

# Tolosa–Hunt Syndrome and IgG4 diseases in Neuro-Ophthalmology

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## Abstract

Tolosa–Hunt syndrome (THS) remains a challenging diagnosis for many neurologists. Often believed to be a rare presentation, the classical presentation is known to involve cranial nerves and tissues surrounding the cavernous sinus. Traditionally, a diagnosis of THS is considered when all secondary conditions have been ruled out. Yet, newer findings have elaborated a complex pathogenetic process with some overlap from the IgG4 spectrum of disorders, with which it shares many phenotypic similarities. In this narrative review, we present an updated picture of the condition focusing on the latest developments in the pathogenesis, diagnosis, and clinical management of these two conditions and use illustrative examples to highlight the salient features of this rare presentation.

**Keywords:** Neuroophthalmology, tolosa hunt syndrome, IgG4, pachymeningitis

## TOLOSA–HUNT SYNDROME

### Anatomical components

Tolosa–Hunt syndrome (THS) is a rare neuro-ophthalmic manifestation characterized by non-specific inflammation of the cavernous sinus, superior orbital fissure, or the orbital apex. Clinically, it is identified by the presence of painful ophthalmoplegia involving the oculomotor (III), trochlear (IV), or the abducens (VI) nerves in varying combinations with oculo-sympathetic paralysis and involvement of the ophthalmic or maxillary division of the trigeminal (V) cranial nerve.<sup>[1]</sup> It has been considered, by some, as a variant of the orbital inflammatory syndrome (orbital pseudotumor) with extension into the orbital apex of the cavernous sinus or focal idiopathic hypertrophic pachymeningitis.<sup>[2,3]</sup> The exact nature of the disease continues to find updated definitions and evades consensus among those who treat it.

### BRIEF HISTORY AND DIAGNOSTIC CRITERIA

THS derives its name from Eduardo Tolosa and William Hunt, the two pioneers who independently described patients with ophthalmoplegia with evidence of granulomatous inflammation in the cavernous sinus, and subsequently, this eponym was applied to patients with “investigation negative” cavernous sinus syndrome (CSS).<sup>[4–6]</sup> Diagnosis of THS is considered to be that of exclusion, and lately, various authors have critically declined the eponymous use of the term THS for the “presumed granulomatous inflammation of the cavernous sinuses”.<sup>[7]</sup>

The International Classification of Headache Disorders-3 (ICHD-3) defines THS under the category of “painful lesions of cranial nerves and other facial pain”. The key diagnostic requirements are the presence of unilateral orbital/periorbital pain in combination with paresis of one or more oculomotor cranial nerves and demonstration of granulomatous inflammation of the cavernous sinus.<sup>[1]</sup> The diagnostic criteria were adopted

by ICHD-3 and are important to consider while diagnosing of THS [Table 1]. These criteria are highly sensitive (~95–100%) but have limited specificity (~50%) to diagnose THS.<sup>[1]</sup>

## EPIDEMIOLOGY AND CLINICAL PROFILE OF THS

THS is considered to be a rare entity with an annual estimated incidence to be 1–2 cases per million per year. Yet, it accounts for nearly 23% of causes of CSSs. No geographical or racial

**Table 1: ICHD-3 Diagnostic Criteria of THS**

- |  |
|--|
| A. Unilateral orbital/periorbital headache fulfilling criteria C   |
| B. Both B1 and B2  |
| 1. Granulomatous inflammation of the cavernous sinus, superior orbital fissure, or orbits, demonstrated by MRI or biopsy |
| 2. Paresis of one or more of the ipsilateral oculomotor, trochlear, and/or abducens nerves                               |
| C. Demonstration of evidence of causation fulfilling both C1 and C2  |
| 1. Headache ipsilateral to the granulomatous inflammation  |
| 2. Headache has preceded the involvement of extraocular motor nerve by $\leq 2$ weeks or developed with it               |
| D. Not better accounted for by any other cause   |

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predominance has been noted. It does not show any gender predilection, and the average age of onset has been noted to be in the fourth decade.<sup>[8,9]</sup>

Involvement can be unilateral, sequential, or bilateral and simultaneous. Pain is usually the defining feature and suggests a localized dural inflammation. Pain is usually around the eye or brow on the involved side or can be retroorbital or even extend to the frontal or temporal regions. It usually precedes ophthalmoplegia by a duration of up to 2 weeks and on average lasts for about 8 weeks in untreated cases.<sup>[8]</sup> Extraocular muscles can be involved in any combination, and it is wise to revise the anatomy of the cavernous sinus and nearby structures. Ishikawa and Jefferson's classification schemes are two popular classification schemes that can help in the anatomical classification of the lesions and also have prognostic importance [Figure 1].<sup>[10,11]</sup>

### CLINICO-ANATOMICAL CORRELATION

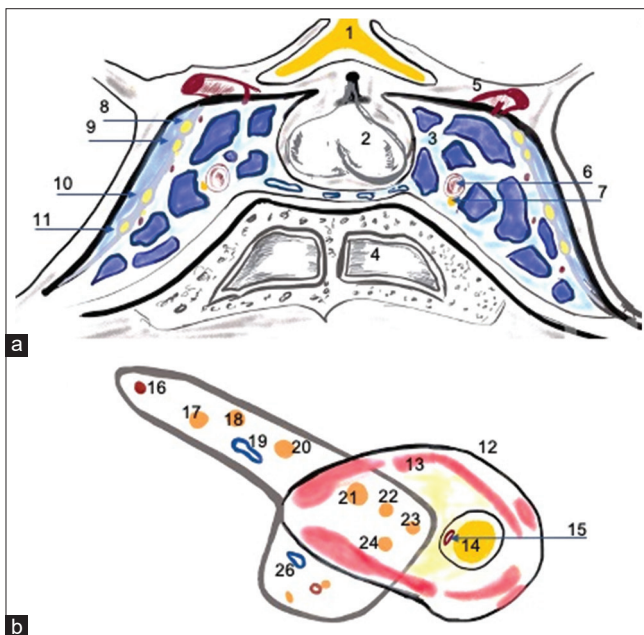
THS often involves the lateral wall of the anterior cavernous sinus; hence, the oculomotor nerve is the most commonly involved in about 80% of the cases. [Figure 1] Involvement of the core of the cavernous sinus may in turn lead to the

involvement of the abducens nerve, which is seen in around 70% of cases. Oculo-sympathetic plexus around the internal carotid artery (ICA) may be involved in another 20% of patients, causing third-order Horner's syndrome. Proptosis may occur in a small subset of patients due to the involvement of pericarotid sympathetic fibers and the resulting contraction of Muller's muscle.<sup>[8,9]</sup>

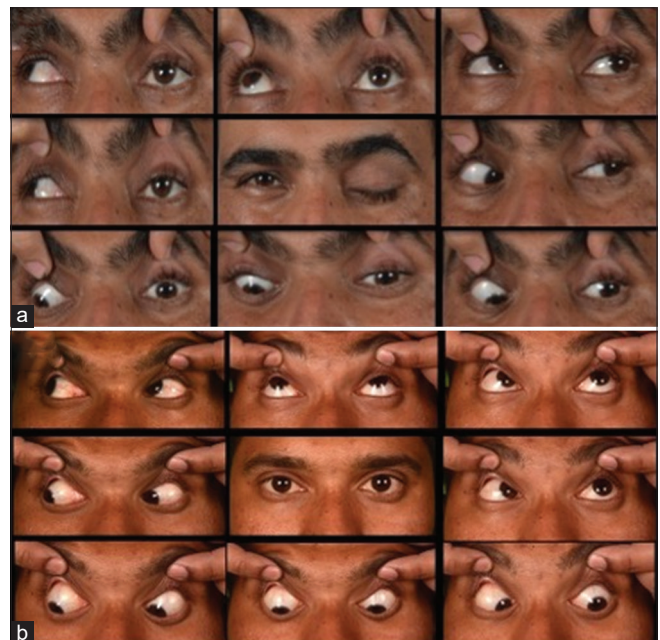
Involvement of the trochlear nerve and ophthalmic and maxillary divisions of the trigeminal nerve can take place in various combinations. The spread of inflammation further anteriorly into the superior orbital fissure or the orbital apex may lead to the involvement of the optic (II cranial) nerve, causing visual loss, optic disc swelling, and consequent optic pallor. An extension may also occur posteriorly in a few cases, leading to the involvement of the facial nerve, vestibulocochlear nerve, and other vital structures.<sup>[9,12,13]</sup> Systemic features such as nausea, vomiting, and fatigue secondary to severe periorbital pain have been reported in anecdotal case reports/series.<sup>[8]</sup> Clinical examination is always essential for diagnosis and should utilize the evaluation of the nine cardinal gazes of the patient to know the involvement of each nerve [Figure 2a and B].

### DIAGNOSTIC EVALUATION

Diagnosis is clinical, and meticulous investigations are needed to exclude other causes of CSS. The ICHD-3 diagnostic criteria mandate the demonstration of granulomatous inflammation



**Figure 1:** Animation depicting anatomical landmarks of the structures in the cavernous sinus (a) and in the orbital apex (b). (1) Optic chiasma; (2) pituitary gland; (3) cavernous Sinus; (4) sphenoid sinus; (5, 6) ICA; (7) abducens nerve; (8) oculomotor nerve; (9, 20) trochlear nerve; (10) ophthalmic division of the trigeminal nerve; (11) maxillary division of the trigeminal nerve; (12) annulus of Zinn; (13) extraocular muscles; (14) optic nerve; (15) ophthalmic artery; (16) recurrent meningeal artery; (17) lacrimal nerve; (18) frontal nerve; (19) superior ophthalmic vein; (20) trochlear nerve; (21) superior division of the oculomotor nerve; (22) nasociliary nerve; (23) inferior division of the oculomotor nerve; (24) abducens nerve; (25) inferior ophthalmic vein



**Figure 2:** (a) Showing nine-gaze photograph of a 34 year-old male with left oculomotor nerve palsy who presented with recurrent complaints of drooping of the left eye and diplopia for 2 years (total of 3 episodes). The patient was diagnosed to be having left THS based on neuroimaging findings. (b) Showing nine-gaze photograph of a 28 year-old male with left abducens nerve palsy THS. The patient presented with the first episode of diplopia with horizontal separation of images on looking toward left

by neuroimaging or biopsy, and hence, a histopathological correlation is always required to establish the same.<sup>[1]</sup>

## MAGNETIC RESONANCE IMAGING (MRI)

### Ideal sequences in MRI

Conventional neuroimaging techniques usually do not cover the proper visualization of the cavernous sinus. Dedicated contrast-enhanced, fat-saturated, TurboSpin Echo T1 and T2 sequences in the coronal and axial sections must be utilized in the study of the cavernous sinus. The orbital apex, superior orbital fissure, and anterior temporal lobe should always be carefully seen in a patient with suspected THS. Akpınar *et al.*<sup>[14]</sup> suggested a dedicated “Tolosa–Hunt protocol” and highlighted the role of dynamic MRI in facilitating the early diagnosis of THS.

### Characteristic findings on MRI

Convexity of the lateral wall of the cavernous sinus due to the presence of soft tissue, which appears isointense on T1, hypointense on T2, enhances upon contrast administration, and is diffusion-weighted imaging restriction is the characteristic description of THS. A bulging contour of the lateral wall of the cavernous sinus, dural meningeal enhancement (focal pachymeningitis) of neighboring structures, and focal narrowing of the intracavernous ICA are other subtle signs suggesting THS<sup>[15]</sup> [Figure 3a–c].

The presence of nasal/paranasal sinus disease should alert a physician to rule out fungal etiology, and lacrimal enlargement should alert the clinician to IgG4 and other noninflammatory granulomatous etiologies such as sarcoidosis. Extension of the lesion should always be looked for by tracing the orbital apex and superior orbital fissure.

### Caveats on neuroimaging

The lack of specificity of the MRI findings is a major limitation. In a retrospective analysis of 61 patients with painful ophthalmoplegia, identification of atypical findings (lesions extending into sella fossa, infratemporal fossa, paranasal sinuses, brain parenchyma, skull or causing bony erosions, or causing a dilated superior orbital vein) on cranial imaging was found to have a useful role in discriminating other etiologies

before labeling THS.<sup>[15]</sup> The abnormal signal intensity may also be confused with orbital pseudotumor, neurosarcoidosis, central nervous system lymphoma, meningiomas, IgG4 disease, and chronic infections such as fungal sinusitis. Indirect signs such as the involvement of sinuses, bony erosions, angioinvasion, etc., although not highly sensitive, may provide vital clues toward the diagnosis of fungal infection in contrast to inflammatory etiologies such as THS [Figure 4a-d].

### Role of Computed Tomography (CT) in the diagnosis of THS

Although high-resolution CT scans may demonstrate soft tissue inflammation and associated bony changes such as erosion, hyperostosis, calcification, or even hemorrhage, it has limited sensitivity for cavernous sinus/orbital apex lesions. Moreover, the use of CT is limited due to superimposed beam hardening and bony artifacts.<sup>[8,16]</sup>

## CEREBRAL ANGIOGRAPHY

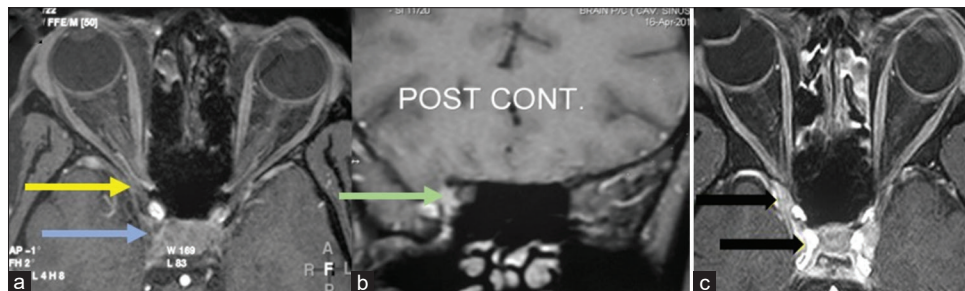
Cerebral angiography is primarily important to rule out aneurysms or fistulae in the carotid–cavernous territory. Segmental narrowing, irregularity, or constriction of the intracavernous carotid artery need to be noted as these findings may provide valuable adjunct information in favor of THS. In some patients, soft tissue inflammation may cause intense stenosis of the carotid siphon, resulting in high resistance flow that was described as the “arterial stationary wave phenomenon” in older literature on THS.<sup>[17]</sup>

## ORBITAL VENOGRAPHY

Orbital venography may disclose abnormal filling of the superior ophthalmic vein or the cavernous sinuses but does not contribute to ruling out other causes of CSS.<sup>[18]</sup>

## ANCILLARY IMAGING AND POSITRON EMISSION TOMOGRAPHY (PET)

It is judicious to screen selected patients for the presence of systemic inflammatory conditions and malignancies by CT of the chest/abdomen or whole-body PET. In addition, fluorodeoxyglucose (FDG) PET/CT may show focal



**Figure 3:** (a) Showing gadolinium-enhanced MRI of the brain, T1 axial image with a bulging convex contour of the right anterior cavernous sinus (blue arrow); isointense soft tissue lesion involving the right anterior cavernous sinus and orbital apex (yellow arrow). (b) Showing gadolinium-enhanced MRI of the brain, T1 coronal image showing contrast-enhanced soft tissue lesion in the right orbital apex (green arrow). (c) Gadolinium-enhanced MRI of the brain showing sheet-like enhanced lesion involving the right cavernous sinus encasing the ICA without invading it

hypermetabolism, suggesting inflammation in THS. Although limited by its low specificity, FDG PET/CT may provide vital clues to differentiate THS from other ominous disorders.<sup>[19]</sup>

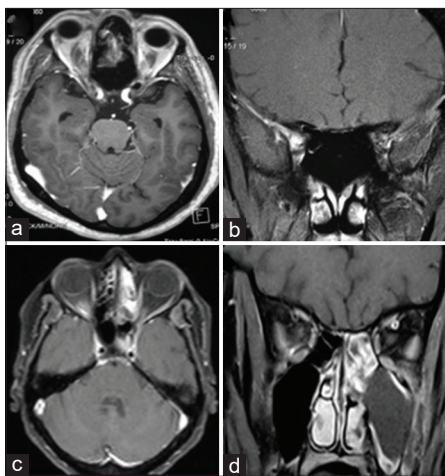
### LABORATORY INVESTIGATIONS AND CEREBROSPINAL FLUID (CSF) EXAMINATION

A raised erythrocyte sedimentation rate (ESR), C-reactive protein, and leucocytosis may occur in the acute stages of THS. Similarly, the presence of antinuclear antibodies, LE cell preparations, and a few extranuclear antibodies may be seen in patients with THS.<sup>[8]</sup>

It is important to note that CSF analysis may be completely unremarkable in these patients, although mild pleocytosis or marginally raised proteins have been documented. These changes are steroid-responsive and the persistence of abnormalities or grossly abnormal CSF should suggest an alternative neuroinflammatory cause.<sup>[8,9]</sup>

### HISTOPATHOLOGICAL EVALUATION

A definitive diagnosis is established by histopathology. However, obtaining a sample may be technically challenging due to the deep location of the cavernous sinus and the presence of important cranial nerves around the involved site. Non-specific chronic granulomatous inflammation with abundant fibroblasts, lymphocytes/plasma cells, epithelioid, and occasional giant cells infiltrating the septa and the walls of cavernous sinuses is the hallmark of the biopsy specimen in patients with THS.<sup>[9]</sup> Lack of IgG4 staining plasma cells, storiform fibrosis, and obliterative phlebitis differentiate THS from similar-looking IgG4-related disorders.



**Figure 4:** (a) and (b) Showing gadolinium-enhanced MRI of the brain T1 W images in a patient with soft tissue inflammation in the right anterior cavernous sinus and orbital apex in a patient of THS. Sparing of paranasal sinuses is seen. In contrast, (c and d) show left cavernous sinus involvement with the involvement of the left sphenoid and ethmoidal paranasal sinuses in a patient of histopathologically proven fungal sinusitis

### DIFFERENTIAL DIAGNOSIS [TABLE 2]

THS is a diagnosis of exclusion. A wide spectrum of medical and surgical causes of painful ophthalmoplegia is included in the differential diagnosis of THS. Association of other autoimmune disorders has been reported in the literature. Table 2 shows the differential diagnosis and conditions which should be adequately ruled out before considering the diagnosis of THS.<sup>[9]</sup>

### TREATMENT OF THS

In general, THS is considered to be self-limiting and even without treatment improvement should occur over a few months.<sup>[9]</sup> Treatment is often offered due to the possibility of residual deficits causing morbidity in these patients. There is no consensus or guideline for treatment, and the agent of choice depends a lot on the choice of the physician and patient suitability.

Corticosteroids are the cornerstone for the treatment of THS. High-dose pulse steroid therapy has been advocated in the recent literature, followed by oral steroids (0.75 mg/kg) in tapering doses for a duration of 6 to 8 weeks. Literature is not clear on the route of administration, optimal dose, duration of therapy, and treatment protocols for a special subset of patients (children, pregnant patients, etc.). Clinical improvement, specifically in periorbital/orbital pain, usually starts within 24 hours. Cranial nerve functions improve over 6 to 8 weeks. Non-responsiveness to steroids should suggest an alternative diagnosis. Clinical improvement usually precedes

**Table 2: Medical Causes of Painful Ophthalmoplegias**

Differential Diagnosis	Causes
Trauma	
Vascular causes	Posterior communicating artery aneurysm Cavernous ICA aneurysm Carotid-cavernous fistula Cavernous sinus thrombosis
Diabetes associated ocular cranial nerve palsy	
Inflammatory lesions	
Infectious:	Bacterial: Sinusitis, periostitis, orbital cellulitis Viral: Herpes zoster Fungal: Mucormycosis Mycobacterium tuberculosis
Non-infectious:	Polyneuritis cranialis, sarcoidosis, IgG4-related disorder, eosinophilic granuloma, vasculitis Wegener's granulomatosis, giant-cell arteritis, orbital inflammatory syndrome, hypertrophic pachymeningitis, THS
Ophthalmoplegic migraine	
Neoplastic lesions	Nasopharyngeal carcinoma, lymphomas, multiple myeloma, parasellar/orbital metastasis, primary intracranial tumors, Pituitary adenoma

the neuroradiological resolution, which may be delayed by weeks or even several months.<sup>[20]</sup> Dramatic improvement in symptoms is noted after steroid administration, but no conclusive data suggests the role of steroids in decreasing the degree or the duration of ophthalmoplegia. Some patients may have residual cranial nerve palsies.

Recurrences are known and may occur even after months after the first episode. Kline noted recurrence in 39% of 146 patients of THS reviewed by him in one of his earlier series.<sup>[8]</sup> Long-term steroids may be required in these subsets of patients. The role of steroid-sparing agents in preventing relapse is not clear. Although there are no clear guidelines on the use of steroid-sparing agents, many immunosuppressive/immunomodulatory drugs such as mycophenolate mofetil, methotrexate, azathioprine, and rituximab have been used successfully in patients who relapse after steroids. Other agents used with variable efficacy include cyclophosphamide, cyclosporine, tacrolimus, infliximab, and adalimumab (anecdotal case reports available in the literature). Various authors have reported complete remission of the disease using therapy with tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) antibody and infliximab.<sup>[21]</sup>

Focal radiotherapy/gamma knife radiosurgery has been found useful in well-selected subsets of patients who are non-responsive, partially responsive, non-tolerant to medical treatment, or in whom conventional treatment is contraindicated.<sup>[22]</sup>

## NATURAL COURSE AND PROGNOSIS

Although THS is often acute to subacute in onset patients, the course of the disease is unpredictable. Symptoms may last from days to many weeks, but the disease is usually self-limited. Spontaneous remissions, as well as recurrences, are known. Residual cranial nerve paresis may lead to significant morbidity, and hence, more often than not, steroids are administered in most cases presenting early to medical attention. The overall prognosis is considered to be favorable, even though up to 40% of patients can relapse after complete improvement.<sup>[8,9,21]</sup>

## IGG4 DISEASES IN NEURO-OPHTHALMOLOGY

One of the emerging causes of painful ophthalmoplegia is the IgG4-related ocular disease which in itself is one of the manifestations of systemic disease.<sup>[23]</sup> IgG4 is a chronic fibroinflammatory condition that is being increasingly recognized with many neurological conditions.<sup>[24]</sup> Neuro-ophthalmological manifestations of this condition are quite commonly observed.<sup>[25]</sup>

IgG4 disease is almost indistinguishable from THS in its ocular presentation. However, tumefactive lesions are additionally seen in many organs outside the ocular system. Ophthalmologic involvement is common but not limited to the orbit, lacrimal glands, and extraocular muscles. Additionally, hypophysitis and hypertrophic pachymeningitis are other conditions of

interest.<sup>[26]</sup> [Figure 5 color plate] Systemic signs are usually found to occur simultaneously with neuro-ophthalmological manifestations. This distinguishes it from THS, and almost all cases of IgG4 were diagnosed earlier as THS until research showed to have a more diffuse involvement. The most important distinguishing feature was its progressive nature and response to immunomodulation.<sup>[27]</sup>

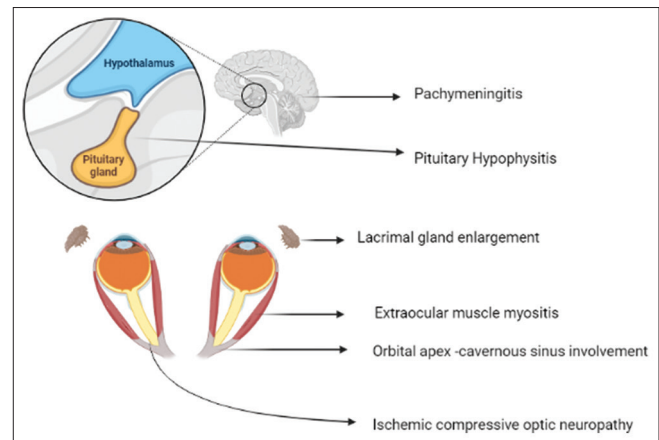
## PATHOGENESIS OF IGG4 DISEASE

Pathogenesis of IgG4 depends on a close interaction between T and B cells. Clonal expansion of T and B cells occurs, which contributes to lymphadenopathy and organ enlargement. The activated IgM plasmablast undergoes class switching to give rise to IgE plasmablasts and IgG4 memory B cells. The latter homes inside the bone marrow, causing chronicity of the condition and multiple relapses despite immunomodulatory therapy. Many markers of inflammation are involved in the interchange, which causes the recruitment of macrophages and inflammatory markers which set up a fibrotic process that is the characteristic feature of IgG4 disease.<sup>[28]</sup>

## NEURO-OPHTHALMOLOGICAL SPECTRUM OF IGG4 DISEASE

Although visceral organ involvement is one of the most common presentations in IgG4 disease, neuro-ophthalmic manifestations are important and often exist with multifocal involvement. It is important to know them because a delay in diagnosis of these conditions can cause increased morbidity and occasionally mortality in the patients.<sup>[25]</sup> It has gradually placed itself as an important differential in the multiple fibro-inflammatory reactions of the orbit previously labeled as idiopathic.<sup>[25]</sup>

IgG4-related ophthalmic disease (IgG4-ROD) is usually seen in three distinctive forms: (1) enlargement of the infra-orbital nerve, (2) extraocular myositis, and (3) compressive optic neuropathy. Symmetric asymptomatic enlargement of the lacrimal glands was the most common finding, with the bilateral



**Figure 5:** Structures in the neuro-ophthalmic system involved in the IgG4-related disorders

orbital disease as well as extraocular involvement. Serum levels of IgG4 were relatively higher in patients with bilateral disease in comparison to those with unilateral disease.<sup>[29]</sup> Pachymeningitis usually presents as nodular meningitis with diffuse thickening of meninges, which can involve even the basal meninges and extend into the spinal canal. It is clinically indistinguishable from the other kinds of hypertrophic meningitis, and symptoms usually occur from mechanical compression of neighboring structures<sup>[30]</sup> [Figure 6a–c].

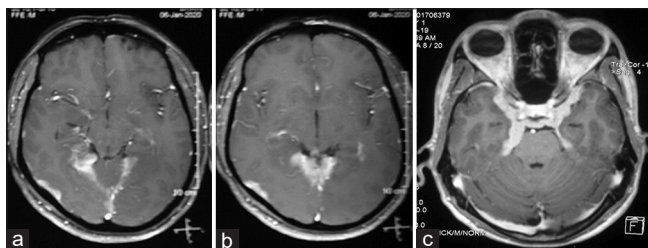
## DIAGNOSIS OF IgG4 DISEASE IN NEURO-OPHTHALMOLOGICAL INVOLVEMENT

Several conditions can result in the elevation of IgG4 levels in a disease condition.

The histopathological hallmark of IgG4-related disease involves lymphoplasmacytic infiltration of IgG4-positive plasma cells, arrangement in the pattern of storiform fibrosis, and obliterative phlebitis.<sup>[31]</sup> However, the pathological picture of IgG4 involvement is different in different organs. Hence, the consensus of two of the diagnostic criteria is the absolute values of IgG4 above 135 mg/dl and over 40% of the plasma cells staining positive for IgG4 with absolute counts of greater than 10 per high power field in the histopathological sample.<sup>[32]</sup>

## OTHER CONDITIONS MIMICKING IgG4 DISEASE

It is important to note that several other conditions can mimic IgG4 disease in their presentation and may also be associated with elevated levels of IgG4 in serum. Many infectious conditions, such as multi-centric Castleman's disease, sarcoidosis, granulomatosis with polyangiitis, etc., are some of the conditions which can present with raised levels of IgG4.<sup>[33]</sup> Rosai–Dorfman disease is another interesting clinical entity than can present with raised levels of IgG4 not amounting to criteria cut-offs than can present with ophthalmic manifestations secondary to raised intracranial pressure due to nodular pachymeningitis or direct orbital infiltration.<sup>[34]</sup> [Figure 6c] Clinical presentations mimicking IgG4 disease must be biopsied, and the presence of Ig4



**Figure 6:** (a–c) Two cases of dura-based nodular pachymeningitis with heterogeneous and florid contrast uptake. Both patients presented with features of raised intracranial pressure and the sixth cranial nerve palsy. Additionally, the second patient had bilateral optic atrophy at presentation with brisk reflexes at presentation. Serum IgG4 was raised in both cases, but the histopathology was positive only in the former, whereas the latter case was found to have markers suggestive of Rosai Dorfman disease

staining cells in the histopathological specimen fulfilling the criteria should be ensured before labeling them as IgG4-related disease.<sup>[35]</sup>

## UPDATED TREATMENT STRATEGIES IN IgG4 DISEASE

The treatment of IgG4 centers is mainly around the control of inflammation and prevention of relapses.<sup>[34]</sup> One of the major concerns of treatment is also to preserve the function of the organs as local pressure and tissue infiltration often compromise vision and cause severe symptoms due to the rise of intracranial pressure. The indolent form of the disease often hampers clinical decision-making. However, one must also be careful in following up on such cases to look for disease relapse or recurrence. We feel that all cases of neuro-ophthalmic IgG4-related diseases must be immediately treated as disease progression can lead to vision impairment and systemic disease is usually associated with neuro-ophthalmic involvement.<sup>[36]</sup> Long-term studies of treatment modalities with neuro-ophthalmic presentation are not available. However, the management of the neuro-ophthalmic disease is the same as for those with systemic disease.

## Steroids

Corticosteroids are the first line of treatment to induce remission and are used as monotherapy in up to 70%, and the efficacy of steroid-based first-line management has well been reported to be over 97%.<sup>[37]</sup> The international consensus for the management of IgG4 disease has recommended a very slow taper of steroids over several months to a minimum dose varying between 2.4 and 10 mg per day. The usual recommended initial dose is 1 mg/kg/day, although higher doses are used for patients with intractable disease in the form of optic nerve involvement or active orbital myositis or those with evidence of systemic disease.<sup>[38]</sup> A dose less than 10 mg is ineffective for maintaining remission<sup>[39]</sup> [Figure 7].



**Figure 7:** Presentation with headache and right-sided sixth nerve palsy. Axial contrast MRI shows strong contrast uptake in bilateral cavernous sinuses with extension into the orbital apex (left > right) and temporopolar region. Meningeal biopsy showed IgG4 disease, and the patient responded to steroids and maintenance immunomodulators

## Maintenance strategies

Because IgG4 is prone to recurrence, maintenance of induction is achieved through steroids as well as various steroid-sparing agents. The duration of maintenance depends on the number of involved organs and baseline levels of IgG4. Low-dose corticosteroids have been used as the sole maintenance agent for up to 3 years in a study by Kamisawa.<sup>[40]</sup> Steroid-sparing regimens have also proven to be effective in maintaining remission, and a variety of agents similar to THS have been used with varying results.<sup>[39]</sup> Methotrexate has been used with good response in patients with intractable orbital inflammation, although no set protocol is available for the treatment regimen owing to the small number of patients encountered in such subgroups. The choice of an agent is often guided by the experience of the patient and acceptability by the patient.

## Role of rituximab in IgG4 disease

A recent meta-analysis looked at the various agents used in the management of IgG4 disease and showed that maintenance therapy with rituximab had the lowest rate of relapse of all the treatments (OR = 0.10, 95% CI [0.01, 1.63]). A combination of steroids in the combination of immunomodulators had a lower relapse rate as compared to steroid monotherapy. Although no consensus of any single agent was shown to be more efficacious in the maintenance of remission, rituximab is efficacious in inducing remission both in steroid-dependent and steroid-refractory cases, with a good safety profile.<sup>[41]</sup> Rituximab has gained a considerable reputation as a safe and effective agent in inducing and maintaining remission in IgG4-related diseases. The special efficacy of rituximab is believed to be due to the pathogenic process involving the persistence of memory B cells, which are targeted specifically by rituximab. A regimen of 1 g every 6 months is believed as a safe and effective dose to maintain remission in IgG4-related disease.<sup>[42]</sup>

## Surgical methods

Surgical methods primarily aim at decompression of orbital contents to prevent compressive ischemic optic neuropathy, but cases have to be individualized and not be a part of the consensus guidelines.<sup>[43]</sup>

## LONG-TERM PROGNOSIS OF IgG4 OPHTHALMIC DISEASE

A long-term follow-up study of IgG4-related orbital disease shows that even if the response to treatment remains satisfactory, up to 37.1% of the cases relapse after discontinuation of therapy, one of the highest in all forms of the disease. Relapse was seen to occur more in patients who received lower doses of corticosteroids or those in whom steroids were tapered earlier.<sup>[44]</sup> In other studies, treatment with steroids alone, higher baseline levels of IgG4 at presentation, involvement of more than 5 organs, eosinophilia, and dacryoadenitis were the risk factors for relapse.<sup>[45]</sup>

## CONCLUSION

There is an imperative need to diagnose every suspected case of THS through histopathological evaluation. This should be done to ensure that no condition mimicking IgG4 disease through raised IgG4 levels gets mistakenly labeled while missing the primary diagnosis. Treatment of the condition needs to be customized, but a longer duration of steroids with a slow tapering with a judicious combination of steroid-sparing immunotherapy for conditions such as IgG4 is required. Rituximab is a safe and effective agent to induce and maintain remission in these cases with a comparable safety profile. The role of meticulous follow-up is crucial considering the potential morbidity associated with THS.

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## Conflicts of interest

There are no conflicts of interest.

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