Dose-dependent valproate-induced alopecia in patients with mental disorders

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Introduction

Valproate is an established treatment for various types of epilepsy, as well as mood disorders such as mania and manic episodes of bipolar disorder. Alopecia is a frequent side effect of valproate-based products. However, few studies have reported a relationship between the plasma valproate concentrations and the occurrence of alopecia. We report three cases of alopecia that occurred in patients who received sodium valproate for mental disorders. In all three cases, alopecia appeared after long-term valproate exposure with a plasma concentration of 100 μg/ml approximately. However, the alopecia resolved in all cases after dose reduction or treatment discontinuation. Therefore, alopecia may develop in patients with chronic exposure to high plasma concentrations of valproate. Based on these findings, we believe that patients with high plasma concentrations of valproate should be closely monitored for the occurrence of side effects, particularly alopecia.

Case Reports

Case 1

A 49-year-old woman had been receiving sodium valproate (VPA-Na) since August 2010 for manic episodes of bipolar disorder, which were stabilized with a constant VPA-Na dose of 800 mg/day. Her plasma concentrations of valproate fluctuated from 76 to 125 μg/ml (n = 9) from the start of treatment until day 773. On day 826, her plasma concentration of valproate was found to be 9 μg/ml, which led to the discovery that the patient had not been complying with the treatment [Figure 1]. In the outpatient clinic, the patient stated that the reason for this noncompliance was hair loss; therefore, we discontinued VPA-Na treatment on day 822. Hair loss was often observed when she washed her hair, and it had advanced to the extent that her scalp was visible. However, her hair loss improved on day 15 after the discontinuation of VPA-Na treatment.

A manic episode occurred again on day 117 after the discontinuation of VPA-Na; therefore, treatment was restarted at a dose of 800 mg/day. The patient’s plasma concentration of valproate increased to 116 μg/ml on day 2, the manic episodes improved on day 15, and VPA-Na treatment was subsequently discontinued; hair loss did not recur.

KEY WORDS: Alopecia, chronic exposure, high plasma concentration, valproate

ABSTRACT

Drug-induced hair loss may occur as a side effect in patients treated with valproate. However, few studies have reported a relationship between the blood levels of valproate and the occurrence of hair loss. We report three cases of alopecia that occurred in patients who received sodium valproate for mental disorders. In all three cases, alopecia appeared after long-term valproate exposure with a plasma concentration of 100 μg/ml approximately. However, the alopecia resolved in all cases after dose reduction or treatment discontinuation. Therefore, alopecia may develop in patients with chronic exposure to high plasma concentrations of valproate. Based on these findings, we believe that patients with high plasma concentrations of valproate should be closely monitored for the occurrence of side effects, particularly alopecia.
Case 2
A 33-year-old man had been receiving sodium valproate (VPA-Na) since July 2007 for mania. VPA-Na treatment was initiated at a dose of 400 mg/day, and the dose was gradually increased. On day 1922 (dose: 900 mg/day), the patient expressed concern regarding hair loss. On day 1938 (dose: 900 mg/day), thinning of the hair was noticed on the parietal region of his head, indicating hair loss (the estimated plasma concentration of valproate was approximately 100 μg/ml). On day 1957, the dose of VPA-Na was increased to 1200 mg/day, although the progression of hair loss caused us to lower the dose to 600 mg/day on day 2003; his alopecia subsequently improved. The dose of VPA-Na was adjusted because of psychiatric symptoms. The patient’s plasma concentrations of valproate were 62 μg/ml on day 2012 (dose: 600 mg/day), 37 μg/ml on day 2201 (dose: 300 mg/day), and 34 μg/ml on day 2306 (dose: 300 mg/day).

Case 3
A 40-year-old woman had been receiving sodium valproate (VPA-Na) treatment since June 2010 for a personality-behavioral disorder that was associated with epilepsy. VPA-Na treatment was initiated at a dose of 600 mg/day. Her plasma concentration of valproate was 67 μg/ml on day 216 (dose: 800 mg/day), and the dose was increased to 1200 mg/day (the estimated plasma concentration of valproate was approximately 100 μg/ml) on day 431. The dose of VPA-Na was adjusted because of psychiatric symptoms. Hair loss was detected on day 1122, and it had increased in severity by day 1152 to the extent that her drain became filled with hair after washing. Therefore, VPA-Na treatment was discontinued [Figure 2], and her alopecia subsequently improved by day 84 after the drug discontinuation.

However, her personality-behavioral disorder recurred on day 237 after the discontinuation of VPA-Na; therefore the treatment was reinitiated at a dose of 400 mg/day. Hair loss was detected again on day 14 after the reinitiation of VPA-Na treatment; consequently, VPA-Na treatment was subsequently discontinued.

Discussion
The three patients had no medical comorbidities. No possible drug that causes alopecia was concomitantly administered other than VPA-Na. Alopecia was resolved in the patients after dose reduction or treatment discontinuation; thus alopecia was likely triggered by or causally related to VPA-Na treatment, as opposed to aging. Using the Naranjo adverse drug reaction probability scale,[2] all three cases of alopecia were found to be in the “probable” category, with scores of 5. The three patients experienced grade 1 alopecia (Common Terminology Criteria for Adverse Events Version 4). Among those, no patient presented with persistent alopecia after treatment discontinuation. In fact, after stopping VPA-Na treatment or decreasing the dose, hair fall decreased and hair regrowth was observed.

Alopecia is a frequent side effect of valproate-based products, and a prospective study of 78 subjects who were receiving valproate found that hair loss occurred in 6% of patients.[3] In addition, when used as mood stabilizer therapy, up to 12% of patients who are receiving valproate experience temporary alopecia.[4] Furthermore, valproate can result in dose-dependent alopecia in up to 12% of patients, including up to 28% of patients who are exposed to high valproate concentrations.[5] Similarly, a double-blind, concentration-response clinical trial of divalproex sodium monotherapy reported that alopecia occurred in 4% of patients in the low plasma valproate group (25–50 μg/ml), compared to 28% of patients in the high plasma valproate group (85–150 μg/ml).[6]

The stages of hair loss are classified into anagen effluvium and telogen effluvium. In anagen effluvium, hair growth ceases owing to damage to the hair matrix cells, whereas, damage to the hair matrix cells slows in telogen effluvium. Thus, hair loss (in excess of the physiologically normal levels) transitions from anagen effluvium to telogen effluvium in most cases. In this context, valproate is known to induce telogen effluvium, with the attached documents listing alopecia under “other side effects” at a frequency that is unclear or <0.1%.

Figure 1: Time course of the plasma valproate levels in case 1

Figure 2: Valproate-induced hair loss in case 3. (a) Illustration of hair loss. (b) Recovery from hair loss
A case report also described the relationship between the plasma valproate levels and the occurrence of hair loss. In the report, a patient with relatively high serum valproate levels (70.14–124.82 μg/ml) complained of hair loss after 10 months of valproate treatment, although hair loss subsided after treatment discontinuation. In that report, the authors discussed whether the high serum concentration of valproate might be the cause of hair loss. In the present report, hair loss in all 3 of our patients resembled that in the case reported by Ramakrishnappa and Belhekar in that hair loss appeared after periods of exposure to high plasma concentrations of valproate (approximately 100 μg/ml) and improved after dose reduction or treatment discontinuation. Furthermore, alopecia occurred when VPA-Na was administered at high doses in all three patients. Therefore, we believe that these findings indicate a strong association between the plasma concentration of valproate and the incidence of hair loss.

Although the Japanese Society of Therapeutic Drug Monitoring’s guidelines for antiepileptic monitoring recommend a therapeutic window of 40–125 μg/ml for valproate concentrations, a correlation between the plasma concentration of valproate and its clinical effect or side effects (toxicity) has not been established. In our three patients, although the plasma concentrations were within the therapeutic window, treatment was discontinued or the dose reduced because of the occurrence of hair loss. Thus, clinicians should be aware that valproate therapy may result in hair loss even when the dose is within the therapeutic window.

Based on these findings, we believe that patients with high plasma concentrations of valproate should be closely monitored for the occurrence of side effects, particularly alopecia.

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**Conflicts of Interest**

There are no conflicts of interest.

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