

## Painful ophthalmoplegia - a hospital based prospective observational study from south Kerala

Kabeer Kaithadiyil Abdul Khayar Kutty<sup>1\*</sup>, Sunil Das<sup>2</sup>, Jyolhish Sivananda Panicker<sup>3</sup>, Sreedevi P.<sup>4</sup>

<sup>1</sup>Additional Professor, Dept. of Neurology, Government T.D Medical College, Alappuzha, Kerala, <sup>2</sup>Assistant Professor, Dept. of Neurology, <sup>3</sup>Additional Professor, Dept. of Neurosurgery, <sup>2,3</sup>Government Medical College, Trivandrum, Kerala, <sup>4</sup>Consultant, Dept. of Pediatrics, General Hospital, Alappuzha, Kerala, India

**\*Corresponding Author:**  
Email: kabeerka4@gmail.com

### Abstract

**Introduction and Objectives:** Painful ophthalmoplegia is a clinical syndrome due to various underlying causes. The objective of the study is to determine the underlying pathological entities responsible for this potentially fatal condition. Various primary headache syndromes, facial pain syndromes and post traumatic and postsurgical pain syndromes were ruled out clinically.

**Materials and Methods:** 107 patients satisfying our research definition of painful ophthalmoplegia were enrolled in this study. The data was collected and analyzed systematically.

**Results and Interpretation:** The common etiological causes for painful ophthalmoplegia are idiopathic inflammation of orbit (22 patients /20.5%), Tolosa hunt syndrome (13 patients /11.21%) followed by orbital cellulitis (11 patients /10.28%) fungal granuloma and mononeuritis multiplex (10 patients each /9.34%) granulomatosis with polyangiitis and tuberculous granuloma (5patients each/4.67%)

**Conclusions:** most cases of painful ophthalmoplegia are amenable to medical management provided an early and prompt diagnosis is made using appropriate diagnostic tools.

**Keywords:** Ophthalmoplegia, Periorbital pain, Tolosa hunt syndrome, Superior orbital fissure, Cavernous sinus, Orbital apex, Fungal granuloma, Tuberculous granuloma.

### Introduction

Painful ophthalmoplegia is a clinical syndrome than a disease entity with various underlying causes. By definition ophthalmoplegia means paralysis or weakness of one or more extra ocular muscle causing diplopia or paralysis of ciliary muscles causing defective accommodation. Based on this definition ophthalmoplegia can be classified into three groups. First one is external ophthalmoplegia where extra ocular muscles alone are affected compared to second group ie internal ophthalmoplegia where only ciliary muscles are involved. Third group the complete ophthalmoplegia where both extra ocular and ciliary group of muscles have been affected together. Pain along the distribution of Trigeminal nerve is an important feature in syndrome of painful ophthalmoplegia. Pain over eye, along the distribution whole of first, second and rarely third division of Trigeminal nerve is the cardinal symptom of this condition. Ophthalmoplegia associated with ipsilateral orbital pain have various etiological factors including inflammatory conditions chronic infections, neoplasms and vascular anomalies.

Superior orbital fissure syndrome is characterized by pain along the distribution of trigeminal nerve with or without sensory loss associated with diplopia due to involvement of extra ocular muscles. Examination reveals ptosis, ophthalmoplegia and decreased corneal sensation. In orbital apex syndrome there is involvement of the same cranial nerves in association with optic nerve dysfunction.<sup>4</sup> The cavernous sinus syndrome includes the features of orbital apex

syndrome with added involvement of the maxillary branch of the trigeminal nerve and oculosympathetic fibers.<sup>3</sup> Patients who have features of superior orbital fissure syndrome may subsequently develop orbital apex and cavernous sinus syndromes. Presence of swelling of the eye lid chemosis, proptosis indicates significant mass extension into the orbit. Detection of etiology will not be easy in all patients with ophthalmoplegia so also formulating a definitive treatment strategy.

Idiopathic orbital inflammation or Orbital pseudo tumor was first described by Birch Hirschfield in 1905.<sup>1</sup> Proposed mechanisms of this entity with elusive pathogenesis include autoimmune, chronic infection, aberrant wound healing and biopsy obtained from tissue specimen showed complement deposition and increased expression of HLA class I antigen. Classification of idiopathic orbital inflammation is based on the tissue affected within the orbit due to inflammatory pathology. It may affect virtually any orbital structures including lacrimal gland, orbital fat, connective tissue and optic nerve. Differential diagnoses of this inflammatory condition include Sarcoidosis, Lymphoma, ANCA associated vasculitis, Crohn's disease, Systemic Lupus Erythematosus, Behcets's disease, and IgG4 related diseases.<sup>1</sup> Tolosa Hunt syndrome was first reported in 1966 by Taxel and Smith based on observation made by Tolosa and Hunt separately. It is defined as a painful ophthalmoplegia with unknown etiology that responds to steroids with in forty eight hours. To make a diagnosis of Tolosa Hunt

syndrome there must be either granulomatous inflammation of cavernous sinus, superior orbital fissure or orbit demonstrated by MRI or biopsy or weakness of one or more ipsilateral third, fourth and sixth nerves.<sup>2</sup> In most of reported cases, pain is confined ipsilateral first and second division of trigeminal nerve precedes the onset of ophthalmoplegia. This is a relatively benign condition usually respond to corticosteroid and other immune modulatory therapies. However relapses have been reported in majority of cases especially with florid presentations. Granulomatosis with polyangiitis or Wegener's granulomatosis is a systemic necrotizing vasculitis associated with granulomatous inflammation of nose and paranasal sinuses, lungs and renal system. This is an ANCA positive vasculitis often presented as orbital apex, superior orbital or rarely petrous apex syndromes.<sup>7</sup> ACR criteria include nasal or oral inflammation, abnormal chest radiograph, abnormal urinary sediment and evidence of granulomatous inflammation on biopsy has a specificity of 92 percent to make a diagnosis of granulomatosis with polyangiitis.<sup>12</sup> Sarcoidosis is a granulomatous inflammation of unknown etiology most commonly affect adults between the age of 20 and 40 and commonly affect lungs. Ocular sarcoid is seen in approximately 12% of case mostly presented as anterior uveitis.<sup>10</sup> Orbital sarcoidosis is still less common and is usually affect lacrimal gland, soft tissue mass, extra ocular muscles. In neurosarcoidosis there is selective involvement of meninges, hypothalamus, spinal cord, peripheral and cranial nerves and muscles.<sup>11</sup> Temporal arteritis is a systemic vasculitis with inflammatory changes with unknown cause which usually affects elderly patients and can presented as various neurological and ophthalmic disorders. This is the most common vasculitis in patients above 50 yrs of age and is presented as head ache, joint pain, facial pain with jaw claudication tenderness over superficial temporal arteries with reduced or absent pulsations. Usually associated with anterior ischemic optic neuropathy and may leads to permanent visual loss and rarely presented as ophthalmoplegia.

Most common orbital fungal infections include mucormycosis and aspergillosis and in both these pathogens cause initial involvement of paranasal sinus followed by secondary infection of orbit. In mucormycosis most common mode of infections are invasion from adjacent paranasal sinus or direct inoculation into orbit via trauma and rarely through respiratory passages especially in immune compromised patients. Rhino cerebral mucormycosis is an acute fulminant often life threatening opportunistic fungal infection usually affect immune compromised individuals eg. Patients with diabetes mellitus & HIV infection. Usually caused by fungus belongs to Mucoraceal family and clinical features are characterized by low grade fever, head ache, facial

edema, orbital and paranasal sinus syndrome. Then the infection cause necrotizing vasculitis and spread into orbit, cranial cavity and eventually to brain through foramina or through meninges. Aspergillosis has three distinct clinical presentations. First is noninvasive sinusitis in immunocompetent host. Second is the locally invasive granuloma causing erosion of bone and extension into the soft tissue of cheek and orbit. Third is the disseminated aspergillosis most commonly involving sinus, lungs, visceral organs, brain and is associated with a mortality of 50-80%.<sup>9</sup> Orbital cellulitis is an infection of soft tissue surrounding eye ball caused by various organisms especially by S.aureus, Streptococci, H. influenzae etc. due to direct injury to periorbital region or spread of infection from adjacent structures like paranasal sinuses.<sup>5</sup> Presenting symptoms include eye lid edema, proptosis, ipsilateral periorbital pain, fever, blurred or double vision. In Hypertrophic pachymeningitis there is significant fibrosis with thickening of duramater of unknown etiology associated with head ache, cranial neuropathies, cerebellar ataxia and csf abnormalities. Diagnosis is based on typical radiological features and biopsy based tissue methods and treatment is mainly immunomodulation.

Ophthalmoplegic migraine has been removed from international classification head ache disorders –beta version. This entity is now been renamed reclassified as recurrent painful ophthalmoplegic neuropathy (ICHD-3, 2018) and is more common in children causing recurrent head ache with ophthalmoplegia.<sup>2</sup> Pain is typically retro or periorbital and is associated with involvement of 3<sup>rd</sup>, 6<sup>th</sup> or 4<sup>th</sup> nerve in that order. According to various population based studies 9-36% of isolated oculomotor nerve palsies are caused by an intracranial aneurysm most commonly at the junction of posterior communicating artery and the internal carotid artery. Aneurysm at top of the basilar and at the junction of and superior cerebellar arteries may also produce oculomotor nerve palsies. Peak incidence of rupture with sub arachnoid hemorrhage is between 50-60 years although they may present at any age. Virtually all aneurysms present with pain as an initial symptom usually associated with ptosis and papillary dilatation.

## Materials and Methods

This hospital based prospective observational study was conducted in Department of Neurology Government Medical College Trivandrum and Government. T.D. Medical College, Alappuzha over a period of ten years. These institutions caters to health needs of people of five districts of Kerala viz Trivandrum, Kollam, Pathanamthitta, Alappuzha and Ernakulam. As we couldn't find a appropriate diagnostic criterion in the literature of painful ophthalmoplegia we have formulated research criteria to conduct this study. Inclusion criteria include (1. Any

patient above the age of 12yrs; (2. Unilateral or bilateral diplopia with or without ptosis or proptosis; (3. Pain around the eye or along the distribution of trigeminal nerve.<sup>4</sup> There will not be any previous history of traumatic brain injury, cranio-facial surgery, glaucoma, brain neoplasia. Cases were selected from medical and neurology wards over a period of ten years. We could collect 107 patients for this study, of which 74 were females and 33 were males. Of the cohort majority of patients were between the age of 25-50yrs (51.4%) followed by age group above 50yrs (38.38%) and rest is constituted by the least common group ie age group below 25yrs (11.2%). 40% of subjects were reported to have diabetes mellitus where as 10 % gave past history of pulmonary tuberculosis and 10% had polyarthralgia in the past. Those with past history of traumatic brain injury, maxilla-cranio-facial surgery, systemic malignancies, glaucoma, diabetic retinopathy were excluded from the cohort. Common clinical syndromes we could enroll are orbital inflammation, superior orbital fissure syndrome, orbital apex syndrome, cavernous sinus syndrome and petrous apex syndrome.

We have done a battery of investigations include blood routine examination, peripheral smear examination, random blood sugar, antinuclear antibody, ANA profile, P-ANCA, C-ANCA, Anti-Cyclic Citrullinated Peptide (Anti-CCP) Antibody, serum angiotensin converting enzyme and cerebrospinal fluid study to diagnose chronic meningitis -TB PCR, fungal stain test, cytology for malignant cells. Imaging study include CT scan brain, CT skull base images & orbits, MRI of Brain, MR angiogram, MR venogram. We used appropriate investigations and criteria to confirm different etiological causes for pain associated with ophthalmoplegia.

## Results

Results were analyzed at the end of the study period. Most common nerve involved was 6<sup>th</sup> nerve (91patients/85%) and optic nerve was least commonly affected (only in 26 patients 24.27%). Proptosis was noticed in 87 patients (81.3%) 3<sup>rd</sup> nerve and 4<sup>th</sup> nerves palsy was seen in 88 (82.24%) and 94 (87.85%) patients respectively. These patients presented with different clinical syndromes like superior orbital fissure syndrome, orbital apex syndrome, etc. Of the cohort of 107 subjects most common presenting symptom was superior orbital syndrome followed by orbital apex syndrome, cavernous sinus syndrome and petrous apex syndromes. Idiopathic inflammation orbit<sup>1</sup> was diagnosed by neuroimaging and biopsy and Tolosa Hunt syndrome was diagnosed using specific criteria<sup>6</sup>. Granulomatosis with polyangiitis (Wegener's granulomatosis) is confirmed by immunological test battery<sup>12</sup> where as fungal<sup>9</sup> and tuberculous granuloma could confirmed on the basis of tissue biopsy as well as cerebrospinal fluid study. Diagnosis of top of the basilar and posterior communicating artery aneurysms were made with MR angiography & CT Angiography. Presence of temporal arteritis recurrent ophthalmoplegic neuropathy were determined on the basis of appropriate criteria.<sup>2</sup> Neuroimaging study was negative in 18 patients.

Most common etiological cause in this cohort of painful ophthalmoplegia was idiopathic inflammation of orbit, 20% (22) followed by Tolosa Hunt Syndrome 11.21% (13), orbital cellulitis 10.28 (11), fungal granuloma, 9.34(10), and mononeuritis multiplex cranialis 9.34% (10). 13 patients (16.82%) didn't show any neuroimaging abnormality. Cases of idiopathic inflammation of orbit were treated corticosteroid and those with orbital cellulites promptly responded to penicillin group of antibiotics. Patients with fungal and tuberculous granuloma received antifungal medications.

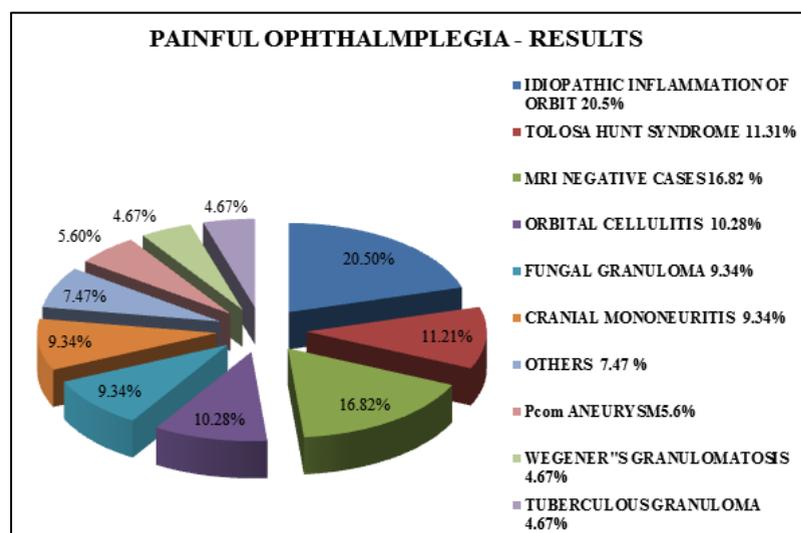


Fig. 1:

## Discussion

As we do not have a previous study entirely dedicated to establish underlying pathological causes of ophthalmoplegia with pain along the distribution of trigeminal nerve, we could not make comparison in this study. There are various studies focusing on Tolosa Hunt syndrome,<sup>6</sup> Orbital pseudo tumors,<sup>1</sup> pituitary mass lesions<sup>14</sup> and infective<sup>9,15</sup> and non infective granulomas.<sup>10,11</sup> If the treating physician is not aware of common underlying causes of this potentially life threatening neurological emergency it is very difficult to formulate an effective algorithm to reach a definitive diagnosis. Establishing a pathological diagnosis is the most essential part of clinical neurology as most of the conditions causing pain associated diplopia are very well responds to appropriate medical or surgical therapy.

In this prospective observational study we were tried to establish common underlying causes of painful ophthalmoplegia from south Kerala. In most cases, the pathology is confined to eye ball, orbit, superior orbital fissure, cavernous sinus or petrous apex. Except for those patients with malignant central nervous system infiltrations and those patients presented with fulminant rhino cerebral infection due mucormycosis most of the patients could come out of danger probably with residual sequelae. Four of our patients lost sight and another sixteen developed atrophy of extra ocular muscles on neuroradiology follow up. Blindness most commonly associated with invasive fungal granulomas and three of our patients died due to vascular invasion.

High degree of suspicion and early and accurate diagnosis and prompt administration of specific therapy will bring back life and prevent sequelae in most of the patients.

## Conclusions

Though the sample size is small, in this work we made an attempt to provide preliminary evidence of various common pathological entities responsible for painful ophthalmoplegia. There are only limited data regarding the heterogeneous etiologies of this syndrome and most the studies focused on single pathological cause. Most common causes were nonspecific inflammation with or without granulomas due to various etiologies and are amenable medical or surgical treatment early and definite and prompt etiological diagnosis helps the treating physician to take early and adequate measures to save the life of many. Based on the current study we could formulate a practically feasible easily adaptable protocol including all possible battery of investigation to make an early and correct diagnosis.

**Conflict of Interest:** None

**Source of Support:** Nil

## References

1. Idiopathic orbital inflammatory Syndrome: Clinical features and treatment outcomes –B.N. Swamy et al *British journal of ophthalmology* 2007;91:1667-1670.
2. The International Classification of head ache disorders, 3<sup>rd</sup> edition – Head ache Classification committee of the *International head ache society (HIS) Cephalalgia* 2018, vol. 38(1) 1-211 *International Head Ache Society* 2018.
3. Cavernous sinus thrombosis and meningitis from community acquired Methicillin resistant staph aureus infection –Munckhof. W.J et al. *Internal medical journal* 2008 April;38(4):283-287.
4. Orbital apex syndrome: a case series– R E Warburton et al *International Journal of Oral maxilla Facial Surgery*. 2016 April, 45(4):497-506.
5. Periorbital and orbital cellulitis in children. William. M Clarke. *Pediatric child Health*. 2004 September 71;471-472.
6. The Tolosa Hunt Syndrome –L.B.Kline, *Journal of Neurology Neurosurgery Psychiatry* 2001;71:577-2827.
7. Clinical feature of childhood granulomatosis with polyangiitis (Wegener's granulomatosis). Marek Bohm et al *Pediatric Rheumatology* 2014;12:18.
8. Overview of neurosarcoidosis: recent advances –Renata Hebel et al. *Journal of Neurology* (2015) 262:258-267.
9. Imaging of granulomatous and chronic invasive fungal sinusitis; Comparison with allergic fungal sinusitis-C Ekambar Eswara Reddy, *Otolaryngology –Head And Neck surgery* (2010)143,294-300.
10. Neurosarcoidosis. Jinny.o. Tavee et al. *Clinics of Chest Medicine-* (2015).
11. Neurosarcoidosis –david Lacomis. *Current Neuropharmacology*. 2011 september; 9(3):429 -436.
12. Diagnosis and classification of granulomatosis with polyangiitis (Wegener's granulomatosis) P.M.K. 2 Lutalo. *Journal of Autoimmunity* xxx (2014) 1e5.
13. Imaging Lesions of the Cavernous Sinus A.A.K. Abdel Razeq *AJNR Am J Neuroradiol* 30:444 –52.
14. Clinical features of non-pituitary sellar lesions in a large surgical Series - Elena Valassi1, Beverly MK Biller. *Clin Endocrinol (Oxf)*. 2010 December;73(6):798–807.
15. Acute invasive fungal rhinosinusitis: Evaluation of 26 patients treated with endonasal or open surgical procedures –Fikret Kasapoglu, Hakan Coskun et al. *Otolaryngology– Head and Neck Surgery* (2010) 143, 614-620.