International Journal of Advances in Medicine
Saraswati SI et al. Int J Adv Med. 2025 Jan;12(1):97-102
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20243786

Case Report

Graves disease induced rapid ventricular response atrial fibrillation in association with hemorrhagic transformation in patient with ischemic stroke

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Received: 20 November 2024
Revised: 10 December 2024
Accepted: 11 December 2024

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ABSTRACT

Graves' disease is the most common etiology of hyperthyroidism caused by the presence of autoantibodies that stimulate the thyroid-stimulating hormone receptor (TSH-R). If graves' disease is not effectively treated, it can result in several complications, including atrial fibrillation, which affects 5-15% of patients with the condition. In this case, we report a 48-years-old male with hemorrhagic transformation in patient with ischemic stroke associated with Graves' disease, which occurred as a result of complications from atrial fibrillation. The patient has a history of ischemic stroke about one month ago and presented to the emergency department with a relapse of symptoms that had previously improved. Based on the history, physical examination, and supporting tests, a triad of graves' disease was identified, which supported the patient's diagnosis, including thyrotoxicosis, diffuse goiter, and ophthalmopathy. This case report discusses the mechanisms and factors that contribute to hemorrhagic transformation with a history of previous ischemic stroke in a patient with graves' disease, as well as comprehensive treatment approaches.

Keywords: Grave's disease, Hemorrhagic transformation, Ischemic stroke

INTRODUCTION

Hyperthyroidism is a pathological disorder due to excessive synthesis and secretion of thyroid hormones by the thyroid gland.[1] Graves' disease is an autoimmune disorder with its main manifestation caused by the presence of autoantibodies that stimulate the thyroid-stimulating hormone receptor (TSH-R) leading to hyperthyroidism and goiter.[2] This condition manifest as increasing level of blood T3 and free T4 hormone levels, with low TSH level.[3] Early diagnosis and treatment of Graves' disease can help prevent severe cardiac complications, including atrial fibrillation, atrial flutter, and high-output heart failure.[4]

Atrial fibrillation (AF) occurs in 5-15% of patients with hyperthyroidism and 13% of patients with new-onset AF have biochemical evidence that support the diagnosis of hyperthyroidism.[5] In the cardiovascular system, thyroid hormones have multiple effects and play a fundamental role in homeostasis, both in physiological and pathological conditions. Hyperthyroidism is associated with significant changes in the cardiovascular system, such as an increase in heart rate, venous return, and stroke volume resulting in increased cardiac output, reduced peripheral vascular resistance, and increased atrial automaticity, which then most of the patients develop specific complications due to the condition of hyperthyroidism.[6]

Stroke is a major complication of atrial fibrillation, with cardio-embolic causing approximately 25% of ischemic strokes, and AF is the most common etiology of those. One of the mechanisms causing stroke in AF is the impaired atrial contractility, which disrupts coordinated myocyte

activity, leading to blood stasis and an increased risk of embolism.[7] Hemorrhagic transformation (HT) is a frequent complication that results from an ischemic event and has been proposed to occur due to minor leakage from small vessels, with blood infiltrating brain tissue with minimal clinical consequences. However, the causative factors that lead to the progression of ischemia into hemorrhagic infarction are not fully understood.[8]

In this case, reported a 48-year-old male patient with graves' disease induced rapid ventricular response atrial fibrillation associated with hemorrhagic transformation following ischemic stroke.

CASE REPORT

A 48-year-old male patient came to the emergency department with chief complaint of left-sided body weakness. The complaint was felt since the morning before admission to the hospital which appeared suddenly when the patient was walking around the house. The patient also complained of palpitations, his lips looked parted, slurred speech and difficulty swallowing. The patient had previously experienced similar complaints and had a history of ischemic stroke about one month ago. Three days after hospitalization, the patient was referred to the internal medicine department with suspicion of thyroid problems because there was mass symmetrical in both side of neck. The patient noticed the mass since one month ago, previously small in size, but gradually getting bigger. This painless mass was colorless, with normal temperature. The patient also complained sudden body weight loss about 25 kg since the last two months, sometimes feels shortness of breath and his hands often tremble.

The patient's consciousness was compos mentis with GCS E4V5M6, blood pressure 133/91 mmHg, pulse rate 164×/min irregular, respiration 20×/min, temperature 36 ^{o}C and oxygen saturation 97% on room air. From physical examination found exophthalmos as seen in Figure 1, no icteric and no anemic. His thyroid glands were palpable, enlarged size of 5×3 cm, painless, mobile, warm and moist (Figure 2). No lymph node enlargement was found. Cardiac, pulmonary and abdominal examinations were within normal limits. The extremities were warm, capillary refill time (CRT) <2 seconds and no edema was found. The patient was evaluated using the Burch-Wartofsky point scale (BWPS) to exclude the possibility of thyroid storm. Based on the scoring, a result of 35 was recorded, which suggestive of impending storm. Neurological examination revealed supranuclear type left N. VII paresis, supranuclear type left N. XII paresis accompanied by dysphagia and left hemiparesis grade 3. Sensory examination found left hemihypoesthesia. The physiological reflexes appeared increased on the left side of the body and a positive Babinski reflex was found on the left leg.

Additional examinations were performed on the patient including laboratory tests, electrocardiography (ECG), thorax X-ray, colli ultrasound and head computed tomography (CT) scan. In the laboratory examination, from the results of complete blood count: white blood cell (WBC) 9.10×103/Ul, haemoglobin (Hb) 14.2 g/dl, hematocrit (HCT) 42.5% and platelet (PLT) 356×103 /Ul. Liver function examination: serum glutamate pyruvate transaminase (SGPT) 23 U/l and serum glutamic oxaloacetic transaminase (SGOT) 30 U/l. Kidney function examination: blood urea nitrogen (BUN) 22 mg/dl and serum creatinine (SC) 0.7 mg/dl, random blood glucose examination: 134 mg/dl, electrolyte examination: Na 141 mEq/l, K 4.0 mEq/l and Cl 104 mEq/l. Thyroid function examination: TSHs: 0.16 mIU/l and FT4: 4.36 ng/dl. ECG examination shows a rapid ventricular response (RVR) atrial fibrillation (AF) (Figure 3). Thorax X-ray shows cardiomegaly with an increase in cardiothoracic ratio (CTR >50%) and pulmonary within normal limits. Colli ultrasonography (USG) showed bilateral thyroiditis (Figure 4). Non-contrast head CT scan showed a sign of bleeding in the right insular region and right frontoparietal with a picture of infarction around it (Figure 5).

Figure 1: Sign of exophthalmos.

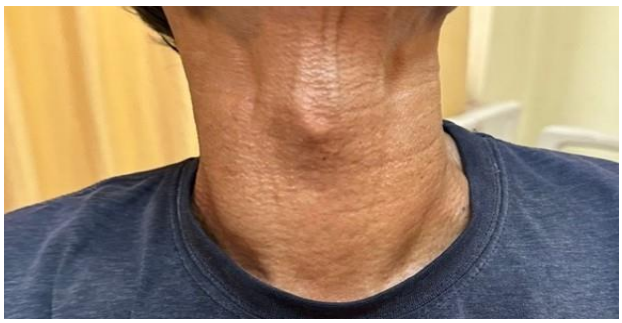

Figure 2: Enlarged of thyroid glands.

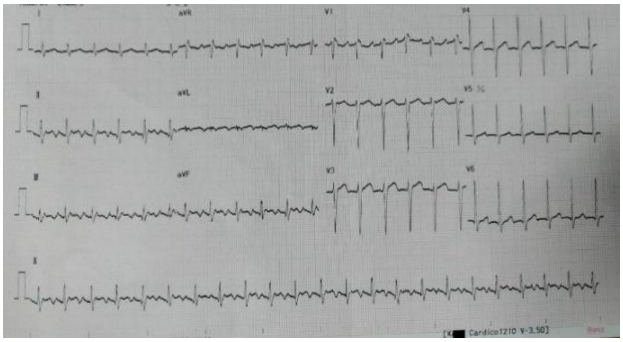

Figure 3: Patient's ECG showed rapid ventricular response atrial fibrillation.

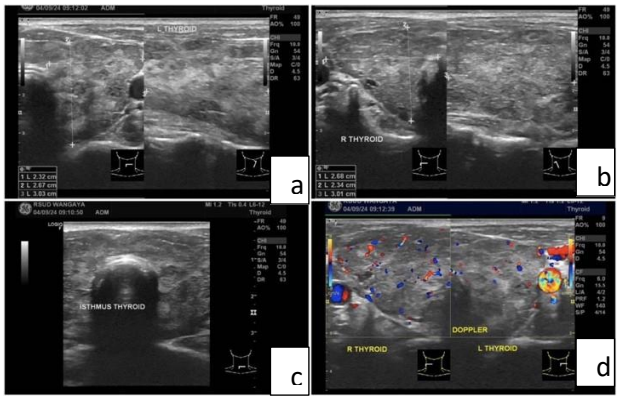

Figure 4 (a-d): Patient's colli USG showed bilateral thyroiditis.

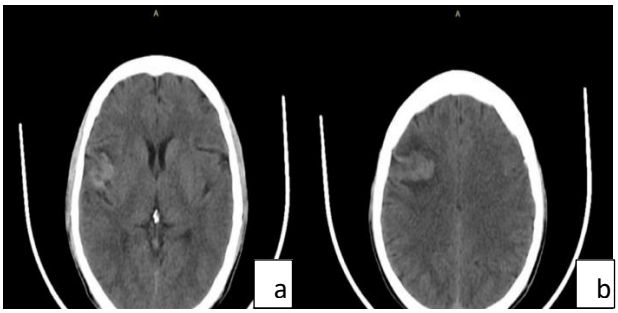

Figure 5: The results of non-contrast head CT scan showed a picture of bleeding in the (a) right insular region and (b) right frontoparietal region with a picture of infarction around it.

From neurology and cardiology department, the patient was diagnosed with non-hemorrhagic stroke of hemorrhagic transformation and rapid ventricular response atrial fibrillation. The patient received initial therapy in the form of O2 4 liters per minute with nasal cannula, IVFD NaCl 0.9% 20 tpm, citicoline 2×250 mg IV, mannitol 6×100 cc tapering off every day 100 cc IV, omeprazole 1×40 mg IV, paracetamol 3×1000 mg IV and bed rest with head up 30 degrees. From the cardiology department, the patient received initial therapy in the form of amiodarone 150 mg drip for 10 minutes, followed by 360 mg for 6 hours and 540 mg for 18 hours. Then the patient was referred to the internal medicine department and diagnosed with graves' disease, then the patient received therapy in the form of thyrozol 2×10 mg PO. Once the patient's condition stabilized, a follow-up examination was scheduled, which included a fine needle aspiration biopsy (FNAB) and testing for thyroid-stimulating hormone receptor antibodies (TRAb) at the polyclinic.

DISCUSSION

Graves' disease is an autoimmune disease and the most common etiology of hyperthyroidism. In this case, hyperthyroidism is caused by an increased production of thyroid hormone due to thyroid-stimulating immunoglobulins (TSIs), also known as TSH receptor antibodies (TRAb), binding to TSH receptors. This binding activates the receptors, leading to enlargement of the thyroid gland and an increased production of thyroid hormones by the thyroid follicles.[9]

Clinical manifestations of Graves' disease are due to increased thyroid hormone activity, with symptoms usually depending on the age, severity and duration of hyperthyroidism.[4] The initial screening for the diagnosis of hyperthyroidism is the examination of thyroid-stimulating hormone (TSH), free T4 (FT4) and triiodothyronine (T3) levels. In graves' disease, there will be an elevation in FT4 and T3 levels, along with a reduction in blood TSH levels.[3] If the diagnosis still cannot be established based on these laboratory tests, additional tests including thyroid receptor antibody (TRAb) examination can be performed.[3,10] Another possible test is radioactive iodine uptake, thyroid ultrasound, CT or MRI.[4] In this case, the patient had three typical symptoms of graves' disease or the merseburg triad, 11 which consists of thyrotoxicosis, diffuse goiter and ophthalmopathy. Thyroid function examination revealed an elevated FT4: 4.36 ng/dl and decreased TSH: 0.16 mIU/l, and bilateral thyroiditis were found from collic ultrasound (USG). This indicated patient had positive graves' disease.

In patients with hyperthyroidism, it is important to evaluate for the possibility of thyroid storm. In 1993, Burch and Wartofsky developed a scale that includes various clinical signs and symptoms to aid in diagnosing thyroid storm. A score above 45 suggests the presence of thyroid storm, a score between 25 and 44 indicates an impending storm and unlikely a thyroid storm when the score is below than 25.[12] In this case, the patient had a total BWPS score of 35, indicating an impending thyroid storm. However, after several days of treatment, the patient showed clinical improvement after receiving antithyroid medication.

AF is the most prevalent cardiac complication of hyperthyroidism, affecting 5-15% of hyperthyroid patients and is associated with higher cardiovascular morbidity and mortality.[13] AF pathophysiology is characterized by electrical and structural remodeling of the atrial myocardium. A number of clinical studies have reported that hyperthyroidism is correlated with an increased risk of AF.[14] There are several mechanisms that can explain the pathophysiology of atrial fibrillation in hyperthyroidism, including: an increase in left atrial pressure caused by an increase in left ventricular mass and disruption of ventricular relaxation, ischemia resulting from increased heart rate at rest, and increase in atrial ectopic activity.[15] The evaluation of the patient with atrial fibrillation is based on clinical history and physical examination findings, including serial ECG, with a focus on risk factors associated with atrial fibrillation.[16] The patient in this case complained of palpitations and the ECG results showed a rapid ventricular response (RVR) of AF with a ventricular rate of 164×/min. Current guidelines support the atrial fibrillation better care (ABC) pathway, which is a four-

pillar strategy emphasizing integrated care, focusing on: avoid stroke or thromboembolism using CHA2DS2-VASc risk score and prevention with anticoagulants drugs (suggested in patients CHA2DS2-VASc score ≥1), better rate control with beta-blockers and rhythm control with pharmacological and non-pharmacological interventions, and cardiovascular risk factor and comorbidities management (primary and secondary AF prevention).[13] Atrial fibrillation in the acute phase with stable hemodynamics can be treated with drugs that control the ventricular response, especially intravenous administration to obtain a faster response. The recommended drugs are digoxin or amiodarone. Amiodarone is among the most frequently prescribed anti-arrhythmic drugs for preventing and treating cardiac arrhythmias, including AF.[17] In this case, the patient was given initial therapy of amiodarone 150 mg drip for 10 minutes, followed by 360 mg for 6 hours and 540 mg for 18 hours. However, when intravenous drugs are not available, or in primary care settings far from secondary or tertiary referral centers, oral antiarrhythmic drugs such as calcium channel blocker (diltiazem or verapamil) and beta-blockers (propanolol, bisoprolol or metoprolol) can be given temporarily.[17]

From the neurology department, the patient was diagnosed with hemorrhagic transformation of non-hemorrhagic stroke. A hemorrhagic transformation (HT) can be defined as an area of hemorrhage in ischemic brain tissue that occurs after an acute ischemic stroke event. HT is a complex and dynamic and condition, and its underlying pathophysiology is not fully understood.[18] Increased risk of hemorrhagic transformation associated with atrial fibrillation and cerebral embolism. A major cause of cardioembolic cerebral infarction is blockage of intracranial vessels due to atrial fibrillation. The embolus can be dislodged either through thrombolytic therapy or spontaneously, resulting in the recanalization of the previously occluded vessels. Ischemia occlusions and undeveloped neovascularization increase the probability of hemorrhagic transformation.[19] Atrial fibrillation is associated with larger volumes of more severe baseline hypoperfusion, leading to greater infarct growth, more frequent severe hemorrhagic transformation, and worse stroke outcomes.[20] Based on a study conducted by Fahmi et al, it was found that the frequency of hemorrhagic transformation patients with AF was higher than the frequency in patients without AF. The results showed that old age, large infarction size, and cerebral microbleeds (CMB) ≥10 were important predictors for HT in ischemic stroke patients with AF. CMB might indicate the severity of cerebral microangiopathy, which may explain the abnormal permeability of the arteriolar blood-brain barrier (BBB) leading to extravasation of blood components. Therefore, it has been suggested that these lesions may be an indication of a bleeding prone state in HT after an acute ischemic stroke. This was consistent with findings in several studies of other ethnicities.[21] There are no specific recommendations for the therapy of hemorrhagic transformation, in general, the management given is the same as the management of hemorrhagic stroke, which aims to improve cerebral perfusion. Therapy is supportive and the most important thing is to control the increase in intracranial pressure by: head up 20-30º, avoid jugular venous pressure, avoid giving glucose or hypotonic fluids, avoid hyperthermia, maintain normovolemia, and give mannitol.[22] In this case, the patient was given initial therapy of O_2 4 liters per minute with nasal cannula, IVFD NaCl 0.9% 20 tpm, citicoline 2×250 mg IV, mannitol 6×100 cc tappering off every day 100 cc IV, omeprazole 1×40 mg IV, paracetamol 3×1000 mg IV and bed rest with head up 30 degrees.

Table 1: Patient Burch-Wartofsky point scale (BWPS) scoring.[12]

Criteria	Point	Patient's score
Temperature		
>37.2	0	0
37.2–37.7	5	
37.8–38.3	10	
38.4–38.8	15	
38.9–39.3	20	
39.4–39.9	25	
≥40	30	
Central nervous system effects		
Absent	0	0
Mild (agitation)	10	
Moderate (delirium, psychosis, extreme lethargy)	20	
Severe (seizure, coma)	30	
Gastrointestinal-hepatic dysfunction		
Absent	0	0
Moderate (diarrhea, nausea/vomiting, abdominal pain)	10	
Severe (unexplained jaundice)	20	
Tachycardia		
90–109	5	25
110–119	10	
120–129	15	
130–139	20	
≥140	25	
Congestive heart failure		
Absent	0	0
Mild (pedal edema)	5	
Moderate (bibasilar rales)	10	
Severe (pulmonary edema)	15	
Atrial fibrillation		
Absent	0	10
Present	10	
Precipitating event		
Absent	0	0
Present	10	
Total patient's score		35

The goal of managing hyperthyroidism in graves' disease is to decrease the activity of thyroid hormones in the body.[23] Treatment modalities for graves' disease consist of various options including anti-thyroid drugs, radioactive iodine (RAI) and surgery. The choice of therapy is based on several factors such as severity of thyrotoxicosis, size of the goiter, age of the patient, history of comorbidities in the patient, availability of modalities and response to treatment.[3] In this case, the patient was given thyrozol 2×10 mg orally as anti-thyroid medication. These medications can reduce the production of thyroid hormone by inhibiting the action of the enzyme thyroid peroxidase, which functions to oxidize iodide ions in the formation of thyroxine and triiodothyronine. Another drug that can be used as an anti-thyroid treatment is propylthiouracil (PTU), but the drug has more severe side effects and is hepatotoxic. Therefore, its use is primarily intended for pregnant patients in the first trimester, patients with thyroid storm and patients who are unable to tolerate thiamazole.[23]

Managing hyperthyroidism leads to a spontaneous restoration of sinus rhythm in approximately two-thirds of patients. Achieving complete normalization of thyroid function is not always required for the conversion to sinus rhythm. However, the study on AF related to graves' disease showed a lower spontaneous conversion rate to sinus rhythm (34.6%), in which patients who were monitored over a longer period and evaluated for the recurrence of both AF and graves' disease. Key factors influencing the reversion of AF include age, the length of hyperthyroidism, the duration of AF before treatment, and the presence of heart disease.[13]

In this patient, additional diagnostic tests, including a fine needle aspiration biopsy (FNAB) and thyroid-stimulating hormone receptor antibodies (TRAb) testing, were scheduled. FNAB may be indicated if there is suspicion of a thyroid nodule or co-existing thyroid cancer in a patient with graves' disease, particularly if there are concerns about nodular thyroid disease or a solitary nodule that could be malignant. TRAb is an essential diagnostic marker for graves' disease. These antibodies target the TSH receptor, causing excessive stimulation of the thyroid gland, which leads to hyperthyroidism. TRAb testing is particularly valuable when the clinical diagnosis is unclear, such as in cases where hyperthyroidism overlaps with other conditions like toxic multinodular goiter or thyroiditis. Elevated TRAb levels are present in 90% to 100% of patients with Graves' disease, especially those with active disease. TRAb levels often correlate with the severity of the condition and can help predict the risk of relapse after treatment.[24]

CONCLUSION

In this case, the patient was diagnosed with Graves' disease and developed a complication in the form of AF, which contributed to the risk of HT. AF is associated with larger volumes of more severe baseline hypoperfusion, leading to greater infarct growth, more frequent severe hemorrhagic transformation, and worse stroke outcomes. Early identification and appropriate management are essential for patients with hyperthyroidism to prevent complications that could lead to higher morbidity and mortality.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Saraswati SI, Wulandari DC, Yuliani D. Graves disease induced rapid ventricular response atrial fibrillation in association with hemorrhagic transformation in patient with ischemic stroke. Int J Adv Med 2025;12:97-102.