Diagnosis and management of thyroid eye disease

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Recent advances are helping elucidate the pathogenesis and improve the management of thyroid eye disease. While biochemical investigations and imaging may be supportive, ophthalmological and medical clinical assessments remain the key to the diagnosis and management of this sight-threatening disorder.

Thyroid eye disease (TED) is an organ specific autoimmune disorder which may be both sight-threatening and disfiguring. Although clinical or biochemical thyroid dysfunction is present in most cases, it should be emphasized that, despite its name, patients with TED may be hyperthyroid, hypothyroid or euthyroid. Likewise, TED may precede, accompany or follow other evidence of thyroid dysfunction.

EPIDEMIOLOGY

The annual incidence of TED is estimated at 16/100 000 in females and 2.9/100 000 in males (Bartley, 1994). It is commoner in middle age. The severe end of the spectrum tends to occur in older males, smokers and diabetics (with their associated microvascular disease). This last is an important issue since the combination of diabetes and TED is not uncommon. Linked genes include human leukocyte antigen (HLA) DR3, HLA B8, cytotoxic lymphocyte associated esterase-4 (CTLA4) and thyroid-stimulating hormone (TSH) receptor (Chistyakov et al, 2000).

PATHOLOGY

Enlargement of extraocular muscles (EOM), fat and connective tissue occurs both as a result of the acute inflammation and as a result of an increase in glycosaminoglycans. Compression and inflammation of muscle fibres may result in fibrosis and atrophy in burnt-out disease. The cellular infiltrate consists of macrophages, T-cells, mast cells and occasional plasma cells (Bahn and Heufelder, 1993). Levels of T-cells (both CD4+ and CD8+) and macrophages are much higher in early active disease (Pappa et al, 2000).

PATHOGENESIS

Interestingly, the identity of both the target cell and the primary antigen remain in doubt. The fibroblast–adipocyte lineage are the strongest contenders based on early histological and cytochemical markers and the clinical parallels with pretibial myxoedema. The primary antigen probably shares epitopes with thyroid follicular cells; the TSH receptor remains one unproven candidate. Having escaped deletion by the immune system, recruitment of activated T-cells to the orbit is facilitated by cytokines (predominantly Th1 spectrum) and adhesion molecules (ICAM1, VCAM1, CD44) with subsequent clonal expansion. The ensuing barrage of cytokines, fibroblast growth factors and oxygen free radicals act upon the target cells to stimulate adipogenesis, fibroblast proliferation and glycosaminoglycan synthesis (Heufelder and Joba, 2000).

CLINICAL FEATURES

TED is a clinical diagnosis. The cardinal features are lid retraction or lag (with characteristic visualization of sclera above the cornea), soft tissue inflammation or infiltration, proptosis and restrictive myopathy of the extraocular muscles (Char, 1996).

Lid retraction or lag

Retraction of the upper lid mainly results from shortening and tethering of the levator palpebrae superioris (LPS) (*Figure 1*). In addition, where there is tethering of the inferior rectus, further LPS elevation may arise from attempted corrective overaction of the superior rectus (neurologically part of the levator–superior rectus complex). Any proptosis will exacerbate the apparent lid retraction. Lastly, overaction of the sympathetic part of the LPS (Muller's muscle)

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may occur as a result of thyroxine-induced sensitivity. Inferior lid retraction may also occur. When recording lid position, it should be remembered that the upper lid normally overlaps the superior limbus by 2 mm, whereas the lower lid rests on the inferior limbus.

Soft tissue signs

Common signs of active disease include conjunctival injection and oedema (chemosis), and oedema of the lids (*Figure 2*). Infiltration and forward prolapse of orbital fat may render the periorbital changes chronic. Inadequate lid closure as a result of proptosis may result in sight-threatening exposure keratopathy (*Figure 3*). This may be compounded by disease involvement of lacrimal glands and ensuing keratoconjunctivitis sicca.

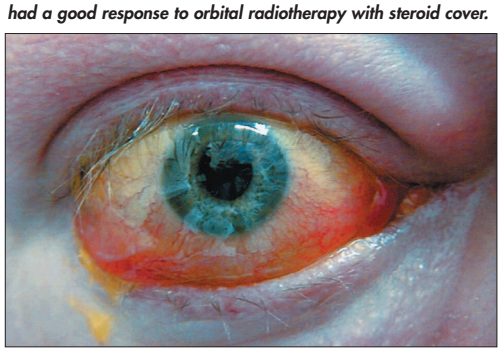
Proptosis

TED is the commonest cause of proptosis (unilateral and bilateral) in adults (*Figures 1* and *2*). The adverse effect on vision at the front of the eye (exposure keratopathy) may be compounded by proptotic stretching of the optic nerve (contributing to optic neuropathy). This may actually be exacerbated by treatment since steroids may induce adipogenesis. It is easily measured with the Hertel's exophthalmometer.

EOM enlargement/myopathy

Ocular motility may be disrupted by EOM changes. Initially, oedema and later fibrosis may restrict movement and cause diplopia. Interestingly, the rectus muscles tend to be affected in order: inferior, medial, superior and lastly lateral (*Figure 4*). Involvement of the inferior rectus may be detected early by noting an increase in intraocular pressure on upward gaze. It should be noted that difficulties may occur in distinguishing inferior rectus restriction from a superior rectus palsy, or medial rectus restriction from a sixth nerve palsy, especially when there is little other evidence of TED.

Figure 2. Chemosis, lid retraction and proptosis. This patient had a good response to orbital radiotherapy with steroid cover.



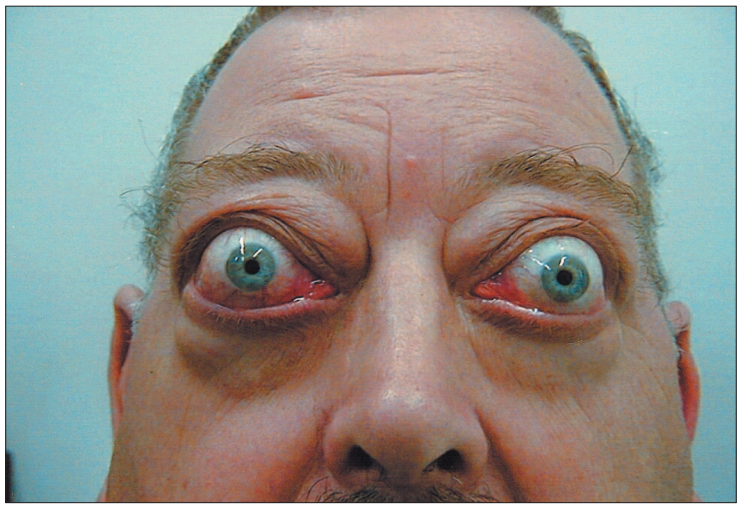


Figure 1. Bilateral lid retraction (with proptosis).

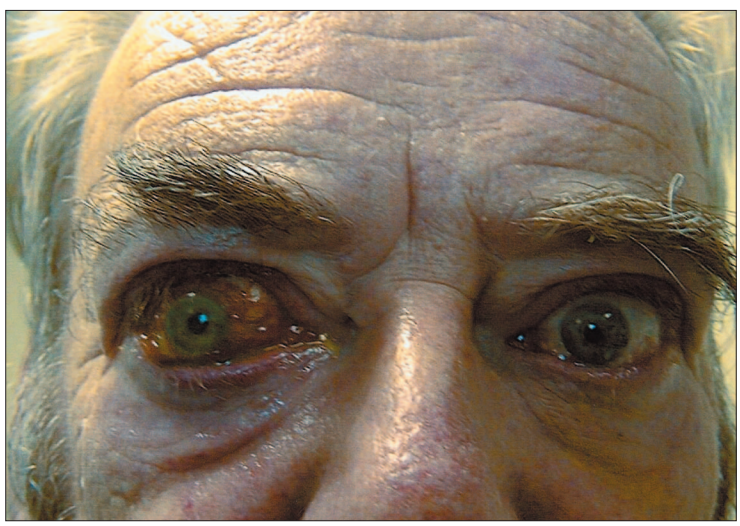
Optic neuropathy

Worsening visual acuity, altered colour perception and scotomata (blind spots) are important signs of optic nerve dysfunction, even though the optic disc commonly appears normal on ophthalmoscopy; in longstanding cases it may be atrophic, and vision will be irreversibly lost. Colour vision may be usefully monitored with Ishihara pseudoisochromatic plates or by comparing colour intensity of a stimulus with both eyes. The neuropathy may be caused by stretch or compression by the surrounding swollen recti muscles (*Figure 4*).

Systemic associations

It is important that a full medical examination is carried out to assess thyroid status, thyroid gland abnormalities, such as a goitre, and systemic features, such as pretibial myxoedema and thyroid acropachy.

Figure 3. Diffuse fluorescein staining with hazy cornea indicative of exposure keratopathy in a proptotic right eye.



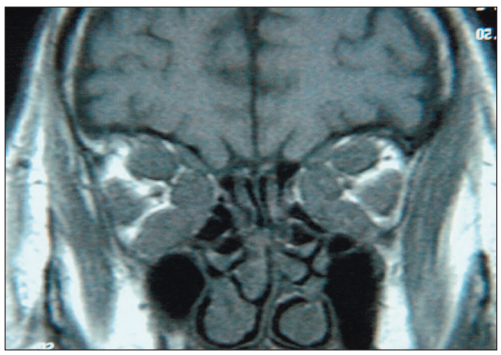


Figure 4. Coronal magnetic resonance image showing the typical pattern of extraocular muscle involvement and compression of the optic nerve; the patient had minimal clinical signs other than ocular dysmotility.

INVESTIGATION

Thyroid function tests

TSH (released from the pituitary) and free thyroxine measurement are the most commonly measured indices of thyroid function. However, if these are normal yet clinical suspicion remains, free tri-iodothyronine (the more active metabolite) should be measured. TSH is commonly suppressed in TED and may be an early marker of thyroid disease. Antithyroglobulin, antiperoxidase and TSH receptor antibodies are commonly associated with TED.

Figure 5. Ophthalmic assessment of the patient with thyroid eye disease.

Check for active eye disease (new or worsening features as listed)

History
- Pain (superficial grittiness/deep ache)
- Pain on eye movement
- Red eye(s)
- Watering eye(s)
- Swollen eye(s)
- Sticking out eye(s)
- Blurred vision
- Double vision
- Blind spot
- Washed out colours

Examination
- Redness of conjunctiva/eyelid
- Chemosis/caruncle swelling/lid oedema
- Increasing proptosis (measure)
- Threatened corneal integrity (stain with fluoroscein)
- Worsening visual acuity
- Relative afferent pupil defect
- Swollen optic disc
- Visual field defects
- Restriction of extraocular movements

→ **Signs of active disease**

Start symptomatic and consider medical therapy: steroids, steroid-sparing agents, orbital

↓

Signs of worsening optic nerve function/presence of high-risk factors

Consider emergency surgery (computed tomography/magnetic resonance imaging may be supportive)

↓

Signs of threatened corneal integrity

Consider emergency surgery
- Lateral tarsorrhaphy
- Lid lengthening procedures
- Orbital decompression

Signs of chronic impaired function or cosmesis

Consider elective surgery
- Orbital decompression
- Ocular motility surgery
- Corrective lid procedures

↓

No active disease but chronic impaired function or cosmesis

- Diplopia (stable)
- Proptosis (stable)
- Poor lid position/impaired closure (stable)
- Restriction of extraocular muscles (stable)

Imaging

Orbital imaging is important for diagnosis and to plan management. Computed tomography (CT) has been largely superseded by magnetic resonance imaging (MRI), although CT bony windows may still have a role in planning decompression operations (Trokel and Jacobiec, 1981). MRI avoids ionizing radiation, permits image reconstruction in any plane and provides much better soft tissue detail, allowing assessment of disease activity and any impending optic neuropathy (Kahaly et al, 1995).

MANAGEMENT

General

In managing TED, assessment (*Figure 5*), counselling, symptomatic measures, medical options for active disease and surgical options (mainly for inactive disease) should be considered. The presence of poor prognostic features may guide towards a more aggressive therapeutic approach (*Table 1*). Multidisciplinary input may be effectively delivered by a combined clinic comprising both endocrine and ophthalmic services. Thus, the aims of euthyroidism and control of eye disease may be coordinated. Counselling should include the reassurance that TED is a self-limiting disease. Local and national support groups are often helpful.

Symptomatic measures include ocular lubricants, tinted glasses, bed-head elevation (to combat morning exacerbation of symptoms) and prisms for diplopia.

Medical

In the active stage, the severe forms of disease are generally predicted by a more aggressive onset. These patients therefore require frequent review and careful documentation of ocular and

TABLE 1. High-risk group

The following are risk factors for a worse final outcome and may require a more aggressive approach:
Older age of onset
Male
Smoker
Diabetes
Reduced visual acuity
Rapid progression at onset
Length of disease

optic nerve function. This is also the group most likely to benefit from medical immunosuppression – with steroids, steroid-sparing agents (e.g. cyclosporin, methotrexate, azathioprine), orbital radiotherapy or a combination of these (Bartalena et al, 2000). Of the steroid-sparing agents, cyclosporin is the best established, with prospective randomized, controlled trials demonstrating improvement in disease control (when given with steroids) and a reduced relapse rate (after steroids withdrawal). However, the benefit was offset by frequent side effects, notably infection, hypertension and hepatic dysfunction (Kahaly et al, 1986).

Similarly, there are promising initial data for the use of methotrexate, but close monitoring is essential in view of potential haematopoietic suppression and hepatic toxicity. However, the side effects of steroids should not be trivialized and may also require monitoring: e.g. hypertension, gastrointestinal side effects (which may be treated prophylactically) and osteoporosis (bone densitometry in prolonged courses). Furthermore, glycaemic control both in patients with pre-existing diabetes and to pick up those who develop diabetes de novo is also required. Immunosuppression by radiotherapy appears to be as effective as steroids with, so far, minimal side effects (Prummel et al, 1993; Mourits et al, 2000). The transient exacerbation of disease severity associated with radiotherapy may be reduced by simultaneous steroid administration, and this is now standard practice. Other immunomodulators under evaluation include intravenous immunoglobulin, plasmapharesis, cytokine antagonists and somatostatin analogues (Krassas and Heufelder, 2001).

There has been widespread debate over the activation or worsening of TED as a result of antithyroid treatments. While this is most marked with the use of radioiodine-131 (^{131}I), it is also seen in association with thyroidectomy and medical antithyroid therapy; it is postulated that this occurs as a result of autoimmune activation to thyroid antigens in the context of thyroid injury. Significantly, the largest randomized study of ^{131}I and its effects on TED demonstrated that the rate of activation or worsening of TED associated with ^{131}I was abolished if steroids were given simultaneously (15% *vs* 0%) (Bartalena et al, 1998); however, this study only included patients with mild or no evidence of TED and was not controlled for other risk factors (e.g. smoking, diabetes). Thyroidectomy appears to have a less dramatic effect on activation or worsening of TED, and there is probably no additional benefit from steroids; debate continues as to whether subtotal has a relatively worse effect on TED compared with total thyroidectomy (reviewed by Bartelena et al, 2000).

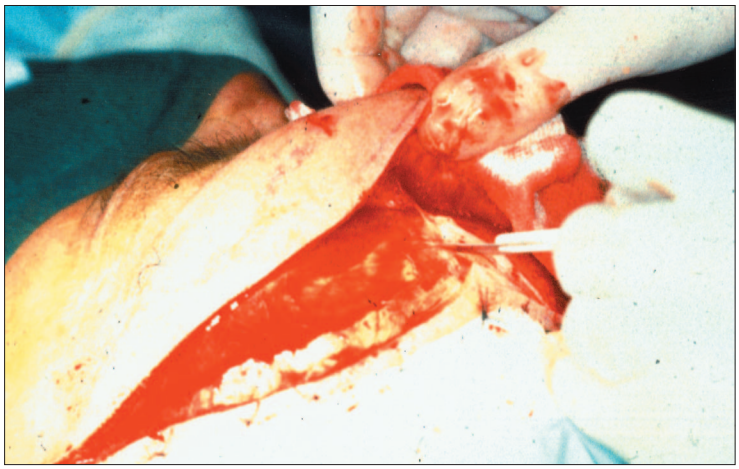


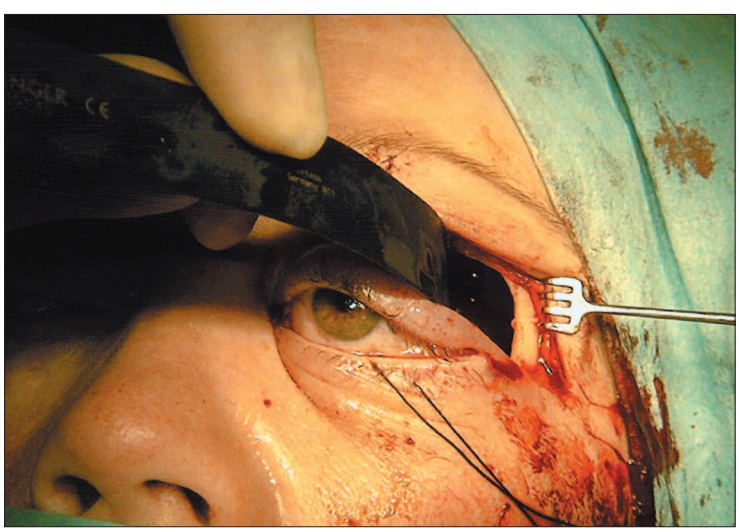
Figure 6. Coronal approach to decompression; incision relatively hidden by the hairline.

Surgical

Where medical treatment proves inadequate, optic nerve compression and severe corneal involvement are indications for emergency orbital decompression. Decompression options include the extent (two-, three- or four-wall) and approach (transorbital, transantral or endoscopic). Most commonly, the two-wall (floor and medial wall) decompression is used (*Figures 6* and *7*). If the cornea is threatened but there is no danger of optic nerve compression, a temporary lateral or central tarsorrhaphy may be sufficient.

In burnt-out or inactive disease, surgery may permit restoration of normal vision and cosmesis (*Figures 8* and *9*). The psychological effects of the changed appearance should not be underestimated. Patients have been known to go into 'voluntary' social isolation because of the perceived

Figure 7. Anterior approach to decompression; incision relatively hidden by a skin crease.



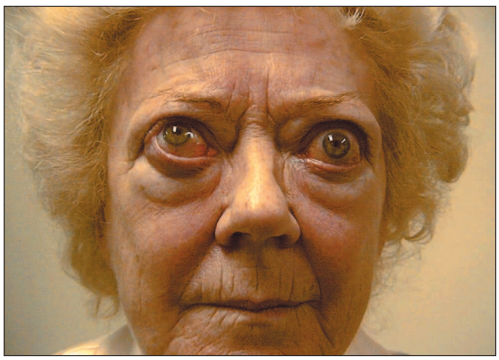


Figure 8. 'Burnt out' thyroid eye disease with proptosis, lid retraction, ocular dysmotility.

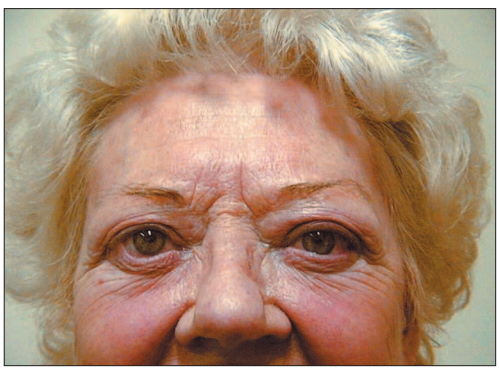


Figure 9. The same patient shortly after orbital decompression. In some cases ocular dysmotility resolves with decompression alone.

frightful appearance (Gerding et al, 1997). Surgical options comprise orbital decompression, motility surgery and lid procedures. Orbital decompression deals with proptosis, which may be both disfiguring and threaten corneal and optic nerve integrity. Motility surgery to regain binocular single vision usually involves recession of the medial and/or inferior rectus, with adjustable sutures. This should only be attempted when motility has been stable for 6 months. Lid operations may improve corneal protection and/or cosmesis by reducing lower lid retraction (recession of lower lid retractors), upper lid retraction (release of levator aponeurosis, excision of Muller's muscle) or both (lateral tarsorrhaphy). Redundant skin and fatty tissues may be removed by blepharoplasty; laser techniques also have an emerging role by making the procedure virtually bloodless.

KEY POINTS

- Thyroid eye disease (TED) is an organ-specific autoimmune disorder which may be both sight-threatening and disfiguring.
- TED may occur in patients who are hyperthyroid, hypothyroid or euthyroid; it may precede, accompany or follow other evidence of thyroid dysfunction.
- Cardinal signs are lid retraction/lag, soft tissue inflammation/infiltration, proptosis and restrictive myopathy of the extraocular muscles.
- Biochemical and radiological investigations may assist in diagnosis; imaging may also help plan detailed radiotherapy or surgery.
- Treatment requires a multidisciplinary approach with counselling, supportive measures, medical immunosuppression, radiotherapy and surgery.

CONCLUSION

TED is a very familiar condition but which has, as yet, no clear cause (the target cell and antigen remain uncertain), no confirmatory test and no specific cure. It may well be that the discovery of the first will lead to both an accurate diagnostic test and a targeted cure. For now, clinical assessment remains the key to both diagnosis and treatment selection. According to disease severity and activity, both immunomodulation and surgery have a role in combating this sight-threatening and disfiguring disease. HM

Conflict of interest: none.

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