Symptomatic and asymptomatic hypohidrosis in children under topiramate treatment

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Topiramate (TPM) has peculiar side effects such as speech difficulties, weight loss, oligohidrosis and hyperthermia. We present the frequency and severity of hypohidrosis in our patients under TPM treatment.

One hundred and two patients treated with TPM were evaluated retrospectively. Five (8 months-15 years of age) of them experienced symptomatic hypohidrosis manifested with prolonged or intermittent fever. Pilocarpine iontophoresis sweat test had been performed on the five patients before they were managed, and no sweat had been collected in 4/5 cases. Of the 102 patients, 42 who started TPM treatment when the study was established were evaluated prospectively regarding oligohidrosis. First, they were questioned about whether hypohidrosis occurred after TPM. Of 42, 11 patients complained of hypohidrosis. A sweat test was then performed on these 11 patients. Sweat could not be obtained in 5/11, and increased chloride concentration was found in 4/11. However, sweat could be obtained in the patients who had no complaint of hypohidrosis.

Pediatricians should be aware of this side effect of TPM to prevent nonrelevant and cumbersome investigations in patients with prolonged or intermittent fever onset during TPM treatment. Our findings suggest that 5% of patients would experience hyperthermia during TPM treatment. Hypohidrosis without hyperthermia would be more frequent. If it is possible to collect sweat in patients who get fever during TPM treatment, it would be highly probable that the fever is not due to hypohidrosis. Increased chloride concentration alone does not seem to be significant for the hyperthermia risk.

Key words: children, epilepsy, hyperthermia, hypohidrosis, prolonged fever, topiramate.

Approximately 25% of epilepsy patients are unresponsive to conventional antiepileptic drugs (AED). Newer generation AEDs have been introduced for those cases in the last decade. Topiramate (TPM) is one of the new AEDs, which has been reported as effective, safe and tolerable in children as well as in adults[1,2]. TPM acts through blocking of sodium channels, enhancing GABA-induced influx of chloride, inhibiting kainate/AMPA glutamate receptors, reducing L-type currents in voltage-activated calcium channels and inhibiting carbonic anhydrase enzyme. TPM has no significant hepatic or hematological side effects. However, some peculiar side effects have been reported. Selective (i.e. speech) or nonselective depression of the central nervous system and weight loss are the most often encountered adverse effects. Although a new AED is introduced and marketed only after phase 4 studies, some adverse effects are noted during postmarketing surveillance. Metabolic acidosis, nephrolithiasis, acute glaucoma, central hyperventilation and hypohidrosis have been reported recently[3,4]. Although oligohidrosis has become more striking in

TPM treatment[5-7], the patients reported in the literature are limited in number. Herein, we present the frequency and severity of hypohidrosis in our pediatric epilepsy patients under TPM treatment.

Material and Methods

One hundred and two patients who had been given TPM as add-on therapy in effective doses (3.4-12 mg/kg/d) were evaluated retrospectively. The cases who had experienced recurrent febrile episodes or heat intolerance manifestations (flushing, dry skin, and irritability in a hot environment or during a physical activity) were accepted as cases with symptomatic hypohidrosis. Of the 102 patients, 42 started TPM treatment during the study, and were evaluated prospectively. They were first questioned regarding asymptomatic hypohidrosis onset after TPM treatment. The patients who had the complaint of hypohidrosis and no hyperthermia were accepted as patients with subjective hypohidrosis. Second, pilocarpine iontophoresis sweat test (3100 Sweat conductivity analyzer, Wescor Company, USA) was performed in all patients who had the complaint of hypohidrosis. Sweat test was also performed in a group of patients selected from the cases without the complaint of hypohidrosis, who were age- and sex- matched to the patients with complaint of hypohidrosis. Sweat test had been performed in all patients with hyperthermia (symptomatic hypohidrosis) before they were managed, and the results of those tests were also considered. The patients were accepted to have objective hypohidrosis (either symptomatic or asymptomatic objective hypohidrosis in accordance with hyperthermia presence) if sweat could not be collected on sweat test. A second sweat test was also performed to verify objective hypohidrosis in such cases.

Results

Of the 102 patients (age: 4 months-18 years; mean: 7.3 years), five patients had experienced either prolonged fever or intermittent hyperthermia, heat intolerance and dry flushed skin after physical activity due to hypohidrosis, and these were accepted to have symptomatic hypohidrosis. Their clinical features and sweat test results are summarized in Table I. Of the 42 patients who were evaluated prospectively about asymptomatic hypohidrosis, 11 patients

Table I. Features of the Symptomatic Cases

Case	Age-Sex	Diagnosis	AED	TPM efficacy	Dose (mg/kg/d)	Symptoms	Sweat test	Prognosis
1	8 months, M	Symptomatic West syndrome	TPM+VGB	No	12	Prolonged fever and anhidrosis	No sweat	After TPM was stopped, body temperature, hidrosis and sweat test returned to normal
2	12 months, M	Symptomatic West syndrome	TPM+VGB	No	8	Prolonged fever and anhidrosis	No sweat	After TPM was stopped, body temperature, hidrosis and sweat test returned to normal
3	6 years, M	Landau-Kleffner syndrome	TPM+VPA	Complete	4	Febrile episodes and hypohidrosis	No sweat	Asymptomatic after keeping the child away from hot environments and excessive exercise
4	10 years, M	Symptomatic complex partial epilepsy	TPM+CBZ+ VPA	Partial (50-100%)	7	Febrile episodes and hypohidrosis	77 mEq/L	After TPM was decreased to 4.3 mg/kg/d, episodes of hyperthermia disappeared, and sweat test decreased to 65 and later to 34 mEq/L.
5	15 years, M	Cryptogenic complex partial epilepsy	TPM+CBZ	Partial (50-100%)	6.5	Febrile episodes and hypohidrosis	No sweat	Asymptomatic after keeping the child away from environmental hyperthermia and excessive exercise

AED: Antiepileptic drug.
CBZ: Carbamazepine.
TPM: Topiramate.
VPA: Valproate.
VGB: Vigabatrin.

expressed, on direct questioning, that they had begun to sweat less after TPM treatment (i.e., asymptomatic subjective hypohidrosis); 31 had no complaint of hypohidrosis. Regarding the sweat test results, sweat could not be collected to measure chloride concentration in five of the 11 patients. However, sweat could be obtained in the entire group that consisted of 11 patients selected from the 31 patients who did not complaint of hypohidrosis. Table II summarizes the findings.

Table II. Number of Patients and Sweat Test Results by Group

Groups	Patients (n)	Sweat test (n)		
		No sweat	Increased chloride concentration	Normal chloride concentration
Patients evaluated retrospectively for symptomatic hypohidrosis	102	4	1	0
• Cases with symptomatic hypohidrosis	5 (5%)			
Patients evaluated prospectively for asymptomatic hypohidrosis	42	5	4	2
• Cases with hypohidrosis complaint	11 (26.1%)			
Control group (*)	11	0	3	8

* Control group was selected from the patients with no hypohidrosis complaint. The patients were age- and sex-matched to the cases with hypohidrosis complaint.

Discussion

Sweating is essential for regulation of body temperature in hot environments and during physical activity. Sweat is mainly produced by skin eccrine glands. An increase in core body temperature is sensed by the anterior hypothalamic preoptic nucleus, which fires sympathetic nerve fibers of sweat glands. The eccrine glands are innervated by the postganglionic C-type nonmyelinated fibers. Although acetylcholine, as opposed to the ordinary sympathetic innervation, is the principal neurotransmitter, some other chemicals such as vasoactive intestinal peptide, histidine, and atrial natriuretic peptide are also important[8].

Seventeen patients with fever secondary to hypohidrosis during TPM treatment have been reported in children to date[5-7]. The characteristic features observed in those cases[5-7] and in our patients could be summarized as follows: Manifestation of hypohidrosis varies from recurrent episodes of hyperthermia in certain conditions to persistent fever. It seems that younger children are more likely to suffer prolonged fever rather than intermittent hyperthermia. Children are inclined to be symptomatic in comparison with adults; adult cases have been reported only rarely[9]. The onset time is likely to be related to length of time until effective doses are reached. It is not clear whether rapid dose escalation might give rise to earlier onset of hypohidrosis. Hypohidrosis is reversible. Decreasing TPM dose relieves the symptoms. However, it might be necessary to stop TPM treatment. Increased physical activity, high ambient temperature and hot seasons have been noted as predisposing factors. Avoidance of those factors by the patients might be sufficient in some cases. TPM was used as add-on therapy in most of the reported patients. Because various AEDs

were used in addition to TPM, it is not clear whether any other AED is also a predisposing factor. It would be reasonable to be cautious in combining TPM with zonisamide since the latter may also cause hypohidrosis[10]. Finally, hypohidrosis may also occur in patients whose seizures do not respond to TPM therapy (Cases 1 and 2).

How TPM causes hypohidrosis has not yet been clarified. TPM might cause a blockade in nerves innervating eccrine glands. However, no such effect of TPM has been demonstrated. TPM might affect electrolyte channels or transporters involved in sweat glands as well as in neurons, but it is not known whether the sodium channels in sweat glands are structurally similar to the neuronal channels. The most likely mechanism is related to the carbonic anhydrase enzymes. Carbonic anhydrase enzymes I and II have been demonstrated in normal sweat glands. TPM has an inhibitory effect on some carbonic anhydrase isoenzymes (II and IV)[11]. Furthermore, metabolic acidosis and nephrolithiasis are likely to be related to inhibition of carbonic anhydrase. Interestingly, zonisamide, which inhibits the carbonic anhydrase enzyme, also has similar side effects. On the other hand, what determines the severity of hypohidrosis is not known at present. The fact that most symptomatic patients were younger may suggest that possible compensation mechanisms such as up-regulation work less in children in comparison with adults. In addition, genetic polymorphism may exist in carbonic anhydrase isoenzymes, which has not been studied to date.

Incidence of hypohidrosis and fever has not been documented well. Asymptomatic hypohidrosis may be overlooked. In our study, symptomatic hyperthermia secondary to severe hypohidrosis occurred in 5% of all patients. In addition, 26.1% of the patients had complaint of hypohidrosis without hyperthermia. Sweat test showed that 45.5% of the patients with the complaint of hypohidrosis had significant hypohidrosis even though they had no hyperthermia. Should milder hypohidrosis be considered, oligohidrosis would be more frequent. Ben-Zeev et al.[7] showed subnormal sweat production in nine (64%) out of 14 patients. Four patients (28.5%) had hyperthermia and heat intolerance.

We did not measure sweat production quantitatively. Our objective was to discover the benefit of the standard sweat test. Our findings suggest that if it is possible to obtain sweat in patients who get fever during TPM treatment, it would be highly probable that fever is not due to hypohidrosis, and any other reason should be considered. Because sweat could not be obtained in some of our patients without hyperthermia, lack of sweating during the sweat test does not seem to be significant for predicting the patients who will get fever due to hypohidrosis. Sweat test would not be normal in most of the patients with hypohidrosis. Increased chloride concentration alone does not seem to be significant for either severity of hypohidrosis or the risk of hyperthermia.

Awareness of a novel side effect of a new drug can prevent nonrelevant and cumbersome investigations, and avoids its use in patients identified to be at special risk. Pediatricians should consider this side effect of TPM for the correct management of patients with persistent or intermittent fever. Parents of patients who are prescribed TPM should be advised to be watchful for possible decrease in sweating and fever. Younger children and patients who have the complaint of hypohidrosis should be followed more carefully and should be advised to avoid hot environments and excessive physical activity, especially in hot seasons. In symptomatic cases, TPM should be decreased or, if necessary, ceased.

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