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Review Article

Ophthalmoplegia syndrome or tolosa hunt syndrome – A review

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ABSTRACT

Ophthalmoplegia syndrome or Tolosa Hunt syndrome (THS) is a rare severe unilateral periorbital headache associated with painful and restricted eye movements (ophthalmoplegia) with no visual deterioration. It is associated with choric inflammation with granulomatous deposition in cavernous sinus and at superior orbital fissure.

This article provides a detail outlook of this syndrome that along with pathophysiology, the present diagnostic considerations and management insights on Tolosa-Hunt syndrome through review of published article.

1. Introduction

Ophthalmoplegia syndrome or Tolosa Hunt syndrome (THS) orbital apex syndrme or Recurrent ophthalmoplegia, is a rare as recognized by National Organization for Rare Disorders (NORD), severe unilateral periorbital headache associated with painful and restricted eye movements. Or Tolosa-Hunt syndrome is an idiopathic inflammatory condition that involves the cavernous sinus and orbital apex and is essentially a clinical diagnosis of exclusion.[1] This is also was included in list of painful cranial neuropathies by the International Headache Society (IHS).

Tolosa Hunt syndrome was first described in the year 1954 by Dr. Eduardo Tolosa, a Spanish neurosurgeon.[2] This type of clinical presentation was then also reported by Hunt et al. in 1961.[3] Further for such disorder the term “Tolosa Hunt Syndrome” was coined by Smith and Taxdal in 1966[4] Since then many cases and studies have been reported around the world.

2. Etiology

Ophthalmoplegia syndrome or Tolosa Hunt syndrome (THS) thought to be from non-specific inflammation in the cavernous sinus and/or superior orbital fissure region. Traumatic injury, tumors or an aneurysm could be the potential triggers of this syndrome.

3. Epidemiology

The estimated incidence of Tolosa-Hunt syndrome is 1 per 1,000,000 person-years with an average age of onset at 41 years.[5] It has been reported globally in all race without any geographical boundaries. The usual onset of this syndrome is above 41yrs of age. It is not found in younger peoples. Although usually unilateral, either side can be affected, and there have been case reports about bilateral

4. Pathophysiology

This disorder is a result of a non-specific inflammation of unknown etiology. Tolosa described the pathophysiology as "non-specific, chronic inflammation of the septa and wall of the cavernous sinus with the proliferation of fibroblasts and

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infiltration with lymphocytes and plasma cells.,[2] and was seconded by Hunt et.al. and added that "such inflammatory changes, in a tight connective tissue, may exert pressure upon the penetrating nerves."[3]

The oculomotor, trochlear, abducent and ophthalmic branch of trigeminal cranial nerves could be affected by the presence of granulomatous material deposits along with epithelioid cells and giant cells and also necrosis rarely. The dura in cavernous sinus is also thickened. Rarely also associated with intracranial infiltration.[5]

That explains the syndrome of painful ophthalmoplegia consists of periorbital or hemi cranial pain, combined with ipsilateral ocular motor nerve palsies, oculo-sympathetic paralysis, and sensory loss in the distribution of the ophthalmic division of the trigeminal nerve. Which localizes the pathological process to the region of the cavernous sinus/superior orbital fissure.[6]

It has been found that this disorder may be associated with other systemic and autoimmune inflammatory disorders such as SLE, Sarcoidosis and Wegener's granulomatosis.[7,8]

5. Clinical Presentation

The hallmark of this syndrome is a periorbital or hemi cranial pain, combined with ipsilateral ocular motor nerve palsies, oculo-sympathetic paralysis, and sensory loss in the distribution of the ophthalmic division of the trigeminal nerve.

The pain may be described as sharp, shooting, stabbing, boring, severe and intense, located in the periorbital region but can often be retro-orbital, extending up to frontal and temporal areas and may precede up to 30 days of eye ball movement restrictions.

This syndrome may have relapsing nature and attacks recurring every few months or years. The 3^{rd} cranial nerve mostly affected around in 80% cases, next is 6^{th} cranial around 70%, ophthalmic br. of 5^{th} cranial nerve around 30%, and 4^{th} cranial nerve trochlear nerve around 29%. This syndrome usually does not have any other neurological or systemic involvement[5]

A sympathetic involvement (3^{rd} order neuron Horner syndrome) around in 20% cases and 3^{rd} cranial nerve associated parasympathetic nerve can cause pupillary abnormalities.[9,10]

Occasionally maxillary and mandibular division of 5^{th} cranial nerve may also be affected. 2^{nd} and 7^{th} nerve involvement suggest an extension of the disease process beyond the cavernous sinus. Optic nerve inflammation if involve orbital apex leads to optic nerve damage and loss of visual acuity.[3,4,11–14]

Nausea, vomiting, chronic fatigue due to pain also may be there and these symptoms may last up to 8 weeks and then resolve spontaneously without any residual neurological effect.[15]

6. Diagnostic Evaluation

This syndrome is diagnosed on basis of the clinical presentation, neuroimaging studies and steroid response.

The supportive test are Laboratory tests and cerebrospinal fluid (CSF) studies, that help in ruling out the other causes of ophthalmoplegia.

Last choice is Tissue biopsy, although it is diagnostic due to high risk and technical difficulties.

International Headache Society (IHS) Diagnostic Criteria.

In international headache society, this disorder under painful cranial neuropathies and other facial pains. The diagnostic criteria laid down for THS gives high sensitivity (95% to 100%) but low specificity (approximately 50%).[16]

That is summarized here as follows: -

6.1. Unilateral headache

Includes both of the following:

1. Presence of granulomatous inflammation of the cavernous sinus, superior orbital fissure or orbit, with or without caseation seen on MRI or biopsy
2. Ipsilateral palsies of one or more of the oculomotor nerves.

Corroboration of the cause as evidenced by both of the following:

1. Ophthalmoplegia happened after 2 weeks or less after headache or developed simultaneously with a headache.
2. Ipsilateral periorbital localization of a headache.

6.2. Neuroimaging

1. MRI brain with contrast, especially the coronal view, is a crucial diagnostic study. It shows thickening of the anterior cavernous sinus, superior orbital fissure +/- orbital apex. because of the presence of abnormal soft tissue.
   Signal characteristics are non-specific[17] (clinical scenario essential to diagnosis) but may include:
   (a) T1: involved region is isointense [18] to hyperintense[19] compared with muscle.
   (b) T2: involved area is hyperintense.
   (c) T1 C+ (Gd): may show contrast enhancement during active phase with resolution of enhancement following treatment[20,21] which is isointense on T1, iso or hypointense on T2, and enhances with contrast.
   Also seen, Lateral wall convexity of the cavernous sinus, orbital apex extension.
   Although MRI findings have low specificity,

2. High-resolution computed tomography (HRCT) can also show changes in the soft tissue but less sensitive. and above-mentioned findings can also be found in lymphoma, meningioma, and sarcoidosis.[6]

There are reports of vascular abnormalities in the intra-cavernous segment of carotid artery which show segmental narrowing, constriction, irregularities. These changes can be detected by MR angiography, CT angiography, digital subtraction angiography and usually resolve with steroids.

6.2.1. Other tests

In case of suspicion on clinical presentation and MRI, blood and CSF studies should be performed to rule out other causes of painful ophthalmoplegia.[6]

Blood tests: - Complete Blood Count, Comprehensive Metabolic Panel, HbA1C, ESR, C-Reactive Protein, angiotensin converting enzyme (ACE), Anti-Nuclear Antibodies, Anti-dsDNA Antibody, Anti-sm Antibody, Lyme Panel, Serum Protein Electrophoresis, Fluorescent Treponemal Antibody Test.

CSF studies: - Glucose, protein, cell count and differential, cytology, culture and gram stain, ACE enzyme, syphilis and Lyme serology.

Blood and CSF markers are usually normal in this syndrome.

6.2.2. Steroid responsiveness

The high doses of systemic steroids lead to a dramatic improvement in pain within 2-3 days. Cranial nerve dysfunction improves due to volume reduction of granulomatous tissue in cavernous sinus or orbital apex. and there is a reduction in abnormal tissue volume as well as signal intensity on MRI over the next few weeks of steroid treatment.[9] This helps in confirmation of diagnosis

Other disease processes such as malignancies, infection, or vasculitis should also be taken into account before confirming the diagnosis of Tolosa Hunt syndrome with steroid response clinically and MRI.

Glucocorticoids have been the mainstay of the treatment ever since the syndrome was first described.[3,4] But there is no specific data to give recommendations about dose, duration or route of administration.[6]

Spontaneous remission of symptoms is known to occur.

Although orbital pain drastically improves with steroid treatment, may be followed improvement in ophthalmoplegia. The treatment involves initial high-dose therapy for few days followed by a gradual taper over weeks to months.[22] That is guided by symptomatic resolution and MRI image improvement.

Rarely used immunosuppressives (Azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, and infliximab) for resistant cases or recurrent cases[3,4] or contraindications to steroids. Usually, these patients would have had a biopsy-proven diagnosis of Tolosa Hunt syndrome before a second-line therapy is initiated.[23]

7. Prognosis

Its symptom dramatically improve with Glucocorticoids, especially pain relief, is often seen in 24 to 72 hours and improve within one week. Cranial nerve palsies improve gradually in two to eight weeks.[4] Relapses occurs in about half patients[3], common in younger patients.[13]

Whether steroids help prevent relapses is not clear.[24]

8. Differential Diagnosis

Cavernous Sinus Syndromes, Cerebral Aneurysms, Cerebral Venous Thrombosis, Diabetic Neuropathy, Epidural Hematoma, Lyme Disease, Meningioma, Migraine Headache, Tuberculous Meningitis, Varicella Zoster.

8.1. Caution

The ophthalmologist should be caution before diagnosing Tolosa hunt syndrome after excluding variou s causes of painful ophthalmoplegia include the following: Trauma, Vascular- Intra-cavernous carotid artery aneurysm, Posterior cerebral artery aneurysm.

Carotid-cavernous fistula, Carotid-cavernous thrombosis, Posterior communicating artery aneurysm.

Basilar artery aneurysm, Internal carotid artery dissection.

Neoplasm-Primary intracranial tumor, Pituitary adenoma, Meningioma, Craniopharyngioma, others.

Primary cranial tumor, metastases, Nasopharyngeal tumour and others.

8.1.1. Inflammation, infection

Bacterial-Contiguous sinusitis,[25] Mucocele (sphenoid sinus), Periostitis, Abscess.

Viral - Herpes zoster, Fungal - Mucormycosis, Actinomycosis, Spirochetal- Treponema pallidum, Mycobacterial- Mycobacterium tuberculosis, Others-Sarcoidosis, Wegener's granulomatosis, Eosinophilic granuloma, Orbital pseudotumor[26]

8.1.2. Miscellaneous

Diabetic ophthalmoplegia, Ophthalmoplegic migraine, Giant cell arteritis.

THS responded well to steroid treatment, but if it was accompanied by optic neuritis as optic nerve involvement, it has been suggested a follow-up with high dose steroid treatment is important.[27,28]

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10. Conflict of Interest

None.

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