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"OCULAR MANIFESTATION IN THYROID EYE DISEASE" A CLINICAL REVIEVE

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ABSTRACT
Thyroid eye disease (also known as Graves' ophthalmopathy) is a complex orbital inflammatory disease, which can be sight threatening, debilitating and disfiguring. People with thyroid disease sometimes develop an eye condition that causes the immune system to attack the muscles and other tissues around the eyes. This can cause the eyes and eyelids to become red, swollen and uncomfortable and the eyes can be pushed forward (_staring' or _bulging' eyes). Thyroid eye disease (TED) has a higher prevalence in women than men. TED is a chronic debilitating condition causing physical discomfort, facial disfigurement and impaired visual function. The physical consequences of TED could have a negative and lasting impact on patients' employment, hobbies and psychosocial function. We discuss the epidemiology, risk factors, pathogenesis, ophthalmic clinical features, investigations and management of Thyroid eye disease.

INTRODUCTION
Thyroid eye disease (TED), sometimes called Graves' ophthalmopathy or Graves' Eye Disease, is an autoimmune disease in which the immune system causes inflammation and swelling and stimulates the production of muscle tissue and fat behind the eye. The overactive thyroid gland (hyperthyroidism) is usually caused by Graves' disease. Up to one-half of people with Graves' disease develop thyroid eye disease. In some people, thyroid eye disease can occur with normal levels of thyroid hormones (euthyroid) or low levels of thyroid hormones (hypothyroidism). Thyroid eye disease may occur in patients who already know they have thyroid disease, or it may be the first sign of Graves' disease. While TED often occurs in people living with hyperthyroidism or Graves' disease, it is a distinct disease and treating hyperthyroidism may not resolve the eye symptoms and signs.

EPIDEMIOLOGY
Most common disease affecting the orbit
Sever cases more frequent in > 50 yr. age group
1. Smoking the strongest modifiable risk factor
2. Women – six times more likely to be affected by ted than men
3. Radioactive iodine- use to treat hyperthyroidism can worsen ted

RISK FACTORS
- Age: Usually affects middle-age adults but can occur at any age
- Gender: Females are affected more than males
- Family history of thyroid eye disease
- Smoking: Smoking increases the risk of thyroid eye disease by 7–8 times, causes thyroid eye disease to have a longer "active phase", and it reduces the effectiveness of treatments
- Radioactive iodine therapy: Radioactive iodine has been used to treat hyperthyroidism and Graves' disease. This treatment should be used with caution in people with active thyroid eye disease as it may worsen the condition unless steroids are given at the same time
- Low blood levels of selenium, a dietary mineral.

ETIOLOGY
TED is most frequently associated with Hyperthyroidism, consisting of approximately 90% of the cases. However about 10% of patients with TED have either a normal-functioning (Euthyroid) or under-functioning thyroid (Hypothyroidism e.g. Hashimoto's thyroiditis). While strict control of thyroid function is crucial in patients with TED, the course and severity of ocular manifestation does not always correlate with thyroid hormone levels. Thus, treatment of thyroid dysfunction does not necessarily affect course of Grave's ophthalmopathy.

PATHOPHYSIOLOGY
Although the underlying mechanisms of action of these processes are not completely understood, the presumed mechanism is activation of orbital fibroblasts by Graves' disease-related autoantibodies, which lead to the release of T cell chemoattractants, initiating an interaction which

ultimately results in fibroblasts expressing extracellular matrix molecules, biologic materials proliferating and differentiating into myofibroblasts or lipofibroblasts and deposition of glycosaminoglycans which bind water that lead to swelling, congestion in addition to connective tissue remodeling. This results in extraocular muscle enlargement and orbital fat expansion.

1) Inflammation of Extraocular Muscles

Pleomorphic cellular infiltration,
Increased secretion of glycosaminoglycan's,
Osmotic retention of water
↓
Muscles become enlarge
↓
Subsequent degeneration of muscle fibres
Eventually leads to fibrosis
↓
Restrictive myopathy and diplopia

2) Inflammatory Cellular Infiltration

Infiltration with lymphocytes, plasma cells, macrophages & mast cells of interstitial fluid, orbital fat & lacrimal glands
↓
Accumulation of glycosaminoglycan's & retention of fluid.
↓
Increase in volume of orbital contents & secondary elevation of intra orbital pressure
Secondary elevation of intra orbital pressure.

SIGNS

Eyelid retraction in patient with TED. Upper lid retraction measured with margin to reflex distance 1 (MRD1) and lower lid retraction measured with margin to reflex distance 2 (MRD2).

1. Eyelid retraction (Dalrymple's sign) is the most common presenting sign of TED, present in upto 90% of patients.[5]
2. Lid lag of the upper eyelid on downward gaze (Von Graefe's sign) and lid edema.[6]
3. TED is the most common cause for both unilateral and bilateral axial proptosis (exophthalmos). There is increased resistance to retropulsion. Hertel's exophthalmometer is used for the measurement of proptosis.
4. Bulbar conjunctiva may be injected (Goldzeiher's sign). Exposure keratopathy ocular emergency can occur further due to lagophthalmos, which is a major cause for decrease visual acuity and blurred vision in TAO apart from compressive optic neuropathy.
5. Extraocular muscles frequently involved in TAO. The most commonly affected muscle Mnemonic "I'M SLOw" Inferior rectus followed by medial, superior, levator, lateral rectus and oblique. Extraocular muscles affected results in ocular misalignment, diplopia. Inability to look up when the eye is adducted i.e. double elevator palsy.
6. Compressive optic neuropathy is an ocular emergency, and occurs in <5% of patients with typical TED resulting in slowly progressive fulminant visual loss. It occurs due to compression from the oversized recti and orbital fat causing compartment syndrome at the apex of orbit. It is characterized by decrease in vision, color vision, contrast sensitivity and relative afferent papillary defect. The characteristic visual fields commonly show central, cecocentral, paracentral, and nerve fiber layer bundle defects. Optic nerve head examination can be normal, optic disc edema, or pallor.
7. Clinical course: TED typically has a progressive inflammatory phase followed by a stable post-inflammatory phase.
8. The pattern of the disease follow the Rundle's curve which describe the plot of orbital disease severity against time

- Initial phase- inflammatory phase duration may last from 6 – 18 months with orbital and periorbital signs i.e. proptosis and retraction.
- Static phase- decrease in the inflammatory phase and minimal improvement.
- Quiescent phase- gradual improvement with improved motility and retraction of the muscles

CLINICAL MANIFESTATION

5 main clinical manifestation of thyroid eye disease are:

1. Soft tissue involvement
2. Lid retraction
3. Proptosis
4. Optic neuropathy
5. Restrictive myopathy

1) Soft Tissue Involvement Symptoms

Grittiness	Lacrimation
Photophobia	Retrobulbar discomfort
Periorbital swelling	Epibulbar hyperaemia
Puffy lids	Red eye

EPIBULBAR HYPERAEMIA

PUFFY LIDS

RED EYE

2) LID RETRACTION

- Occurs in 50% of patient
- Fibrotic contracture of elevator

Worsening of lid retraction in down gaze

SIGN

S Kochers sign

The von graefe sign

Dalrymple sign

3) PROPTOSISIS

Axial, unilateral/ bilateral, symmetrical or asymmetrical and frequently permanent Sever proptosis may compromise lid closure with resultant exposer keratopathy, corneal ulceration.

4) RESTRICTIVE MYOPATHY

30% to 50% of patient develops opthalmoplegia Ocular motility is restricted due to fibrosis

FOUR MOTILITY DEFECTS ARE

1) Elevation- Due to fibrosis of Inf. Rectus
2) Abduction- Due to fibrosis of Med. Rectus
3) Depression - Fibrosis of Sup. Rectus
4) Adduction- Fibrosis of Lat. Rectus

5) OPTIC NEUROPATHY

Is uncommon but serious complication due to compression op optic n. or its blood supply.

DIFFERENTIAL DIAGNOSIS

- Orbital pseudotumour
- Caroticocavernous fistula
- Inflammatory orbitopathy e.g, granulomatosis with polyangitis
- Orbital myositis (OM)
- Orbital tumors
- IgG4 disease

INVESTIGATION

- Serum T3, T4, & TSH level
- **Orbital Ultrasonography**

Both A-scan and B-scan transocular echograms can be used to visualize the orbital structures and determining recti muscle enlargement. Advantage is its low cost, lack of ionizing radiation and relatively short examination time.

Imaging

Computed tomography (CT) scan: This type of imaging without contrast may distinguish normal structures from abnormal structures of different tissue density. It demonstrates enlargement of the bellies and sparing of the tendons. It helps in assessing the relationship between the optic nerve and muscles at the apex, which helps in planning for the surgical intervention if needed.

Exophthalmos noted in axial view of CT-scan. Patient with TED also demonstrates enlargement of extra ocular muscles (asterisk).

Magnetic resonance imaging (MRI)
Fusiform rectus enlargement and orbital fat expansion may be identified. MRI may also aide in assessing water content in the muscles and other soft tissues. This may correlate with active inflammation.

MANAGEMENT
Management of thyroid eye disease has shifted dramatically from conservative measures—observation and surgery—to targeted biologic therapy with a focus on cosmesis and quality of life. Surgical innovations have also allowed for more profound results with significantly less risk of complications. Treatments for active-phase disease have also multiplied, which significantly affects quality of life for these afflicted patients.

Medical Therapies
Medical therapy can be a good initial, non-invasive way to manage certain patients with TED. Following are the pros and cons of the various medical approaches.
Control of Hyperthyroidism
- Iodine
- Anti-Thyroid Drugs

- ***Vitamins***

As discussed in part one of this series, data has shown that supplementation of selenium has reduced the severity and progression of disease in patients with mild thyroid eye disease.[1] Dosing is at 100 µg daily, and is best started as early as possible in the course of the disease, preferably within six months of onset. While there have been no studies of vitamin D supplementation in patients with TED, laboratory studies have shown an anti-inflammatory effect.

- ***Topical medicines***

Topical eye drops are chiefly prescribed to treat ocular surface disease. In the early, active phase of TED, ocular surface inflammation contributes to dry eye; this often responds to a low-dose topical steroid such as loteprednol or fluorometholone.

- ***Steroids***

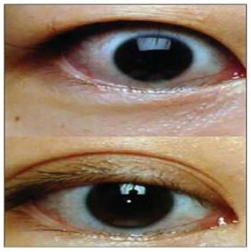
Steroids are excellent for reducing symptoms in TED, but aren't disease-modifying; rather, they improve soft-tissue symptoms in the active phase until the body can pass into the stable phase of the disease.

- ***Orbital radiation***

This may sound scary, but it's a relatively gentle treatment considering the small doses that are used for TED. Radiation is helpful in patients who have persistent inflammation in active disease, and it's synergistic with steroids

1) SURGICAL MANAGEMENT
Surgical Therapies
Surgery for TED is often necessary, but is usually delayed until the disease is in its stable phase. There's a small (<10 percent) risk of reactivating the active phase of the disease after surgery, though this is rare. The surgical options consist of the following:

Orbital decompression
Orbital decompression surgery is the mainstay of rehabilitation for TED; it can improve nearly every aspect of the disease, from vision-threatening optic nerve damage or corneal exposure to cosmesis. Quality of life is often better after surgery, since orbital congestion, pain and dry eye can improve.



For advance proptosis and optic nerve compression.

- ***Strabismus surgery***

Surgery to adjust the extraocular muscles and improve double vision is commonly performed. However, this can be much more complicated than typical strabismus surgery, and needs to be performed by a surgeon who is experienced in thyroid eye disease. This surgery takes between 30 to 60 minutes, can be performed under general or twilight anesthesia, and is done on an outpatient basis. Patients can have significant improvement if the muscles aren't too scarred.

- ***Eyelid surgery***

Surgery to improve eyelid retraction is often the final step in rehabilitation. This step can also be the most temperamental, as the eyelid structures are incredibly minute and unpredictable. However, significant improvement can be achieved *(Figure 4)*. Surgery is performed under twilight anesthesia, can take between 30 to 60 minutes, and is done on an outpatient basis.

- ***Cosmetic surgery***

While thyroid eye disease primarily affects the tissues inside the orbit, there are significant changes in the skin and fat in the eyebrows, cheeks, neck and other areas of the face. In fact, the eyebrow and cheek fat tends to grow alongside the orbital fat, creating a characteristic "hourglass" appearance *(Figure 5)*.

1) To minimise diplopia
2) Lid lengthening surgery

GENERAL MANAGEMENT
Control of ocular discomfort
- Artificial tear

- Topical lubricants
- Sunglasses

ADVICE

Avoid smoking, dust, stress

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