The Canadian Journal of Neurological Sciences (2025), 1–2
doi:10.1017/cjn.2025.34

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Letter to the Editor: New Observation

Occam's Razor Revisited: Myasthenia Gravis and Thyroid Ophthalmopathy

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Keywords: myasthenia gravis; ophthalmoparesis; thyroid ophthalmopathy; extraocular muscles; hypothyroidism

Myasthenia gravis (MG) is an autoimmune disorder that targets the neuromuscular junction and can be associated with autoimmune thyroid disease. While 3%–8% of myasthenia patients have concurrent autoimmune thyroid disease, MG occurs in 0.2% of autoimmune thyroid disease patients.[1] MG usually accompanies hyperthyroidism, especially Graves' disease, although there are rare reports with hypothyroidism. Both MG and Graves' can present with ocular findings, namely, ptosis and diplopia in MG and proptosis and ophthalmoparesis in autoimmune thyroid-related orbitopathy (TRO).[2] We report on the diagnostic nuances of a person who experienced new-onset MG in the context of previously long-standing but treated hypothyroidism and unrecognized TRO.

An 84-year-old right-handed woman presented with gradual, progressive ophthalmoparesis, ptosis and facial weakness associated with a 5-month history of painless fluctuating binocular diplopia and a 3-month history of fatigable left ptosis, prominent later in the day. Her past medical history was significant for hypothyroidism diagnosed in her 20s without a history of Graves' disease or Hashimoto's thyroiditis and treated with levothyroxine 100 mcg daily. Her thyroid-stimulating hormone (TSH) was normal on treatment. Interestingly, both of her biological children had Hashimoto's thyroiditis.

Neurological examination identified bifacial weakness, worse on the left, with left ptosis accentuated by sustained upgaze. The ice pack test of the left eyelid was positive. The left eye had exotropia and hypotropia at primary gaze, and extraocular movements were severely restricted in all directions. There was mildly restricted adduction of the right eye. Pupils were equal and reactive to light. Motor examination revealed fatigable weakness of neck flexors, deltoids and hip flexors. The thyroid was palpable although not enlarged.

Anti-acetylcholine receptor antibody testing was positive, 0.44 nmol/L ($N < 0.25$ nmol/L). The patient was started on pyridostigmine 60 mg TID. Upon follow-up, the patient reported minimal response after 1 month of pyridostigmine therapy. Instead, facial weakness had progressed as the patient had lost the ability to close her left eye independently of her right eye. She also noted mild proximal muscle weakness in the upper extremities, particularly when lifting objects above her head. She denied dysarthria, dysphagia, headache, pain, constitutional symptoms and sensory changes. Due to the antibody titer in the lower range and MRI findings suggesting an alternative diagnosis (below), electrophysiological studies were carried out for further diagnostic clarification, and single fiber electromyography in the right frontalis muscle identified 6 of 15 fiber pairs with abnormal jitter and 4 fiber pairs with blocking.

Further work-up included normal CSF and a normal CT chest without thymoma. Interestingly, the MRI brain with gadolinium was initially reported normal, but on review, there was bilateral enlargement and enhancement of the medial, lateral and inferior rectus muscles (Figure 1A,B). Dedicated MRI orbits revealed the same, more pronounced on the left (Figure 1C,D). These changes of the extraocular muscles were considered consistent with TRO. Anti-TSH and anti-thyroid peroxidase antibodies were negative.

The patient had a limited response to pyridostigmine and prednisone. Intravenous immunoglobulin was added with improvements in limb muscles but only limited extraocular improvement. One year after diagnosis, given ongoing ophthalmoparesis, azathioprine was added as prednisone was tapered, and her condition stabilized over the next 1–2 years. The choice of steroid-sparing therapy was made favoring azathioprine to address her greater risk of disability from MG. Her left eye had persistent but much improved ptosis, weakness with upgaze and downgaze deviation at rest. At 6 years following diagnosis, she had 2 mm ptosis and persistent weakness of left upgaze and adduction but was managing well, mobile and quite independent with most activities. There were no other signs of MG. She continued to experience diplopia and patched one eye regularly and was followed by ophthalmology but did not wish to pursue strabismus surgery or trial other therapies. Repeat MRI orbits approximately 3 years after symptom onset showed partial improvement in extraocular muscle size.

TRO involves enlargement of the extraocular muscles, most notably the inferior, medial and superior recti muscles. Although TRO is most commonly seen in association with hyperthyroidism, up to 10% of TRO cases occur in the context of hypothyroidism.[3]

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Cite this article: DuVal M, Borch LA, and Zochodne DW. Occam's Razor Revisited: Myasthenia Gravis and Thyroid Ophthalmopathy. *The Canadian Journal of Neurological Sciences*, https://doi.org/10.1017/cjn.2025.34

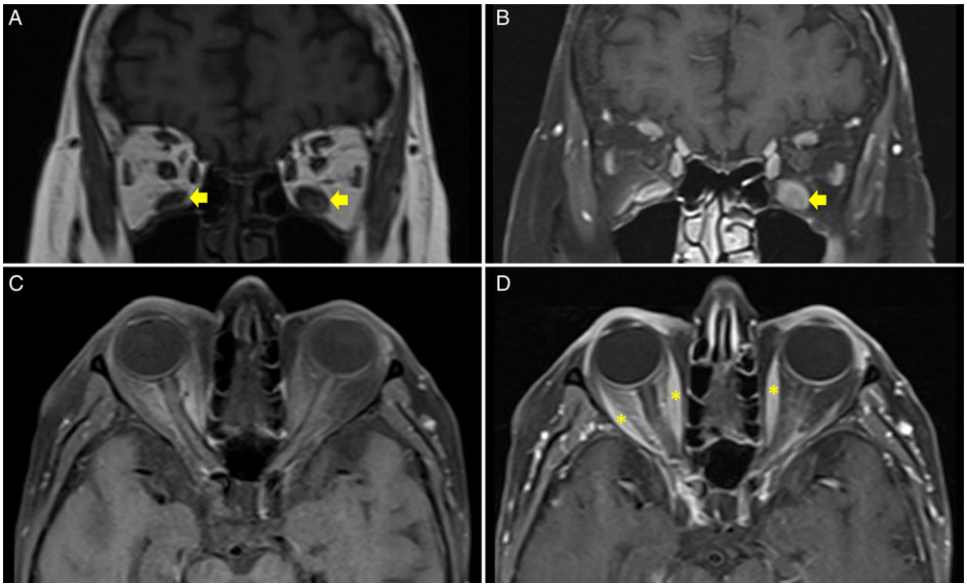

Figure 1. MRI orbits showing thyroid orbitopathy in an 84-year-old patient with myasthenia gravis and hypothyroidism. (A) Coronal T1 section through extraocular muscles showing left > right enlargement of the inferior rectus muscles (arrows) and, to a lesser degree, the lateral and medial rectus muscles. (B) Coronal T1 (fat suppression) post-gadolinium section showing uniform enhancement of the extraocular muscles. (C) Axial T1 (fat suppression) section. (D) Axial T1 (fat suppression) post-gadolinium section showing uniform enhancement of the extraocular muscles (asterisks).

Similarly, MG is more often associated with hyperthyroidism than hypothyroidism. Discerning between MG and TRO is important for proper management but can be challenging. Diplopia due to MG classically has fatigability and fluctuation; however, these symptoms can be nonspecific. TRO classically features proptosis and esotropia due to enlargement of the medial and inferior recti.[4] Ptosis in MG is fatigable and common; in TRO, ptosis is uncommon (unlike lid retraction) but can occur with levator dehiscence (aponeurotic ptosis). Proximal weakness can be found in both MG and hyperthyroidism. Thus, patients with clinical findings suspicious for both MG and thyroid disease require additional testing. Our patient's ptosis, weakness of orbicularis oculi and exotropia are more typical of MG than TRO; however, ancillary testing revealed evidence of both processes.

The co-occurrence of MG and thyroid eye disease in the literature remains very rare, with fewer than 30 cases described since 1980.[4] In general, patients with MG and thyroid disease are more likely to have milder clinical features and are more likely to have ocular myasthenia involvement compared to their counterparts without thyroid disease.[5] Discerning MG and TRO is important for management, especially if vision is at risk. Ocular MG may be responsive to acetylcholinesterase inhibitors alone. MG and moderate-severe TRO can be managed with immunosuppression, though with several differences. Corticosteroids are common for initial management in both. Steroid-sparing agents such as mycophenolate mofetil (MMF), azathioprine and newer agents including biologics targeting Fc-receptor or complement proteins are used first line in MG,[6,7] whereas MMF was introduced as a first-line steroid-sparing therapy for moderate-severe TRO in the most recent update to practice guidelines.[8] Thymectomy is recommended for AChR ab+ MG but not for thyroid disease. Second-line treatment for TRO includes high-dose corticosteroids, other steroid-sparing agents such as azathioprine, orbital radiotherapy and orbital decompression for sight-threatening disease.[8] While these diseases have some similar therapies, the ideal approach to concurrent disease is currently unknown. Collaboration with ophthalmology is thus important to create a personalized plan for these patients.

In summary, our case serves as a useful example for the general neurologist's approach to diplopia and further supports the guidance that MG and TRO together should not be overlooked in the context of ophthalmoparesis. These rare cases require careful multimodal investigations, and while optimal treatment is not known, these patients benefit from multidisciplinary and personalized management.

Author contributions. MD reviewed the clinical features and generated revised and penultimate drafts of the manuscript. LAB reviewed the clinical features and generated an initial draft of the MS. DWZ supervised the report and revised and prepared the final version of the manuscript.

Funding statement. None.

Competing interests. None.

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https://doi.org/10.1017/cjn.2025.34