Case Report ISSN: 2833-034X

Women's Health Care and Issues

A Case of 31 WKS Primi with Acute Hypertensive Left Heart Failure with Severe Pre- Eclampsia Secondary to Graves' Disease

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Received: 07 Feb 2022; **Accepted:** 10 Mar 2022; **Published:** 15 Mar 2022

Citation: Gomes RR. A Case of 31 WKS Primi with Acute Hypertensive Left Heart Failure with Severe Pre- Eclampsia Secondary to Graves' Disease. Womens Health Care Issues. 2022; 1(1): 1-5.

ABSTRACT

Graves' disease, a well-known cause of hyperthyroidism, is an autoimmune disease with multi-system involvement. More prevalent among young women, it appears as an uncommon cardiovascular complication during pregnancy, posing a diagnostic challenge, largely owing to difficulty in detecting the complication, because of a low index of suspicion of Graves' disease presenting during pregnancy. Globally, cardiovascular disease is an important factor for pregnancy-related morbidity and mortality. Here, we report a case of 24 years old primi with Graves' disease detected for the first time in pregnancy presenting with acute hypertensive left heart failure and severe pre-eclampsia. She was found to have abnormal thyroid function tests compatible with the diagnosis of Graves' disease. Emphasis is placed on the spectrum of clinical presentations of Graves' disease, and the importance of considering this thyroid disorder as a possible aetiological factor for such a presentation in pregnancy.

Keywords

Graves' disease, Hypertensive left heart Failure, Pre-eclampsia, Pregnancy.

Introduction

Grave's disease (GD), named after Robert J. Graves, MD, circa 1830s, is an autoimmune disease characterized by hyperthyroidism due to circulating autoantibodies [1]. Thyroid stimulating immunoglobulins bind to and activate thyrotropin receptors, causing the thyroid gland to grow and the thyroid follicles to increase synthesis of thyroid hormone. Grave's disease accounts for 60-80% of cases of hyperthyroidism, with a female/male ratio of 5-10:1 and peak incidence between the ages of 40 and 60 [2]. GD is associated with multisystem involvement chiefly characterized by a diffuse goiter and features of thyrotoxicosis; it may also be accompanied by an infiltrative orbitopathy, ophthalmopathy and occasionally infiltrative dermopathy. Due to the autoimmune nature of GD, and given that pregnancy is a state of immunosuppression, thyrotoxic symptoms generally show a regression as the duration of pregnancy progresses. This can be explained by the diminished functions of both T-cells and B-cells under the influence of local placental factors and regulatory T cells.

Thyrotoxicosis is well known to associate with left ventricular dysfunction due to long-standing effects of thyroid hormones. There are various cardiovascular manifestations for hyperthyroidism, such as cardiomegaly, increased cardiac output, atrial fibrillation, and, in certain cases, congestive heart failure [3,4].

Globally, cardiovascular disease is an important factor for pregnancy-related morbidity and mortality, and complicates 1-4% of all pregnancies [5,6]. In addition to maternal mortality, cardiovascular diseases are responsible for approximately 30% of all deaths globally [7,8]. GD is not a common presentation of cardiovascular complication in pregnancy. We report here a case of acute hypertensive left heart failure and pre-eclampsia in pregnancy due to GD.

Case Report

A 24-year-old Bangladeshi primi in her 31st week of pregnancy, not

known to have hypertension, bronchial asthma, diabetes mellitus or any vulvular heart disease was admitted to our medical college hospital with 7 days history of shortness of breath on exertion (NYHA Class II) which had worsened to dyspnea at rest (NYHA Class IV) for two days and pedal edema, which she noticed two days back. She was not on any medications except iron and calcium supplements, and her family history was noncontributory. She also reported no fever, cough, hemoptysis, chest pain, weight loss or joint pain and had not traveled in the recent past. On initial assessment, she was tachypnoeic with a respiratory rate of 30 breaths per min, pulse 105/min regular, high volume with normal rhythm and blood pressure was raised at 200/110 mm of Hg with wide pulse pressure. She had mild pallor and was apyretic and peripheral oxygen saturation was 82% in room air. There was significant bi-pedal oedema. Jugular venous pressure was not raised. On systemic examination, Apex beat was hyperdynamic in character felt in left 6th intercostal space displaced 2 cm lateral to midclavicular line, Left parasternal heave and palpable P2was absent. Systolic thrill was present in mitral area. Auscultation revealed Soft S1 with Grade 5 pansystolic murmur in mitral area. There was bi basal mid to late inspiratory fine rales over both lung bases. Other systematic examination revealed no abnormalities.

She improved with initial treatment consisting of high doses intravenous diuretics and high flow oxygen and delivered a premature male baby of low birth weight (weight- 1.6 kg) per vaginally, 6 hours later. Upon further evaluation, a moderately enlarged thyroid gland was detected. The goitre was diffuse, non-tender and mobile, with no features of compression, thrills or bruits. However, there were no postural tremors, lid retraction, exophthalmos or other features of thyroid eye disease or thyroid dermopathy. Pulse pressure was wide (90mm Hg). Haemogram, serum electrolytes, serum creatinine and random blood sugar were within normal limit. Urine routine microscopy showed (++++) proteinuria with pus cells 4-5/HPF done before delivery. UTP was 2.2-gram protein/day. Electrocardiography showed sinus tachycardia and echocardiography revealed grade 3 mitral regurgitation (MR) and fair left ventricular systolic function with an ejection fraction of 50%. NT pro- BNP was 4225 pg/ml (normal less than 125 pg/ml).

Thyroid function tests revealed biochemically hyperthyroid state (Free T4- 6.56 ng/dl; Normal 0.71- 1.85 ng/dl and thyroid stimulation hormone [TSH] <0.001 uIU/ml; Normal 0.3 – 2.5 mIU/l). She had positive anti thyroid peroxidase antibodies (>1000 µ/ml; Normal ≤15 µ/ml) and positive TSH receptor antibody. 99m Technetium pertechnetate thyroid scan confirmed a diffuse toxic goiter as evidenced by enlarged thyroid gland with intense radiotracer concentration all over the gland. Thus, the clinical, biochemical and radiological features were consistent with Graves' thyrotoxicosis.

She responded to intravenous diuretics. Her thyroid hyperactivity was controlled with carbimazole 45 mg/day and propranolol 40 mg/day in divided doses, and blood pressure control following delivery was achieved with Lisinopril 10mg/day and nifidepine 20mg/day. Her child also made a healthy recovery. On OPD follow up after 6 weeks, she became euthyroid both clinically and biochemically. Blood pressure was100/70 mm of Hg. Thyroid function tests revealed (Free T4- 1.66 ng/dl; Normal 0.71- 1.85 ng/dl and thyroid stimulation hormone [TSH] 1.32uIU/ml; Normal 0.3 – 2.5mIU/l). A repeat echocardiogram revealed only trivial mitral regurgitation. Anti-hypertensive and propranolol were withdrawn. Carbimazole dose was reduced to 20mg/day. There is a plan to follow her up at a regular interval on outpatient door basis to assess her thyroid functional and cardiac status [9-18].

Discussion

Graves' disease, named after Robert J. Graves was first described in 1825 by Dr. Caleb Hillier Parry [1,19]. Known in Europe as von Basedow's disease, it is an autoimmune disease that may occur at any age, with a peak incidence in the 40- to 60-year age group and female to male ratio of 5–10:1 [2,14].

In this case, the young age of onset of disease (at 42 years) and high levels of anti-thyroid peroxidase antibodies and positive TSH receptor antibody indicate the genetic and epigenetic factors involved in the pathogenesis of GD. Immunochip genetic association analyses have identified 30 single-nucleotide polymorphisms in several genes significantly associated with the young age of onset (AO) GD, i.e. onset <30 years of age, including major histocompatibility complex class I and class II genes, BTNL2, NOTCH4, TNFAIP3 and CXCR4; most of the genes known to be associated with adult-onset GD were also associated with Young AO GD [10]. The epidemiology of GD is the result of complex interactions between genetic, epigenetic and various environmental factors. Gene- gene interactions and gene environment interactions (e.g. viral infection-related production of interferon-α induced alteration in thyroglobulin gene expression through epigenetic changes in histone modification) are mainly accountable for the pathogenesis. The thyroidal CD40 over expression can augment the severity of GD but is not required for disease development; in mice, it increased the level of thyrotropin (TSH) receptor antibodies and thyroid hormone production [11-15]. In humans, it is strongly associated with persistently high levels of post- treatment thyroid antibodies suggesting a role in thyroid antibody production [16]. The risk of developing GD is greatly increased when two or more disease-associated alleles are inherited together [15].

In the vast majority of cases, GD is the chief cause for thyrotoxicosis in pregnancy. However, as both pregnancy and hyperthyroidism are accompanied by thyroid stimulation, hyperdynamic circulation and hypermetabolism, the detection of hyperthyroidism can be challenging during pregnancy. Biochemically, a serum TSH level lower than the trimester-specific lower limit 0.3 mIU/L and an elevated free T4 level greater than the normal range for pregnancy strongly suggests coexistent hyperthyroidism; the detection of TSH receptor antibodies virtually confirms the diagnosis of GD [17]. In this case, confirmation of GD was achieved by the findings of diffuse toxic goiter in 99m Technetium scintigraphy thyroid scans and highly raised anti thyroid peroxidase antibodies and positive

TSH receptor antibody. Severe GD is uncommon in pregnancy as it is related with reduced fertility. For women with milder disease who successfully conceive, hyperthyroidism endows an increased risk of pregnancy loss and established pregnancy complications (Table 1) [18].

Table 1: Potential maternal and fetal complication in uncontrolled hyperthyroidism.

Maternal	Fetal
1. Pregnancy induced hypertension	1. Neonatal hyperthyroidism
2. Pre-eclampsia	2. Intrauterine growth retardation
3. Preterm delivery	3. Small-for-gestational- age
4. Congestive heart failure	4. Prematurity
5. Thyroid storm	5. Stillbirth
6. Increased or recurrent miscarriage	6. Increased perinatal mortality
7. Placenta abruption	
8. Infection	
9. Increased maternal mortality	

Preeclampsia affects 2%–8% of pregnancies worldwide and is a leading cause of maternal and child morbidity and mortality [19]. Although the prevalence is similar across the globe, large differences between high and low-income countries are found for complications and maternal death [19]. Preeclampsia is characterized by new-onset hypertension(systolic blood pressure ≥ 140 mm of Hg or diastolic blood pressure ≥ 90 mm of Hg and proteinuria(≥ 300 mg in 24 hours) after the 20th week of pregnancy and affects multiple organ systems [19]. Features of severe pre-eclampsia are summarized in table 2.

Table 2: Features of severe pre-eclampsia.

Table 1 Severe features of preeclampsia	
Severe hypertension	• SBP >160 mm Hg or • DBP >110 mm Hg • Taken on 2 occasions at least 4 h apart while on bed rest (unless antihypertensives have been administered)
CNS symptoms	• Persistent headache not relieved by analgesics • Visual changes
Pulmonary edema	• Clinically diagnosed
Thrombocytopenia	• Platelet count <100,000/mL
Renal insufficiency	• Serum creatinine >1.1 mg/dL, or • Doubling of the serum creatinine when other renal diseases have been excluded
Liver dysfunction	• Increase in liver enzymes to ≥ twice the upper limits of normal

The pathophysiological mechanisms leading to preeclampsia include impaired placentation, trophoblast invasion, and uterine spiral artery remodeling, followed by an adverse inflammatory, metabolic, and thrombotic response. However, the exact underlying mechanisms remain unknown. Thyroid hormone plays a role in placental development and is an important regulator of various metabolic and inflammatory processes [20-24]. Overt gestational hyperthyroidism is a known risk factor for preeclampsia [25-28]. In line with this, we previously showed that already high normal concentrations of freeT4 (FT4) are associated with a 2.1-fold higher risk of preeclampsia [29]. However, other studies on subclinical changes in thyroid function have shown conflicting results [27,28,30-33]. This might be due to the underlying mechanism causing high gestational FT4.

In this case, GD was first detected during the third trimester of pregnancy and was complicated by the development of acute hypertensive left heart failure, owing to the simultaneous contributions of both thyrotoxicosis and pre-eclampsia. With a blood pressure of 200/110mmHg, we also found a wide pulse pressure in this patient, characteristic of hyperthyroidism. Hyperthyroidism is a secondary cause of isolated systolic hypertension despite low systemic vascular resistance, due to increased arterial stiffness [34,35]. Cardiac output may be increased by 50 – 300% over that of normal subjects as a result of the combined effect of increase in resting heart rate, left ventricular contractility, ejection fraction and blood volume with a decrease in systemic vascular resistance [36,37]. Thyroxin not only affects the heart, but also alters the vascular smooth muscle and endothelial cell function via genomic and non-genomic actions targeting membrane ion channels and endothelial nitric oxide synthesis [38,39]. In addition, research evidence has revealed that the Calcium/ Calmodulin- dependent kinase IV (CaMKIV), which is a major thyroid hormone target gene in the developing brain, plays an important role in blood pressure regulation through the control of endothelial nitric oxide synthase (eNOC) activity. There is also a significant association between the human CaMKIV gene polymorphism and high diastolic blood pressure among hypertensive patients [40,41]. This patient had high diastolic blood pressure (diastolic blood pressure 110 mm Hg) and there is a possibility of presence of CaMKIV gene polymorphism in this case. Dysfunctional CaMKIV, albeit not expressed in the heart, might partake in cardiac organ damage in the context of the hypertensive state that we found in this case [40].

It has been well established that hyperthyroidism is associated with left ventricular dysfunction and heart failure [42]. β - Adrenergic receptors in the myocardium are under thyroid hormone regulation and are positively regulated; the G- protein coupled receptor kinase GRK5 is an important regulator in beta-adrenergic signaling [37,43,44].

Concordant with this patient's finding of MR on Doppler echocardiography, atrioventricular valve regurgitation has been documented to occur in hyperthyroidism with a high prevalence [45-47].

Conclusion

This was a unique case of GD-related acute hypertensive left heart failure and preeclampsia in pregnancy. Albeit uncommon, un-explained left heart failure in pregnancy may very well be explained by pre-eclampsia due to Graves' disease. However, with prompt diagnosis and appropriate therapies, the disorder can be treated successfully and without lasting harm to the mother or fetus. Such a diagnosis requires a high index of suspicion and subsequently specific treatment should be commenced promptly in order to ensure better outcome in such patients. For these reasons, it should remain on the differential for patients with symptoms of preeclampsia, and thyroid studies should be considered.

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