

The Hyperthyroid Stare

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A 69-year-old female was electively admitted to the ophthalmology service for a cataract surgery. She had a background history of Grave's disease, and a thyroid function test showed a hyperthyroid picture with thyroid stimulating hormone (TSH) less than 0.0083 uIU/ml (reference range: 0.35 -4.94 uIU/ml), free T4 19.1 pmol/L (9-19.1 pmol/L) and free T3 5.89 pmol/L (2.43-6.01 pmol/L). At that time, the patient was on carbimazole 10mg once daily. She was subsequently referred to endocrinology team to optimise her thyroid disease before surgery. On review, she was asymptomatic without any symptoms of hyperthyroidism. However, there was presence of small, soft diffuse, non-tender goitre without any bruit any and bilateral exophthalmos and lid retraction (Dalrymple's sign) (Figures).

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Thyroid eye disease (TED), also known as Graves' ophthalmopathy (GO) or thyroid associated ophthalmopathy (TAO) is a chronic inflammatory autoimmune disease of eyes associated with systemic thyroidal disorder mainly Graves' disease.¹ It is one of the most important causes of bilateral and/or unilateral proptosis which gives the hyperthyroid staring glare; Dalrymple sign.

Graves' disease mainly affects women with peak incidence in fifth decades of life. TED is relatively common with studies showing incidence between one third to one half of patients with thyroid dysfunction and 150 to 250 people per 100,000 of the general population. The prevalence of TED in Asia was 44% which was highest amongst the continents, lowest being North America (27%). Southeast Asia has a relative lower prevalence rate (35%).² Environmental factors like smoking, selenium and vitamin D deficiency and genetic factors like family history of thyroid illness predispose to TED.³

The pathophysiology of the TED is not clear. Lehman and colleagues hypothesised that orbital tissues and thyroid both share common antigens like thyroglobulin, TSH receptor, insulin-like growth factor-1 (IGF-1) receptors and extraocular muscle antigens, which activate fibroblasts to release chemokines and cytokines. This in turn stimulates T-cells lymphocytes leading to deposition of extracellular matrix molecules, fibroblast proliferation and adipogenesis seen in TED.⁴

Various classifications are available for the assessment of the clinical manifestations of TED. Historically, the Werner's NO SPECS classification (No physical signs or symptoms, Only signs, Soft tissue involvement, Proptosis, Extraocular muscle signs, Corneal involvement, and Sight loss) had been used but has limited prognostic values. The European Group of Graves' Orbitopathy (EUGOGO), Clinical Activity Score (CAS) or Vision, Inflammation, Strabismus, and Appearance (VISA) classification are the most recent classifications introduced.¹

CAS assessment uses seven criteria each scored as 0 (absent) or 1 (present).^{5,6} These include spontaneous retrobulbar pain, pain on attempted upward or downward gaze, redness of eyelids, redness of conjunctiva, swelling of caruncle or plica, swelling of eyelids and swelling of conjunctiva (chemosis). CAS helps to determine the treatment according to the severity and progression of the disease. CAS values <3 is inactive GO whilst CAS \geq 3 is active GO. A ten-item CAS, including an increase in exophthalmos of \geq 2 mm,

a decrease in eye motility of \geq 8° or a decrease in visual acuity in the last 1–3 months, is useful to assess progression of GO after the first visit.

Clinical features of TED may present before or during the thyroid dysfunction state but can also be seen during euthyroid state on treatment. TED present primarily with eyelid retraction also known as the Dalrymple sign giving a classical staring look or wide-eyed appearance.⁷ The lid lag and staring look become more prominent when the eyeballs are moved upward. This sign is called Kocher's sign. Lid retraction is multifactorial and is due to increased sympathetic stimulation of Muller's muscle, contraction of the levator muscle, and scarring between the lacrimal gland fascia and levator, which specifically gives rise to the lateral flare. Also seen are lagophthalmos presenting with exposure symptoms like foreign body sensation, grittiness, photophobia, and lacrimation. Various other signs are present depending upon the involvement of eyelids, pupils, extraocular muscles and face as a whole. Lid retraction of upward eyelids on downward gaze (Von Graves sign), fine tremors of eyelids when closed gaze (Rosenbach sign), difficulty in eversion of upper eyelids (Gifford sign), inadequate and infrequent blinking (Stellwag's sign), loss of forehead creases of upward gaze (Joffroy's sign), restriction of one or more extra ocular muscles (Jendrassik sign) are other eye signs to name a few.^{1,8}

Diagnosis for TED is usually clinical. The obvious findings maybe unilateral or bilateral proptosis, which can be confirmed by exophthalmometer using a Hertel instrument.⁹ A computed tomography scan is preferred over a magnetic resonance imaging of the eyeballs in investigation of TED due to greater sensitivity of CT scans to look for extraocular muscles.³ Anti-Thyroglobulin (Anti-TG), anti-Thyroid Peroxidase (Anti-TPO) and TSH receptor antibodies (TSH R Ab) positivity indicate any possible autoimmunity. Management of TED depends on the severity of ocular involvement and disease activity. Non-severe cases with ocular involvement and inactive lesions are treated symptomatically, for example with sunglasses (reduces photophobia), artificial tears (to prevent exposure-related dry eyes or keratitis) and head elevation to reduce periorbital oedema. Active and severe TEDs with CAS of 3 or more may need glucocorticoids, orbital decompression, radiotherapy or strabismus and eyelids reconstruction surgery as indicated.¹⁰

Abbreviations

TSH	Thyroid stimulating hormone
TED	Thyroid eye disease
GO	Grave's ophthalmopathy
TAO	Thyroid associated ophthalmopathy

Declarations

Patient Consent

Patient consent has been obtained.

Disclosure and Conflict of Interest

The authors declare that they have no conflicts of interest and no financial disclosures relevant to this case report.

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