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Update on Thyroid Eye Disease

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ABSTRACT

Thyroid-related ophthalmopathy or Graves' ophthalmopathy is the most common orbital pathology occurring in the general population. It is a self-limiting condition with approximately 5% to 7% of patients developing a severe form of the orbital disease. The primary eye care optometrist is well qualified to treat the ocular signs and symptomatology of thyroid-related ophthalmopathy. Additionally, optometrists are well qualified to monitor patients for compressive optic neuropathy during the active disease state. This update should aid the practitioner in his or her delivery of primary eye care to patients.

INTRODUCTION

Thyroid-related ophthalmopathy (TRO), also known as Graves' ophthalmopathy, is an autoimmune disorder of the orbit that primarily affects the extraocular muscles. It commonly affects women about six times more frequently than men.¹ Interestingly, optic neuropathy, soft tissue involvement, and ocular motility impairment occur more frequently in men and in individuals over the age of 50.¹ Recent studies implicate cigarette smoking as a major risk factor for the development of TRO.² The disease typically occurs in association with Graves' disease and hyperthyroidism, but it can also occur in patients with Hashimoto's thyroiditis and hypothyroidism.

It is important to recognize that Graves' disease is self limiting and usually quiescent within three years after diagnosis and treatment.³ Therefore, unless there is an immediate threat to vision, surgical intervention should be avoided until the active phase of the disease subsides. Medical and topical therapies and radiotherapy are useful treatment modalities for patients in the active phase of the disease.

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This article will review some current concepts in the diagnosis, treatment, and management of TRO for the eye care practitioner.

ETIOLOGY OF GRAVES' DISEASE

Graves' disease is an autoimmune disease that appears to be mediated by both humoral and cell-mediated immunity although the cause and precise immunopathy are still unknown.⁴ Thyroid gland stimulation is caused by the circulation of abnormal thyroid-stimulating immunoglobulins (TSI).⁵ Several factors have been implicated as possible inciting causes; including stress,⁶ abnormal immune reaction, human lymphocyte antigen predisposition,⁷ and bacterial infections with certain gram negative organisms such as *Yersinia*.⁸

When the systemic immune response is triggered, the abnormal circulating TSI reacts with the extraocular muscles and orbital fibroblasts. This initiates the histological and inflammatory response in the orbit. Receptor antibodies may stimulate the development of intracellular matrix proteins (glycosaminoglycans) in orbital fat and eye muscles.⁹ One of the most interesting findings on histology are the presence of inflammatory cells and increased deposition of extracellular matrix molecules between muscle fibers.^{10,11} These extracellular matrix molecules are secreted by orbital fibroblasts that proliferate in the response to the presence of lymphocytes. These orbital fibroblasts are very hydrophilic and their ability to attract water may contribute to the tissue edema that is present in the orbits of patients with thyroid-related orbitopathy.¹⁰

DIAGNOSIS OF GRAVES' DISEASE

Hyperthyroid patients can present with an array of systemic symptoms. Common complaints include weight loss with good appetite, intolerance to heat, resting tremors of the small muscles such as the hands, fine silky hair texture, fatigue, and palpitations. Personal history might include agitation with co-workers or family members, inability to sleep through the night, and infertility during the childbearing years.

One must keep in mind that the ophthalmopathy may precede, coincide with, or develop after the systemic

Table I A suggested sequence of clinical laboratory tests that might be helpful in the diagnosis of hyperthyroidism*		
Test Sequence	Laboratory Test	Diagnostic Information
1	TSH levels	TSH level
2	Free T ₄	Estimates free unbound thyroid hormone
3	TSI	Detects the levels of antibodies directed against the thyroid gland

* Note that most patients can be diagnosed via sequence 1 and 2 alone. Sequence 3, determination of thyroid-stimulating immunoglobulin (TSI), is usually reserved for thyroid patients who have normal serum levels of thyroid-stimulating hormone (TSH), thyroxine (T₄), and triiodothyronine (T₃), yet who may still show orbital signs of thyroid-related ophthalmopathy (TRO).

diagnosis of hyperthyroidism.¹² The most useful laboratory test in making the diagnosis of hyperthyroidism is a measurement of the thyroid-stimulating hormone (TSH) level. Current laboratory techniques are very sensitive and rapid, allowing even low levels of TSH to be detected in serum of patients with thyroid dysfunction. Determinations of serum levels of a total or free thyroxine (T₄) is usually done in conjunction with determination of the TSH level (Table I). These tests can be very helpful if the ophthalmopathy precedes the onset of systemic signs of the disease. Other tests such as T₄ binding capacity, antichromosomal antibodies, thyrotropin release hormone stimulation, and TSI may be indicated in cases where the screening tests are normal, but the clinician has a high suspicion for thyroid disease in his or her patient.

Subclinical hyperthyroidism or euthyroidism reflects a condition in which the clinical features of thyrotoxicosis are apparent, the thyrotrophs usually respond to minor increments in thyroid hormone concentrations, which remain within the normal range, by switching off the production and secretion of thyrotropin.¹³ An absence of symptoms was once part of the definition of subclinical hyperthyroidism, but we now understand that subtle symptoms or signs of thyrotoxicosis may be present.

In the absence of clinical signs or symptoms of thyroid disease and equivocal laboratory results, thyroid-function tests should be repeated after 8 weeks.

Diagnosis of Orbital Involvement

Orbital involvement from Graves' disease is very common.¹⁴ The most common orbital disorder that an eye care practitioner may encounter is Graves' orbitopathy.¹⁵ In fact, thyroid associated ophthalmopathy comprises 32% to 47% of all orbital disorders.¹⁵ Suspect patients should have a physical examination of the thyroid gland, which is located in the base of the neck. This simple and very useful diagnostic procedure can easily be accomplished in the office. Instruct the patient to sit in the exam chair and

extend his or her neck slightly outwards. Standing behind the patient and using both hands, position two fingers of each hand on the sides of the trachea just beneath the cricoid cartilage. Request the patient to swallow. This allows the examiner to feel the isthmus of the gland. To palpate the main body of the thyroid, move the fingers of your left hand between the trachea and right sternocleidomastoid muscle, while placing the fingers of your right hand behind the right sternocleidomastoid muscle. Slightly displace the trachea to the left and request the patient to swallow again, allowing the main body of the right lobe of the thyroid to slide under your fingertips. The normal thyroid should feel smooth and not be tender. Thyroid glands that are inflamed feel coarse and are tender to the touch.

Testing of orbital involvement secondary to Graves' disease starts with practical in-office observations of some early clinical signs. Objective signs might include an increase in the vertical palpebral fissure width, lid retraction with associated lid lag,¹⁶ diplopia on upgaze, engorgement of the conjunctival vasculature in front of the recti muscles, asymmetry of exophthalmometry readings, increase of intraocular pressure upon upgaze of 10°, choroidal folds evident with a dilated fundus examination, disc edema evident on extended ophthalmoscopy, and visual field defects within the central 30°. Further investigation might include orbital imaging and orbital ultrasonography.

Orbital imaging. Orbital imaging might include a computed tomography (CT) series or magnetic resonance imaging (MRI). A CT scan is the most useful and important radiologic test for patients with Graves' orbitopathy.^{12,14-17} It gives superb anatomical detail with especially good views of the orbital apex. High resolution axial and coronal scans should be obtained for patients in whom this disease is suspected. Images from high-resolution CT scans are far superior to plain X ray films for excluding retrobulbar tumors as a cause of unilateral proptosis. Additionally, the majority of patients with Graves' disease who lack overt clinical evidence of orbitopathy do, in fact, have demonstrable abnormalities of the extraocular muscles when examined with imaging series.¹⁸

The most characteristic change seen¹⁸ in TRO is the enlargement of multiple extraocular muscles with a sparing of the muscle tendons.¹⁹ Involvement of the tendons might suggest an overall inflammatory disorder such as orbital pseudotumor.²⁰ The extraocular muscles most susceptible to involvement from TRO are the inferior and medial recti.²¹ Optic nerve compression can also be seen with CT imaging. The compression of the optic nerve is caused by extraocular muscle swelling at the orbital apex.¹⁹ A grading scale was devised to assess the degree of optic nerve crowding resulting from

Table II N.O.S.P.E.C.S. classification of TRO*	
Class	Ocular Signs
0 N	No signs or symptoms
1 O	Only signs (i.e., lid retraction, lid lag)
2 S	Soft tissue involvement with signs/symptoms (i.e., lid edema, conjunctival chemosis, superior limbic keratoconjunctivitis, vessel injection over the horizontal recti muscles)
3 P	Proptosis (usually greater than 23 mm)
4 E	Extraocular muscle involvement (most commonly inferior rectus, medial rectus)
5 C	Corneal involvement (secondary to exposure keratopathy)
6 S	Sight loss (secondary to compressive optic neuropathy from swelling at muscles at orbital apex)

* The classification is easy to remember, but does not specify activity of disease and potential of patients being in multiple classes.

enlargement of the extraocular muscles at the orbital apex.^{21,22} Grade 0 reflects no effacement of perineural fat planes by enlarged extraocular muscles, whereas grade 4 reflects a 75% or greater effacement.²² The clinician should always suspect optic nerve involvement from TRO if the patient demonstrates loss of visual acuity, visual field, or color vision in one or both eyes.

The advantages of MRI over CT scanning for initial diagnosis of the ophthalmopathy are not that significant. Several studies²³ have shown that MRI can help differentiate patients with acute inflammatory disease who respond to corticosteroids, radiotherapy, or immunosuppressive therapy, from patients with chronic fibrosis of the extraocular muscles. The use of short-term inversion recovery (STIR) pulse sequences appears to be preferable in this regard.²⁴ This is due to the fact that the increased water content in the muscle is greater when it comes from inflammation versus fibrosis visible in T₂ weighted images.

Orbital ultrasonography. Ultrasonography offers a diagnostic and cost-effective evaluation of the orbit. Standard A-scan ultrasonography allows quantitative estimation of the extraocular muscles and optic nerve widths.²⁵ The acoustic hallmark of the A-scan ultrasonography is the increased heterogeneity and reflectivity of the thickened muscles.^{25,26} Other A-scan findings that are encountered in TRO are thickening of the optic nerve sheath, periorbital edema, and enlargement of the lacrimal gland.²⁷ Results of the ultrasonography can vary depending on the skill of the ultrasonographer. Therefore, if the results are equivocal, a CT scan should be considered.

OCULAR AND ORBITAL COMPLICATIONS OF TRO

During the active phase of TRO, the globe and orbital structures are susceptible to inflammatory and immunological attack, resulting in secondary subjective and



Fig. 1 Graves' patient with lower lid retraction, mild periorbital edema, and bilateral exophthalmos (arrows delineate the lower lid retraction).

objective ocular complications. The ocular structures of most concern to the practitioner are exposure and decreased wetting of the cornea, restriction and inflammation of the extraocular muscles, and finally, the inflammation and compression of the optic nerve secondary to a constricted orbital apex.

The most common classification system used to describe the ocular complications from Graves' disease is N.O.S.P.E.C.S. (Table II). This classification system suffers from several flaws. First, patients do not move systematically from class to class and, second, patients may be in several classes at one time. The system also fails to distinguish if a patient is in an active or inactive phase of the disease. There are other classification systems^{26,27} that can be used to describe the ocular changes from Graves' disease, but the ease and recall of N.O.S.P.E.C.S. maintains its popularity among practitioners.

Various clinical studies have shown that approximately 10% to 70% of Graves' patients have abnormal clinical eye findings at the time of systemic diagnosis.²⁸ The combination of bilateral exophthalmos, lid retraction, stare, and an enlarged thyroid gland are virtually pathognomonic for TRO (Fig. 1). Some other ocular signs specific for TRO include proptosis, lid lag, proptosis with associated restrictive myopathy, engorged blood vessels over the insertion of the medial or lateral recti muscles, conjunctival edema, and periorbital edema.

Restrictive myopathy of the inferior recti results in a tethering affect upon the globe restricting upgaze and resulting in a diplopic response. Increased intraocular pressure that occurs from muscle restriction during attempted superior gaze of 10° or more is sometimes referred to as Braley's sign.

Proptosis is almost always associated with other ocular and/or systemic signs of thyroid disease. It is rarely

Table III Differential diagnosis of TRO

- Ocular myasthenia
- Orbital tumors (primary/metastatic)
- Orbital inflammations (i.e., pseudotumor)
- Orbital infections (cellulitis)
- Arteriovenous fistula
- Axial myopia
- Anterior staphyloma

an isolated sign of TRO. If the only presenting sign or complaint is proptosis, other causes of orbital disease should be considered and ruled out (Table III).

As the proptosis worsens, adequate lid closure is no longer possible, which results in corneal exposure. Infectious keratitis is more common as the proptosis worsens. If the clinician encounters a Graves' patient with symptomatic central corneal staining, an aggressive topical treatment plan should be initiated.

Finally, optic neuropathy occurs in approximately 5% to 10% of patients with Graves' disease.²⁹ The most common presenting complaint is an insidious onset of either visual acuity loss or a visual field defect.³⁰ Common visual field defects that one may encounter from thyroid optic neuropathy are central scotomas, arcuate or altitudinal defects, paracentral scotomas, and generalized depression.^{31,32}

MEDICAL MANAGEMENT OF TRO

The main goals for treatment of TRO include relief of ocular discomfort, elimination of diplopia, and the protection and restoration of visual function. Treatment should be tied not only to the presenting signs and symptoms but to the active or quiescent phase of the disease as well.

Patients in the active stage of the disease respond best to immunological and inflammatory suppression. This is accomplished via administration of steroids or immunosuppressive agents, and orbital radiotherapy.

Patients with acute orbital inflammation should be considered as candidates for steroid therapy. A short course of high-dose systemic steroids in these cases often results in an improvement in acute symptoms within a matter of days. Any patient with evidence of optic neuropathy should be considered as a candidate for immediate steroid therapy. Studies show that about two-thirds of such patients will respond to steroid therapy, regardless of their age, gender, or severity of eye disease.³² Patients with chronic, stable TRO do not respond as well to steroids as patients who have an acute onset of symptoms.³³ Given the numerous side effects associated with long-term steroid use, it is preferable to limit patients' steroid use to only several months duration. All patients need to be warned about the potential side effects

of long-term steroid therapy. Retrobulbar injections of steroids do show localized effects and reduce the risk of systemic side effects of oral or IV steroid therapy.³²

A number of immunosuppressive agents have been used to treat TRO. These include cyclosporine, cyclophosphamide, methotrexate, and azathioprine.³⁴ Cyclosporine has been used both alone and in conjunction with steroids for the treatment of TRO.³⁵ The drawbacks of all immunosuppressive therapy in TRO are the systemic complications associated with the drugs and its variable and unpredictable effect on the ophthalmopathy.³⁶ It is difficult to compare the relative benefits to patients of treatment with immunosuppressive agents alone, because control studies are lacking.³⁷

Orbital radiotherapy is presently debated as to the overall effectiveness in Graves' orbitopathy. Radiotherapy may be considered in patients who are unable to take steroids, or where adjunct therapy is desired to lower patients' steroid dosage. Radiotherapy is usually applied to the orbit in ten small fractions. This treatment regimen reduces the undesirable effects from radiation to the ocular structures. Improvement is typically seen in 2 weeks, but maximum therapeutic effect does not occur for several months.³⁸ Orbital radiotherapy is contraindicated for patients with concurrent microvascular disease (i.e., diabetes) or for patients receiving chemotherapy.^{39,40}

Ocular Therapies

Ocular treatment of TRO is focused on reducing extracellular fluid in the orbit and in turn reducing exposure of the cornea and ocular adnexa. Elevating the head of the bed at night, taking oral diuretics, and following a low-salt diet may all help reduce extracellular fluid build-up, which is typically worse in the morning.⁴⁰ Clinicians have noted that patients who sleep in the supine position have a reduced fluid build-up in the orbit.⁴¹ Oral prednisone may help reduce periorbital edema, if this drug is given in a short-term duration of 1 to 2 months.

Ocular irritation from lagophthalmos, conjunctival and periorbital edema, and corneal exposure can be treated with non-preserved artificial tears during the day and bland ophthalmic ointment at night. The clinician should consider a topical course of a non-steroidal anti-inflammatory agent (e.g., Acular) for symptomatic relief of ocular irritation. If nocturnal lagophthalmos is a problem, patients may attempt taping their lids at night or adhering the edges of a piece of plastic wrap around the orbital rim with petroleum jelly (to try to create a moisture chamber). Commercially made moisture chambers are also available.

Use of spectacles and tints may also be beneficial for reducing photophobia caused by the periorbital and orbital edema. The diplopia associated with extraocular

muscle involvement from TRO is usually handled with prism correction. Prisms are either press-on (i.e., Fresnel) or ground into the spectacle prescription. If prism correction is not feasible, total occlusion of one eye is effective. This is the least sophisticated method of diplopic resolution, and it excludes the possibility of binocularity. The patch used for occlusion should not be alternately switched between the two eyes, as this causes continuous adaptive problems for the patient. It is best to let the patient choose the eye to be occluded, especially if there is doubt as to which eye needs to be patched.⁴²

Use of botulinum toxin injected into the extraocular muscles has been described in the literature, but this treatment is not used routinely in TRO.⁴³ The main drawbacks to this type of treatment are the variability of effects and possible ptosis.⁴⁴

Clinicians and patients must sometimes be inventive in combining the therapies necessary to reduce ocular complications and to allow the patient to continue normal daily activities. This is most important during the active phase of the disease.

Surgical Intervention

When surgical intervention is indicated, a methodical approach is important to optimize the surgical results. If orbital decompression is indicated due to optic nerve dysfunction or cosmesis, it should be performed before eyelid or extraocular muscle surgeries. This is very important for the clinician to recognize, because orbital decompression may dramatically change the satisfactory results of previous eyelid or extraocular muscle surgeries.

Orbital decompression should be considered for patients with optic neuropathy, visual field loss, visual acuity loss, corneal exposure, or severe exophthalmos, or for patients desiring cosmetic enhancement.⁴⁵ A variety of approaches can be used to decompress the orbit, including anterior ethmoidal, transfrontal, maxillary, and transantral approaches.⁴⁶ The results are maximized if the surgery is performed during the quiescent stage of the disease by an experienced surgeon.⁴⁷ The need for an experienced surgeon is a factor that cannot be overemphasized. Patients who elect to have the surgery can expect a reduction of 5 to 7 mm of proptosis from orbital decompression.⁴⁸ The postoperative complications can be very serious, and the patient should be educated about potential outcomes. The most common complication from orbital decompression surgery is diplopia.⁴⁹

Strabismus surgery for TRO-related diplopia is successful if the deviation has been stable for 6 months or more, and if the TRO is in the quiescent stage. An adjustable suture technique is preferred, because it allows for fine-tuning of the final result. These fine-tuning adjustments can be performed during surgery, or on the

same day as surgery, or on the following day.⁵⁰ The patient should always be mentally prepared for the continued use of prisms or the possibility of further eye-muscle surgical procedures.

Many patients with eyelid retraction enjoy spontaneous resolution during the course of their disease. In addition, the above-mentioned surgical procedures can also alter eyelid position. Therefore, surgery of the eyelids should be the last in the sequence of surgical procedures for TRO.

CONCLUSION

The complexities of TRO remain challenging for the clinician. Medical and local therapies provide transient relief for the ophthalmopathy. In the quiescent stage, surgical procedures may reduce the secondary complications of the disease.

Perhaps in time, clinicians will be able to predict who will and will not suffer from the ocular complications of this disease. As we understand more about the pathophysiology of Graves' disease, we may be able to prevent many complications of TRO, rather than merely correcting abnormalities that have occurred as a result of the inflammatory process. □

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