

THYROID ASSOCIATED OPHTHALMOPATHY – A REVIEW

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Conflict of interest: None

ABSTRACT

Thyroid associated ophthalmopathy is an autoimmune disorder affecting the orbital and periorbital tissues. Hyperthyroidism is commonly associated with thyroid associated ophthalmopathy, however in 5% to 10% of cases it is euthyroid. Genetic, environmental and endogenous factors play a role in the initiation of the thyroid ophthalmopathy. Smoking has been identified as the strongest risk factor for the development of the disorder. The pathogenesis involves activation of both humoral and cell mediated immunity with subsequent production of glycoaminoglycans, hyaluronic acid resulting in oedema formation, increase extraocular mass and adipogenesis in the orbit. The natural history of the disease progresses from active to inactive fibrotic stage over a period of years. Diagnosis is mainly clinical and almost all patients with ophthalmopathy exhibit some form of thyroid abnormality on further testing. Treatment is based on the clinical severity of the disease. Non-severe cases are managed by supportive measures to reduce the symptomatology and severe cases are treated by either medical or surgical decompression. Rehabilitative surgery is done for quiescent disease to reduce diplopia and improve cosmesis.

Key words: Thyroid eye disease, autoimmunity, smoking, corticosteroids, radiotherapy, surgical decompression, rehabilitative surgery.

Mallika PS, Tan AK, Aziz S, Syed Alwi SAR, Chong MS, Vanitha R, Intan G. Thyroid Associated Ophthalmopathy – A Review. Malaysian Family Physician. 2009;4(1):8-14

INTRODUCTION

Thyroid associated ophthalmopathy (TAO) is also known as, thyroid eye disease (TED), Graves' ophthalmopathy/orbitopathy (GO), dysthyroid ophthalmopathy, thyrotoxic exophthalmos and other terms. It is an autoimmune process which affects the thyroid gland, orbital and periorbital tissue and uncommonly the pretibial skin or digits (thyroid acropachy). The individual components can occur together or separately. It is the most frequent extrathyroidal manifestation of Graves' disease. Although TAO is often associated with hyperthyroidism, it may occur in primary hypothyroidism, Hashimoto's thyroiditis, and sometimes in euthyroid individuals.¹⁻³ The incidence and prevalence of Graves' disease is 0.1% and 1% respectively. The clinical signs include widening of the palpebral fissure, eye lid retraction, lid lag, conjunctival congestion, chemosis, proptosis, corneal exposure, restrictive myopathy and optic neuropathy. In majority of cases the ocular manifestations are mild, and severe form of the disease affects 3% to 5% of individuals.⁴

METHODOLOGY

All our reference articles were obtained from Pubmed. The key words for search were thyroid ophthalmopathy, thyroid orbitopathy, thyroid associated ophthalmopathy, ocular manifestations of thyroid, ocular features of Graves' disease, thyroid eye disease, and Graves' ophthalmopathy etc. We used the MeSH database and journal database for our search and our search limits were articles in English and age above 1 year.

FREQUENCY

The exact incidence of ophthalmopathy is not clear. The prevalence of TAO (thyroid associated ophthalmopathy) in patients with GD (Graves' disease) in Caucasian population is generally thought to be between 25% and 50%.^{5,6} Bartley⁷ reported, in a population-based setting in USA, an annual incidence rate of 16 cases per 100,000 population per year for women, and 2.9 cases for men. In Malaysia, Lim *et al*⁸

reported a higher prevalence rate (34.7%) of thyroid associated ophthalmopathy in three populations of Asian patients with GD. Most patients without ophthalmopathy have subtle changes noted in orbital imaging.⁹ It is more common in females than males. The female to male ratio in one study was noted to be 9.3 in patients with mild ophthalmopathy, 3.2 in those with moderate ophthalmopathy, and 1.4 in those with severe ophthalmopathy.¹⁰ TAO presents usually in the fourth to fifth decade. In juvenile Graves disease, ophthalmopathy was reported in two-third of the patients in the age group of 11-18 years and one third of cases in the age group of less than 10 years.¹¹ Men and older age are associated with more severe ophthalmopathy.^{12,13}

The natural history of TAO is not clearly understood. In 90% of cases the disease runs a benign course. Untreated, TAO has a tendency to "burn itself out" within 3 to 36 months.¹⁴ Recurrences are usually uncommon and the disease rarely results in blindness.

PREDISPOSING FACTORS

Graves' disease is an autoimmune disorder. Genetic, environmental and endogenous factors are believed to initiate or predispose for its development. Several genes, including HLA,^{15,16} CTLA4,¹⁷ TCR β -chain¹⁸ and Ig heavy chain have been known to increase the susceptibility for the development of Graves' disease, however there are not much evidences to suggest the association between these susceptibility loci and the development of ophthalmopathy.

Environmental factors are thought to be the primary predisposing factors for the developmental of TAO. Among the several environmental factors blamed, smoking represents the strongest risk factor associated with the development of ophthalmopathy.¹⁹ Several studies have shown that the prevalence of smokers in patients with Graves' disease and even more, patients with Graves' ophthalmopathy is much higher than any other auto-immune or non-auto-immune thyroid disorder.²⁰⁻²³ Smoking causes partial hypoxia, which stimulates the orbital fibroblasts to synthesize glycoaminoglycans which exacerbates extra ocular muscle oedema and swelling.²⁴ The cigarette smoke extract (CSE) is also known to increase adipogenesis.²⁵ A systematic review on cigarette smoking and thyroid eye disease also shows a strong evidence for a causal association between smoking and the development of thyroid associated ophthalmopathy.²⁶ Smokers have a higher risk of developing more advanced GO than non-smokers.²⁷ Even in juvenile GD the prevalence of ophthalmopathy is higher among teenage smokers. Other factors found to be associated with thyroid associated ophthalmopathy are infection with *Yersinia enterocolitica*, other auto-immune disorders like myasthenia gravis, Addison disease, vitiligo and pernicious anaemia.

PATHOGENESIS

In Graves' disease, the pathology is due to the presence of an IgG antibody called long-acting thyroid stimulator directed against the plasma membrane of the thyroid cells.^{28,29} However, the pathogenesis of TAO is uncertain. Antibodies directed against thyroid follicular cells recognize antigenic epitopes, which are shared by tissues contained within the orbital space.³⁰ The effector and target cells are probably the periadipocytes and fibroblasts present in the perimysium of the extraocular muscles and the orbital connective tissues. These cells when stimulated differentiate into mature adipocytes which express the TSHr in increased levels.³⁰ Inflammatory mediators released by the inflammatory cells stimulate the periadipocytes and the fibroblasts which results in adipogenesis, enlargement of extraocular muscles and secretion of glycoaminoglycans (GAG) and hyaluronic acid. This results in increase intraocular volume causing proptosis and elevation of the intraocular pressure. This suggest that the TSHr -directed antibodies do not probably have a direct pathogenic role, but only reflect the intensity of the orbital autoimmune response.

CLINICAL FEATURES

The clinical features of thyroid ophthalmopathy depend on the stage of the disease. The initial acute stage of the disease is characterized by active inflammation in which the eyes are red and painful and the disease later progresses to a stable or a quiescent stage in which the eyes are white and unchanging with a painless motility defect.³¹

Ocular symptoms

These may include increased lacrimation, sandy or gritty sensation, photophobia (increased sensitivity to light of normal intensity), puffy eyelids, bulging eyes, dry eyes, retrobulbar discomfort, ocular pain, and double vision, loss of vision, visual field loss and acquired colour vision defect due to damage of the large achromatic fibres and small chromatic fibres.³²

Ocular signs

Ocular manifestations may be divided into infiltrative and non-infiltrative. Non-infiltrative signs precede infiltrative signs and include widening of palpebral fissure, upper eye lid retraction (Dalrymple's sign), lower lid retraction (Collier's sign) and lid lag on down gaze (von Grafe's sign). Lid retraction is the commonest clinical feature of TAO seen in Caucasians.^{7,33,34} In Asians, exophthalmos was the commonest sign reported.⁸ Upper lid retraction is caused by several mechanisms which include: overaction of Muller's muscle due to increase sympathetic drive, proptosis and fibrosis/dehiscence of the levator palpebrae superioris muscle. Normally, the location of the upper lid is 1-1.5 mm below the superior limbus and that of the lower lid is at the inferior limbus.

Infiltrative signs include: exophthalmos, conjunctival injection, chemosis, fullness of the eyelids, enlargement of lacrimal gland, herniation of orbital fat, infrequent blinking (Stellwag's sign) increase intraocular pressure,³⁵ strabismus and restriction of extraocular movements (Ballet sign). The inferior and medial rectus muscle is commonly involved in TAO.³⁶ TAO is the commonest cause of axial proptosis in adults. It can be unilateral or bilateral. Proptosis is usually measured by Hertel exophthalmometer (Figure 3). It measures the distance between the lateral orbital rim and the anterior surface of the cornea. The upper limit of normal for whites is 18 mm and for blacks is 21 mm and for Asians the normal range is 12-18 mm. A difference in reading of more than 2 mm between the two eyes is suggestive of proptosis.



Figure 1. A patient with TED and corneal perforation of the left eye.



Figure 2. A patient with TED and strabismus of the left eye (esotropia).



Figure 3. Hertel exophthalmometer.

THYROID DERMOPATHY / PRE-TIBIAL MYXEDEMA

It is also an autoimmune manifestation of Graves' disease, which is usually associated with severe ophthalmopathy. Ophthalmopathy is said to occur first and dermopathy occurs later. Lesion of pre-tibial myxedema is usually asymptomatic

and has only cosmetic importance. Thyroid-stimulating hormone receptor antibody in the connective tissue is believed to be the antigen initiating the immune process.³⁷

COMPLICATIONS

- Inability to close the eyelids as result of lid retraction and proptosis can lead to exposure keratopathy.³⁸ Corneal defects in TAO also occurs because of widening of the palpebral fissure accelerating evaporation of the tear film and increase in the tear film osmolarity.³⁹
- Compression of the optic nerve or its blood supply due to enlarged extraocular muscles at the orbital apex causes optic neuropathy.⁴⁰ Compressive optic neuropathy occurs in less than 5% of patients.⁴¹ The optic neuropathy produces progressive loss of visual acuity, decreased color vision and defects in the visual field, usually central scotoma.⁴²
- The prevalence of glaucoma is said to be much higher in patients with Graves' disease than in the general population.⁴³

CLINICAL CLASSIFICATION OF DISEASE SEVERITY

There are several classifications available to grade the severity of thyroid ophthalmopathy. The symptoms and signs of TAO are often classified with the modified NO SPECS system.⁴⁴ (Table 1). The CAS system (clinical activity score) is another system which was developed for the selection of therapy, especially for deciding whether or not immunosuppressive therapy should be instituted.⁴⁵

Table 1. Abridged classification of eye changes of Graves' disease

Class	Definition
0	No physical signs and symptoms
I	Only signs, no symptoms (signs limited to upper eyelid retraction, stare and lid lag)
II	Soft tissue involvement (signs and symptoms)
III	Proptosis (3 mm or more)
IV	Extraocular muscle involvement
V	Corneal involvement
VI	Sight loss (optic nerve involvement)

Adapted from Werner⁴⁴

DIAGNOSIS

The diagnosis of TAO is clinical and is based on the triad of characteristic eye findings, thyroid dysfunction, and imaging

studies.⁴⁶ In majority of cases, ophthalmopathy occurs in association with hyperthyroidism. TAO is also said to occur in 5% of patients with Hashimoto's thyroiditis. However in 5% to 10% of cases, ophthalmopathy occurs in the absence of thyroid disease (euthyroid disease). This could be due to lack of TSH control of thyroid function in patients with ophthalmic Graves' disease. Even in patients without overt thyroid disease further tests like triiodothyronine (T3) suppression test, anti-thyroid antibodies abnormal thyroid-releasing hormone stimulation test and TSH antibody tests will demonstrate abnormalities in about 30% of patients.^{47,48} Patients with a euthyroid disease can even become hyper or hypothyroid after sometime. All these findings suggest that thyroid associated ophthalmopathy is heterogeneous either due to different phase of presentation or different pathogenesis in different patients.⁴⁶

The most characteristic findings in TAO are enlargement of the extra ocular muscles, without involvement of their tendons. Ultrasound B-scan of the eye, CT-scan orbit and MRI can be used to show thickened muscles, however CT scan is currently the imaging study of choice. MRI is sensitive for showing compression of the optic nerve.

DIFFERENTIAL DIAGNOSIS

The clinical features of thyroid associated ophthalmopathy are usually identified easily if it is bilateral and associated with hyperthyroidism, however in patients with euthyroid disease and unilateral it is essential to rule out other causes of lid retraction and proptosis. The differential diagnosis of proptosis include vascular conditions like cavernous haemangioma, orbital varices, lymphomas, inflammatory conditions which may be pseudotumour, orbital cellulitis, sarcoidosis, primary orbital tumours like lacrimal gland tumour and metastatic tumours. The other causes of lid retraction include aberrant regeneration of third nerve, Parinaud's syndrome and use of sympathomimetic drugs.⁴⁹

TREATMENT OF GRAVES' OPHTHALMOPATHY

The hyperthyroidism and the eye disease should be treated independently. Most of the mild to moderate TAO cases shows improvement with treatment of the underlying hyperthyroidism. The decision to treat TAO depends on the severity and the activity of the disease. The principal goals of therapy for TAO include pain relief, protection of vision and cosmetic improvement. The major therapeutic options include corticosteroids, radiotherapy and surgical intervention. TAO is categorized as severe and non-severe for treatment purposes. Severe disease can be either active or inactive. Features of severe ophthalmopathy are marked proptosis, diplopia in primary gaze or reading, exposure keratopathy, corneal ulceration or perforation and compressive optic

neuropathy. Treatment options for severe, active cases include either medical decompression (steroids or radiotherapy) or surgical decompression. Majority of them prefer high doses of steroids first and surgical decompression if it fails. For severe, inactive disease, surgical decompression is the only option. Management options for non-severe cases are mainly supportive and are shown in Table 2. Lid retraction in TAO is caused by sympathetic stimulation of the Muller's muscle. Guanethidine or α -blocker eye drops has been tried for the treatment of lid retraction with varying degree of success. In patients with severe ophthalmopathy, if the disease is active the treatment is medical decompression by either steroids or radiotherapy and if the TAO is inactive orbital decompression and rehabilitative surgery is the choice.

Table 2. Treatment of non-severe TAO

Signs / Symptoms	Management Options
Peri-orbital oedema	Elevation head of the bed, anti-diuretics
Dryness, foreign body sensation	Artificial eye drops and ointment
Lagophthalmos	Nocturnal eye taping, eyes shield
Eyelid retraction	Topical Guanethidine or β -blockers eye drops
Diplopia	Prisms
Photophobia	Sunglasses

Glucocorticoids

Corticosteroids therapy is the mainstay and is effective against active disease, soft tissue inflammatory changes and optic neuropathy.⁵⁰ It has no much role to play in long-standing and inactive disease (fibrotic stage). Favourable response rate ranges from 63% -73%. The beneficial effects of steroids are due to its anti-inflammatory, immunosuppressive.⁵¹ and ability to reduce glycoaminoglycans synthesis.⁵² Corticosteroid can be administered orally, locally (subconjunctival or retrobulbar) and intravenously. Intravenous steroids given by weekly pulse doses have a favourable response than daily oral steroids. Intravenous steroids have higher tolerability and success rates.⁵³ Retrobulbar steroids are not preferred as it is associated with pain and increase in the intraocular pressure. Intravenous methylprednisolone 0.5 to 1 g every other day for 3 cycles is associated with much higher tolerability. The dose of oral steroids is 60-100 mg (7-14 days) and dose reduction over several months. The disadvantages of steroids are the frequency and severity of side-effects like Cushingoid features, glucose intolerance, gastritis, hypertension, hepatitis, depression and fatty liver.⁵⁴ Recurrences after cessation or withdrawal of steroids are common.

Orbital radiotherapy

It is effective in for congestive signs, optic neuropathy and extraocular muscle involvement, not very effective against proptosis, eyelid retraction. It has a non-specific anti-inflammatory effect, and reduces the synthesis of glycoaminoglycans. Orbital lymphocytes are highly radiosensitive.⁵⁵ The standard dose is 20 Gy per eye fractionated in ten daily doses for 2 weeks or 1 Gy per week for 20 weeks.^{56,57} Favourable responses are seen in 60% of cases. Radiotherapy is associated with increased inflammation causing temporary exacerbation of the ocular signs. This can be lessened by concomitant administration of steroids. Radiotherapy combined with intravenous steroids is more effective than other modalities of treatment.⁵⁸ Cataract formation, radiation retinopathy, radiation induced optic neuropathy and carcinogenesis are some of the possible risks of radiation of the orbit. Young patients and patients with diabetic retinopathy are contraindications for radiotherapy.

Orbital decompression

It is also known as surgical decompression and involves removal of bony walls of the orbit to increase the orbital space to accommodate the orbital contents. The main indications are optic neuropathy, proptosis, severe orbital inflammation, corneal ulceration and cosmetic improvement. The orbit consists of four walls and in orbital decompression one to four walls can be removed depending on the clinical severity. There are several approaches for doing the decompression procedure. Transantral approach is the most preferred approach for most patients with optic neuropathy. Another approach, the transorbital can be used alone or in combination with transantral approach.⁵⁹ Decompression can be done by either surgical techniques or endoscopically. The complications of surgical decompression are sensory disturbances, sinusitis, oroantral fistula, facial neuralgia, vision loss and diplopia.

Rehabilitative surgery

It is usually done when the TAO is stable and inactive for at least 4-6 months. It is usually done in the following order strabismus surgery, lid-lengthening surgery and blepharoplasty. Strabismus surgery is done to minimize diplopia in primary and reading positions. Lid-lengthening surgeries decreases corneal exposure and blepharoplasty is done to reduce the excess skin and soft tissue.

Other treatment modalities

Somatostatin analogues

Octreotide and lanreotide are synthetic somatostatin analogues which have shown to be beneficial in patients with TAO.⁶⁰ TAO patients with somatostatin-receptor-bearing cells can be identified by orbital scintigraphy and can be subjected to treatment with the somatostatin analogues.

Immunosuppressive agents

Cyclosporin, cyclophosphamide, azathioprine and ciamexone have been tried for the management of TAO due to its auto-immune nature. The results are varying with no clear conclusive evidence for their role. Cyclosporine along with glucocorticoids was found to be effective in patients with either persistent disease or steroid resistance.⁶¹

Intravenous immunoglobulins

Immunoglobulins have better side-effect profile than steroids. It has a beneficial role to play in many autoimmune disorders including TAO, due to its effect on autoantibodies, complement and phagocytes.⁶²

Plasmapheresis

It has shown beneficial effect in patients with severe disease, especially severe progressive ophthalmopathy.

PREVENTION

Refraining from smoking plays a very vital role in primary, secondary and also tertiary prevention of TAO. Smoking influences almost all stages of thyroid eye disease. Stopping smoking prevents Graves' ophthalmopathy (primary prevention).⁶³ In patients who already have TAO, the chances of remission is much less in patients who quit smoking (secondary prevention) and the outcome of immunosuppressive treatment is beneficial in non-smokers than smokers⁶³ (tertiary prevention).

CONCLUSION

Thyroid eye disease even in its mildest form affects the quality of life of the individual considerably. All the currently available treatment modalities for TAO are associated with serious side-effects and complications. Identification of the risk factors and its elimination can help to modify the disease outcome. As smoking is one of the strongest risk factor found to be associated with TAO, refraining from smoking can help to reduce the magnitude of this problem both in developed and developing countries.

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Lumbar imaging for low-back pain without indications of serious underlying conditions does not improve clinical outcomes.

Chou R, Fu R, Carrino JA, Deyo RA. Imaging strategies for low-back pain: systematic review and meta-analysis. *Lancet.* 2009;373(9662):463-472.

This is a meta-analysis of 6 randomised controlled trials that compared immediate lumbar imaging (radiography, MRI, or CT) versus usual clinical care without immediate imaging for low-back pain. There were no significant differences between immediate lumbar imaging and usual care without immediate imaging for primary outcomes at either short-term or long-term follow-up.