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Central sleep apnea caused by low dosage of baclofen: a case report

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Abstract

Background Baclofen can relax muscle spasticity by inhibiting the transmission of both mono- and polysynaptic reflexes at the spinal cord. It has been increasingly used off-label for the management of spinal cord lesions or neurologic disorders. However, the expansion use has led to an increase in baclofen-associated complications.

Case presentation We report the case of a 60-year-old Chinese female patient who suffered from nocturnal choking and daytime sleepiness. Polysomnography identified central sleep apnea after initiation of low-dosage baclofen (10 mg two times a day) treatment, and a complete resolution of central sleep apnea was associated with baclofen withdrawal.

Conclusion This case reminds us that more attention should be paid to the adverse reactions on respiratory control of baclofen, even with low dosage. Regular polysomnography before and after prescription of baclofen is helpful to detect the effects of baclofen on sleep and breathing.

Keywords Baclofen, Muscle spasm, Central sleep apnea, Case report

Introduction

Baclofen, β-(4-chlorophenyl)-γ-aminobutyric acid, with a molecular weight of 213.66 g/mol, is a gamma-aminobutyric acid (GABA)-B agonist with muscle-relaxant and antispasmodic properties [1, 2]. Baclofen has been increasingly used off-label for the management of several disorders, such as musculoskeletal pain, muscle spasms, alcohol use disorder, chronic hiccups, chronic posttraumatic stress disorder, and gastroesophageal reflux disease [1]. Baclofen can be administered orally and by intrathecal injection. After titration from low doses, standard treatment includes daily oral administration of 40–80 mg, which is the commonly accepted maximum daily dosage of baclofen [3]. Dose of intrathecal injection for spasticity begins from 50 μg to 100 μg, which is much lower than the oral dose [1]. Both oral and intrathecal baclofen may produce sleep-disordered breathing [4–6]. It has been reported that central sleep apnea (CSA) was in association within standard-to-high dose baclofen therapy (40–200 mg per day) in patients treated for alcohol withdrawal [6, 7]. One possible pathway is the possibility that baclofen acts on the inspiratory neurons in pre-Bötzinger complex to cause CSA [8]. Here we report a case of CSA induced by low-dose baclofen orally.

Case report

A 60-year-old Chinese woman was referred to the department of Respiratory and Sleep Medicine, Peking University People's Hospital because of snoring, nocturnal choking, and daytime sleepiness for more than 5 years. On 13 November 2023, she underwent a nocturnal polysomnography (PSG) at a local hospital, which showed apnea–hypopnea index (AHI, 65.5 events per hour), and

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the main respiratory events were central apnea (Table 1). She was then admitted to our department on 10 December 2023. Physical examination found no obvious abnormal signs except involuntary head tremor, which lasted for decades. Body mass index (BMI) was 24.4 kg/m^2. Her neck circumference was 34 cm, waist circumference was 85 cm, and hip circumference was 91 cm, which suggested abdominal obesity according to guidelines for Prevention and Control of Overweight and Obesity in Chinese Adults [9]. The Epworth Sleepiness Scale score was 15/24.

The patient had a history of essential head tremor for 34 years, which did not interfere her daily life. Her left lower limb cramped intermittently, as well as cramping of the lower back accompanied by numbness for 5 years. On 11 September 2023, she went to the department of neurology of a general hospital, and was diagnosed painful muscle spasm, essential tremor, anxiety state, and somatization disorder. She began to receive the administration of clonazepam 0.5 mg two times a day, citalopram 20 mg per day, and oxcarbazepine 0.3 g three times a day. On 8 November 2023, the clonazepam was replaced with baclofen at a dose of 10 mg two times per day. The frequency of leg spasm decreased significantly. In recent years, she underwent electromyography (EMG), para-tumor antibody, autoimmune encephalitis antibody of blood and cerebrospinal fluid, and dynamic mutation-whole exome sequencing (dmWES) detection of blood, all of which showed no clear abnormality.

Table 1 PSG reports

	PSG1	PSG2	PSG3
Date	2023-11-13	2023-12-10	2023-12-21
Treatment	Baclofen	Baclofen	
Sleep study			
Total sleep time, minutes	411.0	423.4	322.0
Sleep efficacy, %	71.7	82.0	63.6
N1 sleep, %	14.0	10.7	13.2
N2 sleep, %	69.0	52.4	71.3
N3 sleep, %	6.0	11.3	9.5
REM sleep, %	11.1	25.5	6.1
Respiration, events per hour			
AHI	65.5	51.2	13.6
CAI	36.8	40	1.5
OAI	7.3	1.7	3.2
MAI	5.8	2	0.9
HI	15.6	7.5	8.0
3% ODI	–	35	8.9

Dosage of oral baclofen is 10 mg twice per day. PSG 1: monitored in other hospital before admission. PSG 2, PSG 3: Monitored in our hospital under different treatments

PSG polysomnography, *REM* rapid eye movements, *AHI* apnea–hypopnea index, *CAI* central apnea index, *OAI* obstructive apnea index, *MAI* mixed apnea index, *HI* hypopnea index, *ODI* oxygen desaturation index

In our department, an arterial blood gas analysis did not show CO_2 retention (pH 7.43, PaO_2 70 mmHg, $PaCO_2$ 44 mmHg, HCO_3^- 29.2 mmol/L). PSG revealed severe CSA with a central apnea index of 40 events per hour (AHI 51.2 events per hour, as presented in Table 1). In addition, continuous transcutaneous capnography ($PtcCO_2$) was normal. Central apnea occurs mainly in the Non-rapid Eye movement (NREM) phase (Fig. 1). The patient was titrated on continuous positive airway pressure (CPAP) treatment (ResMed, S10). With a pressure of 10 cmH_2O, the reports downloaded from the device showed residual AHI 18.8 events per hour, of which CAI 14 events per hour. After that, we tried Bi-level Positive Airway Pressure (BiPAP) (9/5 cmH_2O), CPAP (6 cmH_2O) with oxygen 2 L per minute, and CPAP 7 cmH_2O in sequence. However, the residual AHI did not reach satisfactory level.

During admission, we conducted a series of examinations, including head magnetic resonance imaging (MRI), echocardiography, long-term video electroencephalogram, liver and kidney function, lung function, and other examinations. Through these tests and examinations, we excluded cerebral infarction, autoimmune encephalitis, and paraneoplastic syndrome, as well as cardiopulmonary and renal insufficiency. She has had essential tremor for decades, which is relatively stable without significant aggravation. There was no illness history significantly associated with sleep-disordered breathing. Then, we found that oral baclofen was prescribed recently by retrospection of her medical history. We suspected CSA might be caused by baclofen. Obtaining the patient's consent, baclofen was discontinued, and 3 days after withdrawal, a second PSG was conducted and showed a significant decrease of CAI to 1.5 events per hour (AHI 13.6 events per hour, OAI 3.2 events per hour, Table 1). The patient was then treated with CPAP (7 cmH_2O), and 3 days after discharge, we followed up with the patient and found that she tolerated CPAP treatment well, symptoms of night choking were relieved, and daytime drowsiness improved. The downloaded data of the CPAP device showed significant improvement, with AHI dropping to 4.5 events per hour and CAI to 1.1 events per hour. Therefore, we further confirmed that CSA in this patient was associated with baclofen (Fig. 2).

Discussion

This case suggests that CSA could be caused by low dose of baclofen. Firstly, during this hospitalization, with withdrawal of baclofen, PSG found that central sleep apnea hypopnea index decreased significantly (Table 1). Secondly, we ruled out common causes of CSA step by step.

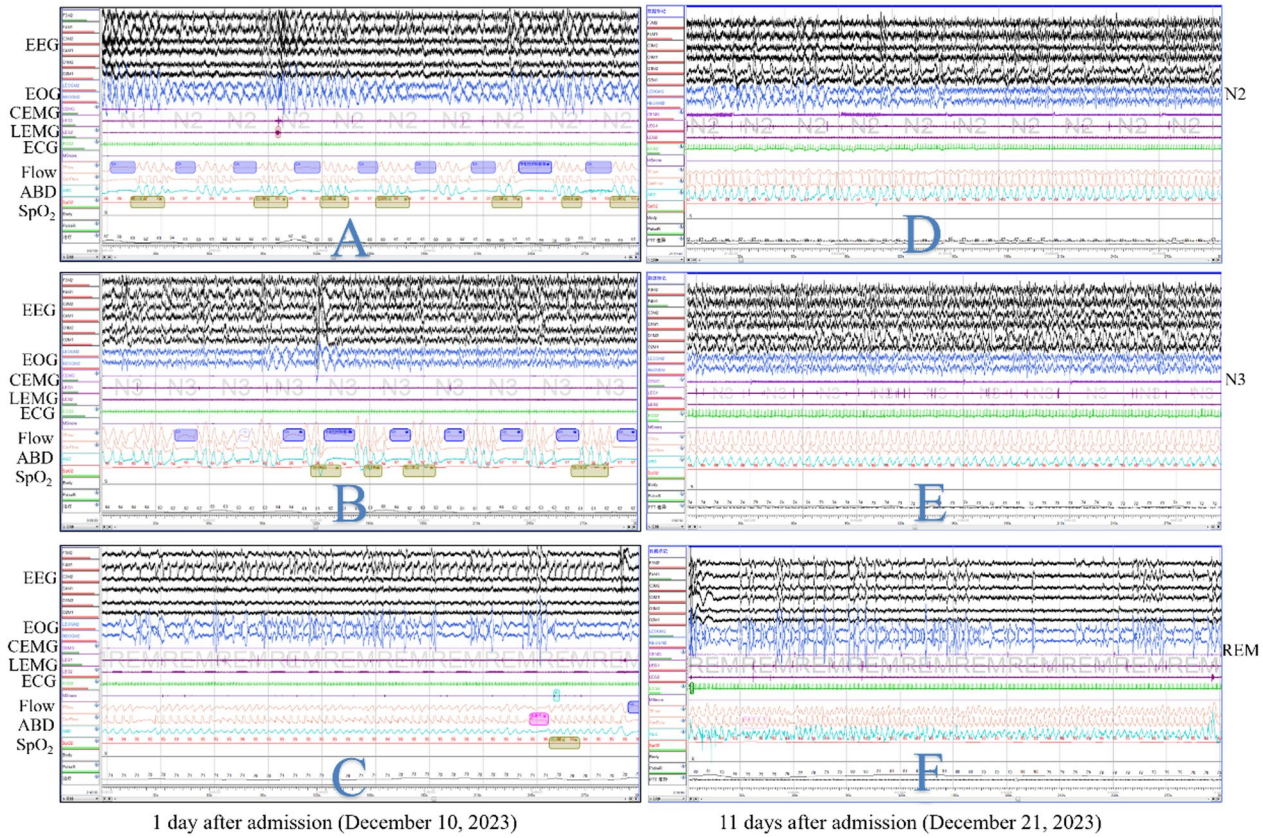

Fig. 1 Comparison of PSG before and after withdrawal of baclofen. **A**–**C** were, respectively, stages of N2, N3, and REM on the night of admission. **D**–**F** were, respectively, stages of N2, N3, and REM after withdrawal of baclofen. *EOG* electro-oculogram, *CEMG* chin electromyogram, *EEG* electroencephalogram, *ECG* electrocardiogram, *LEMG* leg electromyogram, *Flow* nasal flow, *ABD* abdominal band

Her echocardiography, dynamic electrocardiogram, and renal function examination were normal, which ruled out heart failure and renal failure. Brain MRI, video electroencephalogram (EEG), and antibodies related to autoimmune encephalitis and paraneoplastic syndrome showed no abnormalities and did not support neurological disease. The patient had leg muscle spasms, but no muscular atrophy or myasthenia. She had no history of living in high-altitude areas and no experience of CPAP therapy nor oral orthotics or upper airway surgery before and after the onset of the CSA (Fig. 2). In addition to baclofen, she also took citalopram and oxcarbazepine. The effect of citalopram on sleep was decreasing REM sleep and lengthening REM latency [10]. There were no literature reports regarding CSA caused by citalopram and oxcarbazepine [11].

CSA disorders are characterized by disruption of sleep due to repetitive respiratory events characterized by reduction or cessation of airflow due to reduced or absent respiratory effort [12], which can lead to severe comorbidity and increased risk of adverse cardiovascular outcomes [13]. A number of medications have been associated with CSA potentially affecting pre-Bötzinger complex, which is a respiratory rhythm generator in brainstem [14]. Baclofen is on the list of the medications. Baclofen is an agonist for GABA-B receptors on pre- and postsynaptic neurons in the central nervous system (CNS) and peripheral nervous system. Baclofen was approved by the US Food and Drug Administration [10] in 1977 for the treatment of spasticity related to multiple sclerosis, spinal cord injuries, and other spinal cord pathologies. GABA B receptors are present both in Kolliker–Fuse and pre-Bötzinger complex neurons. In animal models, microinjection of baclofen into pre-Bötzinger complex neurons produces a dose-dependent reduction in breathing frequency, eventually eliminating inspiratory discharge resulting in apnea [15]. Some researchers have found that baclofen can affect sleep and breathing in human beings. A study reported that single therapeutic dose (25 mg) of baclofen alters sleep architecture and produces a small reduction in mean sleep oxygen saturation [16]. Another small sample of clinical study in healthy people found that baclofen caused respiratory instability, but the central apnea index was

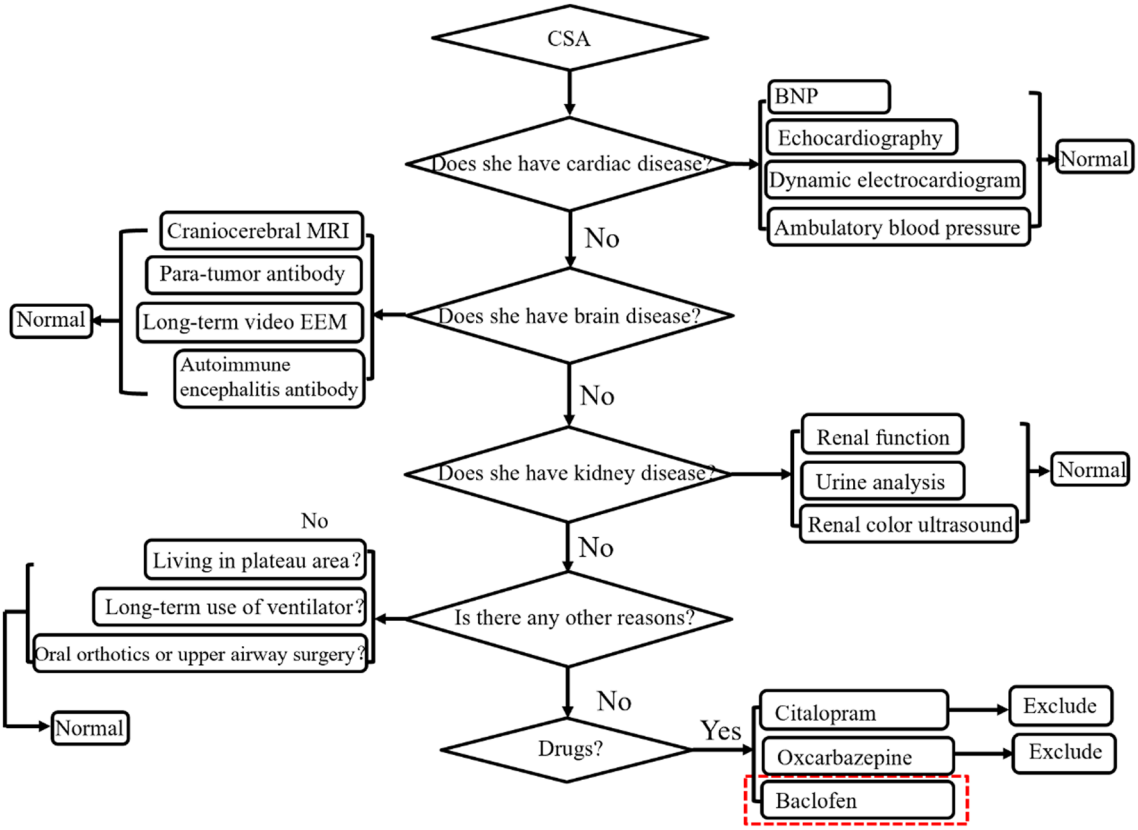

Fig. 2 Flow chart for diagnosis. *CSA* central sleep apnea, *MRI* magnetic resonance imaging, *EEG* electroencephalogram, *BNP* brain natriuretic peptide

not significantly elevated in subjects with baclofen [17]. There was lack of systematic clinic research to support the view of baclofen could cause central apnea.

Since the French health safety agency firstly allowed the prescription of oral baclofen up to 300 mg/day for the treatment of alcohol dependence under a "temporary recommendation for use" license in March 2014, the reports of sleep apnea associated with baclofen in the World Health Organization (WHO) Global Individual Case Safety Reports (ICSRs) database increased significantly compared with other drugs. The adverse effects of baclofen on respiration is dose dependent, therefore, the French health safety agency modified the 2014 "temporary recommendation for use" to a maximum oral daily dose of 80 mg in July 2017 [18]. Olivier *et al.* reported four patients with severe CSA caused by oral baclofen for the treatment of alcohol withdrawal at doses ranging from 40 mg to 190 mg daily [6]. Perogamvros *et al.* also reported one patient with CSA caused by oral baclofen (100 mg twice per day) for alcohol withdrawal (Table 2) [7]. Compared with the reported five cases, the current case is a female patient with confirmed OSA and painful

Table 2 List of reported cases and our case

Author	Gender	Age	BMI	Disease	Dosage (mg/day)	Duration of use (month)	AHI (CAI, %)
Pierre-Yves Olivier [6]	Male	47	29	Alcohol dependence	190	60	59 (90)
	Male	46	30	Alcohol dependence	150	9	73 (98)
	Male	53	31	Alcohol dependence	40	10	100 (100)
	Male	70	31	Alcohol dependence	180	3	73 (98)
Lampros Perogamvros [7]	Male	61	24.4	Alcohol dependence	200	24	81.6 (85.4)
Our case	Female	60	24.4	Spasticity	20	1	65.5 (91.5)

muscle spasms, who suffered CSA after taking a low dose of baclofen (10 mg twice per day). She has no alcohol dependence, which could exclude the confounding factors of alcohol affecting sleep and breathing. In addition, she had a lower BMI, and with a confirmed OSA, we supposed that it would be easier for her to reach the blood level threshold for central apnea. The breathing pattern of baclofen-associated CSA resembles opioid-induced CSA. With both baclofen and opioids, CSA occurs primarily in non-REM sleep, with variable cycles, and is dose dependent.

However, at present, there is no systematic study on baclofen causing CSA, which is limited to case reports. The relationship between baclofen dosage and CSA is also unclear. Future studies are expected to reveal the relationship between baclofen and sleep-disordered breathing and its mechanisms.

Conclusion

With the widespread use of baclofen, there has been a significant increase in the reported cases of central apnea induced by baclofen. More clinical studies are needed to reveal the effect of baclofen on breathing during sleep. We came to the conclusion that oral baclofen may induce CSA even with low dosage. Baclofen was associated with a higher risk of CSA in patients with preexisting sleep-related breathing disorders. After withdrawal of baclofen, CSA can significantly improve. Regular polysomnography before and after prescription of baclofen is helpful to detect the effects of baclofen on sleep and breathing.

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Author contributions
Xiaoqiong Luo and Qidi Ding conceived the idea for the paper and drafted the original manuscript. Yanan Liu and Chenyu Li contributed to the discussion section. Xiaosong Dong and Fang Han reviewed and edited the final manuscript. Xiaosong Dong and Qidi Ding supervised the project. All authors contributed, read, and approved the final manuscript.

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Availability of data and materials
The data related to the case are available from the corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate
The work was carried out in the Sleep Medicine Center, Department of Sleep Medicine, Peking University People's Hospital. The authors complied with the ethical requirements of their institution.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors have no competing interest related to the present study.

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