Thyroid Eye Disease

Synonyms: thyroid ophthalmopathy, dysthyroid eye disease, Graves’ ophthalmopathy, ophthalmic Graves’ disease, Basedow's disease (in German-speaking parts)

Thyroid eye disease (TED) is the most common extra-thyroidal manifestation of Graves' disease. It may also be associated with other forms of thyroid dysfunction and it may also occur in the absence of any biochemical thyroid dysfunction at all.

Management is challenging and requires a team approach. Medical management is only available in the active, early phase. When the disease becomes inactive (no acute inflammation), surgery is the only option. TED is sight-threatening in up to 5% of patients, although most cases are mild and self-limiting. See also separate articles Thyroid Function Tests, Hyperthyroidism, Hyperthyroidism in Pregnancy, Hyperthyroid Crisis (Thyrotoxic Storm), Hypothyroidism, Hashimoto's Thyroiditis and Eye in Systemic Disease.

Description

TED is an organ-specific idiopathic autoimmune disease. It usually begins with an active inflammatory orbital phase lasting 6-24 months, during which expansion of extraocular muscles and orbital fat occurs. This can result in proptosis, compressive optic neuropathy (CON) and compromised extraocular muscle motility. There is progressive deterioration initially, followed by a peak before spontaneously improving.

- The inflammatory phase is followed by an 'inactive' fibrotic phase. The inactive phase is a chronic 'burn-out' phase where further changes are unlikely.
- Sight loss can occur, usually when there has been delay in starting treatment.
- The onset of hyperthyroidism and TED are usually within 18 months of one another. However, TED may also develop years before or after the onset of hyperthyroidism. A small minority of patients never develop any associated thyroid disease. Most patients with TED have clinical and/or biochemical evidence of hyper/hypothyroidism but some are euthyroid (at least at the time of presentation).

Therefore, thyroid dysfunction can precede, proceed or be co-existent with TED.

Pathogenesis

The pathogenesis of TED is still uncertain, but is thought to involve an autoimmune reaction to thyroid-stimulating hormone (TSH) receptors, modulated by T-cell lymphocytes.

Infiltration of lymphocytes into orbital tissue stimulates the release of cytokines (eg, tumour necrosis factor and interleukin-1) which promote the release of mucopolysaccharides from fibroblasts. The resulting hyperosmotic shift leads to oedema of the orbital fat and extraocular muscles, forcing the eyeball forward and leading to the typical appearance of exophthalmos. There are underlying genetic factors which are currently being researched.

Epidemiology

- TED is the most common cause of orbital inflammation and proptosis in adults.
- TED affects an estimated 400,000 people in the UK, a prevalence of 0.7%.
- At least 80% of this is associated with Graves' disease.
- At least 50% of patients with Graves' disease develop clinically significant TED.
- 10-15% of patients with TED have never been hyperthyroid and some are hypothyroid at the time the orbitopathy presents.
Risk factors

- Current smoking increases the risk of developing TED (relative risk of 7 for heavy smokers) although ex-smokers are not at increased risk. Risk increases with the number of cigarettes smoked and reduces on quitting. Smoking also increases the risk of ophthalmopathy after radio-iodine, although this can be reduced by corticosteroids. Smoking also delays and reduces the efficacy of the other methods of treatment such as steroids and radiotherapy.
- Female sex (due to the higher prevalence of thyroid disease in women).
- Middle age.
- There are some associated genes including HLA-DR3, HLA-B8 and the genes for CTLA4 and the TSH receptor.
- Autoimmune thyroid disease.
- Uncontrolled thyroid dysfunction. Thyroid dysfunction is associated with more severe TED, and tight control of thyroid function appears to reduce the severity of TED.
- Radio-iodine therapy is associated with progressive Graves' ophthalmopathy. Thus, it can only be used in the inactive phase of the eye disease (see 'Description', above).

Presentation

- Most patients present with concurrent thyrotoxicosis due to Graves' disease.
- About 20% of patients develop eye problems in the months before becoming thyrotoxic.
- About 10% present with current or previous hypothyroidism.
- Occasionally, TED precedes thyroid dysfunction by several years.
- TED is the most common cause of proptosis in adults and should always be suspected in adults with unexplained diplopia, eye pain or optic nerve dysfunction.

Ophthalmic features

The symptoms reflect the intensity of the inflammatory reaction and the severity of the anatomical, functional and cosmetic aspects. Initially, they relate to an increasingly 'crowded' orbit:

- Ocular irritation.
- Ache (worse in the mornings) behind the eye, especially when looking up, down or sideways.
- Red eyes.
- Cosmetic changes.
- Diplopia (restricted ocular mobility, initially involving the inferior rectus muscles).
- Change in the appearance of the eyes (usually the patient or family notices staring or bulging eyes).
- Dry or watery eyes.
- Mild photophobia.
- Swelling of the upper and lower lids.
Redness of the lids and eyes.
Difficulty moving the eyes.

Proptosis (exophthalmos) may develop gradually, accompanied by:

- Lid retraction and lid lag.
- Conjunctival injection and chemosis (oedema).
- Orbital fat prolapse.
- Exposure keratopathy (photophobia, tearing, grittiness, pain) due to incomplete lid closure.

Exophthalmos does not always develop and it does not correlate with disease severity. Some patients with minimal exophthalmos are at high risk of optic nerve compression. Elderly patients may present with relatively inactive orbitopathy and progressive strabismus.

**Acute progressive optic neuropathy**

If the involved tissues (mainly muscle) begin to compress the optic nerve and if the nerve is further stretched due to proptosis, visual loss can occur. Prompt treatment offers a better chance of a good outcome.

Features suggesting optic neuropathy (and necessitating urgent referral) include:

- Blurred vision.
- Impaired colour perception.
- Reduced visual acuity.
- A relative afferent papillary defect.
- Visual field defect.

See separate Examination of the Eye article. See also below under urgent referral.

**Systemic features**

These depend on the thyroid status and the underlying disease. See the links at the beginning of this article for more information about dysthyroid states.

**Diagnosis**

This is straightforward in patients with obvious bilateral eye disease and a background of thyroid function abnormalities. It can be more difficult in unilateral disease or when the patient is euthyroid.

Diagnosis is confirmed with blood biochemistry and orbital imaging - see ‘Investigations’, below.

**Differential diagnosis**

TED is more often bilateral whereas non-TED proptosis (eg, from a retro-orbital tumour) is usually unilateral.

- **Allergic conjunctivitis** is a common misdiagnosis when periorbital swelling and conjunctival injection are predominant: however, restricted eye movement, lid retraction ± blurred vision occur in TED and are not present in conjunctivitis.
- **Dry eye** is a common misdiagnosis in early disease.
- Orbital myositis.
- Chronic progressive external ophthalmoplegia.
- Idiopathic orbital inflammatory disease.
- Lymphoproliferative disorders.
- Caroticocavernous fistula.
- Myasthenia gravis.
- Cushing's syndrome.
- Obesity can sometimes result in a similar clinical picture.
Investigations

- TSH and free thyroxine (FT4). If normal but clinical suspicion remains, free tri-iodothyronine (T3).
- Thyroid auto-antibodies: anti-TSH receptor, anti-thyroid peroxidase and anti-thyroglobulin antibodies (although these have poor sensitivity and specificity).
- CT or (preferably) MRI of the orbits. MRI is better at showing soft tissue; CT is helpful if surgery for orbital decompression is planned. There will be enlarged extra-ocular muscles (with tendon sparing) ± an increase in orbital fibro-adipose tissue.
- Thyroid uptake scan or orbital biopsy may be helpful.
- Orthoptist review to fully assess ocular movement and visual fields.

Associated diseases[18]

TED is most commonly associated with Graves' disease: clinically apparent TED occurs in about 50% of cases of Graves' disease. It is clinically relevant in 20-30% and sight-threatening (dysthyroid optic neuropathy, corneal breakdown or both) in 3-5%.

Even in the absence of clinical signs, imaging reveals subtle orbital changes in most cases of Graves' disease.

TED shows a significant association with autoimmune thyroiditis, such as in Hashimoto's thyroiditis, where it occurs in about 3% of cases.

Staging[21]

There are various staging systems. The prevailing system is outlined in the European Group on Graves' Orbitopathy (EUGOGO) Consensus statement 2008. It is based on a combination of clinical activity scoring and severity measures, as follows:

Activity measures
- 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.
- Conjunctival oedema.

Scoring 1 for each measure, a score of 3 or more indicates Graves' orbitopathy.

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).
- Degree of exophthalmos (measured using a Hertel exophthalmometer).
- Subjective diplopia score:
  - 0 = no diplopia
  - 1 = intermittent, ie diplopia in primary position of gaze, when tired or when first awakening
  - 2 = inconstant, ie diplopia at extremes of gaze
  - 3 = constant, ie continuous diplopia in primary or reading position.

- Eye muscle involvement (reduction 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).
Management\textsuperscript{[1, 22]}

General points
Ideally TED should be managed in a joint endocrinology and ophthalmology clinic where there is experience and expertise in the condition. The role or primary care professionals includes:

- Identifying sight-threatening eye complications early if the patient is not already under specialist care and referring early (see 'Referral' below).
- Supporting affected patients to stop smoking.
- Achieving and maintaining euthyroid state.
- Prescribing ocular lubricants where there are symptoms of corneal exposure.
- Reminding patients to try sleeping propped up and to avoid dusty conditions.
- Providing support group information (see 'Further reading & references', below).

Referral\textsuperscript{[3]}
Patients with a history of Graves' disease, who have neither symptoms nor signs of TED, require no further ophthalmological assessments and need not be referred to a specialist. Where there is suspected TED, early referral is important because medical treatment is most effective when the eye is acutely inflamed.

- Corneal exposure.
- Strabismus.
- Pressure on the optic nerve.
- Poor cosmetic result.

EUGOGO also recommends urgent referral where:\textsuperscript{[23]}

- There is unexplained deterioration in vision.
- Colour vision changes in one or both eyes.
- There is sudden exophthalmos.
- Corneal opacity is obvious.
- There is restriction of eye movement.
- There is disc swelling.

Treatment\textsuperscript{[1, 21]}
Treatment options include:

- Prisms to control diplopia.
- Botulinum toxin to reduce upper lid swelling.
- Medical treatments:
  - Oral or systemic steroids
  - Octreotide and lanreotide
  - Ciclosporin
  - Intravenous immunoglobulin
- Emerging treatments:
  - Selenium
  - Rituximab
  - Anti-tumour necrosis factor
- Orbital radiotherapy.
- Surgical interventions:
  - Orbital decompression
  - Strabismus surgery
  - Lid-lengthening surgery
  - Blepharoplasty
Treatment of mild TED

- Most patients have mild TED, with symptoms limited to dry eye and mild diplopia.
- These are easily treated with artificial tears, ointment and prisms.
- Conservative therapy has traditionally been recommended for these patients, although there is emerging evidence for early medical treatment.

Treatment of moderate-to-severe TED

- Corticosteroids: the most commonly used medical therapy in active moderate-to-severe TED. They alleviate inflammation and the associated symptoms. It is not clear whether they alter the disease course. Studies suggest intravenous steroids are most effective. Complicating factors include the well-known side-effects of systemic steroid therapy. Periocular and orbital administration have also been evaluated but there is as yet limited evidence for this approach.
- Orbital radiotherapy was an early treatment for TED but now plays only a minor role in the treatment of non-sight-threatening TED because studies and evidence reviews have not clearly demonstrated its efficacy. Additionally, patients with diabetes have an increased risk of radiation-induced retinopathy.
- Ciclosporin is less effective than corticosteroids but it may be of benefit in combination with oral corticosteroids as a steroid-sparing agent.
- Somatostatin analogues such as octreotide and lanreotide have been suggested as there are somatostatin receptors in diseased orbital tissue. Efficacy has not been sustained in several randomised controlled trials so they are not recommended.
- Rituximab is a monoclonal antibody that targets mature B cells. Studies of its use in moderate-to-severe TED, including some steroid-resistant patients, suggest it to be effective in the doses routinely used in rheumatoid arthritis. It was associated with significantly fewer adverse effects than systemic corticosteroids. It is currently recommended in steroid-resistant patients but more evidence is needed before it replaces corticosteroids as a first-line treatment.
- Other studies have found possible roles for etanercept, intravenous immunoglobulin (IVIG), plasma filtration and colchicine.
- Surgical decompression is ultimately needed in up to 80% of patients with moderate-to-severe disease.

Treatment of sight-threatening TED

- This accounts for around 5% of patients.
- Urgent orbital decompression surgery and intravenous corticosteroid therapy both appear effective. Corticosteroids are associated with more adverse effects, although some studies suggest they are also more likely to be effective.

Prognosis

The natural history of the disease is variable: symptoms may progress, remain unchanged or improve spontaneously. Typically, the disease runs its course over a 12- to 24-month period.\(^{[13]}\)

In thyrotoxic patients, 90% of proptosis improves and 30% of restrictive myopathy improves but proptosis rarely improves without further treatment. Poor prognostic factors include:\(^{[24]}\)

- Older age at onset.
- Rapid progression at onset.
- Longer duration of active disease.
- Drop in visual acuity during the active phase.
- Male gender.
- Smoker.
- Diabetes.

More than a third of patients are dissatisfied with the appearance of their eyes when the disease has run its course and more than a quarter have low visual acuity. Between about 10% and 35% will need further treatment.\(^{[25]}\)
Further reading & references

- Thyroid eye disease; Royal National Institute of Blind People (RNIB)
- British Thyroid Foundation
- EUGOGO (European Group On Graves’ Orbitopathy)

5. Cawood T, McBriarty P, OShea D; Recent developments in thyroid eye disease: BMJ 2004; 329. Published 12 August 2004

Disclaimer: This article is for information only and should not be used for the diagnosis or treatment of medical conditions. Patient Platform Limited has used all reasonable care in compiling the information but makes no warranty as to its accuracy. Consult a doctor or other healthcare professional for diagnosis and treatment of medical conditions. For details see our conditions.
Ask your doctor about Patient Access

- Book appointments
- Order repeat prescriptions
- View your medical record
- Create a personal health record (iOS only)

Simple, quick and convenient.
Visit patient.info/patient-access or search ‘Patient Access’