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The Effects of Phenytoin on Thyroid Function Tests: A Case Mimicking Central Hypothyroidism

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ABSTRACT
Introduction: Phenytoin, a widely used antiepileptic, can alter thyroid hormone metabolism and laboratory assays, potentially mimicking central hypothyroidism.
Case Presentation: A 75-year-old woman on long-term phenytoin presented with nonspecific symptoms and thyroid function tests showing low free T4 with a normal TSH. Workup revealed no evidence of pituitary disease. Elevated phenytoin levels and the absence of clinical hypothyroid features suggested phenytoin-induced assay interference or altered metabolism.
Conclusion: In patients on chronic phenytoin therapy, discordant thyroid function tests may not indicate true hypothyroidism but rather drug-induced changes. Clinical correlation is essential before initiating unnecessary treatment.

KEYWORDS: Antiepileptic drugs, Central hypothyroidism, Drug interference, Phenytoin, thyroid function tests.

INTRODUCTION

Antiepileptic drugs (AEDs) are the cornerstone of therapy for individuals with epilepsy, many of whom require lifelong treatment. While these medications are effective in controlling seizures, they are also associated with a range of systemic effects, including alterations in endocrine function. Among these, changes in thyroid hormone levels have been increasingly recognized [1]. Phenytoin, one of the oldest and most widely used AEDs, is known to influence thyroid hormone metabolism and laboratory assay results. This case report explores a patient who presented with symptoms suggestive of hypothyroidism and a thyroid function test profile resembling central hypothyroidism, ultimately linked to long-term phenytoin therapy. The case highlights the importance of considering drug effects when interpreting thyroid tests in patients receiving chronic antiepileptic treatment.

CASE REPORT

A 75-year-old female was referred to the endocrinology department by her pulmonologist following the incidental discovery of thyroid nodules during imaging studies ordered for a pulmonary complaint. Her medical history includes a seizure disorder diagnosed 40 years ago, hypertension, osteoporosis with three fractures in the past year, and migraines.

The patient reported no overt symptoms of thyroid dysfunction, although she had experienced nonspecific complaints such as weight gain of 25 pounds over the past two years, easy bruising for one year, and dry, cold skin for two years. She denied experiencing palpitations, tremors, or heat intolerance.

Her medication regimen included phenytoin 400 mg daily for seizure control, metoprolol 200 mg daily and lisinopril 10 mg twice daily for hypertension, and Prolia, of which she had received two injections for osteoporosis. Additional medications included atorvastatin, sumatriptan, montelukast, and omeprazole. She also used an ipratropium bromide inhaler.

Her family history was notable for her mother having thyroid disease treated with Synthroid and both parents dying of stroke. A brother had prostate cancer, and a sister had skin cancer. Socially, the patient was a former smoker, having quit 25 years ago after smoking for 30 years. She denied alcohol use and noted a reduction in exercise levels, contributing to her weight gain.

A neck ultrasound conducted on February 25, 2025, revealed an enlarged right thyroid lobe measuring 59 x 28 x 26 mm, a left lobe measuring 44 x 16 x 15 mm, and an isthmus of 3 mm. Three thyroid nodules were identified, with one large enough to warrant a biopsy. The biopsy returned benign results, showing no abnormal cells or calcifications.

Thyroid function tests performed on March 31, 2025, showed a TSH level of 1.38 µIU/mL (within the normal range), a free T4 level of 0.7 ng/dL (low), and a free T3 level of 4.45 pg/mL, which was borderline high (normal range: 2.3–4.4 pg/mL). Thyroid-stimulating

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immunoglobulin (TSI), thyroid peroxidase antibodies, and thyroglobulin antibodies were all negative. Her phenytoin level was elevated at 33 µg/mL (therapeutic range: 10–20 µg/mL).

DISCUSSION

Thyroid function tests are usually straightforward to interpret, but certain patient populations, such as those on chronic antiepileptic therapy, can present with misleading results. In this patient, the combination of a low free T4 and a normal TSH could easily suggest central hypothyroidism—a pattern characterized by low thyroid hormone levels in the presence of an inappropriately normal or low TSH due to pituitary or hypothalamic dysfunction [2]. In central hypothyroidism, a low free T4 with a TSH that is inappropriately normal or low supports the diagnosis because it shows the pituitary is not responding as it should. However, to confidently diagnose central hypothyroidism, there must also be clinical, imaging, or biochemical evidence of pituitary or hypothalamic dysfunction. Our patient had none of these findings, with no history of pituitary injury, head trauma, radiation exposure, or signs of adrenal insufficiency.

A more likely explanation for this discordant thyroid function pattern is the long-term use of phenytoin, which can both alter thyroid hormone metabolism and interfere with standard thyroid assays. Phenytoin induces hepatic microsomal enzymes, accelerating the metabolism and biliary excretion of thyroxine (T4) over time. This can lead to reduced total and, eventually, free T4 levels as the body fails to keep up with increased clearance [3]. Additionally, phenytoin displaces T4 from its binding proteins—primarily thyroxine-binding globulin (TBG)—resulting in transiently increased free T4 in undiluted serum, which can suppress TSH slightly. Yet in routine diluted serum assays (such as chemiluminescence-based immunoassays), this displacement effect dissipates during processing, producing falsely low free T4 levels despite normal thyroid status [4,5].

The challenge lies in distinguishing true thyroid dysfunction from assay interference or drug-induced changes. While some patients on phenytoin develop genuine hypothyroidism, many show abnormal labs without clinical hypothyroid symptoms. In our case, the patient exhibited nonspecific symptoms—weight gain, dry skin, and easy bruising—but lacked classic signs of hypothyroidism (e.g., constipation, cold intolerance, lethargy). Furthermore, there was no objective evidence of pituitary disease, and the elevated phenytoin level suggested significant drug exposure as a confounding factor.

The literature supports this interpretation: Pattan et al. (2020) described phenytoin-induced laboratory distortions mimicking central hypothyroidism in patients without true thyroid disease, while Miyake et al. (2018) described a patient receiving phenytoin and gabapentin who developed true hypothyroidism, evidenced by low free T4, elevated TSH, and clinical symptoms that improved with levothyroxine therapy [6,7]. These findings emphasize the importance of correlating clinical presentation with biochemical data before diagnosing central hypothyroidism or initiating unnecessary thyroid hormone replacement.

In practice, when faced with low free T4 and normal TSH in a patient on enzyme-inducing anti-epileptics like phenytoin, clinicians should review the medication history carefully, consider measuring total T4 or conducting ultrafiltration-based free T4 assays if available, and monitor for evolving clinical signs of hypothyroidism. If the patient is asymptomatic or symptoms are nonspecific, repeating thyroid tests after adjusting phenytoin dosing—or using a specialized lab—may clarify the true thyroid status.

Our patient's case highlights that the presence of normal TSH with low free T4 should not reflexively trigger a diagnosis of central hypothyroidism in patients on phenytoin. Instead, clinicians must integrate clinical, biochemical, and pharmacologic data to avoid misdiagnosis and unnecessary treatment.

CONCLUSION

In patients on chronic phenytoin therapy, thyroid function tests may show a misleading pattern of low free T4 with a normal or low-normal TSH, mimicking central hypothyroidism. Clinicians should interpret thyroid tests carefully in patients receiving enzyme-inducing anti-epileptics, correlating laboratory findings with the patient's clinical presentation and considering medication effects.

ETHICAL APPROVAL

Written informed consent was obtained from the patient for publication of this case report.

CONFLICT OF INTEREST

The authors declare no conflict of interes

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AUTHOR CONTRIBUTIONS
Kwame O. Amoh-Mensah compiled the patient's relevant clinical information and documented case details. Ransford Bio conducted the literature review, performed comparative analysis, and drafted the discussion in the context of referenced studies. Both Kwame O. Amoh-Mensah and Ransford Bio collaboratively prepared the initial manuscript draft. Lubna Mirza identified the case, supervised its evaluation and management, and provided critical revisions to the manuscript. All authors read and approved the final version of the manuscript.

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