

A Case of Grave's Disease with Unusual Presentation

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ABSTRACT

Hyperthyroidism is a common metabolic disorder with many cardiovascular manifestations. In rare cases, untreated hyperthyroidism can lead to thyrotoxic cardiomyopathy with severe left ventricular (LV) dysfunction and if its associated with myasthenia gravis it can result into the acute respiratory failure. This case report aims to discuss the pathogenesis of heart failure and respiratory failure in hyperthyroidism and the available treatment options.

A 26 yrs old male patient with a past history of uncontrolled hyperthyroidism has presented with anxiety, difficult breathing and irrelevant talking. After doing examination and full workup he was found to have left ventricular failure and associated acute respiratory failure. Acute respiratory failure was a presentation of masked myasthenia gravis association. Beta-blockers and anti-thyroid medication was started and patient was stabilized.

A good medical history along with clinical examination can reveal the diagnosis and the TSH level should be checked as a part of the initial laboratory workup of every patient with new-onset CHF. One should always keep association of myasthenia gravis in mind.

Key words: Thyrotoxicosis, myasthenia gravis, acute respiratory failure, left ventricular failure.

INTRODUCTION

Graves' disease (GD) is characterized by a hyper functioning thyroid gland due to stimulation of the thyroid stimulating hormone (TSH) receptor by auto antibodies directed against it. It usually presents with the common well-known symptoms and signs (goiter, ophthalmopathy, weight loss, nervousness, tremors, palpitations, sweating, etc.) which are the distinctive features of the disease. Atypical manifestations of GD include cardiopulmonary, hematological, gastrointestinal, periodic paralysis and psychosis.

The cardiovascular manifestations range from sinus tachycardia to atrial

fibrillation and from a high cardiac output state to congestive heart failure (CHF) due to systolic left ventricular dysfunction. In addition to the well-known presentations, a variety of unusual cardiovascular manifestations are increasingly being reported in association with hyperthyroidism. These include pulmonary arterial hypertension (PAH), ^[1,2] right heart failure, ^[1,2] myocardial infarction, ^[3] and heart block. ^[4] Clinically, isolated right-sided heart failure may be the presenting feature of GD. If the underlying hyperthyroidism is recognized and treated early, the CHF in such cases can be cured.

GD is an organ-specific autoimmune disorder and hence is associated with

various other autoimmune disorders. Myasthenia gravis (MG) is one such disease, which is seen with patients of GD and vice versa. Though the association of GD and myasthenia is known, subtle manifestations of the latter can be frequently missed in routine clinical practice. The coexistence of GD and systemic MG poses a significant diagnostic dilemma to treating physicians. This can be demonstrated in the case presented below.

CASE REPORT

A 26 years old male patient presented to the emergency department with severe anxiety, discomfort and irrelevant talking for 4hrs. A day before he had come to casualty with 1-week history of cough and difficulty in breathing. The patient was nebulized and oral antibiotics were prescribed.

The patient was diagnosed with hyperthyroidism 3years ago. He was prescribed with T. carbimazole 20mg bd and Propranolol 40 mg tds; however, was non-complaint with medication.

On general physical examination, the patient was thinly built, and appeared cachectic. He was afebrile, blood pressure was 168/87mmHg, pulse 146 beats per minute synchronous with a regular rhythm. His respiratory rate was 16 breaths per minute, and the oxygen saturation 98%. He had no lymphadenopathy. Neck examination was normal. Respiratory system examination was normal. Cardiovascular examination revealed S1 S2 and tachycardia with regular heart rhythm. No obvious murmur was found. Ocular examination revealed ptosis in both eyes. Neurological examination revealed fine tremors in hands. Reflexes were normal. He had bilateral exophthalmos with binocular diplopia on lateral gaze.

Laboratory tests including thyroid function tests, chest X-ray, neck USG, ECG, and Echocardiography were advised. FreeT4 levels were raised 98pmol/L, free T3 levels were raised 20.05pmol/L, TSH levels were suppressed 0.0005. Chest x-ray

was normal, ECG revealed sinus tachycardia. Neck USG revealed diffuse enlargement of the thyroid gland with heterogenous echo pattern and mildly increased in vascularity. Echocardiography revealed severe LV systolic dysfunction, LVEF 28% by Simson's method. Troponin T levels were raised 0.073 ng/ml. Renal function tests and venous blood gas tests were normal.

Based on clinical presentation and laboratory tests, the patient was diagnosed with a Left ventricular failure secondary to hyperthyroidism.

The patient was admitted and IV propranolol 60mg qid with carbimazole 20 mg qid were started. He developed cardiac arrest while trying to get out of the bed. This is because of the poor cardiac output which the patient had and beta blockers like propranolol can precipitate cardiac arrest in those with cardiac storm and poor cardiac output. During this event after resuscitation his trachea was intubated and ventilated. He got extubated the next day as his condition was stable. However, he could not maintain his oxygen saturation and he developed CO2 narcosis after 24 hours of extubation which was confirmed by arterial blood gas analysis. The patient was re-intubated, the possibility of Thyrotoxic myopathy was considered. On re-evaluation of the patient it was found that he was having bilateral ptosis which could not be explained by thyroid eye disease. So an ice pack test was carried out to rule out associated Myasthenia Gravis and his ptosis almost disappeared. Confirmed the diagnosis of MG by oral neostigmine test and repetitive nerve conduction studies and EMG.

A CT scan chest to rule out thymoma along with Anti-ACH antibody and ANA antibody titers were requested. His Anti-TSH receptor Antibody, anti-AChR Abs and anti-ANA Abs turned out to be positive; however, his CT chest was normal. Based on these findings patient was started on IV immunoglobulin, pyridostigmine 60 mg tds doses, tab. prednisolone 60 mg and mycophenolate

mofetil 250 mg bd. CT scan of orbit and brain were normal. Orbital CT showed normal extra-ocular muscles and fat.

After 2 months of treatment, the patient's thyroid status became normal and his repeat Echocardiography show marked improvement (Ejection fraction 55%). The patient was successfully discharged from the hospital.

DISCUSSION

A case of severe but reversible systolic Left Ventricular dysfunction along with respiratory and ocular muscle weakness due to uncorrected hyperthyroidism with myasthenia gravis has been presented. In our opinion it is a first case which has presented with LVF and respiratory failure due to thyrotoxicosis associated with myasthenia after doing Pubmed search. Failure to recognize the features of hyperthyroidism has probably led to the development of congested heart failure as in our patient. Hyperthyroidism can present with a wide variety of signs and symptoms. Typically, it presents with the features of heat intolerance, weight loss, sweating, palpitation, tremors, and diarrhea, especially in younger patients. In Graves's disease one has to have lid retraction and not ptosis. This finding helped us to reach the proper diagnosis.

In elderly patients with the cardiac disease, it presents with heart failure in the absence of any classic symptoms of hyperthyroidism, palpable thyroid mass may be absent in as many as half of the patients. If left untreated, it can cause heart failure. In addition, if it is associated with systemic myasthenia it can result in ptosis, dysphagia, severe muscle weakness.

One should suspect thyrotoxicosis in a patient who has persistent sinus tachycardia or atrial fibrillation especially when the ventricular rate cannot be slow down with the usual dose of digoxin; in patients with congestive heart failure that has no obvious cause or that is accompanied by weight loss and in patients with worsening of angina pectoris. The single

best method for assessing the possibility of thyrotoxicosis is a measurement of serum thyrotropin [5] If the concentration is low, the serum free T4 should be determined; a higher value for either confirms the diagnosis of thyrotoxicosis. [6] Measurement of total T3 and total T4 in serum may be misleading, since patients with severe cardiac disease, like patients with nonthyroidal illness in general, have decreased peripheral conversion of T4 to T3 and decreased plasma protein binding of both hormones. These disturbances result in a decrease in serum total T4 concentrations and, less often, serum total T4 concentrations. [7] On the other hand, a normal serum total T3 concentration in a patient with severe cardiac disease suggests that thyrotoxicosis may be present.

Hyperthyroidism and effect on heart:

Profound circulatory alterations accompany the thyroid state. They include an increase in total blood volume; the increase in total blood volume increases preload, whereas the decrease in total systemic vascular resistance reduces afterload. In addition, there is an increase in the rate of left ventricular diastolic relaxation, which contributes to the increase in left ventricular end diastolic volume. [8] Thyroid hormone has a direct positive chronotropic action. [9] It increases SA node firing, decreases the electrical threshold of atrial excitation. Increase in preload causes increase stroke volume of patients with thyrotoxicosis and results in an increase in left ventricular end-diastolic volume. [10]

Thyrotoxicosis is an uncommon cause of atrial fibrillation (5%–22% of hyperthyroid patients) [11, 12] and is probably the most common cardiovascular problem that brings this disease to medical attention. The preferential involvement of the atria in hyperthyroidism is thought to be due to an abundance of β receptors in the atria, [13] the difference in the sensitivity of the atria and the ventricle to thyroid hormone, and the difference in autonomic input to the atria and the ventricles. [14-16] In hyperthyroidism, atrial fibrillation is often undertreated

because it is usually resistant to digoxin; serum digoxin levels are low due to the increased volume of distribution and metabolism. [17,18] Therefore, higher than normal doses are required for adequate control of the ventricular rate. Uncontrolled atrial fibrillation of long duration has been linked to the development of "tachycardia-related cardiomyopathy" in hyperthyroidism. [17]

The first line of treatment of CHF secondary to hyperthyroidism is a β blocker, except in patients with marked hypotension, reversible airway disease, and marked bradycardia, especially with second- or third-degree atrioventricular block. Beta-blockers not only help ameliorate the noncardiac symptoms of the disease but also decrease the heart rate, by controlling, sinus tachycardia and/or decreasing the ventricular response to atrial fibrillation by action on the β_1 receptors, in addition to other unproven actions. [19-21] In some patients who cannot tolerate β blockers, such as those with reversible airway disease, a non dihydropyridine calcium channel blocker, such as diltiazem, can be used. Diltiazem has been shown to be safe and effective in ameliorating the hyperadrenergic symptoms of hyperthyroidism when compared with β blockers. [22, 23] In addition to definitive therapy, oral or intravenous diuretics should be used for symptomatic relief. Whether ACE inhibitors should be started as a part of the initial treatment is not clear. It is empirically believed that an ACE inhibitor should be part of the initial drug regimen, especially if the ejection fraction (EF) is markedly depressed and if there is concern about any other etiologic factors. Digoxin is reasonable with a low EF, the fast ventricular rate in atrial fibrillation, and/or moderate to severe CHF. All cardiac medications can be gradually withdrawn once the euthyroid state has been achieved, the LVEF has improved, and sinus rhythm has returned, with a periodic clinical or echocardiographic assessment of LV function. LV function tends to improve

within a few weeks of initiation of treatment of thyrotoxicosis and heart failure. In particular, LV function improves when the rapid ventricular rate, due to either sinus tachycardia or atrial fibrillation, is brought under control.

Association between thyrotoxicosis and myasthenia gravis:

Myasthenia gravis occurs in 0.35% cases of hyperthyroidism while as 1-5% of patients with myasthenia gravis develop hyperthyroidism. [24]

In our case, the patient was having moderate ptosis along with respiratory muscles weakness which raised suspicion of associated myasthenia gravis. On further laboratory tests, anti-Ach receptor and anti-ANA antibodies were present. Ice-pack test was positive. In addition, improvement in his condition after starting immunoglobulins confirmed associated myasthenia gravis. Physical findings can vary in myasthenia as the muscle weakness tends to be more when the muscles are stressed. Muscle strength improves with rest, so the initial physical examination may not reveal any neurological deficit as in our patient. The important factor that distinguishes the disorder from other neuropathies is that sensation and reflexes are preserved.

Diagnostic tests are needed to confirm clinical suspicion, including anticholinesterase test, repetitive nerve stimulation test, and acetylcholine receptor antibody test. Edrophonium is the drug of choice for the anticholinesterase test because of its rapid onset and short half-life (few minutes). The test is considered positive if there is considerable improvement in muscle strength. In the repetitive nerve stimulation test, electricity is delivered to the nerve, and action potentials are recorded on the surface of the muscle. The test is considered positive if there is a decremental response of 15%. [25] Acetylcholine receptor antibody testing is done with a radioimmunoassay and is positive in 85% of patients with generalized

myasthenia gravis patients and 30%–50% of ocular myasthenia gravis patients.

Other differential diagnoses that should be considered are Lambert–Eaton syndrome, drug-induced myasthenia, botulism, and intracranial lesions. Current treatment options for myasthenia gravis include anticholinesterase agents, surgical thymectomy, immunosuppression, and short term but fast-acting therapies such as plasma exchange and intravenous immunoglobulin. In general anticholinesterase agents are used as the first line agents along with surgical thymectomy or immunosuppression. Contemporary opinion is to carry out thymectomy in all patients who have attained puberty and are under 60 years of age even if they do not have a thymoma.

Thyrotoxic myopathy usually appears after 1-3 months of thyrotoxicosis. It is more common in men and can be the presenting feature. In a review of the literature, most common musculoskeletal findings of thyrotoxicosis are painless skeletal muscle wasting, with normal muscle enzymes and nonspecific electromyographic abnormalities. The discovery of anti-AChR Abs yielded useful diagnostic tests. The demonstration of serum anti-AChR Abs proves the diagnosis of MG. However, their absence does not exclude it because anti-AChR Abs are detectable only in 80%-90% of generalized myasthenia gravis (gMG) patients and 30%–50% of ocular myasthenia gravis (oMG) patients. [26]

CONCLUSION

We conclude that hyperthyroidism can cause left ventricular failure and it can also present as the unexplained cause of acute respiratory failure if it is associated with myasthenia gravis. A good medical history along with clinical examination can reveal the diagnosis and the TSH level should be checked as a part of the initial laboratory workup of every patient with new-onset CHF. It should be remembered that, ptosis is not an expected symptom in

thyroid ophthalmopathy. If ptosis or paresis of the orbicularis oculi muscle develops in a patient with thyroid ophthalmopathy, coincidence of myasthenia gravis should be considered.

Consent:

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Abbreviations: Graves' disease (GD), thyroid stimulating hormone (TSH), congestive heart failure (CHF), pulmonary arterial hypertension (PAH), Myasthenia gravis (MG), LV (left ventricle), LVEF (Left ventricular ejection fraction), generalized myasthenia gravis (gMG), ocular myasthenia gravis (oMG)

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