



Case Report

Topiramate-induced periodic limb movement disorder in a patient affected by focal epilepsy



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ARTICLE INFO

Article history:

Received 9 April 2014

Accepted 10 April 2014

Available online 21 May 2014

Keywords:

Topiramate

Focal epilepsy

PLMD

Sleep

Sleepiness

Cyclic alternating pattern

ABSTRACT

Periodic limb movement disorder (PLMD) is characterized by pathological periodic limb movements during sleep, insomnia and/or diurnal sleepiness, and the absence of another primary sleep disorder. We report a patient with complex partial seizures who developed PLMD while taking topiramate (TPM). He had no evidence of metabolic and/or other conditions inducing PLMD. He also had fragmented sleep and disruptive PLMS on polysomnography, and PLMS subsided with change of antiepileptic drug. Topiramate may modulate the dopaminergic pathway by inhibition of glutamate release, thereby inducing PLMD as observed in our patient. Although a single case does not allow any generalization, PLMD should be considered in patients complaining of insomnia and treated with TPM.

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1. Introduction

Periodic limb movement disorder (PLMD) is diagnosed when there are periodic limb movements during sleep (PLMS) exceeding norms for age, clinical sleep disturbance, and the absence of another primary sleep disorder or reason for the PLMS [1]. Pathological periodic limb movement index (PLMI) is defined as >15 movements/h in adults [1]. Periodic limb movement disorder is rarer than restless legs syndrome (RLS), which is characterized by the sensory motor symptoms frequently associated with PLMS, usually occurring at night and leading to disrupted sleep and daytime fatigue as in neuromuscular disorders [2]. Several medications are known to induce and/or to worsen PLMD (i.e., antidepressants, antihistamines, and antipsychotics) [3]. Although alternative RLS/PLMD treatments include antiepileptic drugs (AEDs) [4], in contrast, topiramate (TPM)-induced RLS also associated with PLMS was described in four patients affected by epilepsy [5,6]. We report a case of TPM-induced PLMD in a patient affected by cryptogenic temporal lobe epilepsy lacking a history of previous sleep disorders.

2. Case report

A 34-year-old male affected by cryptogenic temporal lobe epilepsy previously treated with carbamazepine (up to 1200 mg per day)

manifested monthly complex partial seizures. Topiramate slowly titrated up to 250 mg per day induced seizure freedom and, afterward, carbamazepine was discontinued. Concurrently, he complained of insomnia, nonrestorative sleep, and daytime sleepiness (Epworth Sleepiness Scale (ESS) score: 16). In addition, his wife reported the appearance of frequent nocturnal leg movements that were never previously observed. The patient also denied having had prior similar symptoms. Serum examination (blood count, electrolytes, liver and renal function, thyroid hormones, and iron and ferritin levels) was unremarkable. Therefore, our patient underwent a full polysomnography (PSG) that showed a severe PLMD (PLMI: 62.7/h) associated with high PLM arousal index (PLMAI: 11.9/h); low sleep efficiency; high sleep latency, wakefulness after sleep onset, and number of awakenings; high percentage of light sleep (N2); and low percentage of slow-wave sleep (N3) (see Table 1). Periodic limb movements during sleep were strictly associated with periodic electroencephalographic arousals and cyclic alternating pattern (CAP). In particular, CAP oscillations were triggered by PLM with higher presence of CAP subtypes A2 and A3 (see Fig. 1). These CAP subtypes represent an arousal phenomenon that likely leads to clinical correlates of disturbed sleep. Respiratory disturbance index and oxygen desaturation index were normal. Therefore, because of the progressive impairment of insomnia and daytime dysfunction, TPM was slowly discontinued and switched to valproate up to 900 mg per day. During TPM discontinuation and after complete withdrawal, the patient underwent full PSG (TPM: 50 mg per day). Periodic limb movement index and periodic limb movement arousal index showed a significant improvement and, after TPM discontinuation, reached a normal value (PLMI < 15/h). Polysomnography

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Table 1
PSG data during TPM treatment (250 mg and 50 mg) and after TPM discontinuation.

Sleep variables	TPM (250 mg)	TPM (50 mg)	No TPM
TST, total sleep time (min)	399	510	495
Sleep efficiency (%)	81.5%	93.1%	97.2%
Sleep latency (min)	22	12	13
n awakenings	29 (4.4/h)	17 (2/h)	4 (0.1/h)
n REM periods	3	4	5
REM latency (min)	80.5	92	80
WASO (min)	68	43	14.1
% N1	2.3	6.2	0.4
% N2	62.8	32	49.7
% N3	21.5	42.2	23.3
% REM	13.5	19.5	16.6
RDI	0.7/h	1.7/h	1.2/h
CAP rate (%)	66.3	47.7	45.1
A1 (%)	23.7	33.4	42.5
A2 (%)	41.8	44.5	27.7
A3 (%)	34.5	22.1	29.8
ODI	0.8/h	1.4/h	0.7/h
PLMI	62.7/h	21.5/h	11.6/h
PLMAI	11.9/h	3.4/h	0.9/h
PLMW	50.2/h	5.2/h	6.7/h
ESS score	16	11	10

RDI, respiratory disturbance index; ODI, oxygen desaturation index; PLMI, periodic limb movement index; PLMAI, periodic limb movement arousal index; PLMW, periodic limb movements during wakefulness; CAP, cyclic alternating pattern; A1, CAP phase A1; A2, CAP phase A2; A3, CAP phase A3; ESS score, Epworth Sleepiness Scale score.

variables and ESS scores showed remarkable amelioration (see Table 1). In addition, the CAP rate exhibited a slight reduction, an increase of CAP phase A1 and a parallel reduction of phases A2 and A3. All PSG data are summarized in Table 1. In order to evaluate the association between TPM and PLMD, the Naranjo probability scale [7] documented a probable association (Naranjo score: 8/13) between PLMD and TPM intake.

3. Discussion

This is the first publication, to our knowledge, to describe TPM-induced PLMD in a patient affected by cryptogenic temporal lobe epilepsy previously not complaining of sleep disorders. Although there is a high night-to-night variability of PLMI in PLMD/RLS that may influence our results, this issue is still controversial, and the nocturnal pattern of PLM occurrence was highly reliable across nights, suggesting that a single-night study may be sufficiently sensitive to confirm diagnosis and associated sleep disturbances [8]. Therefore, we can state that PLMD was probably induced by TPM in our patient.

In addition, RLS and PLMD pathophysiology is highly debated; a common central dysregulation of dopaminergic system seems to be implicated [9]. This hypothesis is supported by the efficacy of dopaminergic treatment for both sleep disorders. Several drugs with a dopamine-modulating profile may provoke RLS and/or PLMD [3]. Although such AEDs may be effective treatments for RLS and PLMD, TPM-induced

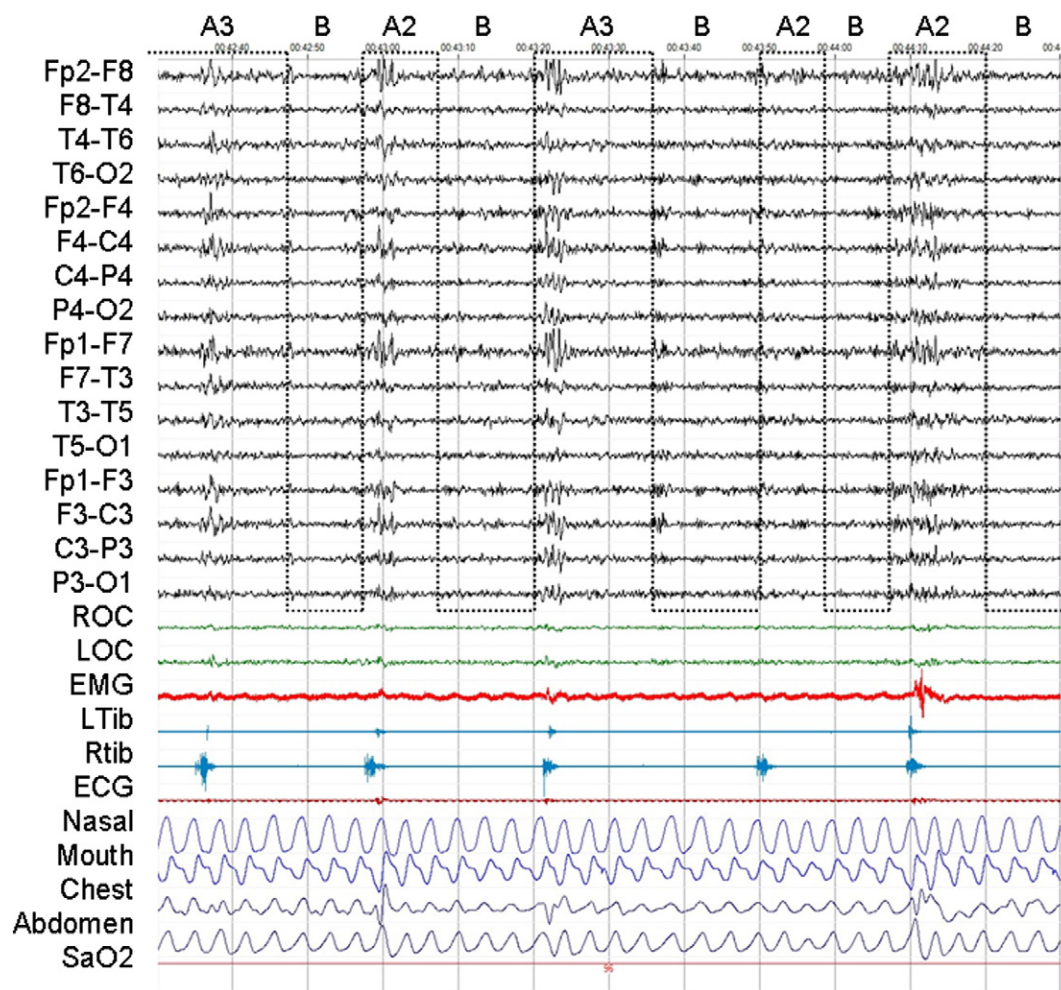


Fig. 1. Two-minute segment of full polysomnography (TPM: 250 mg per day) showing periodic limb movement during NREM sleep (N2). The muscle contractions of the anterior tibialis (RTib and LTib) and of the chin (EMG) occur after the onset of the A phase (A2 and A3) of the cyclic alternating pattern and follow the same cyclic recurrence. The TPM withdrawal induced the progressive reduction of PLMS and CAP rate, particularly phases A2 and A3, considered a marker of sleep instability.

RLS was previously described in a few cases [5,6]. Topiramate shows multiple mechanisms of action. Topiramate enhances GABA function and inhibits AMPA and kainate glutamate pathways, inducing an extracellular modulation of dopamine release in the mesocorticolimbic dopamine system [10]. These experimental lines of evidence are confirmed by its efficacy against alcohol, nicotine, and cocaine addictions [11,12]. Therefore, we can hypothesize that TPM may modulate the dopaminergic pathway, thereby inducing PLMD in subjects with specific individual susceptibility.

On the other hand, the clinical significance of PLMS lacking RLS symptoms is still debated. Patients showing PLMS may complain of insomnia and daytime dysfunction. High levels of EEG arousals and/or CAP sequences prior to leg movements confirm the presence of sleep impairment in these patients [13,14]. Periodic limb movements are short movements that can be entrained by central pattern generators in reciprocal oscillatory coupling. Specifically, CAP phases A2 and A3 that represent arousal phenomena are more probably associated with disturbed sleep [14] as also demonstrated polygraphically in our patient (Fig. 1). The patients are typically not aware of these limb movements, but quality of sleep may be compromised, and the bed partners might recognize PLMS. Even though the literature failed to document a clear correlation between PLMS severity and sleep disruption [13], Haba-Rubio et al. [15] found a correlation between PLMS and tiredness, sleep efficiency, and psychological well-being.

Periodic limb movement disorder, insomnia, and diurnal symptoms promptly recovered after drug discontinuation in our patient suggesting a probable association with TPM. We are aware that, regarding the mutual interactions between sleep and epilepsy, not only sleep deprivation and daytime sleepiness but also abnormal sleep per se represent well-known potential triggers for seizures and are themselves influenced by epilepsy in a sort of reciprocal effect. Notwithstanding, comorbidities and pharmacological treatment are other commonly accepted major factors that influence this interplay. Therefore, an accurate clinical history and PSG study in selected cases could be useful in order to recognize potential drug-induced sleep disorders.

Conflict of interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

- [1] American Academy of Sleep Medicine. The International Classification of Sleep Disorders: Diagnostic and Coding Manual. 2nd ed. Westchester, Ill.: American Academy of Sleep Medicine; 2005.
- [2] Romigi A, Izzi F, Pisani V, Placidi F, Pisani LR, Marciani MG, et al. Sleep disorders in adult-onset myotonic dystrophy type 1: a controlled polysomnographic study. *Eur J Neurol* 2011;18(9):1139–45.
- [3] Lesage S, Hening WA. The restless legs syndrome and periodic limb movement disorder: a review of management. *Semin Neurol* 2004;24(3):249–59.
- [4] Lee YA, Huynh P, Neher JO, Safranek S. Clinical inquiry. What drugs are effective for periodic limb movement disorder? *J Fam Pract* 2012;61(5):296–8.
- [5] Romigi A, Izzi F, Placidi F, Sperli F, Cervellino A, Marciani MG. Topiramate-induced restless legs syndrome: a report of two cases. *J Neurol* 2007;254(8):1120–1.
- [6] Bermejo PE. Restless legs syndrome induced by topiramate: two more cases. *J Neurol* 2009;256(4):662–3.
- [7] Naranjo CA, Busto U, Sellers EM, Sandoz P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239–45.
- [8] Sforza E, Haba-Rubio J. Night-to-night variability in periodic leg movements in patients with restless legs syndrome. *Sleep Med* 2005;6(3):259–67.
- [9] Siddiqui F, Strus J, Sun YJ, Walters AS. No significant difference in cytokine levels in patients with restless legs syndrome versus controls – preliminary data. *Sleep Med* 2007;8(1):98–9.
- [10] Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. *Epilepsia* 2000;41(Suppl. 1):S3–9.
- [11] Johnson BA, Ait-Daoud N, Wang XQ, Penberthy JK, Javors MA, Seneviratne C, et al. Topiramate for the treatment of cocaine addiction: a randomized clinical trial. *JAMA Psychiatry* 2013;70(12):1338–46.
- [12] Kampman KM, Pettinati HM, Lynch KG, Spratt K, Wierzbicki MR, O'Brien CP. A double-blind, placebo-controlled trial of topiramate for the treatment of comorbid cocaine and alcohol dependence. *Drug Alcohol Depend* 2013;133(1):94–9.
- [13] Karadeniz D, Ondze B, Besset A, Billiard M. Are periodic leg movements during sleep (PLMS) responsible for sleep disruption in insomnia patients? *Eur J Neurol* 2000;7(3):331–6.
- [14] Parrino L, Boselli M, Buccino GP, Spaggiari MC, Di Giovanni G, Terzano MG. The cyclic alternating pattern plays a gate-control on periodic limb movements during non-rapid eye movement sleep. *J Clin Neurophysiol* 1996 Jul;13(4):314–23.
- [15] Haba-Rubio J, Staner L, Krieger J, Macher JP. What is the clinical significance of periodic limb movements during sleep? *Neurophysiol Clin* 2004;34(6):293–300.