

Thyroid Disorders

Chapter 4

Thyroid Eye Disease: A Case Report, Review of Current Literature and Usefulness of Joint Specialist Clinics

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Abstract

Grave's disease is a common endocrine condition often associated with eye disease resulting in Graves' orbitopathy (GO). We report a case of GO which was successfully managed in a combined thyroid eye disease (TED) specialist clinic. We also review the literature and discuss diagnostic criteria for GO, EUGOGO severity classification, Amsterdam declaration for prevention and care of TED and the UK TEAMeD audit survey, recommendations and combined specialist TED clinics to improve outcome for TED patients.

Keywords: Graves' Disease; Grave's Orbitopathy (GO); Radioiodine; EUGOGO classification; Thyroid Eye Disease Amsterdam Declaration Implementation Group (TEAMeD); Thyroid Receptor Antibody (TRaB); Thyroid Eye Disease (TED)

1. Introduction and Case Report

Thyroid Eye Disease (also known as Graves' Orbitopathy [GO]) is a disfiguring condition that affects an estimated 50,000-100,000 people in the UK. GO is a self-limiting autoimmune disease resulting in diplopia, grittiness, eyelid erythema and retraction. It manifests with pain, loss of vision and exposure keratopathy in the initial active stage [1]. Smoking causes an inflammatory response and can worsen the manifestation [2,3].

We report a patient with Grave's disease and severe thyroid eye disease who underwent a combination of intravenous and oral steroids, and orbital decompression to restore vision.

A 48 years old gentleman was diagnosed with Grave's thyrotoxicosis in mid 2013. He was a smoker and had family history of thyroid disease. Blood results revealed high Free T3 (21.6 pmol/L), Free T4 (36 pmol/L), strongly positive TPO antibody titres (704 IU/ml), positive TSH receptor antibody and low TSH levels (<0.01 mUL). He was started on 20 mg Carbimazole which was subsequently increased to 40mg due to poor control of thyroid function. However, this led to hypothyroidism within a few months and Carbimazole was stopped. In mid-2014, he relapsed and became thyrotoxic again with resting tremor and palpitations, for which 10mg Carbimazole was re-commenced. The dose was increased to 15 mg after 16 months of euthyroidism. He had developed only mild thyroid eye disease at this stage with some lid retraction and conjunctival hyperemia. Examination revealed good visual acuity of 6/6, full colour vision, 20 mm proptosis on exophthalmometer and 1/7 clinical activity score (CAS) bilaterally.

Three years later in mid 2016, with normal T3 and T4 level and suppressed TSH, he became sub clinically hyperthyroid and presented with resting pain in his eyes, conjunctival hyperaemia, eyelid swelling and erythema, reduced visual acuity (6/18), reduced colour vision, 26 mm proptosis and high CAS score (7/10). He was thus diagnosed with bilateral active severe thyroid eye disease with dysthyroid optic neuropathy. He was commenced on 3 doses of 1gm intravenous methylprednisolone on consecutive days followed by tapering doses of oral prednisolone. Consequently, his visual acuity and colour vision were restored to normal, although he developed steroid induced central serous retinopathy in his left eye.

3 months later, he had another flare up of active thyroid eye disease in Oct 2016, with decreased visual acuity and colour vision in both eyes. His visual acuity recorded was 6/9 in right eye and 6/36 in left eye. His clinical activity score was 6/10 at this stage. CT orbits revealed marked enlargement of extra-ocular muscles in both eyes with apical crowding. VEP recording suggested bilateral dysthyroid optic neuropathy, worse in the left. He remained biochemically euthyroid and was on no anti thyroid medication. He was given another course of 3 days of 1gm Methylprednisolone followed by oral prednisolone. Subsequently he underwent urgent bilateral orbital decompression surgery with rim advancement to treat his progressive dysthyroid optic neuropathy. At the conclusion of treatment, his vision was restored to 6/6 in both eyes with good colour vision, minimal soft tissue swelling and upper and lower lid retraction. His exophthalmometer reading had improved to 22mm in each eye.

2. Discussion

Thyroid eye disease is a term used to describe a combination of adnexal and orbital findings that occurs most commonly with Grave's hyperthyroidism - patients may be hypothyroid or euthyroid [4]. Thyroid eye disease may precede or follow endocrine manifestations.

The common symptoms of Grave's orbitopathy include changes in appearance of eyes;

ocular surface irritation such as grittiness, watering, photophobia, orbital ache and double vision. Typical signs associated are eyelids retraction, lid lag, conjunctival swelling and redness, lid swelling, redness, proptosis and restriction of ocular movement [1].

Diagnostic criteria for Graves' orbitopathy (derived from Bartley et al, 1996 [5])

Eyelid retraction present and one or more of following features are associated with >90% probability of the diagnosis of GO being correct:

- Thyroid dysfunction
- Exophthalmos
- Optic neuropathy
- Extraocular muscle involvement

If eyelid retraction is absent and the patient has a history of thyroid dysfunction, any one of the following features, there is >90% probability of the diagnosis of GO being correct:

- Exophthalmos
- Optic nerve dysfunction
- Extra ocular muscle involvement

All the other presentation or atypical presentation despite above features eg lid retraction, restrictive strabismus

- Consider alternate diagnosis

Women in their third to fifth decade of life are most commonly affected. Despite this, the severity tends to be worse in male patients [6]. Risk factors of developing thyroid eye disease include cigarette smoking, older age of diagnosis of Graves' hyperthyroidism, longer duration of hyperthyroidism, uncontrolled thyroid dysfunction and prior radioiodine treatment [7].

Graves' orbitopathy is a self-limiting condition that manifests in 2 phases. The active phase is characterized by fluctuating inflammatory response that eventually transitions into a non-progressive phase. The mainstay of therapy in active phase is systemic corticosteroids to alleviate symptoms [8]. Newer non-steroidal immunomodulatory agents are now being considered as an alternative with promising results [9]. Once the disease reaches a non-progressive phase, the mainstay of treatment is surgical rehabilitation.

EUGOGO has classified thyroid orbitopathy based on severity [10]. Sight threatening disease requires urgent intervention. Patients with moderate to severe thyroid eye disease have sufficient impact on daily life to justify the risks of immunosuppressive (if active) or surgical intervention (if inactive). Mild thyroid eye disease only needs supportive management.

EUGOGO (severity classification): (derived from EUGOGO, reported in Clinical medicine 2015)

Sight threatening thyroid eye disease:

- Dysthyroid optic neuropathy and/or
- Corneal breakdown

Moderate to severe thyroid eye disease

- Lid retraction \geq 2mm
- Moderate to severe soft tissue involvement
- Exophthalmos \geq 3 mm above normal for age and gender
- Inconstant or constant diplopia

Mild thyroid eye disease:

- Mild lid retraction <2mm
- Mild soft tissue involvement
- Exophthalmos \leq 3mm above normal for race and gender
- Transient or no diplopia
- Corneal exposure responsive to lubricants

The Amsterdam Declaration (AD) set up in 2009-10, aims to improve prevention, care and access to care for thyroid eye disease (TED) and they set 3 targets as follows (adapted from TEAMED first report April 2014):

1. Halving the time from presentation to diagnosis,
2. Halving the time from diagnosis to referral to a Centre of excellence,
3. Optimal treatment of thyroid disease including appropriate use of radioiodine, avoidance of hypothyroidism and vigorous anti-smoking measures in patients at risk of or with thyroid eye disease.

The UK Thyroid Eye Disease Amsterdam Declaration Implementation Group (Teamed) was formed in 2010 to take forward the above initiative in the UK and comprised representatives from all the key stakeholder organizations.

The key points arising from the work of the first TEAMeD report in UK (adapted from TEAMED first report April 2014):

- A significant delay remained (mean of five months) from the onset of symptoms to diagnosis (inter-individual variation 0-216 months). However, this was better than previous rates (> 6 months, Estcourt et al 2009).
- 50% of patients were referred to a specialist clinic and only 20% were actually seen in a joint clinic. This was reported as inadequate but represented an improvement on previous rates (Estcourt et al 2009 – 25% attending a specialist clinic)
- Once referred, patients were seen promptly in a specialist clinic (median delay to first appointment -2 months).
- Awareness of smoking risks once diagnosed seemed high (100%), although smoking rates among patients who are newly referred to tertiary centres were still high.

Nearly 26% of patients with Graves' disease in endocrine clinics had thyroid eye disease and roughly 8% would benefit from specific interventions over and beyond what endocrinologists would offer. The use of a questionnaire screening tool could aid in identifying these patients.

- More than 30 centres in the UK treated moderate-severe thyroid eye disease. Of these, around 38% had clinics conducted jointly between an ophthalmologist and an endocrinologist. 65% of centres saw less than two severe cases of TED per year and 61% (47/77) of all severe cases were seen in 3 centres.
- Provision of specialist procedures (like orbital decompression) and rates of referral for TED specialist care for patients varied quite widely (more than 30-fold) by PCT/region.
- Advice leaflets on the risks of smoking specifically designed for patients with TED were drafted by the Group which contained practical advice and promoted shared decision making.

The above findings seemed to suggest that care of patients with TED in specialist centres had improved in recent years. However, there were significant delays in diagnosis, and potential to increase the number of patients seen in these specialist clinics. The provision of specialist clinics, working jointly with endocrinology, and reducing inequalities in workload, maintenance of specialist expertise and access to specialist services by region could also be significantly improved.

Ongoing work included an observational study and audit of the use of radioiodine in across endocrine units, development of best practice guidelines for referral to specialist centers, preparation and dissemination of an eye disease awareness card for patients with Graves' disease, audit of rates of optic neuropathy due to TED (severe disease) and an audit of patient journey and referrals to specialist clinics.

Thyroid Eye Disease Amsterdam Declaration Implementation Group (TEAMeD) recommendations on 5 steps to improve outcomes in patients with TED [11-13]

- 1) Diagnose Graves' Disease accurately (e.g. using TSH receptor antibody TRaB testing to identify patients at risk of TED)
- 2) Screen all patients with Graves' disease for early symptoms and signs of TED using the DiaGO clinical assessment tool
- 3) Alert patients with Graves' Disease to the early symptoms of TED using a TEAMeD early warning card
- 4) Prevent TED in Graves' disease by smoking reduction, early induction and maintenance of euthyroidism and avoidance of Radio-Iodine in active TED
- 5) Promptly refer patients who develop TED to a specialist multi-disciplinary joint thyroid-eye clinic

The management of Grave's orbitopathy require multidisciplinary collaboration of ophthalmologist, endocrinologist, radiologist, surgeon and occasionally oncologist for management of the varied spectrum of the disease [14,15]. EUGOGO recommends patient-centered multi-disciplinary approach towards management of thyroid eye disease [15].

Here, we describe the importance of combined thyroid eye clinics where an ophthalmologist and an endocrinologist simultaneously examine the patients in planning treatment programs which aims at correcting both hyperthyroidism and treating orbitopathy. Careful and coordinated consideration of individual patient needs requires input from various specialties throughout the disease process. The advantages of such clinics are numerous. Early diagnosis and intervention of Grave's Orbitopathy is possible. It also avoids any sort of communication error or delay in referral between treating physicians. The management plan is better understood by patients, which positively influences compliance. The outcome of combined treatment is far better monitored in a joint clinic. The patients are also managed efficiently with reduced number of hospital visits. Hence, this is not only important from public health perspective but also economically. Multi-disciplinary TED clinics offer an optimal setting for a cost-effective and specialized management of patient with TED [16].

The relationship between the treatment of Grave's hyperthyroidism and its effect on orbitopathy is controversial. It is well established that anti-thyroid drug treatment and surgery (thyroidectomy) do not worsen orbitopathy. Treatment with Radio-Iodine (RI) is associated with development or worsening of orbitopathy in 15% cases [17]. Although, there is no definite explanation for this, many risk factors are associated with the worsening of ocular symptoms. These include smoking, pre treatment severe hyperthyroidism, high TRAb concentration, pre-existing orbitopathy and post treatment uncontrolled hypothyroidism [18-20]. Bartalena et al showed that prophylactic prednisolone treatment not only prevents worsening of Graves' orbitopathy after Radio-Iodine (RI), but actually also improves Graves' orbitopathy in some patients [20,21]. The ocular signs following RI are very subtle and can be easily missed if the patients are not examined meticulously and frequently.

Patients with mild Graves' orbitopathy benefit from supportive care, which includes ocular surface management. Smoking cessation is also important as smoking has been shown to increase the incidence and severity of the disease [2,3]. Selenium supplementation has shown to improve clinical activity score in mildly active disease [22]. Patients with mild disease do not need referral to specialist TED clinics. In moderate to severe active disease, corticosteroids and often, urgent orbital decompression is required to prevent vision loss – these patients benefit from referral to combined specialist clinics according to current recommendations by TEAMeD. Orbital radiation is helpful especially in patients who are intolerant to steroids [23]. Surgical rehabilitation, in non progressive phase, is undertaken and includes orbital surgery, strabismus surgery and eyelid surgery.

In conclusion, our patient being a male and a smoker with fluctuating thyroid function was at high risk of developing severe thyroid eye disease. He was serially managed in joint thyroid eye clinic where subtle worsening of eye signs were picked up early and treated. His condition was managed collectively in a multi-disciplinary specialist setting to stabilize endocrine function and promote visual rehabilitation.

3. References

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