

Clinical assessment of patients with thyroid eye disease

Graves' ophthalmopathy – also referred to as Graves' orbitopathy, thyroid eye disease or thyroid-associated orbitopathy – is an autoimmune condition arising most commonly in the context of Graves' autoimmune thyrotoxicosis. Thyroid eye disease is characterized by inflammation of the orbital and periorbital fibro-adipose tissues that leads to a spectrum of ophthalmic manifestations – typically causing significant aesthetic morbidity and, in some cases, sight-threatening complications. This article discusses the disease epidemiology, manifestations, clinical evaluation and differential diagnosis. An accompanying article (p. C6) looks at the management of this condition.

Epidemiology of thyroid eye disease

The estimated annual incidence of thyroid eye disease is about 16 women and three men per 100 000 population (Bartley et al, 1995). About 25% of patients with Graves' hyperthyroidism have evident signs of ophthalmopathy (Burch and Wartofsky, 1993), but occasionally asymptomatic disease – such as raised intraocular pressure or extraocular muscle enlargement – may occur for many years (Villadolid et al, 1995). Ophthalmopathy appears concurrently with thyrotoxicosis in approximately 40% of patients, beforehand in about 20% and after manifest thyrotoxicosis in about 20%

(Bartley et al, 1996); in the remaining cases, thyroid eye disease appears after the treatment of thyrotoxicosis – particularly after use of radioactive iodine (Tallstedt et al, 1992).

Except for about 10% of cases that constitute 'euthyroid Graves' disease', most patients with thyroid eye disease have thyroid gland disease and such patients may exhibit high circulating levels of anti-thyroid antibodies and/or specific T-cells (Salvi et al, 1990). Thyroid eye disease can also arise with hypothyroidism in the context of Hashimoto's autoimmune thyroiditis.

While thyroid eye disease is commonly bilateral and symmetrical, it can be solely unilateral or occur sequentially – occasionally with many years before involvement of the second orbit (Burch and Wartofsky, 1993). The disease is commonly accepted to have an initial inflammatory phase lasting 6–24 months (the 'active' phase), followed by a plateau phase, and then a phase of partial remission (the 'inactive' phase) (Bartalena and Tanda, 2009). The natural history is variable: ocular symptoms may progress, remain unchanged or remit spontaneously (Perros et al, 1995), with estimated frequencies of ~15%, 20% and 75% respectively. The disease is severe or sight-threatening in about 5% of cases (Bartalena and Tanda, 2009).

Although occurring at any age, thyroid eye disease is commonest in the fifth and seventh decades (paralleling the age incidence peaks for autoimmune thyrotoxicosis) (Perros et al, 1993). Thyroid eye disease mainly affects women, although men tend to have more severe disease. Smoking is a well-established risk factor (Szucs-Farkas et al, 2005; Cawood et al, 2007) – with probable immunomodulatory effects – and is associated with increased volume of orbital connective tissues (as shown by

magnetic resonance imaging) and increased adipogenesis and hyaluronic acid production within in-vitro cultured orbital fibroblasts. Other risk factors include extreme physical or psychological stress (Perros et al, 1993), treatment of thyrotoxicosis with radioactive iodine (Tallstedt et al, 1992), and greater titres of anti-thyroid-stimulating hormone-receptor antibodies that correlate with disease course and severity (Eckstein et al, 2006).

Clinical manifestations and evaluation of patients with thyroid eye disease

Clinical and biochemical evaluation of thyroid status is important for the assessment of each patient.

Symptoms and signs

The earliest symptoms of thyroid eye disease are typically ocular redness, grittiness, bursts of lacrimation, photophobia, and a 'stary or frightened' appearance. 'Lid lag' and 'downgaze hangup' are two common signs that are frequently confused and their terminology misused: lid lag is a dynamic phenomenon whereby, during slow eye movement from upgaze to downgaze, the eyelid lags behind the movement of the globe and catches up at the end of eye movement. In contrast downgaze hangup is a static sign where, in downgaze, the upper eyelid assumes a position higher than normal.

Rarer or more significant symptoms include an oppressive orbital 'pressure', 'bulging' of the eye ('exophthalmos' or 'proptosis'), diplopia or blurred vision. Visual impairment usually arises from localized corneal drying or excess tear-lake (when the blurring tends to improve after eyelid closure), but is occasionally caused by compressive optic neuropathy – when blurring persists after a period of eyelid closure. The onset of eyelid retraction, oedema of the eyelid or

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“ most patients with thyroid eye disease have thyroid gland disease and ... may exhibit high circulating levels of anti-thyroid antibodies and/or specific T-cells. ”

Figure 1a. Left upper eyelid retraction in a patient with unilateral Graves' ophthalmopathy. The staring appearance is often misinterpreted as exophthalmos, but proptosis leads to a downward displacement of the lower eyelid margin, with increased scleral show, that is largely absent in this patient.

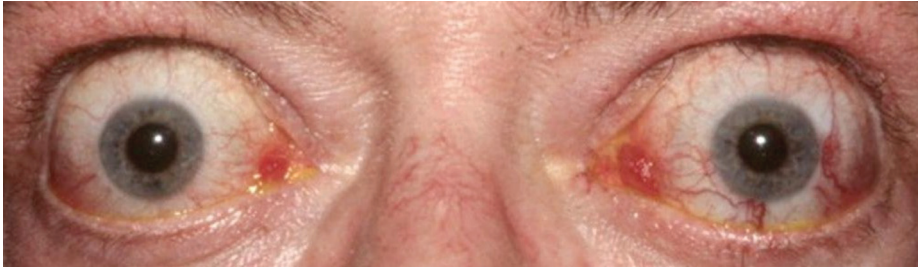


Figure 1b. Severe thyroid eye disease. Severe and neglected thyroid eye disease, leading to bilateral ulcerative keratopathy and spontaneous perforation of the left globe.

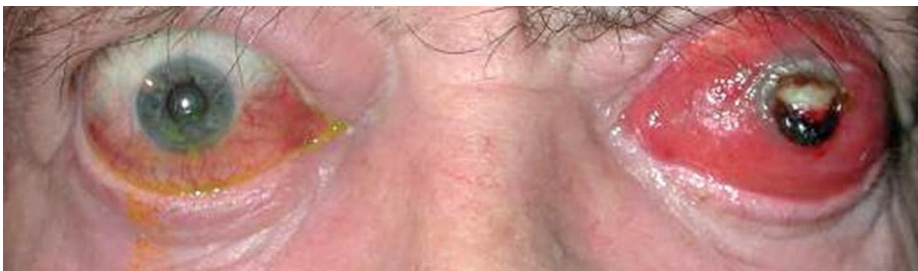


Figure 1c. Upper eyelid retraction and gross proptosis as a result of Graves' ophthalmopathy. The presence of marked lower scleral show caused by the proptosis should be contrasted with the minimal show in Figure 1a.



conjunctiva, diplopia, proptosis and visual impairment should all merit ophthalmic referral and if blurring, visual field defect, or impaired colour vision suggest dysthyroid optic neuropathy the patient should have urgent assessment.

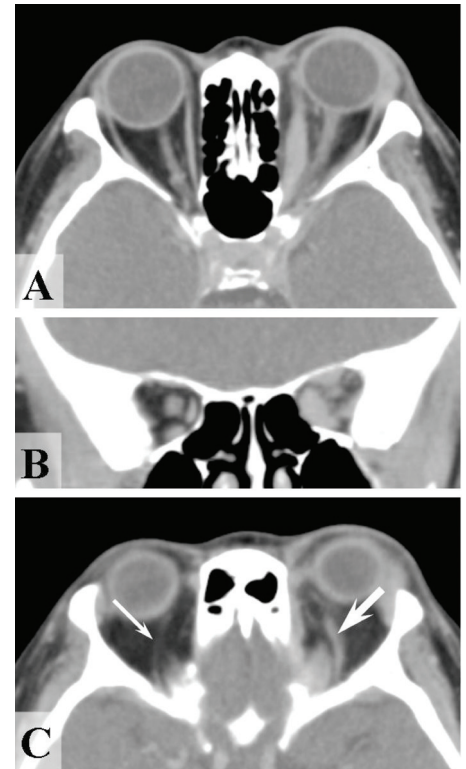
The cardinal sign of eye disease with Graves' thyrotoxicosis is retraction of the upper eyelid, the 'staring' giving the false impression of 'apparent exophthalmos'; as expansion of the orbital fat and muscles occurs, the patient will also develop proptosis and periorbital swelling. While the upper eyelid retraction is commonly attributed to the excess of thyroid hormones and will often improve with treatment, in many patients there is persistent retraction, with secondary corneal exposure as a result of incomplete blinking and failure of eyelid closure (*Figure 1a*).

The clinical assessment of patients with thyroid eye disease should include the following:

Inspection of periorbital tissues and conjunctiva

The periorbital tissues and conjunctiva should be inspected for periorbital swelling and erythema, conjunctival hyperaemia and chemosis (oedema), and inflammation of the caruncle or plica; validated grading systems for these signs are available for clinical use (European Group Of Graves' Ophthalmopathy; www.eugogo.eu). Eyelid closure should be checked, as incomplete closure (lagophthalmos) caused by lid retraction and proptosis may lead to corneal epithelial damage (punctate keratopathy), ulcerative keratitis or ocular perforation (*Figure 1b*).

Figure 2. Congestion of orbital tissues and apical crowding in a patient with left compressive optic neuropathy, shown (a) on axial computed tomography, where a large medial rectus is evident, and (b) on coronal section. c. The left orbital vascular congestion is also manifest as enlargement of the left superior ophthalmic vein (large arrow), as compared with the normal right vein (small arrow).



Optic nerve function

Notably, dysthyroid optic neuropathy tends to occur in the absence of proptosis, and thorough clinical assessment is key to timely diagnosis. In practical terms, visual acuity and colour perception can be assessed with a Snellen chart and Ishihara colour test-plates, with impairment of colour vision being a sensitive marker of dysthyroid optic neuropathy. The patient should be referred for ophthalmic assessment if there is persistence of a corrected acuity below Snellen 6/12, impairment of colour vision, visual field defect or optic disc swelling. Crowding of the optic nerve at the orbital apex (*Figure 2*) is commoner with dysthyroid optic neuropathy, but may be tolerated with no impairment of visual functions.

Assessment of ocular motility

Impairment of extraocular muscle function is the result of inflammatory oedema or fibrosis,

Table 1. Single-visit components of the seven-point clinical activity score

Spontaneous retrobulbar pain
Pain with eye movements
Eyelid erythema
Redness of the conjunctiva
Eyelid swelling
Swelling of the caruncle
Conjunctival oedema (chemosis)

The short clinical activity score is derived on the basis of each of the features, the patient scoring 1 point for each of the features present at a single visit (minimum score = 0, maximum score = 7). A score of 0–2 indicates inactive ophthalmopathy, whereas a score of 3–7 indicates active ophthalmopathy. From Mourits et al (1997), Bartalena et al (2008b)

Table 2. 'NO SPECS' classification for severity of thyroid eye disease

Class 0	N	No symptoms or signs
Class I	O	Only signs, no symptoms (e.g. lid retraction, stare, lid lag)
Class II	S	Soft tissue involvement
Class III	P	Proptosis
Class IV	E	Extraocular muscle involvement
Class V	C	Corneal involvement
Class VI	S	Sight loss (optic nerve involvement)

'NO SPECS' thyroid eye disease assessment (Villalodid et al, 1995) classifies the disease into seven classes of severity; the combination of the first letter of each class makes up the mnemonic 'NO SPECS'

Table 3. Clinical features in mild and more severe ophthalmopathy

Feature	Mild ophthalmopathy	Severe ophthalmopathy
Eyelid retraction (mm)	<2	≥2
Exophthalmos (mm)	<3	≥3
Soft tissue involvement	Mild	Moderate to severe
Diplopia	None or intermittent	Inconstant or constant
Corneal involvement	Absent or mild	Moderate

From Bartalena et al (2008a)

and leads to restricted eye movements and impairment of binocular fusion, the latter causing true diplopia. Contracture of the inferior recti – the most commonly affected muscles in thyroid eye disease – limits upgaze and may be associated with a 'chin-up' head posture. Diplopia can be constantly present, or else intermittent – either present only on first waking or when tired, or else at the extremes of gaze.

Measurement of the degree of proptosis

Exophthalmos is suggested by the presence of scleral show below the lower corneal limbus, but can be formally measured using a Hertel (or other) exophthalmometer, which measures the position of the anterior corneal surface relative to the lateral orbital rim. Typical upper limits for Hertel exophthalmometry are 21 mm for Caucasians and 23 mm for Afro-Caribbeans, but may reach 30 mm or more in severe thyroid eye disease (Figure 1c).

Intraocular pressures

Intraocular pressures are commonly elevated in patients with thyroid eye disease, especially on upgaze, and this can rarely lead to glaucomatous optic disc damage.

Table 4. Differential diagnosis of thyroid eye disease

Obesity-related increase in orbital fat
Cushing's syndrome
Idiopathic orbital inflammation and myositis
Primary and metastatic orbital tumours
Vascular abnormalities in the cavernous portion of the carotid artery (i.e. thrombosis, aneurysm, fistula)
Infiltrative disorders
Physiological asymmetry of orbits
Unilateral axial myopia (different axial lengths to globe)
Contralateral enophthalmos caused by old blow-out fracture or scirrhous tumours

Assessment of disease activity and severity

As active inflammation often merits immunosuppression, assessment of the degree of disease activity is particularly important (Bartalena et al, 2008b). A widely-used score for evaluation of disease activity is the clinical activity score (Table 1) (Mourits et al, 1997), with a clinical activity score ≥3 suggesting significant inflammatory disease (Bartalena et al, 2008b).

Disease inflammatory activity relates poorly to the final severity (morbidity) of the eye disease. A widely-used tool for severity assessment is the NO-SPECS system of the American Thyroid Association (Table 2) (Villalodid et al, 1995). Other parameters of value are listed in Table 3.

Differential diagnosis of proptosis and extraocular muscle enlargement

Most patients with bilateral thyroid eye disease will have an evident diagnosis, based on symptoms and clinical signs, although it is important to differentiate true exophthalmos from 'apparent exophthalmos' caused by upper eyelid retraction. However, diagnosis is more difficult with unilateral or asymmetrical disease, or in the absence of thyroid gland disease.

Several conditions may cause unilateral or bilateral proptosis and should be considered in the differential diagnosis (Table 4). Orbital imaging (computed tomography or magnetic resonance imaging) is warranted with unilateral or atypical thyroid eye disease, and thyroid-stimulating hormone-receptor antibody titres can aid diagnosis because of their high specificity and

sensitivity for thyroid eye disease. Orbital imaging typically reveals tendon-sparing enlargement of the rectus muscles, with or without increased orbital fat. With dysthyroid optic neuropathy, imaging may show marked crowding of the optic nerve at the orbital apex and intracranial bulging of the orbital fat at the superior orbital fissure. Octreotide scan, although not routinely used, can help identify patients with active ophthalmopathy.

Conclusions

This article discusses the pathophysiology and clinical manifestations of thyroid eye disease. The management of thyroid eye disease requires multidisciplinary approach and depends on disease severity and activity. The management of thyroid eye disease is discussed in the accompanying article. **BJHM**

Conflict of interest: none.

Bartalena L, Baldeschi L, Dickinson A et al (2008a) Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO. *Eur J Endocrinol* **158**: 273–85 (doi: 10.1530/EJE-07-0666)

Bartalena L, Baldeschi L, Dickinson AJ et al (2008b) Consensus statement of the European group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy. *Thyroid* **18**: 333–46 (doi: 10.1089/thy.2007.0315)

Bartalena L, Tanda ML (2009) Clinical practice. Graves' ophthalmopathy. *N Engl J Med* **360**: 994–1001 (doi: 10.1056/NEJMcp0806317)

Bartley GB, Fatourechhi V, Kadrmas EF, Jacobsen SJ, Ilstrup DM, Garrity JA, Gorman CA (1995) The incidence of Graves' ophthalmopathy in Olmsted County, Minnesota. *Am J Ophthalmol* **120**: 511–17

Bartley GB, Fatourechhi V, Kadrmas EF, Jacobsen SJ, Ilstrup DM, Garrity JA, Gorman CA (1996) Chronology of Graves' ophthalmopathy in an

incidence cohort. *Am J Ophthalmol* **121**: 426–34

Burch HB, Wartofsky L (1993) Graves' ophthalmopathy: current concepts regarding pathogenesis and management. *Endocr Rev* **14**: 747–93

Cawood TJ, Moriarty P, O'Farrelly C, O'Shea D (2007) Smoking and thyroid-associated ophthalmopathy: A novel explanation of the biological link. *J Clin Endocrinol Metab* **92**: 59–64

Eckstein AK, Plicht M, Lax H et al (2006) Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. *J Clin Endocrinol Metab* **91**: 3464–70

Mourits MP, Prummel MF, Wiersinga WM, Koornneef L (1997) Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. *Clin Endocrinol (Oxf)* **47**: 9–14

Perros P, Crombie AL, Matthews JN, Kendall-Taylor P (1993) Age and gender influence the severity of thyroid-associated ophthalmopathy: a study of 101 patients attending a combined thyroid-eye clinic. *Clin Endocrinol (Oxf)* **38**: 367–72

Perros P, Crombie AL, Kendall-Taylor P (1995) Natural history of thyroid associated ophthalmopathy. *Clin Endocrinol (Oxf)* **42**: 45–50

Salvi M, Zhang ZG, Haegert D, Woo M, Liberman A, Cadarso L, Wall JR (1990) Patients with endocrine ophthalmopathy not associated with overt thyroid disease have multiple thyroid immunological abnormalities. *J Clin Endocrinol Metab* **70**: 89–94

Szucs-Farkas Z, Toth J, Kollar J et al (2005) Volume changes in intra- and extraorbital compartments in patients with Graves' ophthalmopathy: effect of smoking. *Thyroid* **15**: 146–51

Tallstedt L, Lundell G, Topping O, Wallin G, Ljunggren JG, Blomgren H, Taube A, and the Thyroid Study Group (1992) Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. *N Engl J Med* **326**: 1733–8 (doi: 10.1056/NEJM199206253262603)

Villalodid MC, Yokoyama N, Izumi M et al (1995) Untreated Graves' disease patients without clinical ophthalmopathy demonstrate a high frequency of extraocular muscle (EOM) enlargement by magnetic resonance. *J Clin Endocrinol Metab* **80**: 2830–3

KEY POINTS

- Thyroid eye disease is an autoimmune disease affecting predominantly the orbital and periorcular tissues.
- The cardinal features of the disease are inflammation causing ocular redness, upper eyelid retraction, periorbital tissue swelling, proptosis and diplopia.
- The annual incidence of thyroid eye disease is estimated at ~16 women and three men per 100 000 population.
- Thyroid eye disease is usually bilateral, but can be asymmetrical or unilateral. Some patients with unilateral disease may develop contralateral disease many years later.
- At diagnosis, ~20–25% of patients with Grave's hyperthyroidism have clinically evident signs of ophthalmopathy.
- Risk factors for thyroid eye disease are female sex, smoking and stress. Although thyroid eye disease is more common in women, affected men tend to manifest more severe disease.
- The natural history of thyroid eye disease is variable; ocular symptoms may progress, remain unchanged or remit spontaneously.
- The disease has an initial inflammatory phase lasting 6–24 months, followed by a plateau phase and then by an invariably partial remission phase (inactive phase). The disease is mild in the majority of cases, moderate in 20–25% of cases, and severe and potentially sight-threatening in ~3–5% of cases.
- Diagnosis of thyroid eye disease is clinical, and the evaluation and treatment should be multidisciplinary.



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