Severe Fatigue Due to Valproate-induced Hypothyroidism in a Case of Bipolar Disorder

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Case report

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Abstract

Background: Valproate-induced hypothyroidism is a rare condition and has been considered asymptomatic. Here, we report a case of bipolar I disorder who developed symptomatic valproate-induced hypothyroidism.

Case presentation: A 44-year-old woman with bipolar I disorder complained of severe fatigue after starting valproate. She showed a hormonal pattern of central hypothyroidism. Thyroid autoantibodies were negative, and no pituitary abnormality was seen on magnetic resonance imaging. After stopping valproate, her severe fatigue rapidly improved with normalizing thyroid function.

Conclusions: Our case suggests that valproate-induced hypothyroidism should be considered when patients complain of excessive fatigue under treatment with valproate.

Background

Valproate, which is recognized to be much safer than lithium, the archetypal mood stabilizer, in terms of effects on thyroid function, is widely used in the treatment of bipolar disorder [1]. However, previous reports have suggested that valproate can also cause hypothyroidism [2, 3]. Here, we report a case of bipolar disorder showing severe fatigue due to valproate-induced hypothyroidism.

Case Presentation

A 44-year-old woman was referred to our outpatient clinic with a 2-month history of manic episodes. She developed her first episode of depression when she was 42 years old. She had no history of thyroid disease. When she presented at our clinic, she had been treated with quetiapine for 1 month, but still had elevated mood, irritability, and mood-congruent delusions. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, we diagnosed her as having bipolar I disorder, and added 200 mg of valproate on 100 mg of quetiapine. Valproate was later increased to 400 mg, after which, her manic symptoms ameliorated.

Despite her mood being well controlled, she developed severe fatigue 30 days after starting valproate. She had no depression-related symptoms other than fatigue, and no findings suggesting sedation with medication such as somnolence or impaired attention. A physical examination and laboratory test found no abnormalities except for low values of free thyroxine 0.50 ng/dL (F-T4; normal range 0.8–1.5 ng/dL) and free triiodothyronine 1.85 pg/mL (F-T3; normal range 2.0–3.8 pg/mL). Although F-T4 was decreased, thyroid-stimulating hormone 2.97 µU/mL (TSH; normal range 0.34–3.8 µU/mL) was within the normal range, suggesting central hypothyroidism. Since other fatigue-causing medical conditions were ruled out by further examinations, we considered that the severe fatigue was associated with hypothyroidism. Thyroid autoantibodies were negative, and gadolinium-enhanced magnetic resonance imaging of the pituitary gland showed no evidence of a pituitary lesion. Based on previous reports suggesting that
valproate can cause hypothyroidism [2, 3], we suspected that her hypothyroidism was caused by valproate, and stopped it 33 days after its introduction. Her severe fatigue then improved, completely disappearing in about 20 days. A laboratory test 35 days after stopping valproate confirmed that her thyroid function had normalized (TSH 2.17 µU/mL, F-T3 2.99 pg/mL, F-T4 1.10 ng/dL).

**Discussion**

In this case, severe fatigue was relieved by discontinuation of valproate with normalizing thyroid function. Therefore, we concluded that the severe fatigue was due to hypothyroidism induced by valproate. Valproate-induced hypothyroidism has been considered to be asymptomatic, even if it occurs [2, 3]. To our knowledge, this is the second report of a case of symptomatic valproate-induced hypothyroidism. Similar to our case, Rao et al. reported a case of bipolar disorder who presented with excessive fatigue under treatment with valproate [4]. While their report noted that symptomatic hypothyroidism can be caused by valproate, whether this can be improved by discontinuation of valproate has remained unclear, because their report did not include a description about the treatment for hypothyroidism. Our case firstly demonstrates that valproate-induced hypothyroidism can be rapidly improved by discontinuation of valproate, even if it is symptomatic. Our case showed fatigue, but no other symptoms of hypothyroidism such as weight gain and myxedema; this may have been due to the mild decline in thyroid hormones.

Clinical manifestations of hypothyroidism such as fatigue and psychomotor retardation are similar to those of depression. Therefore, hypothyroidism that develops during the course of treatment for depression is often overlooked. In such cases, patients can be considered as having treatment-resistant depression [5]. In patients with bipolar disorder who develop treatment-resistant depressive episodes, mood stabilizers such as valproate and lithium are continued, and patients are often supplemented with other treatments. Thyroid function is regularly screened for lithium, but is less likely to be tracked in patients using valproate [6]. Although the incidence of hypothyroidism due to valproate is speculated to be low, our case suggests that valproate-induced hypothyroidism should be considered when patients complain of excessive fatigue under treatment with valproate.

The mechanism of valproate-induced hypothyroidism is unclear. In our case, F-T4 was decreased, but TSH did not increase in reactivity, suggesting central hypothyroidism. Central hypothyroidism is caused by a malfunction of the hypothalamic–pituitary–thyroid (HPT) axis. Previous studies have suggested that γ-aminobutyric acid (GABA), whose action is enhanced by valproate, affects the HPT axis [7]. Given this finding, the central hypothyroidism in the present case might have been caused by the enhancing effect of valproate on the action of GABA. On the other hand, another mechanism in children using valproate has also been previously reported. Secondary deficiency of zinc and selenium due to valproate may decrease the synthesis of thyroid hormone and cause hypothyroidism with elevated TSH [8, 9]. However, in adults with bipolar disorder, the mechanism of valproate-induced hypothyroidism has been poorly studied. The effects of valproate on thyroid function have important implications for the treatment of bipolar disorder, so the elucidation of this mechanism is needed in future studies.
Conclusion

We reported the second case of symptomatic valproate-induced hypothyroidism. Our case suggests that valproate-induced hypothyroidism can be rapidly improved by discontinuation of valproate, even if it is symptomatic. Valproate-induced hypothyroidism should be considered when patients complain of excessive fatigue under treatment with valproate.

Abbreviations

F-T4  
free thyroxine
F-T3  
free triiodothyronine
TSH  
thyroid-stimulating hormone
HPT  
hypothalamic–pituitary–thyroid
GABA  
γ-aminobutyric acid

Declarations

Ethics approval and consent to participate:
Not applicable

Consent for publication:
We have obtained written consent from the patient for the publication of this case report.

Availability of data and materials:
Not applicable

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Authors’ contributions:
TK and HK were involved in patient care and treatment. TK and TS both mainly wrote the manuscript. YK, KY, and MU interpreted the patient data and were involved in revisions to the manuscript.

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