Case Reports

Intractable Insomnia as a Major Comorbidity of Grand Mal on Awakening: Case Report with Diagnostic Polysomnographic Findings and Successful Treatment Outcome

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Abstract-

Purpose: We report a novel case of "grand mal on awakening" from sleep presenting with intractable insomnia associated with interictal epileptiform activity (IEA) during sleep.

Case Report: A 36-year-old woman with a seizure history of grand mal on awakening since age 13 years suffered from severe, persistent insomnia despite seizure control with daytime valproic acid therapy. Bedtime hypnotic therapy with zolpidem and clonazepam was ineffective. An overnight polysomnographic (PSG) study with expanded EEG seizure montage found IEA with microarousals or full arousals from sleep, with a mean rate of IEA events of 19.0 per hour. The sleep macrostructure (the cycling and distribution of sleep stages) was disturbed by the IEA events, and the sleep efficiency was 67.2%. Bedtime valproic acid therapy, 500 mg, was rapidly effective. A follow-up PSG study documented a reduced mean rate of IED events of 5.8 per hour, and an improved sleep efficiency of 87.7%.

Conclusion: Severe persistent insomnia with sleep-related IEA can occur as a major comorbidity of grand mal on awakening despite full seizure control. Although standard hypnotic therapy (benzodiazepine receptor agonist; benzodiazepine) was ineffective, bedtime monotherapy with valproic acid was promptly effective, with objectively-documented improvement. Therefore, when remitted epilepsy patients complain of persistent insomnia, clinicians should consider sleep-related IEA activity, with sleep disruption and poor sleep efficiency, in the differential diagnosis. A diagnostic PSG study with expanded EEG seizure montage should be considered.

Key Words: insomnia, epilepsy, grand mal on awakening, valproic acid, polysomnography

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INTRODUCTION

Insomnia is defined as difficulty initiating or maintaining sleep, or sleep that is non-restorative with poor quality, with negative daytime consequences[(1)]. Insomnia is a common complaint in patients with epilepsy,

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with an estimated prevalence of 25% to 54%, which is 2–4 times greater than insomnia reported in the United States general population[2]. In epilepsy patients, antiepileptic drugs (AED), nocturnal seizures, sleep apnea, and medical or psychiatric comorbidities can disrupt sleep and promote insomnia[3]. Polysomnographic (PSG) studies of patients with epilepsy have shown disrupted sleep with increased sleep onset latency, increased number of nocturnal awakenings, and altered sleep architecture[4]. We report a case of remitted grand mal seizures on awakening from sleep, presenting as intractable insomnia, with full response to bedtime valproic acid therapy, confirmed by follow-up PSG findings and by major improvement in the following validated clinical scales: CPSQI (Chinese version of the Pittsburgh Sleep Quality Index)[5], and ISI-C (Insomnia Severity Index- Chinese Version)[6]. The CPSQI measures self-reported sleep quality and disturbances over the previous month. The CPSQI global score differentiates "good sleepers" (CPSQI total score ≤ 5) from "poor sleepers" (CPSQI > 5). The ISI-C is a self-report questionnaire measuring the patient's perception of his or her insomnia over the previous two weeks. ISI-C scores < 9 indicates a healthy sleeper.

CASE REPORT

A 36 y.o. woman presented to a neurologist (S-B Y) at the age of 23 years because of generalized tonic-clonic convulsions with unconsciousness upon awakening from sleep. These events had emerged 10 years previously, at the age of 13 years. Once while riding on a school bus she had fallen asleep and was awakened by a classmate when it was time to leave the bus. This triggered a grand mal (GM) convulsion. Throughout adolescence there was an increasing frequency of GM seizures both upon awakening from nocturnal sleep and from daytime naps. All the GM attacks occurred in the context of sleep deprivation, or by sleep interruption, such as a phone call awakening her. A traditional Chinese medicine specialist was eventually consulted, but therapy was ineffective. During her university years, when she had minimal sleep deprivation, she had only one GM attack from sleep.

After starting a job as a school teacher, the sleep-related GM attacks reemerged with increasing frequency. She then presented to the neurologist (S-B Y) at the age of 23 years. The medical history, physical examination, and neurologic evaluation were negative. There was no history of birth injury, head trauma, nor any positive medical, psychiatric or family history. She reported being a good sleeper in childhood. A routine awake brain EEG examination (fig. 1) revealed generalized 3-4 Hz spike-and-wave activity bilaterally over the hemispheres. Brain MRI was unremarkable. The presumptive diagnosis was epilepsy with GM seizures upon awakening from sleep.

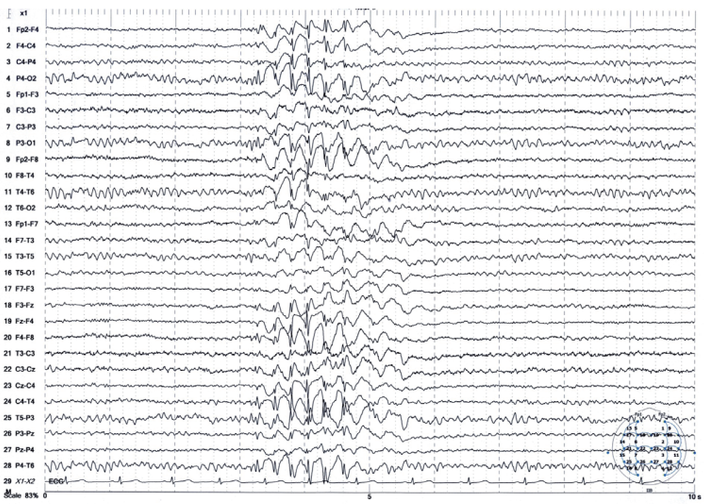

Figure 1. Daytime awake EEG study revealed a run of the generalized spike and waves (3-4 Hz) over bilateral hemispheres.

Carbamazepine therapy, 200 mg bid, was started, which was ineffective and induced daytime myoclonic jerks. Valproic acid therapy was substituted, 200 mg bid, with prompt, full seizure control that was maintained for three years, until January of 2004, when she stopped valproic acid therapy on her own, and remained seizure-free.

In January 2011 she spontaneously developed disrupted, very light and unsatisfactory sleep with considerable recall of mundane dreams and early morning awakenings, which she had never experienced before. Consultation with a Chinese medicine doctor was again not helpful. Her nocturnal sleep disruption with sleep deprivation became progressively worse until her GM seizure attacks upon awakening reappeared in July 2011. She then presented to a neurologist, and valproic acid therapy, 200 mg bid, was reinstituted, along with clonazepam therapy, 0.5 mg at bedtime due to her insomnia complaint that also included leg kicking during sleep. Her seizures were promptly controlled, but she still had prominent insomnia and sleep deprivation symptoms. She was then referred to the hospital sleep clinic (S-B Y), where zolpidem 10 mg at bedtime was added to the clonazepam therapy, 0.5 mg; valproic acid therapy, 200 mg bid, was continued. Her insomnia minimally improved, and she continued to complain of poor sleep quality. Her CPSQI was 18 and ISI-C was 27. The score of the Chinese version of the Beck Depression Inventory (BDI-II)[7] was 26 (severe depression) and the score of the Chinese version of the Beck Anxiety Inventory (BAI)[8] was 47 (severe anxiety).

An overnight, hospital-based PSG study was undertaken, utilizing standard recording and scoring methods[9]. The patient took zolpidem 10 mg and clonazepam 0.5 mg 30 minutes before the PSG study. The PSG monitoring included eye movements (EOG); expanded EEG (seizure montage) with fast paper speed; submental and leg electromyograms; airflow, chest and abdomen respiratory effort; electrocardiogram; and continuous time-synchronized audiovisual recording. The sleep EEG revealed interictal epileptiform activity (IEA) consisting of spike-and-waves with microarousals or full arousals (fig. 2 & 3), with an hourly event index

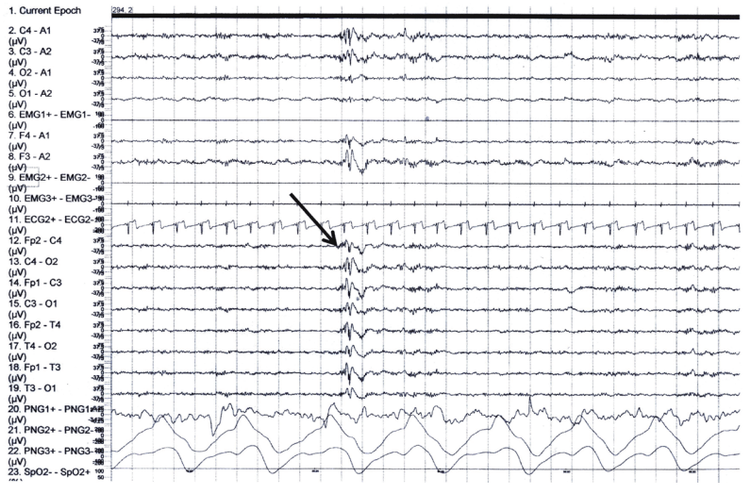

Figure 2. Nocturnal PSG (30 seconds per epoch) during N2 sleep and the emergence of an interictal epileptiform discharge (IED) with spike-and- wave complex (black arrow) following fast-wave EEG activity.

Ep294.2 refers to the 294th epoch, with this epoch being in N2 sleep. EEG montage (channels 12-19) shows a run of spike-and-waves. The electrooculogram (channel 7-8) indicates no rapid eye movements. The electrocardiogram (channel 11) shows no change in heart rate during the IED event. Channels 20-23 represent the nasal/oral airflow, chest respiratory effort, abdomen respiratory effort and O_2 saturation, which do not show any sleep apnea or oxygen desaturation during the IED event.

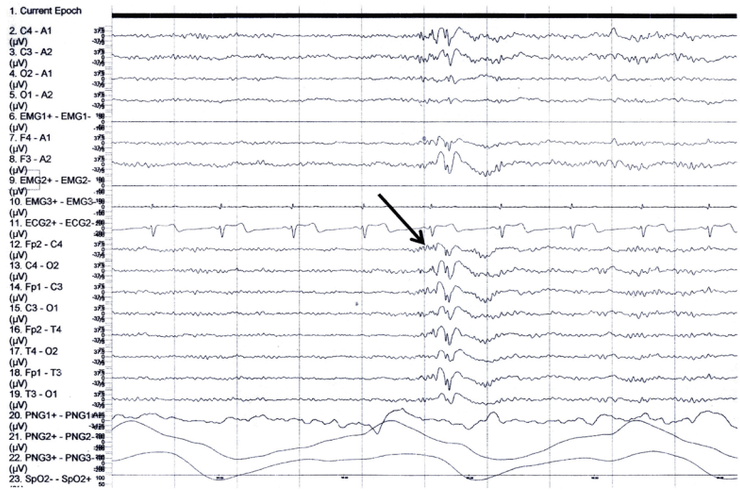

Figure 3. Shift from 30 seconds per epoch in Figure 2 to 10 seconds per epoch. The epileptiform discharge with spike-and-wave complex is more clear (black arrow).

Table 1. Polysomnographic and Questionnaire Data: Before vs. After Bedtime Valproic Acid Treatment

	Before	After
Sleep onset latency (min)	50.5	49.0
REM sleep latency (min)	72.0	75.5
N1 sleep (% TST)	6.3	4.8
N2 sleep (%TST)	72.3	68.6
N3 sleep (%TST)	0.0	2.0
REM sleep (%TST)	21.4	24.6
WASO (%)	25.3	9.2
Sleep efficiency (%)	67.2	87.7
PLMI (hourly)	11.8	0.0
IED (hourly)	19.0	5.8
CPSQI	18	6
ISI-C	27	8
BDI-II-C	26	13
BAI-C	47	34

TST: total sleep time

WASO (wake after sleep onset): % wake time after sleep onset during the entire night in bed.

Sleep efficiency: total sleep time divided by total time in bed

PLMI: periodic limb movement index

IED: Interictal Epileptiform Discharge

CPSQI: Chinese version of the Pittsburgh Sleep Quality Index

ISI-C: Insomnia Severity Index- Chinese Version

BDI-II-C: Chinese Version of the Beck Depression Inventory-II

BAI-C: Chinese Version of the Beck Anxiety Inventory

of 19.0. Periodic limb movements (PLMs) were also present, with an hourly PLM index of 11.8. The dose of clonazepam was increased to 1 mg at bedtime, and valproic acid therapy was switched to 500 mg at bedtime (with cessation of the 200 mg bid regimen). At one month follow-up, her insomnia and psychological status had much improved (Table 1.). The patient continued taking valproic acid 500 mg and clonazepam 0.5 to 1 mg at bedtime since September of 2011. During 2013-2014 the clonazepam dose was tapered down and then discontinued. She remains on valproic acid monotherapy, 500 mg at bedtime, and has been seizure-free with full control of her insomnia. A follow-up PSG study revealed a remarkably improved sleep macrostructure with consolidated sleep, and the IEAs with arousals were considerably reduced (Table 1.). Her sleep, depression and anxiety rating scales also were normalizing with insomnia control (Table 1.).

DISCUSSION

Epilepsy with grand mal on awakening is a benign generalized idiopathic epilepsy, first occurring around the time of puberty. The recognized diagnostic criteria[10] are as follows: (1) a form of epilepsy with an onset around puberty; (2) occurring in previously normal children; (3) seizure pattern characterized by generalized tonic-clonic

seizures shortly after awakening, regardless of the time of day. Shian et al. found that the most frequent initial EEG finding in grand mal on awakening was a 3-4 Hz generalized spike-wave complex, and good response to valproic acid[11]. The clinical history and objective findings in our patient satisfy the diagnostic criteria for epilepsy with grand mal on awakening[10], and also correspond closely to the findings by Shian et al[11].

Nocturnal seizures and IEA can disturb the normal sleep architecture. Marked sleep instability is often observed in epileptic patients, even in the absence of nocturnal seizures[12]. Our patient presented with a novel complaint of severe, persistent insomnia with documented sleep-related IEA that was a major comorbidity of grand mal on awakening despite full seizure control. Although standard hypnotic therapy was ineffective, bedtime monotherapy with valproic acid was promptly effective, with objectively-documented improvement. Therefore, when remitted epilepsy patients complain of persistent insomnia, clinicians should consider sleep-related IEA activity, with sleep disruption and poor sleep efficiency, in the differential diagnosis. A diagnostic PSG study with expanded EEG seizure montage should be considered.

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