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Case Series

Pharmacology Section

Sodium Valproate Induced Alopecia: A Case Series

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ABSTRACT

Drug induced alopecia may range from a barely detectable shedding to an irreversible baldness. Alopecia associated with valproate is a dose-dependent and reversible side effect. We hereby report, three cases of alopecia that occurred in patients who received sodium valproate for various neurological conditions. In all three cases, long term exposure of valproate therapy led to the development of alopecia which eventually resolved after dose reduction or discontinuation. The Naranjo's causality assessment scale indicated valproate as the probable cause of the alopecia in all our patients.

Keywords: Adverse drug reaction, Anticonvulsant, Hair loss, Naranjo's scale

CASE SERIES

Sodium valproate was originally developed as an anti-epileptic and later approved for its use in bipolar disorders, migraine prophylaxis and off labelly in the treatment of alcohol dependence, bipolar depression and aggression. Therefore, it is important to keep a watch at the common and uncommon Adverse Drug Reactions (ADR) occurring with this drug. Diffuse and non-scarring alopecia is one of the uncommon ADR associated with valproate and has to be looked into and treated with utmost caution. We hereby report, three cases of sodium valproate induced alopecia which was reversed following its withdrawal.

CASE 1

A premorbidly normal 35- year- old lady, was brought to the Psychiatry Outpatient Department (OPD) in December 2010 with symptoms of generalized slowness of movement, crying spells, neglect of daily activities and poor self-care, decreased interaction with family members, insomnia, fearfulness, irrelevant talk, disinhibition and inappropriate behaviour. A close scrutiny of the various systems and laboratory parameters did not reveal any abnormalities. Hence, after the conclusion of the history, physical and psychological evaluation, a diagnosis of a psychosis not otherwise classified was made and she was initiated on oral olanzapine 5 mg. Later on, in 2012 she presented with a picture resembling mania with altered lipid profile and hence olanzapine was changed to aripiprazole 10 mg and valproate was initiated at a dose of 500 mg once a day along with lithium 400 mg, risperidone 4 mg and trihexyphenidyl 4 mg. In view of frequent complaints of mania and hypomania dose of valproate was increased to 1000 mg. Subsequently during her follow up in January 2016, she complained of an enormous amount of hair loss, which was persistent in nature for 10 days. On examination diffuse alopecia was present associated with scaling, hair pull test was negative and she was prescribed anti- hair fall serum in February 2016, in view of no improvement in hair fall, a diagnosis of valproate induced alopecia was made and drug was tapered and stopped. Lithium, an established cause for hair loss was ruled out as the serum levels of lithium were within normal range [{Serum lithium-1.1 mmol/L (0.8-1.2 mmol/L)}]. Patient showed improvement in symptoms of hair fall during her subsequent visit the next month

CASE 2

A 20- year- old adult male, suffering from Generalized Tonic Clonic Seizures (GTCS) for the past three years presented to Psychiatry Outpatient Department of our hospital with complaints of severe hair loss since 1 year. The hair loss had worsened over the past three months and was associated with dandruff and itching as well. On scalp examination there was non-scarring and bitemporal recession of hair. His 1st episode of GTCS was at the age of 15 years, when he was started on tablet phenytoin 500 mg twice a day. A 2nd episode of GTCS occurred the next year, when phenytoin was changed to valproate 500 mg. Metabolic and other laboratory parameters [{Fasting blood sugar–99 mg/dl (70-100 mg/dl), Total cholesterol-180 mg/dl (140-200 mg/dl), Triglycerides-142 mg/dl (60-150 mg/dl), HDL-37 (40-65 mg/dl), LDL-114.6 mg/dl (50-130 mg/dl), Serum sodium-138 mmol/L (136-144 mmol/L), Serum potassium-4.2 mmol/L (3.6-5.1 mmol/L)}] were within the normal limits, ruling out any other causes of seizures. Electroencephalogram (EEG) was taken, which revealed abnormal and bifrontal sharp and slow wave discharges with right hemispherical spike discharges but CT scan did not reveal any significant intracranial abnormality. However, he had another episode the next year and hence dose of valproate was increased to 1500 mg. One year after an increased dose of valproate, patient came back with complaints of severe hair loss and after a detailed evaluation, a diagnosis of valproate induced alopecia was made. The suspect drug (valproate) was stopped and changed to levetiracetam 1000 mg. The signs of common conditions like anemia and hypothyroidism, which are often associated with diffuse hair loss, were excluded since hemogram, thyroid hormones profile and electrolytes were within normal limits. Alopecia was treated using zinc supplements and lotions containing azelaic acid, minoxidil and tretinoin as active ingredients and his symptoms improved within two months following treatment with the above medications.

CASE 3

A 24-year-old female patient suffering from GTCS, came to the Dermatology Outpatient Department of our hospital on January 2017 with complaints of diffuse hair loss for the past five months. During the last two years she was receiving lamotrigine, however within a period of one year, patient developed allergic reactions to lamotrigine in the form of maculopapular rashes, hence lamotrigine was stopped and she was started on valproate 500 mg. After one year of valproate therapy, she developed severe hair loss. A complete physical examination revealed non-scarring and diffuse alopecia. Other comorbidities such as hypothyroidism, lichen planus, scalp infection and cancer or any hereditary predisposition were ruled out and laboratory parameters were within normal limits. Hence, a diagnosis of valproate induced hair loss was thought of and drug was withdrawn. Alopecia was treated using zinc supplements and her symptoms improved subsequently within a month

DISCUSSION

Valproate is an anticonvulsant that has been used for years in the treatment of generalized tonic-clonic, absence seizures and

in cases of bipolar disorders [1]. Most common psychotropic drugs associated with hair loss are: Lithium with an incidence of 12-19 % in long-term users, carbamazepine with an incidence of 6%, sodium valproate causes alopecia in upto 8%-12 % patients in a dose-dependent manner and incidences are almost rare with newer antidepressants such as fluoxetine, sertraline, paroxetine, venlafaxine and nefazodone [2]. Sodium valproate is known to cause hair loss, change in hair colour (graying) and structure and curling of hair in as much as 6-12 % of patients [3, 4]. The Japanese Society of Therapeutic Drug Monitoring recommends a therapeutic window of 40-125 µg/ml for valproate concentration as ideal for antiepileptic monitoring [5]. A study conducted by Chen B et al., concluded that the time to development of alopecia in patients treated with valproate was 93 days [3].

Mechanism of Drug Induced Hair Loss

Drug induced alopecia occurs through two different modalities:

Interference at the anagen effluvium phase and thereby inducing a cessation of the mitotic activity of the hair follicles.

Interference at the telogen effluvium phase, thereby facilitating a premature arrest of the hair follicles.

In the anagen effluvium phase, hair loss usually occurs within days to weeks of drug administration, while in telogen effluvium, hair loss occurs within two to four months after therapy. Withdrawal of drug leads to a complete hair regrowth [4, 6].

Study conducted by Hoseinahali E et al., revealed an incidence of 3.5% of hair loss and curling of hair in a mean age group of 8 years, suggesting a predominance of younger age group in the development of alopecia [6]. These side effects were observed as early as within three months and in some alopecia developed within a period of two to three years.

Zinc deficiency is also another feature associated with drug induced alopecia as a high dose and long term use of valproate is related to zinc deficiency [6]. There is no clear understanding of the pathophysiology to explain how valproate and zinc deficiency causes alopecia. Animal and human data suggest that these agents can chelate zinc and selenium minerals that are believed to be important in the metabolism of the integument of hair. Management of drug induced hair loss includes reassurance, use of mineral supplements, treatment with minoxidil, hair care and hair replacement techniques.

A study conducted by Watanabe S et al., concluded that valproate at a median dose of 800 mg/day is able to reduce hair loss in patients receiving radiation therapy for glioma [1].

Alopecia developed in all our cases within a period of one to three years at a dose ranging from 500-1500 mg/day and was resolved after a dose reduction or discontinuation. We can also suspect that, the patients who develop drug induced hair loss could have predisposing factors like hypothyroidism, lichen planus, scalp infection and cancer or any hereditary predisposition. However, none of our patients had any predisposing factors, medical comorbidities or any drug interactions.

Causality assessment according to Naranjo's scale showed a probable relationship between the drug and the reaction with a score of 5 [7]. It was also found that the adverse drug reaction was of mild severity and was preventable as per Hartwig's and Thornton's scale, respectively [8,9]. According to the Common Terminology Criteria for Adverse Events Version 4.0, all three patients experienced grade 1 alopecia [10].

CONCLUSION

Drug-related hair loss is not always easy to diagnose and requires an understanding of normal hair growth and many different causal factors that are involved in it. Alopecia might not be frequently reported by every patients, but physicians should be aware of this potential problem which may contribute to noncompliance.

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