

# Thyroid-associated ophthalmopathy: a neuro-ophthalmologist's perspective

Andy C. O. Cheng, MMedSc, MRCSEd, DPD, FCOphthHK, FHKAM (Ophthalmology)

Department of Ophthalmology, Hong Kong Eye Hospital, Hospital Authority; Department of Ophthalmology & Visual Sciences, The Chinese University of Hong Kong, Hong Kong Eye Hospital, Hong Kong.

Correspondence and reprint requests:

Dr. Andy C. O. Cheng, Department of Ophthalmology, Hong Kong Eye Hospital, 147K Argyle Street, Kowloon, Hong Kong.

Email: acocheng@gmail.com

## Abstract

Thyroid-associated ophthalmopathy is an autoimmune process representing the commonest and most important extra-thyroidal manifestation of Graves' disease. Ophthalmologists are often the first doctors to see these patients. Due to a wide range of ocular features, patients with thyroid-associated ophthalmopathy may be seen by more than one ophthalmic sub-specialist. Neuro-ophthalmologists are often involved in the management of patients with thyroid-associated ophthalmopathy since diplopia is one of its common and debilitating symptoms. Moreover, visual loss due to dysthyroid optic neuropathy is a potentially irreversible sight-threatening complication if treatment is delayed. This article focuses on the management of patients with thyroid-associated ophthalmopathy with diplopia or dysthyroid optic neuropathy, from a neuro-ophthalmologist's perspective. Practical issues and pitfalls in the management of these patients are elucidated.

*Key words:* Diplopia; Graves ophthalmopathy; Optic nerve diseases

## Introduction

Thyroid-associated ophthalmopathy (TAO), also known as Graves' ophthalmopathy / orbitopathy or thyroid eye disease, is an autoimmune process, which is the commonest and most important extra-thyroidal manifestation of Graves' disease.<sup>1,2</sup> Less commonly, TAO may be associated with hypothyroidism in Hashimoto's thyroiditis, euthyroid state

in ophthalmic Graves' disease, thyroid carcinoma, or neck irradiation.<sup>1</sup> It has been estimated that about 20 to 25% of patients with Graves' disease have clinically evident TAO at the time systemic hyperthyroidism is diagnosed and up to 25 to 50% have TAO during the course of their disease.<sup>1,3</sup>

The diagnosis of TAO may precede, coincide or follow the clinical manifestations of the dysthyroid state. About 20% of the patients with TAO are euthyroid at the time of presentation. Among the latter, 25% manifest dysthyroidism within the first year, 50% within the first 2 years, and possibly up to 80% manifest thyroid hormone disturbances during the disease course. Hence, ophthalmologists are often the first doctors to see these patients.

The detailed pathophysiology of TAO is beyond the scope of this article. In brief, it is part of an autoimmune inflammatory disease affecting the orbital tissue, thyroid gland and skin. Existence of at least 2 well-defined thyroidal antigens, namely thyroid-stimulating hormone-receptor (TSH-R) and thyroglobulin, which are present in orbital tissue may help explain why periocular tissue is a site of predilection.<sup>3</sup> Subsequent activation of T-lymphocytes and orbital fibroblasts, with release of cytokines and production of mucopolysaccharides, results in inflammation, edema, orbital volume expansion and fibrosis that are its characteristic features. Autoimmune thyroid disease can also be associated with other autoimmune diseases, including pernicious anemia, vitiligo, type 1 diabetes mellitus, autoimmune adrenal insufficiency, systemic sclerosis, myasthenia gravis (MG), Sjögren syndrome, rheumatoid arthritis, and systemic lupus erythematosus.<sup>4</sup>

Symptoms and signs of TAO differ depending on the stage

of the disease. Traditionally, it was arbitrarily divided into the acute inflammatory phase and subsequent chronic fibrotic phase (with some degree of overlap), which was elucidated by the Rundle's curve. In the acute stage, inflammatory signs dominate and include conjunctival and eyelid injection, chemosis, swollen caruncle, proptosis and eyelid swelling. When the inflammatory process is burnt out, the chronic fibrotic phase ensues. In this phase there can be ocular motility restrictions, lid retraction and residual proptosis, which may dominate the clinical picture. Sight-threatening complications occur in 3 to 5% of the patients, which may result from dysthyroid optic neuropathy (DON), corneal complications due to exposure keratopathy or lid abnormality (e.g. acquired epiblepharon), glaucoma, or choroidal folds.<sup>5</sup>

Owing to such wide-ranging presentations, patients with TAO may be seen by more than one ophthalmic subspecialist. Commonly that might be an oculoplastic specialist, a neuro-ophthalmologist, a strabismologist, and less commonly, a corneal specialist or glaucomatologist. Neuro-ophthalmologists are often involved in the management of patients with TAO, since diplopia is one of its common and debilitating symptoms and visual loss due to DON is a potentially irreversible sight-threatening complication if treatment is delayed.

In this article, we focus on the management of TAO from a neuro-ophthalmologist's perspective, with an emphasis on patients presenting with diplopia or visual loss (with or without a prior diagnosis of Graves' disease).

## General management

TAO poses a significant clinical and therapeutic challenge to both the patient and doctor.<sup>6</sup> Optimal management requires a multidisciplinary team approach, including endocrinologists, ophthalmologists, surgeons and radiation oncologists.<sup>7,8</sup> Despite knowledge about the importance of such an approach, a survey on physicians treating TAO reported widespread suboptimal management.<sup>9</sup> A quality-of-life study on TAO patients also showed low scores in the categories of physical functioning, social functioning, mental health, health perceptions and bodily pain.<sup>10</sup> These findings indicate a pressing need to facilitate collaboration among different healthcare providers, enhance the training of clinicians, and undertake more research on TAO.

Evidently, severe TAO is associated with older age at presentation, male gender, smoking, and suboptimal control of thyroid function. Regrettably, the first 2 factors cannot be altered. The latter 2 are potentially modifiable and every effort should be made to do so.

### Smoking

Smoking has been shown to have a strong and consistent association with TAO.<sup>6</sup> Studies have suggested that smoking is associated with more severe TAO,<sup>11-14</sup> probability of developing TAO (with a dose-response relationship),<sup>15</sup>

increased likelihood of progression of TAO after radioactive iodine (RAI) treatment,<sup>6,16</sup> and delay or worsen the outcome of TAO after treatment.<sup>6,17</sup> More important still, evidence suggests that smoking cessation is associated with an improved TAO outcome.<sup>6</sup> Hence, all patients with TAO should be advised to stop smoking, and referral to professionals in local smoking cessation programs may help to increase success rates. In fact, all patients should be advised to stop smoking even without TAO!

### Thyroid function control — drugs, surgery and radioactive iodine

Although optimization of thyroid function does not abort the course of TAO, studies have shown that suboptimal control resulting in hyper- or hypo-thyroidism is associated with more severe TAO than in well-controlled euthyroid patients.<sup>18,19</sup> Hence, close collaboration with the endocrinologist is essential to minimize undue TAO progression. Modalities commonly used for controlling thyroid function include anti-thyroid drug treatment (e.g. carbimazole, propylthiouracil), surgical thyroidectomy and RAI. Anti-thyroid drugs and surgical thyroidectomy have no other influence on the course of ophthalmopathy.<sup>6,20</sup> RAI, however, is associated with increased risk of exacerbations, especially in high-risk patients with pre-existing ophthalmopathy.<sup>6,20</sup> In one series, about 15% of patients receiving RAI developed new or more marked exacerbations of pre-existing ophthalmopathy within 6 months, and in 5% the deterioration persisted at 1 year.<sup>16</sup> Such risks can almost be eliminated by a course of steroids and avoiding post-treatment hypothyroidism.<sup>16</sup> However, there is currently no consensus on the steroid regimen use with respect to when it should be initiated, its duration, and the necessary cumulative dosage.<sup>21</sup> The European Group on Graves' Orbitopathy (EUGOGO) suggests using prednisolone 0.3 to 0.5 mg/kg/day orally 1 to 3 days after RAI and then tapering the dosage until withdrawal at about 3 months.<sup>6</sup>

### Visual loss

Several mechanisms may result in visual loss in patients with TAO. They include DON, corneal complications related to significant lagophthalmos or acquired lid abnormalities, glaucoma, choroidal folds, and rarely, globe subluxation.<sup>6</sup> Patients with DON are often referred to neuro-ophthalmologists. Alternatively, they may be referred to a neuro-ophthalmologist for unexplained visual loss (with or without a diagnosis of TAO).

### Dysthyroid optic neuropathy

DON is generally believed to occur in the context of apical crowding with compression of optic nerve at the orbital apex due to pathologically enlarged, non-pliable extraocular muscles (EOM), which can be visualised by computed tomography (CT) or magnetic resonance imaging (MRI).<sup>22</sup> In a minority of affected patients however, orbital imaging only shows increased fat compartment volumes, normal EOM volumes and straightened optic nerves without evidence of direct optic nerve compression.<sup>23</sup> In these patients, it is

believed that both expansion of orbital soft tissue volume within the fixed bony boundaries and fibrosis of tissue (especially EOM and intermuscular septae) limit anterior displacement of the globe and result in an elevation of orbital pressure.<sup>23</sup> The elevated orbital pressure and stretching of the optic nerve possibly cause the DON, which mostly occurs during the active phase of TAO.

Sight-threatening DON requires early recognition and prompt medical attention. Treatment involves high-dose systemic corticosteroids, surgical decompression or both. Radiotherapy alone is not recommended, unless it is used as an adjuvant in other proven therapies.<sup>6</sup>

Corticosteroids have been shown to be effective in the treatment of DON. Various routes of administration have been studied. Intravenous high-dose corticosteroids given in pulses are more efficacious and associated with less adverse effects than oral and retrobulbar steroid administration.<sup>6,8,24</sup> Intravenous pulses improve optic nerve function, which can be expected within 1 to 2 weeks of initiating treatment.<sup>25</sup> Relapses are quite common, however, especially if systemic dosing is tapered too rapidly.<sup>6</sup>

Surgical decompression is an effective means for treating DON; the response is rapid and improved optic nerve function can be expected within days of surgery. Traditionally, decompression of the medial orbital wall (with or without other walls) is the method of choice for relieving the optic nerve compression. Recent case series suggest that lateral wall decompression alone or orbital decompression by fat removal may also be useful in selected cases.<sup>23</sup> However, some surgeons avoid removing fat during the active phase of TAO, based on the theoretical risk of exacerbating the inflammatory response. Evidence suggests that immediate orbital decompression surgery as the first treatment for DON is not associated with outcomes that are superior to pulsed intravenous steroids, nor does it reduce recourse to the subsequent use of steroids.<sup>26</sup>

There is currently no well-defined protocol on the treatment of DON in terms of dosage and duration of corticosteroid use, protocol for monitoring side-effects, optimal timing for surgical intervention, and the mode of decompression.<sup>6,8</sup> One of the more popular approaches which we adopted is to promptly initiate high-dose intravenous pulse methylprednisolone (1 g/day) for 3 days, then switch to oral prednisolone (1 mg/kg/day) and then slowly taper the dosage. Once steroid therapy is initiated, early surgical bony decompression (including the medial wall) is undertaken to avoid relapses that are not uncommon during the tapering of steroids. Input from endocrinologists is valuable so as to optimize the systemic treatment of hyperthyroidism before surgery.

Occasionally, patients with DON without known autoimmune thyroid disorder may be referred to a neuro-ophthalmologist for workup of unexplained visual loss, for which a carefully taken history and physical examination are

essential for identification of Graves' disease. In fact, most such patients will have clinical signs including: lid retraction, conjunctival injection, chemosis, lid puffiness and proptosis (usually not severe in patients with DON). Blood testing for TSH, free thyroxine, anti-thyroglobulin antibodies, anti-microsomal or anti-thyroid peroxidase antibodies, and anti-TSH-R antibodies (by the commercially available thyrotropin binding inhibitory immunoglobulin assay [TBII] or thyroid-stimulating immunoglobulin [TSI] bioassay) may be helpful, especially in situations where clinical signs are not obvious.<sup>3</sup> The prevalence of these antibodies in euthyroid and hypothyroid individuals with TAO has been shown to exceed 90%.<sup>27,28</sup> Moreover, TSI positivity has been shown to be a predictor of TAO.<sup>3</sup> Other investigations include CT or MRI of the orbit showing enlarged EOM with sparing of tendons, expansion of fat compartment volume and apical crowding of the orbit all suggest TAO-associated optic neuropathy. In some centers with availability of skilled ultrasonographers, scanning of the orbit may allow subtle enlargement of EOM to be identified.<sup>29</sup>

## Diplopia

Restricted extraocular motility causing diplopia is a common and troublesome symptom in patients with TAO and can occur in its active and fibrotic phases. Neuro-ophthalmologists are commonly being referred for such complaints, with or without any prior diagnosis of a systemic thyroid disorder. In these patients too, a thorough history and physical examination may provide hints to the diagnosis.

Most common EOM involved in TAO are the inferior and medial recti, causing patients to have vertical, horizontal or oblique binocular diplopia, depending on the muscles involved. Apart from the classical clinical features of TAO, there may be hypotropia and esotropia with restricted upward gaze on the affected side. Intraocular pressure may be elevated when measured in the restricted gaze direction. The forced duction test may also be useful in confirming the restrictive extraocular motility defect.

Patients with TAO or systemic thyroid disease may occasionally present with binocular diplopia due to other causes, including co-existing MG, which is yet another associated autoimmune disorder. Further workup with ice test (for ptosis), neostigmine test (for diplopia) and serology for anti-acetylcholine receptor antibodies may be necessary to exclude MG. Diagnosis of MG is essential, since treatment with cholinesterase inhibitor (e.g. physostigmine) or steroids may alleviate the symptoms and more importantly, to exclude the possibility of associated thymoma, which may be malignant in nature in some cases. Hence, patients suspected to have TAO-associated diplopia should be carefully examined and the cause of their complaint must not be 'taken for granted'. Further workup is prudent in the presence of atypical features.

Management depends on whether the patient has active inflammatory or quiescent fibrotic phase of the disease. It

is thus essential to grade TAO disease activity, for which Mourits et al<sup>30</sup> developed a widely used clinical activity score (CAS) based on 10 items. The score has been helpful for predicting the outcome of immunosuppressive treatment in patients with TAO.<sup>30</sup> A modified version was adopted by the EUGOGO (Table 1) using 7 items, in which a CAS of  $\geq 3/7$  signified active disease.<sup>6</sup>

**Active phase**

Presence of diplopia usually signifies moderate-to-severe TAO (Table 2). For patients with active (CAS of  $\geq 3/7$ ) and moderate-to-severe TAO, immunosuppression is usually warranted. A large systematic review and meta-analysis concluded that intravenous pulse corticosteroids were significantly better at reducing the CAS and were associated with fewer adverse events than oral steroids.<sup>6,8</sup> However, there was no difference between the groups in terms of proptosis, diplopia, lid aperture, and visual acuity.<sup>8</sup> Orbital radiotherapy had no advantage over sham radiotherapy for influencing the CAS, proptosis, and lid aperture, though it was superior for controlling diplopia.<sup>8</sup> Combination of corticosteroids (intravenous or oral) and orbital radiotherapy was associated with significantly better treatment outcome scores than either treatment alone.<sup>8,31</sup> Other treatment modalities including somatostatin analogues, azathioprine, cyclosporine, intravenous immunoglobulin and colchicine were of only marginal benefit, or the sample sizes were too small to draw definite conclusions.<sup>6,8</sup> New treatments (e.g. rituximab, etanercept) are being evaluated and no randomized controlled trial has been performed to date. Acupuncture was shown to have no benefit in patients with TAO.<sup>32</sup> The consensus statement of the EUGOGO on the management of TAO suggests intravenous corticosteroids as

the first-line treatment for patients with active moderate-to-severe disease.<sup>6</sup> Orbital radiotherapy could be considered if pulse steroid therapy is contraindicated, and patients do not have evidence of diabetic retinopathy, severe hypertension (considered as absolute contraindications for orbital radiotherapy) or diabetes mellitus (relative contraindications for orbital radiotherapy).<sup>6</sup>

The regimen of intravenous pulse corticosteroids used varies in different centers.<sup>6,8</sup> We currently use intravenous methylprednisolone 500 mg/day for 3 days, switching to oral prednisolone (1 mg/kg/day) thereafter and slowly taper the dosage (over 2-3 months). Notably, the total cumulative dose of methylprednisolone in one course of therapy should not exceed 8 g (due to risk of hepatic failure).<sup>6</sup>

Symptomatic control of diplopia includes the use of prisms or eye occluders. Patients should be warned about the risks of machinery, driving and working at heights.

**Fibrotic phase**

Management of diplopia in the fibrotic phase mainly involves strabismus surgery. This is an effective means of correcting TAO-associated diplopia.<sup>6</sup> Such rehabilitative surgery yields best results when the TAO is inactive.<sup>6</sup> It is beyond the scope of this article to discuss the different methods of eye muscle surgery in treating TAO. Before considering strabismus surgery, patients should (a) have no signs of orbital inflammation, (b) be euthyroid without the need for anti-thyroid drugs, (c) have proptosis (if present) being corrected by surgical decompression, and (d) be stable in terms of ocular motility for at least 3 to 6 months. Correction of strabismus should be undertaken before lid lengthening procedures or blepharoplasty.<sup>6</sup> In unfit patients or those not suitable for strabismus surgery, prisms or eye occluders may provide symptomatic relief.

**Conclusion**

Management of TAO remains a challenge for patients and clinicians. There is much to be explored about its pathogenesis and optimal management of this functionally, psychologically and socially debilitating disease. Affected patients require a holistic multidisciplinary team approach for optimal management. Good communications between patients and their healthcare providers are essential for optimizing treatment outcomes.

**Table 1. Seven-item clinical activity score (CAS)<sup>6,30</sup>; a score of  $\geq 3/7$  indicates active disease.**

Activity measures based on features of inflammation
Spontaneous retrobulbar pain
Pain on attempted up or down gaze
Redness of the eyelids
Redness of the conjunctiva
Swelling of the eyelids
Swollen caruncle and / or plica
Chemosis

**Table 2. Severity grading of thyroid-associated ophthalmopathy (TAO) [adopted from the consensus statement of EUGOGO<sup>6</sup>].**

Severity of TAO	Description
Sight-threatening	Dysthyroid optic neuropathy and / or corneal breakdown. Require immediate intervention.
Moderate-to-severe	Absence of sight-threatening Graves' ophthalmopathy but sufficiently severe to have impact on daily life justifying the risks of immunosuppression (if active) or surgical intervention (if inactive). Usually have any one or more of the following: Lid retraction $\geq 2$ mm, moderate or severe soft tissue involvement, proptosis $\geq 3$ mm above normal for race and gender, inconstant or constant diplopia.
Mild	Features of Graves' ophthalmopathy have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment.

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