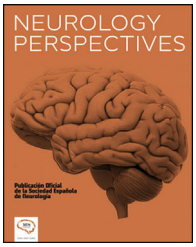
Neurology Perspectives 3 (2023) 100134

NEUROLOGY PERSPECTIVES

www.journals.elsevier.com/neurology-perspectives



ORIGINAL ARTICLE

Obstructive sleep apnea induced bilateral tonic- clonic seizure of unknown origin: A case series of a novel association

R. Mondal[a], A. Maitra[b], S. Saha[c], S. Deb[d], A.G. Roy[e], M. Mahata[f], D. Lahiri[g,*], J. Benito-León[h,i,j,*]

[a] *Department of Clinical Pharmacology and Therapeutic Medicine, IPGMER and SSKM Hospital, Kolkata, India*
[b] *Department of Cardiology, Bellevue clinic, Kolkata, India*
[c] *Department of Critical Care Medicine and Sleep Studies, Bellevue clinic, Kolkata, India*
[d] *S.N.Pradhan Centre for Neuroscience, Kolkata, India*
[e] *Department of Internal Medicine, IPGMER, and SSKM Hospital, Kolkata, India*
[f] *Department of Interventional Neurology, Bellevue clinic, Kolkata, India*
[g] *Department of Cognitive Neurology, Baycrest Health Sciences and Rotman Research Institute, University of Toronto, Toronto, Canada*
[h] *Department of Neurology, University Hospital "12 de Octubre", Madrid, Spain*
[i] *Centro de Investigación Biomédica en Red Sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain*
[j] *Department of Medicine, Complutense University, Madrid, Spain*

Received 11 April 2023; accepted 11 July 2023
Available online 4 October 2023

KEYWORDS
Obstructive sleep apnea;
Seizures;
Polysomnography

Abstract
Background: Obstructive sleep apnea is a highly prevalent disorder, characterized by recurrent events of upper airway obstruction during sleep and associated with recurrent cycles of desaturation and re-oxygenation, sympathetic hyperactivity, and intra-thoracic pressure fluctuations, resulting in fragmentation of sleep and subsequent daytime fatigue with excessive sleepiness. Obstructive sleep apnea-induced bilateral tonic–clonic seizures are unheard of. We aimed to report 3 patients with previously undiagnosed obstructive sleep apnea who presented to the emergency department with new onset bilateral tonic–clonic seizure without any evidential neurological or metabolic cause.
Methods: Patient data were obtained from medical records from the Department of Internal Medicine, IPGMER and SSKM Hospital, Kolkata, and Belle Vue Clinic, Kolkata, India.
Results: Three male patients (67, 58, and 44 years old) presented with bilateral tonic–clonic seizure disorder without any underlying cause of seizures after rigorous investigations except for moderate to severe obstructive sleep apnea on polysomnography. All 2 patients were seizure-free after being treated with levetiracetam, chronic continuous positive airway pressure therapy in 2, and only continuous positive airway pressure in the other. The patients remained

* Corresponding authors.
E-mail addresses: dlarihi1988@gmail.com (D. Lahiri), jbenitol67@gmail.com (J. Benito-León).

https://doi.org/10.1016/j.neurop.2023.100134

seizure-free on continuous positive airway pressure, even when levetiracetam was withdrawn, suggesting obstructive sleep apnea's causality in their new-onset acute seizures.
Conclusion: Although further investigation is required to clarify this association, underlying obstructive sleep apnea should be ruled out in patients with a first-ever bilateral tonic–clonic seizure. Whether or not continuous positive airway pressure alone could effectively treat hypoxia and deranged cortical excitability, which may lead to seizures in cases with long-standing obstructive sleep apnea, is yet to be explored.

PALABRAS CLAVE
Apnea obstructiva del sueño;
crisis;
polisomnografía

Crisis tonicoclónicas bilaterales de origen desconocido inducidas por apnea obstructiva del sueño: una serie de casos de una asociación novedosa

Resumen
Introducción: La apnea obstructiva del sueño es una enfermedad con una alta prevalencia que se caracteriza por episodios recurrentes de obstrucción de las vías respiratorias altas durante el sueño, lo que conlleva ciclos repetidos de hipoxia y reoxigenación, hiperactividad simpática y fluctuaciones en la presión intratorácica. Todos estos procesos dan lugar a una fragmentación del sueño, lo que provoca fatiga diurna y somnolencia excesiva. Las crisis tónico-clónicas bilaterales inducidas por apnea obstructiva del sueño son poco conocidas. Presentamos los casos de tres pacientes con apnea obstructiva del sueño sin diagnosticar previamente que acudieron a urgencias por crisis tónico-clónicas de nueva aparición sin causa neurológica o metabólica aparente
Métodos: Los datos de nuestros pacientes se recogieron de los historiales médicos del servicio de Medicina Interna del Institute of Post-Graduate Medical Education and Research and Seth Sukhlal Karnani Memorial Hospital y de la Belle Vue Clinic, ambos en Kolkata (India).
Resultados: Tres pacientes varones de 67, 58 y 44 años de edad presentaron convulsiones tónico-clónicas bilaterales sin causa identificada tras examen riguroso, exceptuando una apnea obstructiva del sueño de gravedad moderada a grave observada en la polisomnografía. Los tres pacientes recibieron tratamiento con levetiracetam durante el ingreso; al alta, se pautó tratamiento crónico con presión positiva continua de las vías respiratorias más levetiracetam en dos pacientes, y en el tercero solo presión positiva continua de las vías respiratorias. Ninguno presentó nuevas crisis tras la retirada de levetiracetam, lo que sugiere que la causa de las convulsiones era la apnea obstructiva del sueño.
Conclusión: Aunque es necesario realizar más estudios para aclarar esta asociación, debemos descartar la apnea obstructiva del sueño en pacientes con crisis tónico-clónicas bilaterales de nueva aparición. Queda aún por determinar si la presión positiva continua podría tratar de forma efectiva la hipoxia y las alteraciones en la excitabilidad cortical, que podrían provocar crisis en casos de apnea obstructiva del sueño de larga evolución.

Introduction

Obstructive sleep apnea is a highly prevalent disorder, characterized by recurrent events of upper airway obstruction during sleep and associated with recurrent cycles of desaturation and re-oxygenation, sympathetic hyperactivity, and intra-thoracic pressure fluctuations, resulting in fragmentation of sleep and subsequent daytime fatigue with excessive sleepiness.[1,2] Obstructive sleep apnea is defined by combining symptoms and a respiratory disturbance index ≥ 5 or ≥ 15 without symptoms,[3] whereas obstructive sleep apnea severity is categorized through the apnea–hypopnea index (AHI).

Obstructive sleep apnea is more prevalent in patients with neurological disorders, affecting more than one-third of epileptic patients and about two-third of stroke survivors. The neurological disorders that may improve after treating underlying obstructive sleep apnea include dementia, stroke, and headache, among others. Thus far, ischemia or hypoxia and hypoperfusion are major manifestations of chronic obstructive sleep apnea and related sleep-disordered breathing.[4] Fluctuations in blood oxygen supply and pressure may lead to hypoperfusion, hypoxia, or ischemia of major brain areas, potentially representing a major etiopathology for obstructive sleep apnea-induced

neurological disorders.[5] Interestingly, obstructive sleep apnea is an important comorbid condition in late-onset epilepsy[6] and cerebrovascular disease,[7] establishing a 2-way relationship between obstructive sleep apnea and neurological health. Neuro-inflammatory predisposition might be an additional contributing factor toward obstructive sleep apnea-induced neurological and neurocognitive impairments. In this sense, a significant causal effect of leukocytic count on the association between obstructive sleep apnea and brain aging was reported.[8]

Obstructive sleep apnea-induced bilateral tonic-clonic seizures of unknown origin are unheard of.[9] We aimed to report 3 patients with previously undiagnosed obstructive sleep apnea who presented to the emergency department with bilateral tonic–clonic seizures of unknown origin and no neurological or metabolic cause.

Methods

Patient data were obtained from medical records from the Department of Internal Medicine, IPGMER, and SSKM Hospital, Kolkata, and Belle Vue Clinic, Kolkata, India.

Results

Patient 1

A 67-year-old hypertensive, moderately controlled type-II diabetic (for the last 10 years) man with a body mass index of 32.33 kg/m^2 was admitted to the emergency room for a generalized seizure with tongue bite which took place immediately after waking up from sleep at around 6:30 AM on that day. He also complained of acute shortness of breath. His medical history was unremarkable except for a percutaneous transluminal coronary angioplasty, and excessive daytime sleepiness.

The vital signs were within normal range with a blood pressure of 130/80 mmHg, pulse rate of 98 bpm, a temperature of 36.2 °C, and a respiratory rate of 18/min; capillary blood glucose was 186 mg/dl. General and neurological examinations and a digital chest X-ray were unremarkable.

The patient was transferred to the intensive care unit, where intravenous levetiracetam (1 g) was initiated. The basic laboratory parameters were within normal range, including complete blood cell count, cardiac markers, thyroid function test, and renal and liver function parameters, but increased N-Terminal Pro-B-Type Natriuretic Peptide levels (401.4 pg/ml). An electrocardiogram showed non-specific ST changes in V2–V4; a 2D-echocardiographic showed concentric left ventricular hypertrophy with anteroseptal thickening and an ejection fraction of 60% without wall motion abnormalities. An electroencephalogram (EEG) was performed after 6 h following his emergency admission, which was within normal limits without any evidence of focal epileptiform discharges. Brain magnetic resonance imaging (MRI) showed generalized cerebral cortical atrophy with bilateral periventricular white matter subacute ischemic changes and old lacunar infarcts in the bilateral basal ganglia, right thalamus, and bilateral periventricular white matter (Fig. 1A and B). There was no evidence of diffusion restriction and no acute infarct or intracerebral hemorrhage.

Epworth sleepiness scale reading was 13/24 (moderate excessive daytime symptoms). Polysomnography evaluation for over 8 h revealed an apnea–hypopnea index of 9.2/h and a respiratory disturbance index of 13.1. The oxygen desaturation index was 16.7/h, with a minimum saturation of 81% (Fig. 1C). Upon discharge, the patient was initiated on oral levetiracetam (500 mg twice daily) for 6 months and maintenance of continuous positive airway pressure during sleep with close follow-up. He was then advised to gradually taper off the levetiracetam and continue only with continuous positive airway pressure. He remained asymptomatic and seizure-free 1 year after discharge, with an improved Epworth sleepiness score.

Patient 2

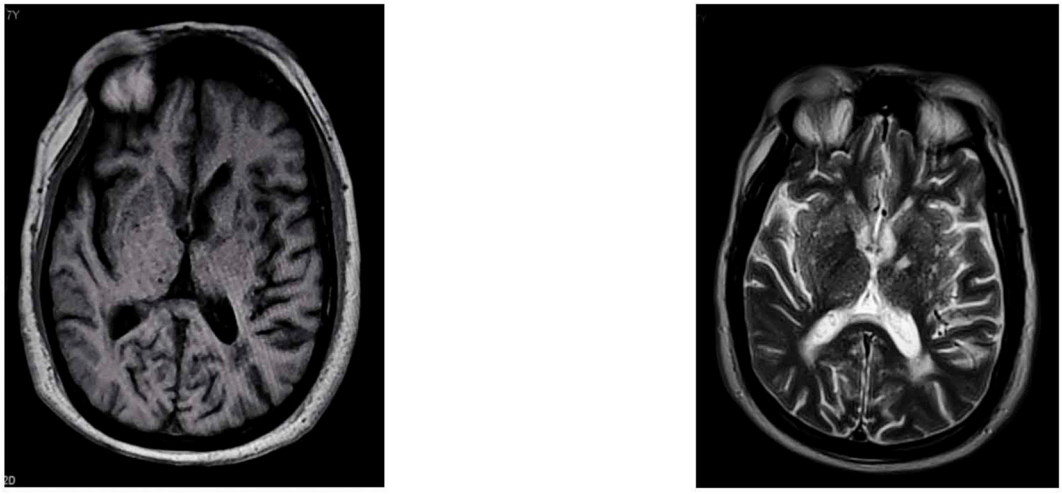
A 58-year-old type-II diabetic (for the last 10 years), hypertensive, obese man (body mass index >35 kg/m^2) presented to the emergency room with complaints of weakness over the right side of the body, slurring of speech, and sudden episodes of unresponsiveness. He referred weakness in all 4 limbs, predominantly over the right side (MRC score: right −3/5 and left −4/5), and an episode of generalized seizure that occurred at around 5:30 AM the same day. Upon further inquiry, history was remarkable for a percutaneous transluminal coronary angioplasty of the left anterior descending artery, snoring, and excessive daytime sleepiness.

The patient was shifted to the intensive care unit, and intravenous levetiracetam (1 g) was started. His vital signs showed a blood pressure of 148/96 mmHg, pulse rate of 88 bpm, SpO2 of 99%, a temperature of 36.3 °C, and a respiratory rate of 18/min; capillary blood glucose of 192 mg/dl. General and neurological examinations and a digital chest X-ray were unremarkable.

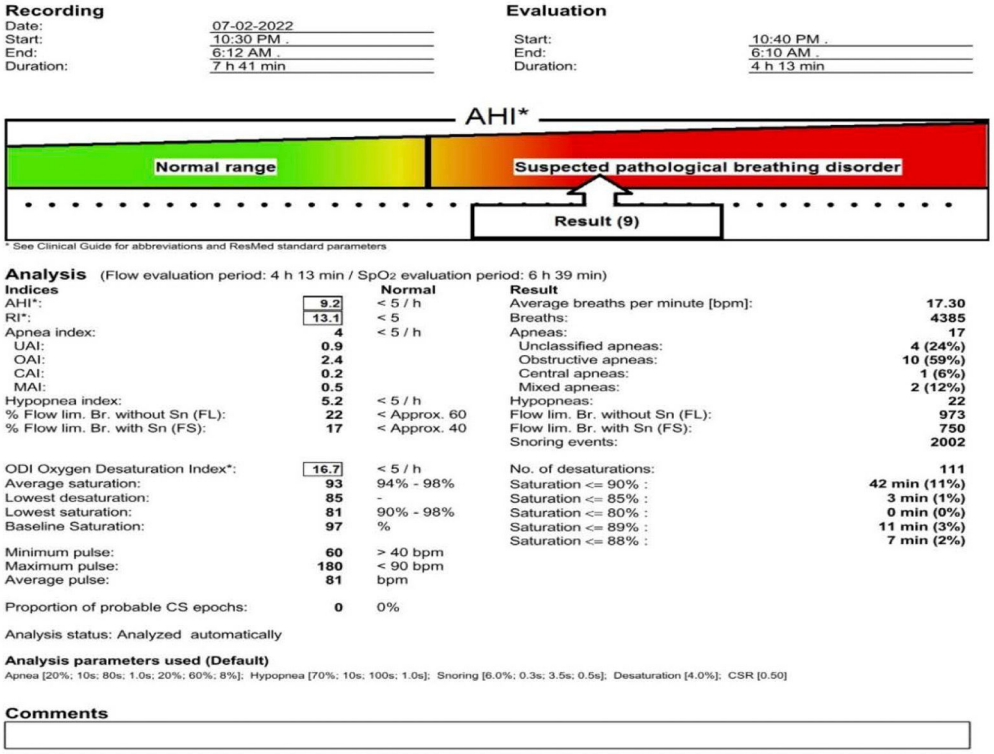
Blood cell count, serum electrolytes, cardiac troponins, and thyroid and renal function tests were within normal range. Electrocardiogram findings were non-significant; a 2D echocardiographic showed eccentric left ventricular hypertrophic with an ejection fraction of 60% without wall motion abnormalities. An EEG was performed after 4 h following admission, which was within normal limits without any significant focal changes.

A non-contrast brain computed tomography and a brain MRI revealed mild frontoparietal cortical atrophy and bilateral mild focal periventricular leukomalacia without any evidence of acute ischemic or hemorrhagic stroke (Fig. 2A and B).

Epworth sleepiness scale reading was 13/24 (moderate excessive daytime symptoms). On performing polysomnography for 538 min, both apnea–hypopnea and respiratory disturbance indexes were found to be 44.3 and oxygen desaturation index of 31.7/h, respectively, with a minimum oxygen saturation of 63% (Fig. 2C). Upon discharge, he was initiated on a low-dose prophylactic oral levetiracetam (500 mg twice daily) for 6 months and maintenance of continuous positive airway pressure during sleep with closed follow-up. Levetiracetam was then withdrawn. The patient remained asymptomatic and seizure-free 1 year after discharge, with an improved Epworth sleepiness score.



A B



Recording

Date:	07-02-2022
Start:	10:30 PM .
End:	6:12 AM .
Duration:	7 h 41 min

Evaluation

Start:	10:40 PM .
End:	6:10 AM .
Duration:	4 h 13 min

AHI*

Normal range | Suspected pathological breathing disorder

Result (9)

* See Clinical Guide for abbreviations and ResMed standard parameters

Analysis (Flow evaluation period: 4 h 13 min / SpO_2 evaluation period: 6 h 39 min)

Indices		Normal	Result	
AHI*:	9.2	< 5 / h	Average breaths per minute [bpm]:	17.30
RI*:	13.1	< 5	Breaths:	4385
Apnea index:	4	< 5 / h	Apneas:	17
UAI:	0.9		Unclassified apneas:	4 (24%)
OAI:	2.4		Obstructive apneas:	10 (59%)
CAI:	0.2		Central apneas:	1 (6%)
MAI:	0.5		Mixed apneas:	2 (12%)
Hypopnea index:	5.2	< 5 / h	Hypopneas:	22
% Flow lim. Br. without Sn (FL):	22	< Approx. 60	Flow lim. Br. without Sn (FL):	973
% Flow lim. Br. with Sn (FS):	17	< Approx. 40	Flow lim. Br. with Sn (FS):	750
			Snoring events:	2002
ODI Oxygen Desaturation Index*:	16.7	< 5 / h	No. of desaturations:	111
Average saturation:	93	94% - 98%	Saturation <= 90% :	42 min (11%)
Lowest desaturation:	85	-	Saturation <= 85% :	3 min (1%)
Lowest saturation:	81	90% - 98%	Saturation <= 80% :	0 min (0%)
Baseline Saturation:	97	%	Saturation <= 89% :	11 min (3%)
			Saturation <= 88% :	7 min (2%)
Minimum pulse:	60	> 40 bpm		
Maximum pulse:	180	< 90 bpm		
Average pulse:	81	bpm		
Proportion of probable CS epochs:	0	0%		

Analysis status: Analyzed automatically

Analysis parameters used (Default)

Apnea [20%; 10s; 80s; 1.0s; 20%; 60%; 8%]; Hypopnea [70%; 10s; 100s; 1.0s]; Snoring [6.0%; 0.3s; 3.5s; 0.5s]; Desaturation [4.0%]; CSR [0.50]

Comments

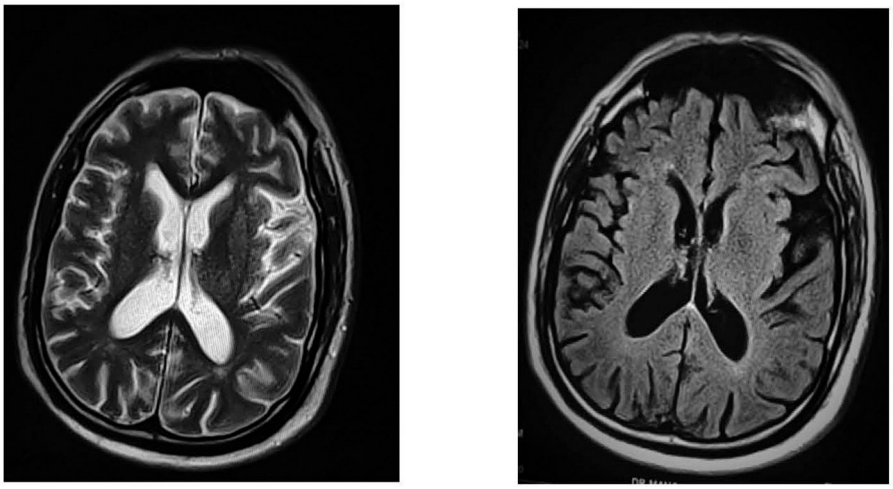
C

Fig. 1 Axial-T1- (A) and T2-weighted (B) images reveal generalized cortical atrophy with bilateral periventricular white matter subacute ischemic changes, and old lacunar infarcts in bilateral basal ganglia, right thalamus as well as in periventricular white matter. Fig. C shows alterations in polysomnography parameters.

Patient 3

A 44-year-old type-II diabetic, hypertensive, and morbidly obese (BMI > 35 kg/m^2) man was admitted to the emergency room with weakness in all 4 limbs and an episode of involuntary movement of hands and legs earlier on the same morning following his wake up at around 8:00 AM. A long history of snoring and excessive daytime sleepiness also became evident.

The patient was drowsy and disoriented. A tongue bite was noted. His vitals showed a blood pressure of 134/80 mmHg, pulse rate of 116 bpm, SpO2 of 92%, a



A B

Sleep Summary

		Stage	Duration	% TST
Lights Out:	21:31:17	N1	0.0 min	0.0%
Lights On:	07:03:59	N2	116.0 min	21.6%
Total Recording Time:	572.7 min	N3	405.0 min	75.3%
Total Sleep Time (TST):	538.0 min	R	17.0 min	3.2%
Sleep Period Time:	553.0 min			
Sleep Onset:	21:41:17			
Sleep Efficiency:	93.9 %	Latencies	From Lights Out	From Sleep Onset
Sleep Latency (from LOff):	10.0 min	N1	min	min
R Latency (from Sleep Onset):	136.5 min	N2	12.0 min	2.0 min
Wake After Sleep Onset (WASO):	24.7 min	N3	10.0 min	0.0 min
Wake During Sleep:	15.0 min	R	146.5	136.5
Total Wake Time:	34.7 min			
% Wake Time:	6.1			

Respiratory Summary

By Event Classification	Central			Mixed			Obstructive		
	Count	Mean	Max	Count	Mean	Max	Count	Mean	Max
Apneas, NREM	0	0.0	0.0	1	12.0	12.0	274	25.4	84.0
Apneas, REM	0	0.0	0.0	0	0.0	0.0	11	17.0	20.5
Apneas, Total	0	0.0	0.0	1	12.0	12.0	285	25.0	84.0

*Hypopneas scored based on 3% or greater desaturation.

Hypopneas, NREM	108	25.3	54.5	RERAs, NREM	0	0.0	0.0
Hypopneas, REM	3	28.3	45.5	RERAs, REM	0	0.0	0.0
Hypopneas, Total	111	25.4	54.5	RERAs, Total	0	0.0	0.0

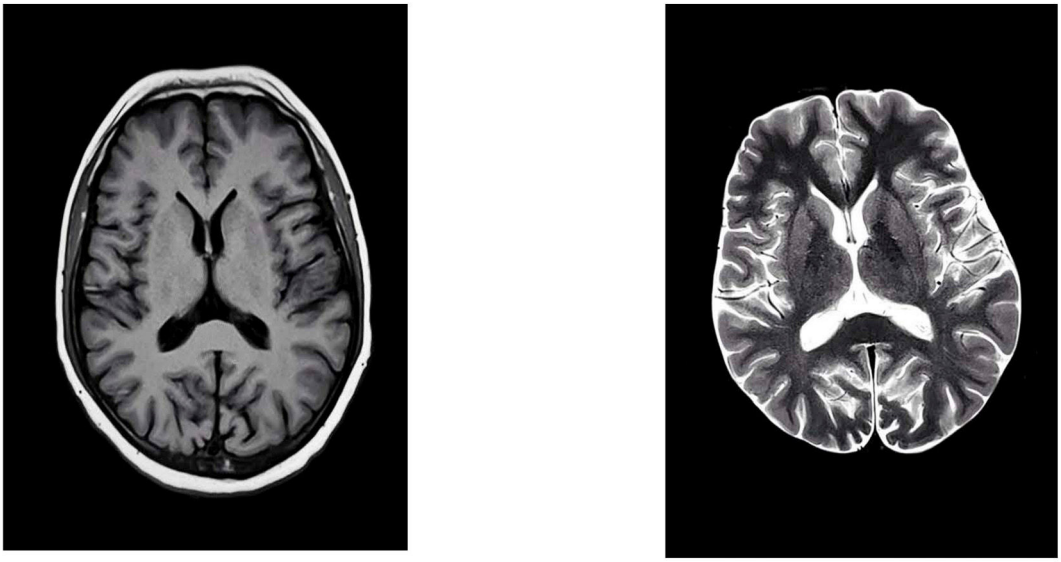
Event Statistics	Total		With Arousal	
	Count	Index	Count	Index
Apneas, Total	286	31.9	129	14.4
Hypopneas, Total	111	12.4	28	3.1
Apnea + Hypopnea Total	397	AHI: 44.3	157	17.5
Apnea + Hypopnea NREM	383	AHI: 44.1	154	17.7
Apnea + Hypopnea REM	14	AHI: 49.4	3	10.6
RERAs, Total	0	0.0	0	0.0
Total Events (A+H+RERA) Total	397	RDI: 44.3	157	17.5
Total Events (A+H+RERA) NREM	383	RDI: 44.1	154	17.7
Total Events (A+H+RERA) REM	14	RDI: 49.4	3	10.6

C

Fig. 2 Axial T1-weighted (A) and FLAIR (B) images reveal bilateral mild focal hyperintense signals involving periventricular and supraventricular white matter regions. Fig. C shows alterations in polysomnography parameters.

temperature of 36.9 °C, and a respiratory rate of 21/min; capillary blood glucose of 140 mg/dl.

The patient was managed in the intensive care unit, and intravenous levetiracetam (1 g) was initiated. After the stabilization, general and neurological examinations were normal, and the digital chest X-ray was unremarkable. Biochemical parameters from the initial investigation showed normal findings. Complete blood cell count, thyroid, liver, kidney functions, electrolytes, and arterial blood gas analysis were normal. An electrocardiogram was normal; a



A B

Sleep Summary

		Stage	Duration	% TST
Lights Out:	21:28:18	N1	20.5 min	4.7%
Lights On:	04:45:42	N2	119.9 min	28.7%
Total Recording Time:	437.4 min	N3	235.0 min	56.2%
Total Sleep Time (TST):	417.9 min	R	43.5 min	10.4%
Sleep Period Time:	418.4 min			
Sleep Onset:	21:47:18			
Sleep Efficiency:	95.5 %	Latencies	From Lights Out	From Sleep Onset
Sleep Latency (from LOff):	19.0 min	N1	18.0 min	0.0 min
R Latency (from Sleep Onset):	33.0 min	N2	38.0 min	19.0 min
Wake After Sleep Onset (WASO):	0.5 min	N3	48.0 min	29.0 min
Wake During Sleep:	0.5 min	R	52.0	33.0
Total Wake Time:	18.5 min			
% Wake Time:	4.2			

Respiratory Summary

By Event Classification	Central			Mixed			Obstructive		
	Count	Mean	Max	Count	Mean	Max	Count	Mean	Max
Apneas, NREM	1	12.0	12.0	0	0.0	0.0	221	17.1	36.5
Apneas, REM	0	0.0	0.0	0	0.0	0.0	36	17.4	42.0
Apneas, Total	1	12.0	12.0	0	0.0	0.0	257	17.1	42.0

*Hypopneas scored based on 3% or greater desaturation.

Hypopneas, NREM	103	22.2	54.0	RERAs, NREM	0	0.0	0.0
Hypopneas, REM	16	25.5	52.0	RERAs, REM	0	0.0	0.0
Hypopneas, Total	119	22.6	54.0	RERAs, Total	0	0.0	0.0

Event Statistics	Total		With Arousal	
	Count	Index	Count	Index
Apneas, Total	258	37.0	25	3.6
Hypopneas, Total	119	17.1	27	3.9
Apnea + Hypopnea Total	377	AHI: 54.1	52	7.5
Apnea + Hypopnea NREM	325	AHI: 52.1	50	8.0
Apnea + Hypopnea REM	52	AHI: 71.7	2	2.8
RERAs, Total	0	0.0	0	0.0
Total Events (A+H+RERA) Total	377	RDI: 54.1	52	7.5
Total Events (A+H+RERA) NREM	325	RDI: 52.1	50	8.0
Total Events (A+H+RERA) REM	52	RDI: 71.7	2	2.8

C

Fig. 3 Axial-T1- (A) and T2-weighted (B) images reveal normal findings. Fig. C shows alterations in polysomnography parameters.

2D echocardiographic showed an ejection fraction of 60% without wall motion abnormalities. An EEG and a brain MRI did not reveal significant findings (Fig. 3A and B).

Epworth sleepiness scale reading was 17/24 (severe excessive daytime symptoms). Polysomnography evaluation for over 7 h revealed an apnea–hypopnea index of 54.1 and a respiratory disturbance index of 54.1. The oxygen desaturation index was 16.3/h, with a minimum saturation of 88% (Fig. 3C). Twenty-four-hour Holter monitoring revealed very few supraventricular ectopic beats without ST changes. Upon discharge, the patient was only advised on continuous positive airway pressure. During the 1-year follow-up visit, the patient was completely asymptomatic and seizure-free, significantly improving his overall functionality, Epworth sleepiness scale score, and glycemic regulatory status.

Discussion

All 3 patients presented with bilateral tonic–clonic seizures at the emergency room, and no cause was identified after exhaustive investigations. Polysomnography, however, revealed the presence of moderate to severe obstructive sleep apnea in all cases. The first 2 patients were initiated on low-dose antiepileptic drugs, i.e., levetiracetam, with maintenance continuous positive airway pressure therapy, while the third patient was only advised to remain on continuous positive airway pressure throughout the follow-up duration. The patients improved with continuous positive airway pressure, allowing the tapering of antiepileptic drugs over the follow-up period of 6 months with better sleep regulation, as evidenced by their Epworth sleepiness scale scores. Based on these findings and in the absence of any other obvious underlying etiology, it can be inferred that the seizures may have been related to undiagnosed obstructive sleep apnea. Whether this association is a causative one is yet to be explored. It is important to note that the intimate relationship between obstructive sleep apnea and chronic epilepsy disorders has already been recognized for a long time because obstructive sleep apnea predisposes these patients to have more seizures.[10]

According to Beebe and Gozel,[11] frequent sleep disruption and dissociation of maintenance in blood oxygenation level due to underlying obstructive sleep apnea can attenuate the restorative sleep phase and result in neuronal and neuroglial injury. Prefrontal cortical dysfunction due to intermittent sleep disruption and phasic hypoxia with hypercarbia may result in behavioral disturbances, disinhibition, emotional lability, and memory disturbances with blunted cognitive abilities, including executive dysfunction.[11] Obstructive sleep apnea can negatively impact sleep staging, a major precipitant of seizures.[12,13] For instance, the non-rapid eye movement sleep state is associated with accelerated cerebral hyper-synchrony reflecting a progressive increase in synchronized neuronal discharge.[13] It could be an important facilitator for seizure induction and spread, while rapid eye movement sleep suppresses epileptiform activity and has been associated with low rates of seizure onset.[14] In addition to the sleep stage, obstructive sleep apnea-induced sleep deprivation has been a well-recognized precipitant for seizures and epileptiform discharges.[15] According to Hrnčić et al.,[16] sleep disruption significantly increases seizure susceptibility in an experimental model of sleep apnea. Park et al.[17] recently identified that synapsin-II expression is significantly reduced in rat hippocampus due to increased sleep disruption. The

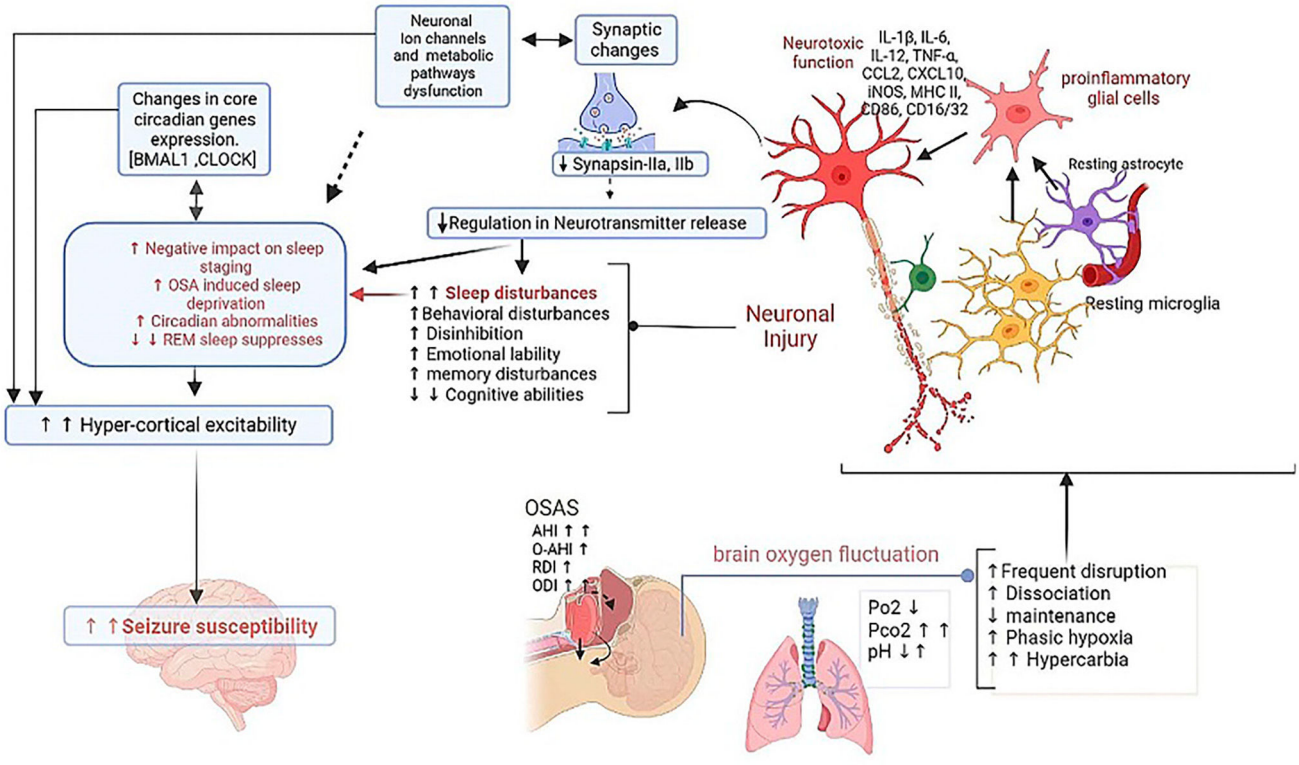


Fig. 4 A proposed pathogenic mechanism for the bilateral tonic–clonic seizures of unknown origin disorders in patients with long-standing severe obstructive sleep apnea. *Abbreviations* – AHI: Apnea–Hypopnea Index; O-AHI: Obstructive Apnea–Hypopnea Index; RDI: Respiratory Disturbance Index; ODI: Oxygen Disturbance Index; pO2: Partial Pressure of Oxygen (PO_2); pCO_2: Partial Pressure of Carbon Dioxide; IL: Interleukins; iNOS: Inducible nitric oxide synthase; CCL2: C-C Motif Chemokine Ligand 2; CXCL10: C-X-C Motif Chemokine Ligand; TNF-α: Tumor necrosis factor alpha; MHC-II: Major Histocompatibility Complex class-II; BMAL1: Brain and Muscle ARNT-Like 1; CLOCK: Circadian Locomotor Output Cycles Kaput.

deficiency of synapsin-IIa and IIb isoforms is crucially associated with epileptiform and seizure-related phenomena due to its regulation of neurotransmitter release.[17] Grubač et al.[18] reported that chronic sleep fragmentation increases seizure susceptibility and modulates neuronal production of IL-1β and IL-6. According to Grippo et al.,[19] the PaCO2 level in patients with obstructive sleep apnea may interact on various ion channels or metabolic pathways, changing the excitability of the motor cortex and modifying excitatory and inhibitory cortical circuits.

Interestingly, core circadian genes like BMAL1, CLOCK, and PER1 are associated with cortical excitability and seizure threshold regulation.[20] Several circadian regulatory proteins like DEPDC5, NPRL-2, and NPRL-3 are crucial as their mutations are specifically associated with sleep hypermotor epilepsy.[21] Patients with obstructive sleep apnea are at high-risk for developing circadian misalignment disruption. Studies have revealed that increased levels of hypoxia-inducible factor 1α in obstructive sleep apnea patients are associated with overexpression of circadian CLOCK proteins such as BMAL1 and PER1 and misalignments of these core clock genesmay lead to increased epilepsy susceptibility.[22,23] Fig. 4 shows a proposed pathogenic mechanism for the bilateral tonic–clonic seizure of unknown origin disorders in patients with long-standing severe obstructive sleep apnea.

Most importantly, accurately detecting such seizure onset from the large surface of the buried frontal cortex is challenging, especially in the ventromedial prefrontal region, which is particularly far from the reach of scalp electrodes. Of note, obstructive sleep apnea can cause sleep fragmentation with lightened sleep and altered sleep-stage transition resulting in reduced seizure threshold.[24] To such effect, antiepileptic drugs might benefit seizure control not only by their direct effect on neuronal excitability but also through the stabilization of sleep, altered sleep transition, and possibly by reducing sleep deprivation and increasing sleep efficiency.[25]

In the emergency room, a bilateral tonic–clonic seizure of unknown origin is not an uncommon presentation. However, polysomnography is not frequently recommended in these cases, even when the underlying etiology is unclear. We recommend that polysomnography be a component of prescribed investigations in cases of bilateral tonic–clonic seizure of unknown origins when the etiology is not obvious after thorough routine investigations. Besides, it is equally important to emphasize the therapeutic implications in such clinical scenarios with the appropriate introduction of continuous positive airway pressure. This can allow the tapering of antiepileptic drugs in the long run, thereby saving the patients from antiepileptic drug-related chronic side effects. Timely obstructive sleep apnea treatment can help control many other adverse health conditions, including cardio- and cerebrovascular mortality.

The other important clinical challenge in this case series is the decision to continue antiseizure medications in the long run. There is, in fact, no clear guideline available in this context. One approach would be to treat these cases as acute symptomatic seizures, which usually do not warrant the continuation of antiseizure medications beyond the first 3–4 weeks.[26] Two important determinants favoring long-term antiseizure therapy could be the presence of epileptiform discharges in the EEG and any structural abnormalities in routine brain scans, preferably MRI. In none of the index cases, however, any epileptiform discharge was noted when the EEG was obtained within hours of the convulsive episodes. Brain MRI did not reveal any potentially epileptogenic lesion. All the patients remained seizure free when the medications were tapered off over 6 months and in the subsequent follow-up period up to another 6 months. That said, each case might be different from another, and therefore individualized treatment approach might be more beneficial than using the same clinical approach for all these patients. A larger cohort of such cases must be studied to arrive at an evidence-based conclusion on these individuals' long-term continuation of antiseizure medication.

Conclusion

Current guidelines emphasize the effectiveness of continuous positive airway pressure as a mainstream treatment of obstructive sleep apnea. We have reported the first-ever case series describing obstructive sleep apnea-induced bilateral tonic–clonic seizure of unknown origins without any underlying neurological or metabolic cause. The patients remained seizure-free on continuous positive airway pressure, even when levetiracetam was withdrawn, suggesting obstructive sleep apnea's causality in their new-onset acute seizures. Although further investigation is required to clarify this association, underlying obstructive sleep apnea should be ruled out in patients with a first-ever bilateral tonic–clonic seizure. Whether or not continuous positive airway pressure alone could effectively treat hypoxia and deranged cortical excitability, which may lead to seizures in cases with long-standing obstructive sleep apnea, is yet to be explored.

Disclosures and Conflict of Interests

None of the authors has a conflict of interest.

Ritwick Mondal (ritwickraw@gmail.com) reports no relevant disclosures.

Arindam Maitra (drarindammaitra@yahoo.com) reports no relevant disclosures.

Somesh Saha (someshsaha96@gmail.com) reports no relevant disclosures.

Shramana Deb (shramanadeb1995@gmail.com) reports no relevant disclosures.

Aakash Guha Roy (guharoyaakash@gmail.com) reports no relevant disclosures.

Manoj Mahata (manojmahata85@gmail.com) reports no relevant disclosures.

Durjoy Lahiri (ddlahiri1988@gmail.com) reports no relevant disclosures.

Julián Benito-León (jbenitol67@gmail.com) reports no relevant disclosures.

Study funding

Nil.

Patient consent (informed consent)

Written informed consent was obtained from the patients to publish this article and any accompanying images.

Ethical considerations

No ethics approval was necessary as it is a case series.

Author contributions

All authors contributed significantly to the creation of this manuscript; each fulfilled criterion as established by the ICMJE.

Acknowledgments

J. Benito-León is supported by the National Institutes of Health, Bethesda, MD, USA (NINDS #R01 NS39422), the European Commission (grant ICT-2011-287739, NeuroTREMOR), the Spanish Ministry of Economy and Competitiveness (grant RTC-2015-3967-1, NetMD—platform for the tracking of movement disorder), and the Spanish Health Research Agency (grant FIS PI12/01602 and grant FIS PI16/00451).

References

1. Sforza E, Roche F. Sleep apnea syndrome and cognition. Front Neurol. 2012 May 29;3:87. https://doi.org/10.3389/fneur.2012.00087. PMID: 22661967; PMCID: PMC3361858.
2. O'Connor GT, Caffo B, Newman AB, Quan SF, Rapoport DM, Redline S, Resnick HE, Samet J, Shahar E. Prospective study of sleep-disordered breathing and hypertension: the Sleep Heart Health Study. Am J Respir Crit Care Med. 2009 Jun 15;179(12):1159–64. https://doi.org/10.1164/rccm.200712-1809OC. Epub 2009 Mar 5. PMID: 19264976; PMCID: PMC2695498.
3. Obstructive sleep apnea in adults: epidemiology, clinical presentation, and treatment options. Adv Cardiol. 2011;46:1–42. https://doi.org/10.1159/000327660. Epub 2011 Oct 13. PMID: 22005188.
4. St Louis EK. Diagnosing and treating comorbid sleep apnea in neurological disorders. Pract Neurol (Fort Wash Pa). 2010 Jul 1;9(4):26–30. PMID: 22298957; PMCID: PMC3268511.
5. Vitale GJ, Capp K, Ethridge K, Lorenzetti MS, Jeffrey M, et al. Sleep apnea and the brain: neurocognitive and emotional considerations. J Sleep Disord Manag. 2016;2:008.
6. Maurousset A, De Toffol B, Praline J, Biberon J, Limousin N. High incidence of obstructive sleep apnea syndrome in patients with late-onset epilepsy. Neurophysiol Clin. 2017 Feb;47(1):55–61. https://doi.org/10.1016/j.neucli.2016.11.002. Epub 2016 Dec 14. PMID: 27988205.
7. Salas RE, Chakravarthy R, Sher A, Gamaldo CE. Management of sleep apnea in the neurology patient: five new things. Neurol Clin Pract. 2014 Feb;4(1):44–52. https://doi.org/10.1212/01.CPJ.0000442583.87327.5d. PMID: 29473567; PMCID: PMC5765590.
8. Weihs A, Frenzel S, Wittfeld K, Obst A, Stubbe B, Habes M, Szentkirályi A, Berger K, Fietze I, Penzel T, Hosten N, Ewert R, Völzke H, Zacharias HU, Grabe HJ. Associations between sleep apnea and advanced brain aging in a large-scale population study. Sleep. 2021 Mar 12;44(3):zsaa204. https://doi.org/10.1093/sleep/zsaa204. PMID: 33017007; PMCID: PMC7953208.
9. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshé SL, Nordli DR, Perucca E, Tomson T, Wiebe S, Zhang YH, Zuberi SM. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia. 2017 Apr;58(4):512–21. https://doi.org/10.1111/epi.13709. Epub 2017 Mar 8. PMID: 28276062; PMCID: PMC5386840.
10. Malow BA, Weatherwax KJ, Chervin RD, Hoban TF, Marzec ML, Martin C, Binns LA. Identification and treatment of obstructive sleep apnea in adults and children with epilepsy: a prospective pilot study. Sleep Med. 2003 Nov;4(6):509–15. https://doi.org/10.1016/j.sleep.2003.06.004. PMID: 14607344.
11. Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res. 2002 Mar;11(1):1–16. https://doi.org/10.1046/j.1365-2869.2002.00289.x. PMID: 11869421.
12. Chihorek AM, Abou-Khalil B, Malow BA. Obstructive sleep apnea is associated with seizure occurrence in older adults with epilepsy. Neurology. 2007;69:1823–7. https://doi.org/10.1212/01.wnl.0000279334.78298.d5.
13. Shahveisi K, Jalali A, Moloudi MR, Moradi S, Maroufi A, Khazaie H. Sleep architecture in patients with primary snoring and obstructive sleep apnea. Basic Clin Neurosci. 2018;9(2):147–56. https://doi.org/10.29252/NIRP.BCN.9.2.147.
14. Kumar P, Raju TR. Seizure susceptibility decreases with enhancement of rapid eye movement sleep. Brain Res. 2001 Dec 20;922(2):299–304. https://doi.org/10.1016/s0006-8993(01)03174-2. PMID: 11743963.
15. Malow BA. Sleep deprivation and epilepsy. Epilepsy Curr. 2004 Sep-Oct;4(5):193–5. https://doi.org/10.1111/j.1535-7597.2004.04509.x. PMID: 16059497; PMCID: PMC1176369.
16. Hrnčić D, Grubač Ž, Rašić-Marković A, Šutulović N, Šušić V, Bjekić-Macut J, Stanojlović O. Sleep disruption increases seizure susceptibility: behavioral and EEG evaluation of an experimental model of sleep apnea. Physiol Behav. 2016 Mar 1;155:188–94. https://doi.org/10.1016/j.physbeh.2015.12.016. Epub 2015 Dec 17. PMID: 26705666.
17. Park DS, Yoon DW, Yoo WB, et al. Sleep fragmentation induces reduction of synapsin II in rat hippocampus. Sleep Biol Rhythms. 2014;12:135–44. https://doi.org/10.1111/sbr.12052.
18. Grubač Ž, Šutulović N, Jerotić D, Šuvakov S, Rašić-Marković A, Macut D, Simić T, Stanojlović O, Hrnčić D. Experimental chronic sleep fragmentation alters seizure susceptibility and brain levels of interleukins 1β and 6. Acta Neurobiol Exp (Wars). 2021;81(1):96–109. https://doi.org/10.21307/ane-2021-010. PMID: 33949166.
19. Grippo A, Carrai R, Romagnoli I, Lanini B, Bianchi R, Gigliotti F, Scano G. Cortical excitability in obstructive sleep apnea syndrome: transcranial magnetic stimulation study. Sleep. 2005 Dec;28(12):1547–53. PMID: 16408414.
20. Wu H, Liu Y, Liu L, Meng Q, Du C, Li K, Dong S, Zhang Y, Li H, Zhang H. Decreased expression of the clock gene Bmal1 is involved in the pathogenesis of temporal lobe epilepsy. Mol Brain. 2021 Jul 14;14(1):113. https://doi.org/10.1186/s13041-021-00824-4. PMID: 34261484; PMCID: PMC8281660.
21. Li Y, Zhao X, Wang S, Xu K, Zhao X, Huang S, Zhu S. A novel loss-of-function mutation in the NPRL3 gene identified in Chinese familial focal epilepsy with variable foci. Front Genet. 2021 Nov 12;12:766354. https://doi.org/10.3389/fgene.2021.766354. PMID: 34868250; PMCID: PMC8633433.
22. Jehan S, Auguste E, Pandi-Perumal SR, Kalinowski J, Myers AK, Zizi F, Rajanna MG, Jean-Louis G, McFarlane SI. Depression, obstructive sleep apnea and psychosocial health. Sleep Med Disord. 2017;1(3):00012 Epub 2017 Oct 27. PMID: 29517078; PMCID: PMC5836734.
23. Gabryelska A, Turkiewicz S, Karuga FF, Sochal M, Strzelecki D, Białasiewicz P. Disruption of circadian rhythm genes in obstructive

sleep apnea patients-possible mechanisms involved and clinical implication. Int J Mol Sci. 2022 Jan 10;23(2):709. https://doi.org/10.3390/ijms23020709. PMID: 35054894; PMCID: PMC8775490.
24. Malow BA. The interaction between sleep and epilepsy. Epilepsia. 2007;48(Suppl 9):36–8. https://doi.org/10.1111/j.1528-1167.2007.01400.x. PMID: 18047600.
25. Hermann B, Meador KJ, Gaillard WD, Cramer JA. Cognition across the lifespan: antiepileptic drugs, epilepsy, or both? Epilepsy Behav. 2010 Jan;17(1):1–5. https://doi.org/10.1016/j.yebeh.2009.10.019. PMID: 19931492.
26. Gunawardane N, Fields M. Acute symptomatic seizures and provoked seizures: to treat or not to treat? Curr Treat Options Neurol. 2018;20(10):41 Published 2018 Aug 23. https://doi.org/10.1007/s11940-018-0525-2.