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Optic Neuropathy and Diplopia from Thyroid Eye Disease: Update on Pathophysiology and Treatment

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Abstract

Purpose of review—Thyroid eye disease (TED) is a disfiguring disease that can lead to neuro-ophthalmic manifestations including diplopia and optic neuropathy. The aim of this review is to shed light on the diagnosis of thyroid eye disease based on clinical examination findings and diagnostic imaging. We will also discuss gold standard as well as newly emerging therapies for TED.

Recent Findings—We discussed diagnostic criteria for thyroid eye disease and differentiating TED from other causes of binocular diplopia. We also reviewed the pathophysiology and differential diagnoses for dysthyroid optic neuropathy as well as recent developments on controversial etiologies. New imaging techniques are available for evaluation and prognosis of TED comorbidities. Most of the recent developments in thyroid eye disease have been focused on new treatment modalities that have thus far had promising results. We reviewed recently approved and novel potential therapies that are helpful in treating both diplopia and dysthyroid optic neuropathy.

Summary—Thyroid eye disease is a complicated disorder with many clinical manifestations as well as treatment modalities. Our aim of this review was to outline new developments in the diagnosis and management of TED.

Keywords

Thyroid eye disease (TED); Grave's ophthalmopathy (GO); Dysthyroid optic neuropathy (DON); Teprotumumab

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Introduction

Thyroid Eye Disease (TED) also known as Graves' orbitopathy and/or Graves' ophthalmopathy, is a fascinating condition that highlights the importance of basic science, clinical medicine, and multidisciplinary treatment teams. Neurologists need to recognize that this thyroid disorder can present with diplopia and/or an optic neuropathy that may mimic other neurological diseases including myasthenia gravis, idiopathic orbital inflammation, cranial nerve palsies, orbital apex syndrome and carotid cavernous fistulas. This broad differential is especially important when external manifestations of TED are not readily apparent. To start to understand the pathogenesis of TED, one must begin at the cellular level in the orbit. Orbital adipocytes and fibroblasts contain the thyrotropin receptor. Autoantibodies generated against the thyrotropin receptor, characteristic of Graves' disease, can reach these orbital cells leading to activation of an inflammatory cascade mediated by cytokines and ultimately ending in the deposition of glycosaminoglycans in the extraocular muscles (EOM) of the orbit [1]. This inflammation and deposition can lead to expansion of the EOM and subsequent compression of the optic nerve, proptosis of the eye, and exposure of the corneal surface that may ultimately lead to a compromise in visual integrity. About 40% of patients with Graves' disease experience TED, but it should be noted that TED can occur in other autoimmune thyroid conditions where thyroid hormone levels are normal or decreased [2]. In addition to the biologic stress experienced by TED, patients can experience significant distress from changes in cosmetic appearance and facial disfigurement. This is of critical importance, as rates of suicide can be higher in TED patients [2].

TED is characterized by an active, inflammatory phase with a subsequent progressive, fibrotic phase. The active phase typically lasts 6 to 18 months, whereas the fibrotic phase can persist indefinitely. An important tool for monitoring disease severity is the clinical activity score (CAS). The CAS is scored from 0 to 10 and has been shown to predict response to anti-inflammatory therapies [3]. The CAS is composed of the following 7 components:

- Painful feeling behind the globe over last 4 weeks
- Pain with eye movement during last 4 weeks
- Redness of the eyelids
- Redness of the conjunctiva
- Swelling of the eyelids
- Chemosis (edema of the conjunctiva)
- Swollen caruncle (flesh body at medial angle of eye)

Of note, upon completion of the initial CAS, the following components can be incorporated:

- Increase in proptosis >2 mm
- Decreased eye movements >5°
- Decreased visual acuity >1 line on Snellen chart

By using objective clinical parameters, the CAS score has become widely adopted in TED for both clinical research and monitoring disease progression [3].

Diplopia in TED

The double vision that is associated with thyroid eye disease is a restrictive strabismus which results from enlargement of the extraocular muscles causing an exaggeration of the function of involved muscles due to mechanical tethering. This is in contrast to a paralytic strabismus, in which the function of the muscle is deficient resulting from various neuromuscular etiologies, the most common of which are discussed below. It is helpful to remember the mnemonic “IMSLO” for the order in which the extraocular muscles are typically involved in TED – starting with the inferior and medial rectus, then superior rectus, lateral rectus and less frequently the obliques. Due to the restrictive nature, an involvement of the inferior rectus, for example, would cause a hypotropia (depression of the eye) rather than hypertropia (elevation of the eye), which may be expected with a paralytic inferior rectus.

Among some of the more common differential diagnoses are myasthenia gravis, idiopathic orbital inflammation and cranial nerve palsies. Diplopia in TED may be differentiated from myasthenia gravis in that with ocular myasthenia patients the diplopia may be associated with fatigability and ptosis, whereas TED patients will likely have associated eyelid retraction, proptosis, and conjunctival injection to varying degrees. Five percent of myasthenic patients may also have thyroid eye disease, and thus we often evaluate for both with serologic studies when sending patients for initial diplopia workup. TED, especially when asymmetric may be mistaken for idiopathic orbital inflammation (IOI). Imaging studies help to differentiate the two, showing muscle enlargement without tendon involvement in TED and inflammation of all of the orbital contents in IOI. Cranial nerve palsies have characteristic signs and measurements that can be evaluated on clinical examination to assist in the diagnosis – i.e. ptosis and anisocoria in oculomotor nerve palsies, positive Parks Bielschowsky 3 step test in trochlear nerve palsies and esotropia with abducens nerve palsies. Depending on the etiology, cranial neuropathies will often improve with time and should not have the enlargement of extraocular muscles seen on imaging. See Table 1 for additional signs and symptoms that assist with differentiation.

Matsuzawa and colleagues looked specifically at imaging in patients with thyroid eye disease with refractory diplopia and came to an interesting conclusion. The study included 61 thyroid eye disease patients with varying activity and degrees of diplopia and 35 control subjects. When they compared signal intensities of the extraocular muscles on T1 weighted MRI images, they found lower intensities seemed to be correlated with refractory diplopia after intravenous glucocorticoid treatment [4]. While imaging has been common place for diagnosis of TED, this study implicates its utilization also for choosing treatment modalities and prognosis.

Dysthyroid Optic Neuropathy (DON)

There are currently two accepted theories for the mechanism in which TED causes optic neuropathy. The least controversial is a compressive optic neuropathy caused by crowding of the nerve at the orbital apex by enlarged extraocular muscles. In about 5% of DON cases, there does not appear to be significant crowding at the orbital apex, rather there is marked proptosis leading to what has been termed stretch optic neuropathy [1]. Stretch optic neuropathy has been very controversial and a recent study by Rose and Vahdani has negated this as a causative factor for DON. Their study was a retrospective comparative case series including 75 patients with DON and age- and sex-matched controls with TED but without DON. The goal was to compare optic nerve compliance between the two groups, with the hypothesis that there would be reduced compliance in DON patients. They determined optic nerve compliance by examining the relationship of optic nerve limits to the maximum dimensions, looking for a phase in which the optic nerve had reached its elastic limit. While they did conclude that patient's with DON had significantly longer optic nerves, the compliance in both groups was very similar. They concluded that because the compliance is similar in both groups, the stretch is unlikely causing metabolic stress causing the optic neuropathy [5].

The differential diagnosis for dysthyroid optic neuropathy is broad and can include nutritional/toxic (particularly if symmetric involvement), infectious, inflammatory, ischemic, traumatic, paraneoplastic or other compressive etiologies [6]. For the purposes of this article, we will focus on alternative etiologies that can have similar presentations, in particular idiopathic orbital inflammation, orbital apex syndrome, and carotid cavernous fistulas. Idiopathic orbital inflammation as described above can cause diplopia, but may also cause an optic neuritis with disc edema that may or may not be similar to that seen in acute DON. Orbital apex syndrome can present similar to TED with ophthalmoplegia, chemosis, conjunctival injection, and proptosis. However, orbital apex syndrome will also involve the ophthalmic division of the trigeminal nerve and thus the patient may express decreased sensation to the forehead and have a diminished blink reflex that should not be seen in pure TED cases. Carotid Cavernous Fistulas (CCF) also present very commonly to TED with proptosis, chemosis, elevated intraocular pressure and conjunctival injection. A few symptoms that may lead a physician to consider alternative etiologies, in particular CCF, would be pulsatile tinnitus, pulsatile exophthalmos and orbital bruit. The extent of conjunctival injection and presence of corkscrew vessels also point to a possible CCF. Additional neurologic deficits may be seen with CCF that are uncommon with TED including involvement of the ophthalmic and maxillary divisions of the trigeminal nerve causing hypesthesia of the face and absent or diminished corneal reflex, and ipsilateral Horner's syndrome.

With any cause of dysthyroid optic neuropathy, patients may present with acute loss of central vision and dyschromatopsia. A relative afferent pupillary defect (RAPD) can be seen if the disease is asymmetric, though approximately 50% will have no RAPD given the presumed bilateral more or less symmetric involvement. Visual field testing can show paracentral, arcuate or altitudinal defects [1]. A study by Wu et al. showed thinning of the nerve fiber layer, ganglion cell layer and inner plexiform layer as well as the ganglion cell

complexes on optical coherence tomography (OCT) imaging for both DON and non-DON TED patients [7]. This could be a helpful tool to monitor for structural changes prior to functional decline.

Updates in Management

Significant advancements regarding the treatment options for Thyroid Eye Disease reflect the exciting possibility that quality of life for this disease can be dramatically improved. A spectrum exists regarding possible treatment options: early recognition of TED during the active phase of disease should be promptly treated with glucocorticoids or other disease modifying agents whereas moderate to severe inactive TED may need surgical treatment. By treating the active phase of the disease, the patient's quality of life can be improved as orbital remodeling can be reduced. Focusing on inflammation is not enough in TED; there is a need for disease modifying therapy. Rehabilitative surgery options for TED include orbital decompression, strabismus surgery, and periorbital and eyelid functional and cosmetic surgery, often in a staged fashion over an extended period of time [8]. These options should be reserved for patients who have significant altered visual function or quality of life after ocular findings have been stably present [8]. Surgical options, while beneficial, can hopefully be avoided or minimized if TED is treated during its earlier stages.

Early and active TED, without DON, has traditionally initially been managed with steroids. Intravenous methylprednisolone (IVMP) 500mg weekly for 6 weeks and then 250mg weekly for 6 weeks is the current accepted regimen for treatment of moderate to severe and active TED. For those patients with DON, the recommended dose increases to 500–1000mg of IVMP for 3 consecutive days or alternating days in the first week. If the response is not substantial after 2 weeks, urgent decompression may need to be performed [9].

Strianese and Rossi provide an excellent overview of the other nonspecific and specific immunosuppressants that have been used to treat TED. They conclude that azathioprine and cyclosporine can be used as first line therapy in combination with steroids to reduce relapse rates and need for surgery. Methotrexate and mycophenolate can be considered when steroids are ineffective or need to be withdrawn due to adverse effects. Tocilizumab and rituximab have been used in steroid-resistant cases; however, rituximab seems to have mixed results on efficacy. Etanercept and adalimumab have been shown to reduce inflammatory signs. One patient with steroid and decompression resistant DON was successfully treated with infliximab. In patients with severe TED, radiotherapy has been used alone or in combination with steroids with hopes to reduce the need for emergent surgery or to increase effectiveness if surgical intervention is required [10].

Teprotumumab offers exciting possibilities for patients battling TED. Immunomodulatory mechanisms remain under investigation; however, evidence exists that the TSH receptor (TSH-R) and IGF-1 receptor (IGF-1R) both co-localize to the perinuclear, cytoplasmic, and plasma membrane compartments of human orbital fibroblasts [11]. There is evidence that immunoglobulins from patients with Graves' disease can activate the IGF-1R [11]. This relationship between IGF-1R and the TSH-R has led to the development of Teprotumumab, a monoclonal antibody against the IGF-1R. Teprotumumab was shown to reduce IGF-1R

and TSH-R surface display on fibrocytes taken from patients with Grave's Disease [12]. Thus, blocking IGF-1R signaling may attenuate disease pathogenesis in TED.

Work done in 2017 by Smith et. al. demonstrated the effects of teprotumumab in TED. Patients recruited for this study had Graves' disease, a CAS score of 4 or more, and ophthalmopathy diagnosis for no more than 9 months after the onset of symptoms [13]. The primary endpoints for this study were reduction of 2 points or more in CAS and a reduction of 2 mm or more in proptosis in the study eye. Patients were studied over 24 weeks, and teprotumumab (given once every 3 weeks starting with an initial dose of 10 mg/kg followed by 20 mg/kg for remaining infusions) was compared to placebo (normal saline infusions). The results were notable: when compared with placebo, patients receiving teprotumumab had clinically significant reductions in CAS, Graves' ophthalmopathy quality of life scores, proptosis, and subjective diplopia [13]. The amount of proptosis reduction was surprisingly comparable to orbital decompression surgery.

Building upon this, Douglas et. al. has further demonstrated a case for the use of teprotumumab in TED. The OPTIC trial was run across 13 sites in the US and Europe, with patients requiring a diagnosis of Graves' disease, active moderate-to-severe TED, and a CAS of at least 4 [14]. Again, teprotumumab was compared to placebo. The primary endpoint was a proptosis response (defined as reduction in proptosis of >2 mm from baseline in the study eye without a corresponding increase of >2 mm in the fellow eye) at week 24. The OPTIC trial also had important secondary outcomes: A CAS score as low as 0 or 1, diplopia response, and responses in the Graves Quality of Life survey (GQoL). After screening, a total of 42 patients received teprotumumab (vs. 41 in the placebo group), and after 24 weeks 83% in the teprotumumab group had a proptosis response, compared with 10% in the placebo group. The median time to respond was 6.4 weeks. The number needed to treat for the study was 1.36. Diplopia, proptosis, and GQoL scores were all significantly improved in the teprotumumab group compared to placebo. Diplopia response, as measured by the Gorman subjective diplopia score, was seen in 68% of the patients in the Teprotumumab group at 24 weeks whereas the placebo group only saw a 29% diplopia response. Orbital imaging was conducted in six patients getting teprotumumab at one center with all six showing decreased extraocular muscle volume [14].

Limitations in these studies regarding teprotumumab include the lack of more objective orbital imaging studies, restricting patient populations to only the United States and Europe, the lack of patients with TED refractory to steroid use, and the lack of patients with euthyroid or hypothyroid TED. Teprotumumab appeared to be well-tolerated with few adverse reactions [13] [14]. Specifically, mild hyperglycemia was observed in 2 patients, reports of hearing impairments that mostly self-resolved, and weight loss of at least 5 kg. There were no deaths reported, and 2 serious adverse events reported were pneumothorax (determined probably unrelated to the trial drug by an investigator) and an infusion reaction that led to withdrawal [15]. Despite these potential shortcomings, teprotumumab shows considerable promise for patients with moderate to severe TED. Future studies examining teprotumumab in TED should include steroid-resistant populations as well as patients with TED not associated with Grave's disease.

Another therapy in development for TED is RVT-1401, a novel anti-FcRN monoclonal antibody. The neonatal fragment crystallizable receptor (FcRn) was originally identified as responsible for IgG transport from maternal to fetal circulation across the placenta; it also plays a role in the long half-life of IgG by facilitating IgG recycling and preventing its degradation [15] [16]. By inhibiting FcRn, the destruction of IgG is increased via lysosomal degradation [15]. ASCEND-GO 2, a Phase 2a study in TED, is assessing the role of RVT-1401 in TED; specifically, whether or not RVT-1401 can alter disease mechanisms in TED by decreasing pathogenic IgG against the TSH-R [17]. Primary endpoints in ASCEND-GO 1 include percentage change from baseline in total IgG and IgG subclasses (1–4) and percentage change in levels of anti-TSH-R antibodies.

Conclusion

Thyroid eye disease is a disfiguring condition that may be seen by neurologists and neuro-ophthalmologists due to the clinical manifestations of diplopia and vision loss. It is critical to differentiate this disease from alternative causes in order to manage appropriately. There are many new medical therapies available and being studied that could decrease the need for surgical intervention in these patients.

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Key points

1. The diagnosis and assessment of cranial neuropathies is essential to the practice of neurology; any patient presenting with an optic neuropathy or diplopia should be screened for thyroid eye disease as part of an initial evaluation.
2. Binocular diplopia in TED is restrictive caused by enlargement of the extraocular muscles and must be distinguished from alternative etiologies.
3. Dysthyroid optic neuropathy is a sight threatening condition that must be evaluated and treated promptly to avoid permanent vision loss or need for surgical intervention.
4. The early recognition and diagnosis of TED should facilitate treatment in a multidisciplinary center with experience in disease modifying therapies to slow disease progression and ultimately increase the quality of life for these patients.
5. New disease modifying therapies in TED show promise in better controlling the active phase of disease.

Table 1:

Differential Diagnosis for Diplopia in TED patients

Below is a description of the discussed differential diagnoses for TED with corresponding signs and symptoms of each. Of note, (+) in the column would indicate this is a possibility for the disease, but all of the symptoms listed do not have to be present at the same time to make the diagnosis. A (−) indicates less likely with a particular disease.

	Supraduction deficit	Infraduction deficit	Adduction Deficit	Abduction Deficit	Ptosis	Lid Retraction	Decreased Visual Acuity	Chemosis	Conjunctival Injection	Proptosis
Thyroid Eye Disease	+	+	+	+	−	+	+	+	+	+
Myasthenia Gravis	+	+	+	+	+	−	−	−	−	−
Idiopathic Orbital Inflammation	+	+	+	+	+	−	+	+	+	+
Cranial Nerve 3 Palsy	+	+	+	−	+	−	−	−	−	−
Cranial Nerve 4 Palsy	−	+	−	−	−	−	−	−	−	−
Cranial Nerve 6 Palsy	−	−	−	+	−	−	−	−	−	−