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Heart Complications of Graves 'disease: About 2 Cases

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Abstract **Case Report**

Graves' disease is associated with cardiac arrhythmias especially in the suprventricular stage, cardiac ischemia and cardiomyopathy - all rare in young adults without a history of heart disease. We present two young individuals who developed cardiac complications after periods of uncontrolled Graves' disease. ***Subject 1***: A 51-year-old woman, thyrotoxic for several months, developed atrial fibrillation (AF) and heart failure. Echocardiography showed cardiomegaly - EF 30%. It maintains sinus rhythm after early total thyroidectomy (EF 50%). ***Subject 2***: A 21 year old man developed thyrotoxic symptoms One month after starting carbimazole; he developed acute heart failure (HF) due to severe dilated cardiomyopathy - 15-20% LVEF. He partially recovered after treatment - 28% LVEF and had early treatment for his dysthyroidism. Significant heart complications can occur in previously physically fit young adults who have had Graves' disease that have not been controlled for weeks or even months. The majority of heart function is restored, but early definitive treatment should be discussed to prevent relapse of Graves' disease and other heart conditions.

Keywords: Cardiac complications, Thyrotoxicosis, Heart failure, Atrial fibrillation, Graves' disease, Case report.

INTRODUCTION

Thyrotoxicosis causes well-known short-term cardiac effects – increased heart rate, stroke volume, improved left ventricular stroke function and relaxation time. These changes are mediated by genomic and non-genomic effects of thyroid hormones. However, in the longer term and if left untreated, Graves' disease, the most common form of thyrotoxicosis, leads to increased cardiovascular morbidity and death [1]. Heart failure estimated at 16% in cases of overt hyperthyroidism contributes to this increased risk of cardiovascular morbidity, even in people without pre-existing heart disease [2].

Thyroid hormones have direct effects on the myocardium (mediated by triiodothyronine – fT3), the systemic vascular system and the autonomic nervous system [3]. Supraventricular tachycardias, heart failure, cardiomyopathy, pulmonary hypertension, and pericardial effusion are recognized cardiac complications of thyrotoxicosis [4, 5]. The risks of developing these cardiovascular complications are higher in middle-aged and older people and in people with pre- existing heart disease. However, there are increasing reports of these occurring in young adults without a history of heart disease [4]. The majority of these subjects [usually untreated or partially treated for months) make a full recovery after Graves' disease treatment and cardiac surgery. Reversible dilated cardiomyopathy, pericardial effusion, and heart failure, among others, have been previously reported in young patients with Graves' disease [4-6].

We present two young subjects with no cardiac history, who developed major cardiac complications of Graves' disease following significant periods of uncontrolled thyrotoxicosis. We emphasize the importance of the diagnosis of heart disease in this group of young and previously healthy individuals, particularly if they present with persistent symptoms despite adequate control of Graves' disease. We also highlight the reversibility of their heart disease when Graves' disease is controlled.

CLINICAL CASE PRESENTATION

Patient Information:

Subject 1: A 51-year-old woman with no previous cardiovascular history presented to the emergency room

with abrupt onset of palpitations, shortness of breath and leg swelling. She had been treated 3 years earlier for Graves' disease but had had an untreated relapse for at least 2 months prior to her visit to the emergency room. She had no significant medical history.

Subject 2: A 21-year-old, previously physically fit male presented with weight loss, palpitations, sweating, and diarrhea with no symptoms of Graves' orbitopathy. He did not smoke and consumed very little alcohol. His medical and social history was unremarkable.

Clinical Findings:

Sujet 1: Clinically, she was tachycardic with an irregular pulse, BP 136/81 mmHg, and heart failure. On the ECG, she had atrial fibrillation with a ventricular rate of 120/min.

Sujet 2: Clinically, he appears thyrotoxic with a regular pulse of 96/min, a BP of 111/79 mmHg, hand tremors and a smooth and symmetrical goitre**.**

Diagnostic Approach

Subject 1: Thyroid assessment showed fT4: 44.3 pmol/L; fT3 > 49 pmol/L; TSH < 0.01 and anti-TSH receptor antibody (Anti RTSH Ab) = 15.5. A chest x-ray showed cardiomegaly. Echocardiography showed cardiomegaly, impaired left ventricular function with an EF of 30% and a small pericardial effusion (4 mm) with spherical heart geometry.

Subject 2: FT4 was 33.1 (9–19.1 pmol/L), fT3: 12 (2.6–5.7 pmol/L), TSH < 0.01 and anti RTSH Ab=20.1. Cervical ultrasound showed an enlarged thyroid, with regular contours, hyper-vascularized without a clearly circumscribed nodule. At the time of decompensation, echocardiography revealed signs of severe dilated cardiomyopathy (DCM) with a left ventricular EF of 19% and spherical heart geometry. Comprehensive investigations (including coronary angiography, extensive etiologic workup for cardiomyopathy) ruled out other causes of DCM. EF partially recovered in 28% after definitive treatment of Graves' disease.

Therapeutic Intervention and follow-up:

Subject 1: She was initiated on Carbimazole, slowed down by Bisoprolol 10 mg. The heart failure episode was controlled with Furosemide 40 mg per day and Ramipril 1.25 mg per day. We decided not to anticoagulate her because of rectal bleeding which was being explored and a CHA_2DS_2-VASc score of 1. After a period of stability, she underwent an early total thyroidectomy.

After treatment, his ejection fraction improved to 40-45% with regression of ventricular dilation; as well as a transition to sinus rhythm.

Subject 2: He received 15 mg of carbimazole daily and propranolol, in addition to the treatment of dilated cardiomyopathy and heart failure: ramipril 2.5 mg, furosemide 40 mg, spirinolactone 25 mg which also been administered.

Currently, his ejection fraction has partially recovered to 35% after initiation of treatment for Graves' disease, and his cardiac geometry is now ellipsoid. It maintains cardiovascular stability under drug treatment.

DISCUSSION

We described three young subjects with no previously known heart disease, who had well-known but uncommon cardiac complications of Graves' disease in this age group. Thyroid dysfunction with elevated fT3 and fT4 had been present and untreated or partially treated for several weeks to months prior to presentation in each. All three patients had substantial recovery of cardiac function after effective control of Graves' disease and cardiac therapy.

Thyroid hormones exert their effects on cardiac myocytes, vascular smooth muscle, and vascular endothelium through both genomic (fT3) and non-genomic (fT3 and fT4) actions [7]. Although these mechanisms mediate effects on heart rate and rhythm, other effects such as changes in autonomic function may also contribute to cardiovascular actions [8]. These effects of thyroid hormones are mediated by the activation of genes controlling cardiac muscle function and chronotropy [8]. Cardiac contractility improves in the short term and in the long term cardiac mass increases. However, if the thyrotoxicosis is prolonged or severe, heart failure can often develop when tachycardia such as atrial fibrillation (AF) occurs Age, pre-existing coronary and valvular diseases are risk factors for AF and its complications. But it is now increasingly recognized that Graves' disease causes significant cardiac morbidity and mortality, even in young individuals who have no previously known heart disease [4, 9]. None of our subjects had a history of heart disease and, at presentation, had no clinically apparent vascular risk factors or comorbidities other than Graves' disease. Of note, they also had untreated or partially treated Graves' disease for several weeks to months prior to presentation. Despite previously normal cardiac function, Graves' disease treated suboptimally over several months may place physiological burdens on even relatively young cardiovascular systems, causing acute decompensation.

Pericardial effusion (PE) complicating Graves' disease is relatively rare – 7 of 12 case reports of pericardial effusion in subjects with thyrotoxicosis had Graves' disease [10]. Serous and bloody effusions have been reported. Two subjects were reported to require pericardiocentesis for cardiac tamponade [10]. None of these subjects had a history of heart disease. Although the exact mechanism of pericardial effusion in Graves' disease is not known, immune mechanisms are increasingly considered relevant. Our Subject 1 had a pericardial effusion complicating Graves' disease that developed a few weeks after starting treatment. Further shortness of breath at a time when thyroid function was

improving after a thyroid storm alerted doctors to this rare cause of her symptoms. His effusion responded to standard treatment and there was complete cardiac recovery.

Severe cardiomyopathy in adults with hyperthyroidism is rare – it is estimated to occur in only about 5.8% [11, 12]. But among them, only <1% develop dilated cardiomyopathy with LV involvement. Although most are recovering, some deaths have been reported. The exact mechanism of dilated cardiomyopathy in Graves' disease is uncertain, and prolonged and uncontrolled hyperthyroidism and autoimmunity have been postulated as causative [13]. Tachycardia- related cardiomyopathy can also complicate Graves' disease, and in a recent study of rhythmic heart disease, LV dysfunction did not normalize despite adequate rhythm and rate control, implying a possible anomaly underlying heart disease before the onset of tachycardia. Our subject 3 had cardiomyopathy likely related to tachycardia presenting as decompensated dilated cardiomyopathy for which no obvious cause other than Graves' disease was found. His cardiac recovery was partial (improving to 28%) despite adequate cardiac and endocrine control. We can only speculate if an underlying heart defect was present in him prior to the development of Graves' disease.

There is an increased prevalence of AF in people with hyperthyroidism compared to the general population (10- 15% vs. 0.5%) and the prevalence is higher in people with coronary or valvular disease and CI. The development of AF in thyrotoxicosis is related to multiple actions of fT3 – increased systolic and diastolic depolarization, decreased action potential duration, and decreased refractory period of the atrium and auriculo node -ventricular. The role of the pulmonary veins has also been recognized. The risk of ischemic stroke is increased in people with AF complicating hyperthyroidism. The view that hyperthyroidism is a "procoagulant state" should also be taken into account when assessing the risk of ischemic stroke in this condition [15]. The role of the reported increase in fibrinogen, factor X and von Willebrand antigen levels is currently only speculative [16]. However, there have been no clinical trials evaluating the benefit of anticoagulation.

CONCLUSION

We demonstrated that significant cardiac complications of Graves' disease (dilated cardiomyopathy and rate- related cardiomyopathy and AF causing heart failure) can occur in young, previously healthy patients without heart disease. All had Graves' disease partially treated or untreated for several weeks or months. It is therefore important to exclude Graves' disease-related heart disease in people who develop significant cardiorespiratory symptoms inconsistent with their thyroid status and under appropriate clinical circumstances. The majority of patients respond well to thionamides and specific cardiac intervention with complete or partial reversal of cardiac abnormalities [17], but definitive treatment should be discussed early to avoid Graves disease relapse and potential recurrence of decompensation cardiac [18].

What is known about this subject?

- Thyroid hormones act directly on the heart and the circulatory system, by increasing the myocardial inotropic effect, heart rate and peripheral vasodilation leading to an increase in cardiac output.
- A high level of thyroid hormones exposes patients to cardiovascular complications which are not uncommon in hyperthyroidism and can be revealing. Graves' disease is associated with heart rhythm disorders, especially at the supraventricular level, cardiac ischemia and cardiomyopathy in patients.
- Prior cardiac involvement exposes you to an increased risk of cardiac complications during hyperthyroidism, as in Graves' disease.

What is new about our study?

- We demonstrated that significant cardiac complications of Graves' disease (dilated cardiomyopathy and rate- related cardiomyopathy and AF causing heart failure) can occur in young, previously healthy patients without heart disease. This should push us to watch for complications in all patients presenting with Graves' disease.
- It is always necessary to eliminate a cause secondary to heart conditions, in particular hyperthyroidism as in the case of Graves' disease, which remains a significant and frequent cause.
- It has also been shown that early and well-conducted treatment can partially or totally reduce heart disease secondary to hyperthyroidism. This exempts patients from lifelong cardiac treatment and its potentially serious side effects.

Patient Consent: The patient has given consent.
Conflicts of Interest: The authors declare no conflicts of interest.

Author Contributions

All authors contributed to the drafting of the manuscript, all authors read and approved the final version of the manuscript.

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