

# Perampanel-induced hair curling in a patient with epilepsy associated with Pitt Hopkins syndrome

Yamile Calle-Lopez<sup>1,2,3</sup>, Prakash Kotagal<sup>1</sup>,  
Elia Pestana Knight<sup>1</sup>

<sup>1</sup> Epilepsy Center, Cleveland Clinic, Cleveland, USA

<sup>2</sup> Neurology section, University of Antioquia, Medellin, Colombia

<sup>3</sup> Neuroclinica, Medellin, Colombia

Received April 19, 2019; Accepted July 20, 2019

**ABSTRACT** – Antiepileptic drug side effects are frequent, 42% of them corresponding to cosmetic changes. The most frequent effects are weight gain, gingival hyperplasia, and hair loss. Hair changes in texture or colour are rarely reported in the literature. We present a case of hair curling after the introduction of perampanel. A 13-year-old girl with genetically confirmed Pitt-Hopkins syndrome with uncontrolled seizures, while on treatment with levetiracetam and valproic acid, was started on perampanel, reaching seizure control. After a few weeks of the introduction of the new antiepileptic drug, she developed hair curling. Hair curling is a rare cosmetic side effect, reported mainly in patients under valproic acid treatment. Perampanel is a recently introduced pharmaceutical molecule with no prior reports of hair changes as a side effect. There is no clear explanation for this side effect, but it should be discussed with patients taking valproate whenever perampanel is added to the treatment.

**Key words:** perampanel, antiepileptic drugs, valproic acid, hair, epilepsy, adverse events

Up to 88% of patients treated with antiepileptic drugs (AED) experience at least one adverse event (AE) (Baker *et al.*, 1997). A recent study indicated that 42% of AED side effects are cosmetic. These side effects can increase the economic burden of treatment by necessitating the addition of more expensive medications and more clinic visits, not to mention the emotional implications of

modifications to physical appearance (De Kinderen *et al.*, 2014). The most frequent cosmetic side effects are weight gain, associated with valproic acid and pregabalin, hair loss with valproic acid, and gingival hyperplasia with phenytoin (Chen *et al.*, 2015).

We present the case of a 13-year-old girl who developed curled hair without hair loss after the introduction of perampanel.

## Correspondence:

Elia Pestana-Knight  
Epilepsy Center,  
Cleveland Clinic,  
9500 Euclid Ave. 44195,  
Cleveland, Ohio, USA  
<pestane@ccf.org>

## Case study

The patient had medically refractory epilepsy, developmental delay, and stereotypes due to genetically confirmed Pitt-Hopkins syndrome. Since 2016, she had had 3-4 seizures per year on valproate and levetiracetam (*figure 1*). Her seizures were controlled with the addition of 2 mg daily of perampanel. The patient's mother noticed hair curling in the occipital area a few weeks after the introduction of perampanel; the curling extended to the whole head in the following weeks (*figure 2*). No change in hair texture was noticed while the patient was on stable doses of valproic acid and levetiracetam for 16 months. The family declined weaning off perampanel because of its efficacy in seizure control. The new hair texture remains unchanged to date, with a dose of perampanel of 6 mg daily (*figure 1*). No blood tests for perampanel are commercially available to assess the correlation between level and side effect. Valproate blood level was 139 mcg/mL before the onset of this side effect. Medroxyprogesterone was administered to the patient from 2016 to date for contraception, with no changes in dose around the time of the side effect. Naranjo score for drug-related side effects was 6.

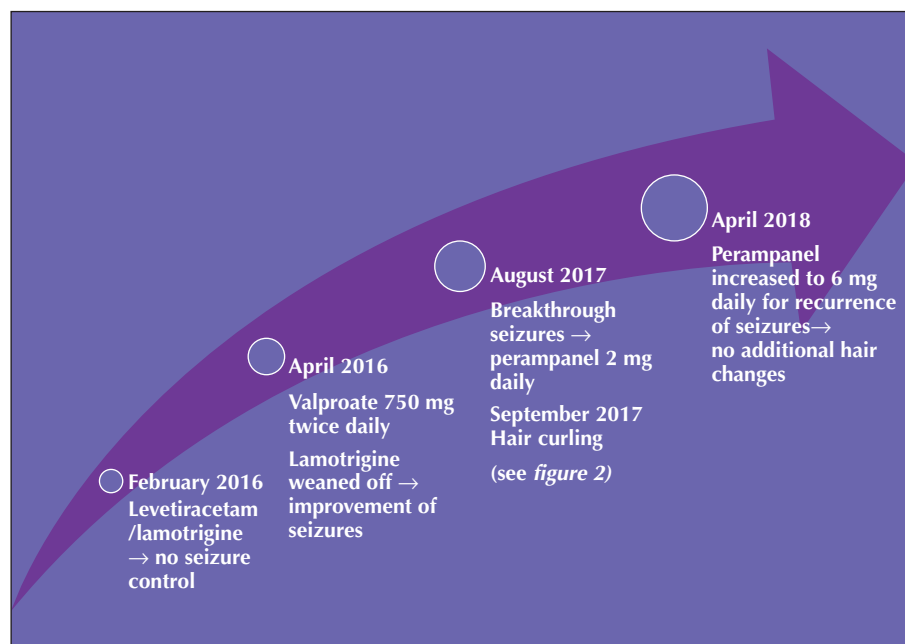
## Discussion

Hair changes in volume, texture, and colour have been reported with several medications, including the older AEDs (especially valproic acid, phenytoin

and phenobarbital) (Chen *et al.*, 2015; Ricci *et al.*, 2016) and some of the newer AEDs, such as levetiracetam (Zou *et al.*, 2014). A decreased concentration of zinc has been proposed as the cause of hair loss (Yilmaz *et al.*, 2009). There are no clear possible explanations for changes in colour and texture. Hair curling is an infrequent AE for AEDs. It was first described in 1977 in five patients taking valproic acid (Jeavons *et al.*, 1977). Since then, several reports have described the presence of curly hair, weeks after the first administration of this AED (Caneppele *et al.*, 2001), some of them showing improvement of the condition after down-titration of the dosage (Wilting *et al.*, 2007).

Our patient was treated with valproic acid for 16 months, but experienced no changes in hair texture until perampanel was added. This new AED is a partially selective, non-competitive antagonist of the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor that reduces neuronal excitability. The most frequently reported side effects are dizziness and fatigue. The only reported cosmetic side effects were weight gain in 7.4 to 19.2% of the analysed population (French *et al.*, 2012, 2015) and skin rash in 10.6% of Asian patients (Lin *et al.*, 2018). A comprehensive search in PUBMED, EMBASE, and Scielo using the MESH terms "hair", "antiepileptic drug side effects", and "perampanel" did not reveal any articles about hair changes associated with perampanel.

The mechanism of action of perampanel is so far unclear, and AMPA receptor deactivation has not previously been associated with hair growth or texture. When the Naranjo assessment for drug-related side



**Figure 1.** Evolution of AED doses.



**Figure 2.** Hair texture before and after introduction of perampanel.

effects was applied, however, the patient obtained a score of 6, which means that perampanel was a probable cause of the hair curling (Naranjo *et al.*, 1981). Given the scarce evidence of hair texture changes associated with the first AED, it is impossible to rule out an additive effect between valproate and perampanel. Medroxyprogesterone is another medication that was started years before the time of the hair curling side effect, with no known effects on hair texture and no reported inducing/inhibiting effects on the metabolizing enzymes for perampanel or valproate. Our patient was also afflicted with Pitt-Hopkins syndrome, a genetic disorder caused by mutations in the transcription factor TCF4 that causes several complications, affecting the central nervous system such as developmental delay and epilepsy. We found no case reports of changes in hair texture related to this disease, which provides further support for the causative effect of perampanel in this patient's hair curling (Zollino *et al.*, 2019).

## Conclusion

Hair curling is a rare cosmetic side effect of AEDs, reported mainly in patients undergoing valproic acid treatment. Perampanel is a recently-introduced pharmaceutical agent with no prior reports associated with hair change. We report on a change in hair texture, from straight to curly, after the introduction of perampanel. There is no clear explanation for this side effect, but it should be discussed with patients taking valproate whenever perampanel is added to the treatment. □

## Supplementary data.

Summary didactic slides are available on the [www.epilepticdisorders.com](http://www.epilepticdisorders.com) website.

## Disclosures.

Dr. Pestana Knight is a principal investigator in the clinical trial EISAI 338 for perampanel in Lennox-Gastaut syndrome. Dr. Kotagal is a member of the speaker bureau of EISAI Co.,Ltd. Dr. Calle-Lopez has no conflict of interest to declare.

## References

- Baker G, Jacoby A, Buck D, *et al.* Quality of life of people with epilepsy: a European study. *Epilepsia* 1997; 38: 353-62.
- Caneppele S, Mazereeuw-Hautier J, Bonafé J. Cheveux crépus acquis induits par le valproate de sodium. *Annales de Dermatologie et de Vénéréologie* 2001; 128: 134-5.
- Chen B, Choi H, Hirsch LJ, *et al.* Cosmetic side effects of antiepileptic drugs in adults with epilepsy. *Epilepsy Behav* 2015; 42: 129-37.
- De Kinderen R, Evers S, Rinkens R, *et al.* Side-effects of antiepileptic drugs: the economic burden. *Seizure* 2014; 23(3): 184-90.
- French J, Krauss G, Biton V, *et al.* Adjunctive perampanel for refractory partial-onset seizures. *Neurology* 2012; 79: 589-96.
- French J, Krauss G, Weschler R, *et al.* Perampanel for tonic clonic seizures in idiopathic generalized epilepsy. *Neurology* 2015; 85: 950-7.
- Jeavons P, Clark J, Harding GF. Valproate and curly hair. *Lancet* 1977; 1: 359.
- Lin K, Lin J, Chou M, *et al.* Efficacy and tolerability of perampanel in children and adolescents with pharmacoresistant epilepsy: the first real-world evaluation in Asian pediatric neurology clinics. *Epilepsy Behav* 2018; 85: 188-94.

Naranjo C, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30: 239-45.

Ricci F, De Simone C, Del Regno L, et al. Drug-induced hair colour changes. *Eur J Dermatol* 2016; 26: 531-6.

Wilting I, van Laarhoven J, de Koning-Verest I, et al. Valproic acid induced hair-texture changes in a white woman. *Epilepsia* 2007; 48(2): 400-1.

Yilmaz Y, Tasdemir HA, Paksu MS. The influence of valproic acid treatment on hair and serum zinc levels and serum biotinidase activity. *Eur J Paed Neurol* 2009; 13(5): 439-43.

Zollino M, Zweier C, Van Balkom I, et al. Diagnosis and management in Pitt-Hopkins syndrome: first international consensus statement. *Clin Genet* 2019; 95(4): 462-78.

Zou X, Hong Z, Zhou D. Hair loss with levetiracetam in five patients with epilepsy. *Seizure* 2014; 23: 158-60.

## TEST YOURSELF



- (1) What are the most frequent cosmetic side effects of AEDs?
- (2) What is the proposed mechanism for AED-related hair loss?
- (3) Which AED has previously been associated with hair curling?

*Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, [www.epilepticdisorders.com](http://www.epilepticdisorders.com), under the section "The EpiCentre".*