Thyroid eye disease (TED) is an autoimmune disorder representing the commonest extrathyroidal manifestation of Graves’ disease, but it may also occur in euthyroid patients or in patients who are hypothyroid due to chronic autoimmune (Hashimoto’s) thyroiditis. TED often mild and self-limiting, and probably declining in frequency, with only 3–5% of cases posing a threat to eyesight (Figure 1).1,2

Severity classification in TED
EUGOGO (European group on Graves’ orbitopathy) recommends the following classification of patients with TED/GO (Graves’ Orbitopathy)3.

1. Sight-threatening GO: patients with dysthyroid optic neuropathy (DON) and or corneal breakdown. This category warrants immediate intervention.

2. Moderate to severe GO: patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Patients with moderate to severe GO usually have any one or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, exophthalmos ≥ 3 mm above normal for race and gender, inconstant or constant diplopia.

3. Mild GO: patients whose features of GO have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually only have one or more of the following: minor lid retraction (< 3 mm above normal for race and gender, transient or no diplopia, corneal exposure responsive to lubricants.

Activity and severity assessments in TED
EUGOGO recommends the following assessments for patients with TED.

- Activity measures based on the classical features of inflammation: clinical activity score (CAS) is the sum of all items present.
  - Spontaneous retrobulbar pain
  - Pain on attempted up- or down gaze
  - Redness of the eyelids
  - Redness of the conjunctiva
  - Swelling of the eyelids
  - Inflammation of the caruncle and or plica semilunaris
  - Conjunctival oedema
  - A CAS ≥ 3/7 indicates active TED

- Severity measures
  - Lid aperture (distance between the lid margins in mm with the patient looking in the primary position, sitting relaxed and with distant fixation)
  - Swelling of the eyelids (absent/equivocal, moderate, severe)
  - Redness of the eyelids (absent/present)
  - Redness of the conjunctivae (absent/present)
  - Conjunctival oedema (absent/present)
  - Inflammation of the caruncle or plica (absent/present)
Exophthalmos (measured in mm using the same Hertel exophthalmometer and same intercanthal distance for an individual patient)

Subjective diplopia score (0- no diplopia; 1- intermittent, i.e. diplopia in primary position of gaze, when tired or when first awakening; 2- inconstant, i.e. diplopia at extremes of gaze; 3- constant, i.e. continuous diplopia in primary or reading position)

Eye muscle involvement (ductions in degrees)

Corneal involvement (absent/punctate keratopathy/ ulcer).

Optic nerve involvement (best corrected visual acuity, colour vision, optic disc, relative afferent pupillary defect (absent/present), plus visual fields if optic nerve compression is suspected.

Medical Treamentnet

Mild TED (Figure 2)
The mainstay of treatment in mild cases of TED is to

- Control thyroid function,
- To cease smoking,
- Topical lubrication for ocular symptoms.

Oral Selenium- Oxygen free radicals are known to play a role in the pathogenesis of TED, with serum selenoprotein P, an index of the oxidative state, being reduced in TED patients. Selenium is an essential component of antioxidant enzymes, several studies have shown that oral selenium can slow progression of the disease in patients with mild TED. Marcocci et al. have shown that Compared with placebo, at the end of 6 months treatment, and 6 months after cessation of treatment, oral selenite (oral sodium selenite 100 mg twice daily) was associated with a significant improvement in the quality of life, reduced ocular disease, and less risk of disease progression.
Progression to severe disease is seen in around 15%-25% of the mild cases of TED despite of early treatment.8

**Moderate to severe TED**

First line of treatment in moderately active TED is mainly medical, which aim to diminish and shorten the acute inflammatory phase, rarely it requires surgical treatment.

**Steroids** - Although their exact mechanism of action remains unclear, they are thought to reduce transcription of intra- and extracellular pro-inflammatory proteins in orbital fibroblasts and Th1 lymphocytes. There are no clear consensus on the optimum dosage, dosing intervals, and duration of treatment of steroids in TED. Treatment is most effective when given early in the course of active disease, with the literature now favouring high-dose intravenous glucocorticoid pulses for moderate to severe TED, with response rates of about 80% for parenteral treatment as compared to 60% with oral steroids.9 Parenteral steroids should be avoided in patients with a history of hepatic, cardiovascular or renal morbidity, uncontrolled hypertension, and diabetes.

Steroid-sparing agents: Azathioprine (AZT) is used not as a monotherapy, but may be along with low dose orbital radiotherapy/ steroids can be considered.10 Oral cyclosporine alone has been reported to be less effective than oral steroids, but if both are combined, then it is considered to be more effective in patient refractory to treatment with either as monotherapy. Salvi et al, have shown that using parenteral Rituximab (RTX) (a chimeric mouse monoclonal anti-human CD20 antibody that blocks B-cell proliferation and maturation) in a non-randomised cohort study, a greater improvement was noted in clinical activity after treatment (1000mg intravenous infusion, twice at two-week interval), and with fewer side effects, than those treated with a standard intravenous steroids.

High serum TNF-α levels have been associated with more severe forms of TED and studies have shown that Infliximab and Etanercept (monoclonal antibodies against TNF-α) can rapidly reduce orbital inflammation and improve visual function, with relatively few side effects.11,12

Radiotherapy- radiotherapy is a well established adjunctive treatment in TED. Low-dose orbital radiotherapy can be considered not as monotherapy, but combined with intravenous steroids. Although a typical radiotherapy dose is 20 Gy, given in 10 fractions of 2 Gy, lower doses may be equally as effective.13

Exposure keratopathy- Intensive topical lubricants and
antibiotics should be started, and the use of moist chambers can be considered in these patients.

Optic neuropathy- As the orbital apex pressure increases it causes compressive optic neuropathy (or dysthyroid optic neuropathy, DON) which results in blurred vision, impaired colour vision, and/or new visual field defects. In these patients high dose of systemic steroids should be considered, with surgical decompression performed when the response to medical treatment is inadequate.

Surgical Treatment

Orbital Decompression

Surgical decompression creates more space for the swollen tissues by expanding the walls of the orbit (bony decompression) or by removing excess orbital fat (fat decompression). The objective is to relieve the hydrostatic pressure at the orbital apex and, by doing so, reduce orbital congestion and improve vascular perfusion and axonal flow within the optic nerve.

Most common indications for orbital decompression are compressive optic neuropathy and excessive proptosis causing globe subluxation, corneal ulceration, and cosmetic disfigurement.

Several clinical studies have demonstrated that the amount of proptosis reduction increases with the number of orbital walls decompressed. A one-wall decompression typically yields 0–4 mm proptosis reduction, a two-wall decompression 3–7 mm, a three wall decompression 6–10 mm, and a four-wall decompression 10–17 mm14 (Figure 3 & 4).

Squint surgery

Restriction of the extraocular muscles will result in the motility imbalance with both vertical and horizontal components, hence the patient will have diplopia. Diplopia is known to fluctuate as the patient progresses from acute inflammatory phase to later fibrotic phases of the disease. Therefore surgeons are advocated to wait for the stable measurements at least for 6 months and 4-6 weeks after the decompression surgery. The goal of strabismus surgery is to achieve single binocular vision in primary and downgaze positions15,16. Most commonly performed surgical procedure for TED associated strabismus is recession of the medial rectus or inferior rectus muscle. Sometimes these procedures can be combined with adjustable suture to prevent large over or undercorrection.

Lid surgery

Exposure keratopathy- In those who remain markedly hyperthyroid, a prompt endocrinological assessment should be obtained, and one has to consider for urgent upper lid lowering procedure with, or without, temporary tarsorrhaphy and topical lubricants to prevent corneal exposure and its sequelae. When the thyroid activity is controlled, high-dose intravenous corticosteroids should be started, in the presence of marked exophthalmos, orbital decompression should be considered with simultaneous lid lowering procedures. One such example for lid lowering procedure is LPS recession, it can be achieved through the posterior (conjunctival) approach, or via an anterior (skin crease) approach. This procedure requires extensive release of the central aponeurosis, lateral horn and Muller’s muscle from the tarsus and conjunctiva17,18. Botulinum toxin is not recommended in these patients as results are unpredictable, and delayed by up to 48 h or longer. Corneal protection is further jeopardised if the neighbouring superior rectus muscle is affected, as this reduces Bell’s phenomenon (Figure 5).

References


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