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CASE REPORTS

Knuckle cracking at night associated with sodium oxybate treatment

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During upward titration of a dose of sodium oxybate therapy for narcolepsy with cataplexy, a 25-year-old woman was observed by her husband to have new onset of knuckle-cracking and moaning behaviors during sleep ≥1 nights each week. The patient did previously occasionally crack her knuckles during the day (but never at night). These behaviors had not been evaluated by polysomnography. After transition of care, polysomnography with video monitoring was ordered and revealed 2 knuckle-cracking episodes that developed out of stage N2 sleep and were likely a non-rapid eye movement sleep parasomnia associated with sodium oxybate treatment.

Keywords: parasomnia, sodium oxybate, catathrenia

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INTRODUCTION

Sodium oxybate (SO) is approved for the treatment of both excessive sleepiness and cataplexy in adult patients with narcolepsy by the US Food and Drug Administration. Treatment starts at 2.25 g orally while in bed ready for sleep, and the dose is repeated 2.5–4 hours later.[1] Slow upward titration is needed to minimize adverse effects. The usual target dose is 6 to 9 g at night. In general, higher doses are needed for sleepiness whereas cataplexy may respond to lower doses. Common adverse effects include nausea, dizziness, vomiting, somnolence, enuresis, and headache.[1] Confusion and anxiety can also occur. Sleepwalking episodes[2] (including sleep driving), sleep-related eating,[2] catathrenia[3] (expiratory groaning), and sexsomnia[4] have also been reported. Prescribing information for SO[1] lists the prevalence of sleepwalking at 6% of 781 patients with narcolepsy treated with SO in adult controlled trials and long-term open label studies, but a postmarketing study found that sleepwalking was present in a very low percentage of patients treated with SO (0.4%).[5] However, 1 review of medication-induced sleepwalking found the evidence to be strongest for patients treated with SO or zolpidem.[6]

REPORT OF CASE

A 25-year-old woman developed incapacitating excessive sleepiness and fatigue. During episodes of laughter, her head sometimes bobbed and her knees buckled. However, only the severe sleepiness concerned the patient. Because of daytime impairment, she developed anxiety and depression and was started on bupropion and sertraline by her psychiatrist. A sleep specialist at an outside institution evaluated the patient using polysomnography and a Multiple Sleep Latency Test (bupropion and sertraline were appropriately withheld), and the results were consistent with a diagnosis of narcolepsy including Multiple Sleep Latency Test findings showing a mean sleep latency of 1.45 minutes and 2 rapid eye movement sleep onset periods.

The patient was started on modafinil and later armodafinil, but the medications were not effective and worsened her anxiety. Methylphenidate was prescribed but also resulted in worsening anxiety. The patient's psychiatrist changed sertraline to fluoxetine because of adverse effects. The sleep specialist initiated treatment with SO starting at 4.5 g nightly. The dose was increased very slowly over several months because the patient had severe nausea. When a total dose of 7 g per night was reached, the patient's husband noted that she had episodes of moaning and knuckle cracking (KC) during sleep that had never been previously observed. His bedtime was several hours later than that of the patient. Therefore, before falling asleep he was able to carefully observe his wife's behaviors. Because she still complained of significant daytime sleepiness, SO was titrated to 9 g per night with improvement in sleep and daytime alertness. In addition, because some residual sleepiness was still noted, solriamfetol at 75 mg daily was added (a higher dose worsened anxiety). Notably, the KC episodes during sleep were observed before this solriamfetol was started. Before the patient started taking SO, she was also noted to have body movements during sleep (thrashing around) and at one point had hit her husband on the nose. However, these behaviors had never been evaluated with video polysomnography. The patient transitioned her care to our facility and presented for ongoing treatment of narcolepsy and concern for nocturnal behaviors. Although the nocturnal KC did sometimes awaken her husband, the major concern was the etiology of the violent body movements during sleep.

Further history was obtained from the patient and her husband. The patient had a history of sleep talking as a child but had

never had a sleepwalking episode. She had no recall of the KC events in the morning. The patient's husband noted that her eyes were typically open during the episodes. He confirmed that the patient did occasionally crack her knuckles while awake before SO treatment was started, but never during sleep. At 9 g of SO per night, both daytime sleepiness and cataplexy were much improved, but KC and moaning/groaning were present at least 3 nights per week. The occurrence of more than 1 episode of KC in a single night was sometimes noted. Since starting SO the patient had only been off the medication twice, each time for a period of approximately 1 week. Neither the patient nor her husband recalled KC episodes at night occurring during these periods. When the patient's husband attempted to converse with her during the episodes of violent movements during sleep, her answers were not always understandable but sometimes revealed dreamlike mentation.

Physical examination was normal. Specifically, the patient had a normal body mass index, a Mallampati score of 1, and a neck circumference of 14 inches. A neurological examination was normal. Polysomnography with synchronized video and audio monitoring was performed using bilateral frontal, central, and occipital electroencephalogram derivations as recommended by *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*[7] and additional temporal electrodes (T3, T4). The patient took her usual SO medication before and during the sleep study. A summary of the polysomnography results is shown in **Table 1.** An episode of KC is shown in **Video 1** in the supplemental material. Two episodes of KC after arousal from stage N2 sleep were recorded. The first episode occurred approximately 2 hours after the patient took the second dose of SO. During the episodes, the patient raised both hands above her head, then lowered her hands, intertwining her fingers and cracking her knuckles (**Video 1**). In addition, brief moaning was heard during nonrapid eye movement sleep, including 1 long episode of an expiratory moan/growl consistent with catathrenia. During stage R sleep there were epochs meeting the criteria for rapid eye movement sleep without atonia (based on chin and leg electromyography), and a few small arm and leg movements and 1 body jerk were visualized during stage R sleep (no complex movements).

Table 1—Polysomnography results.

	Values
Total recording time (min)	491
TST (min)	469
Stage N1 sleep (min)	16.5 (3.5% TST)
Stage N2 sleep (min)	199.0 (42.4% TST)
Stage N3 sleep (min)	128.5 (27.4% TST
Stage REM sleep (min)	125.0 (26.7% TST)
Sleep efficiency (%)	96
Sleep latency (min)	9
REM sleep latency (min)	61
Wake after sleep onset (min)	13
Arousal index (events/h)	8.4
AHI (events/h)	0.5
Number of obstructive apneas	1
Number of mixed apneas	0
Number of central apneas	1
Number of hypopneas	2
AHI, NREM sleep (events/h)	0.5
AHI, REM sleep (events/h)	0.5
AHI, supine (events/h)	0.6
AHI, nonsupine (events/h)	0.0
% TST supine (%)	84
Number of desaturations	4
Low SpO_2 (%)	91
PLMS index (events/h)	0
PLMS arousal index (events/h)	0

AHI = apnea-hypopnea index, NREM = nonrapid eye movement, PLMS = periodic limb movements of sleep, REM = rapid eye movement, SpO_2 = arterial oxygen saturation by pulse oximetry, TST = total sleep time.

DISCUSSION

SO treatment has been associated with sleep talking, sleep-related eating disorders, sleepwalking, and catathrenia. However, KC as a nonrapid eye movement sleep parasomnia has not been reported. The patient's history strongly suggests that the KC was associated with SO treatment. Stage N3 sleep is increased by SO, but at least on the night of monitoring in our sleep center the KC events followed awakening from stage N2 sleep. Many patients who exhibit nonrapid eye movement sleep parasomnias as adults have a history of sleepwalking or other nonrapid eye movement sleep parasomnias in childhood. The patient was noted to have had sleep talking as a child but no other overt parasomnias. The history of moving around and sometimes hitting her husband suggests that rapid eye movement sleep behavior disorder could be present. Some epochs of rapid eye movement sleep without atonia were present during polysomnograph but were only associated with simple arm and leg movements. Narcolepsy is associated with the presence of rapid eye movement sleep behavior disorder.[8]

Because the patient has entered a stressful professional training program, she is hesitant to attempt a trial of lowering the SO dose (or temporarily discontinuing SO) to determine whether the KC episodes will diminish or resolve. Neither the KC nor the moaning have caused a significant issue for the patient or her husband. On her current medication regimen, for the first time in many years she has finally been able to maintain good sleep and alertness. The fact that KC had never been observed until an SO dose of 7 g nightly was reached suggests that the behavior is associated with SO treatment. Precautions for sleepwalking and violent dream enactment were discussed with the patient and her husband. The use of clonazepam is contraindicated in a patient taking SO, and the addition of melatonin was declined in favor of environmental precautions because no potentially injurious behavior had been noted over the previous 3 months.

ABBREVIATIONS

KC, knuckle cracking
SO, sodium oxybate

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The authors report no conflicts of interest.