Thyroid Ophthalmopathy

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Introduction

Thyroid ophthalmopathy often termed as Graves ophthalmopathy, is a part of an autoimmune process that can affect the orbital and periorbital tissue, the thyroid gland and rarely the pretilial skin or digits. The condition primarily affects women and has an incidence of approximately 4/10,000 per annum. During their lifetime approximately 1% of the population is affected. The condition has disfiguring and sight threatening complications and it’s the commonest cause of orbitopathy and thyroid induced sensitization of Muller’s muscle to circulating catecholamines resulting in a staring look (Fig. 2).

1. Lid signs: Lid lag, globe lag, proptosis, restrictive extraocular myopathy and optic neuropathy.

2. Soft tissue signs: These are common in active eye disease and include eyelid oedema (Fig. 3) and conjunctival erythema and chemosis. Dilated episcleral veins over insertion of recti can be seen in inactive disease.

3. Proptosis: Proptosis is commonly seen in thyroid eye disease. Its extent is partly dependent on compliance of orbital septum. Choroidal folds can occasionally be seen and there is often an increased resistance to retropulsion. Proptosis combined with lid retraction and inferior rectus restriction may lead to corneal exposure and ulceration. (Fig. 4)

4. Restrictive extraocular myopathy: This is due to oedema, inflammation and fibrosis due to lymphocytic infiltration of the extraocular muscles. This causes tethering of the globe by the tight recti muscles. The muscles (recti) involved in decreasing order of severity and frequency are the inferior rectus, superior rectus and lateral rectus.

5. Anterior segment signs: They include superficial punctuate keratitis, superior limbal keratoconjunctivitis, conjunctival injection usually over the rectus muscle insertions, and conjunctival chemosis.

6. With severe proptosis, corneal exposure with frank corneal ulceration may occur. A chronic, often recurrent condition of ocular irritation, which may be attributable to mechanical trauma transmitted from the upper eyelid to the superior bulbar and tarsal conjunctiva and is purported to be a prognostic marker for severe thyroid ophthalmopathy is superior limbal keratoconjunctivitis.

7. Strabismus is common and it often represents as hypotropia or esotropia because the inferior rectus muscle and the medial rectus muscle are the most commonly involved extraocular muscles.
   - Since asymmetric proptosis and lid retraction may mask the true relative positions of the globe, corneal light reflexes should be examined closely.
   - Forced ductions or elevated intraocular pressure with eye movement (e.g. upgaze in hypotropic patients) can help confirm restrictive myopia in cases in which the diagnosis of thyroid ophthalmopathy is difficult.
   - Inferior rectus muscle restriction may mimic double elevator palsy.
   - Pseudo-fourth nerve palsies have been described with thyroid ophthalmopathy.
   - Although esotropia is a more common finding with thyroid ophthalmopathy, convergence insufficiency has been described.
   - In patients with thyroid ophthalmopathy and esotropia, the possibility of concurrent myasthenia gravis should be considered.

8. Optic nerve compression may occur with seemingly mild proptosis. Also, in most cases of compressive thyroid optic neuropathy visible optic nerve oedema occurs. For this
reason, documenting visual acuity, colour vision, and the presence or absence of a relatively afferent papillary defect is important during each visit.

9. **Glaucoma** may result from decreased episcleral venous outflow. Restrictive myopathy may cause an increase in intraocular pressure of more than 8mm Hg on upgaze (differential IOP).

10. **Choroidal folds** may be seen with thyroid ophthalmopathy.

11. **Other eponymous signs** are associated with thyroid ophthalmopathy, including the following:

   - Vigouroux sign (eyelid fullness)
   - Stellwag sign (incomplete and infrequent blinking)
   - Grave sign (resistance to pulling down the retracted upper lid)
   - Goffory sign (absent creases in the forehead on superior gaze)
   - Mobius sign (poor convergence) (Fig. 5)
   - Ballet sign (restriction of one or more extraocular muscles)

12. **Deep glabellar rhytids** has been found to be significantly associated with thyroid ophthalmopathy, presumably as a result of hypertrophy of brow depressor muscles compensating for lid retraction.

13. ** Pretibial dermopathy** and thyroid acropachy (which mimics the appearance of clubbing) are less commonly encountered dramatic, cutaneous signs of dysthyroidism.

Many a times, in cases of periorbital swelling and conjunctival redness as the predominant features, thyroid eye disease is often misdiagnosed as allergic conjunctivitis. Differentiating between the thyroid eye disease and other causes of periorbital edema is possible by (exophthalmometry – Fig. 6) examining the presence of eyelid retraction and restricted eye movements, which occurs in thyroid eye disease.5

**Differential Diagnosis**

- Allergic conjunctivitis
- Myasthenia gravis
- Orbital myositis
- Chronic progressive external ophthalmoplegia
- Orbital tumors (primary or secondary).
- Carotid cavernous fistula
- Any inflammatory orbitopathy
- Sarcoidosis
- Preseptal cellulitis
- Orbital cellulitis

**Classification for Thyroid Ophthalmopathy**

Simplest classification for thyroid ophthalmopathy is1:
Type 1 is characterized by minimal inflammation and restrictive myopathy.

Type 2 is characterized by significant orbital inflammation and restrictive myopathy

NOSPECS classification (Table 2) for remembering clinical features |

<table>
<thead>
<tr>
<th>Score</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No signs or symptoms</td>
</tr>
<tr>
<td>1</td>
<td>Only signs</td>
</tr>
<tr>
<td>2</td>
<td>Soft tissue involvement, with symptoms and signs</td>
</tr>
<tr>
<td>3</td>
<td>Proptosis</td>
</tr>
<tr>
<td>4</td>
<td>Extraocular muscle involvement</td>
</tr>
<tr>
<td>5</td>
<td>Corneal involvement</td>
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- Pain Painful, oppressive feeling on or behind the globe during the last 2 weeks.
- Pain on attempted up, side or down gaze during the last 4 weeks.
- Redness Redness of the eye lids.
- Diffuse redness of the conjunctiva covering at least one quadrant.
- Swelling Swelling of the eyelids.
- Chemosis Swollen caruncle
- Increase of proptosis ≥2mm during a period of 1-3 months.
- Impaired Function Decrease of eye movements in any direction ≥5° during a period of 1-3 months.
- Decrease of visual acuity of ≥1 line on the Snellen chart (using a pin hole) during a period of 1-3 months.

Diagnosis

**Blood**
- In screening for thyroid disease, the combination of T4 (thyroxine) and TSH (thyroid-stimulating hormone) or serum TSH (thyrotropin) are highly sensitive and specific.
- Serum TSH is useful to establish a diagnosis of hyperthyroidism and hypothyroidism. The TSH is low in hyperthyroidism and high in hypothyroidism.
- Other blood tests that may be useful include calculated free T4 index, thyroid-stimulating immunoglobulin, antithyroid antibodies and serum T3.
- Thyroid peroxidase antibodies and antibodies to thyroglobulin may be useful when trying to associate eye findings with a thyroid abnormality, such as euthyroid Graves' disease.

**Imaging Studies**

**Ultrasound**
- Orbital ultrasound can quickly confirm if the patient has thickened muscles or an enlarged superior ophthalmic vein.

**CT Scan and MRI**
- If the diagnosis of thyroid opthalmopathy can be established clinically, then it is not necessary to routinely order a CT scan or an MRI.
- If the above studies are required, obtain axial and coronal views.
- Neuroimaging usually reveals thick muscles with tendon sparing.
  - The inferior rectus muscles and the medial rectus muscle usually are involved.
  - Isolated rectus muscle involvement may occur in up to 6% of patients. In this sub group of patients, the superior rectus muscle may be the most frequently involved muscle.
  - Bilateral muscle enlargement is the norm; unilateral cases usually represent asymmetric involvement rather than normality of the less involved side.
- Neuroimaging may show a dilated superior ophthalmic vein.
- Apical crowding of the optic nerve is well visualized on
neuroimaging

- MRI is more sensitive for showing optic nerve.
- CT scan is performed prior to bony decompression because it shows better bony architecture.
- Occasionally the proptosis results in straightening of the optic nerve.

Atypical features requiring confirmation of the diagnosis of thyroid eye disease by orbital imaging (CT or MRI)⁵:- (Fig. 7, 8)

- Unilateral disease
- Unilateral or bilateral disease in patients with no previous or present evidence of thyroid dysfunction
- Absence of upper eyelid retraction
- Divergent strabismus
- Diplopia sole manifestation
- History of diplopia worsening towards the end of the day

Histologic findings

- Lymphocytic cell infiltration
- Enlargement of fibroblasts
- Accumulation of mucopolysaccharides
- Interstitial oedema
- Increased collagen production
- Fibrosis with degenerative changes in the eye muscles

Management

TEARS mnemonic for remembering initial management.⁵

T – Tobacco abstinence is immensely important
E – Euthyroidism must be achieved and maintained
A – Artificial tears are helpful for the majority of the patients and can afford rapid relief from symptoms of corneal exposure
R – Referral to a specialist centre with experience and expertise in treating thyroid eye disease is indicated in all but the mildest of cases
S – Self help groups can provide valuable additional support

Medical care

- Inform patients that thyroid ophthalmopathy usually runs a self limited but prolonged course over 1 or more years. Patient should realize that no immediate care is available.¹³
- Most patients with thyroid ophthalmopathy should be observed and the follow up interval depends on disease activity.

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Radiotherapy

This has a non specific anti-inflammatory effect and destroys the radiosensitive lymphocytes and reduces glycosaminoglycans production.¹⁵, ¹⁶, ¹⁷ Usually a cumulative dose of 20 Gy per eye fractioned in 10 daily doses over a two week period is used. Orbital radiotherapy may cause a transient exacerbation of inflammation, but this can be prevented by concomitant glucocorticoid administration.¹⁷

Glucocorticoids

These are highly effective in soft tissue changes and optic neuropathy, whereas decrease in proptosis and ocular motility is less impressive.¹⁶ Intravenous glucocorticoids seem to be associated with higher success rate and better tolerability as compared to oral glucocorticoids.¹⁸,¹⁹ Since recurrences are not infrequent, treatment may prolong.¹⁹ Patients may be treated with one gram of intravenous methyl prednisolone daily for three days followed by oral steroids which may be tapered as condition improves.

Antioxidants

Treatment with anti oxidants like nicotinamide and allopurinol, has shown encouraging results in mild and moderately severe newly diagnosed active disease.²⁰ Nicotinamide and allopurinol have been used in doses of 300mg daily. The effect was found to be more pronounced in cigarette smokers. Though soft tissue inflammation responds well to treatment, effect on proptosis is not very impressive.¹⁶
Somatostatin analogues

These receptors can be visualized in Vivo in orbital tissue of Graves’ ophthalmopathy patients. Somatostatin analogues are postulated to bind to certain somatostatin receptors on surface of various orbital cells like lymphocytes, fibroblasts and muscle cells, thereby altering their immunologic and metabolic activities. Recent studies have shown successful therapy with octreotide and lanreotide in patients with moderately severe Graves’ ophthalmopathy and a positive Octreoscan, but the number of treated patients is too small to draw conclusions.

Monoclonal antibodies

Rituximab, a chimeric monoclonal antibody, is being evaluated for its possible role in Graves’ ophthalmopathy. Rituximab causes an immediate depletion of circulating b cells which usually lasts for 4-6 months but may last up to 4 years. T cells and natural killer cells are usually not affected.

Immunosuppressive drugs

The autoimmune origin of Graves’ ophthalmopathy has prompted the use of immunosuppressive drugs however their efficacy is yet to be proven. Cyclosporine has a lower effectiveness than glucocorticoids but a combination may be more effective than either treatment alone. Low dose treatment with Methotrexate is being used with apparent success, however data to conclusively prove its efficacy is still lacking. Other drugs that have been tried include Azathioprine and cyclophosphamide. However these drugs are yet to prove their efficacy.

- In patients with diplopia, prisms may be beneficial to those with small angle and relatively comitant deviations.
  - Tape occlusion of one lens or segment of the glasses may be helpful. An occluder or an eye patch can also be tried, but with care not to compress the orbit.
  - Oral steroids usually are reserved for patients with severe inflammation or compressive optic neuropathy. Steroids may decrease the production of mucopolysaccharides by the fibroblasts. Pulse intravenous steroids may be considered.

- Orbital radiation
  - This procedure sometimes is prescribed for moderate to severe inflammatory symptoms, diplopia and visual loss.
  - The radiation is administered via lateral fields with posterior angulation. Radiation is believed to damage orbital fibroblasts or perhaps lymphocytes.
  - Radiation requires several weeks to take effect, and it may transiently cause increased inflammation. Thus, most patients are maintained on steroids during the first few weeks of treatment.
  - Better response to radiation is observed in patients with active inflammation who are treated within 7 months of thyroid ophthalmopathy onset. Radiation may be more effective if combined with steroid treatment.
  - Cataract, radiation retinopathy and radiation optic neuropathy are possible risks. They are not common if treatment is appropriately fractioned and the eyes are shielded. In Marquez’s study, 12% of patients developed cataracts after irradiation with median follow up of 11 years.
  - Wakelkamp also believed that orbital irradiation is a safe treatment modality, except possibly for patients with diabetes mellitus.
  - Although improvement of motility disturbances can occur with radiotherapy, radiation is limited when used in isolation to treat diplopia.

- Optic nerve compression
  - Compressive optic neuropathy may present with blurry vision, visual loss, dyschromatopsia or field loss. Patients may not have marked proptosis but they usually show markedly decreased retroillumination.
  - If necessary, high-dose steroids and higher intravenous doses are given. In case of non-response to high-dose steroids and higher intravenous doses after 24 hours, it must be borne in mind that steroids may not work. Such patients should undergo surgical decompression while being maintained on steroids.
  - If a good steroid response occurs, orbital irradiation may be considered. In severe cases, combined steroids, radiation and surgery may be required.

Surgical care

Few patients may require surgical care. Patients must be informed that surgical care will involve multiple staged procedures.

Orbital decompression

Patients undergoing surgical care should be explained the probable complications that may occur with orbital decompression prior to the procedure. These include blindness, haemorrhage, diplopia, periorbital numbness, globe malposition, sinusitis, and lid malposition. In patients with compressive optic neuropathy, orbital decompression may be employed as initial therapy or if medical treatment is found to be ineffective. A medical and surgical treatment may be required in compressive optic neuropathy.

Strabismus surgery

Although studies have described the practice of early strabismus surgery during active thyroid ophthalmopathy, this is not preferred. Strabismus surgery generally is delayed until ophthalmopathy is inactive and the prism measurements have been stable for a minimum of 6 months. Patients should be informed of the expectations after strabismus surgery; the goal of surgery is to minimize diplopia in primary and reading positions and expecting binocular single vision in all positions of gaze may be unrealistic. Strabismus surgery predominantly involves resections rather than resections because of the presence of restrictive myopathy. Adjustable suture surgery is recommended in all possible cases.

Lid-lengthening surgery

Lid-lengthening surgery should be considered if restoration of the euthyroid state does not improve lid retraction. Corneal exposure is reduced by this surgery which helps in camouflaging mild-to-moderate proptosis. A Muller muscle excision can be used to ameliorate a 2 to 3 mm upper lid retraction. The temporal flare may be reduced by employing lateral levator tenotomy. For further lid recession, levator recession is a good option.

Blepharoplasty

- This is the last phase of restorative surgery in thyroid ophthalmopathy. Lower lid blepharoplasty can be approached transconjunctivally if no excess lower lid skin is present.
Upper lid blepharoplasty is performed transcutaneously with conservative skin excision. Brow fat resection may be considered. Dacryopexy may be required if lacrimal gland prolapsed occurs.

**Consultations**

- Patients with thyroid ophthalmopathy benefit from consultation and follow up care with an endocrinologist.
- When endoscopic procedures are contemplated together with orbital decompression, an otorhinolaryngologist should be part of the surgical team.
- Neurosurgical consultation is required when decompression of the orbital roof is performed.

**Conclusion**

- Thyroid ophthalmopathy (Graves ophthalmopathy), is an autoimmune disorder with clinical signs which are characteristic and include a combination of eye lid retraction, lid lag, globe lag, proptosis, restrictive extraocular myopathy and optic neuropathy.
- Diagnosis is confirmed on various clinical signs and investigative studies like ultrasonography, CT scan and MRI.
- The primary protocol of managing thyroid eye disease is patient counseling emphasizing the self limited but prolonged course of disease with not immediate care available.
- Various pharmacotherapy and surgical options are available depending on the various stages of ophthalmopathy.

**References**