Thyroid Eye Disease: a Comprehensive Review

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Nomenclature of Thyroid Eye Disease

Thyroid eye disease (TED) is also known as Graves' ophthalmopathy / orbitopathy, thyroid associated ophthalmopathy / orbitopathy (TAO), or thyrotoxic/ endocrine exophthalmos. It is the most important extrathyroidal manifestation of autoimmune thyroid diseases such as Graves’ Disease and Hashimoto thyroiditis. It is also the most common orbital disorder in adults worldwide and the commonest causes of unilateral or bilateral axial proptosis (exophthalmos), acquired strabismus or lid retractions. TED may lead to visual dysfunction, ocular discomfort, facial disfigurement and significantly decreased quality of life.

Disease Spectrum of Thyroid Eye Disease

Patients with TED may not have any clinical or biochemical evidence of thyroid dysfunction or autoimmunity. They may have only orbital involvement known as ophthalmic Graves’ Disease or euthyroid Graves’ Ophthalmopathy; or they may also have isolated thyroid dysfunction with minimal (subclinical) TED.

Epidemiology of Thyroid Eye Disease

TED tends to have a bimodal presentation during the fourth or sixth decade. While the female to male ratio of patients with all forms of clinical TED is about 9:1; for those with the severe form of disease it drops to 3:1. A previous research from a Caucasian TED cohort of 120 patients, 90% had Graves’ Disease, 7% was euthyroid, 3% had Hashimoto thyroiditis and 1% had primary hypothyroidism.

Chronology of Thyroid Eye Disease

Around 4% of TED patients present more than 6 months before diagnosis of thyroid problems, while 19% within 6 months before. In about 20% of patients, there are concurrent ocular and endocrine features on presentation, while 22% and 35% had ocular manifestations within 6 months or more after being treated for thyroid dysfunction respectively.

Risk Factors of Thyroid Eye Disease

The main risk factors for the development of TED in patients with thyroid disease include the male gender, advancing age of onset, smoking, use of radioactive iodine (RAI) and post-ablative hypothyroidism. Previous studies have demonstrated that smokers have a higher risk of developing GD, as well as additional chances of TED developing or worsening and a reduced response to immunosuppressants or orbital radiotherapy.

Thyroid Eye Disease in Paediatric Patients

TED is not uncommon in the paediatric population but is usually far less severe than their adult counterpart. Among 83 Chinese children aged 16 or below with GD, 65% had ocular findings including 38.6% had lower lid retraction, 13% had punctate epithelial corneal erosion, 12% had mild proptosis (<3mm), and 1.2% had limited extraocular movement. None of the children developed visual threatening complications.

Pathophysiology of Thyroid Eye Disease

With genetic susceptibilities and permissive environmental triggers, individuals with the risks factors are prone to develop autoantibodies which can stimulate the thyroid gland to cause goitre and hyperthyroidism (Fig. 1A), some attack the orbits leading to TED/TAO while a minority are responsible for pretibial myxoedema (Fig. 1B). A T-cell mediated response appears to be important in orbital autoimmunity. In addition, autoantibodies to Thyroid Stimulating Hormone receptor and Insulin-like Growth Factor-1 receptor were found to be implicated in TED. The physical co-localisation and functional linkage of the two receptors were recently reported. Orbital fibroblasts are the primary cells responding to autoimmune stimuli leading to adipogenesis, accumulation of glycosaminoglycan (GAG) particularly hydrophilic hyaluronan causing tissue oedema, infiltration by lymphocytes, mast cells and secondary involvement of the extraocular muscles.
with subsequent tissue fibrosis and remodelling. The anatomically confined orbital space further exacerbates compressive effects and congestive changes. While extraocular muscle enlargement has been used to be considered as the cardinal feature in TED, there is now growing molecular, radiological and clinical evidences that adipogenesis is universal in all patients with TED particularly the younger patients. The dual differentiating pathways of orbital fibroblasts, or more recently circulating fibrocytes may determine such fat or muscle predominant phenotypes of TED.

There are still many missing links between the thyroid and orbit in TED. How these two anatomically and embryologically distinct organs are related during the autoimmune attack is still unknown. The diagnosis of GD and Hashimoto thyroiditis with TED can be chronologically discordant. The asymmetric involvement (Fig 2A), predilection of certain EOM (inferior > medial > superior > lateral recti > obliques) are atypical of systemic conditions. As opposed to other autoimmune diseases, inflammation in TED will eventually quiet down but fibrotic and congestive features often persist and progress. Reactivation of TED does occur in rare circumstances.

Clinical Features of Thyroid Eye Disease

Typical signs of TED from a Caucasian cohort include eyelid retraction (90%) (Fig. 2B), lid lag (50%) (Fig. 2C&D), exophthalmos (60%) (Fig. 2E), restrictive myopathy (40%) (Fig. 2F), optic nerve dysfunction (5%) (Fig. 2G) while classical presentation with the above (except optic nerve dysfunction) comprised only 5%. Physical findings may be grouped as extraocular: lid puffiness, lid retraction, lid lag, lagophthalmos (incomplete eyelid closure) (Fig. 2H), axial non-pulsatile proptosis (exophthalmos), restrictive strabismus, acquired lower lid epiblepharon in Asians, and conjunctival injection (Fig. 3A), exposure keratopathy (Fig. 3B), chemosis (Fig. 3C), raised intraocular pressure (IOP), optic disc swelling, retinal venous congestion or choroidal folds. Vision loss in TED can be caused by optic nerve dysfunction (dysthyroid optic neuropathy), exposure keratopathy, raised IOP or globe subluxation.

Dysthyroid Optic Neuropathy

Dysthyroid optic neuropathy (DON) is usually due to apical compression by enlarged extraocular muscles (Fig. 4A). Other mechanisms involved include inflammation, ischaemia or mechanical stretching. Patients often present with diplopia (particularly abduction deficits secondary to medial rectus enlargement) while patients with fat predominant subtype may have relative normal motility but severe proptosis and straightening of optic nerve on axial orbital scans (Fig. 4B). Signs of optic neuropathy include drop in vision, colour vision, visual field and afferent papillary defect or optic disc swelling. Patients with existing diabetes or of Asian origin (due to shallow orbits) have higher chances of developing DON. Medical decompression (e.g. intravenous methylprednisolone 1gm daily for 3 days) and often surgical (medial wall or fat) decompression are required subsequently.

Lid Retraction

Lid retraction is the commonest sign in TED (Fig. 2B to 2D). Practitioners should note that the normal upper lid rests at 1-2mm below the superior limbus (corneal-scleral junction) and the lower lid should be just below the inferior limbus. On the other hand,
while the commonest cause of lid retraction is also TED, its differential diagnoses include myasthenia gravis, myotonia dystrophy, Marcus Gunn jaw winking, metabolic diseases (uraemia, cirrhosis), Parinaud’s (midbrain) syndrome, Parkinson’s disease, contralateral ptosis or aberrant third nerve regeneration.

**Proptosis (exophthalmos)**

Patients with TED have axial non-pulsatile proptosis (exophthalmos) secondary to orbital venous congestion, accumulation of GAG and adipogenesis. Exophthalmos can be quantified by the exophthalmometer or radiologically with axial orbital scans.

**Diplopia**

Diplopia or double vision is often the most debilitating visual symptom in TED. Strabismus is restrictive (fibrotic) rather than paralytic in nature. As mentioned earlier, the inferior rectus is the most commonly involved, followed by the medial, superior then lateral rectus. Movement is therefore usually worst in elevation or abduction (Fig. 2F). Radiologically involved muscles are often enlarged but not infrequently sparing the tendons.

TED can be graded according to the severity (tissue remodelling or deformities) against activity (inflammation). The NOSPECS grading (Normal, Only sign, Soft tissue involvement, Proptosis, Extraocular Motility, Corneal exposure, Sight-threatening) can be used to define the degree of deformities, while the clinical activity score (CAS) utilises the parameters of inflammation (erythema, swelling, tenderness, loss of function).

Diagnosis of TED is largely clinical based on history and typical ocular examination findings. However, all patients should have appropriate endocrinological referrals for evaluation with thyroid function test for serum sensitive thyrotropin (sTSH) and free thyroxine (free T3, free T4) levels. Thyroid-related antibodies including anti-thyroglobulin, anti-microsomal and TSH receptor antibodies may be used adjunctively. Other ancillary ocular investigations involve the use of visual field (automated perimetry), colour vision assessment (Ishihara pseudoisochromatic plates), Hess chart (for extraocular movement) and binocular field (of single vision).

**Diagnosis, Grading and Investigation of Thyroid Eye Disease**

For patients with features suggestive of infiltrative TED (motility restriction and/or proptosis), DON or before surgical decompression, orbital imaging should be considered. Non-contrast computerised tomography (CT) of the orbits performed in axial and coronal (direct or reformatted) planes readily reveals proptosis, EOM enlargement (Fig. 4A), apical compressions and bony anatomical variants for preoperative planning. Alternatively, orbital magnetic resonance imaging is superior in delineating the soft tissue component and T2 relaxation times on extraocular muscles have been used to assess the degree of oedema for disease.
activity or response to immunosuppressants. Orbital scintigraphy, positron emission tomography (PET) CT scan or more recently digital infrared thermal imaging have been introduced to measure disease activity for research purposes. The threshold of imaging should be lower if there are atypical features suggestive of alternative diagnosis.

Differential Diagnoses of Thyroid Eye Disease

Differential diagnoses of TED include other orbital disorders such as carotid-cavernous fistula, idiopathic orbital inflammation (pseudotumour), orbital or preseptal cellulitis, and orbital tumour. Appropriate orbital imaging might be warranted to differentiate these conditions.

Management of Thyroid Eye Disease

The multidisciplinary approach in managing TED requires close collaboration between physicians and ophthalmologists for early diagnosis, triaging, referral, symptomatic topical and systemic anti-inflammatory therapies, as well as staged surgical rehabilitation.

General Recommendations

Although the thyroid status does not always correlate with the presence, severity or activity of TED, we do recommend early stabilisation of thyroid functions (see section on prognosis). Ophthalmologists are often consulted on the risk of using RAI in patients with GD. It was reported that about 15-20% of patients receiving RAI have progression or development of TED. Patients who are current smokers, with unstable thyroid function, high levels of thyroid-stimulating immunoglobulin (TSI) and in particular active (CAS≥3/10) TED are at risk. This may be controlled with a short tapering course of moderate dose (0.5mg/kg/day) oral prednisolone. RAI causes progression of TED by releasing intrathyroidal autoreactive lymphocytes and antigens while subsequent hypothyroidism (even subclinical) may promote accumulation of GAG by slowing down its turnover. It was reported that about 15-20% of patients receiving RAI have progression or development of TED. Patients who are current smokers, with unstable thyroid function, high levels of thyroid-stimulating immunoglobulin (TSI) and in particular active (CAS≥3/10) TED are at risk. This may be controlled with a short tapering course of moderate dose (0.5mg/kg/day) oral prednisolone. RAI causes progression of TED by releasing intrathyroidal autoreactive lymphocytes and antigens while subsequent hypothyroidism (even subclinical) may promote accumulation of GAG by slowing down its turnover. Frequent biochemical monitoring and timely thyroxine supplementation are therefore crucial.

All patients except those with the mildest form of TED would benefit from topical lubricants including eye drops and gel during day time and thicker ointment at bed time with or without taping the eyelids closed. Sunglasses may be valuable for those with photophobia or pending surgical rehabilitation. Stick-on (Fresnel) or spectacles-incorporated prism lens may alleviate small to moderate amount of diplopia.

Immunosuppressants

Immunosuppressants are occasionally required for patients with active (CAS>3) TED. Systemic corticosteroid with oral prednisolone of 1mg/kg/day for 1-2 weeks is usually the first-line treatment of active TED. This is followed by slow tapering depending on the response. The treatment regime of using intravenous administration is more variable and common regimes include 500-1000mg pulse methylprednisolone for 3 days followed by oral prednisolone, or 500mg pulse methylprednisolone weekly for 6 weeks then 250mg for another 6 weeks. Recent reports suggest that intravenous corticosteroid were better tolerated and more effective than the oral route, though idiosyncratic hepatic failure and arrhythmia might occur at cumulative doses over 8g. Periocular steroid injections, e.g. triamcinolone acetonide (40mg/ml) can be used in asymmetric orbitopathy, mild relapses during tapering, or when the patient is contraindicated or reluctant for systemic steroids. In patients with persistent active disease despite a full course of steroid treatment, steroid-sparing agents (e.g. methotrexate, azathioprine, rapamycin, cyclosporin, cyclophosphamide) or newer biologics (e.g. rituximab, adalimumab) may be administered by rheumatologists.

Radiotherapy

Orbital radiotherapy (fractionated external beam irradiation of 20Gy over 10 sessions) has been shown to have comparable effects with oral prednisolone for moderate to severe orbitopathy. It may be used with systemic corticosteroids concurrently or after surgical decompression for resistant or residual disease activity although younger patients or those with diabetic retinopathy are relatively contraindicated.

Anti-glaucomatous Medication

Anti-glaucomatous eye drops may be required to control secondary increased intraocular pressure. Topical alpha-agonists (e.g. brimonidine) have an added benefit of decreasing conjunctival and episcleral congestions compared with other eye drops.

Surgical Intervention

In general, stability in an endocrine and orbital status for at least 6-9 months is often recommended before surgical rehabilitation. A staged approach is undertaken as follows: orbital decompression, followed by strabismus surgery, correction of lid retraction, then finally blepharoplasty and other aesthetic operations. Orbital decompression and/or expansion are classified into bone removal orbital decompression (BROD) and fat removal orbital decompression (FROD) which can be performed in isolation or in combination. The design of BROD is by the choice of surfaces and incisions for bone removal, e.g. medial (via transcaruncular, transcutaneous Lynch or endonasal), inferior (transconjunctival fornical/swinging eyelid, transcutaneous subciliary or transantral) and lateral walls (transcutaneous upper lid crest/swinging eyelid, coronal). Complications include diplopia, globe dystopia, periocular sensory changes, orbital haemorrhage, infection, lid malposition, lacrimal gland or lacrimal drainage injury, cerebrospinal fluid (CSF) leak and rarely subarachnoid/cerebral haemorrhage.

FROD involves removing intraconal and sometimes extraconal orbital fat via a transcutaneous (upper lid crest or lower lid subciliary) or transconjunctival approach. Fat pockets are usually debulked in the following sequence: inferolateral, superonasal, inferomedial, and superotemporal (to avoid lacrimal gland and its neurovascular structures). FROD may cause fewer cases of new-onset diplopia or worsening of pre-existing diplopia compared to pure BROD (for
Conclusions
TED is the most common cause of proptosis or lid retraction in adults and can be markedly asymmetric. One in five patients with TED has normal thyroid functions on presentation. In some cases, visual threatening TED can present as subacute blurring of vision with minimal proptosis but upper lid fullness (DOP) or severe eye pain, incomplete lid closure (exposure keratopathy). Most thyroid patients do not require eye surgery but smokers and those who present with ocular symptoms or findings should be referred for assessment. Smoking cessation and early stabilisation of thyroid functions are the most important primary or secondary measures to prevent TED. More than one operation may be required to correct established or iatrogenic deformities in TED patients.

References

Prognosis of Thyroid Eye Disease

Upon achieving euthyroidism, up to 90% of lid retraction, 30% of restrictive myopathy but rarely does proptosis improve. For patients having clinically evident TED (NOSPECS class 3 or above) the typical disease course usually runs for 12 to 24 months before it quiets down.

Prevention of Thyroid Eye Disease

While the aetiology/pathogenesis of GD/TED is still unknown, primary prevention of TED (avoid occurrence) is not impossible by encouraging subjects at risk (family or personal history of autoimmune thyroid diseases, autoantibodies or biochemical dysthyroidism) to quit active and to avoid passive smoking. Secondary prevention (avoid progression of subclinical TED) involves early and accurate control of dysthyroidism (particularly post ablative treatment). Tertiary prevention (avoid development of visual threatening complications) requires early and judicious use of immunosuppressive therapies, orbital irradiation and timely surgical rehabilitation.

Similar amount of proptosis reduction). Anecdotal experience reports occasional improvement of motility restriction after RFD. Orbital haemorrhages and periocular sensory loss may develop.

Strabismus correction in TED is typically challenging due to the fibrotic nature of EOM involvement. Usually EOM recession instead of resection is performed to correct the limitation of movement rather than the amount of ocular deviation at primary gaze. For example bilateral asymmetric inferior rectus (IR) muscles recession is performed to correct vertical diplopia, to improve upgaze and to avoid late progressive overcorrection. Detachment of capsulopalpebral fascia (lower lid retractor) has been proven to minimise postoperative lower lid retraction/scleral show. Different techniques have been proposed to improve the outcome in strabismus surgery including an intraoperative relaxed muscle positioning technique, the use of adjustable sutures and operating under monitored aesthetic care or topical anaesthesia.

To correct upper lid retraction, mullerotomy, Muller’s muscle extirpation, levator aponeurosis disinsertion/ resection, levator muscle myotomy with/without the use of adjustable or hangback sutures can be used. Recently full thickness blepharotomy has gained much popularity because of technical simplicity. Spacers are often required for lower lid retraction (against gravity) after retractor disinsertion / lysis. Available materials include hard palate graft, dermis fat/strip graft, auricular/nasal septal cartilage, donor sclera and synthetic materials such as Medpor, Alloderm, aluminium foil, and Polytetrafluoroethylene with or without intraoperative anti-metabolites including mitomycin C (MMC) and 5-fluorouracil (5FU). Transcutaneous/transconjunctival Botulinum toxin A (BTA), steroid (triamcinolone acetonide) or filler (Restylane) injections have been used to alleviate lagophthalmos and exposure keratopathy before surgical intervention.

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