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UNCONTROLLED GRAVES' DISEASE AS A DRIVER OF AMPLIFIED WARFARIN SENSITIVITY

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ABSTRACT

Background: Thyroid function abnormalities can alter the pharmacokinetics of various drugs, including warfarin. Although a few case reports in the literature have highlighted this phenomenon, ours is the first in the region.

Case description: We report a case of a 40-year-old female known to have uncontrolled Graves' disease due to non-compliance with medication and follow-up, with a history of mitral valve replacement, on warfarin 3 mg daily. She presented with a headache and was found to have a subdural haematoma and an INR of 10.58. It was observed that as she was approaching euthyroid state with antithyroid treatment; her warfarin requirement slowly increased to maintain the target INR.

Conclusion: Our case highlights the relationship between hyperthyroidism and exaggerated response to vitamin K antagonists. Literature suggests there is an amplified response to warfarin in a hyperthyroid state. Therefore, a timely and close follow-up of INR and thyroid function test is warranted in patients with hyperthyroidism on anti-coagulation with warfarin.

KEYWORDS

Warfarin, INR, hyperthyroidism, anticoagulation

LEARNING POINTS

- Uncontrolled hyperthyroidism can significantly increase warfarin sensitivity, leading to unpredictable and potentially dangerous INR elevations even on low doses.
- Improvement in thyroid function decreases warfarin sensitivity, often necessitating careful dose adjustment and frequent INR measurement to maintain therapeutic anticoagulation and prevent thrombotic and bleeding complications.
- Effective management of anti-coagulation in patients with thyroid dysfunction and mechanical heart valves requires multidisciplinary collaboration and patient adherence to optimise outcomes.

INTRODUCTION

Thyroid hormones play an essential role in regulating metabolism, cell proliferation, and haemostasis[1]. Evidence suggests that hyperthyroidism is linked with hypercoagulability through mechanisms such as increased erythropoiesis, insensible fluid loss as a result of increased

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metabolism, enhanced hepatic protein synthesis and upregulation of coagulation factors such as tissue factor, thrombin and plasmin[1]. Thyroid hormone receptor beta may regulate the transcription of genes for coagulation proteins, and elevated thyroid hormones can alter endothelial function through increased expression of endothelial proteins and adhesion molecules[1,2].

A meta-analysis by Elbers et al.[2] concluded that the thyrotoxic state shifts the haemostasis towards a hypercoagulable and hypofibrinolytic state. This alteration is marked by elevated levels of factor VIII, factor IX, fibrinogen, von Willebrand factor (vWF) and plasminogen activator inhibitor-1. It was observed in both endogenous and exogenous thyrotoxicosis, as well as in subclinical and overt hyperthyroidism[2]. A prospective Serbian study involving 200 patients assessing thrombosis risk across thyroid states reported that thrombotic events occurred in 6.25% of hyperthyroid patients, compared to 2.9 and 1.4% in hypothyroid and euthyroid groups, respectively. Notably, 79.4% of hyperthyroid individuals had factor VIII levels above 1.50 U/ml, among whom 8.3% developed thrombosis, whereas none with lower factor VIII levels experienced events[3].

Warfarin is an oral vitamin K antagonist (VKA), commonly used to prevent thromboembolic events, which inhibits vitamin K epoxide reductase, thereby reducing the activation of vitamin K-dependent clotting factors[4,5]. Warfarin is known for its narrow therapeutic index and is metabolised by CYP2C9 mutations that can reduce clearance[6,7]. Drugs, diet and comorbidities may also affect pharmacokinetics, causing labile international normalised ratio (INR) and complicating management[8].

Additionally, hyperthyroidism accelerates the catabolism of vitamin K-dependent clotting factors and increases the affinity of warfarin to its receptors in the liver, resulting in a higher overall bleeding tendency[9]. Despite the clinical importance of this interaction, literature on hyperthyroidism and warfarin remains limited, with most studies dating back from the mid-to-late twentieth century and only a few recent reports, indicating to a gap in up-to-date, high-quality evidence to guide recommendations[4,9].

CASE DESCRIPTION

We report a case of a 40-year-old female who presented to the emergency department with a one-day history of sudden-onset, left-sided, dull headache of moderate intensity, without visual changes, photophobia, vomiting or focal neurological deficits. She also reported fatigue and irritability over the preceding days but denied palpitations, heat intolerance, or weight loss. Her medical history included poorly controlled Graves' disease diagnosed five years prior, with no recent follow-up or medication adherence. She also had a mechanical mitral valve replacement and a pacemaker for complete heart block and was maintained on warfarin 3 mg daily with regular monitoring. She denied alcohol, smoking or illicit drug use. Other potential confounding factors that could affect warfarin metabolism, including liver dysfunction, alcohol use, inconsistent dietary vitamin K intake, drug interactions or non-adherence, were excluded.

On examination she was irritable and pale, with mild lid retraction, exophthalmos, and grade 1 goitre. Cardiac examination revealed normal heart sounds and a mechanical valve click; she did not have a neurological deficit.

Initial investigations showed haemoglobin of 7.4 g/dl and an INR of 10.58. Thyroid function tests revealed elevated T4 (46.3 pmol/l) and suppressed TSH (0.008 μIU/ml). Liver function was normal. The Burch-Wartofsky score was 10, indicating a low likelihood of thyroid storm; ECG revealed a normal sinus rhythm with left-sided axis deviation.

A non-contrast CT scan of the brain revealed a minimal subdural haematoma along the interhemispheric fissure, right tentorial margin and over the right cerebellar hemisphere, with hyperdense cortical veins bilaterally. CT cerebral venography excluded cerebral venous thrombosis.

Warfarin was reversed with four units of fresh frozen plasma and 1 mg of intravenous vitamin K. The following day, INR fell to 2.02 and subsequently to 1.18. The patient was started on bridging therapeutic enoxaparin 50 mg BID, and warfarin was reinitiated three days later with a target INR of 3.5. Thyrotoxicosis was managed with carbimazole 15 mg TDS and propranolol as needed. On day 6, the patient was discharged against medical advice with an INR of 1.72. She was discharged on warfarin 3 mg daily, carbimazole 15 mg twice daily, and bisoprolol 2.5 mg daily, with follow-up in cardiology, endocrinology, and anticoagulation clinics.

As shown in *Table 1* and *Figure 1*, the patient's INR initially spiked while hyperthyroid on 3 mg/day warfarin. As her thyroid function returned to normal, the warfarin dose was gradually escalated to 5 mg once daily to maintain the target INR. These changes are illustrated in *Figure 1*, which highlights the inverse relation between thyroid state and warfarin requirement over time.

DISCUSSION

Our case describes a forty-year-old female with uncontrolled Graves' disease and a history of atrial fibrillation and a mechanical mitral valve replacement, who is receiving warfarin for anticoagulation, presenting with intracranial haemorrhage and supratherapeutic INR.

The complex relationship between hyperthyroidism and coagulation disorders was first described at the beginning of the twentieth century, and most studies are from the early to mid-twentieth century, with a handful of studies in recent years.

Our case highlights the relationship between hyperthyroidism, coagulation status, and fluctuating warfarin requirement. Our patient required increasing doses of warfarin as she approached euthyroid status.

One of the most recently published case reports was Lilihata et al. (2020) who reported a 24-year-old man with a mechanical mitral valve and thyroid storm who developed GI bleeding and INR 15.8, worsened by hypoalbuminaemia

Date	Warfarin dose (mg/day)	INR	TSH (µIU/ml)	T4 (pmol/l)
Sep 2023	3	10.58	0.008	46.3
Dec 2023	4	4.88	1.85	29.34
Jun 2024	4	3.01	2.53	15.186
Oct 2024	5	2.23	3.91	15.2

Table 1. Relevant laboratory tests and warfarin dose over time.

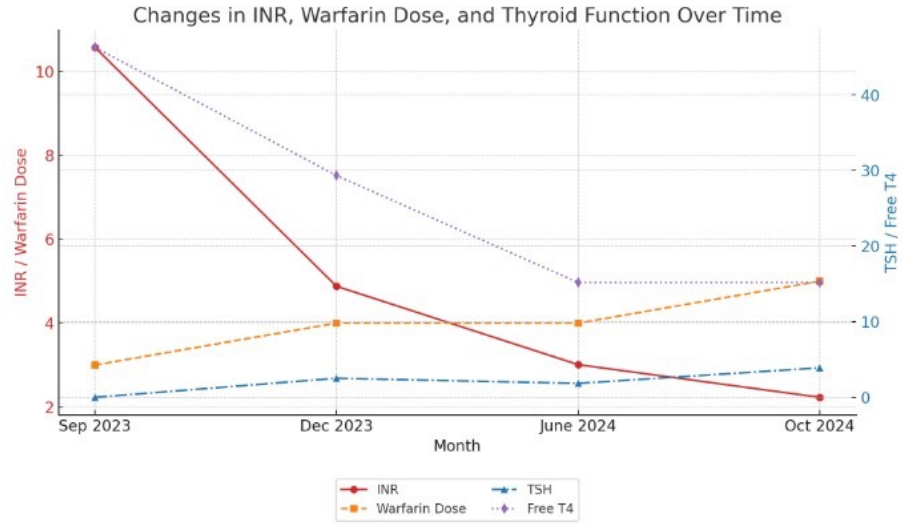


Figure 1. Changes in INR, warfarin dose, and thyroid function over time.

and thrombocytopenia, likely secondary to hyperthyroidism. Analogous to our patient, he required urgent warfarin reversal and thyroid management[9].

Howard-Thompson et al. (2014) described a 48-year-old female with new-onset Graves' disease and atrial fibrillation (AF) who had persistently unstable INR despite escalating warfarin doses, stabilising only after thyroid ablation, illustrating that definitive hyperthyroidism treatment may be required to achieve target INR[4]. In contrast, our patient responded to carbimazole alone.

Lee et al. (2014) reported a 73-year-old male with AF, INR 15 and bleeding due to hyperthyroidism in the context of CYP2C9 and VKORC1 variants resulting in an exaggerated warfarin response[7].

Bucerius et al. (2007) reported a sixty-year-old female with a mechanical valve who developed amiodarone-induced thyrotoxicosis, with INR fluctuations mirroring thyroid shifts[10].

Busenbark et al. (2006) described a 54-year-old man with Graves' disease and AF who had supratherapeutic INR while hyperthyroid, followed by subtherapeutic INR after methimazole[11]. Similarly, as our patient approached euthyroidism, the warfarin dose increased to maintain a therapeutic INR.

Our case demonstrated the presence of bleeding complications alongside supratherapeutic INR in a patient with uncontrolled Graves' disease on warfarin for a mechanical mitral valve, which requires more vigilant INR monitoring to avoid therapeutic complications.

VKAs are the anticoagulation drugs of choice for patients with mechanical heart valves [12]. The recommended INR for a mechanical prosthetic mitral valve ranges between 2.5 and 3.5, with a target of 3. This range minimizes the risks of bleeding and thromboembolic events in patients with a mechanical mitral valve[12].

There are no standardised guidelines regarding warfarin dose and frequency of follow-up in patients with thyroid disorders, which necessitates more robust evidence to direct patient care. The relationship between antithyroid medications and coagulation indices is not well established in the literature. As described in case reports, patients who were started on methimazole required higher doses of warfarin as they approached euthyroid. However, it remains uncertain if fluctuations in INR are also linked to a direct interplay between antithyroid agents and warfarin rather than an altered thyroid state alone[9].

CONCLUSION

Available evidence suggests that there might be an exaggerated response to warfarin in a hyperthyroid state. Therefore, a timely and close follow-up of INR with thyroid function test is warranted in patients with hyperthyroidism on anticoagulation with warfarin. As patients approach the euthyroid state, they will require up-titration of warfarin to achieve the target INR.

Research about the complex interaction between hyperthyroidism and warfarin is limited to only a few studies published in recent years. This emphasises the significant gap in the literature and the need for more robust evidence to draw conclusions and guide recommendations.

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