CASE REPORT

Hickam's dictum: Myasthenia Gravis presenting concurrently with Graves' disease

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SUMMARY

We present two patients with Graves' disease and concurrent myasthenia gravis. The impact of the dual diagnosis on the clinical course and the potential for a delayed diagnosis of myasthenia gravis is discussed. Patient 1, a 28-year-old man was diagnosed with Graves' disease following his second respiratory arrest. His history was strongly suggestive of a second pathology. Patient 2, a 66-year-old Cantonese woman with established Graves' disease presented with thionamide-related neutropaenia. Examination revealed bilateral ptosis and right lateral rectus palsy. Both patients had thyrotoxicosis secondary to Graves' disease with concurrent myasthenia gravis. Although neuromuscular weakness is common in Graves' disease, coexisting myasthenia gravis (MG) is rare and can cause profound morbidity. Ocular signs in both diseases may cause diagnostic confusion although ptosis suggests coexisting MG. In both cases, the thyrotoxicosis delayed the diagnosis of MG.

BACKGROUND

Graves' disease is a common cause of thyrotoxicosis and is due to stimulation of the thyroid stimulating hormone (TSH) receptor by TSH receptor antibodies (TRAb).¹ Proximal muscle weakness is common in thyrotoxicosis, is due to the disease itself and slowly improves with the development of a euthyroid state.¹ Thyrotoxicosis particularly that due to Graves' disease is also associated with thyrotoxic periodic paralysis (TPP) with an increased incidence in men especially those of Asian and Polynesian ethnicity.² The muscle weakness associated with TPP is typically acute and reversible and most commonly affects proximal muscles with sparing of bulbar and ocular muscles.^{3,4}

Myasthenia gravis (MG), similar to Graves' disease is autoimmune but is less common with an incidence of between 3 and 30 patients per million.⁵ Although thyroid disease is relatively common in patients with MG affecting 5%–10% of patients, the converse is not true with a prevalence of MG in patients with Graves' disease of only 0.14%.^{6,7} Myasthenia is commonly associated with fluctuating muscle weakness and fatigability. MG has a preference for the ocular muscles, with fluctuating ptosis or diplopia occurring in 85% of patients.⁸

MG can mimic some of the neuromuscular signs of Graves' disease and when these disorders coexist, especially if MG signs are subtle, these signs can

easily be missed or mistakenly be attributed to the Graves' disease.⁹ This may result in a delay in diagnosis and treatment of MG. As such, a high degree of suspicion is needed when the clinical features of Graves' disease are atypical.

CASE PRESENTATION

Patient 1

A 28-year-old Māori (indigenous) man was admitted to hospital acutely, having been witnessed to choke while he was eating. He received both bystander and in-hospital cardiopulmonary resuscitation and had spontaneous circulation return after two cycles. He was intubated following the arrest and he had two failed attempts at extubation due to respiratory distress and hypoxia. A respiratory opinion was sought following the failed extubation. Bronchoscopy revealed old blood and purulent secretions. CT head was unremarkable and CT chest showed interstitial changes of the lung. A persistent sinus tachycardia (115/min) was noted on ECG at admission. Successful extubation was finally achieved on day 7 after admission following the addition of dexamethasone and bronchodilators, and he was discharged from intensive care on day 10.

After 10 days in the community, he represented to the emergency department, having become unresponsive and short of breath following a meal. On initial assessment, he had a Glasgow coma scale (GCS) of 3/15 and was intubated. He was noted to be in rapid atrial fibrillation with a ventricular rate of 150/min. He received intravenous amiodarone therapy and direct current (DC) cardioversion. Thyroid function tests were performed at the time of initial assessment and prior to amiodarone revealed moderate biochemical hyperthyroidism as shown in [table 1](#). The thyrotoxicosis with elevated TRAb was consistent with Graves' disease. Family history was remarkable only for a multinodular goitre in a grandmother.

Two further attempts at extubation were unsuccessful and he was referred to endocrinology to evaluate potential links between his neuromuscular weakness and thyrotoxicosis.

On examination he was intubated, tachycardic and hypertensive with bilateral ptosis and exophthalmos. His skin was warm and dry. Thyroid exam revealed no palpable goitre and no bruit. Neurological examination revealed bilateral ptosis, with an inability to assess other voluntary motor movements due to his impaired level of consciousness.

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Table 1 Pertinent laboratory results

	TSH (0.27–4.2mU/L)	FT3 (3.1–6.8 pmol/L)	FT4 (12–22 pmol/L)	TRAb (<1.3 IU/L)	AChR antibody (<4 IU/L)	MuSK antibody
Patient 1	<0.01	20.2	44	6.8	>20.0	Negative
Patient 2	<0.02	20.6	67	31	5.35	Negative

AChR, acetylcholine receptor; FT4, free thyroxine; FT3, free triiodothyronine; MuSK, muscle specific kinase; TSH, thyroid stimulating hormone; TRAb, TSH receptor antibodies.

A collateral history from his partner revealed a 3-month history of motor fatigability, worsening ptosis with progressive dysphagia to both solids and liquids, resulting in several near-choking episodes. He had also experienced several months of weight loss, tremors and palpitations. He had been evaluated for dry eyes by an ophthalmologist 3 years earlier and at that time was noted to have proptosis. Unfortunately, no thyroid function tests were collected at that time.

His clinical history with recurrent choking episodes and difficulties with extubation suggested an additional concurrent diagnosis, as he did not have significant thyromegaly. There was no documented hypokalaemia to suggest TPP and the marked bulbar involvement would have been atypical. A neurological opinion was recommended and measurement of nicotinic acetylcholine receptor antibodies (nAChR) arranged. Despite treatment of the thyrotoxicosis, his muscle weakness did not improve. His nAChR levels were markedly elevated at >20.0 (<4.00 Mu/L), with negative muscle-specific kinase (MuSK) antibodies. Electromyography (EMG) demonstrated reduced recruitment across all muscle groups consistent with MG (table 2).

Patient 2

A 66-year-old Cantonese woman with Graves' disease was transferred from a secondary hospital, for definitive treatment of her thyrotoxicosis following the development of thionamide-associated neutropaenia. After cessation of her antithyroid medication, she rapidly became severely thyrotoxic (FT₄ 67 pmol/L (12–20), TSH <0.02 mU/L and was referred to our service for consideration of definitive surgical therapy. Neutropaenia was managed with a single dose of granulocyte colony-stimulating factor. She had been commenced on prednisone 20 mg as an adjunctive treatment for possible Graves' eye disease prior to transfer.

She reported 8 kg of weight loss, tremors and palpitations consistent with the severity of her hyperthyroidism. Further collateral history from her daughter revealed gradual onset ptosis for 2 weeks together with diplopia on right lateral gaze. Dysphagia and other bulbar signs were absent.

There was no family history of thyroid disease or other autoimmune disease.

On examination she was noted to have bilateral ptosis—right greater than left—with no lid lag, proptosis, retro-orbital pain, oedema, inflammation or chemosis but a right partial VI nerve

palsy was also present. Tone was normal in both the upper and lower limbs bilaterally. Power in both upper limbs was reduced globally to 4/5 on the National Health and Medical Research Council scale with no evidence of fatigability on clinical exam.

As the ocular signs were not consistent with Graves' ophthalmopathy alone, a further opinion was sought from the Neurology and Ophthalmology services. An ice pack test was negative. Subsequently, a diagnosis of ocular MG was made based on elevated acetylcholine receptor antibodies.

INVESTIGATIONS

Other investigations:

Patient 1:

ECG: atrial fibrillation with rapid ventricular response

Echocardiogram (ECHO)—left ventricle (LV): Normal size. LV function globally moderate to severely reduced, estimated ejection fraction 30%–35%.

CT brain: No acute intracranial abnormality identified.

CT thorax: Small amounts of dependent secretions noted in the trachea and right main bronchus; however, no overt obstructing foreign body is identified in the main bronchial tree. No asymmetrical volume loss is noted. There was no evidence of a thymoma.

EMG: reduced recruitment across all muscle groups consistent with MG

Key to EMG table

Ampl.mv- Baseline amplitude of recruited nerve fibres in millivolts

Table 2 Electromyography response following right abductor digiti minimi stimulation for patient 1

Train	Amplitude mV	d.Ampl1%	Time (min)
Baseline	6.9	–9.2	0:00:00
Facilitation	6.7	–8.7	0:01:03
@0.30	7.5	–16.9	0:01:44
@1.00	7.6	–22.6	0:02:14
@2.00	6.7	–22.1	0:03:13
@3.00	8.1	–14.3	0:04:13
@5.00	7.4	–16.8	0:06:13

Figure 1 MRI brain of patient 2 demonstrating early Graves' ophthalmopathy in a patient with ocular myasthenia.

d.ampl.1%- Percent decremental response from baseline

Patient 2:

- ▶ ECG: sinus rhythm, rate 80/min, normal axis (on beta-blocker)
- ▶ ECHO: normal LV function
- ▶ CT chest: demonstrated a 58 mm anterior mediastinal mass consistent with a thymoma.
- ▶ MRI orbits: features consistent with early stages of thyroid eye disease (figure 1)

The following differential diagnoses were considered for the presentation of neuromuscular weakness for each patient.

Patient 1

Thyrotoxic periodic paralysis—is due to intracellular potassium shifts and is usually reversed by propranolol, acute onset, may last hours but not days.

Thyrotoxic myopathy—but history here was of bulbar weakness which would be atypical.

Lambert Eaton syndrome—antibody negative and pattern of weakness different, no evidence of underlying malignancy.

Critical illness myopathy—but history of weakness preceded hospitalisation.

Patient 2

'Graves' orbitopathy—bilateral ptosis is an unusual finding for this condition.

Infiltrative orbital tumour—not found on MRI.

TREATMENT

Patient 1

The elevated TRAb was consistent with Graves' disease. He was commenced on carbimazole. MG was confirmed following EMG. He received a 5-day course of intravenous immunoglobulin followed by an intravenous infusion of pyridostigmine and methylprednisolone. His motor function improved dramatically and he was breathing spontaneously without pressure support. He was extubated 17 days following admission to intensive care unit (ICU). He was discharged from ICU to a rehabilitation ward 3 days following extubation. Following 1 week of intensive rehabilitation he was discharged home, on prednisone and carbimazole having fully recovered his muscle strength.

Patient 2

Following a course of Lugol's iodine, and with prednisone cover, she underwent a total thyroidectomy, which was uncomplicated. Three weeks later, once the nAChR results were back, she was seen by the neurology service and started on pyridostigmine.

OUTCOME AND FOLLOW-UP

Patient 1 was reviewed in outpatient clinic 6 weeks following discharge. He was both clinically and biochemically euthyroid. He had no ptosis or fatigability on clinical examination and his thyroid function tests had normalised on carbimazole. Carbimazole was down titrated with close monitoring of his thyroid function and definitive therapy for his Graves' disease planned.

Patient 2 was reviewed in her local hospital post-thyroidectomy. Apart from subclinical hypothyroidism requiring dose titration of her levothyroxine, there were no postoperative complications. There was no evidence of fatigability or ptosis on examination. CT chest demonstrated an anterior mediastinal mass consistent with a thymoma for which she is awaiting resection.

DISCUSSION

We report two cases of Graves' disease with concurrent MG. Graves' disease is associated with a number of autoimmune

diseases, including MG. Both disorders can cause ocular symptoms. In a large British cohort study, 52% of all MG patients had ocular symptoms at presentation.¹⁰ Patients with Graves' disease and MG have also been reported to have a higher prevalence of ocular myasthenia signs.¹¹ Both of our patients were noted to have ptosis. Ptosis is uncommon in Graves' ophthalmopathy and if present may suggest coexisting MG.^{12 13}

The first case presented with multiple respiratory arrests, which is rare in the developed world.⁹ Unfortunately, despite having a clear history of progressive dysphagia, this was not identified until his second ICU admission. Dysphagia is not a commonly recognised symptom of MG, and is the presenting symptom in 6% of patients at presentation.¹⁴ MG patients reporting dysphagia have a significant risk of aspiration (35%) and laryngeal penetration (65%).¹⁴ A Turkish study reported that pharyngeal and laryngeal involvement in MG rapidly resolves following initiation of anticholinesterase treatment.¹⁵ While dysphagia rarely can occur in Graves' disease, this is due to significant thyromegaly, which was absent in this case.

The reason for the increased risk of myasthenia in patients with Graves' disease is not fully understood but may be due to shared genetic susceptibility. For example in a Japanese case series, a common human leukocyte antigen (HLA) type (HLA-DQ3) was present in all patients with both disorders.¹⁶ An increased prevalence of acetylcholine receptor antibodies has also been demonstrated in patients with Graves' ophthalmopathy.¹⁷

Diagnosing MG in Graves' disease using acetylcholine receptor antibodies alone can be challenging. The proportion of myasthenia patients with Graves' disease that have positive acetylcholine receptor antibodies may be less than that of patients with myasthenia alone. In a large Taiwanese cohort, 70% of those with concurrent autoimmune thyroid disease and MG had positive AChR antibodies compared with 76.5% of all patients with MG.¹⁸ In these situations, the Tensilon (edrophonium) test may be the diagnostic method of choice to detect the presence of MG.¹⁹ Once the diagnosis of MG is confirmed, mediastinal imaging should be performed as a thymoma is present in approximately 10% of cases; however, a recent randomised trial suggests even non-thymomatous MG may benefit from thymectomy.²⁰

The prognosis of MG in the presence of Graves' disease is poorly understood. A reverse 'see saw' relationship was thought to exist between the clinical courses of the two diseases, where improved thyroid function produced an increase in myasthenic weakness, but this has not been observed in more recent works.^{16 21} One African study suggested that MG worsens with hyperthyroidism in 40% of cases.²² Other studies suggest that myasthenia coexisting with autoimmune thyroid disease appeared to follow a milder course than MG alone.^{21 23}

When both MG and Graves' disease coexist, medications used in the management of hyperthyroidism may precipitate a myasthenic crisis.^{24 25} Deterioration of MG following methimazole treatment has been documented postulated to be related to the immunomodulatory properties of methimazole.²⁵

If thyroid surgery is considered for definitive management in a patient with both Graves' disease and MG, there is a significant risk of poor outcomes.²⁶ In a cohort of thymectomy patients, 11.5% developed myasthenic crises postsurgery, including requiring prolonged intubation and ventilation postoperatively.²⁶

Anaesthesia induction and maintenance carry an increased risk in patients with both MG and Graves' disease. At induction, patients with MG may have low respiratory reserve, so benzodiazepines and respiratory depressants need to be used with caution.²⁷ In terms of maintenance, there may be resistance

to the action of long-acting neuromuscular depolarising agents, and increased sensitivity to non-depolarising relaxants such as vecuronium.²⁷ To date, there is little data on the clinical course of MG in patients with Graves' disease who have received radio-iodine as definitive therapy.

Both of these cases highlight the need for clinicians to recognise that Graves' disease and MG can coexist. In the first case, both diagnoses were unnecessarily delayed particularly given that he had a clear history of both thyrotoxic symptoms and a second pathology to explain the bulbar symptoms. As a result of the delay, he was fortunate to have survived. In the second case, the clinical signs were also suggestive of MG but again the diagnosis was delayed until after she had undergone a total thyroidectomy under general anaesthesia. Due to concerns by the endocrine team, the anaesthetist was made aware that there was strong clinical suspicion for MG so that he could minimise the risk of a myasthenic crisis following surgery.

A history of fatigability, weakness or dysphagia may suggest MG in a patient with Graves' disease. Given the increased incidence of ocular myasthenia in Graves' disease, clinicians need to be aware of ptosis as a clinical sign that suggests the presence of MG. The impact of each disease on the other is not well understood but the presence of Graves' disease can be expected to worsen the myasthenic weakness. The treatment of Graves' disease may be complicated by the presence of MG and general anaesthesia needs to be given only after careful discussion with the patient and anaesthetist regarding potential complications. In a patient with Graves' disease who demonstrates atypical neuromuscular symptoms the possibility of coexisting MG should be considered for both conditions to be treated in a timely fashion to minimise adverse outcomes.

Learning points

- Both Graves' disease and myasthenia gravis (MG) share common autoimmune mechanisms.
- A careful history and examination should always be performed and consideration of additional diagnosis/ diagnoses if the clinical symptoms and signs are not consistent with the presence of a single pathology.
- Both Graves' disease and MG complicate the presentation, evaluation and successful medical and surgical management of each other.
- Recognising that Graves' disease and MG may coexist is the key to preventing adverse outcomes including respiratory arrest.

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