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TREATMENT DILEMMA IN PATIENTS SUFFERING FROM MYASTHENIA GRAVIS AND HYPERTHYROIDISM

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ABSTRACT Myasthenia gravis (MG) is a rare auto-immune disease characterised by antibodies against Acetylcholine receptors on the post synaptic neuromuscular junction leading to progressive weakness of different muscle groups. Graves' disease is another auto-immune condition involving antibody mediated activation of TSH receptors leading to hyperthyroidism. The two pathologies may co-exist in a single patient or one may precede the other. MG and hyperthyroidism may have similar clinical features making it difficult for the clinician to distinguish the two. The two conditions, moreover, have a see-saw relationship, wherein treating one may worsen the other. Here we present a unique case of a patient admitted in the ICU with MG showing features of thyrotoxicosis.

KEYWORDS : myasthenia gravis, thyroid disease, autoimmune disease, thyrotoxicosis

INTRODUCTION

In a normal neuromuscular junction, the action potential prompts the release of ACh from the synaptic vesicles which combine with the AChRs (consisting of five subunits - 2 , 1â, 1 , 1 or å) producing depolarisation at the end plate region of the muscle fibre. In MG, the fundamental defect is an autoimmune mediated decrease in the number of available AChRs at the post synaptic muscle membrane. Therefore, even though the ACh is normally released, it produces small end plate potentials that may fail to trigger muscle action potentials.

Thyrotoxicosis is a clinical state of inappropriately high levels of circulating thyroid hormones (T3 and/or T4) in the body. The major etiology of thyrotoxicosis are hyperthyroidism caused by Graves' disease. The hyperthyroidism in Graves' disease is caused by thyroid stimulating immunoglobulins (TSI). Symptoms include hyperactivity, irritability, sweating, palpitations, fatigue and weakness, weight loss, diarrhoea etc.

The overlap in symptoms between MG and thyrotoxicosis may make the diagnosis of either condition difficult and often time subtle clinical signs may be missed or may be confused for another.[1]

The treatment modalities of thyrotoxicosis may worsen the clinical picture of MG. MG is worsened by antithyroid medications through immunomodulatory effects. Moreover, â-blockers and corticosteroids may worsen the weakness of MG. Here, we report a rare case of a 24 year old man with a known case of hyperthyroidism who presented with features of myasthenic crisis.

Case Report

A 24 year old male presented to the emergency department with complaints of difficulty in swallowing, breathing, speech and movement in shoulders since 1 day. He also complained of generalised weakness and fatigue with double vision and drooping of eyelids. Past medical history revealed that he was diagnosed with hyperthyroidism 2 years back and with ocular myasthenia gravis 3 months back following a positive decremental response to a neostigmine challenge test. Patient was taking Tab. Carbamizole 20 mg TDS for hyperthyroidism for the past 2 years and was on Tab. Pyridostigmine 60 mg BD for ocular MG.

On examination in the emergency department his vitals were as follows: HR- 98/min; BP- 160/80 mmHg; SpO2- 93% on room air; GCS- 15/15 with intact orientation to time place and person. The patient was unable to hold his neck up and had a single breath count of <10 seconds. Systemic examination was unremarkable except for CNS which revealed weakness in the extra-ocular eye muscles - CN III, IV, VI (upward movement affected in b/l eyes); CN VII - b/l ptosis (orbicularis oculi); CN XI - weakness in shrugging the shoulders; and CN XII - weakness in protruding the tongue. CN I, II, V, VIII, IX, and X were found to be normal in clinical examination. Motor examination revealed a loss of power in all limbs (4/5) except hip and shoulder joints that had a power of 3/5. There was no atrophy or loss of bulk in any of the muscle groups. DTRs were preserved. There was no history of similar episodes in the past. The patient did not report any history of similar disease or any other autoimmune condition in his family.

Suspecting acute myasthenic crisis with thyrotoxicosis, the patient was started on IVIg @ 2g/kg given over a period of 5 days. He was also given Inj. Methyl prednisone 1 g iv OD; Tab carbamizole 20 mg TDS; Tab propanolol 40 mg OD; Tab pyridostigmine 60 mg TDS; tab paracetamol 650 mg sos. The condition worsened in the emergency department with a decrease in power in b/l shoulder and hip joints from 3/5 at initial presentation to 2/5. A fall in SpO2 with tachypnoea and a falling GCS prompted a call to the Anaesthesia and ICU department for intubation. After thorough evaluation the patient was shifted to the general icu and tracheal intubation was performed following which the patient was put on mechanical ventilation with adequate sedation and analgesia. A central venous line was secured via the right internal jugular vein and a foleys catheter was inserted along with a nasogastric tube for enteral feeding.

During the course of the icu stay the patient started developing intermittent episodes of fever (101 to 104°F) and sinus tachycardia on ECG (110 - 130 bpm) for which Tab metoprolol was added to the treatment. Obvious causes of fever and tachycardia were ruled out. Blood and urine cultures were sent and the patient was started on appropriate antibiotics. CVP

guided fluid therapy was given and lab investigations were sent included a thyroid panel. Along with intermittent tachycardia the patient also developed episodic spikes in blood pressure with systolic pressures of 220-180 mmHg and diastolic pressures of 110-130 mmHg. Inj. Nitroglycerin infusion was started @ 3ìg/kg/min with intermittent boluses of â-blockers for hemodynamic control. Intra-arterial access was secured in right radial artery for beat to beat blood pressure monitoring.

The fever became unresponsive to antipyretics and could only be controlled with continuous cold sponging and surface cooling. Several differentials were kept in the diagnosis including pheochromocytoma, intracranial pathology, and thyroid storm. USG abdomen failed to reveal any mass in the abdomen and urine VMA (vanillylmandelic acid) was negative which ruled out pheochromocytoma. MRI brain also did not reveal any intracranial pathology.

While the thyroid results were awaited an empirical diagnosis of thyroid storm was made in view of fluctuating heart rate, blood pressure and body temperature along with waxing and waning sensorium. Investigations revealed a TSH of 0.04 mU/L with elevated free T3 and T4. The dose of Tab. Propranolol was increased to 20 mg QID and super saturated potassium iodide drops (SSKI) 3 drops BD were added.

After 17th day of endotracheal intubation, elective percutaneous dilatation tracheostomy was done. Patient gradually showed improvement in hemodynamics and other clinical parameters and after satisfactory spontaneous breathing, T-piece trials were given. He was gradually weaned off of mechanical ventilation. He was shifted to medicine ICU at 2 L/min of oxygen and after another round of IVIg he was discharged with tracheostomy in situ.

DISCUSSION

Myasthenia gravis is an autoimmune disease caused by circulating antibodies against post synaptic AChR on the muscle membrane. The incidence of MG in India is 2.1 to 5.0 per 100,000 people per year. The onset is between 20-40 years of age with 60% of cases being diagnosed in women. Men show a higher incidence later in life than women. Even though the autoimmune response involved in the initiation and maintenance of MG is not clearly understood, thymus is thought to play an important role in this process, being abnormal in 75% of AChR antibody positive MG.

The distribution of muscle weakness in MG has a characteristic pattern. Initial muscle groups involved are the cranial ones, particularly eyelids and extra-ocular muscles. In 85% of patients the weakness becomes generalised, affecting the proximal limb muscles. Ocular MG is characterised by weakness of only the ocular muscle groups. Despite muscle weakness, deep tendon reflexes (DTRs) are preserved. If respiratory weakness develops requiring ventilatory support, the patient is said to be in myasthenic crisis.

There are several diagnostic tests available for MG such as ice-pack test, electrophysiological studies, anticholinesterase test, autoantibodies measurements.

Treatment options include acetylcholinesterase inhibitors, corticosteroids, immunosuppressants and thymectomy.[2]

Being an autoimmune condition, MG has associations with other autoimmune diseases, autoimmune thyroid disease being the most common one.[3] Seropositive MG (AChR positive) is linked to endocrinological conditions.[4] MG association with other diseases was studied in a study on a group of 127 people with subsequent follow up for ten years. The outcome of the survey showed that the onset of disease before the age of 50, being more prevalent in women, 65% of patients also showed another condition, out of which 15% had an autoimmune disease. Associated diseases were systemic lupus erythematosus (SLE), hypertension, heart disease, and dyslipidemia. Around 10.2% were diagnosed with extrathymic tumors.[5]

A retrospective study found the relationship between MG and endocrinological disorders. 109 MG patients participated and distinguished based on AchR antibodies presence or absence. 66% were seropositive MG patients in the study and had thymic hyperplasia, thymoma, or thyroid disease.[6] Cross reaction between thyroid receptors and neuromuscular junction immunologically may be seen in patients with MG and Graves' disease leading to their simultaneous presence in the same patient.[7] Another retrospective study was done from 2008 to 2009 on 300 patients of MG for linkage of MG with thyroid disease. The study results showed that MG patients with positive thyroid antibodies have a higher number of AchR antibodies and more abnormalities with T cells.[8] Of all the thyroid diseases, Graves' disease is more frequent in patients with MG. The underlying cross reactivity of antibodies and receptors involved in MG and Graves' disease may give rise to this clinical scenario which can make the diagnosis of either disease challenging due to the overlapping clinical presentation. Furthermore, the anti thyroid medicines such as carbamizole are known to worsen the weakness seen in myasthenia gravis.[9]

Because of diagnostic confusion, there are also different approaches in treating MG with and without thyroid disease, and treatment of one pathology may worsen the other one. A literature study by Nicole MW et al. presented a patient with exophthalmos, right-sided lid retraction, and diplopia. Graves' disease was confirmed after running lab investigations with TSH antibodies. Symptoms improved with antithyroid medications and steroids but came back two weeks later with new left-sided ptosis and diplopia recurrence. Diagnostic testing for MG came out to be positive also diplopia and ptosis improved with pyridostigmine.[10]

Our patient had established hyperthyroidism for which he was regularly taking carbamizole which improved his initial symptoms of hyperthyroidism but also brought to surface his myasthenic weakness which was diagnosed as ocular MG. Continued therapy with carbamizole could have led to severe worsening of MG symptoms landing the patient in myasthenic crisis which brought him to our emergency department.

The stress of respiratory insufficiency and subsequent intubation and mechanical ventilation could have triggered the thyroid storm in this patient during the hospital stay. The treatment of thyrotoxicosis in a pt of myasthenia gravis is complicated by the see saw relationship between the two. Aggressive treatment of thyroid storm with â-blockers and corticosteroids may prolong the recovery of myasthenia induced muscle weakness and may make weaning from mechanical ventilation difficult or delayed.[11] Knowledge of coexistence of these clinical entities may help the clinician to better tailor the treatment of either disease.

CONCLUSION

Myasthenia gravis and graves' disease are well known autoimmune diseases. Despite advancements in understanding pathology and treatment strategy, there is still an increased number of myasthenic crisis episodes. Similarities in clinical presentation among both the pathologies have resulted in not detecting the other autoimmune disease. Furthermore, treating thyroid disease sometimes leads to worsening of myasthenia gravis symptoms. Further studies and research is needed to discover new distinguishing tests for both pathologies. More research is required to better understand the association and yield a better management strategy so that we have a better

guideline to follow. More case-control studies, case series, and randomised clinical trials are needed as we do not have much data available at the moment, to get more knowledge about the association between these two pathologies and devise a better management plan.

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