Acta Neurochirurgica (2021) 163:3075–3082
https://doi.org/10.1007/s00701-021-04717-2

CASE REPORT - NEUROSURGERY GENERAL

CO_2-induced intracranial hypertension and high-amplitude B-waves in a patient with Chiari 1 malformation and sleep apnea syndrome that resolved following CPAP therapy

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Received: 8 July 2020 / Accepted: 11 January 2021 / Published online: 2 February 2021

Abstract

Headaches and cognitive impairment in the elderly population have been described as symptoms related to obstructive sleep apnea (OSA). Although papilledema has been observed in some of these patients, suggesting intracranial hypertension (ICH), there are only a few studies in which intracranial pressure (ICP) has been continuously measured in patients with OSA without neurological disease. We present a patient diagnosed with Chiari Type 1 malformation and OSA, who present normal ICP recording during the day and nocturnal ICH associated with high amplitude B-waves and hypercapnia during obstructive apneas, which disappeared following continuous positive airway pressure (CPAP) therapy. The normalization of the cerebral and respiratory parameters with CPAP therapy is important for performing the correct treatment in these patients.

Keywords Chiari malformation type 1 · Continuous positive airway pressure · Hypercapnia · ICP B-waves · Intracranial hypertension · Obstructive sleep apnea

Introduction

Sleep-related breathing disorders (SRBD), which include nocturnal hypoventilation and central or obstructive sleep apnea (OSA), represent a highly prevalent chronic condition that is associated with disruption of sleep continuity and intermittent hypoxemia, which can lead to serious adverse effects. SRBD can cause daytime hypersomnolence and is a well-documented risk factor for an increased incidence of cardiovascular disease, impaired quality of life, motor accidents, and increased mortality [12, 18]. Duran et al. estimated that 28% of women and 26% of men in the general Spanish population, aged between 30 and 70y, have OSA syndrome based on the presence of an apnea-hypopnea index (AHI) score ≥ 5 [5]. We reported a high prevalence (50%) of SRBDs in patients with Chiari type 1 malformation (CM-1), with a predominant obstructive component [6].

One of the mechanisms responsible for OSA adverse effects is the increase in intracranial pressure (ICP) that might be induced by $paCO_2$ retention during sleep [7]. The increase in $paCO_2$ induces cerebral vasodilation, a secondary increase in cerebral blood volume (CBV), and a variable increase in ICP. Even though intracranial hypertension (ICH) has been confirmed by the presence of papilledema in some of these patients [15], there are no specific studies that show the direct repercussion of these phenomena on ICP and effect of CPAP therapy on this parameter.

This article is part of the Topical Collection on *Neurosurgery general*

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Here we report the results of continuous ICP and transcutaneous CO_2 ($TcCO_2$) monitoring in a patient with CM-1 and OSA, before and after CPAP therapy. A secondary aim was to present the cognitive status of the patient before and 7 years after the use of this therapy.

Report of the CASE

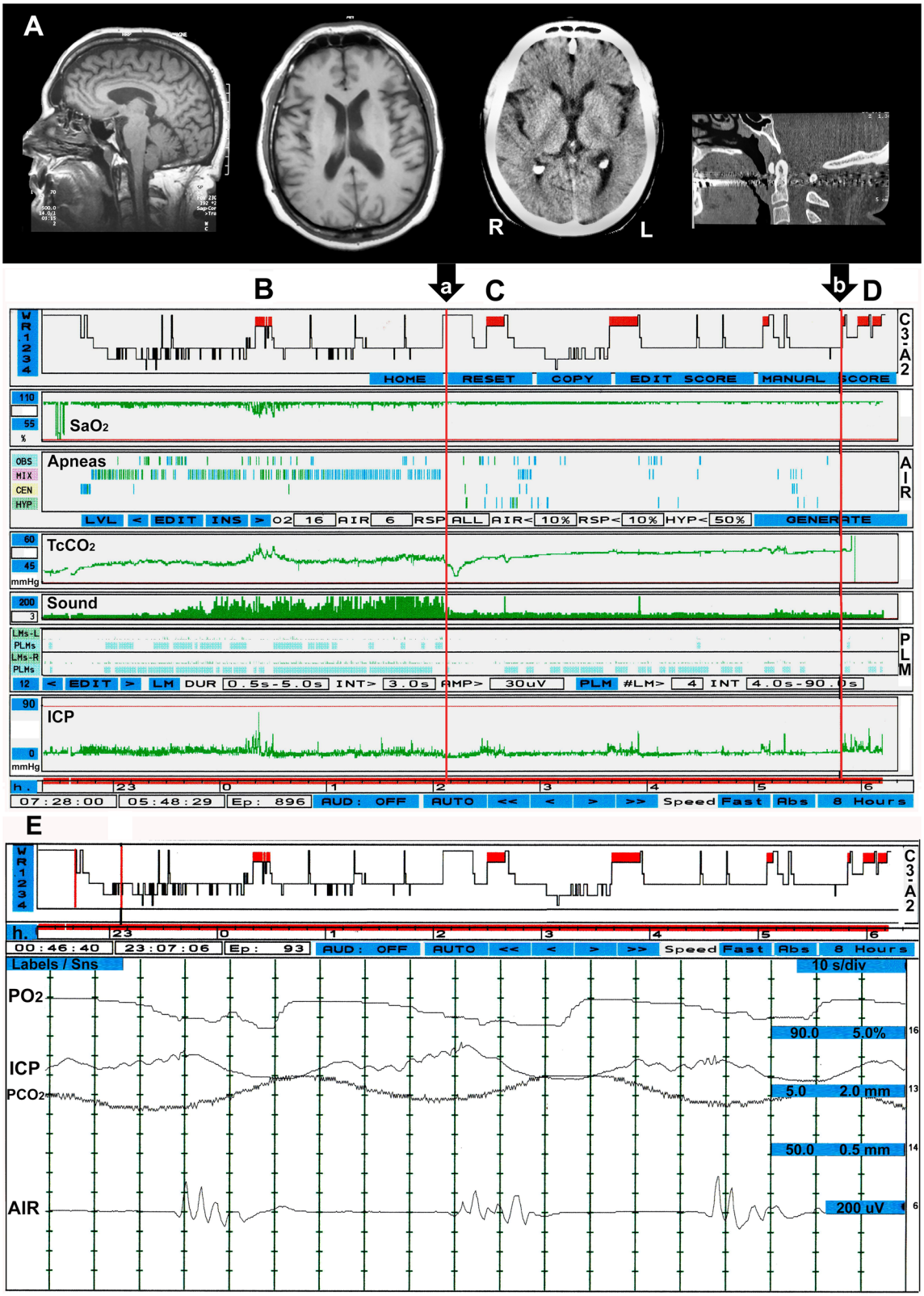
A 55-year-old obese white man with well-controlled hypertension and a diagnosis of CM-1 without hydrocephalus (Evans' index: 0.28) or syringomyelia was admitted for ICP monitoring. The patient had a medical history of high arterial blood pressure, episodic diplopia, and episodes of holocranial headaches. The patient was a university professor and reported subjective mild cognitive impairment in short-term memory. He denied being sleepy during the daytime but had a history of habitual loud snoring at night. The memory disorders he referred, in addition to the nighttime snoring and headaches, led to suspicions of benign intracranial hypertension without papilledema, so the patient accepted the implantation of a cranial sensor for continuous ICP monitoring to complete the sleep study.

The patient body mass index was 30.6 kg/m^2. His neck circumference was 43 cm, and the tongue, the upper airway tonsils, and adenoids were normal. However, the patient had a small maxilla and elongated soft palate with a very reduced velopharyngeal space (Fig. 1). The neurological examination was normal. Visual acuity was normal in both eyes and he did not have papilledema. No cognitive impairment was detected in a neuropsychological assessment. The MRI showed a small posterior fossa with a short and horizontal occipital scale and a tonsillar descent (TD) of 4 mm through the foramen magnum (FM), without any other MRI abnormality (Fig. 1). However, the patient did not present any symptoms or signs attributable to the CM-1. Visual-evoked potential, brainstem auditory-evoked potential, and somatosensory-evoked potential were normal. The study protocol in our center in CM-1 patients includes conventional nocturnal polysomnography (PSG) [6]. Polysomnographic methods and respiratory scoring criteria have been described in supplementary material.

ICP was monitored using a fiberoptic extradural device (LADD Research Industries, Inc., Burlington, Vermont, USA) for 72 h. An ICP above 30 mmHg with 100% of high amplitude B-waves (0.5–3 ICP waves/min with an amplitude > 10 mmHg) were present when the patient was asleep (Fig. 2). According to these results, the next night a split PSG was performed according to the American Academy of Sleep Medicine criteria, including simultaneous ICP and $TcCO_2$ continuous monitoring (Radiometer TCM). In addition to the analog printer that recorded the $TcCO_2$ and the ICP record (which allowed us to have a more defined record of the waves of both parameters, Fig. 2), both signals were entered into the automatic sleep recording software, together with the rest of the parameters, so that in this register all variables are registered in real time (Fig. 1). The first part of the study had a diagnostic purpose, and the second part was used for CPAP titration when severe obstructive sleep apnea was detected. The first part of the sleep study demonstrated an apnea-hypopnea index (AHI) of 62, with a predominance of obstructive and mixed phenomena and a mean duration of 40 s and was related hypercarbia. All the PSG parameters are summarized in Fig. 1 and Table 1. During the first part of the PSG recording, high ICP (> 20 mmHg) and high-amplitude B-waves were present in 100% of the recording that reached an amplitude up to 68 mmHg during REM sleep. In the second part of the night, the patient underwent CPAP titration (Table 1), which started at 4 cmH_2O and ended with 8 cmH_2O. At 8 cmH_2O, the residual AHI was 6.5, with the lowest SpO_2 of 97%. $TcCO_2$ was stabilized, and the mean ICP and the B-waves significantly reduced their amplitude during REM sleep or even disappeared in some stages of NREM-sleep (Fig. 2). Abnormalities in $TcCO_2$ and in ICP reappeared when CPAP was disconnected at 04:50 (Fig. 2).

The patient was discharged with a home CPAP. Two years after diagnosis, the cranial and spinal neuroimaging studies were repeated, with no changes observed from the initial tests. Seven years after treatment with CPAP, a new neuropsychological evaluation was performed, demonstrating that he maintained normal cognitive functions with an improvement in several scores in memory (Table 2).

Fig. 1 **A** MRI and CT scans of the patient that show a normal ventricular size, and cerebellar tonsillar descent of 4 mm through the foramen magnum and small posterior fossa. The tongue, the upper airway tonsils, and adenoids are normal. However, the patient has a small maxilla and elongated soft palate with a very reduced velopharyngeal space. Below the anatomical information, the image shows the summary of the polysomnography, including a hypnogram. The black arrow (a): CPAP was initiated. The b arrow (b): the CPAP device was switched off. ICP: intracranial pressure; L: left; PLM: Periodic limb movements; R: right; $TcCO_2$: transcutaneous CO_2. **B**: High ICP values during the polysomnographic study without CPAP. **C:** The $TcCO_2$ and the ICP values are reduced when a CPAP was initiated. **D**: High values of the CO_2 and ICP reappear at the end of the night when the CPAP device is switched off. **E**. Details of an obstructive sleep apnea during the NREM period (stage 2) with simultaneous changes in paO_2, ICP, $TcCO_2$, and oronasal flow. In this image, a progressive increase of the ICP is observed during the apnea period, which could be related to the progressive respiratory efforts and caused by the reduced PO_2 values. However, transcutaneous monitoring of $paCO_2$ can produce a delay, which explains the absence of the expected simultaneous increase of ICP and $TcCO_2$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07:28:00
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Ep: 93
Labels / Sns
10 s/div
PO2
PCO2
AIR
90.0
5.0%
5.0
2.0 mm
50.0
0.5 mm
200 uV

Table 1 Split night polysomnography evaluation in a patient with Chiari malformation type 1 and obstructive sleep apnea, before and after continuous positive airway pressure (CPAP) therapy

	First part of the night basal PSG	Second part of the night PSG with CPAP titration*
Sleep parameters		
Total sleep time	231 min	229 min
Sleep efficiency	98%	95.6%
Sleep latency	21 min	1 min
REM latency	98 min	8 min
REM	4.2%	19.4%
NREM	95.8%	80.6%
Stage 1	7.0%	8.0%
Stage 2	71.9%	59.8%
Stage 3	16.7%	12.0%
Number of sleep cycles	1	4
Arousal index	60 e/h	16 e/h
Periodic limb movement index	45.5 e/h	19 e/h
Respiratory parameters		
Number of sleep apneas/h	62 e/h	6.5 e /h
Central apnea	2.5 e/h	1.7 e/h
Basal $SatO_2$	98%	99%
Mean $SatO_2$	94%	97%
Min $SatO_2$	82%	95%
Basal $TcCO_2$	48 mmHg	44 mmHg
Max $TcCO_2$	60 mmHg	45 mmHg
Mean $TcCO_2$	53 mmHg	44 mmHg
Intracranial pressure (ICP) information		
Mean ICP (mmHg)	25	12
Low amplitude B-waves	0%	65.5%**
High amplitude B-waves	100%	17%

*Data corresponding to the complete CPAP titration, which started at 4 cm H_2O and ended with 8 cm H_2O. At a pressure of 8 cm H_2O, the number of residual sleep apneas/h was 6.5, with a lowest SpO_2 value of 97%

**Very low B-waves (< 5 mmHg). Only the nocturnal recording was considered

PSG polysomnography, *REM* rapid eye movement sleep, *NREM* non-REM sleep, *RS* raw score, *SS* standard score, *TS* T-score. A more complete table on all the cognitive domains assessed can be found in the supplementary material. *$TcCO_2$* transcutaneous CO_2, *Max* maximum, *Min* minimum

Discussion

In our patient, the diagnosis of CM-1 was made according to Barkovich's criteria, which requires a TD below the FM of at least 3 mm [1]. Patients with CM-1 have a higher prevalence of SRBD than the prevalence described in population-based studies or control patients. Our group found a very high prevalence of SRBD (50%) in adult patients with CM-1, which was moderate to severe in ~ 30% of cases. In most of these patients, we found obstructive hypopneas or apneas and poor sleep efficiency and sleep quality [6]. However, despite this diagnosis, the patient did not present any symptoms or signs attributable to the CM-1 and had a correct cerebrospinal fluid (CSF) circulation through the craniocervical junction, as shown in Fig. 1A, where it can be seen that when the patient sits, there is a physiological ICP decrease, which is usually absent when the TD hinders the CSF circulation at this level [14]. Therefore, in this patient, sleep disorders cannot be explained by the cerebellar ectopy. In this patient, the PSG showed frequent ICP abnormalities, which were objectively related to the impact of the apneas on ICP and showed that these alterations could disappear with the CPAP treatment.

Despite much indirect evidence on the potential impact of apneas on a nocturnal increase in ICP (e.g., morning headaches and visual disturbances), only a few studies have continuously monitored ICP in OSA patients [9, 15, 17]. Purvin

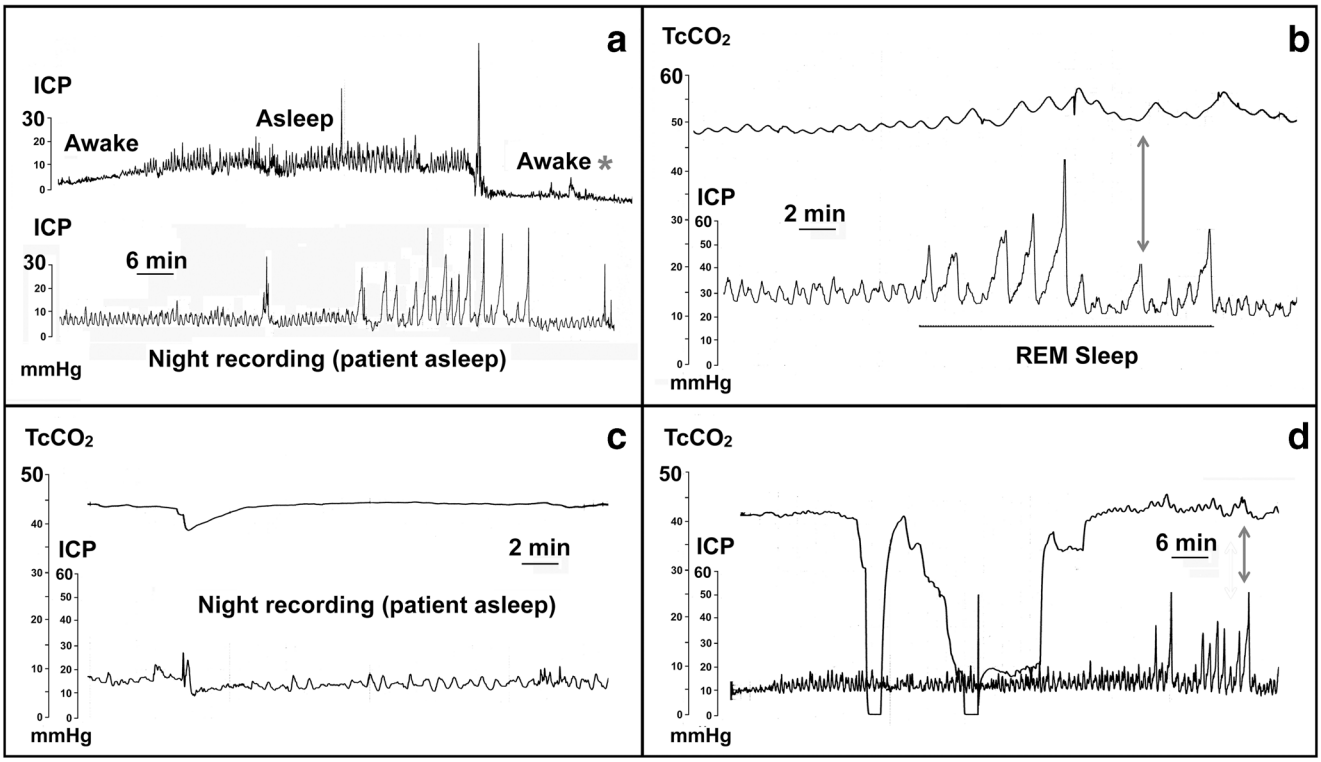

Fig. 2 **(a)**. **Top**: continuous intracranial pressure (ICP) recording during the day. In this monitoring period, we can see the presence of low (≤ 10 mmHg) and high (> 10 mmHg) amplitude B-waves when the patient sleeps, but the ICP recording was completely normal when he was awake, both lying and sitting (*). **Bottom:** pathological ICP waves were present practically during all the night, but we can see ICP waves of different morphology, with a period with very high amplitude (> 40 mmHg), corresponding to a REM-sleep period. **(b)**. ICP recording (**bottom**) with simultaneous transcutaneous CO_2 ($TcCO_2$) monitoring (**top**) during the polysomnographic study without CPAP (B in fig. 1). Note the simultaneous presence of $TcCO_2$ and ICP waves, which also increase during REM sleep (arrow). **(c)**. In the same sleep study (C in fig. 1), when a CPAP was initiated (black arrow, a in fig. 1), we can observe how the $TcCO_2$ (**top**) and the ICP (**bottom**) values are reduced and that the CO_2 waves disappear, and the ICP waves are also greatly reduced. **(d)**. At the end of the night (D in fig. 1), when the CPAP device is switched off (black arrow, b in fig. 1), the CO_2 (**top**) and ICP (**bottom**) waves reappear, showing very pathological findings (arrow)

et al. performed nocturnal ICP monitoring in one patient and demonstrated repeated episodes of marked ICP elevation associated with apnea and arterial oxygen desaturation [15]. Sugita et al. [17] measured the CSF pressure continuously at the lumbar level during nocturnal sleep in three patients with apnea-hypopnea syndrome, using a pressure transducer connected to a lumbar catheter. When the patients were awake and relaxed in the supine position, their CSF pressure was stable and within the normal range. Episodic marked elevations of CSF pressure frequently occurred during sleep (always more marked during REM-sleep than during NREM-sleep). Each CSF pressure elevation was preceded by an episode of sleep apnea or hypopnea, with significant correlations between the duration of apneic episodes and the decrease of SaO_2 or $TcPO_2$ and the increase of CSF pressure. Unfortunately, in this relevant study, the $paCO_2$ was not monitored. Jennum et al. found parallel results when they placed an epidural ICP sensor in six patients with OSA. In this study, the authors monitored $TcCO_2$ and found parallel increases in $TcCO_2$ and ICP, with significant decreases in cerebral perfusion pressure during apneas. REM sleep was associated with longer apneas and greater pressure variations than NREM sleep [9]. However, the impact of CPAP treatment was not analyzed in these patients.

To our knowledge, this is the first reported case in which it is evident that high ICP values and B-waves improved or disappeared when CPAP therapy was instituted. This explains the reported improvement in patients with papilledema after treatment with CPAP in OSA patients [8, 10].

Various mechanisms have been postulated to explain increases in ICP during apnea. In chronic OSA, high blood pressure disturbances in cerebral autoregulation have been observed [2]. In this context, the nocturnal increase in blood pressure can produce a simultaneous increase in ICP in patients with reduced compliance. However, the most plausible mechanism is that hypercapnia and hypoxia provoke cerebral arterial vasodilation, decrease cerebral resistance, and increase cerebral blood flow (CBF), cerebral blood volume (CBV), and ICP. Additionally, Loeppky et al. found an abnormal cerebrovascular response to $paCO_2$ in awake patients with sleep apnea, supporting that the physiological mechanisms of control of CBF might be altered in these patients s[11].

Table 2 Complete neuropsychological evaluation of the patient at the diagnosis (baseline study) and 7 years after continuous positive airway pressure (CPAP) therapy (long-term study)

Assessment tool	Normal score	Basal	Results	Long-term*	Results
Functional status and screening tests					
RDRS-2	≤21	20	No disability	21	No disability
EDAS		10	Normal	10	Normal
MMSE Folstein	≥24	29	No cognitive impairment	29	No cognitive impairment
WMS-R: Information and orientation	14	14	Average	14	Average
Memory					
WMS-R: Visual reproduction. Immediate recall	PC 50 (17–82)	PC 88 (RS 35)	High average	PC 88 (RS 35)	High average
WMS-R: Visual reproduction. Delayed recall	PC 50 (17–82)	PC 85 (RS 33)	High average	PC 85 (RS 33)	High average
RAVL immediate recall: Auditory Verbal. Learning Test	TS 50 (40–60)	TS 62 (RS 57)	High average	TS 81 (RS 67)	Very superior
RAVL delayed recall: Auditory Verbal. Learning Test	TS 50 (40–60)	TS 64 (RS 13)	High average	TS 71 (RS 15)	Superior
Attention and executive functions (frontal functions)					
Digits total recall	TS 10 (40–60)	SS 17 (RS 22)	Superior	SS 14 (RS 16)	High average
Forward Span Digits	PC 50	PC 98 (RS 8)	Superior	PC 89 (RS 6)	High average
Backward Span Digits	PC 50	PC 98 (RS 6)	Superior	PC 95 (RS 5)	Superior
Verbal Fluency Test (letter S)	TS 50 (40–60)	TS 55 (RS 16)	Average	TS 55 (RS 16)	Average
Verbal Fluency Test (animals)	SS 10 (8–12)	SS: 12* (RS 30)	Average	SS: 11* (RS 27)	Average
TMTA	SS 10 (8–12)	SS: 9* (RS 33)	Average	SS: 10* (RS 31)	Average
TMTB	SS 10 (8–12)	SS: 9* (RS 63)	Average	SS: 7* (RS 79)	Below average

RDRS-2 Rapid Disability Rating Scale-2, *MMSE* mini-mental state examination, *EDAS* Everyday Activities scale, *WMS-R* Wechsler Memory Scale-Revised, *RAVL* Rey Auditory Verbal Learning Test, *TMTA* Trail Making Test A, *TMTB* Trail Making Test B, *PC* percentile, *RS* raw score, *SS* standard score, *TS* T-Score. * corrected for age and educational level (NEURONORMA scales). Although the results of all tests were normal at the baseline study, 7 years after the use of CPAP, the patient preserved all functions (except for TMTB), and in some of them, even had improved scores

The increase in the ICP values may also be related to the respiratory efforts against a closed glottis and the consequent increase in intrathoracic pressure, which is directly transmitted through the jugular veins into the intracranial space and also to the increases in CBV. In a recent paper, Riedel et al. suggest that the mechanical changes during respiration could also have a previously unrecognized role in the generation of B-waves [16] (2020). This mechanism could also be observed in our Fig. 1E in which ventilatory flow was used as a surrogate marker of respiratory movements, and B-waves reach the highest amplitude at the same time airflow restarts. However, in our opinion, this point needs further evaluation. B-waves could be explained by the increasing hypercapnia and hypoxia that this patient presented and not only justified by the mechanical respiratory efforts (Figs. 1E and 2). We believe that B-waves may be present in patients with sleep-breathing disorders as occurred in our patient. However, the increases in the intrathoracic pressure as with any Valsalva maneuver induces an increase in the absolute ICP values but does not generate B-waves directly but indirectly by causing an increase in $paCO_2$ and/or causing a decrease in paO_2.

To clarify this issue is beyond the goal of this paper, but in brief, we need to move on from the time-domain to the frequency-domain analysis of the B-waves. In the later, signals are analyzed in reference to frequency instead of time; therefore, this type of analysis shows how many times a wave appears within a given frequency band. In the frequency-domain, the respiratory cycle ranges from 8 to 20 cycles/min that produces a signal in the 0.13 to 0.33 Hz frequency band [4]. B-waves occur at 0.5–2 oscillations/min in ICP with a spectral representation within the frequency of 0.005–0.05 Hz [3]. This difference in frequency between B-waves and respiratory cycles makes difficult to explain that a 0.33 Hz wave can directly trigger a 0.05 Hz wave, but without a delayed trigger,

the apnea/hypopnea-induced increase in $paCO_2$/decrease in paO_2 occurs. However, findings from a study by Riedel et al. provide a fresh approach to the physiopathology of B-waver that merits further investigation [16].

In addition to the recurring increases in ICP during sleep in OSA patients, the repeated decreases in arterial paO_2 associated with apnea induced increases in sympathetic activity, oxidative stress, inflammation, endothelial dysfunction and carotid body activity, and decreased nitric oxide bioavailability, which have detrimental effects on the brain/cerebrovasculature and the heart/cardiovascular systems that contribute to the increased risk of stroke, white matter hyperintensities, cognitive decline, hypertension, tachycardia, myocardial infarction, arrhythmia, and heart failure. [2]

Untreated OSA patients also suffer from long-term cognitive impacts, which can manifest as deficits in attention, memory, executive function, psychomotor function, and language abilities [13]. This suggests that recurrent ICP increases during sleep in patients with OSA might be an important determinant of cognitive impairment [13]. Seven years after starting CPAP therapy, our patient preserved his cognitive functions, some of which were improved relative to the first evaluation. Our report does not intend to say that ICP should be monitored in OSA patients but rather emphasizes the importance of starting and maintaining CPAP treatment as early as possible when indicated to help maintain normal ICP values at night as this may favorably influence the maintenance of cognitive functions.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00701-021-04717-2.

Authors' contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Maria A Poca, Alex Ferre, Maria D de la Calzada, and Sara Fernandez-Torrelles. The first draft of the manuscript was written by Maria A Poca and Juan Sahuquillo, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statements The study received ethical approval from VHUH Ethics Committee with reference: AGE- 26/06/2020 and was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The patient has given written informed consent to publish his case.

Financial disclosure This study was partially supported by grant FIS PI18/00468, co-financed by the European Regional Development Fund (ERDF), awarded to M.A. Poca.

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