

Thyroid orbitopathy

A review

Thyroid orbitopathy (thyroid eye disease, thyroid ophthalmopathy) is a self-limited, organ specific, autoimmune disorder with the potential to cause severe functional and psychosocial effects. This article reviews the clinical features with particular emphasis on current management.

Thyroid orbitopathy (TO) is most prevalent among females in the fourth and fifth decades and is usually associated with thyroid dysfunction. Clinical manifestations include soft tissue signs, lid retraction, lid lag, proptosis, restrictive myopathy, corneal exposure and optic neuropathy. Thyroid function tests are essential, while thyroid antibodies and imaging to demonstrate extraocular muscle enlargement, may also aid diagnosis. Correction of thyroid dysfunction and supportive measures are necessary in all cases. Immunosuppression is reserved for moderate to severe active orbitopathy and rehabilitative surgery is generally used once the disease is quiescent. A good visual and cosmetic outcome requires close cooperation between the optometrist, general practitioner, endocrinologist and ophthalmologist.

TO is an organ specific autoimmune disorder which may result in severe functional and psychosocial sequelae. Although there is an association with Graves' disease or Hashimoto thyroiditis in 90% of cases, patients may be hyper, hypo or euthyroid^{1,2}. In addition, orbital disease may precede, coincide with or follow the onset of thyroid dysfunction. An estimated 30-40% of Graves' disease sufferers demonstrate clinical signs of TO, while 90% have radiological evidence of extraocular muscle involvement^{3,4}. The incidence of TO is approximately 16/100,000 in females and 2.9/100,000 in males and although it is most prevalent in the fourth and fifth decades, a wide age range exists^{3,5}.

Pathophysiology

Despite evidence for an autoimmune aetiology, the precise pathophysiology of TO remains unknown. The inflammatory response is centred on the extraocular muscles and orbital connective tissue, and is thought to arise from autoantibody cross-reactivity between thyroid and orbital antigens⁶. There are two distinct stages – an active inflammatory stage followed by a quiescent stage. The inflammatory phase is characterised by lymphocytic infiltration, interstitial oedema and mucoglycoprotein deposition within the extraocular muscles and orbital fat^{2,3,7}. Inactive disease is distinguished by fibrosis and fatty infiltration of the orbital tissues^{2,3,7}.

Clinical features

The major signs and symptoms are outlined in **Table 1**. Common complaints include red, gritty, photophobic and watery eyes. Patients often report a change in the appearance of their eyes and perusal of old photographs may be helpful. Periorbital swelling is worse in the mornings, and diplopia, retrobulbar discomfort, and pain on eye movement are other presenting symptoms (**Figure 1a**). The cardinal signs are axial proptosis, eyelid retraction and lid lag (**Figure 1b**). In fact, TO is the most common cause of bilateral, asymmetric and unilateral proptosis in adults³ (**Figure 1c**). Although progression of signs such as muscle restriction and the presence of soft tissue inflammation are suggestive of activity, the differentiation of active from inactive orbitopathy can be problematic. The

Table 1:
Symptoms and signs of thyroid orbitopathy

Symptoms	Signs
Impaired lid closure	Lid retraction
Protruding eyes	Lid lag
Eye pain	Proptosis
Eye grittiness	Conjunctival injection
Photophobia	Conjunctival oedema
Watery eyes	Corneal exposure with corneal erosion
Double vision	Lid oedema
Blurred vision	Restricted extraocular movements
Washed out colour vision	Reduced visual acuity
Blind spot	Reduced intensity of colour perception Central or paracentral scotoma



Figure 1
Signs of thyroid orbitopathy

- Periorbital swelling due to mild active thyroid orbitopathy
- Axial proptosis and eyelid retraction
- Right axial proptosis due to thyroid orbitopathy
- Axial computerised tomography (CT) scan of orbits showing enlarged extraocular muscles causing crowding of the optic nerve at the left orbital apex



Figure 2
Coronal CT scan of orbits showing enlarged recti, in particular inferior, medial and superior recti



Figure 3
Patient receiving Linear accelerator external beam radiotherapy to posterior orbit for thyroid orbitopathy



Figure 4
Intraconal fat excision during an orbital decompression procedure

distinction is of particular importance as medical treatment is effective only in active disease and surgery is generally reserved for stable TO^8 .

It should be noted that there is a broad spectrum of clinical presentation. Mild disease may present solely as prominence of the eyes due to lid retraction. On the other hand, severe myopathy may cause crowding of the optic nerve at the orbital apex leading to dysthyroid optic neuropathy (Figure 1d). Loss of vision may also occur as a consequence of gross

proptosis resulting in severe corneal exposure and ulceration. Smoking, diabetes, male gender and increasing age are risk factors for more severe disease⁹.

With regard to differential diagnosis, active disease may require differentiation from non-specific orbital inflammatory syndrome, and unilateral proptosis may need exclusion of an orbital mass.

Natural history

As with other autoimmune disorders, TO is characterised by an active dynamic phase with spontaneous remissions and exacerbations, thought to reflect a period of self-limited autoimmune inflammation, which then leads to static fibrotic changes¹⁰. The active phase of the disease usually encompasses an average period of 18 to 36 months, but late reactivation does occur in the occasional patient.

Investigations

Thyroid function tests should be performed in all cases. Thyroid stimulating hormone receptor antibody and antithyroglobulin antibody levels may be useful in making the diagnosis in euthyroid patients². The diagnosis can also be confirmed by computerised tomography (CT) or magnetic resonance imaging (MRI) showing enlarged extraocular muscle bellies with relative sparing of the tendons^{3,7} (Figure 1d). Muscle involvement is generally bilateral and symmetrical with the inferior, followed by medial, superior and lateral recti being most often affected³ (Figure 2). In the majority of cases, a strong presumptive diagnosis can be made on the clinical presentation in the context of thyroid dysfunction, and imaging is only appropriate in severe disease or if the diagnosis is doubtful.

Management

The management of TO remains controversial as much of the literature refers to small, uncontrolled studies. Nevertheless, the treatment plan shown in Algorithm 1 summarises the current philosophy used by the majority of orbital clinicians. Referral to an ophthalmologist should be considered if the diagnosis is unclear, in moderate to severe active inflammatory disease, especially if vision is threatened, and in inactive disease with significant functional or cosmetic sequelae.

Correction of thyroid status

The initial management in all TO patients is restoration of euthyroid state, as this will often ameliorate the orbitopathy. It should be noted that there is a risk of exacerbation of TO following I 131 therapy particularly in those with pre-existing active orbitopathy^{11,12}. Simultaneous prednisolone administration or alternative therapy should be considered in these patients^{6,11}.

Supportive therapy

Supportive therapy is applicable to all patients with cessation of smoking being the single most effective measure¹³. Exposure symptoms can be alleviated with wrap-around sunglasses, lubricant eye ointment at bedtime and artificial tears during the day². Cool compresses and head elevation whilst sleeping help reduce periorbital oedema². Diplopia can be temporarily managed with monocular occlusion or prisms¹. The majority of patients can be managed with these supportive measures alone, however, in the presence of moderate or severe disease activity, immunosuppression either in the form of steroids or radiotherapy should be considered.

Immunosuppression

Steroid therapy has a 65% response rate and is most effective for soft tissue signs rather than motility problems, and least efficacious for proptosis¹⁴. The treatment regime is 1mg/kg of prednisolone tapered over a six to 12-week period. However, steroid related side effects are relatively common and symptoms may return with cessation of therapy¹⁵. Pulsed intravenous (IV) steroid (1g for three days and repeated second weekly) is usually reserved for optic neuropathy¹⁶. Low-dose orbital radiotherapy also has a 65% response rate, primarily in soft tissue signs, and is given as 10 fractions of 2 Gy to the posterior orbit¹⁷ (Figure 3). It is better tolerated than steroid therapy with side effects including hair loss at the temples (14%) and transient increase in soft tissue involvement (14%)⁸. Radiation retinopathy is extremely rare¹⁸. The combination of steroids and radiotherapy is commonly used and appears more effective than monotherapy^{19,20}. Although, the efficacy of radiotherapy has been recently questioned, it remains widely used²¹.

Cyclosporin is used in combination with steroids for refractory cases and also as a steroid sparing agent²². Intravenous IgG, somatostatin analogues and cyclophosphamide have been reported in small series as having similar response rates to steroids, but are not commonly used^{19,23-25}.

Surgery

Surgery is generally reserved for quiescent disease. The exception is urgent orbital decompression for dysthyroid optic neuropathy. However, with the advent of aggressive immunosuppression, emergency decompression has become rare. Surgical intervention follows a step-wise approach, with orbital decompression, if required, being performed prior to any strabismus surgery, which precedes eyelid surgery. The reason for this is that decompression may result in ocular misalignment requiring strabismus surgery. Similarly, strabismus surgery may affect eyelid position and should therefore be done before any lid

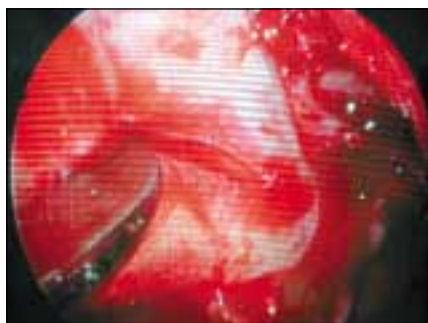


Figure 5

Endoscopic transnasal view of right orbital medial periorbital (periosteum) after removal of bony medial orbital wall. Periosteum is being incised in order to release orbital contents into ethmoid sinus

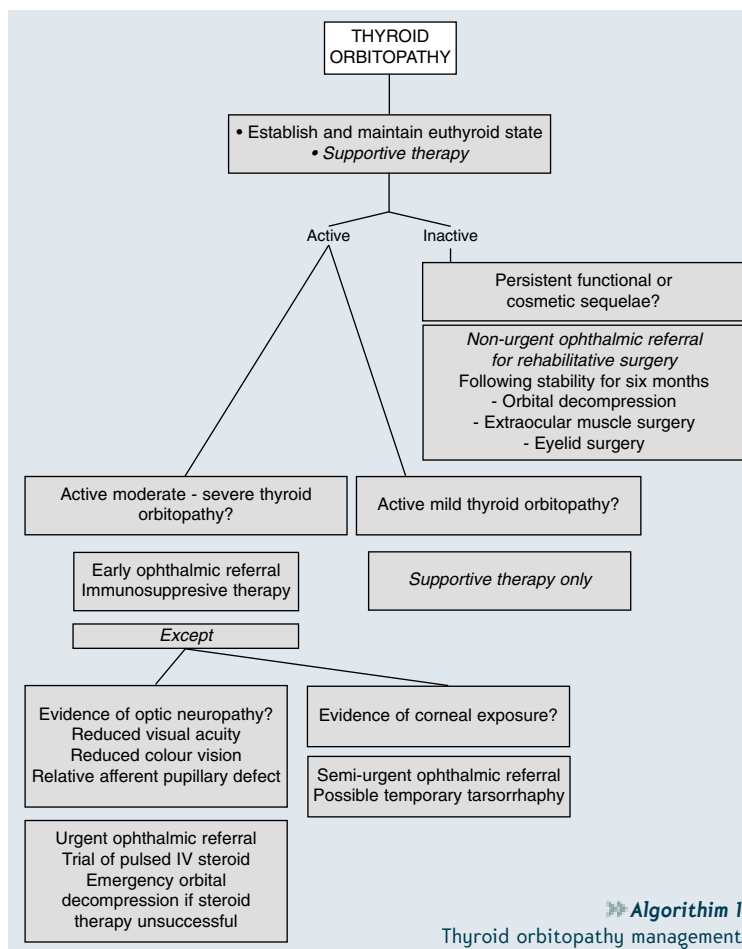


Figure 6

a. Right sided proptosis and lid retraction prior to orbital decompression surgery
b. Cosmetic result after right orbital decompression surgery in the same patient

procedures. Currently, the most common indication for orbital decompression is disfiguring proptosis. It is important to make patients aware of the possibility of rehabilitative surgery and not underestimate the effect this has on a patient's appearance and their psyche.

Orbital decompression involves removal of two to four orbital walls. This is often combined with orbital, including intraconal fat excision (Figure 4). There are a variety of techniques including transconjunctival, lateral canthal and endoscopic approaches (Figure 5), and each wall removed results in approximately 2-3mm of globe retroplacement² (Figure 6). The most common complication is diplopia (15%) and the low risk of blindness (<1/600) is commensurate with that for cataract surgery⁵. Extraocular muscle surgery is performed for strabismus and usually involves recession of the affected muscles. Retraction of the upper eyelids is corrected with levator recession or mullerectomy, whilst elevation of the lower lids requires insertion of a tarsal or hard palate mucosal graft as a spacer. Finally, upper and lower blepharoplasties to debulk excess skin and fat prolapse from the eyelids can also help restore the patient's appearance closer to the premorbid state (Figure 6).



Summary

- TO is an organ specific autoimmune disorder, most frequent in women between 40 to 50 years old and usually associated with thyroid dysfunction
- The clinical manifestations include periorbital soft tissue inflammation, lid retraction, lid lag, proptosis, restrictive myopathy, corneal exposure and optic neuropathy
- Thyroid function tests are essential, while thyroid antibodies and imaging (CT or MRI) showing extraocular muscle enlargement, may also aid diagnosis
- Referral to an ophthalmologist is advisable if there is uncertainty about the diagnosis, significant disease activity or marked functional or cosmetic complications
- Management should be individualised to the patient and often requires collaboration between the optometrist, general practitioner, endocrinologist and ophthalmologist
- Treatment involves correction of thyroid dysfunction, supportive therapy, immunosuppression for moderate to severe active disease and surgery once stable

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