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Case Report

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Hickam's Dictum: Coexistence of Graves Thyrotoxicosis and Myasthenia Gravis in a Young Bangladeshi Male

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Abstract

Myasthenia gravis (MG) is a rare autoimmune neuromuscular junction disorder. In myasthenia gravis, autoimmune antibodies develop against postsynaptic neuromuscular junction disrupting the neuromuscular transmission, resulting in fluctuating muscle weakness and fatigue. Graves' disease (GD) is the most common autoimmune thyroid disorder, in which antibodies develop against thyroid receptors. Although neuromuscular weakness is common in Graves' disease, coexisting myasthenia gravis (MG) is rare but well recognized and can cause profound morbidity. It would be consistent with a genetic predisposition for autoimmune disease. Here we report a 35 years Bangladeshi male who presented with episodic fatigable weakness and weight loss later diagnosed with myasthenia gravis with coexistent graves' disease.

Introduction

Robert Graves' disease, although first described by Parry in 1825 [1], is best known as Graves' disease and is characterized by diffuse goiter (Thyrotoxicosis), infiltrative orbitopathy & ophthalmopathy and occasionally infiltrative dermopathy. It occurs in up to 2% of women and 0.2% in men. The disorder rarely begins before adolescence and typically occurs between 20 and 50 years of age and rarely occurs in elderly as well. It is an autoimmune disorder with autoantibodies directed against the TSHR (TSHR Abs) and behaves as thyroid-stimulating antibodies [2,3]. Clinically it is characterized by hyperactivity, irritability, dysphoria, heat intolerance, sweating, palpitations, fatigue, weakness, weight loss despite increased appetite, diarrhea, polyuria, oligomenorrhea, loss of libido, tachycardia, atrial fibrillation, tremors, goiter, warm, moist skin, muscle weakness, muscle weakness, proximal myopathy, lid retraction/lag, gynecomastia [4]. Myasthenia gravis (MG) is an autoimmune neuromuscular condition characterized by the presence of post synaptic anti-acetylcholine receptor antibodies and to a lesser extent against muscle-specific kinase protein resulting in fluctuating muscle weakness. MG is more prevalent in women. Most of the patients present with ptosis and diplopia initially and then progress rapidly to generalized disease. It may cause acute respiratory failure. It can be associated with other auto-immune conditions such as Hashimoto's thyroiditis, Graves' disease [5], systemic lupus erythematosus (SLE), or rheumatoid arthritis. Although the association of Graves' disease and MG is known [6], it has been rarely described in medical literature [7,8]. The incidence of autoimmune thyroid disease is relatively common in patients with MG (5-10%), however, the association between GD and MG is only 0.14% [9]. Treating one pathology may worsen the other which will make it a challenge to treat both pathologies. Myasthenia gravis gets worse by the use of antithyroid drugs through immunomodulatory effects. Beta-blockers and corticosteroids cause a worsening of weakness in myasthenia patients [10]

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 report

A 35-year-old Bangladeshi male, non-smoker, non-alcoholic patient, businessman by occupation presented to hospital with a history of gradually increasing painless swelling in the neck of 6 months duration associated with insomnia, generalized weakness, palpitations and weight loss despite having good appetite. It was not associated with hoarseness of voice, difficulty in breathing or swallowing. Patient also complained of low-grade fever of 2 months duration, intermittent, not associated with chills and rigors or any diurnal variations. Patient had no such complaint in past or no such history was found in family or first-degree relatives. On examination patient was conscious, oriented. Look was lethargic and had proptosis and ptosis. Large thyroid swelling was visible, bilaterally symmetrical, non-tender, smooth, firm in consistency, non-fluctuant, with audible bruit present. B.P-110/60 mmHg, Pulse-108/min, regular. Temp- 100^{o}F and respiratory rate of 16/min. Palms were warm and sweaty. Investigations revealed Hb-12.6 g/dl, TLC-8600/cmm, DLC- N-68%, L-27%, Platelets - 2.25 lacs/cmm, ESR - 55 mm in 1st hour, P.B.F - Normal, Urea-13 mg/dL, Bl. Glucose (R)- 6.6mmol/L, S. Creatinine-0.5 mg/dL, SGPT -30 U/L, Sr.Ca++= 8.7 mg/dl, S.sodium-135 meq/l, Sr. K+-3.9 meq/l, Chest X-ray-Normal, routine urine exam- normal,

ECG- normal, TSH- 0.005 µIU/ml, (Normal: 0.1 to 4 µIU/ml) Free T4- 6.89 ng/dL (Normal 1.2-2.8 ng/dL). On the thyroid ultrasound and Doppler ultrasound examination, enlarged lobes, inhomogeneous echo structure, markedly increased flow was described, which was consistent with the image of autoimmune thyroiditis (Figure 1). Thyroid scan showed thyromegaly with intense diffuse radiotracer uptake in both thyroid lobes (Figure 2). TRAb was highly raised to 6.65IU/L (Normal less than 1.75IU/L).

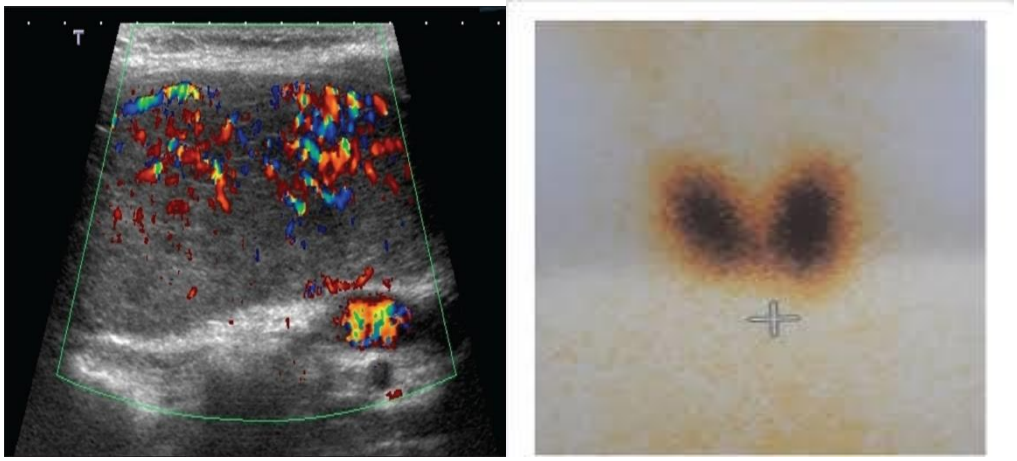

Figure 1: Doppler ultrasonography of thyroid revealed enlarged both thyroid lobes with hypervascularization, Figure 2: Thyroid scintigraphy showed intense radiotracer uptake in both thyroid lobes with diffuse thyromegaly.

He was started treatment with carbimazole 40 mg daily with propranolol 40 mg daily. With treatment, his complaints were alleviated and his general condition showed a marked improvement, and after seven days he was discharged with follow up after 8 weeks with TSH and FT4 reports. After 6 weeks he presented with diplopia on downward gaze, drooping of eyelids on both sides. Neurological examination revealed complete ptosis of both eyelid with paresis of both inferior recti. There was no other focal neurological deficit. Bed side ice on eyes test was positive. Repeat thyroid function tests revealed TSH- 0.164 µIU/ml, (Normal: 0.1 to 4 µIU/ml) Free T4- 2.19 ng/dL (Normal 1.2-2.8 ng/dL). Anti-Acetylcholine Receptors antibodies: positive (26.3 nmol/L, N<0.2 nmol/L.). Computed Tomography (CT) scan of the thorax showed no abnormalities, apart from a small (15 mm) thymic remnant. Treatment was initiated as follows: pyridostigmine 240 mg/ day, prednisolone 10 mg/day, with a reduction in the dose of carbimazole from 40 mg to 20 mg daily. The patient improved on treatment with a regression of myasthenic signs, including reduced fatigability and an improvement of ptosis and diplopia.

Discussion

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).[11] Proximal muscle weakness is common in thyrotoxicosis, is due to the disease itself and slowly improves with the development of a euthyroid state.[11] Myasthenia gravis (MG), similar to Graves' disease is autoimmune but is less common with an incidence of between 3 and 30 patients per million.[12] Myasthenia is commonly associated with fluctuating muscle weakness and fatigability. MG has preference for the ocular muscles, with fluctuating ptosis or diplopia occurring in 85% of patients [13].

Patients with myasthenia gravis may have coexisting autoimmune thyroid disease (AITD), which include Hashimoto's disease Type 2A and Graves' disease Type 3A. Epidemiological studies show that AITD occurs in approximately 5-10% of patients with MG, whereas MG is reported in a fairly low frequency (0.2%) of patients with AITD. The reasons for the co-occurrence of the two conditions have not yet been elucidated. The chemokine CXCL10 and its receptor CXCR3 seem to play an important role in the pathogenesis of systemic or organ specific autoimmune diseases. High levels of CXCL10 are found in case of organ specific autoimmune disease like Grave disease or systemic autoimmune diseases and seems to be marker of amplified host immune response that perpetuate the autoimmune process and could lead to the association of the two diseases [14]. The clinical presentation of MG associated with AITD is frequently restricted to eye muscles. The reason for the association of AITD with ocular MG is unknown, but several hypotheses can be considered. First, ocular MG and generalized MG might actually represent separate diseases with different spectra of associated conditions. Second, an immunological cross-reactivity against epitopes or auto-antigens shared by the thyroid and the eye muscles might be the basis of this association. A third explanation for the higher frequency of ocular MG in AITD could be that these disorders have a common genetic background [15]. In three-quarters of patients with both conditions, thyrotoxic symptoms occur before or concurrently with those of myasthenia [16]. Our patient had thyrotoxicosis symptoms 2 months before his ptosis developed. The ocular changes in Graves' disease may include exophthalmos, periorbital edema, lid lag, chemosis and ophthalmoplegia. The extraocular muscles most commonly involved in Graves' disease are the superior and lateral recti [17]. Two-thirds of the patients with both disorders show improvement in myasthenia gravis after treatment of thyroid disease [17]. In a Japanese case series, a common human leukocyte antigen (HLA) type (HLA-DQ3) was present in all patients with both disorders [18]. An increased prevalence of acetylcholine receptor antibodies has also been demonstrated in patients with Graves' ophthalmopathy. [19]

In our case, Graves' disease preceded MG by two months. According to the literature, the diagnosis of MG preceded that of hyperthyroidism in 30-35% of cases, the conditions were diagnosed simultaneously in 20-25% of cases, and hyperthyroidism preceded the MG diagnosis in the majority (40-50%) of cases. The most common etiology of hyperthyroidism is Graves' disease [8], as in our case.

Thymus anomalies which may be associated with MG are follicular thymus hyperplasia in 65% of cases; thymoma (epithelial tumor) in 10-15% of cases [20,21]. Thymus hyperplasia has also been described in cases of Graves' disease without associated myasthenia. In these cases, the thymus mass was assessed, and a shrinkage or regression was universally observed following medical anti-thyroid treatment [20]. These findings justify investigation for a thymus anomaly, but in our case thoracic CT scan showed a non-significant thymus remnant.

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 (AchR) 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. [9] In these situations, the Tensilon (edrophonium) test may be the diagnostic method of choice to detect the presence of MG.[6] 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 randomized trial suggests even non-thymomatous MG may benefit from thymectomy.[22] Anti-TSH receptor antibodies were positive, as in a quarter of cases of MG [7]. Anti-acetylcholine receptor antibodies are positive in 85% of cases of generalized MG, and 66% of cases of ocular myasthenia, but only in 35 to 50% of cases where there is an associated hyperthyroidism [20,23]. In our case anti-Ach R antibodies were strongly positive.

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. [24,25] One African study suggested that MG worsens with hyperthyroidism in 40% of cases [26]. Other studies suggest that myasthenia coexisting with autoimmune thyroid disease appeared to follow a milder course than MG alone [25,27].

When both MG and Graves' disease coexist, medications used in the management of hyperthyroidism may precipitate a myasthenic crisis. [28,29] Deterioration of MG following methimazole treatment has been documented postulated to be related to the immunomodulatory properties of methimazole [29].

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 [30]. In a cohort of thymectomy patients, 11.5% developed myasthenic crises post-surgery, including requiring prolonged intubation and ventilation postoperatively [30].

Anesthesia 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 [31]. In terms of maintenance, there may be resistance to the action of long-acting neuromuscular depolarizing agents, and increased sensitivity to non-depolarizing relaxants such as vecuronium [31]. To date, there is little data on the clinical course of MG in patients with Graves' disease who have received radioiodine as definitive therapy.

Both of these cases highlight the need for clinicians to recognize 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 anesthesia. Due to concerns by the endocrine team, the anesthetist was made aware that there was strong clinical suspicion for MG so that he could minimize the risk of a myasthenic crisis following surgery.

A history of fatigability, diplopia, ptosis, 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 anesthesia needs to be given only after careful discussion with the patient and anesthetist 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 minimize adverse outcomes.

High dose corticosteroids may achieve remission of both pathologies. In our case, we started with a low dose of steroids, because a transitory worsening of MG that is sometimes observed on initiation of corticosteroids would have carried significant risk.

Conclusion

In conclusion, a co-occurrence of myasthenia gravis (MG) and Graves' disease (GD) is not a coincidence, and it is one that clinicians should always have in mind. The coexistence of MG with GD might have prognostic relevance and occur in a subgroup of MG patients with a mild form of the disease. The presence of GD may obscure the diagnosis of associated MG due to symptom similarity; therefore, it is a clinical task to think about the possible association of MG in case of progression and neurological symptoms. Hyperthyroidism and administration of ß-blockers may worsen the symptoms of MG, so co-occurrence of the two diseases may result in poorer prognosis and therapeutic response.

Conflict of interest: None declared

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