Thyroid orbitopathy

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BACKGROUND Thyroid orbitopathy (thyroid eye disease, thyroid ophthalmopathy) is an organ specific, autoimmune disorder with the potential to cause severe functional and psychosocial effects.
OBJECTIVE This article reviews the clinical features with particular emphasis on current management.
DISCUSSION Thyroid orbitopathy is most prevalent in women aged 40–50 years 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 general practitioner, endocrinologist and ophthalmologist.

Thyroid orbitopathy (TO) is an organ specific autoimmune disorder that 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 39–40% of patients with Graves disease 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 women and 2.9/100 000 in men, and although it is most prevalent in women aged 40–50 years, 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 centered on the extraocular muscles and orbital connective tissue, and is thought to arise from autoantibody cross reactivity between thyroid and orbital antigens.[6] 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 of TO 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 which is worse in the mornings, diplopia, retrobulbar discomfort, and pain on eye movement are other presenting symptoms (Figure 1a). The cardinal signs are proptosis, eyelid retraction and lid lag (Figure 1b). Thyroid orbitopathy is the commonest cause of bilateral, asymmetric and unilateral proptosis in adults (Figure 1c).[3,8] The distinction of disease activity is particularly important, as medical treatment

Table 1. Symptoms and signs of thyroid orbitopathy

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

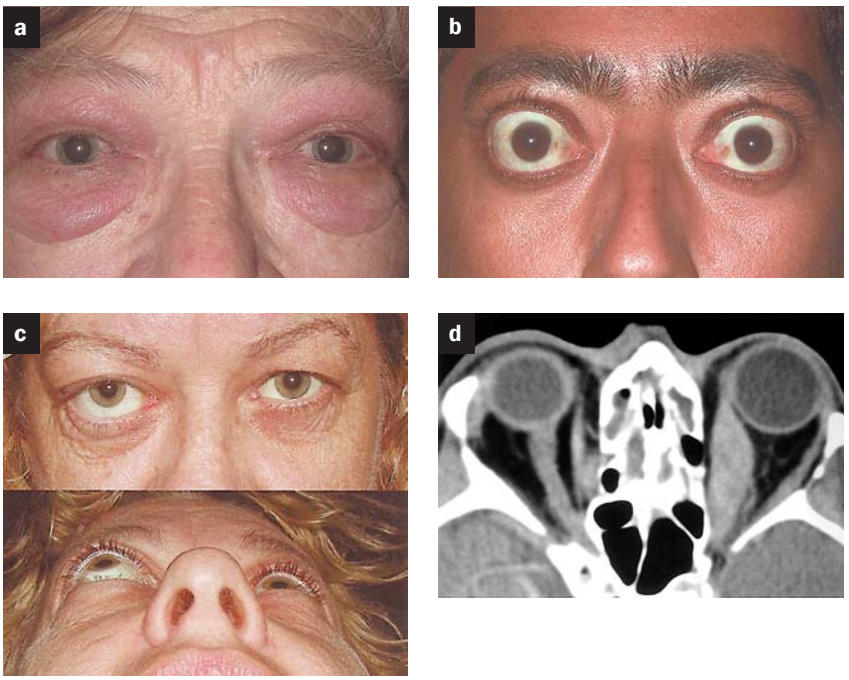

Figure 1a-1d. Signs of thyroid orbitopathy
a) Periorbital swelling due to mild active thyroid orbitopathy
b) Proptosis and eyelid retraction
c) Right proptosis due to thyroid orbitopathy
d) Axial CT scan of orbits showing enlarged extraocular muscles causing crowding of the optic nerve at the orbital apex

is effective only in active disease and surgery is generally reserved for stable TO.[9] Although progression of signs such as muscle restriction and the presence of soft tissue inflammation such as conjunctival injection, chemosis and lid oedema are suggestive of activity, the differentiation of active from inactive orbitopathy can be problematic.[2,9,10] Spontaneous retrobulbar pain or eye pain on extraocular movement can also be symptoms of active disease.[8,10]

It should be noted that there is a broad spectrum of clinical presentation, with the majority of patients exhibiting mild thyroid orbitopathy. Mild disease may present solely as prominence of the eyes due to lid retraction. On the other hand, in severe disease, muscle infiltration or oedema 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 disease.[11]

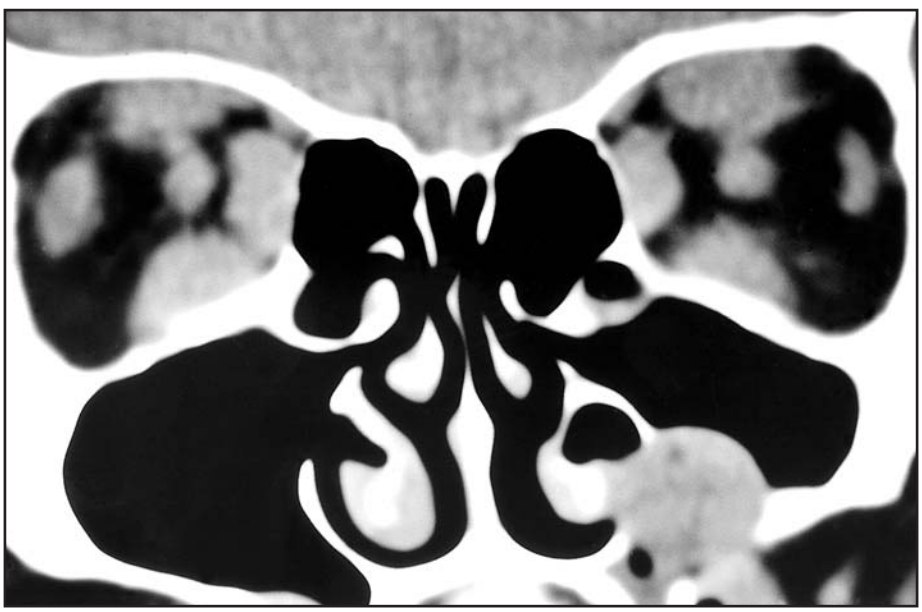

Figure 2. Coronal CT scan of orbits showing enlarged recti, especially inferior, medial and superior recti

With regard to differential diagnosis, active disease may require differentiation from other noninfectious orbital inflamma-

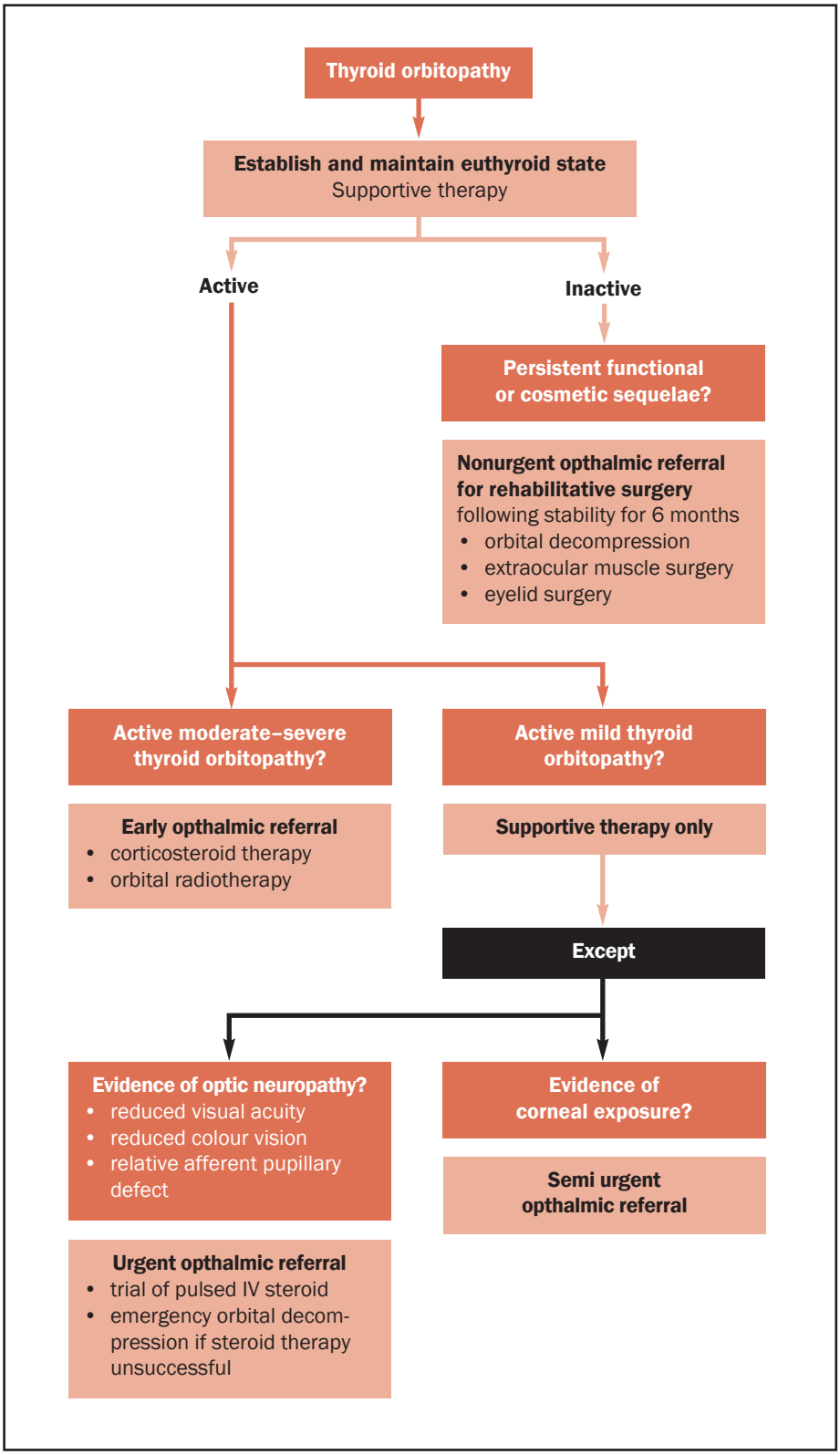

Figure 3. Thyroid orbitopathy management

tory syndromes that may be associated with specific autoimmune systemic disorders but more often are idiopathic (nonspecific). Nonspecific orbital inflammatory syndrome is a relatively uncommon disorder characterised by an inflammatory process involving any, or all of the soft tissue components of the orbit. Patients are generally aged 20–50 years and often present with an abrupt painful onset of unilateral lid oedema, chemosis and conjunctival inflammation, diplopia and proptosis.[3,8] This is opposed to the more insidious onset of superficial eye pain most commonly associated with lid retraction and lid lag in thyroid orbitopathy.[3] Thyroid dysfunction is not present in nonspecific inflammation and it responds dramatically rather than slowly to corticosteroid therapy.[3] Unilateral proptosis may also 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 autoimmune inflammation which then leads to static fibrotic changes.[10] The active phase of the disease usually encompasses an average period of 18–36 months, but late reactivation does occur in the occasional patient.

Investigations

Thyroid function tests should be performed in all cases. Thyroid stimulating hormone receptor, antithyroglobulin and other antibody levels may be useful in making the diagnosis in euthyroid patients.[2] 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 (Figure 1d).[3,7] Muscle involvement is generally bilateral and symmetrical with the inferior, followed by medial, superior and lateral recti being most often affected in caucasian populations (Figure 2).[3] It must be noted that iodine contrast should be used with caution, as it may worsen thyrotoxicosis and could render the disease refractory to medical treatment for some weeks to months. In the majority of cases a strong presumptive diagnosis can be made on

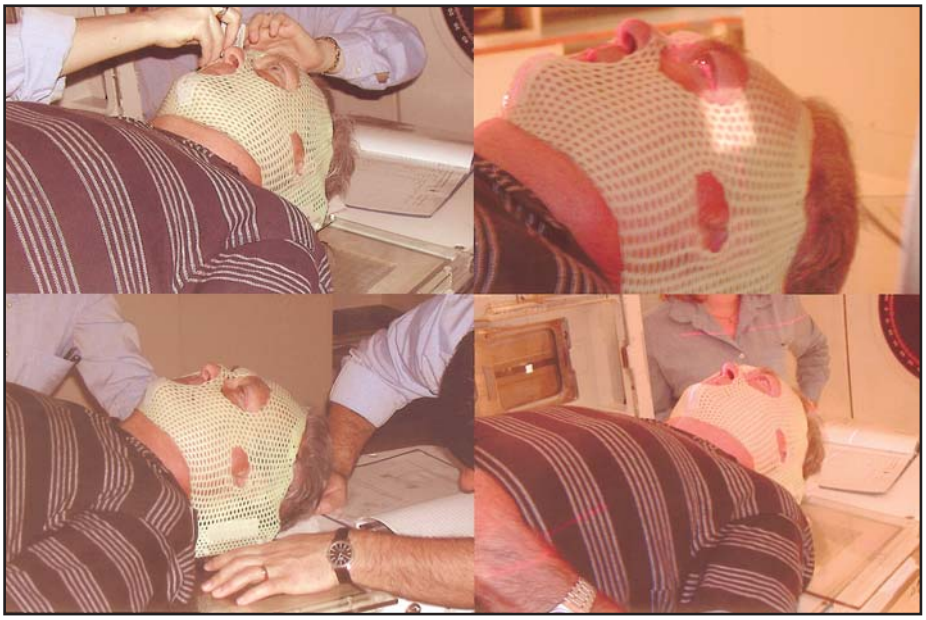

Figure 4. Patient receiving linear accelerator external beam radiotherapy to posterior orbit for thyroid orbitopathy

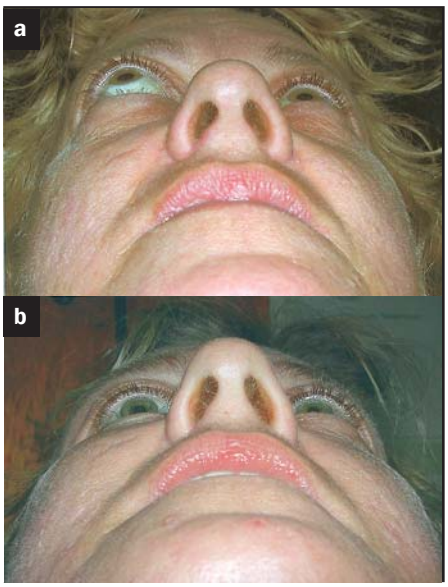

Figure 5a) Right sided proptosis and lid retraction prior to orbital decompression surgery
b) Cosmetic result after right orbital decompression surgery in the same patient

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 Figure 3 summarises the current philosophy used by the majority of orbital clinicians. Early 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 appears to be a risk of exacerbation of TO following I^{131} therapy primarily in those with pre-existing active orbitopathy.[13,14] Bartalena et al found the risk of orbitopathy development or worsening following radioactive iodine to be 33% as opposed to 12.3% with medical therapy and 14.1% with surgery.[13] This should not be considered an absolute contraindication to therapy since any increase in activity may be mild and transient and can be avoided with simultaneous prednisolone administration.[6,9,13]

Supportive therapy

Supportive therapy is applicable to all patients with cessation of smoking being the single most effective adjunctive measure.[15] Exposure symptoms can be alleviated with wrap-around sunglasses, lubricant eye ointment at bedtime, and artificial tears during the day.[2] Cool compresses and head elevation while sleeping may help reduce periorbital oedema.[2] Diplopia can be temporarily managed with monocular occlusion or prisms.[1] 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 corticosteroids or radiotherapy should be considered.

Immunosuppression

Corticosteroids

Corticosteroid therapy has a 65% response rate and is most effective for soft tissue signs rather than motility problems, and least efficacious for proptosis.[16] The treatment schedule is 1 mg/kg of prednisolone tapered over a 6–12 week period. However, glucocorticoid related side effects are relatively common and symptoms may return with cessation of therapy.[17] Pulsed intravenous methylprednisolone was found to be effective in one randomised single blind study.[18] It is usually reserved for optic neuropathy due to its potential for serious side effects.[8,18] It is given as 1 g for three days and then repeated every second week (0.5 g in 200 mL isotonic saline solution given over 30 minutes).[8]

Cyclosporin

Cyclosporin is used in combination with corticosteroids for refractory cases and also as a corticosteroid sparing agent.[28] Intravenous IgG, somatostatin analogues and cyclophosphamide have been reported in small series as having similar response rates to corticosteroids, but are not commonly used.[26,29–31]

Radiotherapy

Low dose orbital radiotherapy also has been found to have a 65% response rate, primarily in soft tissue signs, and is given

as 10 fractions of 2 Gy to the posterior orbit (Figure 4).[19] The likely response time is around 4–6 weeks, with the maximum response at four months.[8,10] It is better tolerated than corticosteroid therapy with side effects including hair loss at the temples (14%) and transient increase in soft tissue involvement (14%).[9] Radiation retinopathy is extremely rare.[20] Indications for radiotherapy are:

- rapidly progressive severe orbitopathy
- troublesome soft tissue changes, or
- when corticosteroids are ineffective or contraindicated.[10]

Radiotherapy is contraindicated in those with known diabetes mellitus or vascular disease as it can accelerate the course of vascular retinopathy.[10] More recently doubts have arisen regarding the efficacy of orbital radiotherapy, as the studies demonstrating a benefit were noncontrolled and the only two randomised controlled trials either failed to show a significant improvement or reported only a minimal improvement in myopathy.[19,21,22] However, there are some reservations about the selection criteria in the study by Gorman et al, such as the possible inclusion of subjects in the stable phase of the disease while excluding those with severe active disease.[23–25] Hence, many orbital clinicians continue to utilise radiotherapy particularly for severe active orbitopathy. The combination of corticosteroids and radiotherapy is also commonly used and is perhaps more effective than monotherapy.[26,27]

Surgery

Surgery is generally reserved for quiescent disease. The exception is urgent orbital decompression for dysthyroid optic neuropathy. However, with the advent of effective immunosuppression, emergency decompression has become rare. Surgical intervention follows a step wise approach, with orbital decompression, if required, being performed before 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 carried out before any lid procedures. Currently, the commonest indication for orbital decompression is disfiguring proptosis. It is important that patients are aware of the possibility of rehabilitative surgery and that clinicians do not underestimate the effect this has on a patient's appearance and their psyche. Orbital decompression involves removal of 2–4 orbital walls. There are a variety of techniques including transconjunctival, lateral canthal and endoscopic approaches, and each wall removed results in approximately 2–3 mm of globe retroplacement (Figure 5).[2] The commonest complication is diplopia (15%) and the low risk of blindness (<1/600) is commensurate with that for cataract surgery.[5] Excision of orbital fat (orbital fat decompression) may also be used to treat proptosis or may on occasion be combined with bony decompression. 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, while 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.

Future research

Further research is required in thyroid orbitopathy particular regarding its pathophysiology and natural history. Uncertainties such as whether radioactive iodine antithyroid therapy significantly worsens thyroid orbitopathy and the effectiveness of orbital radiotherapy need to be clarified with further double blind randomised controlled trials.

Conclusion

Thyroid orbitopathy is a relatively uncommon problem in general practice, but general practitioners are integral members of the management team because of their continuing relationship with their patient. They play an important role in the diagnosis, early specialist referral, patient support and coordination of care.

SUMMARY OF IMPORTANT POINTS

- TO is an organ specific autoimmune disorder, most frequent in women aged 40–50 years and is 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.
- Early 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 GP, endocrinologist and ophthalmologist.
- Treatment involves correction of thyroid dysfunction, supportive therapy and immunosuppression for moderate to severe active disease and surgery once stable.

Conflict of interest: none declared.

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