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THYROID EYE DISEASE: A CRITICLE REVIEW

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ABSTRACT

Thyroid eye disease (TED) is a complex orbital inflammatory disease, which can be sight threatening, debilitating and disfiguring. This overview discuss the epidemiology, risk factors, pathogenesis, ophthalmic clinical features, investigations and treatment of thyroid eye disease.

INTRODUCTION

Thyroid eye disease (TED) is a complex orbital inflammatory disease, which can be sight threatening, debilitating and disfiguring. Thyroid eye disease (TED), also known as thyroid-associated orbitopathy and Graves ophthalmopathy, named after Robert J Graves, an Irish physician who first described thyrotoxicosis in a woman presenting with goiter, it is a very common orbital disorder and most common cause of both bilateral and unilateral proptosis in an adult. TED was originally associated strictly with Graves triad of hyperthyroidism. More recently TED has also been noted in Hashimoto's Thyroiditis as well as in absence of thyroid disfunction. The most common presenting signs are orbital and periorbital edema, eyelid retraction, restrictive strabismus, compressive optic neuropathy and exposure keratopathy. The disease course of TED does not always coincide with thyroid activity or the treatment of underlying thyroid dysfunction.

AIM AND OBJECTIVE

- To review the concept of thyroid eye disease.
- To understand the etiopathogenesis & management of thyroid eye disease.

MATERIAL AND METHODS

Material has been collected from modern textbooks research articles and electronic databases.

What is Thyrotoxicosis ?

Thyrotoxicosis (hyperthyroidism) is a condition involving excessive secretion of thyroid hormones. [3]Graves disease, the most common form of hyperthyroidism, is an autoimmune disorder in which IgG antibodies bind to thyroid stimulating hormone (TSH) receptors in the thyroid gland and stimulate secretion of thyroid hormones. It is more common in females and may be associated with other autoimmune disorders. Presentation is often in the fourth or fifth decades with symptoms including weight loss despite good appetite, increased bowel frequency, sweating, heat intolerance, nervousness, irritability, palpitations, weakness and atigue. There may be enlargement of the thyroid gland, tremor, palmar erythema, and warm and sweaty skin. Thyroid acropachy is a phenomenon similar to clubbing of the fingers, occurring in 1%; pretibial myxoedema (1-5%) is indurated thickening of the skin of the shins. Cardiac manifestations may include sinus tachycardia and other arrhythmias. Other autoimmune disorders can be associated. Thyroid function is commonly tested initially with a TSH level; if this is low, or normal but thyroid disease is still suspected, a range of additional investigations can be carried out. Treatment options include carbimazole, propylthiouracil, propranolol, thyroid ablation with radioactive iodine, and partial thyroidectomy.

[1]Risk factors for TED

Once a patient has Grave's disease, the major clinical risk factor for developing TED is smoking. The greater the number of cigarettes smoked per day, the greater the risk, and giving up smoking seems to reduce the risk. Women are five times more likely to be affected by TED than men, but this largely reflects the increased incidence of Graves disease in women. Radioactive iodine used to treat hyperthyroidism can worsen TED. TED can also, though less commonly, occur in euthyroid and hypothyroid (including treated hyperthyroid) patients. It can sometimes be the presenting manifestation of thyroid-related disease.

[2]Pathogenesis of TED

Thyroid ophthalmopathy involves an organ-specific autoimmune reaction in which an antibody that reacts against thyroid gland cells and orbital fibroblasts leads to inflammation of extraocular muscles, interstitial tissues, orbital fat and lacrimal glands characterized by pleomorphic cellular infiltration, associated with increased secretion of glycosaminoglycans and osmotic imbibition of water. There is an increase in the volume of the orbital contents,

particularly the muscles, which can swell to eight times their normal size. There may be a secondary elevation of intraorbital pressure, and the optic nerve may be compressed. Subsequent degeneration of muscle fibres eventually leads to fibrosis, which exerts a tethering effect on the involved muscle, resulting in restrictive myopathy and diplopia.

[1,2]Clinical features of TED

TED typically proceeds through a congestive (inflammatory) stage in which the eyes are red and painful; this tends to remit within 1-3 years and only about 10% of patients develop serious long term ocular problems. A fibrotic (quiescent) stage follows in which the eyes are white, although a painless motility defect may be present. Clinical features broadly can be categorized into.

A) Soft tissue involvement.

B) Lid retraction.

C) Proptosis.

D) Optic neuropathy.

E) Restrictive myopathy.

[4]A commonly used classification for the severity of TED has been issued by the European Group on Graves Orbitopathy (EUGOGO).

- Sight-threatening due to optic neuropathy or corneal breakdown.
- Moderate-severe, with one of moderate-severe soft tissue involvement, lid retraction of 2 mm or more, diplopia and proptosis of 3 mm or more.
- Mild, with only a minor impact on daily life.

A) Soft tissue involvement

• **Symptoms:** Gritiness, 1Wred eyes, lacrimation, photophobia, puffy lids and retrobulbar discomfort.

- Epibulbar hyperaemia - This is a sensitive sign of inflammatory activity. Intense focal hyperaemia may outline the insertions of the horizontal recti.
- Periorbital swelling is caused by oedema and infiltration behind the orbital septum; this may be associatd with chemosis and prolapse of retroseptal fat into the eyelids.
- Tear insufficiency and instability is common.
- Corneal signs are exacerbated by lid retraction and can include punctate epithelial erosions, superior limbic keratoconjunctivitis and occasionally bacterial keratitis, thinning and scarring.

B) Lid Retraction

Retraction of upper and lower lids occurs in about 50% of patients with Graves disease. Humorally induced overaction of Müller muscle is postulated to occur as a result of sympathetic overstimulation secondary to high levels of thyroid hormones. Fibrotic contracture of the levator palpebrae and inferior rectus muscles associated with adhesion to overlying orbital tissues is another probable mechanism, together with secondary overaction in response to hypo- or hypertropia produced by fibrosis.

Symptoms- Patients may complain of a staring or bulging eyed appearance, difficulty closing the eyes and ocular surface symptoms.

Signs

- The upper lid margin normally rests 2 mm below the limbus. Lid retraction is suspected when the margin is either level with or above the superior limbus, allowing sclera to be visible
- The lower eyelid margin normally rests at the inferior limbus; retraction is suspected when sclera shows below the limbus. Lid retraction may occur in isolation or in association with proptosis, which exaggerates its severity.
- The *Dalrymple sign* is lid retraction in primary gaze.
- The *Kocher sign* describes a staring and frightened appearance of the eyes which is particularly marked on attentive fixation.
- The *von Graefe sign* signifies retarded descent of the upper lid on downgaze.

C) Proptosis

Symptoms are similar to those of lid retraction.

Signs - Proptosis is axial, unilateral or bilateral, symmetrical or asymmetrical and frequently permanent. Severe proptosis may compromise lid closure and along with lid retraction and tear dysfunction can lead to exposure keratopathy, corneal ulceration and infection.

D) Restrictive myopathy

Between 30% and 50% of patients with TED develop ophthalmoplegia and this may be permanent. Ocular motility is restricted initially by inflammatory oedema, and later by fibrosis.

Symptoms - Double vision, and often discomfort in some positions of gaze.

Signs - in approximate order of frequency.

- Elevation defect - caused by fibrotic contracture of the inferior rectus, may mimic superior rectus palsy and is the most common motility deficit.
- Abduction defect - due to fibrosis of the medial rectus, which may simulate sixth nerve palsy.
- Depression defect - secondary to fibrosis of the superior rectus.
- Adduction defect - caused by fibrosis of the lateral rectus.

E) [5]Optic neuropathy

Optic neuropathy is a fairly common (up to 6%) serious complication caused by compression of the optic nerve or its blood supply at the orbital apex by the congested and enlarged recti and swollen orbital tissue. Such compression, which may occur in the absence of significant proptosis, may lead to severe visual impairment if adequate and timely treatment is not institute.

Symptoms - Impairment of central vision occurs in conjunction with other symptoms of TED.

Signs

- Visual acuity (VA) is usually reduced, but not invariably.
- Colour desaturation is a sensitive feature.
- A relative afferent pupillary defect, if present, should give cause for marked concern.
- There may be diminished light brightness appreciation
- Visual field defects can be central or paracentral and may be combined with nerve fibre bundle defects. These findings, in concert with elevated IOP, may be confused with primary open-angle glaucoma.
- The optic disc may be normal, swollen or rarely atrophic.

Investigation for TED

Investigations other than blood tests for thyroid disease are not necessary if the diagnosis is evident clinically.

Visual field testing is carried out if there is a suspicion of optic nerve compromise.

MRI, CT and ultrasonographic imaging to confirm an equivocal diagnosis by identification of the typical pattern of extraocular muscle involvement in TED, consisting of muscle belly enlargement with tendon sparing.

Imaging is also used in the assessment of optic nerve compression and prior to orbital wall surgery.

Visual evoked potentials are sometimes utilized in optic neuropathy.

[6,7]Treatment of TED

Treatment can be classified into that of mild disease (most patients), moderate to severe active disease, and treatment of post inflammatory complications.

Cessation of smoking.

Thyroid dysfunction should also be managed adequately; if radioiodine treatment is administered in patients with pre-existing TED, a short course of oral steroids should be given in concert.

- **Mild disease**

➢ Lubricants for superior limbic keratoconjunctivitis, corneal exposure and dryness.

➢ Topical anti-inflammatory agents (steroids, non-steroidal anti-inflammatory drugs (NSAIDs), ciclosporin) are advocated by some authorities.

➢ Head elevation with three pillows during sleep to reduce periorbital oedema.

➢ Eyelid taping during sleep may alleviate mild exposure keratopathy.

- **Moderate to severe active disease**

Clinical activity score. EUGOGO suggests calculating a 'clinical activity score' to aid in determining a threshold for the use of immuno-suppressives, assigning one point for each feature present from the following list and considering treatment for a score of 3 or more out of 7.

1. Spontaneous orbital pain.
2. Gaze-evoked orbital pain.
3. Eyelid swelling considered to be due to active (inflammatory phase) TED.
4. Eyelid erythema.
5. Conjunctival redness considered to be due to active (inflammatory phase) TED.
6. Chemosis.
7. Inflammation of caruncle or plica.

During subsequent review, a point is allocated for an increase in proptosis of 2 mm or more, a decrease in uniocular excursion in any one direction of 8° or more, or a decrease in Snellen acuity of one line.

- [7]Systemic steroids are the mainstay of treatment for moderate to severe disease. Oral prednisolone 60-80 mg/ day may be given initially, and tapered depending on response. Intravenous methylprednisolone is often reserved for acute compressive optic neuropathy (see below), but tolerability is better and outcomes may be superior compared with oral treatment; a lower-intensity regimen in the absence of acute sight-threatening disease is 0.5 g once weekly for 6 weeks followed by 0.25 g once weekly for 6 weeks. A reduction in discomfort, chemosis and periorbital oedema usually occurs within 24 hours, with a maximal response within 2-8 weeks. Ideally, oral steroid therapy should be discontinued after several months, but long-term low-dose maintenance may be necessary.
- Orbital steroid injections are occasionally used but are considerably less effective than systemic treatment.
- Low-dose fractionated radiotherapy may be used in addition to steroids or when steroids are contraindicated or ineffective. Adverse effects include cataract, radiation retinopathy, optic neuropathy and an increased risk of local cancer.
- Combined therapy with irradiation, azathioprine and low-dose prednisolone may be more effective than steroids or radiotherapy alone.
- **Optic neuropathy** and less commonly intractable corneal exposure, requires aggressive treatment. Pulsed intravenous methylprednisolone is commonly used, regimens including 0.5-1 g on three successive days with conversion to oral treatment (e.g. 40 mg/day prednisolone) or 0.5-1 g on alternate days, 3-6 times, keeping the maximum dose below 8 g to reduce the risk of liver compromise, followed by oral prednisolone; appropriate monitoring should be instituted, including liver function tests, as well as gastric protective treatment and osteoporosis prophylaxis if necessary.
- Several drugs targeting specific aspects of the immune response in TED are under investigation, notably monoclonal antibody treatment with rituximab.
- Post-inflammatory complications - Eyelid surgery should be performed only after any necessary orbital and then strabismus procedures have been undertaken, as orbital decompression may impact both ocular motility and eyelid position, and extraocular muscle surgery may affect eyelid position.
- **Proptosis** - After active inflammation has remitted, the patient can be left with cosmetically and functionally significant proptosis, the treatment of which is essentially

surgical. Surgical decompression increases the volume of the orbit by removing the bony walls and may be combined with removal of orbital fat.

- **Restrictive myopathy** - Surgery is required in most cases experiencing persistent diplopia in the primary or reading positions of gaze, provided the inflammatory stage has subsided and the angle of deviation has been stable for at least 6-12 months.
- **Lid retraction** - Mild lid retraction frequently improves spontaneously so does not require treatment. Control of hyperthyroidism may also be beneficial. Botulinum toxin injection to the levator aponeurosis and Müller muscle may be used as a temporary measure in patients awaiting definitive correction. Mullerotomy is effective for mild lid retraction, Recession of the lower lid retractors when retraction of the lower lid is 2 mm or more.

DISCUSSION

Thyroid eye disease is a complex and poorly understood inflammatory disease that causes a wide variety of clinical problems. Clinical management is often frustrating for both the physician and the patient, because no immediate or dramatic cure exists. Each treatment modality has significant side effects and complications, and treatment decisions are rarely easy. Thyroid disease, being autoimmune disorder mostly, effects in 4th and 5th decade of life and commonly in females as cited by many previous studies. Ocular manifestation of thyroid disease includes eyelid retraction, periorbital oedema, chemosis, proptosis, extraocular muscle restriction, exposure keratopathy, and optic nerve compromise. Sympathetic stimulation of the Müller muscle may be responsible for most of the medically reversible cases of eyelid retraction in patients with Graves disease. Similarly, the periorbital oedema, conjunctival injection, proptosis, extraocular muscle restriction all are attributed to the inflammation of intraorbital fat as well as extraocular muscle. The exposure keratopathy is due to severe proptosis and the compressive optic neuropathy is also due to severe proptosis.

Other severe ocular manifestations of thyroid ophthalmopathy include diplopia, corneal ulcer due to exposure keratopathy and dysthyroid optic neuropathy.

CONCLUSION

Thyroid eye disease affects the majority of thyroid disease patients. The ocular manifestation ranges from mildest to the most severe form. Early diagnosis and intervention can be beneficial in saving sight and globe. Hence a proper referral system between

ophthalmologists and physician is mandatory. Also, many thyroid disorders are first time diagnosed form ocular manifestations so a regular health check up including eye check up is needed to pick the cases in early stage and referred among each other for better treatment outcome.

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