Thyroid eye disease and ocular myasthenia gravis

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Purpose of review
An overview of two ocular diseases, which significantly impact quality of life: thyroid eye disease (TED) and ocular myasthenia gravis (OMG). Additionally, we describe the clinical challenge when they occur simultaneously. We will describe the pathophysiology of both conditions, the currently available diagnostic tools, and the therapies available.

Recent findings
Recent literature has described newer diagnostic modalities, predictors of disease severity and co-occurrence of TED and OMG, and novel therapies. There is also critical analysis of current therapeutics and risk factors.

Summary
The findings from this review suggest a need for heightened clinical awareness and early detection strategies for TED and OMG due to their overlapping clinical presentation. Emerging therapies and diagnostic techniques should be integrated into practice. Further research is warranted to explore the long-term safety and efficacy of novel treatments and the potential genetic links between these conditions.

Keywords
diplopia, disease modulation, myasthenia gravis, ocular motility disorder, thyroid eye disease

INTRODUCTION

Thyroid eye disease (TED) and ocular myasthenia gravis (OMG) are two autoimmune conditions with significant clinical overlap. Rennie first described the coexistence of Graves' disease (exophthalmic goiter) and generalized myasthenia gravis (GMG) in 1908 [1]. Autoimmune thyroid disorders, including Graves' disease, hypothyroidism, and thyroiditis, are the conditions most commonly associated with myasthenia gravis [2–4]. Recognizing the co-occurrence of these diseases is crucial to maximize quality of life. This review aims to describe the ocular manifestations, diagnosis, and treatment options of TED and OMG, with a special focus on the co-occurrence of the two diseases.

CLINICAL SIGNS, SYMPTOMS, AND PATHOPHYSIOLOGY

Thyroid eye disease

Thyroid eye disease, also known as Graves' ophthalmopathy or thyroid-associated orbitopathy, is an extrathyroidal manifestation of Graves' disease that can also occur in patients with autoimmune hypothyroidism or in euthyroid patients [5▪▪]. The diagnosis is established based on clinical and radiographic features and can be phenotypically divided into three subtypes: congestive, myopathic, and mixed [6].

Signs of TED include eyelid retraction, periorbital edema, chemosis, conjunctival injection, exophthalmos, lagophthalmos, strabismus, and compressive optic neuropathy. Diplopia may occur due to the infiltration and restriction of extraocular muscles. The Rainbow Brow, associated with brow fat pad hypertrophy may aid in diagnosing TED [7▪]. The disease is most often bilateral and asymmetric but is unilateral in 10% of cases. TED is more common in females, but older men are over-represented in cases of severe ophthalmopathy [6,8]. Disease activity can be monitored with the Clinical Activity Score (CAS) in many cases. However, as North *et al.* [7▪] and Oeverhaus *et al.* [9▪] report, CAS is less helpful in the youngest and oldest patients.

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KEY POINTS

- This study discusses the clinical overlap between thyroid eye disease (TED) and ocular myasthenia gravis (OMG), two autoimmune conditions with distinct features but frequent co-occurrence.
- TED is typically linked to Graves' disease and presents with symptoms like eyelid retraction, exophthalmos, and strabismus, while OMG primarily involves ptosis and diplopia caused by neuromuscular junction dysfunction.
- The co-occurrence of these diseases may be due to shared genetic and immune mechanisms, with significant implications for diagnosis and treatment.
- Modifiable risk factors such as smoking and obstructive sleep apnea may influence disease progression.
- Proper recognition of overlapping symptoms is essential for accurate diagnosis, and treatment strategies should address each condition independently to optimize patient outcomes.

Bartalena *et al*. [5▪▪] authored a comprehensive review of the epidemiology, natural history, and risk factors of TED. The authors summarize the prevalence of TED, the phases of disease and reviewed the endogenous and exogenous risk factors associated with TED. The natural history of TED follows a biphasic course: an initial active phase lasting 12–18 months followed by stabilization or regression of the disease in the quiescent stage [5▪▪,10]. Early diagnosis, control, and management of modifiable risk factors can limit the development of TED and progression to the more severe forms [5▪▪]. Patients may continue to deal with sequelae from the active phase of disease throughout their lifetime. Up to 15% of patients experience reactivation of the disease [11].

The pathophysiology of TED is not fully understood but involves cross-reactivity between orbital and thyroid antigens, resulting in inflammation, adipogenesis, and fibrosis of the extraocular muscles and surrounding orbital adipose. It is hypothesized that T-cells bind to thyroid-stimulating hormone (TSH) receptors on orbital fibroblasts and extraocular muscles, leading to increased orbital fibroblast glycosaminoglycan production and muscle inflammation [6,12]. Anti-TSH receptor antibodies and TSH receptor stimulating immunoglobulin (TSI) are the most common antibodies implicated in TED [13]. TSI levels tend to correlate with disease activity [14–16]. Insulin like growth factor-1 (IGF-1) and inhibition of the IGF-1 receptors have recently come into the limelight as therapeutic targets for TED. IGF-1 receptors are overexpressed in several cell types in TED, including orbital fibroblasts [17]. The exact relationship between IGF-1 and TSHR and the mechanism by which their cross-reactivity promotes disease activity is not fully understood.

OCULAR MYASTHENIA GRAVIS

Myasthenia gravis is a neuromuscular junction disorder characterized by abnormal function of acetylcholine receptors (AChR) at the postsynaptic membrane, most often due to autoantibodies directed against these receptors and less commonly due to autoantibodies directed against proteins affecting AchR function, such as anti-MuSK (muscle-specific kinase) and anti-LRP4 (low-density lipoprotein receptor-related protein 4) antibodies. When the manifestations of myasthenia gravis are limited to ptosis or diplopia, it is categorized as OMG.

Up to 85% of patients present with ocular symptoms [18,19]. Reported rates of lifetime conversion from OMG to GMG range from 23.3 to 80% [19–21]. In one retrospective multicenter study, median time to conversion from OMG to GMG was 20 months in the nonimmunosuppressed group and 24 months in the immunosuppressed group [20]. OMG represents 14–25% of all patients with a diagnosis of myasthenia gravis [3,18,19,22,23]. The overall incidence of OMG is highest in men above the age of 40 [18,22].

Approximately 85% of patients with GMG have highly specific anti-AChR antibodies [24,25]. However, the sensitivity of AchR antibodies is low for OMG [26,27], and frequency of positive AchR antibodies in OMG is lower compared to the frequency in GMG [3,18,22]. Conversion from OMG to GMG is associated with anti-AChR antibody positivity, higher AchR titers, male sex, and later onset of disease [26–29,30▪▪]. Of the AchR-negative patients, 30–50% have anti-MuSK antibodies [24,25]. An additional 2% of patients have anti-LRP4 antibodies [24]. Other antibodies and biomarkers implicated in myasthenia gravis include Anti-Titin, Anti-Kv1.4 (voltage-gated K channel), Anti-Rapsyn, Anticortactin, antiagrin, antiryanodine receptor, and anticollagen Q [24,31,32].

CO-OCCURRENCE OF THYROID EYE DISEASE AND OCULAR MYASTHENIA GRAVIS

The reported prevalence of thyroid disease in GMG ranges from 7 to 18% [33–35], and a reported 40% of patients with OMG may have antithyroid antibodies [3]. Conversely, 0.2% of patients with thyroid disease also have GMG [4]. The prevalence increases

when looking specifically at patients with hyperthyroidism, with one study reporting a rate of 0.99% [36]. Of patients with thyroid disorders who develop TED, 0.7–1.3% will be diagnosed with GMG [37]. Myasthenia gravis associated with autoimmune thyroid disease often has a milder clinical expression, with preferential ocular involvement [2,38,39]. Notably, there are no population studies reporting the prevalence of OMG with TED.

In a retrospective study of patients with AchR antibody-positive OMG, Supawongwattana *et al.* [30▪▪] found that higher AchR antibody titer was associated with thyroid autoimmune antibodies as well as presence of thymoma. Of note, the statistically significant threshold AchR titer values were different for the presence of thyroid autoimmune antibodies and the presence of thymoma.

Several explanations have been advanced for the coexistence of these two diseases, including cross-reactivity of antibodies, defective immune tolerance, and shared genetic predispositions. It is likely that both TED and OMG are mediated by cytotoxic T-cells recognizing another cell membrane antigen as foreign, including the thyroid and eye muscle shared protein G2 s [29]. The cytotoxic T-cells may therefore cross-react, with antithyroid antibodies targeting AChR and AChR antibodies targeting TSH receptors. Both OMG and TED are associated with the HLA gene locus, particularly HLA-DR on MHC II is the main susceptibility gene for autoimmune thyroid disease and is also related to GMG [40,41]. Another genetic predisposition for co-occurrence of TED and GMG is tumor necrosis factor-alpha-863 polymorphism [42]. Finally, both conditions may involve abnormalities of central and peripheral B-cell tolerance. Patients with GMG who have thyroid antibodies have a higher percentage of B-cells compared to those without thyroid antibodies [39]. Patients with GMG are also at higher general risk of developing other autoimmune diseases [43,44].

Both conditions have been reportedly triggered by COVID illness or vaccination [45▪,46▪]. De Giglio *et al.* [45▪] reported a case of simultaneous TED and OMG onset following SARS-CoV-2 infection. In a review of patients with ocular motility disorders diagnosed within 4 weeks of COVID-19 vaccination, Park *et al.* [46▪] reported several cases of OMG and of orbital disease including TED.

DISTINGUISHING FEATURES

Understanding the differences in clinical presentation is requisite to recognizing the co-occurrence of the two diseases. The hallmark features of OMG are variability and fatigability of diplopia and ptosis while TED is characterized by inflammatory signs and symptoms as well as the progression of proptosis and restrictive strabismus. Variability can be established through clinical examination and patient history. A prospective study of patients with OMG by Keene *et al.* [47▪▪] compared orthoptic measurements of patients with OMG with those of healthy controls and disease controls including patients with TED. Orthoptic measurements of drift during persistent gaze on a Hess chart was both specific and sensitive for OMG [47▪▪]. This study offers proof of an inexpensive, noninvasive, and readily available clinical test to differentiate OMG from TED.

Ptosis is very rarely seen in TED and may result from levator palpebrae muscle compression [48]. Alternatively, ptosis may be seen early in the course of TED when periorbital edema predominates, is worse due to relative dependent head position upon rising in the morning, and predates the ultimate development of fibrosis and eyelid retraction. More commonly, patients may present with "pseudoptosis" in the noninvolved eye due to eyelid retraction in the contralateral eye [49]. Patients with either disease report diplopia. TED most commonly produces progressive esotropia and/or hypotropia, whereas exotropia and highly variable ocular alignment is more commonly seen in OMG.

"Rundle's curve" has been used to illustrate the natural history of TED [50–52]. The severity of diplopia in TED and OMG can similarly be plotted on a graph of diplopia severity versus time. Figure 1 illustrates on three curves the different behavior of diplopia associated with TED and OMG and the clinical picture when TED and OMG coexist. TED diplopia worsens typically slowly and steadily over the course of the 1 to 2-year active phase, after which the constancy of the ocular misalignment is a highly reliable indication of disease stability. If there is reported variability in TED diplopia, it is briefly worse upon arising from sleep until maximum fusional amplitudes can be reestablished. Conversely, OMG demonstrates variability throughout the day as well as throughout the disease course in a range, which is generally constant until the disease remits. When the conditions co-occur, there is an overlap in behavior such that there is progression of the magnitude of the ocular deviation over months superimposed over daily diurnal variability.

DIAGNOSTIC APPROACHES

With a subset of overlapping signs and symptoms, diagnosing TED, OMG, and the coexistence of the two conditions can present a diagnostic challenge. Imaging, serology, and clinical testing can aid in diagnosis.

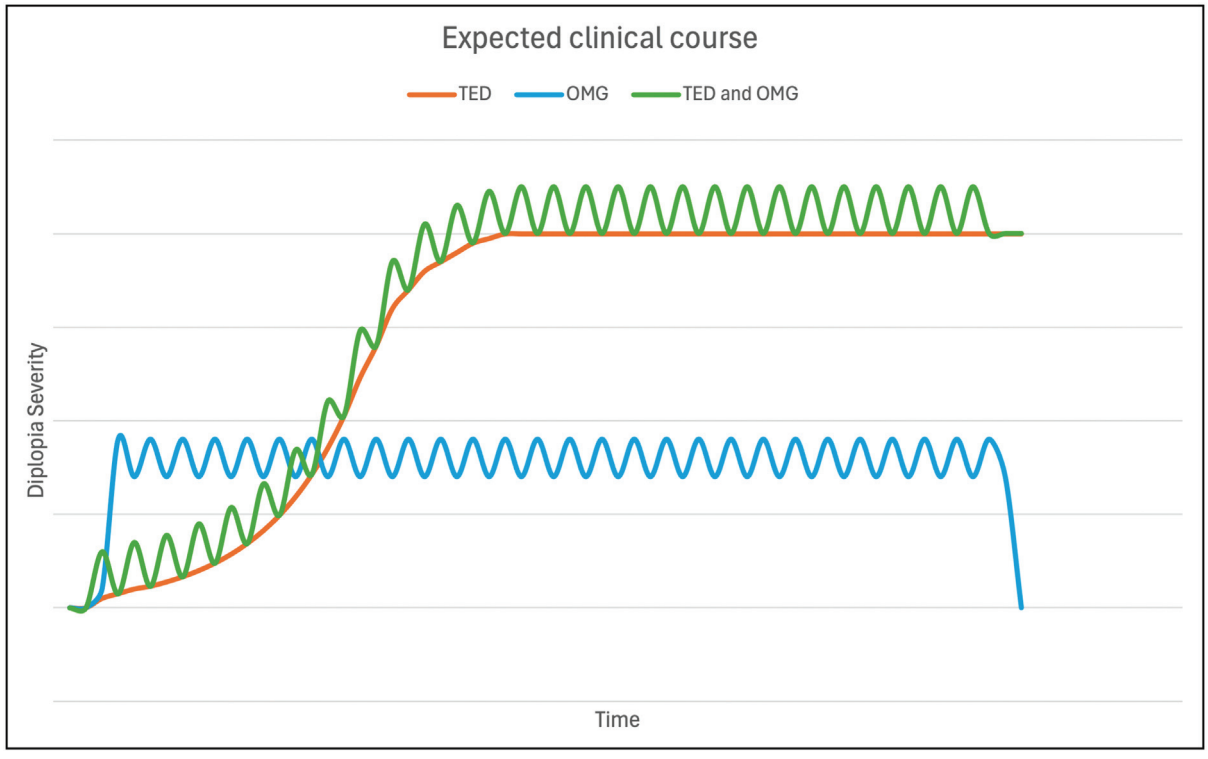

FIGURE 1. Expected clinical course of diplopia severity. The course of concurrent TED and OMG (green) displays variability in severity similar to OMG (blue) while exhibiting an active period followed by stability similar to that seen in isolated TED (orange).

CLINICAL TESTS

Diagnosis of OMG often begins with the ice pack test, where improvement in ptosis or diplopia after application of a cold pack for 2 min suggests OMG. The edrophonium (Tensilon) test results in elevation in eyelids or improvement in diplopia within 2–5 min following its administration, indicating OMG. However, Tensilon can be difficult to obtain. Other easily conducted clinical tests for OMG include the sleep test [53], sustained gaze fatigue [54], quiver eye movements [55], and Peek sign [56].

IMAGING

Imaging techniques used in the diagnosis of TED include orbital computed tomography and MRI, which identify fusiform enlargement of extraocular muscles sparing the tendons and expansion of orbital fat in patients with TED.

SERUM STUDIES

erum studies can be useful in differentiating TED and OMG. Thyroid function tests like TSH, free T4, and T3 levels, as well as thyroid antibodies (e.g. TSH receptor antibodies, TSI) are important diagnostically and for monitoring of thyroid dysfunction but may not correlate with ocular manifestations.

While less sensitive in OMG compared to GMG, testing for AChR or anti-MuSK antibodies can support the diagnosis. It is important to note that the absence of these antibodies does not rule out OMG.

ELECTROPHYSIOLOGY

Repetitive nerve stimulation test or single-fiber electromyography (EMG) can be used to confirm neuromuscular transmission defects. Single-fiber EMG is highly sensitive for OMG, particularly in patients presenting with ptosis [57]. Abnormal orbicularis oculi single-fiber EMG in patients with seronegative OMG has a high predictive value for response to therapy [58].

TREATMENT MODALITIES

Thyroid eye disease

In a recent review of disease management, North *et al.* [59▪▪] advanced a novel classification of TED treatment options distinguishing disease modulators from disease modifiers. The key difference is

that disease modifiers shorten and thereby favorably change the natural history of the disease, whereas modulators suppress the clinical manifestations, which recur when the drug is withdrawn.

Modulators of TED include corticosteroids, tocilizumab, and teprotumumab. Corticosteroids reduce inflammatory signs and symptoms of TED, but long-term use comes with significant side effects [60▪▪,61]. Tocilizumab has been used mainly in steroid nonresistant or relapsing cases. Duarte *et al.* [62▪] conducted a systematic literature review of studies demonstrating the effect of tocilizumab in TED, specifically in reducing inflammatory signs during active TED. Teprotumumab is a human mAb inhibitor of the insulin-like growth factor 1 receptor typically given as an infusion every 3 weeks for a total of eight infusions [63]. It has demonstrated efficacy in reducing CAS, proptosis, and diplopia in moderate-to-severe TED; however, the rates of reactivation approach 50% and there is a 10% rate of permanent neurosensory hearing loss [63–66].

Modifiers, which affect the natural history of TED, include radiotherapy and rituximab. Orbital radiotherapy, typically given over 10 sessions, has shown efficacy in improving pain, motility, and proptosis. Furthermore, radiotherapy can reduce the need for acute-phase decompression surgery and reduce the likelihood of developing compressive optic neuropathy [67–70]. Rituximab is a chimeric monoclonal anti-CD20 antibody, which depletes B-cell populations. Observational studies have shown that rituximab can reduce CAS in active TED and may relieve compressive optic neuropathy [71,72]. In a prospective, randomized controlled trial comparing intravenous methylprednisolone to rituximab in patients with moderate-to-severe TED, patients receiving rituximab did not experience recurrence [73].

Moledina *et al.* [60▪▪] reviewed changes in therapeutic targets for the treatment of TED. Historically, therapies have had broad targets accompanied by significant side effects. Recently, there has been a shift toward a more targeted approach, focusing on the molecular pathway of TED.

Selenium supplementation in European populations, known to be deplete in serum levels, has been shown to have beneficial effects on cases of mild TED [74▪]. Selenium has antioxidant and immunoregulatory actions that can improve the quality of life in mild TED and may prevent progression to moderate or severe TED [60▪▪,74▪]. However, Foos *et al.* [74▪] highlight the limited data demonstrating a role for selenium in TED outside of a 6-month course of supplementation or in a Selenium replete population.

OCULAR MYASTHENIA GRAVIS

The treatment of GMG primarily involves cholinesterase inhibitors such as pyridostigmine. However, OMG responds poorly to pyridostigmine, and most patients move to other treatment options [75]. Immunosuppressors such as corticosteroids and antimetabolites are frequently used. Steroids should be used as the initial immunosuppressant agent [76]. Low-dose prednisone has proven effective in treating OMG and the fluctuations in diplopia amplitude. Prednisone has also been shown to delay conversion from OMG to GMG [77–80]. In OMG patients who do not generalize by 3 years and receive low-dose prednisone and/or other immunomodulatory therapy, conversion to GMG after 3 years is uncommon [81]. Studies have also shown that azathioprine reduces the risk of progression from OMG to GMG [82]. If OMG is associated with thymoma, thymectomy is indicated. However, without associated thymoma, evidence for the efficacy of thymectomy in OMG is limited [76]. Intravenous immunoglobulin (IVIG) and plasma exchange have been effective for acute GMG flares [76]. There are insufficient data to assess the efficacy of IVIG and plasma exchange in OMG, though one case series reports improvement of ocular symptoms with the use of IVIG in steroid-refractive OMG [83].

MANAGEMENT OF THE CO-OCCURRENCE OF THYROID EYE DISEASE AND OCULAR MYASTHENIA GRAVIS

When TED and OMG co-occur, control of each disease independently is essential in minimizing impact on quality of life. In addition to the aforementioned treatment options, special attention should be paid to the role for prisms and strabismus surgery. When the diplopia is relatively stable, Fresnel temporary prisms can provide symptomatic relief until definitive strabismus surgery can be performed. If not, monocular occlusion of the nondominant eye may be practical. Surgery for TED strabismus should be delayed until TED is in the stable phase and in general the motility has recovered from the influence of OMG variability. This would be best assured by stability of orthoptics measurements for an interval of 6 months.

There are a number of modifiable risk factors affecting both TED and OMG. Active smoking has been associated with symptom severity of both OMG and TED and smoking cessation can improve outcomes for both diseases [6,84]. Previous literature posits that smoking produces relative tissue hypoxia which increases circulating inflammatory cytokines and in turn an increase in orbital glycosaminoglycan synthesis [85]. Active smokers are

more likely to require surgical intervention and have higher rates of recurrence [11,86]. TED patients who are active smokers are less likely to respond to medical treatment [6]. O'Dell *et al*. [87▪▪] found that proptosis reduction in patients treated with teprotumumab is greater in nonsmokers compared to smokers.

Hsu *et al*. [88▪▪] conducted a retrospective case–control study to evaluate protective factors and risk factors for the development of TED in patients newly diagnosed with Graves' disease. They found that the use of statins decreased the risk of developing TED by 80%. Interestingly, they report no correlation between lipid profile or smoking status and the development of TED in patients with Graves' disease.

Obstructive sleep apnea (OSA) is another potential modifiable risk factor in TED. In a retrospective case-control study, Habib *et al*. [89] found that patients with TED-associated compressive optic neuropathy were more likely to be at a high risk for OSA compared to TED patients without compressive optic neuropathy. Evidence for an association between GMG and either statin use or OSA is mixed in the literature, though there are case reports of statin-induced GMG [90].

CONCLUSION

Recognizing and understanding the clinical overlap between TED and OMG is crucial for appropriate diagnosis and management. Clinicians should be aware of the potential for co-occurrence of these diseases. Early and accurate diagnosis combined with tailored treatment strategies can improve outcomes and quality of life.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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