



World Journal of Pharmaceutical Science & Technology

Journal homepage: www.wjpst.com

Review Article

A REVIEW OF TOLOSA HUNT SYNDROME A RARE NEURO-OPHTHALMIC DISORDER: DIAGNOSIS CHALLENGES AND THERAPEUTIC GOALS.

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Received: 02-02-2025, Revised: 01-03-2025, Accepted: .03-04-2025

ABSTRACT

Occurring in very rare cases, Tolosa-Hunt syndrome impacts the retro-orbital and orbital regions. Due to its similarities to various illnesses impacting neurological and vascular issues, accurate diagnosis of THS can be challenging. The most typical symptoms of tolosa-hunt syndrome are a lack of sensation in the area supplied by the trigeminal nerve, discomfort in the orbit, edema, headache, and palsies of the cranial nerves. These symptoms can last anywhere from a few months to a few years until they go away. High dosage steroids are administered to treat painful ophthalmoplegia when other possible reasons have been ruled out. The diagnosis and main treatment plan can be solidified when the patient's clinical response to corticosteroid treatment is rapid in THS. With an emphasis on the pharmacist's responsibility to monitor adverse drug reactions (ADRs), ensure medication safety, and educate patients, this article examines the disease's origins, clinical presentation, diagnostic criteria, and treatment methods.

KEYWORDS: Tolosa Hunt Syndrome, Neuro, Ophthalmic, Therapeutic

INTRODUCTION

Tolosa Hunt Syndrome is also known as painful, recurring, and ophthalmoplegia syndrome. An unknown cavernous sinus or superior orbital fissure infection rarely causes severe ophthalmoplegia of the third, fourth, and sixth cranial nerves. A severe, one-sided periorbital headache and limited, painful eye movement characterize Tolosa-Hunt syndrome. NORD considers Tolosa-Hunt syndrome one of the rarest diseases. The International Headache Society calls it excruciating cranial neuropathy. In Tolosa-Hunt syndrome, relapses and remissions occur months to years apart. Exclusion is achieved after exhausting all other causes of painful ophthalmoplegia, and high-dose corticosteroids are given. The rare illness Tolosa-Hunt syndrome affects the orbit and retro-orbital regions.

In 1954, Spanish neurosurgeon Eduardo Tolosa discovered Tolosa Hunt syndrome. Hunt et al. described similar events in 1961. It was first called Tolosa Hunt Syndrome by Smith and Taxdal in 1966. Before then, it was a medical mystery. Since then, worldwide instances and study have been reported. Symptoms of painful ophthalmoplegia syndrome include eye discomfort, paralysis of the eye muscles, and trigeminal nerve abnormalities (ophthalmic and, rarely, maxillary division). Many cranial nerve palsies at once are likely localized around the superior orbital fissure or cavernous sinus. Tolosa-Hunt Syndrome (THS) is normally benign, although it may cause long-term brain damage and progress abruptly, needing immunosuppressive medicine. No test exists to distinguish THS from more severe illnesses,

making diagnosis difficult. Since THS symptoms may also be caused by vascular abnormalities, infections, tumors, and malignancies, this difference is crucial. Imaging studies are typically used to rule out alternative reasons and assess the patient's response to corticosteroid therapy to confirm THS. [1,9]

Etiology

The etiology of the inflammatory condition underlying Tolosa-Hunt syndrome remains elusive. Histopathological examination reveals the presence of lymphocyte and plasma cell infiltration, the formation of giant cell granulomas, fibroblast proliferation, and nonspecific inflammatory changes within the cavernous sinus wall and septa [2,3]. The cranial nerves III, IV, and VI, along with the upper branches of cranial nerve V, are situated within the cavernous sinus and may experience secondary dysfunction as a result of the pressure induced by inflammation. The four primary potential sources of the constellation of symptoms include trauma, cancer, aneurysm, and inflammation.

Additional causes of THS

Some examples of disease that may affect the orbit include contiguous sinusitis, mucormycosis, idiopathic ocular inflammation (pseudotumor), and various fungal infections. Advancement of cancer
Eye problems caused by diabetes: mononeuropathy and palsies of many cranial nerves
Back of the neck aneurysm: The basilar artery and the posterior connecting artery

Epidemiology

Tolosa Hunt syndrome has an estimated annual incidence of around one case per million persons. The average age of onset is 41 years; however, cases have been recorded in persons younger than 30. In rare cases, children under the age of 10 have been diagnosed with Tolosa-Hunt syndrome. [24]

Pathophysiology

It is yet unknown what causes the inflammation that presents as Tolosa-Hunt syndrome. Histopathological characteristics of non-specific inflammation affecting the cavernous sinus walls and septa include fibroblast growth, giant cell granulomas, and lymphocytic and plasma cell infiltration. This inflammation causes the top branches of cranial nerve V as well as cranial nerves III, IV, and VI to become compressed and dysfunctional within the cavernous sinus.

There is an unexpected correlation between cavernous sinus inflammation and intracranial inflammation. Although there is no known autoimmune cause for Tolosa Hunt syndrome, it may be an early symptom of sarcoidosis, systemic lupus erythematosus, or another autoimmune inflammatory disease. When the parasympathetic (oculomotor) or sympathetic (third-order neuron Horner syndrome) pathways are activated, aberrant pulses may result. According to the accounts, the illness process extended beyond the cavernous sinus and involved the maxillary and mandibular branches, the optic nerve, the facial nerve, and the third cranial nerve (trigeminal).

This is often caused by idiopathic granulomatous inflammation of the cavernous sinus. Inflammation compresses and disrupts nearby neurovascular systems, leading to the rapid development of cranial nerve issues. When corticosteroid therapy results in a considerable improvement in symptoms, the diagnosis is often accurate [7,12].

Physical Evaluation

This condition is readily recognized and is characterized by a propensity for acute, intense, stabbing pain. While the most typical site for this kind of headache is the periorbital area, it is also possible for retro-orbital pain to migrate to the frontal and temporal areas. Most patients say that their initial symptom is discomfort, which may start as early as 30 days before ophthalmoplegia appears. Relapsing and remitting is the pattern of Tolosa Hunt syndrome relapses, which might occur every few months or even years. THS symptoms may last up to eight weeks until they go away on their own if therapy is not received. It is located in the periorbital region and continuously expands into the frontal, retroorbital, and temporal regions.

Other Test

Haematological tests:

- Complete blood count
- Serum chemistry (glucose, electrolytes, liver and renal function)
- Erythrocyte sedimentation rate
- C reactive protein
- Antinuclear antibody

- Anti-dsDNA antibody
- Anti-sm antibody
- Serum protein electrophoresis
- Antinuclear cytoplasmic antibody
- Cerebrospinal fluid
- Cell count
- Culture: bacterial, fungal, mycobacterial
- Serology
- Cytology

Differential diagnosis

- Cavernous sinus thrombosis
- Orbital pseudotumor
- Aneurysm
- Posterior cerebral artery aneurysm
- Carotid- cavernous fistula
- Intracavernous carotid artery aneurysm
- Neoplasms
- Multiple sclerosis
- Sarcoidosis

Diagnostic criteria

Clinical features, neuroimaging evaluations, and steroid responsiveness are the cornerstones of a THS diagnosis. To help rule out other possible causes of ophthalmoplegia, further diagnostics such as laboratory testing and cerebrospinal fluid (CSF) analysis might be performed. The diagnostic procedure of tissue biopsy is seldom used because of the high risks involved and the technical hurdles that must be overcome. Multiple nearby cranial nerves in a clinical diagnosis of THS point to a cavernous sinus or subarachnoid space lesion. There is only one nerve that is not completely enclosed in the dural wall of the cavernous sinus, and it is probably the sixth cranial nerve.

International Headache Society (IHS) Criteria for diagnosis

1. Retrobulbar discomfort may manifest days before the onset of ophthalmoplegia or may arise thereafter.
2. Neurological symptoms may affect the third, fourth, and sixth cranial nerves, as well as the first (and infrequently the second) division of the trigeminal nerve. The optic nerve and oculosympathetic fibers may occasionally be involved.

Symptoms may last for weeks or months.

3. Spontaneous remission may transpire; nevertheless, enduring neurological deficits may remain.

Attacks may reoccur after intervals of months or years.

4. Comprehensive examinations, including angiography and surgical exploration, have revealed no involvement of tissues beyond the cavernous sinus.

Neuroradiological diagnosis of THS

Affected patients with Tolosa-Hunt syndrome exhibit soft tissue lesions in the cavernous sinus, superior orbital fissure, and orbital apex, according to new imaging techniques like MRI and computed tomography. A magnetic resonance imaging (MRI) scan may help rule out serious medical conditions including cancer and vascular abnormalities that might be causing the symptoms. Tolosa-Hunt syndrome is associated with magnetic resonance imaging (MRI) findings of a convex lateral wall resulting from an extension of the cavernous sinus, which is caused by a soft tissue lesion inside the sinus. Although CT scans aren't always the best option, they may be useful in some cases. The area around the orbital apex may show signs of bone degradation or thickening. The evaluation of vascular involvement and the exclusion of differential diagnoses like thrombosis or aneurysm are common uses for magnetic resonance imaging (MRA).

MRI

In order to rule out less serious but potentially dangerous possibilities, such as a cavernous sinus biopsy—the only way to provide histological proof of this condition—a brain MRI is essential for diagnosis. It is possible to see inflammation at the orbital apex, superior orbital fissure, and anterior cavernous sinus.

A contrast-enhanced magnetic resonance imaging (MRI) scan with several views, particularly coronal sections, should be the primary diagnostic test performed. To better see the cavernous sinus and/or superior orbital fissure, an MRI scan is recommended. An key diagnostic test is the contrast-enhanced magnetic resonance imaging (MRI) of the brain, specifically the coronal view. Because it is quite unusual in cases with Tolosa Hunt syndrome, it helps rule out other medical conditions that cause painful ophthalmoplegia. Sign features are not diagnostically specific (clinical status is necessary for diagnosis), but they may include a wide range of attributes, such as:

- T1: After gadolinium injection, the afflicted area may appear as an isointense to slightly hyperintense mass in the cavernous sinus (T1 C+). (Depending on the clinical situation, this might indicate a range of tissue changes, such as inflammatory changes or edema.)
- Hyperintense is the damaged area on T2. In comparison to the muscle, the bulk could seem more intense.
- T1 C+ (Gd): During the active period, there may be contrast enhancement. After treatment, the enhancement will decrease.

On T1 and intermediate-weighted images, the anomaly often shows intermediate signal strength, which might indicate an inflammatory condition. Additionally, if paramagnetic contrast is infused intravenously, the aberrant region becomes much more noticeable.

3D CT scan

Although MRI is more sensitive, high-resolution CT may still identify soft tissue alterations in the cavernous sinus/superior orbital fissure area. On occasion, contrast enhancement may be seen, which might indicate abnormal development in the cavernous sinus region at the site of impact. This is caused by a lack of sensitivity to changes in soft tissue, which is worsened by aberrations such as bone streaks and superimposed beam hardening. Occipital apex and superior orbital fissure advancement and internal carotid artery constriction are secondary criteria.^[15]

MRA

MRA generally shows the Focal stenosis with deformation of cavernous segment of the internal carotid artery typically due to inflammatory involvement. ^[15]

Differential diagnosis

Painful ophthalmoplegia can have a variety of causes, including cavernous sinus syndromes (e.g., tumors, aneurysms, thrombosis, fungal infections, carotid-cavernous fistulas, and granulomatosis with polyangiitis), brainstem ischemia, ischemic oculomotor nerve palsy, masses in the brainstem, lesions in the brainstem caused by multiple sclerosis, oculomotor nerve schwannomas, diabetes, traumatic oculomotor nerve palsy, meningeal infections or inflammatory diseases, Miller Fisher syndrome, idiopathic intracranial hypertension, thyroid ophthalmopathy, orbital masses, and narrow-angle glaucoma.^[3]

Treatment

Since it helps with both diagnosis and therapy, the glucocorticoid response is mentioned here. Within two or three days of administering large dosages of systemic steroids, the patient reports a significant decrease in pain. As steroid therapy progresses over the next several weeks, aberrant tissue volume and MRI signal intensity decrease, and functioning of the cervical nerves improves. It is important to exercise care when relying exclusively on steroid response to establish a diagnosis of Tolosa Hunt syndrome. Improvements in both clinical and radiological aspects may be seen in other pathological conditions, such as infections, cancer, or vasculitis. In most cases, patients with THS will first take high doses of glucocorticoids for a short period of time, then taper off the medication over the course of many weeks or months. Once clinical signs and symptoms have subsided, the usual course of treatment comprises weaning down from an initial dosage of 50 mg/day of oral methylprednisolone or 1 g/day intravenously. Ten days up to six weeks was the greatest amount of time that oral corticosteroids were given. A tapering phase of intravenous steroids might last anywhere from two weeks to eight months. Diagnostic imaging scans, such as magnetic resonance imaging (MRI), may be useful, but the results won't be visible for a few weeks after symptoms have subsided. The main treatment for THS is the use of oral steroids. Over the course of three to four months, a patient using oral steroids will gradually reduce their dosage, which should alleviate symptoms and improve physical examination findings including ophthalmoplegia, ptosis, and headache. The patient may be managed in a collaborative fashion with the neurology department in order to rule out other possible diagnoses. Before starting steroid treatment, make sure there aren't any fungal infections in the orbit, especially fungal

sinusitis (such mucormycosis in those with diabetes or impaired immune systems), since steroids may make fungal infections worse.

To control illness or lessen the negative effects of long-term steroid therapy, patients may sometimes need additional immunosuppressive drugs. The following medications are available as second-line treatments: azathioprine, infliximab, methotrexate, cyclosporine, and mycophenolate mofetil. When steroids are not an option, or when there are recurring flare-ups that cause the patient to become dependent on steroids, radiotherapy has been used as a main treatment or a secondary intervention. Corticosteroids remain a fundamental treatment for Tolosa Hunt syndrome, although standardized guidelines are still needed. Alternative therapies include infliximab (300 mg infusion), azathioprine, methotrexate, and acupuncture. Recently, surgical options have been explored, but concerns about the potential for permanent cranial nerve VI palsy and the risk of late-onset malignancy have been raised.

Antimetabolic agents like methotrexate, infliximab, and mycophenolate mofetil have demonstrated significant improvement in patients who are considered steroid-resistant. In most instances, the pain linked to Tolosa Hunt syndrome diminishes with the short-term use of steroid medications.^[4-6]

Managing comorbidities in THS

It is well-known that corticosteroids hinder glucose metabolism and might cause hyperglycemia or relapse in patients with diabetes mellitus. Diabetic treatment may need to be adjusted, thus it's crucial to test blood glucose levels often.

Patients with hypertension should be closely watched over the course of therapy with steroids because of the potential for an increase in blood pressure. Patients may also need medications to control their blood pressure. Osteoporosis and osteopenia are conditions that may worsen with prolonged use of corticosteroids. Therefore, it is recommended to have bone density tests and take calcium and vitamin D supplements. Peptic ulcer formation may be accelerated with long-term steroid usage, particularly when combined with nonsteroidal anti-inflammatory drugs (NSAIDs). Proton pump inhibitors and other gastroprotective medications are often recommended to reduce this risk.

Increased susceptibility to infections is a result of steroids' immunosuppressive effects. Keep a watchful eye on the patient; antibiotics or other preventative measures may be necessary.

Pharmacy practice perspective

Pharmacist's role is essential in the management of corticosteroid therapy, especially for rare disorder like THS. Responsibilities includes ensuring the safe administration of medication by monitoring adverse effects, guiding patients through tapering regimens to prevent withdrawal or relapse, to provide patient education on medication adherence.

Therapeutic role of clinical pharmacist

Providing thorough information about corticosteroid medication, including its therapeutic aim, correct dose, administration methods, and any side effects, is an important part of a pharmacist's job. In order to prevent the return of the illness and the onset of withdrawal symptoms, patient counseling should also highlight the need of tapering and the dangers of abrupt termination.

Mood swings, hyperglycemia, weight gain, and fluid retention are common side effects of corticosteroids, therefore pharmacists should keep a close eye on their patients. In more serious instances, they need to be vigilant for the emergence of mental symptoms or steroid-induced psychosis. Mania, sadness, or delirium might be the symptoms.

Check the patient's current prescription list for any drugs that might interact with the corticosteroid, especially those that could increase the risk of side effects or reduce the drug's therapeutic impact. Emphasize the need of following the recommended corticosteroid schedule precisely, including dosing, timing, and duration of treatment. To aid patients in maintaining adherence and managing side effects and concerns related to medication, pharmacists should provide both informative resources and supporting measures.

DISCUSSION

Ophthalmoplegia is a hallmark of the mysterious Tolosa Hunt syndrome, which is defined by subacute, strong, and long-lasting pain in the orbit and retro-orbital areas. This is related to the process of granulation tissue production in the anterior cavernous sinus or superior orbital fissure.

Despite having some telltale symptoms, Tolosa Hunt syndrome is not always easy to diagnose.

It is possible that more cranial nerves are involved in THS in addition to the IIIrd, IVth, and VIth cranial nerves. Research shows that different cranial nerves are involved to different degrees. The second, third, seventh, and eighth cranial nerves have all been the subject of documented cases. The intracavernous segment of the carotid artery is characterized by segmental constriction, irregularity, and narrowing, according to the reports. The use of corticosteroids often alleviates these changes, which may be seen using magnetic resonance angiography (MR), computed tomography (CT) angiography, and digital subtraction angiography. Serious or chronic illnesses, including tumors or infections, may look quite similar, so doctors often rule them out as possible causes before making a diagnosis. In certain cases, a biopsy could be necessary. Since corticosteroid therapy usually has a positive effect on THS, confirming the condition requires a proper diagnosis.

Despite its mostly benign nature, Tolosa Hunt syndrome may sometimes impact the optic nerve, leading to blindness. Therefore, neurohospitalists must be able to detect the symptoms and clinical indications of THS promptly and provide therapy appropriately. The eyes and their ability to move around are better protected in this manner, and any problems down the road are less likely to occur. On rare occasions, symptoms of Tolosa Hunt syndrome may go away without treatment. Within three days of starting corticosteroid medication, most patients report less discomfort, and within a week, they see an increase in muscular strength. A recurrence may occur in 30% to 50% of patients, even though the prognosis is typically positive. Recurrences may occur anywhere from a few months to many years after the original episode, and they tend to occur more often in younger people.

Despite the significant improvement in THS with corticosteroid medication, recurrence rates of 30% to 40% may be seen, even after years of recovery. Relapse may be more common in younger patients, according to Zhang et al. The ipsilateral, contralateral, or both ocular areas might be affected by these relapses. Both the original and revised ICHD used a high responsiveness to steroid treatment as a diagnostic criterion for THS. Although steroid response is no longer included in the THS criteria in the current third edition, it is still included as a supplementary characteristic that might support a diagnosis. When it comes to treating THS, steroids have a lot of support from clinical studies. In order to rule out cancer, vascular causes, or other inflammatory disorders in the cavernous sinus or superior orbital fissure region, a thorough patient evaluation is required for a diagnosis of exclusion in Tolosa-Hunt syndrome [10-11].

CONCLUSION

Unilateral orbital discomfort and ocular muscle paralysis due to nonspecific expansion of the cavernous sinus characterize the rare Tolosa-Hunt Syndrome (THS). Although THS is usually harmless, it does have the potential to damage the optic nerve and cause blindness in rare cases. Because THS is so uncommon and its symptoms might be similar to those of other diseases, making a correct diagnosis is challenging. The exclusion of more serious diseases, such as tumors or infections, that display similar symptoms makes a rapid and accurate diagnosis all the more important. Treatment of THS is most effective when started as soon as symptoms appear; this is because corticosteroid medication frequently reduces symptoms significantly. However, the patient has a good chance of making a full recovery with prompt diagnosis and appropriate treatment. In order to assess the impact of the illness, rule out other possible causes, and track the success of treatment, imaging is essential. Timely and effective treatment, which reduces the risk of long-term consequences, requires radiologists and clinicians to be well-versed in both conventional and unusual imaging findings of THS. In order to provide the best possible therapy outcomes for THS patients, pharmacists play a crucial role in patient education and close monitoring.

Healthcare outcomes

Patients complaining of headaches are common presentations for primary care physicians, nurse practitioners, and internists. It is crucial to send the patient to a neurologist when they have ophthalmoplegia in addition to a severe headache. Corticosteroids and immunosuppressive medication are used to treat Tolosa-Hunt syndrome, which is different from other headache conditions. Patients often suffer from worse quality of life and recurring episodes even after receiving these therapies. The possible side effects of corticosteroid medication must be closely monitored by nurse practitioners and other essential care assistants. Better patient outcomes may be possible as a consequence of an interdisciplinary effort to manage this scenario^[1].

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