore, other causes of painful ophthalmoplegia including tumors, vasculitis, basal meningitis, sarcoidosis, migraine, cranial herpes zoster, giant cell arteritis, myositis, pseudotumor, and thyroid ophthalmopathy were excluded. Patients who did not show confirmed recovery within a follow-up duration of less than six months were excluded.

Case notes were reviewed to obtain data on patient demographics (age, sex), previous medical history (hypertension, diabetes mellitus, or cancer), symptoms (recorded as orbital pain, diplopia, ptosis, visual loss, and facial numbness), the involved cranial nerves, laboratory results, neuroimaging, the symptom-resolution interval, and treatment. All patients were given oral methylprednisolone (MPD) at 50 mg/day or intravenous (IV) MPD 1 g/day initially and then switched to a gradually decreased dose until the signs and symptoms resolved. The patients with previously diagnosed paralytic or restrictive strabismus, congenital strabismus, or with previous extraocular muscle surgery were excluded. At the first visit, the patients underwent ophthalmologic assessments including slit-lamp, intraocular pressure measurements, ocular motor limitation assessment, and fundus photography. At the final follow-up visit, THS recovery was deemed complete or non-recovered based on ocular motor limitation and visual acuity. Complete recovery was defined as the absence of ocular motor limitation and other CN abnormalities and non-recovery was defined as sequelae of cranial nerve function.

## Results

A total of eleven patients (eight males and two females) were included in this study and the mean follow-up time was  $201.27 \pm 31.36$  days after the initial visit. The average age at THS onset was  $57.18 \pm 15.32$  years (range, 35–78 years). All eleven patients had orbital or periorbital pain as the first symptom followed by diplopia or ptosis. Diplopia and ptosis were found in eleven patients (100%) and five patients (45.45%), respectively. Sixth CN palsy was most common (eight cases, 72.73%), followed by fourth and sixth CN palsy (five cases, 45.45%, respectively), optic nerve (ON) (two cases, 18.18%), and trigeminal nerve and facial nerve palsy (one case, 9.09%, respectively). At the initial examination, four patients had one CN involved, three patients had two CNs involved, and two patients had three CNs involved. Complete recovery was seen in ten (90.91%) patients and in one patient, the ocular motor limitation was completely recovered but visual acuity was not recovered. The mean duration of recovery was  $26.91 \pm 24.35$  days (range, 8–73 days) (Table 2).

The clinical summary and MRI findings of the patients are presented in Table 3. All patients were initially treated with steroid. Six patients received oral MPD at 50 mg/day and five patients received IV MPD at 1g/day. The laboratory test results showed an elevated erythrocyte sedimentation rate (ESR) in three patients and no patients had elevated C-reactive protein (CRP) values. In two patients with ON involvement, one had fourth CN palsy at the first visit with a history of facial nerve palsy before four months. ON swelling was observed three days later, and IV MPD at 1 g/day was administered. Another patient had third, fourth, and sixth CN palsy at the first visit and oral MPD at 50 mg/day was administered. After five weeks, decreased visual acuity was observed and IV MPD at 1 g/day was injected. The first patient recovered completely after treatment, but the second patient did not recover from visual impairment. Of all the patients, two patients relapsed, and one patient had recurrence of visual impairment at 5 weeks interval. The other patient had a history of treatment for THS five years prior according to the medical record and was included as a relapsed patient.

Table 2  
Demographics of patients with Tolosa-Hunt syndrome.

Parameters	
Total patients (n)	11
Male : Female (n)	9 (81.12%) : 2 (18.18%)
Age at time of onset (years)	57.18 ± 15.32 (range : 35–78)
Involved eye (right : left)	5 (45.45%) : 6 (54.55%)
Duration of follow-up (days)	201.27 ± 31.36
Duration of recovery (days)	26.91 ± 24.35 (range : 8–73)
Complete recovery state (n)	10 (90.91%)
ESR (mm/hour)	16.73 ± 13.76 (range : 2–52)
CRP (mg/L)	1.15 ± 0.84 (range : 0.3–2.6)
Diplopia (n)	11 (100%)
Periorbital pain (n)	11 (100%)
CN nerve involvement cases (n)	2 (18.18%)
Optic nerve	5 (45.45%)
Third CN	5 (45.45%)
Fourth CN	1 (9.09%)
Trigeminal nerve	8 (72.73%)
Sixth CN	
Ptosis (n)	5 (45.45%)
Hypertension (n)	3 (27.27%)
Diabetes mellitus (n)	2 (18.18%)
Recurrence state (n)	2 (28.18%)
Values are presented as mean ± SD.	
SD = standard deviation	
ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; CN = cranial nerve	

Table 3. Clinical summary of patients with Tolosa-Hunt Syndrome.

Case	Sex	Age	Clinical findings	Involved CN	MRI findings	ESR (0-20)	CRP (0-5)	Treatment (per day)	Relapse
1	M	73	Diplopia	6 CN	Enhanced left cavernous sinus and clinoid process	15	0.9	Oral MPD 50mg	-
2	M	74	Diplopia, Ptosis	Optic nerve, 3/4/6 CN	Enlarged and enhanced left cavernous sinus/apex/optic nerve	52	2.6	Oral MPD 50mg	5 weeks interval
3	M	52	Diplopia	Optic nerve, 4 CN	Mild thickening and enhanced right cavernous sinus/apex (superior/inferior orbital fissure)	10	2.5	IV MPD 1g	-
4	F	46	Diplopia, Ptosis	3/4/6 CN	Enhanced focal triangular shaped right cavernous sinus with enlarged right superior ophthalmic vein	21	0.3	IV MPD 1g	-
5	M	68	Diplopia, Ptosis	3 CN	Enhanced focal right superior orbital fissure	12	2.0	Oral MPD 50mg	5 years ago
6	M	46	Diplopia	6 CN	Slightly bulging of right cavernous sinus	2	0.5	Oral MPD 50mg	-
7	M	46	Diplopia	6 CN, facial nerve	Suspicious enhanced left superior orbital fissure	10	0.7	Oral MPD 50mg	-
8	M	69	Diplopia	4 CN	Enhanced left cavernous sinus/superior orbital fissure	8	0.8	Oral MPD 50mg	-
9	M	78	Diplopia, Ptosis	3/6 CN	Enlarged and enhanced left cavernous sinus	11	0.7	IV MPD 1g	-
10	F	42	Diplopia, Ptosis	3/4/6 CN	Enhanced right cavernous sinus and extending to orbital apex	30	0.5	IV MPD 1g	-
11	M	35	Diplopia	Trigeminal nerve, 6 CN	Enhanced left cavernous sinus and extracranial portion of mandibular division of trigeminal nerve	13	1.1	IV MPD 1g	-

MRI = magnetic resonance imaging; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein  
 CN = cranial nerve; MPD = methylprednisolone; IV = intravenous

## Discussion

This retrospective study of nine cases of THS based on ICHD-3 beta criteria showed that the clinical manifestations were variable. The sixth CN (72.73%) was most commonly involved, followed by the third (45.45%), and fourth CN (45.45%). Previous studies reported a high rate of third CN (78–91%) involvement[6, 7], however, Curone et al. reported a low rate of third CN (39%) involvement.[8] As such, CN involvement has been variably reported in each study. THS is usually treated with steroid, but there are no rules regarding drugs, formulations, routes of administration, or therapeutic doses. Steroid treatment generally includes prednisone, MPD, and dexamethasone given orally or by IV injection. In this study, five patients were treated with IV MPD at 1 g/day for three days, and six patients received oral MPD at 50 mg/day for seven days, then the dosage was tapered. The difference in treatment dose was determined in consideration of the patient's age, the severity of their symptoms, and underlying diseases. After the initiation of MPD treatment, pain resolved within two days in all patients, and ocular motor limitation gradually improved. Other studies reported that most patients achieved pain relief within 72 hours and that CN palsy resolved over two to eight weeks.[6, 7] In the patients in this study, the recovery period varied from one to eight weeks, similar to the previous report. Steroid treatment relieves the pain quickly, but the signs do not resolve immediately after treatment. As in this study and previous studies, because steroid administration had dramatic effects, when THS is diagnosed, it is important to start steroid therapy immediately.

An accurate diagnosis is important for quick and appropriate treatment, but many diseases must be considered in the differential diagnosis of painful ophthalmoplegia. The role of MRI in the criteria has been included as "granulomatous inflammation demonstrated by MRI or biopsy" in the ICHD 3 beta criteria. In most studies and our study, no patient had a biopsy or pathological examination.[3, 4, 6, 7] Also, the lesion location is an important factor in the differential diagnosis, especially an orbital pseudotumor with characteristics and steroid response similar to THS.[9] Therefore, MRI plays a key role in the diagnosis of THS. Since THS can be diagnosed by anatomical location, MRI should be performed if THS is suspected in a case of painful ophthalmoplegia. The recurrence rate in our study (18.18%) was similar to that of Rui et al. (23%)[6] and Colnaghi et al. (21%)[3] but was lower than that reported by Zhang et al. (37%).[7] Two patients in this study experienced recurrences, one recurred after five weeks and the other had a history of THS diagnosis five years earlier. THS patients have a good prognosis but recurrences occur in about 21–50% of the cases over an interval of months to years. [3, 7, 10] Thus, because THS often recurs after a full recovery, it is important to consider follow-up and the possibility of a recurrence. In this study, the laboratory test results showed elevated ESR values in three patients, which were the patients with third, fourth, and sixth CN involvement. It is thought that blood test results can be considered a factor predicting the severity of inflammation.

Meanwhile, ON dysfunction has been reported, indicating that the pathological process may involve the orbital apex.[10] Two patients in this study had ON involvement and enhanced apex lesions were confirmed by orbit MRI. One patient had fourth CN palsy and ON involvement and recovered completely after steroid treatment. In contrast, in other patients with third, fourth, and sixth CN palsy, relapsed five weeks later with ON dysfunction and third, fourth, and sixth CN palsy. After high-dose steroid treatment, the ocular motor limitation was completely recovered, but the vision loss (recognition of hand motion) did not improve and a pale optic disc was observed at follow-up. Kline and Hoyt[10] reported that the optic disc may be normal, swollen, or pale in appearance, with visual decline ranging from minimal to blindness, and variable final visual acuity. In the two cases in this study, the opposite results were found. In one case, the visual acuity was completely recovered and in the other case, it was not recovered despite the same treatment. Although ON involvement is not common in THS, the occurrence of ON dysfunction should be confirmed through a visual acuity examination during the follow-up period and immediate treatment should be initiated. In addition, even if the ocular motor limitation have improved, it is necessary to check for recurrence or ON function through sufficient follow-up.

Our study had several limitations. First, it was a retrospective, single-hospital-based study, suggesting possible selection bias. Second, the sample size was small due to the relatively uncommon occurrence of the disease. Third, the follow-up

intervals were not standardized and were not long-term. Nevertheless, this study showed the strength of analyzing nine cases and reporting various THS clinical symptoms. In conclusion, considering that THS may cause ON involvement, immediate treatment should be performed at the time of diagnosis. In addition, since there is a possibility of recurrence, long-term follow-up is necessary.

## Declarations

- Ethics approval and consent to participate: The IRB for Human studies at Samsung Changwon Hospital (Changwon, Republic of Korea) reviewed and approved this study protocol (IRB No. 2020-06-014). Informed consent was obtained from all patients (retrospective study)
- Consent for publication: Not applicable
- Availability of data and materials: All data generated or analysed during this study are included in this published article (supplementary information files)
- Competing interests: The author declare that they have no competing interests
- Funding: No-financial competing interests
- Authors' contributions: Dr. Shin Yeop Oh contributed to study concept and design, acquisition of data, analysis and interpretation of data, and draft and revision of the manuscript for content. Dr. Oh reports no disclosure.
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- [THSdata.xlsx](#)