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A Jane Dickinson, Consultant Ophthalmologist, Royal Victoria Infirmary, Newcastle

Thyroid-associated Ophthalmopathy

Thyroid-associated Ophthalmopathy (TAO) is an immensely debilitating condition. Half of patients experience anxiety or depression, quality of life is impaired comparable to chronic diseases such as diabetes or some cancers[1], and the socio-economic impact is considerable. Research shows that the worldwide management of patients with TAO is currently suboptimal, including the UK[2] and so, in 2009, an important worldwide initiative was launched.

The 'Amsterdam Declaration', as it is known[3], aims to raise awareness of TAO, improve the experience of patients undergoing treatment and improve outcomes. TEAMeD (Thyroid Eye disease AMsterdam Declaration) Implementation Group UK is a multidisciplinary initiative supported by the RCOphth, BOPSS and other UK professional and patient led organisations, which is driving the Amsterdam Declaration in the UK. TEAMeD is currently preparing national guidelines on referral pathways and will soon launch a national audit.

Although much of TAO is not yet preventable, the hope is that earlier recognition and appropriate referral will help patients to access optimal management. Through optimal early management, the worst sequelae will be prevented; through optimal later treatment, appearance and visual functioning will be normalised as much as possible. The aim of this review is to highlight aspects of TAO that may help ophthalmologists to achieve the goals of the Amsterdam Declaration.

Objectives: For newly presenting patients, there are three mandatory objectives: the diagnosis of TAO must be securely established; the phase of the disease must be identified; and disease severity must be assessed. While severity will indicate whom to treat and how quickly, disease phase determines therapeutic options i.e. how to treat. In addition, for all patients with TAO at any stage of their disease, euthyroidism must be rapidly achieved then maintained, and smoking cessation measures implemented where applicable.

Diagnostic signs and pitfalls: Patients presenting with bilateral signs comprising upper eyelid retraction, soft tissue swelling and inflammation, proptosis and muscle restriction in the context of abnormal thyroid regulation need no further investigations for a secure diagnosis of TAO. Rarely, TAO presents with no detectable thyroid abnormality, no upper lid retraction, divergent strabismus or purely unilateral signs. The diagnosis of TAO is then not secure and needs further investigation. Note that misdiagnosis of TAO as allergy is common; however, TAO does not itch.

Disease phase: TAO is partially self-limiting: active (inflammatory) phases of progression, plateau and regression lasting six to 18 months are followed by inactivity – the 'burnt-out' phase, where abnormalities often persist. Determining phase is important, as disease-modifying treatment is only appropriate during active TAO, while surgical rehabilitation must await the inactive phase. Active disease is usually highly symptomatic. Apart from recent change in appearance or visual function, aching and surface irritation are common. Early muscle restriction provokes diplopia on waking. Active TAO usually shows signs of inflammation, with swelling and redness of eyelids and conjunctivae viewed as surrogates for orbital inflammation. The clinical activity score (CAS)[4], although not infallible helps identify active TAO and predict treatment response. Clinical assessment plus duration of TAO will determine phase in most patients[5]. Occasionally alternative strategies are needed for moderately severe disease with low CAS. These include re-assessment over time, trial of medical therapy or further investigations e.g. quantitative MRI.

Severity: Severity refers to the degree of deficit in any feature of TAO. 'NOSPECS' provides a good aide memoire, however, a stricter measurement protocol e.g. *www.eugogo.eu* helps future comparison. It is worthwhile noting that Hess charts are poor for assessing TAO unless strictly unilateral, and late change is difficult to interpret as it does not necessarily denote relapse. Uniocular excursions and binocular fields are far more helpful. Management decisions are simplified by grouping patients into three categories of severity[6]: sight-threatening; moderately severe but not sight-threatening; and mild. Apart from the rare situation of subluxation, all patients with new sight threatening disease are active, whereas lesser degrees of severity can apply equally to inactive patients or those where phase is uncertain. Alternatively, the VISA system[7] uses a slightly different protocol and provides a useful proforma and management paradigm, although the principles of treatment remain the same.

Sight-threatening TAO: All patients with active TAO should have dysthyroid optic neuropathy (DON) positively excluded as its signs may be subtle. Older male diabetic smokers are at greater risk. As proptosis signifies self-decompression then those with muscle restriction but minimal proptosis (tight orbits) are at highest risk. Visual acuity and field loss may be mild, but are usually preceded by loss of colour appreciation, plus an afferent pupil defect if DON asymmetrical (60%). Imaging can suggest risk of DON, but the diagnosis is purely clinical. It relies on detecting either a swollen disc or at least two of the four features above. The risk of lagophthalmos and corneal ulceration relates principally to poor levator function (rather than upper lid retraction per se), in the context of a tight inferior rectus and poor Bells'. It may be further aggravated by proptosis. Corneal exposure is an emergency.

Moderately severe but not sight-threatening TAO

If motility restriction, appearance or aching impact significantly on daily life, then TAO may be severe enough to justify disease modulation if active, or surgery if inactive. This decision rests on balancing anticipated benefits against side effects of treatment[6,8], so assessing quality of life can help[9].

Mild TAO: If the risks of disease modulation or major surgical treatment are not justified by the benefits then TAO is mild. However, these are not absolute categories and lid surgery may still be indicated once inactive.

Management of active TAO: All patients should have optimal thyroid control and be helped to stop smoking as both measures reduce the risk of worsening disease and show a significant benefit on outcomes[10,11]. Both gel and nocturnal ointment lubricants are a major help, and fresnel prisms may be indicated.

Sight-threatening TAO: Treatment is mandatory and evidence suggests that intravenous methylprednisolone (IVMP) is optimal first line treatment[12]. There is no evidence-based protocol, however, 500mg–1g daily for three days before assessing response is commonly used. Patients who fail to respond adequately require prompt surgical decompression. Radiotherapy is inappropriate as sole therapy as its time course for response is too long, however, it may be useful adjunctive therapy. The place of other agents in DON is less clear.

Moderately severe but not sight-threatening TAO: For active patients of this severity, the first line treatment is generally corticosteroids. IVMP has greater efficacy and fewer side effects than oral steroids[6,13], with a mean of 79% patients responding to IVMP monotherapy versus 56% for oral regimes. Additionally, any response is seen early so non responding patients can quickly be withdrawn and offered alternatives. When radiotherapy is combined with IVMP 88% of patients respond, and it may have a more lasting benefit, particularly on motility. Radiotherapy should be avoided in diabetic patients or those under 35 years of age. Oral prednisolone plus radiotherapy is less efficacious than IVMP, and similar to oral prednisolone plus cyclosporine, although the latter has more side effects[13]. Of prime importance is the avoidance of prolonged oral prednisolone. This increases the likelihood of cushingoid change, which has a major negative impact on patients. Additionally, fatty change in the orbit can increase venous congestion making it difficult to differentiate from active disease, although imaging and intraocular pressure can help. The place of azathioprine in combination is yet to be proven, however, a trial is in progress.

Mild TAO: In addition to supportive measures, oral selenium 200 µcg daily for six months improves TAO outcomes[14].

Post treatment relapse: Some relapse after 12 weeks of steroids and radiotherapy is common but, unless the patient returns to a severity warranting treatment, this period can usually be weathered. Few patients require other therapy, but cyclosporine can be effective.

Management of inactive TAO: Surgical rehabilitation follows a logical sequence based on anticipated side effects: namely decompression precedes strabismus surgery, which precedes eyelid lengthening and finally debulking. As patients with significant TAO rarely return to normal appearance and function, such surgery offers the chance to transform patients and help restore quality of life. Orbital decompression is immensely valuable, with low morbidity in experienced hands. However, a recent study has shown that decompression rates vary widely across the UK, dropping off significantly with increasing distance from the few major centres[15]. Proptosis readings do not have to be above an arbitrary cut-off before offering orbital decompression; premorbid appearance and quality of life assessment[9] can help select suitable patients. Hence it behoves us all to appreciate the scope of current surgical rehabilitation; to develop it or refer as necessary for optimal care. Close Liaison with the endocrinologist to optimise thyroid treatment is so crucial in TAO that multidisciplinary clinics have developed in many areas. Their advantages include patient convenience, shared expertise in difficult decisions and ease of flow of information between clinicians. Additionally, patients being considered for radio-iodine can have eye assessment to ensure they do not have active TAO, which may worsen unless steps are taken.

Current theories of pathogenesis and novel therapies: TAO is an autoimmune process where the main target is the orbital fibroblast. Fibroblasts are stimulated by cytokines and induced to interact with immune cells. This results in excessive glycosaminoglycans (with fluid accumulation and swelling of muscles), further cytokines and chemo attractant production, and also their differentiation into adipocytes thereby increasing the fat of the orbit[16]. Increasing understanding of these processes suggests potential roles for new agents, some of which are starting to be tested. One such agent is rituximab. This is currently undergoing randomised trials; however, until results are available it is inappropriate for this expensive agent to be used outside of specialist centres.

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