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LETTER TO THE EDITOR

Topiramate-induced hair loss in a patient using valproate and levetiracetam

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Dear Editor,

Cosmetic side effects are the fourth most common adverse effects associated with antiepileptic drugs and are estimated to incur an average financial burden of approximately 3,500 USD per patient (1). Among these, hair loss significantly affects treatment adherence and is reported to occur four times more frequently in women (2). Topiramate (TPM) is an antiepileptic medication known to act on voltage-dependent sodium channels as well as gamma-aminobutyric acid (GABA) and glutamate receptors (3). In a U.S.-based study involving 1,903 patients, cosmetic side effects were reported in 1.7% of those using TPM (2). To our knowledge, only two cases of TPM-induced hair loss have been documented. In one, a 15-year-old female patient with frontal lobe epilepsy developed hair loss two months after TPM was added to carbamazepine (CBZ) therapy (4). In another case, an 18-year-old woman developed hair loss three months after starting TPM 50 mg for migraine treatment (5). In this report, we present a case of probable TPM-associated hair loss in a female patient following its addition to a treatment regimen that included valproic acid (VPA) and levetiracetam (LEV).

A 25-year-old female patient with a diagnosis of epilepsy was admitted to the psychiatry outpatient clinic in August 2023 with complaints of nervousness, restlessness, constant anxiety, palpitation, and shortness of breath. Her symptoms had started approximately three months earlier. At another hospital, she was initially prescribed escitalopram 10 mg/day. However, due to side effects such as dizziness and drowsiness, the medication was discontinued two months ago, and sertraline 50 mg/day was initiated. The patient did not experience any side effects from sertraline but reported only partial improvement in her symptoms. She had been diagnosed with myoclonic epilepsy five years earlier due to throbbing-like movements in her upper and lower extremities and was started on VPA 1000 mg /day. Her seizures were well-controlled until two months ago, when she began experiencing generalized tonic-clonic seizures. As a result, LEV 1000 mg twice daily was added to her treatment regimen, though seizures persisted. One month ago, she was admitted to the emergency department of our hospital after sustaining a right shoulder dislocation due to a seizure-related fall. The patient was evaluated prior to surgery, and her LEV dose was increased to 3000 mg/day. She subsequently underwent surgery and remained seizure-free for one month.

In the mental state examination, the patient was conscious, oriented, and exhibited no psychotic symptoms. She had a dysphoric mood and no history of alcohol or substance abuse. No apparent pathology was found on physical examination. She was diagnosed with an unspecified anxiety disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Due to her ongoing symptoms, the sertraline dose was increased to 75

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mg/day. Since the patient had experienced excessive weight gain and her seizures were under control, a switch from VPA to TPM was planned. Initially, TPM was introduced at 25 mg twice daily without discontinuing the existing antiepileptic drugs. One month later, her anxiety symptoms had completely resolved, and she had not experienced any seizures. However, she reported hair loss that had been ongoing for the past two weeks. She had no previous history of significant hair loss related to antiepileptic drugs. The patient was not pregnant at the time TPM was initiated. There was no known history of dermatitis, weight loss, endocrine, or autoimmune disorders. Laboratory tests, including thyroid function tests, biochemistry, hemogram, beta-human chorionic gonadotropin (β-HCG), serum ferritin, folic acid, and vitamins B12 and D, all yielded normal results. The hair loss was diffuse, non-scarring, and particularly prominent at the vertex. Dermatology consultation found no specific cause. The pull test was positive, revealing normal club hairs. There were no changes in hair texture such as curling, graying, or a dirty appearance. TPM was discontinued due to its suspected role in the hair loss. Subsequently, hair shedding stopped and new growth was observed gradually. Two weeks later, the patient no longer complained of hair loss and remained seizure-free. The Naranjo Adverse Drug Reaction Probability Scale (6) was scored at 6 points, indicating a probable adverse effect associated with TPM. The patient was evaluated monthly for six months, during which no further cosmetic side effects were observed. She had remained seizure-free for the past eight months. In February 2024, as her anxiety symptoms were in remission, sertraline was gradually discontinued. Her antiepileptic therapy was adjusted to LEV 3000 mg/day and VPA 750 mg/day.

Drug-induced alopecia can be classified into two types, depending on the phase of hair growth affected by the drug. Anagen effluvium refers to hair loss during the active division of hair matrix cells and is most commonly associated with chemotherapy drugs (7). Telogen effluvium, on the other hand, is caused by several antiepileptic drugs that lead to premature damage to hair follicles. In most cases, hair loss improves with dose reduction or discontinuation of the drug (8). In a recent systematic review, VPA was identified as the antiepileptic most frequently associated with hair loss (9). With the exception of two studies conducted in China, many studies have reported VPA-related hair loss in more than 1% of patients (9). Drug-related hair loss is typically diffuse, non-scarring, and reversible. However, VPA has also been associated with changes in hair texture, including curling, graying, and a dirty appearance (10). Although our patient had been receiving VPA at 1000 mg/day for approximately five years, she had not experienced significant hair loss, suggesting that the current episode was unlikely to be related to VPA. Furthermore, while the patient experienced diffuse, non-scarring hair loss, no other changes in hair texture were noted. In a U.S.-based study using an antiepileptic drug database, hair loss was reported in 0.4% of patients taking LEV (2). In a separate case study, diffuse, non-scarring hair loss was observed in five patients using LEV at doses ranging from 500 to 1000 mg/day. Hair loss in these patients occurred between the third and eighth weeks of LEV therapy (7). In our case, LEV was added to VPA due to generalized tonic-clonic seizures, and the dose was increased to 3000 mg/day. Similarly, our patient developed hair loss within the first two months of LEV therapy. However, the improvement in hair loss following discontinuation of TPM, and the absence of recurrence during the subsequent six-month follow-up, suggest that LEV was not the causative agent of this side effect. The patient has also been using sertraline for two and a half months at the time she reported hair loss. However, sertraline was not considered responsible, as hair regrowth was observed after stopping TPM, despite no changes in sertraline dosage.

The gradual resolution of hair loss after discontinuing TPM strongly indicates a causal relationship. To our knowledge, only two prior cases of TPM-induced hair loss have been reported. In one case, a 15-year-old female developed hair loss two months after TPM 200 mg/day was added to CBZ 1200 mg/day (4). In the other, an 18-year-old woman developed hair loss three months after initiating TPM 50 mg/day (5). For antiepileptic-induced alopecia, the most commonly reported onset occurs between one and six months after starting the drug or increasing the dosage (11). In our patient, hair loss began within two weeks, suggesting a possible influence from drug interactions between VPA and TPM. According to the Medscape Drug Interaction Checker, TPM and VPA may enhance each other's toxicity, and close monitoring is therefore recommended. While sertraline does not show a clear interaction with existing antiepileptics, LEV appears to increase sedation when used in combination with TPM and VPA (12). Although the exact mechanism of the interaction between TPM and VPA is unknown (13), TPM has been reported to exacerbate VPA-induced side effects such as hyperammonemia and hypothermia (14, 15).

Although the patient was not given a rechallenge test, TPM was determined to be the most likely cause of the hair loss. While hair loss is not life-threatening, it can negatively affect quality of life and treatment adherence. Therefore, clinicians should remain vigilant for antiepileptic-induced hair loss. Large-scale studies are needed to better understand the etiological mechanisms of antiepileptic-associated hair loss.

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