

# Hypothyroidism induced by phenytoin and gabapentin

## A Case Report

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### Abstract

**Rationale:** Antiepileptic drugs (AEDs) are one of the causative drugs of drug-induced hypothyroidism. In most cases, AED-induced hypothyroidism is subclinical and indicated only by abnormalities of free thyroxine (T4) and/or thyroid-stimulating hormone (TSH) levels. Severe symptomatic hypothyroidism following AEDs is rarely reported in the literature.

**Patient concerns:** A 75-year-old man experienced neurologic symptoms including memory impairment, ataxic gait, sensory polyneuropathy and myopathy, lethargy, and edema of the face and lower extremities. He had been administered phenytoin and gabapentin for the treatment of symptomatic traumatic epilepsy 8 years before.

**Diagnoses:** The patient had low free T4 (0.21 ng/dL) and high TSH (113.2  $\mu$ IU/mL), which indicated hypothyroidism. Negative thyroid-related autoantibody tests and the lack of goiter excluded the possibility of Hashimoto disease. Phenytoin and/or gabapentin were strongly suspected as causing his hypothyroidism.

**Intervention:** The patient was treated with replacement therapy (levothyroxine 25  $\mu$ g/day).

**Outcomes:** His symptoms markedly and promptly improved alongside continued antiepileptic therapy.

**Lessons:** In this case, the patient's hypothyroidism was assumed to result from different mechanisms of the 2 AEDs leading to thyroid hormone reduction. AEDs can not only cause asymptomatic thyroid hormone abnormalities but also clinically observable hypothyroidism. Therefore, clinicians should be aware of the association between anticonvulsants and symptomatic hypothyroidism.

**Abbreviations:** AED = antiepileptic drug, CK = creatine kinase, CYP = cytochrome P450, GABA = gamma-aminobutyric acid, MMSE = mini-mental state examination, MRI = Magnetic resonance imaging, T3 = triiodothyronine, T4 = thyroxine, Tg = thyroglobulin, TPO = thyroid peroxidase, TRH = thyrotropin-releasing hormone, TSH = thyroid-stimulating hormone, UGT = uridine diphosphate glucuronosyltransferase, VPA = valproic acid.

**Keywords:** antiepileptic drug, case report, gabapentin, hypothyroidism, phenytoin

## 1. Introduction

Various drugs, including amiodarone, lithium, tyrosine kinase inhibitors, interferon-alpha, thalidomide, monoclonal antibodies, and antiepileptic drugs (AEDs), are known to be associated with the development of hypothyroidism.<sup>[1]</sup> Thyroid abnormalities have been reported in one-third of patients on AEDs.<sup>[2]</sup> However, in most cases, patients treated with AEDs present with subclinical hypothyroidism. Indeed, clinically significant thyroid disorders are reported to occur very rarely following AED use, including after phenytoin or gabapentin administration.<sup>[3,4]</sup>

Here, we report a patient who developed neurologic and systemic symptoms because of hypothyroidism induced by AEDs. Our case suggests that administration of gabapentin and/or phenytoin can lead to symptomatic hypothyroidism.

## 2. Case presentation

A 75-year-old man was admitted to our hospital because of memory impairment and lethargy. He had a traumatic and acute subdural hematoma following an accident and developed post-traumatic seizures approximately 10 years before his admission. Conventional craniotomy had been performed at the time of the accident, and he was also prescribed 200 mg/day phenytoin at this time. Subsequently, 600 mg/day gabapentin was started at 2 years after the accident.

### 2.1. Clinical findings

Six months before his admission, the patient had noticed himself wandering while walking, accompanied by swelling of his face and legs. He also experienced abnormal sensations in his fingers and plantar surfaces. Moreover, it was noticed that he asked the same questions repeatedly and could not choose clothes according to the weather 2 months before admission. In addition, his voice had become hoarse. A blood test was performed at a different hospital, showing a serum thyroid-stimulating hormone (TSH) level of 93.06  $\mu$ IU/mL. Therefore, we suspected clinical hypothyroidism.

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A physical examination revealed a body temperature of 36.2°C, blood pressure of 126/87 mmHg, pulse rate of 81 beats/min, and respiration rate of 18 breaths/min. His voice was still hoarse, and his eyebrows were thin. Thyroid enlargement was not clearly observable. Pitting edema was noted in the lower extremities, and mounding phenomena were observed in his arms and legs. Neurological examination revealed a Mini-Mental State Examination (MMSE) score of 24/30, as well as ptosis, dysesthesia in the palms of his hands and soles of his feet, decreased vibration sensation in his lower extremities, and an ataxic gait.

Urine analysis and blood cell analyses were normal. The patient's blood urea nitrogen was 10.5 mg/dL, creatinine was 0.96 mg/dL, sodium was 137 mEq/L, potassium chloride was 100 mEq/L, total protein was 6.9 g/dL, and albumin was 3.8 g/dL. Serum muscle enzymes were elevated: with a creatine kinase (CK) level of 504 IU/L, aspartate aminotransferase of 63 IU/L, and lactate dehydrogenase of 311 IU/L. Serum concentration of free triiodothyronine (T3) was 1.4 pg/mL, free thyroxine (T4) was 0.21 ng/dL, and TSH was 113.2  $\mu$ IU/mL. Tests for serum anti-thyroglobulin (Tg) antibody and anti-thyroid peroxidase (TPO) antibody were negative, and antinuclear antibody was also negative.

Atrial fibrillation was noted in an electrocardiogram. However, there were no abnormalities on chest x-ray. A thyroid ultrasonography showed a low-echoic mass in the left lobe that was suspected to be an adenomatous nodule. A cardiac ultrasound showed enlarged atria. Magnetic resonance imaging (MRI) of the patient's head revealed only old changes owing to the previous brain contusion in his right frontal and temporal lobes. I-123 iodoamphetamine-single photon emission computed tomography showed focal low uptake in the right frontal lobe. On electroencephalography, basic rhythms were composed of alpha waves, and no paroxysmal discharge was noted.

## 2.2. Treatment and outcomes

Levothyroxine was initiated at a dose of 12.5  $\mu$ g/day from the day after admission. Although phenytoin and gabapentin were administered at the same doses as before, the patient's ataxic gait and dysesthesia of the hands and feet gradually improved. From the 8th day, his levothyroxine dose was increased to 25  $\mu$ g/day. On the 10th day, his MMSE score was 26/30, the increase in which considered to result from a therapeutic effect of thyroid hormone replacement therapy. On the 12th day, neurological examination revealed that sensation in the patient's lower limbs had normalized, and results of laboratory tests showed that serum TSH was 7.15  $\mu$ IU/mL, and free T4 and CK levels were normal. The patient was discharged on day 14 of his admission, and he did not experience any recurrence of clinical hypothyroidism during 2.5 years of follow-up.

The ethical approval was not necessary because this was a case report. The patient provided informed consent for the publication of his clinical data. The presented data are anonymized and risk of identification is minimal.

## 3. Discussion

We present a patient presenting with clinical hypothyroidism while treated with the AEDs gabapentin and phenytoin. Several previous reports have suggested that various AEDs can lower blood thyroid hormones, especially T4.<sup>[3–6]</sup> Several mechanisms

induced by AEDs can act to change thyroid function, including competitive binding of AEDs and thyroid hormones to thyroxine-binding globulin and accelerated metabolism of thyroid hormones owing to the induction of the hepatic cytochrome P450 (CYP) and increased peripheral conversion of T4 to active T3.<sup>[7–10]</sup>

In addition, a higher level of uridine diphosphate glucuronosyltransferase (UGT) has been observed after exposure to AEDs in some studies.<sup>[11,12]</sup> UGT has been reported to be responsible for glucuronidation and plays a role in the metabolic pathway of thyroid hormone.<sup>[10]</sup> Moreover, Anderson<sup>[13]</sup> reported that phenytoin, phenobarbital, and carbamazepine induced both CYP and UGT enzymes, whereas gabapentin, ethosuximide, tiagabine, and vigabatrin did not act as either inducers or inhibitors of drug metabolism.

Consistent with a mechanistic approach, a previous nationwide observational study revealed that phenytoin was associated with a high risk of hypothyroidism, whereas no significant associations were shown for most of the new-generation AEDs, including gabapentin.<sup>[14]</sup> Therefore, focusing only on liver metabolism, phenytoin is more likely to cause hypothyroidism by inducing CYP and UGT enzymes. In contrast, gabapentin has been shown to promptly elevate brain gamma-aminobutyric acid (GABA).<sup>[15]</sup> A previous study with rats revealed that GABA is not only produced and metabolized in the brain but also the thyroid gland, and that the thyroid gland is able to accumulate exogenously administered GABA.<sup>[16]</sup> Furthermore, the inhibition of TSH-stimulated thyroid hormone release by GABA has been shown in studies with adult mice.<sup>[17]</sup> Therefore, these studies suggest that gabapentin-induced GABA production might affect the thyroid gland, possibly via short-loop negative feedback for thyroid hormone homeostasis. Phenytoin has been reported to inhibit nuclear binding of T3 in a dose-dependent fashion and to partially inhibit thyrotropin-releasing hormone (TRH)-stimulated TSH release from cultured rat anterior pituitary cells.<sup>[17]</sup> However, there have been no reports that indicate that phenytoin acts directly on the thyroid gland. Therefore, phenytoin and gabapentin can induce thyroid hormone imbalance in different ways and administering these AEDs concomitantly could increase the possibility of severe clinical hypothyroidism.

In our case, the possibility of primary hypothyroidism (e.g., Hashimoto disease) was very low because tests for anti-Tg antibody and anti-TPO antibody were negative, and thyroid ultrasonography revealed no surface irregularities or internal echoes. Moreover, there was no possibility of transient hypothyroidism after thyrotoxicosis because a test for TSH receptor antibody was negative and there were no symptoms of Basedow disease. In addition, the fact that low-dose levothyroxine promptly improved clinical symptoms was consistent with our diagnosis.

In the present case, the patient developed clinical hypothyroidism after long-term administration of AEDs. Lai et al<sup>[14]</sup> reported the acute onset of hypothyroidism after phenytoin exposure. However, another group reported that AED treatment of >24 months was a risk factor for hypothyroidism.<sup>[18]</sup> Nonetheless, some reports have suggested that length of treatment with AED was not associated with TSH levels.<sup>[19–21]</sup> Therefore, AED-induced hypothyroidism may appear even after a long period of time since initiation of AED administration.

Most previous studies have focused on laboratory abnormalities or other subclinical outcomes of thyroid hormones induced by AEDs. Thus, our case is important in that it demonstrates that AEDs can also induce symptomatic hypothyroidism.

#### 4. Conclusion

This case suggests that the different mechanisms of thyroid hormone reduction induced by 2 AEDs can provoke not only thyroid hormone abnormalities but also clinically observable hypothyroidism. Therefore, clinicians should be aware that anticonvulsants could induce symptomatic hypothyroidism.

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