Review Article

Thyroid Associated Ophthalmopathy (TAO): A Review

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Abstract

Thyroid-associated ophthalmopathy is an orbital autoimmune disease, the exact nature of which is not yet clearly understood. The Clinical features shows a variety of spectrum from eyelid retraction to dysthyroid optic neuropathy. The management strategies of thyroid associated ophthalmopathy have changed time to time. The gold standard treatment modality of active thyroid associated ophthalmopathy is systemic glucocorticoids. Recent modality includes Monoclonal antibody against CD-20, IL-6 receptor, and Insulin like growth factor-1 (IGF-1) receptor inhibitor. Surgeries include orbital decompression, extraocular muscle surgery, and lid surgery. Endoscopic decompression is the recent advancement.

Keywords: Thyroid Ophthalmopathy, Monoclonal Antibodies Therapy.

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Introduction

Thyroid-associated ophthalmopathy (TAO) is the most common cause of proptosis in the people above the age of 15 years but it may occur in children. The strong association between orbitopathy and thyroid dysfunction is known for more than 3 centuries.[1] The clinical presentation of TAO can vary from minimal soft tissue changes like mild lid retraction to a very severe inflammatory phase leading to a painful congestive orbitopathy and very serious complications like corneal perforation and optic nerve compression. Restricted ocular motility leading to troublesome diplopia and secondary glaucoma are other significant manifestations.[2-7]

Incidence and Epidemiology

A 1996 epidemiological study has revealed that the prevalence of TAO was 16 cases per 100,000 population per year.[8] The peak incidence rates occurred in the age groups 40-44 years and 60-64 years in women and 45-49 years and 65-69 years in men. Between 2 and 16 years of age, the rate of TAO is approximately 10%, Between the ages of 17 to 64 years, the rate of TAO is approximately 43%. Among the patients 65 years and above, TAO remain the most common lesion approximately 40%.[9,10]

Pathogenesis

TAO is an orbital autoimmune disease, the exact nature of which is not yet clearly understood. The thyroid-stimulating hormone receptor (TSH-R) located on the thyroid follicular cells acts as an antigen. It shared the same antigenic epitope with the orbital tissue i.e. orbital fibroblast and perimycium of extra ocular muscles, making them a target for autoimmune assault.[11,12]

In Grave's disease, antibodies are produced against TSH receptors which cross react with antigens present on the EOM fibres & also retro bulbar fibroblasts. This immunological reaction recruits T-lymphocytes and macrophages.[13.14]

Recently, Various mechanisms were postulated to explain the pathogenesis of TAO. A circulating immunoglobulin (GD-IgG) is also present in patients with active orbitopathy and acts through the IGF-l receptor on orbital fibroblasts of patients with thyroid disease to stimulate hyaluronan synthesis.[12,15] The insulin like growth factor 1 receptor (IGF-1R) is an autoantigen that may be important in TAO. Cyclooxygenase 2 (COX-2) is expressed at higher levels in the orbital fibroadipose tissues of TAO. Variants in the *IL-23R* gene and HLA-DR histocompatibility loci are associated with TAO.[15] In TAO, the increase in orbital volume from the extraocular muscles and fat causes protrusion of the eye (proptosis or exophthalmos). Occasionally the optic nerve can get compressed at the narrow posterior apex of the orbit by the enlarged extra ocular muscles.[12,16]

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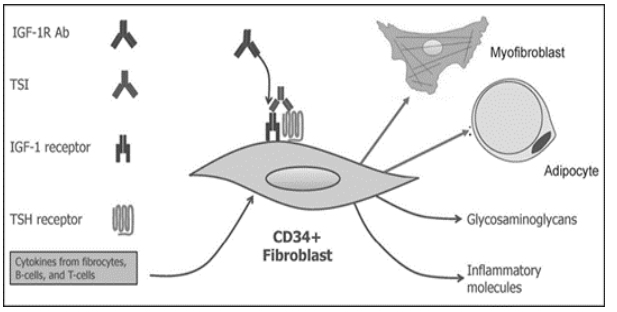

Fig-1 Pathogenesis of TAO. Ab=antibody; IGF-1=insulin-like growth factor-1; IGF-1R= insulin-like growth factor-1 receptor; TSH=thyroid-stimulating hormone; TSI=thyroid-stimulating immunoglobulin. Source: Smith TJ[18]

Risk Factors

Several factors may increase the risk in patients with TAO, namely tobacco, gender, genetics, type of treatment for hyperthyroidism, TSH receptor antibodies, drugs, advanced age and stress.[19],[20] The incidence of TAO among Cigarette smokers is 7.7 folds more than that of non-smokers.[21] TAO is more common in women but men are more likely to be affected by increase in severity during follow up. Radioiodine treatment may also lead to the development or worsening of TAO.[22] TSH-R auto-antibodies (TRAB) might be involved in the disease process of TAO. Other possible risk factors for TAO include advanced age, stress, neck irradiation for Hodgkin disease, and drugs such as lithium or interferon-α.[23] Patient with TAO have an increased probability of developing associated immune diseases, including Superior limbic keratitis (SLK), Myasthenia gravis, Diabetes mellitus, Alopecia and vitiligo. Psychiatric condition such as bipolar affective disorder and anxiety occur more frequently in patients with thyroid dysfunction and with TAO.[24,25]

Course of Disease

There are two stages in the development of disease: 1. Congestive (infiltrative) stage in which eyes are red and painful, [26,27] and 2. fibrotic (Quiescent/Non-infiltrative) stage tends to be occur in younger individuals.[28,29] This pattern of the disease was first described by Rundle.[29] Reactivation of disease is fairly uncommon, occurring in less than 5% of individuals.[30]

The relationship of TAO and hyperthyroidism: Various studies showed that 64–90 % 0f patients with TAO have hyperthyroidism. Of the remaining patients 15-20% had primary hypothyroidism, 3-5% were Hashimoto's thyroiditis and 6-20% were euthyroid,[31,32] only about 30% of patients with autoimmune hyperthyroidism have or will develop TAO.[2,33]

Clinical manifestations: Systemic features of thyroid disease

Systemic signs of hyperthyroidism: Tachycardia / palpitations**,** Nervousness**,** Diaphoresis**,** Heat intolerance**,** Skeletal muscle weakness**,** Tremor**,** Weight loss**,** Hair loss**,** Irritability**,** Goitre.

Systemic signs of hypothyroidism: Bradycardia, Drowsiness, Poor mentation, Muscle cramps, Weight gain, Dry skin, Husky voice, Depression, Cold intolerance.[1,34]

Ocular features of TAO

The most frequent ocular symptom in TAO is dull, deep orbital pain or discomfort, which affects 30% of patients. [35] The five main clinical manifestations are i. soft tissue involvement, ii. Lid retraction, iii. proptosis, iv. optic neuropathy v. restrictive myopathy. *Eyelid retraction* is the most common ophthalmic feature of TAO, [12] fibrosis of inferior rectus muscle induces retraction in the lower lid. Various factors can contribute for the lid retraction: (i). Fibrotic contracture of the levator muscle (ii). Secondary over action of the levator-superior rectus complex (iii). Humorally-induced over action of Muller's muscle as a result of sympathetic over-stimulation secondary to high level of thyroid hormones[19]

Exophthalmos of one or both eyes affect approximately 60% of patients, restrictive extraocular myopathy is apparent in about 40% of patients, and optic nerve dysfunction occurs in one or both eyes in 6% of patients with TAO. Only 5% of patients have the complete constellation of classic findings: eyelid retraction, exophthalmos, optic nerve dysfunction, extraocular muscle involvement, and hyperthyroidism.[36] Retropulsion could be negative if the proptosis is because of increase in the fat volume in the orbit, whereas it could be positive when there is significant increase in the volume of extraocular muscles.[37] The increase in IOP is due to the pressure exerted upon the eyeball by the contracting normal muscle and the nonrelaxing tight muscle. Choroidal folds may also be rarely seen with thyroid ophthalmopathy.[38,39]

Eyelid signs in TAO: There are several classical clinical signs described in literature in TAO.[24,26,40,41]

Dalrymple sign:	Upper lid retraction
Von Graefe sign:	Lid lag on down gaze
Kocher sign:	A staring and frightened appearance of eyes
Vigouroux sign:	
Stellwag sign:	Eyelid fullness
Gifford's sign:	Incomplete and infrequent blinking
Grove sign:	Upper lid is difficult to evert (due to lid edema)
	Resistance to pulling down the retracted upper lid.

Clinical Classifications

There are various classification systems for thyroid-associated orbitopathy. They are (A) Type 1 and Type 11, (B) NOSPECS, (C) The clinical activity score, (D) The VISA classification which is the most recent. [25,36]

The VISA Classification

VISA classification system is based on four disease end points: vision, inflammation, strabismus, and appearance/ exposure. [25]

Appearance/Exposure: Appearance concerns such as proptosis, eyelid retraction, blepharochalasis, periorbital oedema and exposure complaints of foreign body sensation, glare, dryness, or secondary tearing require attention.[25,43]

Investigations:

Thyroid profile: In screening for thyroid disease, the combination of free T4 (thyroxine) and TSH (thyroid-stimulating hormone) or serum TSH (thyrotropin) are highly sensitive and specific..[35,45]

Orbital Imaging

CT scan of the orbit shows two important changes (1) increase in the fat volume of the orbit (2) enlargement of the extraocular muscles sparing the tendon.[28]

Counselling a patient with TAO: The patient should be reassured that the disease is self-limiting over a period of usually 2yrs and that recurrence is seen in only 5% of patients. Orbital decompression is the first surgical procedure performed when indicated followed by extra ocular muscle surgery which will be undertaken to improve ocular motility and reduce diplopia. Lid surgeries are the last to perform.[25,32,35,43]

Management of Thyroid Eye Disease: Management of TAO comprises of topical medication, systemic medical management especially in the active inflammatory phase or during optic nerve compression, radiation and surgical options.[35] Till the time of the surgery the optic nerve is protected by administering high doses of corticosteroids.[28,35]

Surgical decompression: The classical indication for surgical orbital decompression is compressive optic neuropathy. Decompression may be performed via transorbital or endoscopic approaches.[37,38]

i. **Two wall** (antral-ethmoidal), involves removal of a part of the floor and the posterior portion of the medial wall.[35,46]

ii. **Three wall**, involves an antral-ethmoidal decompression and removal of the anterior and deep lateral wall. The amount of retro placement achieved is 6-10 mm.

iii. **Four wall**, involves a three-wall decompression, removal of the lateral half of the orbital roof and a large portion of the sphenoid at the apex of the orbit. This affords 10-16 mm of retro placement and is reserved for very severe proptosis.[26,47] In recent years there is an increased interest in removing orbital fat to decrease the proptosis. It can be a primary procedure or can be combined with bony decompression based on the need.[48]

Treatment of active phase (Active TAO)

Medical management is considered when TAO is clinically active (clinical activity score of 5 or more of VISA classification). Systemic corticosteroids are most commonly used. Depending upon the severity of inflammation the dose can vary from 30-60mg/ day of Prednisolone orally for a period of 2wks which is gradually tapered over a period of 3-4 months. The currently recommended regimen for IVMP therapy is a cumulative dose of 4.5 gm divided into 12 weekly infusions, six weekly infusions of 0.5 gm, followed by six weekly infusions of 0.25 gm.[49] Some others prefer IV Methyl Prednisolone (IVMP) in doses varying from 1gm on alternate day for 3 injections to 500mg IV every day.[35,36,50] When once the inflammation is controlled, some orbital surgeons prefer radiotherapy. Radiotherapy is contraindicated in Diabetics and in patients with retinal vascular diseases.[24,35] During this period the radiation induced inflammation is controlled with oral Prednisolone 30mg/day tapered over a period of 2-3weeks.[51,52] The exact mechanism how the radiation acts is not known.[53] Rituximab infusion (Monoclonal antibody against CD20 antigen on B-lymphocytes), and Tocilizumab subcutaneous injections (Monoclonal antibody against 1L-6 receptor) are effective modality treatment for active TAO.[54,55] Intravenous infusions of IGF-1 receptor inhibitor (Teprotumumab) reported good response to reduce proptosis, CAS, and diplopia.[56]

Local treatment measures: Ocular discomfort may be due to associated dryness as a result of lid retraction, lid lag, lagophthalmos, infrequent and incomplete blinking, changes in the tear film composition which lead to corneal and conjunctival exposure related manifestations. They often respond to topical lubrication. Carboxymethylcellulose artificial tear drops may be used during the day, and lubricant ointment during night. Taping of lids during night or using goggles to provide humidified chamber may be needed in a few. When there is evidence of corneal epithelial breakdown, topical antibiotic eye ointment and even partial eyelid closure with surgical tarsorrhaphy/induction of ptosis by injection of Botox should be considered. In severe situations, surgical levator and Muller's muscle recessions or orbital decompression may be required.[9,35] Mild eyelid retraction may be alleviated transiently by the use of topical adrenergic blocking agents.[25,43] Diplopia from extraocular muscle restrictive imbalances

is most troublesome in primary and down gaze – the most functional gaze positions. Prisms can be incorporated in the glasses which eliminate diplopia in one gaze position only. It may be adequate for small degrees of diplopia. In severe cases of diplopia, patching may be tried till surgery is performed.[35,57]

Surgical management: The timing of surgery is at the cessation of the orbital disease which is usually 2-3yrs after the onset. After an interval of 3 to 4 months restrictive myopathy is attended to by doing recession of the involved muscles. The main objective of this procedure is to eliminate binocular diplopia as far as possible and certainly in the central 30 degrees visual field. Muscle surgery is always done after orbital decompression because the alteration that occurred due to displacement of the extra ocular muscles (as a result of orbital decompression) can be taken care off. The lid surgery is always performed as the last surgical procedure to take care of changes in the lid position that have resulted from the orbital decompression and extra ocular muscle surgeries.[25,26,35]

Lid retraction can be corrected by 1) Mullerectomy with or without LPS recession. This could be either trans conjunctival approach or trans cutaneous. LPS disinsertion can be combined with this procedure when needed.[43] 2) Blepharotomy: For lid retraction in TAO, [58] is another popular procedure. In this procedure, a lid crease incision is made up to the depth of anterior lamella, The Tarsus is exposed and dissection is carried out upwards.

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Figures with Legends of the Figures

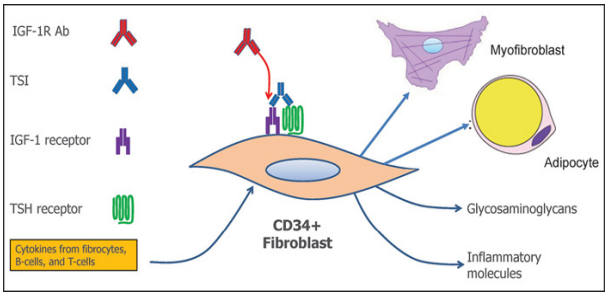

Fig-1 Pathogenesis of TAO.

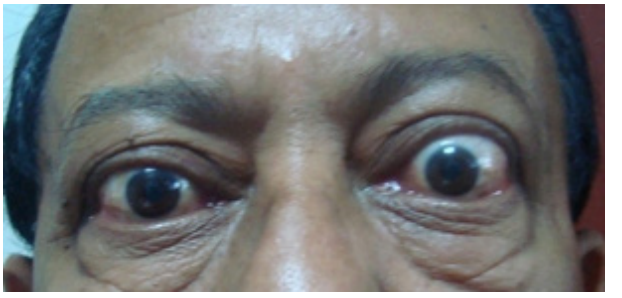

Fig. 2 A patient of asymmetrical bilateral TAO with 4 mm proptosis of the left eye, mild right upper lid retraction and severe left upper lid retraction.

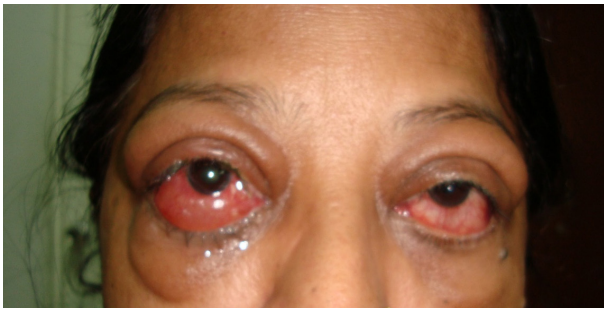

Fig.3 shows a patient of TAO with active bilateral asymmetrical bilateral thyroid associated Ophthalmopathy grade-III chemosis of the conjunctiva (right eye). Note that the chemosis conjunctiva overhangs the lid margin on to the skin of the lower lid. VISA score 7/10.

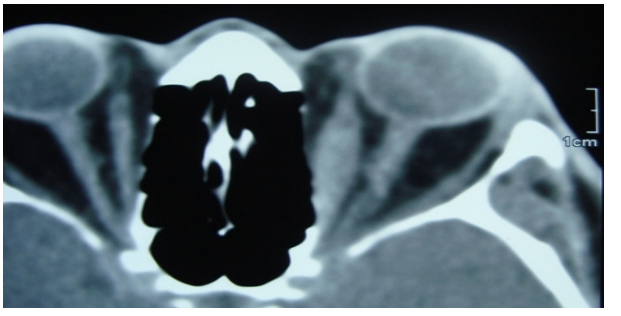

Fig. 4A- Axial sections of CT scan shows enlarged left medial rectus muscles with sparing of the muscle tendon.

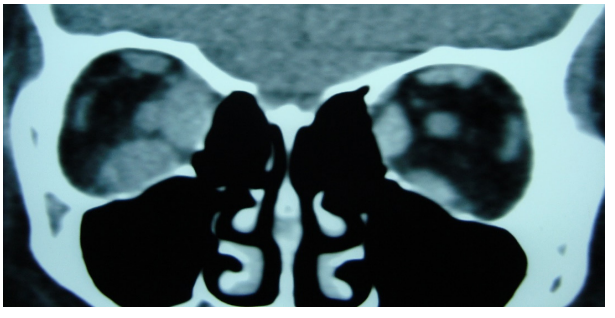

Fig.4B- Coronal section of the same patient shows enlarged medial and inferior rectus muscles on both sides.