

# Hypertrichosis Induced by Topiramate: Report of Two Cases

## Topiramata Bağlı Olarak Gelişen İki Hipertrikoz Olgusu

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**ABSTRACT** Topiramate is a structurally novel broad-spectrum antiepileptic drug (AED) with established efficacy as monotherapy or adjunctive therapy in the treatment of adult and paediatric patients with epilepsy and migraine. The most recent studies in the topiramate treatment show numerous adverse effects such as nephrolithiasis, glaucoma, and metabolic acidosis. We describe two patients with hypertrichosis, probably related to topiramate. These are the first two reported cases of hypertrichosis due to topiramate.

**Key Words:** Topiramate; hypertrichosis; cytokines; anticonvulsants

**ÖZET** Topiramate, yapısal olarak yeni geniş spektrumlu bir antiepileptik ilaç olup (AED) yetişkin ve pediatrik hastalarda migren ile epilepsi ve tedavisinde monoterapi ya da ek tedavi olarak kullanılmaktadır. Topiramate ile ilgili yapılan son çalışmalarda, nefrolitiazis, glokom ve metabolik asidoz gibi çok sayıda yan etkiler gösterilmiştir. Biz topiramate tedavisine bağlı olarak hipertrikoz gelişen iki hastayı sunuyoruz. Bunlar topiramata bağlı olarak hipertrikoz bildirilen ilk iki olgudur.

**Anahtar Kelimeler:** Topiramate; hipertrikozis; sitokinler; antikonvülzanlar

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Topiramate is licensed in the United Kingdom for the management of epilepsy and migraine prophylaxis and is used in the management of essential tremor, alcohol dependence, mood disorders and bulimia nervosa.<sup>1-3</sup> Topiramate has both major side effects, such as kidney stone, glaucoma, metabolic acidosis, and minor side effects, such as nausea, headache, dizziness, fatigue, cognitive slowing, difficulty in retrieving words from memory, weight loss and decreased perspiration, and trichomegaly.<sup>1-4</sup>

In this study we present two child cases in which topiramate was used for the treatment of childhood epileptic seizures and developed hypertrichosis in the early stages of treatment.

## CASE REPORTS

### CASE 1

An 11-year-old girl arrived at the dermatology outpatient clinic with complaints of a rapid onset of 'unwanted hair' that began two months after top-

iramate treatment was started. The patient who developed hirsutism on the forehead, sideburn area, and upper and lower extremities in particular did not suffer from acne or hoarsening of the voice.

The patient's history revealed that she has had epilepsy for 3 years and began topiramate treatment 4 months ago for generalized tonic-clonic seizures. Topiramate was started at a dose of 1 mg/kg/day and increased by 0.5 mg/kg/day weekly up to 5 mg/kg/day, which was the current dose. About 2 months after topiramate treatment was started, the patient developed hirsutism on the face, and the upper and lower extremities. Her neurological evaluation revealed mental and motor retardation. Tonus was increased bilaterally on the upper and lower extremities, and articular spasticity was present. Deep tendon reflexes were hyperactive, and Babinski's reflex was positive. Dermatological examination of the patient showed long, black hair on the back, shoulders, extremities, face and mustache area, but no hirsutism on the chest or genital area (Figure 1).

Investigations for serum testosterone and free testosterone, 17 hydroxyprogesterone, dehydroepiandrosterone sulfate (DHEA-S), androstenedion, prolactin, cortizol, and luteinizing-follicle stimulating hormone levels were all within normal range for her age. The patient was clinically and biochemically euthyroid. Serum concentrations of Topiramate were within the therapeutic range (ref-

erence range 5-20 mcg/ml). Scalp electroencephalography (EEG) revealed sharp waves and spike-and wave complexes. In the brain magnetic resonance imaging (MRI), hyperintense signal changes were determined as basal ganglia, cerebellum and deep gray matter. Topiramate treatment was ended and another anti-epileptic drug was started.

## CASE 2

An eight-year-old girl was admitted to our clinic for the investigation of hypertrichosis of recent onset. According to her history, it was found that the case was diagnosed with epilepsy a year ago by the pediatric neurology department and was put on 1 mg/kg/day topiramate, which was gradually raised up to 5 mg/kg/day. About 3 months after topiramate treatment was started, the patient developed hirsutism on the body, shoulders, upper extremities, lower extremities, forehead, cheeks, back, face and sideburn area in the form of black hair. The patient did not show any virilization signs, such as clitoris hypertrophy, hoarsening of the voice or increased sebum production. No symptoms of Cushing's disease were present. Topiramate treatment was ended upon the demand of the family and another anti-epileptic drug was started.

Dermatological examination of the patient showed long, black hair on the back, shoulders, extremities, face and mustache area, but no hirsutism on the chest or genital area (Figure 2).

Investigations revealed normal scalp EEG, abdominal ultrasonography and brain MRI. Serum prolactin, testosterone and free testosterone, cortizol, 17 hydroxyprogesterone, DHEA-S, androstenedion, and luteinizing-follicle stimulating hormone levels were all within normal range for her age. Haematological investigations, including haemoglobin, white blood count, erythrocyte sedimentation rate, blood glucose, thyroid, renal and liver function tests, serum electrolytes, urine analysis and abdominal ultrasonography findings were all normal for both patients. The fact that the complaints started after the use of the drug, the hirsutism pattern, and lack of a specific hormonal or biochemical abnormality all pointed to drug-in-



**FIGURE 1:** Long, black hair on the forehead, mustache and sideburn areas. Increased hair growth on the lower extremities and thigh.



**FIGURE 2:** Growth of hair on the shoulders, back, forehead and upper extremities.

duced hypertrichosis. The control examinations following the discontinuation of the topiramate treatment showed a marked decrease in both patients' hirsutism at the end of one year (Figure 3).

## DISCUSSION

Hypertrichosis, a rare condition, can be defined as an excessive growth of hair (terminal, vellus or lanugo) in areas of the body that are not predominantly androgen-dependent and is independent of age, race or sex. Hypertrichosis may be congenital or acquired, localized or generalized.<sup>5</sup>

Lanugo hair growth should be differentiated from hair growth due to hirsutism. On clinical examination, the two types of hair growth are clearly different. In hirsutism (male pattern hair growth in a female or child), the hair is of the adult type—thick, coarse, pigmented, and medullated. It appears mostly in the body regions furnishing androgen-sensitive follicles, such as on the beard and moustache area and the chest, and is due to androgenic action, either by increased levels of androgens or via local increased sensitivity to these hormones. The development of lanugo type hair, with fine, thin hair shafts that can reach unusual lengths, is usually located on the face, within eyebrows and eyelashes, and on the forehead, ears, and nose. It may also appear over the trunk, axillae, and extremities. It does not follow a sex-specific pattern on the face, chest or genital areas.<sup>6</sup>

Acquired hypertrichosis lanuginosa (AHL) has often been associated with metabolic and endocrine disorders, such as hyperthyroidism, anorexia nervosa and porphyria, and can also be pharmacologically induced. Some of the drugs reported to cause AHL are cyclosporine, minoxidil, diazoxide, interferon, corticosteroids, valproate and phenytoin.<sup>7,8</sup> However, this is the first reported case of topiramate. The exact mechanism of how topiramate causes hypertrichosis is unknown. This may either be a result of the idiosyncratic effect of the drug on hair growth or it is hypothesized that cytokines produced by drugs can promote proliferating cells. Research has revealed that some AEDs have an important influence on cytokine production. Increase in cytokine production was observed in some studies and also a decrease was observed in others.<sup>9</sup> Hair follicles are highly active structures that may easily be affected by stimulatory cytokines.<sup>6</sup> As a result of the effects of cytokines produced by the cells in the dermal papilla, stem cells in the hair follicle divide and start to differentiate when migrating to the matrix. We think that at this stage topiramate



**FIGURE 3:** Marked decrease in patient's hirsutism on the shoulders, back, forehead and upper extremities.

stimulates cytokines to increase cell division and lead to an abnormal growth of hair.

An alternate explanation for the association between hypertrichosis and AEDs is that they may affect pituitary hormone function via a direct effect on cortical input to the hypothalamic-pituitary-ovarian axis or alter gonadal hormonal

feedback, which could affect gonadal and adrenal sex steroid output.<sup>10</sup>

Our cases demonstrate the importance of drugs as a cause of hypertrichosis, and topiramate should be added to the list of causative drugs. Physicians need to be aware of hypertrichosis as a rare side effect of this drug.

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