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CASE REPORT

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Adaptive servo-ventilation for the treatment of intrathecal baclofen-induced central sleep apnea: A case report

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Abstract

Baclofen is a common muscle relaxant agent used in a number of neurological disorders acting at central level and potentially causing adverse respiratory events, still largely unknown at therapeutic doses. We present the case of a young woman with spastic tetraparesis secondary to perinatal asphyxia treated with a standard dose of intrathecal baclofen who developed nocturnal symptoms, somnolence and memory loss during the day. Nocturnal cardio-respiratory sleep monitoring showed a high number of central sleep apneas (CSA). The patient was adapted and treated with a positive air pressure device, Adaptative Servo-Ventilator, specific designed to treat CSA particularly in patients with heart failure. The treatment was well tolerated and within few days CSA was reversed. The patient reported a feeling of restful sleep and disappearance of morning tiredness. The efficacy of the treatment was verified with nocturnal cardio-respiratory monitoring after 2 months and complete resolution of all symptoms was also confirmed.

KEYWORDS

baclofen, central sleep apnea, CPAP, servo-ventilation, sleep-disordered breathing, spastic tetraparesis

INTRODUCTION

Baclofen is a muscle relaxant GABA-B agonist prescribed to alleviate chronic spasticity either through oral or intrathecal administration.[1] Baclofen, for its central GABAergic activity can cause unstable breathing and ventilatory depression.[1] Unstable breathing is associated with central sleep apnea (CSA), however only few case reports have been published on the occurrence of baclofen-induced nocturnal respiratory disturbance. Adaptative-servo-ventilator (ASV) is a positive air pressure device stabilizing breathing pattern, first proposed to control periodic breathing and CSA in heart failure.[2] We present the case of a young woman with spastic tetraparesis who developed CSA during intrathecal (IT) baclofen therapy and was successfully treated with ASV.

CASE REPORT

A 28-year-old woman with spastic tetraparesis and epilepsy secondary to perinatal asphyxia was evaluated in our Sleep Laboratory. She denied smoking, alcohol/drugs, allergies, previous history of cardiovascular disease or respiratory symptoms. She was treated with lacosamide 100 mg b.i.d, brivaracetam 100 mg b.i.d, and in the last 2 years, with IT baclofen at 630 mcg/die.

The patient was able to communicate with the doctors also with the help of a care giver. She was not dysphagic, had a good cognitive state, an active social life and she had just graduated from the university. She reported the occurrence of disrupted sleep with sudden waking, the subjective feeling of not-refreshing sleep, daytime somnolence, tiredness and episodes of memory loss. As she recalled, symptoms initiated 2 years earlier, after initiation of baclofen,

and worsened over the time. Routine blood test, cardiological evaluation with ECG and echocardiography were normal. Sleep studies, periodically performed in the past for regular follow-up, were negative for sleep-disordered breathing. However, the last nocturnal poligraphy (PG), performed in another Sleep Laboratory 1 year before our evaluation, evidenced an apnea/hypopnea index (AHI) of 15.7 (mainly central apneas). At that time the patient remained untreated. Clinical and instrumental data are shown in Tables 1 and 2.

TABLE 1 Clinical data and functional tests.

BMI (kg/cm^2)	23
Epworth Sleepiness Scale	9
Arterial blood gas	
PaO_2 (mmHg)	72.6
$PaCO_2$ (mmHg)	45.3
pH	7.40
SaO_2%	98
Pulmonary function tests	
Forced vital capacity, L (% predicted)	1.55 (42.3%)
Forced expiratory volume in one second (FEV_1), L (% predicted)	1.22 (38%)
FEV_1/FVC	85%

TABLE 2 Nocturnal respiratory data at baseline and during treatment with adaptive servo-ventilator (ASV).

Nocturnal polygraphy	Basal	ASV treatment
Total apneic events	170	4
Apnea-hypopnea index, no. events (h)	25.7	0.5
Total obstructive apneas/hypopneas	21	0
Total central apneas	112	4
Total mixed apneas	37	0
Mean SaO_2%	96	99
Oxygen desaturation index (h)	0.7	0

We performed a new home PG showing a high number of central apneas determining an AHI of 25.7, causing no relevant desaturation (Table 2, Figure 1). Breathing was regular in waking state.

We therefore initiated nocturnal treatment with ASV (AirCurve 10 CS-A Pace Wave, ResMed) by nasal mask. During the first night of treatment the ASV was set to deliver 3 cmH_2O expiratory positive airway pressure (EPAP) and suitable minimum-maximum inspiratory support (PS), which was within the minimum manufacturer's setting range of 3–10 cmH_2O. As residual events were present we increased pressures to EPAP 5 cmH_2O, PS 4–11 cmH_2O. The treatment was well tolerated and after 5 days of adaptation (according to our standard protocol) central apneas were completely reversed (Figure 2). Treatment data downloaded from the ASV software were: mean use 7 h/night for 100% of the nights, residual AHI 1. After 2 months of treatment PG during ASV confirmed regular nocturnal breathing associated with a significant improvement in sleep quality and daytime symptoms with great satisfaction of the patient.

DISCUSSION

This report highlights two important aspects. First, it suggests a causal relationship between the administration of IT baclofen and the occurrence of CSA. In addition, CSA is

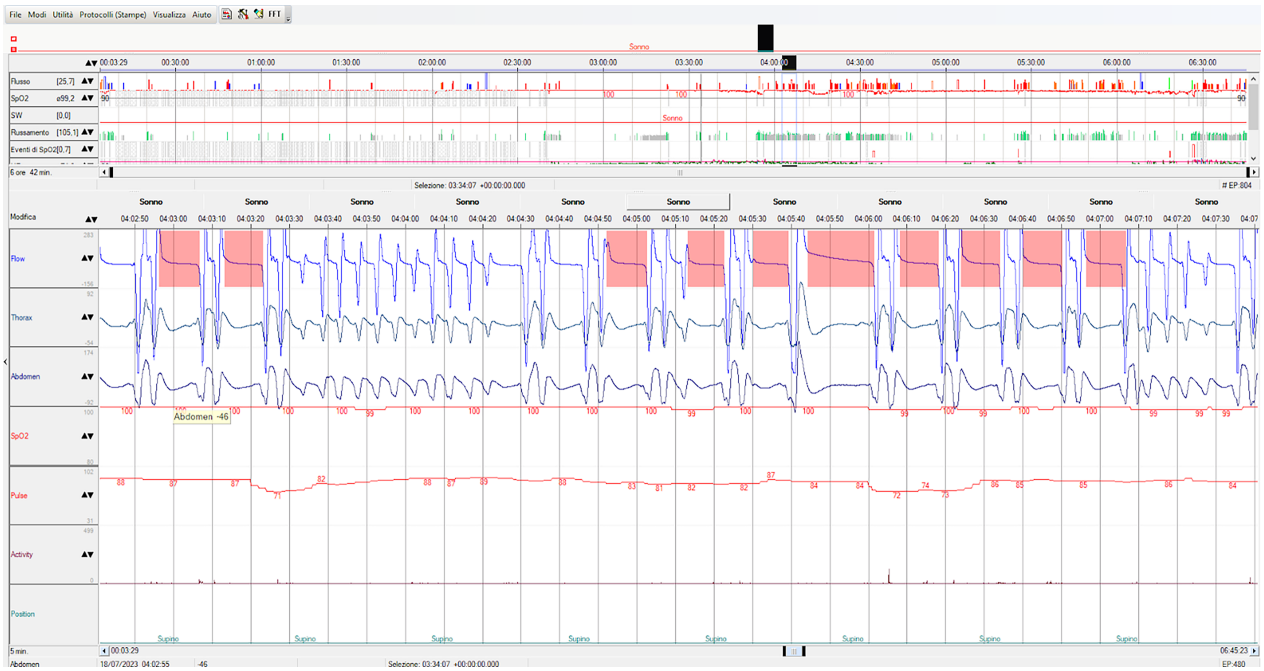

FIGURE 1 Nocturnal home polygraphy at baseline. A 5-min of recording screenshot is shown.

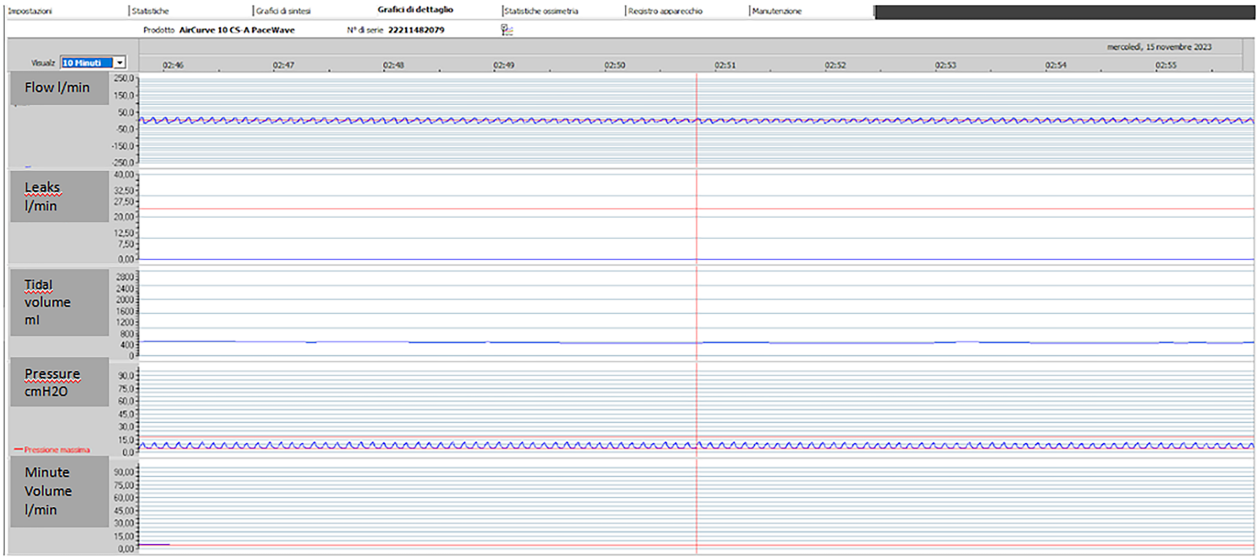

FIGURE 2 Screenshot of nocturnal recording of flow, pressure and leaks during treatment with adaptative- servo-ventilator (ASV). The recording has been downloaded from the ASV device and shows regular uninterrupted flow, no mask leaks and perfect adaptation to the device.

promptly reversed by treatment with ASV, that improves symptoms avoiding the necessity to taper the dose or to stop baclofen.

In our patient we assumed that CSA was associated with intrathecal baclofen administration as both symptoms and abnormal sleep studies were documented for the first time after initiation of the drug and worsened over the time. None of the concurrent medication taken by the patient is known to cause respiratory sleep disorders. Other factors commonly causing CSA, (e.g., cardiac disease, hypocapnia, and alkalosis) were also excluded.

Little has been published on the respiratory consequences of baclofen and studies generally focus on oral administration of high doses for alcoholism treatment. In four patients (41–70 years) treated with oral baclofen (50–100 mg/die) to help alcohol withdrawal, severe CSA was found (mean AHI 73) associated with modest oxygen desaturation.[3] Bensmail et al. did not found an effect of IT baclofen on the respiratory distress index of patients with severe spasticity.[4] It has been therefore suggested that the effect of IT baclofen on nocturnal breathing (particular if administered continuously) is milder compared to oral administration and that adverse effects are dose-dependent and diminish over the time.[4] Conversely, in a 8-year-old girl with brain injury CSA increased with increasing intrathecal doses of baclofen and resolved after dose tapering.[5] However, in our patient the intrathecal dose (continuous administration) was constant and CSA still worsened over the time.

It is widely accepted that CSA can be difficult to reverse and while treatment of opioids-induced CSA has been explored, it is unknown how to manage CSA occurring during IT baclofen administration, in order to avoid that the patient has to discontinue such an important treatment. The choice to treat our patient with ASV is based on available guidelines (that mainly focus on CSA in chronic heart failure (CHF)) and some previous experiences reported in literature. According to the American Academy of Sleep Medicine either continuous positive air pressure (CPAP) or ASV should be the choice for CSA associated with CHF, while synchronized Bilevel positive air pressure (BiPAP) is indicated only when these modes fail.[6] However, in the available studies CPAP failed to completely normalize specific drugs-induced CSA, only producing a reduction in the number of central events,[7] whereas in one study ASV completely reversed severe CSA in two patients on oral baclofen.[3] It is noteworthy that in addition to the adverse physiological effects of CSA on the cardio-respiratory system, this kind of sleep-disordered breathing negatively affects the quality of life of patients with chronic neurological conditions causing daily symptoms. It is relevant that in our patient treatment with ASV greatly improved diurnal and nocturnal symptoms, thus allowing to continue therapy with an effective dose of baclofen.

Currently, taken together a report of two patients on oral baclofen and our only case of a patient on IT baclofen suggest that this mode of ventilation is likely to reverse nocturnal CSA allowing the patient to continue its neurological treatment controlling side effects.

We conclude that, given the increasing population of patients on prolonged IT baclofen treatment, further studies are necessary to understand prevalence and mechanisms of CSA and the potential treatment with nocturnal ASV.

AUTHOR CONTRIBUTIONS

Matteo Schisano: Acquisition of clinical data. **Alessandro Libra**: Analysis or interpretation of data for the work. **Giorgio Morana**: Drafting the work. **Carlo Vancheri**:

Final approval of the version to be published. **Lucia Spicuzza**: Reviewing the work critically for important intellectual content.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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