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# Hypohidrosis induced by topiramate in an adult patient

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**ABSTRACT** – Hypohidrosis is an uncommon and reversible side effect of topiramate treatment, reported mainly in children. This report presents an adult patient with complex partial seizures who was treated with topiramate and developed hypohidrosis coupled with hyperthermia, related to high environmental temperature and physical exercise. Reduced sweat response was confirmed using the Neuropad test. Signs and symptoms ceased after drug discontinuation. During topiramate treatment, it is important to recognise this side effect, although the exact causal mechanism has not yet been clarified.

**Key words:** topiramate, hypohidrosis, adverse effect, sweat function

Topiramate (TPM) is a highly efficacious, broad-spectrum antiepileptic drug and appears to exhibit a favourable safety profile. The most common side effects are somnolence, cognitive dysfunction, speech problems, behavioural changes, nervousness, anorexia, weight loss, lability of mood, paraesthesia, metabolic acidosis, nephrolithiasis, and acute glaucoma (Arcas *et al*., 2001; Ben-Zeev *et al*., 2003; Cerminara *et al*., 2006). Hypohidrosis, often associated with hyperthermia, has been recently noted as a rare and reversible adverse effect of TPM, especially in children (10.5-39.1% of children treated with TPM) (Arcas *et al*., 2001; Ziad *et al*., 2005; Kim *et al*., 2010; Cerminara *et al*., 2006; Incecik *et al*., 2008) and rarely in adults (Ben-Zeev *et al*., 2003; De Carolis *et al*., 2003; Galicia *et al*., 2005).

## Case report

A 32-year-old male had been suffering from complex partial seizures with secondary generalisation for two years. His neurological examination and brain MRI were normal and the interictal EEG examination showed sharp waves on the right frontotemporal region *(figure 1)*. He was initially treated with oxycarbazepine (2,400 mg/day) for six months, but seizures were reduced only by 40%. Subsequently, TPM treatment was added starting with a dose of 25 mg/day and increased by 25 mg every week to a maximum of 300 mg/day in two equally divided doses. TPM was at first well tolerated and the patient's seizures were reduced by 80%. Two months after reaching the target dose, the patient complained of an inability to

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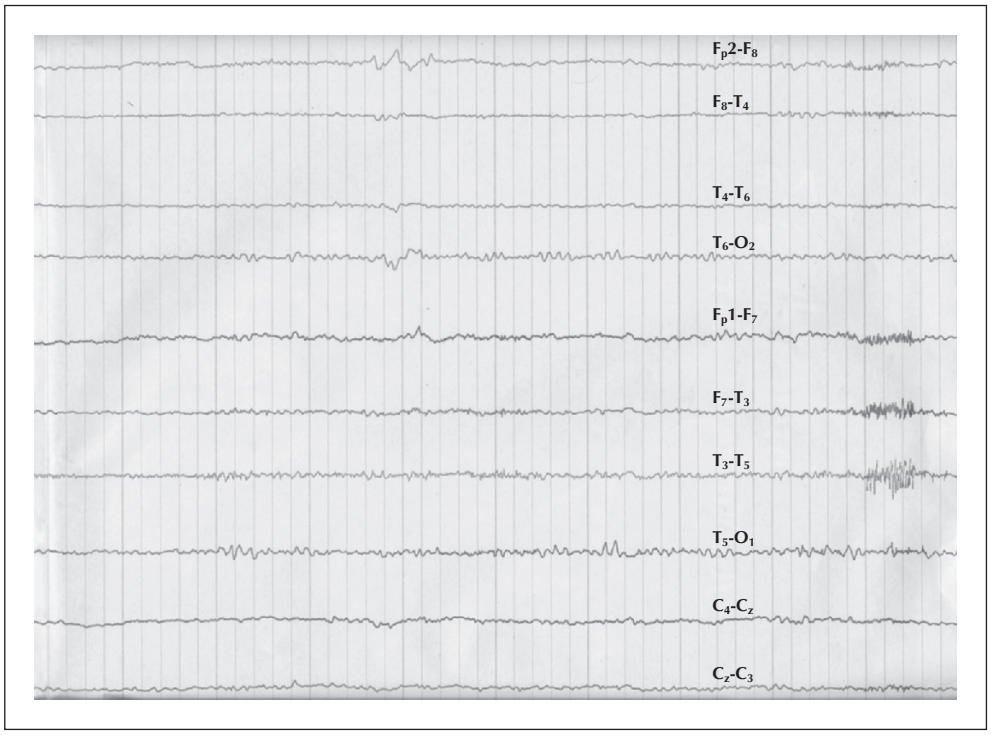


**Figure 1.** EEG recording shows sharp waves on the right frontotemporal region.

produce sweat, dryness of the skin, flushing of the face, fatigability, and irritability, all related to high environmental temperature and physical exercise. These manifestations were sometimes associated with episodes of hyperthermia reaching 39°C.

The Neuropad test is a non-invasive simple method for checking sweat function. The Neuropad is a transdermic patch which contains cobalt. For normal sweat production, the Neuropad changes colour from blue to pink when placed on the sole of the foot for ten minutes, based on the water-inducing colour change of cobalt (Kim *et al*., 2010). Our patient ran for 20 minutes outside, around the hospital, in the summer sun and on his return inside he was evaluated using the Neuropad test which showed no colour change. This result confirms the hypohidrosis he asserted earlier. Furthermore, his rectal temperature increased by 1.8°C (from 37.2°C before the run to 39°C after the run). The patient stayed in hospital, in an air-conditioned environment, for four days without febrile episodes.

His subsequent MRI was normal, the EEG showed the same discharges as those before treatment, and a thorough investigation for infectious, inflammatory, and malignant causes for fever proved to be negative. TPM was gradually discontinued and treatment was switched to pregabalin; the patient reverted to normal sweating without febrile episodes. The Neuropad test was repeated following the same procedure and, under the same conditions, a change from blue to pink occurred when the rectal temperature rose by 0.6°C, from 36.8°C to 37.4°C.

## Discussion

We describe an adult patient with severe hypohidrosis and consequential heat intolerance during treatment with TPM. In the adult series of Ben-Zeev *et al*. (2003) and Ziad *et al*. (2005), TPM was reported not to affect sweat production, however, a small number of such cases have been reported in the literature (Ben-Zeev *et al*., 2003; De Carolis *et al*., 2003; Galicia *et al*., 2005; Markowitz et al., 2010). In one such case, the patient developed residual cerebellar and cognitive dysfunction (Galicia *et al*., 2005). The increased risk of hypohidrosis in children rather than adults may be related to incomplete development of the neurophysiological and biochemical mechanisms of sweating, a smaller blood volume relative to body surface area, a reduced sweating rate per gland, and a greater surface area-to-mass ratio (Arcas *et al*., 2001; Ziad *et al*., 2005; Margari *et al*., 2008; Kim *et al*., 2010). Furthermore, Arcas *et al*. (2001) and Kim *et al*. (2010) noticed that hypohidrosis was not related to the mean dose or duration of TPM treatment in children, whereas Ziad

*et al*. (2005) observed that a TPM dose ≥ 6 mg/kg/day induced hypohidrosis in the same age group.
Topiramate consists of a sulphamate-substituted monosaccharide that acts by blocking the sodium channel in neuronal membranes, which enhances ã-aminobutyric acid-induced (GABA) activity at GABA receptors, inhibits kainate/á-amino-3-hydroxyl-5-methyl-4-isoxazolepropiorate (AMPA) glutamate receptors, reduces L-type currents in voltage-activated calcium channels, and inhibits carbonic anhydrase (CA) isoenzymes (particularly II and IV) (De Carolis *et al*., 2003; Incecik *et al*., 2008; Kim *et al*., 2010).

Hypohidrosis is the inability to produce or deliver sweat by skin eccrine glands. Since sweating is one of the major mechanisms responsible for regulating body temperature in a hot environment and during physical exercise, this may lead to hyperthermia or heat stroke (Arcas *et al*., 2001; Margari *et al*., 2008; Kim *et al*., 2010). With core temperature elevation, there is increased firing of sympathetic nerve fibres originating from the anterior hypothalamic preoptic nucleus (Briggman *et al*., 1983; Arcas *et al*., 2001; Margari *et al*., 2008). The sweat glands are innervated by the sympathetic post-ganglionic C-type non-myelinated fibres using mainly acetylcholine, which increases the secretion of plasma-like fluid by the secretory coil, starting with calcium influx to the basal coil cells, followed by potassium chloride efflux from the cell accompanied by water. The electrolyte concentration of sweat is determined by backward absorption of sodium chloride in the duct of the glands by a sodium/potassium adenosine triphosphatase pump (Sato *et al*., 1989; Ben-Zeev *et al*., 2003). There is evidence that CA isoenzymes I and II are localised immunohistochemically to the sweat glands and may play a role in generating alkaline sweat by catalysing the reaction between $H_2O$ and $CO_2$ to produce of $HCO_3^-$ and $H_+$ and by delivering $HCO_3^-$ (Briggman *et al*., 1983; Ben-Zeev *et al*., 2003).

The precise mechanism by which TPM causes hypohidrosis has not yet been clarified, however, hypohidrosis may be the result of dysfunction of one or more of the above-mentioned mechanisms underlying sweating regulation. De Carolis *et al*. (2003) demonstrated that the central and peripheral thermoregulatory function and the cardiovascular autonomic function tests remain intact in patients with hypohidrosis under TPM. This suggests that the site at which TPM appears to block sweating is probably at the level of the sweat glands. The same conclusion was reached by Margari *et al*. (2008), after an electrophysiological study in two cases with hypohidrosis related to TPM, which showed normal peripheral sensory conduction with normal laser-evoked potential and absent sympathetic skin responses which recovered to normal after TPM discontinuation; findings which might suggest a transitory autonomic dysfunction. As mentioned above, TPM has an inhibitory effect on CA isoenzymes which may alter primary sweat composition and reduce formation of water, leading to an impaired sweat rate (Cerminara *et al*., 2006; De Carolis *et al*., 2003; Kim *et al*., 2010). Another potential mechanism causing sweat reduction could be a specific and reversible effect on one of the electrolyte channels or transporters mainly in the secretory coil, involved in sweat production. TPM has an effect on neuronal voltage-gated sodium channels but it is unclear whether the sodium channels in the sweat gland secretory coil are structurally related to these neuronal channels (Ben-Zeev *et al*., 2003). Finally, Ma *et al*. (2007) reported that TPM in mice induced hypohidrosis and decreased aquaporin-5 expression in membranes of secretory glands, whereas CA activity and CA II expression were unaltered. It should be noted, however, that the experiment had some limitations and the function of aquaporin-5 in sweat glands is not clearly understood. In conclusion, hypohidrosis, related to TPM in adults, to date, is more common than previously reported. Recognition of this may help to avoid unnecessary investigations which are both costly and troublesome to the patient. □

**Disclosures.**
The authors have no financial disclosures to report. The authors have declared that no conflict of interest exists.

## References

Arcas J, Ferrer T, Roche MC, Martinez-Bermejo A, Lopez-Martin V. Hypohidrosis related to the administration of topiramate to children. *Epilepsia* 2001; 42: 1363-5.

Ben-Zeev B, Watemberg N, Augarten A, *et al*. Oligohydrosis and hyperthemia: pilot study of a novel topiramate adverse effect. *J Child Neurol* 2003; 18: 254-7.

Briggman JV, Tashian RE, Spicer SS. Immunohistochemical localization of carbonic anhydrase I and II in eccrine sweat glands from control subjects and patients with cystic fibrosis. *Am J Pathol* 1983; 112: 250-7.

Cerminara C, Seri S, Bombardieri R, Pinci M, Curatolo P. Hypohidrosis during topiramate treatment: a rare and reversible side effect. *Pediatr Neurol* 2006; 34: 392-4.

De Carolis P, Magnifico F, Pierangeli G, *et al*. Transient hypohidrosis induced by topiramate. *Epilepsia* 2003; 44: 974-6.

Galicia SC, Lewis SL, Metman LV. Severe topiramate-associated hyperthermia resulting in persistent neurological dysfunction. *Clin Neuropharmacol* 2005; 28: 94-5.

Incecik F, Herguner M, Altunbasak S. Topiramate associated hypohidrosis and hyperthermia. *Indian Pediatr* 2008; 45: 238-40.

Kim SC, Seol IJ, Kim SJ. Hypohidrosis-related symptoms in pediatric epileptic patients with topiramate. *Pediatr Int* 2010; 52: 109-12.

Ma L, Huang YG, Deng YC, *et al*. Topiramate reduced sweat secretion and aquaporin-5 expression in sweat glands of mice. *Life Sci* 2007; 80: 2461-8.

Margari L, Ventura P, Buttiglione M, *et al*. Electrophysiological study in 2 children with transient hypohidrosis induced by topiramate. *Clin Neuropharmacol* 2008; 31: 339-46.

Markowitz SY, Robbins MS, Cascella C. Reversible hypohidrosis with topiramate therapy for chronic migraine. *Headache* 2010; 50: 672-4.

Sato K, Kang WH, Saga K, Sato KT. Biology of sweat glands and their disorders I. Normal sweat gland function. *J Am Acad Dermatol* 1989; 20: 537-63.

Ziad Ek, Rahi AC, Hamdan SA, Mikati MA. *Neurology* 2005; 65: 1139-40.