Guest Editorial

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Thyroid Eye Disease Simplified

I distinctly remember being scared of my maternal aunt as a child whilst visiting her in Osmanabad during my school holidays. She had prominent bulgy eyes and a stern stary look. I never dared be naughty around her. It was in medical school in Pune, years later that I realised that she wasn't scary but had untreated thyroid eye disease causing change in her appearance. As the regional orbital lead in South Yorkshire, UK,this experience has helped me empathise with my thyroid eye disease patients, many of whom require medical management or rehabilitative surgery for their prominent bulgy eyes or appearance.

Thyroid eye disease (TED) is more common than generally believed. Although 80% of the time it occurs in patients with hyperthyroidism (Graves disease), 10% patients are hypothyroid and 10% patients may be euthyroid. These euthyroid patients may have had thyroid problems in the past or may go on to develop thyroid issues years later and hence need yearly thyroid function tests checked. It can affect children too though thankfully, they do respond well to treatment.

So who is at risk of developing thyroid eye disease?

1. *Thyroid dysfunction: this is the obvious one*
2. *Smoking: smoking significantly increases risk of TED*
3. *Other autoimmune problems such as ulcerative colitis, vitiligo, HLA DR-3, HLA B 8*
4. *Stressful life events: loss of job/bereavement can trigger TED*
5. *Family history of thyroid eye disease*

How does it happen?

TED is an autoimmune process. Patients develop antibodies which act against the thyroid gland causing thyroid dysfunction. The same antibodies also work against the ocular soft tissues, mainly fat and muscles in the orbit in the active phase. This causes localised inflammation and then secondary changes by causing water retention, deposition of glycosaminoglycans and thus thickening and enlargement of orbital fat and muscles as well as scarring causing restriction. After the active phase, the disease will plateau and eventually burn out 18 months to 2 years down the line (Rundle's curve), but in the meanwhile, would have caused permanent debilitating changes such as proptosis, eyelid retraction, restriction of eye movements/squint or periocular severe fat prolapse (all of which my aunt had). By diagnosing and treating TED early, we can dampen and shorten the inflammatory active phase thus reducing the long term secondary sequalae.

What symptoms do TED patients present with?

1. *Change in appearance such as eyelid retraction/ prominent eyes/ peri ocular swelling*
2. *Unexplained watery red eyes or ocular surface irritation*
3. *Unexplained ocular discomfort or heaviness feeling/ ache*
4. *Double vision*
5. *Visual symptoms*

How to assess/examine a patient with TED?

The prime questions are:

1. *Is the disease sight threatening: needs urgent intervention/ referral to orbital surgeon?*
2. *Is there "active" inflammation: what is the clinical activity score?*
3. *How severe is the disease: what changes have already occurred?*

The response to these questions is as follows:

1. *A small percentage of patients may present with or are at risk of developing visual loss.*
   These patients usually have a tight orbital septum and rather than the eyes bulging out secondary to enlarged orbital fat and muscles they get increased orbital pressure. The orbital apex gets crowded and the optic nerve starts getting compressed causing visual deterioration. Thus, the first thing to do in TED patients is to check vision, pupils for relative afferent pupillary defect (RAPD) (TED is often asymmetrical), colour vision, red desaturation, reduced brightness sensitivity, reduced peripheral vision and disc hyperaemia/ papilloedema.

2. *Clinical activity score (CAS):*
   The inflammation caused by TED in the ocular tissues is similar to that caused by arthritis in the joints. There is ache/ pain at rest as well as pain on movement. There is eyelid redness and eyelid swelling; conjunctival redness and swelling (chemosis) as well as caruncular/plical inflammation. At first presentation CAS is measured as out of the 7 clinical indicators (Image 1). At follow up,in addition to these indicators, we also look to see if there is worsening of proptosis (more than 2 mm), reduced eye excursion (more than 8 degrees) or reduced vision by 1 or more Snellen lines.

3. *Severity: mild, moderate or severe: (Image 3)*
   I prefer using a combination of the following changes to describe the severity
   Changes in eyelid: lid retraction, lateral flare, lid lag (dynamic change), hangup (static change) on downgaze, lagophthalmos (Image 4)
   Changes in muscle: restriction of eye movements, double vision in extremes of gaze or primary position
   Changes in globe position: proptosis on exophthalmometry, any vertical or horizontal globe dystopia (usually secondary to tight inferior rectus or medial rectus)
   Changes in peri-ocular tissue: Fat hypertrophy, changes in procerus and corrugator muscles and appearance

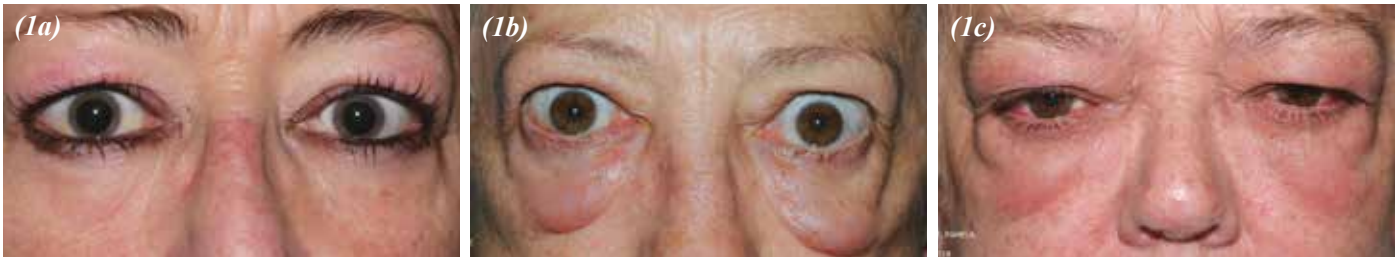

Image 1: Activity of TED based on Clinical activity score (CAS).

(1a): *mildly active TED: CAS of 2: Patient has upper eyelid redness and oedema.*

(1b): *moderately active TED: CAS of 4: Patient has ache at rest, lower eyelid redness, lower eyelid oedema and caruncular injection.*

(1c): *moderately active TED: CAS of 7: patient has ache at rest, pain on eye movements, eyelid redness, eyelid oedema, conjunctival injection, conjunctival chemosis and caruncular injection.*

Note: Patient 1a has mild eyelid retraction (eyelid sitting at upper limbus), patient 1b has severe eyelid retraction which patient 1c has no eyelid retraction. Eyelid retraction is not considered while measuring clinical activity score.

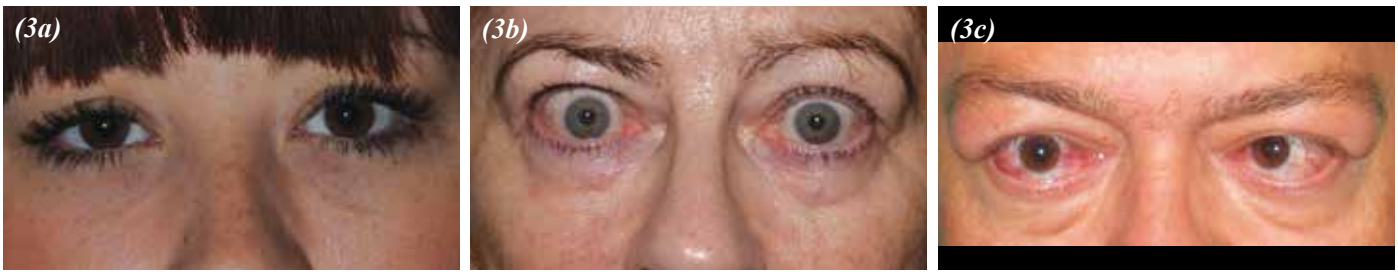

Image 3: Severity of TED

(3a): *Patient's TED is mild with only 2 mm of left proptosis. This was successfully treated with fat decompression of left eye.*

(3b): *Patient had moderate TED with peri orbital fat hypertrophy, eyelid retraction and 4 mm of proptosis with restriction of eye movements causing peripheral diplopia but no diplopia in primary position. Patient required decompression surgery and eyelid lowering surgery.*

(3c): *Patient has severe TED with severe diplopia in primary position with significant restriction of eye movements in addition to peri orbital fat hypertrophy, upper and lower eyelid retraction, 8 mm proptosis. Patient required orbital decompression surgery, squint surgery, upper and lower eyelid retraction surgery and blepharoplasty.*

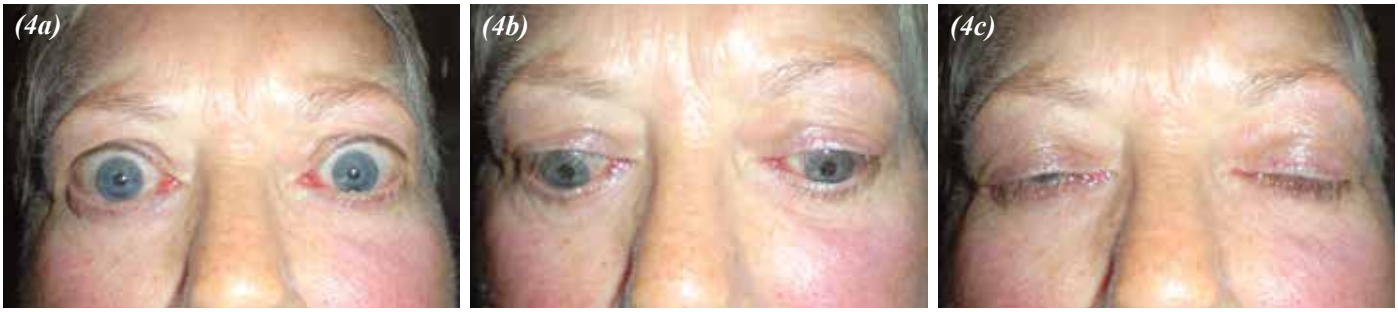

Image 4: Eyelid retraction. Normally the upper eyelid rests 2 mm below upper limbus. In mild eyelid retraction, the eyelid is positioned at the limbus, in moderate eyelid retraction, the eyelid is positioned up to 2 mm above limbus and in severe eyelid retraction; it is more than 2 mm above limbus.

(4a): *Severe eyelid retraction. Note lateral flare.*

(4b): *Hang up of upper eyelids: This is a static sign where the eyelids are higher than they should be when the patient is looking down. Lid lag is a dynamic sign where the upper eyelids lag behind the globe movement when the patient looks down.*

(4c): *Lagophthalmos: There is incomplete closure of eyelids when the patient shuts her eyes. Please note the right cornea is exposed due to absent Bells phenomenon due to tight inferior rectus. Patient is at risk of corneal ulcer and perforation.*

How to investigate patients with TED?

1. *Thyroid function tests (TSH/T3/T4)*
2. *Thyroid antibodies (TSH receptor antibodies/thyroid peroxidase antibodies/ thyroglobulin antibodies)*
3. *Orthoptic assessment*
4. *MRI orbits is usually only necessary in ambiguous cases/ sight threatening thyroid eye disease*
5. *Full blood count, liver function tests, renal profile, vitamin D levels, DEXA bone scan, X Ray chest (if previous history of TB etc.) if possibility of starting the patient on steroids*
6. *TPMT levels if possibility of starting the patient on Azathioprine*
7. *CT orbits if decompression surgery necessary*

How to treat a patient with TED?

All patients should have the following general management:

1. *Control of thyroid dysfunction: The best practice is to recruit the help of an endocrinologist colleague. I run a regular joint thyroid eye disease clinic with my endocrinologist, Dr Amit Allahabadia in which we review these patients together. We favour the use of block and replace therapy (combination of carbimazole and thyroxine) in patients with Graves' disease which in our experience improves control of hyperthyroidism. Block and replace therapy is usually continued until TED is burnt out for at least six months and this may mean a total duration of treatment for 12 – 24 months. There is a small risk of reactivation of TED in patients who need radioiodine therapy (lesser with thyroidectomy) later on and hence any definitive treatment of Graves' disease should be done under steroid cover.*
2. *Stop smoking: This is the single most patient modifiable risk factor. Patients should be actively encouraged to stop smoking. Alternative strategies include e-cigarettes, nicotine patches/gum, hypnotherapy.*
3. *Stress management: Joining lessons such as mindfulness/ Yoga or psychological support should help.*
4. *Patient support groups: I direct patients to TEDCt, a charitable support group in UK. Equally, patients find speaking to other patients with a similar condition therapeutic.*

Patients with sight threating thyroid eye disease: (Image 5)

1. *Intravenous methylprednisolone 10mg/kg alternate days for 3 injections is my preferred regimen.*
2. *If there is reversal of disease, I continue i/v steroid therapy as per the severe TED protocol (see below).*
3. *If no improvement in vision, then urgent medial 1.5 wall orbital decompression surgery is done. The decompression surgery is a sight saving procedure, but patients need to be made aware of high risk of post operative diplopia and requiring squint surgery.*
4. *This decompression surgery simply buys time and patients still need management of their underlying severe, active TED (as below).*

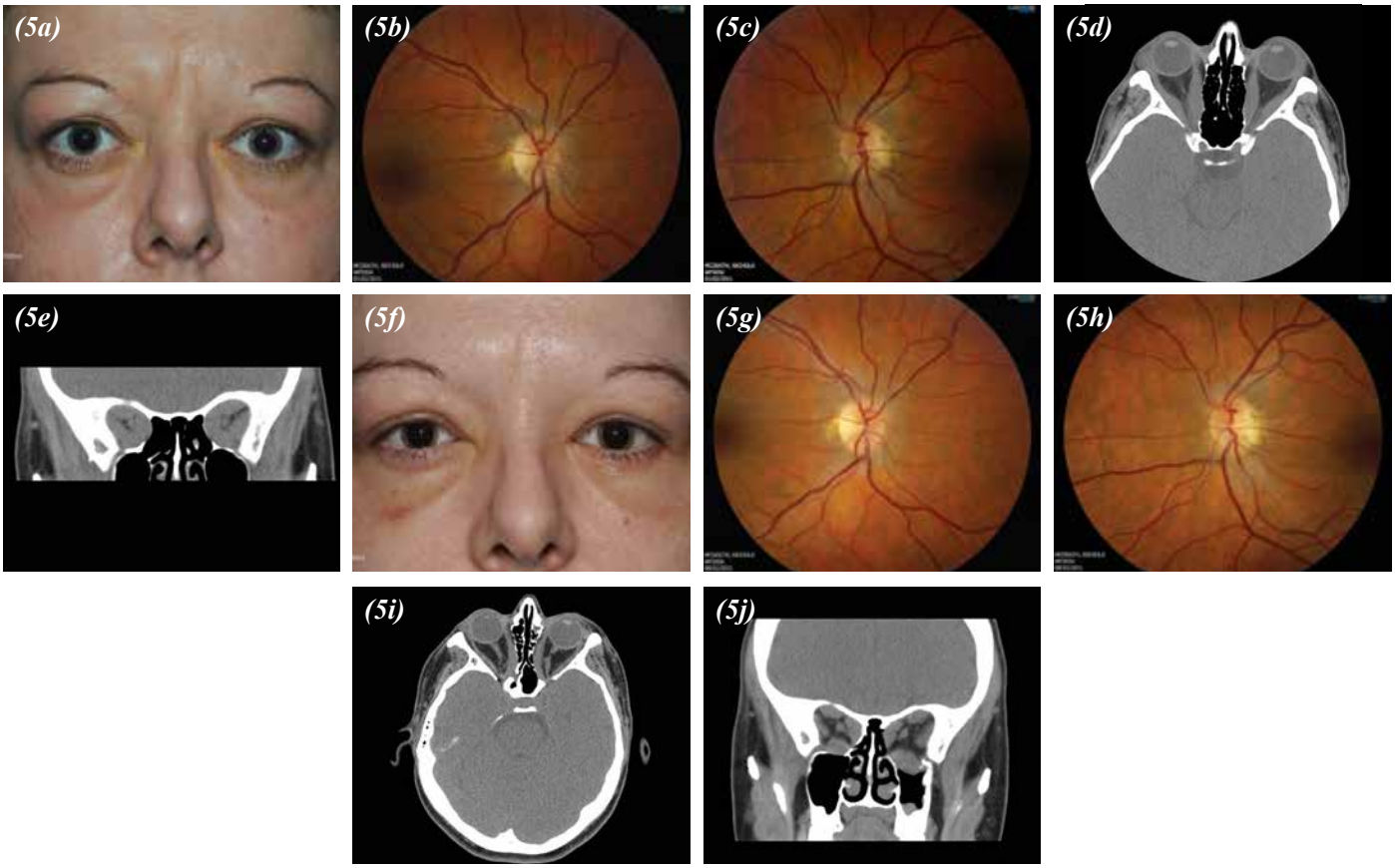

Image 5: Patient with severe sight threatening thyroid eye disease managed with 3 injections of I/V Methylprednisolone followed by bilateral medial 1.5 wall orbital decompression surgery.

(5a): *Patient presented with reduced vision, colour vision and right mild RAPD. She had tense sockets which were hard to retropulsion.*

(5b): *Right optic disc swelling*

(5c): *Left optic disc swelling*

(5d): *Axial view of CT scan showing enlarged medial and lateral rectus muscle compressing the optic nerve*

(5e): *Coronal view of CT scan showing tight orbital apex. All 4 rectus muscles are enlarged with minimal orbital fat space seen at orbital apex and optic nerve compressed secondary to this.*

(5f): *1 week post bilateral medial 1.5 wall orbital decompression surgery; the patient's visual acuity and colour vision had returned to normal. The sockets were no longer tense with retropulsion being near normal.*

(5g): *Reduced right optic disc swelling*

(5h): *reduced left optic disc swelling*

(5i): *Axial view of CT scan showing the space created by removal of the mid and posterior ethmoids into which the medial rectus muscles protrude thus removing the compressive effect onto the optic nerve.*

(5j): *Coronal view of CT scan showing the orbital apex is no longer crowded. All 4 rectus muscles are still enlarged but as the medial rectus and inferior rectus muscles protrude into the space created by surgical decompression; the orbital fat space is clearly visible at orbital apex and optic nerve is no longer compressed.*

Management of mild TED: (CAS 1-2)

1. *Ocular lubricants such as dry eye drops on topical non-steroidal drops.*
2. *Sleeping propped up will help reduce peri-ocular oedema.*
3. *I am not a big fan of oral acetazolamide / antihistamines, though some colleagues use it.*
4. *Selenium 100mcg twice a day for 6 months*
5. *Vitamin D replacement if patient has low levels*

Management of moderate TED: (CAS 3-4)

1. *In addition to above, oral ibuprofen 400mg three times a day for 2 weeks, twice a day for 2 weeks, once a day for two weeks should help control TED.*

2. *Some colleagues will consider oral prednisolone. If oral ibuprofen does not help, I prefer intravenous methylprednisolone.*
3. *In unilateral cases, I prefer orbital floor depomedrone 40mg injection given 6 weekly for 3 injections.*
4. *In patients with eyelid retraction as the only sign, triamcinolone 20mg injection into upper eyelid is effective. It can be repeated if required. Intraocular pressure needs to be monitored in all patients receiving steroid therapy.*

Management of severe TED: (CAS 4-7)

1. *Pulsed intravenous methylprednisolone (I/V MPA). My regimen is 500mg weekly for 6 weeks, followed by 250mg weekly for 6 weeks (based on EUGOGO recommendations). I prefer giving a short tail of oral prednisolone at 30mg/day for a week, 20mg a day for a week and then 10mg a day for a week.*
2. *I give adjuvant calcium and vitamin D3 supplements twice a day, aledronic acid 70mg a week and omeprazole 20mg a day for the duration of treatment*
3. *Patients need to be warned about side effects of high dose steroids including mood swings, unmasking of underlying psychological issues, diabetes, infection, risk of weight gain or bone thinning.*
4. *Towards the end of treatment, my endocrinologist colleague prefers to perform a short synacthen test, to ensure that steroids can be stopped safely.*
5. *In patients with severe TED, I recommend adjuvant radiotherapy to orbits. This helps burn out the active disease, "dry out" the underlying inflammation from muscles and fat as well as prevent recurrence of TED in my experience. My radiation oncologist colleague, Dr Richard Crossley, typically will aim to treat with 20Gy of radiation fractionated over 2 weeks (2 Gy daily for 5 days per week). Patients are warned about radiation side effects including radiation dermatitis, fatigue and tiredness. There is a theoretical risk of secondary cancers in the radiotherapy field, hence I avoid it in patients below 45 years of age. Uncontrolled diabetes is another contraindication as there is risk of worsening of diabetic retinopathy after radiotherapy.*
6. *In my experience, a combination of I/V MPA and radiotherapy have a control rate of over 90%. (Image 2)*
7. *Patients who still have smouldering TED may benefit from azathioprine 150mg/day for upto 18 months. This or other immunosuppressive drugs should be given by rheumatologists/medical ophthalmologists trained in their use.*
8. *In the small group of patients who do not respond to above standard regimen, I haven't had major success with Rituximab. In a couple of patients, thyroidectomy helped reduce the thyroid antibody levels and thus helped control TED.*

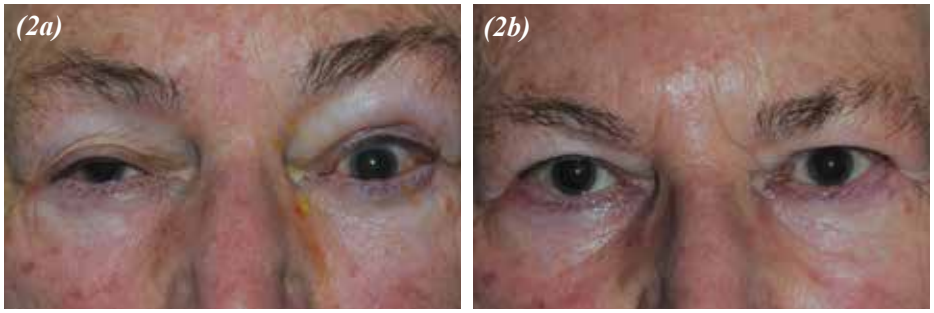

Image 2: Successful treatment of severely active TED with combination of i/V Methylprednisolone regime and orbital radiotherapy.
(2a): *Image showing CAS of 7*
(2b): *Image showing burnt out TED after treatment*

Surgical management:

Medical management of TED as described above has certainly improved outcomes with these groups of patients having fewer sequalae of their TED. The number of patients who require orbital decompression surgery has fallen over the last 10 years in my experience. There is, however,a significant proportion of patients who still require some form of surgical intervention. Surgery is usually reserved for rehabilitative purposes once the thyroid eye disease is completely burnt out for at least 6 months and is usually performed in the following order:

1. *Orbital decompression surgery (Image 6)*
   a. *Orbital fat decompression surgery for proptosis of around 2 mm*
   b. *Lateral wall decompression surgery for proptosis 3-12 mm*
   c. *2.5 wall orbital decompression surgery for severe proptosis over 12 mm*

2. *Squint surgery (Image 7)*
3. *Eyelid lowering surgery (Image 8)*
4. *Blepharoplasty and fat debulking surgery (Image 9)*

Patients with TED, therefore,require significant multidisciplinary team (MDT) input from orbital/oculoplastic/squint surgeon, orthoptist, specialist nursing team, endocrinologist, radiation oncologist and psychologist(Image 10). Formation of dedicated MDT groups and joint TED clinics with endocrinologists in the major centres should be encouraged as they can be effective in improving outcomes. Patient support groups should also be encouraged as they can raise awareness and provide a support network for patients suffering from the effects of TED.

I hoped to share my approach to TED in a simplified fashion with the readers of DJO via this guest editorial. If it helps improve the care of patients with TED in any way, it would have achieved its purpose.

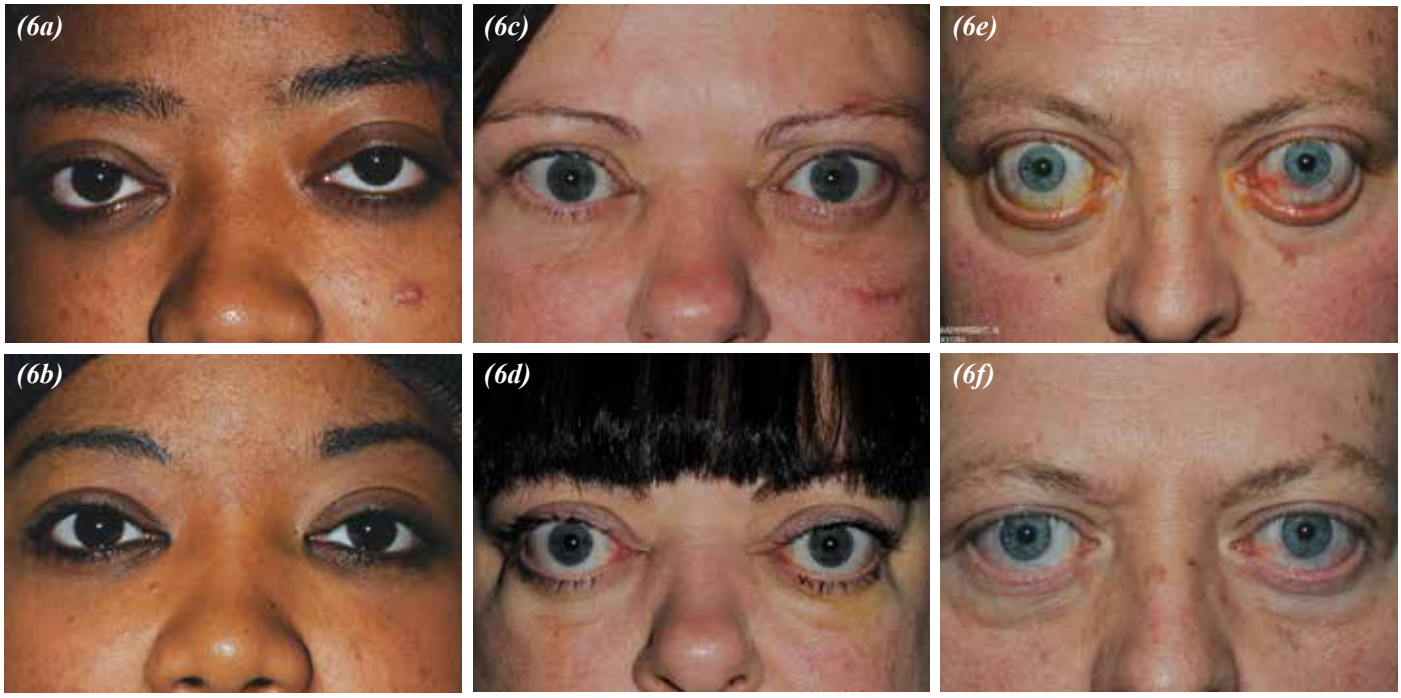

Image 6: Lateral wall decompression surgery for proptosis secondary to TED. Lateral wall decompression surgery alone can be utilised to get successful results for patients with proptosis ranging from 3 -12 mm. Fat decompression surgery alone can be used for patients with 2 mm or less of proptosis. Patients with more than 10-12 mm proptosis may require 2.5 wall orbital decompression surgery.

(6a &6b): *Pre and post op images of patient with 3 mm proptosis*

(6c & 6d): *Pre and post op images of patient with 6 mm proptosis*

(6e & 6f): *Pre and post op images of patient with 12 mm proptosis*

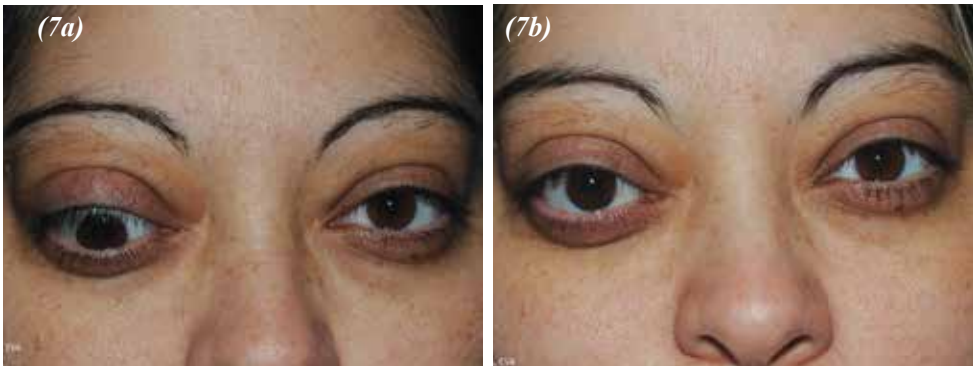

Image 7: Squint correction surgery for TED

(7a and 7b): *Pre and post right inferior rectus recession surgery (All squint surgeries performed by Strabismologist colleague, Mr John P. Burke)*

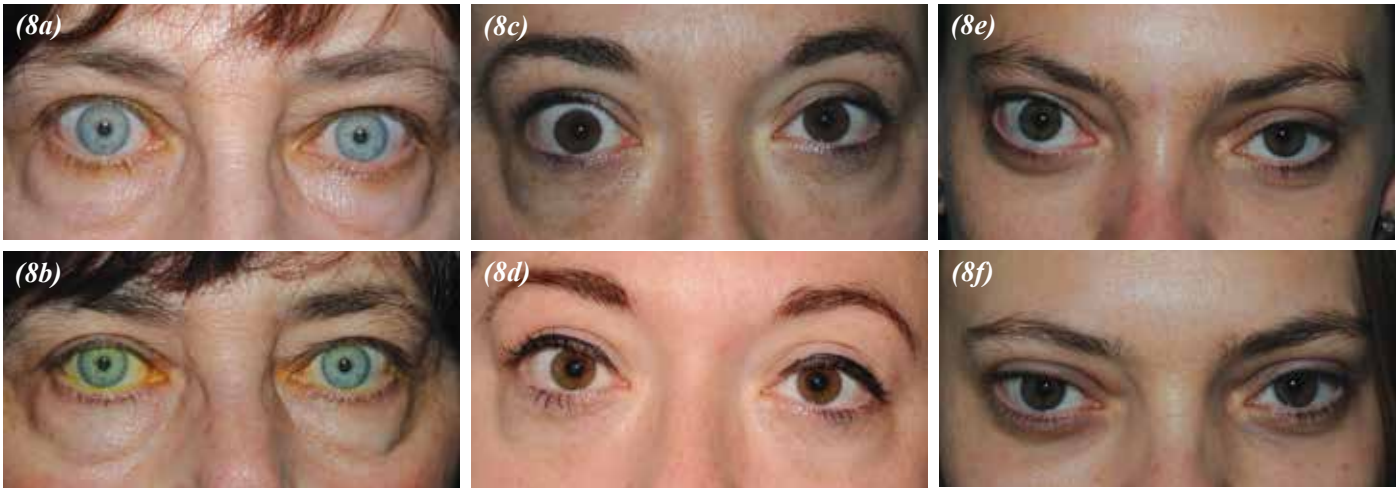

Image 8: Management of eyelid retraction

(8a & 8b): *Spontaneous improvement in eyelid retraction after patient's Graves disease was medically controlled and patient stopped smoking*

(8c & 8d): *Right upper eyelid retraction successfully treated with transconjunctival upper eyelid injection of triamcinolone 20mg into the mullers muscle levator complex*

(8e & 8f): *Successful right upper eyelid lowering surgery to treat right upper eyelid retraction and lateral flare and improve symmetry*

Image 9: Management of fat hypertrophy and dermatochalasis

(9a & 9b): *Pre and post bilateral upper eyelid fat debulking and blepharoplasty surgery*

(9c & 9d): *Pre and post bilateral upper eyelid blepharoplasty surgery*

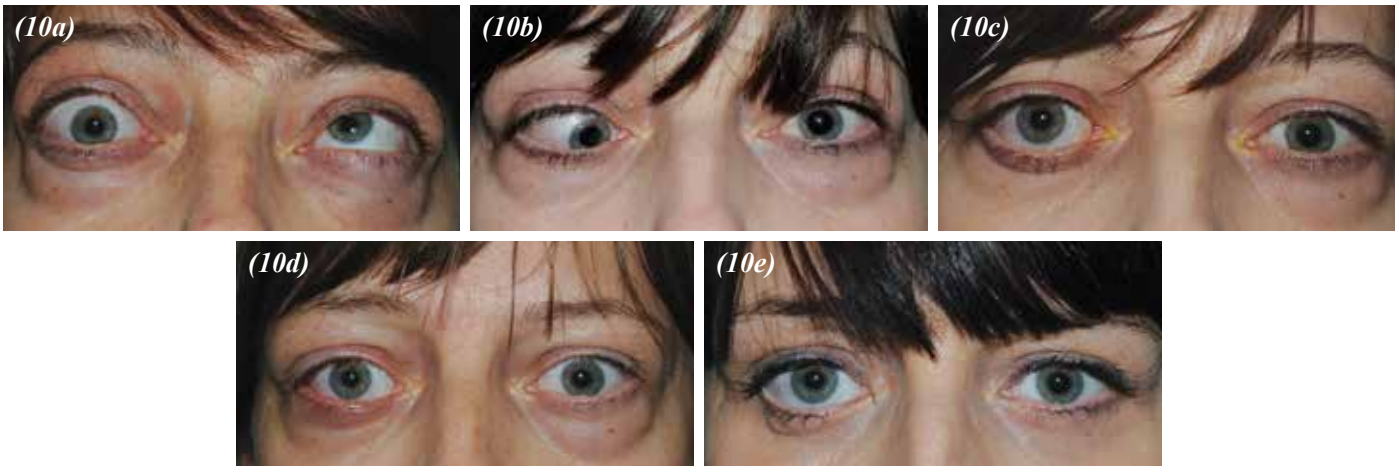

Image 10: Example of patient with severe TED requiring multidisciplinary input and management:

10a: *Severe burnt out TED after i/v Methylprednisolone and radiotherapy treatment showing severe proptosis, squint, lid retraction and fat hypertrophy*

10b: *Post bilateral orbital decompression surgery.*

10c: *Post squint correction surgery. Note spontaneous improvement in lid retraction which was secondary to tight inferior rectus muscles*

10d: *Post right lower eyelid heightening procedure with ear cartilage graft*

10e: *Post left lower eyelid blepharoplasty*

Top 10 Tips

1. *If patient with TED has droopy eyelids rather than lid retraction, rule out associated myasthenia gravis; both are autoimmune conditions after all!*
2. *TED can be unilateral and is often asymmetrical.*
3. *TED can reactivate, especially in patients who continue to smoke. Also consider orbital lymphoma in patients suspected to have recurrence of thyroid eye disease.*
4. *Patients are at a risk of corneal ulcer/ perforation in severe TED due to eyelid retraction and exposure; lagophthalmos and incomplete blink; absent bells phenomenon due to tight inferior rectus; lower lid retraction and proptosis; and lacrimal gland scarring causing dry eyes.*
5. *Patients with tight orbital septum can develop "hydraulic variant" of thyroid eye disease. They develop orbital congestion which may mimic active TED. They have tense sockets, engorged episcleral veins at outer canthus, raised IOP especially in upgaze or frank glaucoma. They require lateral wall orbital decompression surgery rather than i/v steroids.*
6. *TED patients can rarely develop visual loss secondary to severe proptosis and optic nerve stretch; again, decompression surgery should help in this group of patients.*
7. *I/V MPA over 8 gm can cause acute liver failure and can be fatal; I prefer keeping the dose 4.5 gm for the severe TED patients. Always consider joint care with a physician.*
8. *Don't rush into rehabilitative surgery until the disease has burnt out.*
9. *Use of human monoclonal antibodies (mAb) such as teprotumumab are still in research phase and yet to be proven to be superior to the above regimes discussed.*
10. *TED can cause severe psychosocial issues. These patients require empathy and support to help them deal with the disease. My aunt wasn't scary at all. On the other hand, she was one of the kindest people around I am told. Had I been made aware of TED changes that she had undergone then, I perhaps would have been more sympathetic to my aunt rather than being scared!*

References

1. Jefferis JM, Jones RK, Currie ZI, Tan JH, Salvi SM. Orbital decompression for thyroid eye disease: methods, outcomes, and complications. *Eye (Lond)* 2018; 32:626-636.

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