International Journal of Basic & Clinical Pharmacology
Shihab AB et al. Int J Basic Clin Pharmacol. 2026 Jul;15(4):787-790
https://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20261970

Case Report

A novel approach in treating Tolosa-Hunt syndrome with injectable dexamethasone and cyclophosphamide: a case report

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Received: 06 January 2026
Revised: 29 March 2026
Accepted: 15 May 2026

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ABSTRACT

This case report describes about the treatment efficacy of the combination therapy of injection dexamethasone followed by single dose of pulsed intravenous cyclophosphamide in a 53-year-old male patient diagnosed with Tolosa Hunt syndrome (THS) with normal immunoglobulin G4 (IgG4) level. This patient with history of type 2 diabetes mellitus, systemic hypertension, coronary artery disease presented with complaints of left sided headache, blurring of vision with diplopia. On further examination and investigation patient was diagnosed with THS. The patient was managed with intravenous steroid followed by single dose of intravenous steroid sparing agent. Treatment with intravenous steroid sparing agent led to rapid and significant clinical remission. He was discharged with a plan of combination therapy with oral steroid and steroid sparing agent and follow up recommendation.

Keywords: Tolosa Hunt syndrome, Immunoglobulin G4, Dexamethasone, Cyclophosphamide, Steroid, Steroid sparing agent

INTRODUCTION

A rare neuro-ophthalmic symptom, Tolosa-Hunt syndrome (THS), also known as idiopathic orbital inflammation syndrome, is characterized by non-specific inflammation of the orbital apex, superior orbital fissure, or cavernous sinus. In conjunction with periorbital or hemicranial pain, this syndrome of painful ophthalmoplegia includes ipsilateral cranial nerve palsies involving the oculomotor (III), trochlear (IV), or abducens (VI) nerves, oculosympathetic paralysis, and sensory loss in the distribution of the ophthalmic or maxillary division of the trigeminal (V) cranial nerve.[1-6]

THS is acknowledged as a rare condition by the National Organization for Rare Disorders (NORD) and is classified as one of the painful cranial neuropathies by the International Headache Society (IHS) in their headache classification.[3] Comprehensive epidemiological statistics on the incidence and prevalence of TSH are scarce, and the precise figures remain unclear; nonetheless, it is globally estimated to be around 1 to 2 cases per million. The average age of onset has been reported to be in any decade of life, exhibiting no gender, geographic, or racial bias.

THS is caused by an inflammatory process and its etiology remains unknown. But there are various etiologies like craniocerebral trauma, various vascular causes (intracavernous carotid artery aneurysm, posterior cerebral artery aneurysm, carotid cavernous fistula), contiguous or metastatic spread of a neoplasm(meningioma, pituitary adenoma, lymphoma), inflammatory causes(sinusitis, mucocele, periostitis, herpes zoster, mucormycosis, mycobacterium tuberculosis, treponema pallidum) due to specific infectious agents(bacteria, virus, fungi), IgG4-associated disease, multiple sclerosis, ischemic mononeuropathy, autoimmune disorders (Guillain -barre syndrome, myasthenia gravis), Ophthalmoplegic

migraine, neuromuscular disorders, giant cell arteritis that cause painful ophthalmoplegia.[2,3] Various studies have shown that about 30% of cavernous sinus syndrome (CSS) are due to tumors and nearly about 23% is due to TSH.[4] Hence TSH is diagnosis of exclusion requiring careful differential diagnosis.

Diagnostic evaluation of THS is made by a combination of clinical and radiological findings. Laboratory investigations like complete blood count, serum electrolyte, serum glucose, renal and liver function test, C-reactive protein (CRP), angiotensin converting enzyme (ACE), Thyroid stimulating hormone (TSH) levels, autoimmune antibodies (ANA, ANCA, ENA and AMA), rheumatoid factor, serum complement levels, Erythrocyte sedimentation rate (ESR).Cerebrospinal fluid (CSF) investigations like opening pressure, cell count and differential count, protein, glucose, cytology, syphilis and Lyme serology, culture, and gram stain (bacterial, fungal, mycobacterial). Neuroimaging studies like magnetic resonance imaging, computed tomography, cerebral angiography, orbital venography, ancillary imaging and positron emission tomography (PET). Biopsy of the nasopharynx and cavernous sinus can be considered when infectious and malignant causes are considered. Collectively, these investigations and biopsy aid in excluding other etiologies.

According to International Classification of Headache Disorder-3 diagnostic criteria for THS include unilateral orbital and peri orbital headache associated with weakness or paresis of one or more cranial nerves (oculomotor, trochlear, or abducens) on the same side as the headache, MRI or biopsy evidence of granulomatous inflammation in the orbit involving the superior orbital fissure or cavernous sinus, granulomatous inflammation and the headache are located on the same side and the headache typically started before the cranial nerve weakness (within 2 weeks) or developed at the same time as the weakness, no other illness can account for the clinical presentation.[8]

In view of its inflammatory nature, THS is most effectively managed with corticosteroids. High-dose pulse steroid therapy has been advocated in the recent literature, followed by oral steroids in tapering doses.[10] It cause a significant alleviation of pain and accelerates the radiological clearance of the lesions, which further acts as diagnostic confirmation of THS. Steroid-sparing agents, such as mycophenolate mofetil, methotrexate, azathioprine, cyclophosphamide, cyclosporine, tacrolimus, infliximab, rituximab, and adalimumab are the other therapeutic modality. Recurrences are frequent and overall quality of life is low even with therapy.

Purpose

This case report aims to describe the clinical presentation, treatment, and outcome of a patient with THS who was treated with pulsed intravenous dexamethasone and cyclophosphamide. The report highlights the potential benefits and considerations of using cyclophosphamide in THS, contributing to the limited literature on this topic and providing insights on managing similar cases.

CASE REPORT

A 53-year-old male with medical history of type 2 diabetes mellitus (T2DM) and systemic hypertension (SHTN) for past eight years and with history of coronary artery disease (CAD) status post percutaneous transluminal coronary angioplasty for past four years was presented with complaints of left sided headache for one year, blurring of vision with diplopia on looking to the left side and numbness over the left frontal region for past one month. Patient was examined and evaluated outside the hospital and provisionally diagnosed with idiopathic inflammatory disease or IgG4 related disease.

He was presented to our neurology team for further evaluation and management of the prevailing condition. On hospitalisation patient was conscious, oriented, and cooperative. His vitals were within the normal range. He was non-alcoholic, nonsmoker, with no surgical and head trauma history. He was under medications for T2DM, SHTN and CAD. On examination patient had no neck stiffness. Ocular and neurological examination showed vertical diplopia and left lateral rectus paresis or left abducens nerve palsy, hypoesthesia over the left frontal region respectively. All other general and systemic examinations were found to be normal.

On laboratory investigation done on current admission, his systemic inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were found to be slightly elevated with a value of 19 mm/hr (normal range: 0-20 mm/hr) and 5.33 mg/l (normal range:<10 mg/l) respectively and serum-angiotensin converting enzyme level is found to be 35 U/l (normal range: 8-52 U/l). His renal and liver function tests were found to be normal and glycosylated haemoglobin (HBA1C) showed 7.9 % (normal range: <5.7%). His IGG4 value (121 mg/dl) (normal range: 3-201 mg/dl) was found to be normal. Lumbar puncture was done and cerebrospinal fluid (CSF) analysis showed normal protein with a value of 29.6 mg/dl (normal range: 15-45 mg/dl) and chloride 126 mEq/L (normal range: 118-132 mEq/L) but slightly raised glucose 97 mg/dl (normal range: 50-80 mg/dl). CSF gross examination was normal, bacteriology and XPERTMTB examination showed negative. MRI Brain showed enhancing lesion on left orbital and anterior duramater suggested an inflammatory condition probably as THS.

As of current admission, on day one patient was treated with analgesics Tab. Paracetamol and caffeine as stat medication for pain management and then he was treated with intravenous steroid injection dexamethasone 8mg as twice daily dose along with his regular medications and pantoprazole 40 mg. A total of 5 doses of intravenous dexamethasone (16 mg/ day) was given, followed by

which on day 3 of admission patient was treated with single dose of injection cyclophosphamide 700 mg. There was a significant remission in the clinical symptoms of the patient within 24 hours after treating with injection cyclophosphamide. The patient was discharged on day 4 with oral methyl prednisolone 32 mg once daily and mycophenolate mofetil 500mg as twice daily for 1 month and advised to follow up in neurology OPD (Table 1).

Table 1: Clinical timeline illustrating clinical presentation, diagnostic evolution, and therapeutic management of the patient with THS treated with intravenous dexamethasone and cyclophosphamide.

Time	Clinical events
Day 0	Patient was presented with unilateral headache, diplopia and left frontal hypoesthesia. MRI brain revealed enhancing lesion on left orbital and anterior duramater.
Day 1	Diagnosis of THS was considered after reviewing MRI and exclusion of other causes. Patient treated with analgesic and intravenous dexamethasone.
Day 2	Significant improvement in symptoms observed.
Day 3	Patient was treated with single dose of injection cyclophosphamide. Marked remission in the clinical symptoms of the patient
Day 4	Patient was discharged with oral methyl prednisolone 32 mg once daily and mycophenolate mofetil 500 mg as twice daily for 1 month

DISCUSSION

A 10-year retrospective study by Aurther et al involving 44 patients diagnosed with THS, 90% reported pain as the primary symptom.[4] Notably, 25% experienced unilateral headache as the first symptom, and 77% reported diplopia during the course of the syndrome. Left-sided involvement was observed in 61% of cases, and oculomotor nerve involvement was present in all patients. These findings are consistent with the clinical presentation of our patient.

Our case involved a patient presenting with left-sided headache, followed by diplopia, cranial nerve paresis, and facial hypoesthesia. Given the overlapping features with other neurological and vascular conditions, a meticulous evaluation was undertaken to exclude alternative diagnoses.[2] The differential diagnosis for THS includes craniocerebral trauma, and various vascular pathologies which often present with acute onset and mimic THS but were excluded in our patient based on clinical and radiological findings.

Magnetic resonance imaging (MRI) was performed to rule out space-occupying lesions and demyelinating disease. Laboratory investigations, including CSF analysis, were conducted to exclude other inflammatory and infectious etiologies.[6] Inflammatory markers such as ESR and C-reactive protein were mildly elevated-findings reported in some THS cases. Serum ACE levels were within normal range, ruling out sarcoidosis.[7] Neurological examination and appropriate testing excluded Guillain-Barré syndrome and myasthenia gravis. IgG4-related disease and ophthalmoplegic migraine were also considered; however, normal IgG4 levels, absence of systemic involvement, and no family history made these diagnoses less likely.[1]

The patient was initially treated with intravenous dexamethasone 8 mg twice daily, which resulted in significant resolution of orbital pain within 72 hours. After five doses of corticosteroids, a single dose of pulsed intravenous cyclophosphamide was administered. The dramatic symptomatic improvement in response to corticosteroids served as a confirmatory diagnostic marker for THS.

While corticosteroids remain the mainstay of treatment, THS can exhibit a relapsing course. For patients who are steroid-refractory or require prolonged high-dose corticosteroids, steroid-sparing agents may be considered. Although their role in relapse prevention remains under investigation, emerging evidence supports their utility in long-term management.[5]

In a report by Hyuk Sung Kwon et al methotrexate induced sustained clinical remission has seen in two patients with recurrent THS. Aurther et al also noted that in her cohort, 15 out of 44 patients were managed with corticosteroids followed by steroid-sparing agents, with 2 patients receiving pulsed intravenous cyclophosphamide, aligning with our treatment approach.[5]

Cyclophosphamide exerts its anti-inflammatory effect in THS by suppressing autoreactive B and T lymphocytes, inhibiting pro-inflammatory cytokine production, and inducing immune cell apoptosis, thereby reducing granulomatous inflammation within the cavernous sinus.

Pulsed intravenous cyclophosphamide offers a rapid immunosuppressive effect with reduced cumulative toxicity compared to continuous oral administration. When combined with corticosteroids, it enhances therapeutic efficacy and enables early tapering of steroids.

In our case, a single pulsed IV dose of cyclophosphamide resulted in complete remission of symptoms, reinforcing the inflammatory autoimmune nature of the disease. The patient was subsequently discharged on oral methylprednisolone 32 mg once daily and mycophenolate mofetil 500 mg twice daily as a maintenance immunosuppressive strategy for one month.

CONCLUSION

This case highlights a novel and effective therapeutic approach in the management of THS using a combination

of injectable dexamethasone followed by a single dose of pulsed intravenous cyclophosphamide. The rapid and significant clinical remission observed in our patient underscores the potential benefit of incorporating steroid-sparing agents early in the treatment course, particularly in patients with a high risk of relapse or those requiring prolonged corticosteroid therapy. The use of cyclophosphamide not only enhanced clinical recovery but also allowed for early steroid tapering, reducing the risk of long-term steroid-related complications. This case contributes to the limited but growing evidence supporting the role of immunosuppressive therapy in THS and suggests that early intervention with agents like cyclophosphamide may improve patient outcomes. Further studies are needed to establish standardized treatment protocols and evaluate the long-term efficacy and safety of such combination therapies in THS.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Shihab AB, George MA, Yadav KAC, Selvan VLA. A novel approach in treating Tolosa-Hunt syndrome with injectable dexamethasone and cyclophosphamide: a case report. Int J Basic Clin Pharmacol 2026;15:787-90.