

Tolosa-Hunt Syndrome: A Rare Cause of Painful Ophthalmoplegia

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Abstract Tolosa-Hunt syndrome (THS) is a rare inflammatory disorder of unknown etiology with an incidence of one case per million each year. The syndrome is characterized by painful diplopia due to cranial nerve III, IV, or VI palsy. No specific risk factors have been reported, however, in some cases it has been associated with a recent upper respiratory tract infection. THS usually responds well to steroids and they remain the mainstay of treatment. Here, we report a case of a young Hispanic male with no previous health conditions presenting with ophthalmoplegia and retro-orbital pain. After excluding other etiologies of his presentation, a final diagnosis of THS was made. He initially responded well to a course of high-dose steroids, however, he later developed recurrent symptoms and worsening Magnetic resonance imaging (MRI) findings for which he needed an extended course of steroids.

Keywords: *tolosa-hunt, ophthalmoplegia, diplopia, steroids*

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1. Case Presentation

A 29-year-old Hispanic male presented to the emergency room after a three-day history of right retro-orbital pain and dry cough followed by vertical diplopia that he noticed upon awakening. The patient denies any past medical history or family history of headaches or migraines. The patient presented to a different hospital on day two of the diplopia but was sent home. He then presented to our emergency room on day three after an optometrist urgently sent him to the hospital.

Upon physical examination, the patient had mild right medial rectus and superior oblique palsy. Adduction and downward gaze of the right eye was slightly limited, while abduction and upward gaze remained intact. On the second day of admission, the patient developed ptosis in his right eye and his downward gaze palsy significantly worsened. Both pupils were equal, round, and reactive to light. The patient also reported mild blurry vision in his left eye, but denied any other neurological symptoms such as paresthesia, limb weakness, dizziness, or loss of consciousness.

MRI orbit, MRI brain, and magnetic resonance angiography (MRA) head and neck were ordered immediately. While the MRI brain and MRA were unremarkable, the MRI orbit revealed subtle infiltrative enhancing soft tissue at the right orbital apex, lateral aspect of the right cavernous sinus and right foramen rotundum (Figure 1). Computed tomography (CT) chest,

abdomen and pelvis were also performed which showed no evidence of hilar lymphadenopathy or malignancy.

A lumbar puncture was performed and infectious etiologies of meningitis/encephalitis were ruled out. Cerebrospinal fluid (CSF) culture and smear were also negative. The following values were within normal range in both serum and CSF: angiotensin converting enzyme, erythrocyte sedimentation rate (ESR), C-reactive protein and a multiple sclerosis panel. The following values were within normal range in CSF: glucose, protein, Borrelia burgdorferi total antibodies, venereal disease research laboratory test (VDRL), IgG index, and filariasis IgG4 antibody. Myeloperoxidase and protease 3 antibody levels in the serum were also within normal range.

After ruling out an infectious etiology, IV methylprednisolone 500mg daily was initiated two days after admission. After the first day of treatment, the patient reported mild improvement in diplopia and complete resolution of retro-orbital pain. However, the physical exam still revealed significant right medial rectus/superior oblique paralysis with persistent right eye ptosis. By day two of treatment, the patient reported significant improvement in diplopia and was subsequently discharged on day three of treatment. He was discharged on prednisone 60 mg tapering doses for 11 days with follow-up appointments with neurology.

The patient returned to baseline following the prednisone taper and had a normal neurological and eye exam at his one-month follow-up. However, approximately 3 months following his initial presentation, he began to experience right-sided ptosis associated with frequent headaches.

Notably, he did not have any ophthalmoplegia at that time. Repeat MRI orbit demonstrated diffuse inflammation involving the lateral wall and roof of right orbit including the rectus muscles (Figure 2). Additional lab testing that was ordered at this time included lactate dehydrogenase, immunoglobulin levels, myeloperoxidase antibody, serine protease 3 antibody, and IL-2 receptor. All of which were all within normal range. Urine protein electrophoresis was also unremarkable.

The patient was given IV methylprednisolone 1g for 5 days followed by a prednisone taper. His symptoms completely resolved by the end of the duration of the second steroid taper.

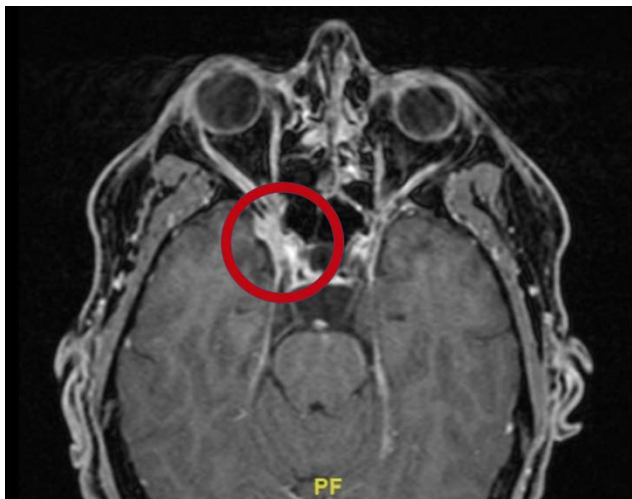


Figure 1. Initial MRI orbit demonstrates subtle thickened enhancing tissue within the right orbital apex and the lateral aspect of the anterior right cavernous sinus.

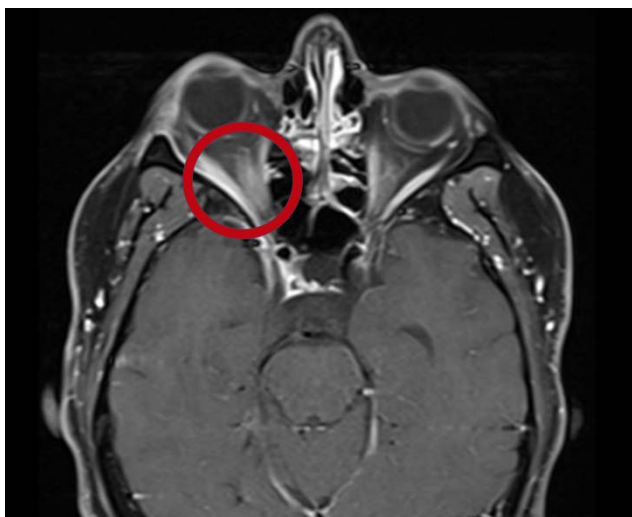


Figure 2. MRI at 3 months shows an infiltrative process along the lateral wall and roof of right orbit including the superior and lateral rectus muscles. The right optic nerve is mildly compressed by this process at the right orbital apex

2. Discussion

The diagnostic criteria for THS was first classified by the International Headache Society in 2004 [1]. Most cases of THS present with painful unilateral diplopia that

responds well to steroids. This condition is due to idiopathic granulomatous inflammation, most commonly of the cavernous sinus, that compresses the CN III, IV, or VI resulting in paresis of the extraocular muscles [2]. Rarely, the condition may cause pupillary dysfunction due to inflammation of the sympathetic fibers of the optic nerve, in addition to paresthesia of the forehead if the V1 branch of the trigeminal nerve is affected [3].

THS may present in any age group. It affects both men and women at the same frequency. Patients oftentimes report a dull or aching retro-orbital pain up to 30 days before the onset of diplopia. In up to 5% of cases, the pain is bilateral. Most patients make a full recovery; the average time it takes from onset to complete resolution of oculomotor palsy is 26 days [4]. A standard treatment regimen includes prednisone 80 to 100mg for three days [5]. If the pain has improved, the dosage may be tapered by 20mg every two weeks over the course of several weeks. Younger patients tend to improve more quickly; however, about 21% of patients do experience relapses which require chronic corticosteroid treatment [6]. On rare occasions, patients do not respond to steroid treatment and biopsy is indicated to confirm the diagnosis [7]. Biopsy most commonly demonstrates granulomatous inflammation with no evidence of infection or neoplasm. In these cases, other immunosuppressive therapies such as cyclosporine, azathioprine, or mycophenolate mofetil are necessary [4].

Although there is no single confirmatory test to diagnose THS, the absence of any other etiology for granulomatous inflammation of the cavernous sinus points us to this diagnosis. It is a diagnosis of exclusion; therefore it is essential to rule out other malignancies or more common causes of inflammation. The International Headache Society defines the following as the diagnostic criteria for THS [1]:

- a) Unilateral orbital/periorbital headache
- b) Ipsilateral paresis of CN III, IV, or VI, within 2 weeks of the onset of headache
- c) MRI or biopsy evidence of granulomatous inflammation of cavernous sinus, superior orbital fissure or orbit, ipsilateral to the headache
- d) Not better accounted for by a different diagnosis

The differential diagnosis should include sarcoidosis, IgG4 disease, and lymphoma. CSF and serum lab values are oftentimes unremarkable. Biopsy of the lesion would provide a more definitive diagnosis. However, if the patient responds well to steroids, biopsy may not be indicated. Some experts also suggest that resolution of symptoms with a course of high dose steroids can help confirm the diagnosis. The lack of generalized inflammatory markers and lack of mediastinal lymphadenopathy in our patient rules out other causes. The isolated findings of the MRI orbit allow us to confidently diagnose this patient with THS. Close follow-up is necessary to ensure there are no complications or a misdiagnosis.

3. Conclusion

THS is a rare inflammatory condition that most commonly presents as painful ophthalmoplegia due to

compression of cranial nerve III, IV, or VI. The incidence rate is approximately one case per million each year. The exact etiology is unclear, however the majority of patients respond well to steroids [5]. It is usually a diagnosis of exclusion with MRI imaging consistent with cavernous sinus inflammation. Biopsy is rarely used due to its invasiveness. Although THS has historically responded well to steroids, it is important for healthcare providers to recognize that this might not always be the case, especially in younger patients. This condition is commonly misdiagnosed because it is so rare; however its prognosis is generally favorable and treatment is simple, so early diagnosis is beneficial. Other granulomatous etiologies should be considered, however this is unlikely if all lab values continue to be within normal limits. THS remains a diagnosis of exclusion for these patients.

Recurrent MRI imaging should be considered in patients with repeated episodes. As in our patient, inflammation may actually worsen in subsequent attacks. Further research is required to determine whether worsening MRI findings is a common feature of recurrent THS.

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