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CASE REPORTS

Polysomnographic Analysis of a Pediatric Case of Baclofen-Induced Central Sleep Apnea

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Respiratory disorders may follow brain injury and may also occur because of comorbidities and drug use, especially central depressants or muscle relaxants. Sleep can precipitate respiratory disorders, thus polysomnography can be a powerful diagnostic tool. By revealing breathing patterns that identify specific sleep disorders, polysomnography may unmask adverse pharmacological effects, for instance connecting central depressant drugs with central sleep apneas. We describe the case of a pediatric patient in rehabilitation from brain injury who developed a central sleep apnea following a baclofen dose increase within the therapeutic range, while assuming an under-dosed benzodiazepine. Polysomnography identified a typical respiration pattern, previously observed in adults treated with baclofen and other central depressants. Baclofen tapering resolved the central sleep apnea. Polysomnography, and this specific pattern, may be proposed as diagnostic tools in patients with high dose baclofen that can be used to prevent potential respiratory disorders in children.

Keywords: rehabilitation, pediatric, sleep-disordered breathing, polysomnography, baclofen

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INTRODUCTION

Polysomnography is the standard examination for measuring sleep-disordered breathing, especially in children affected by acquired brain injury (ABI)[1] who present with risk factors comprising swallowing difficulties, use of sedatives, hypnotics, opioids, and muscle relaxant drugs.[2,3] Baclofen is a standard therapy for muscle spasticity and hypertonicity following ABI.[3] The muscle relaxant properties of baclofen can facilitate upper airway collapse during sleep and increase obstructive apneas. The depressant effect of baclofen on the respiratory drive may also lead to central apneas or sleep hypoventilation.[4] The more efficient intrathecally-administered baclofen (ITB) can severely affect the respiration of children and increase their oxygen desaturation index (ODI).[4] A typical polysomnography pattern has been reported in association with baclofen therapy in 4 adult patients treated for alcohol withdrawal.[5] Their central sleep apnea was characterized by short hyperpnoea episodes between apneas, without the typical crescendo-decrescendo pattern. The breathing pattern was similar to that seen with methadone maintenance treatments,[6] which also have a central depressive effect. If confirmed and clearly attributed to baclofen, rather than to all GABAergic drugs, this polysomnographic pattern could be a useful diagnostic tool to guide the tapering of over-dosed baclofen/ITB therapies.

REPORT OF CASE

The parents of this female patient reported that the she had a previous history of sleep-related breathing disorders, characterized by irregular breathing with episodic apneas and snoring. No examinations were performed for this patient's breathing issues before brain injury. At the age of 8 she had an encephalitis of undetermined origin, with bilateral thalamic ischemia and secondary biventricular haemorrhage due to a thrombotic occlusion of the deep cerebral venous system. An ITB pump was implanted during intensive care. The patient was admitted to our rehabilitation unit 2 months after ABI, under treatment with ITB at a maintenance dose of 450 µg/d (therapeutic dosing 300–800 µg/d) and delorazepam 0.04 mg/kg/d in oral administration (therapeutic dosing 0.02–0.08 mg/kg/d). Concomitant therapies included enoxaparin, omeprazole, and acetaminophen when needed for hyperpyrexia. The child was not using opioids. She was admitted in a state of minimal consciousness, with spastic-dystonic tetraparesis, dysphagia and vomiting. No other comorbidities were detected by objective examination. MRI reported bitalamic necrotic-haemorrhagic lesions, which were reduced as compared to the subacute phase after injury. Gliotic/malacic sequelae were evidenced in the semi-oval centres bilaterally, and in frontal regions. An electroencephalogram (EEG) performed during wake showed an irregular

organization of the electric activity, with background activity around 8–9 Hz, with slower intermixed components of the delta-theta band, with no epileptiform abnormalities.

We increased ITB to 600 µg/d, which improved spasticity. Concomitantly, the patient showed severe nocturnal oxygen desaturations, without blood gas alterations.

PEG implantation and fundoplication subsequently resolved vomiting and, to resolve spasticity, we increased ITB to 700 µg/d. Meanwhile, patient's consciousness gradually improved, with recovery of dysphagia and intentional smiles and movements.

Nocturnal pulse oximetry showed an ODI worsening with the last ITB dose increase; therefore, we started tapering at first delorazepam, then ITB. With 0.01 mg/kg/d delorazepam and 650 µg/d ITB, the patient underwent an overnight polysomnography with cardiorespiratory evaluation (nasal pressure transducers, thoracic and abdominal respiratory inductance plethysmography, pulse oximetry, electrocardiogram and manual sleep diary (**Figure 1A** and magnification). The saturation nadir was 75.4% during polysomnography. No capnography was available contextually. However, after wake, an arterial blood gas analysis (paO_2 78, $paCO_2$ 39, blood pH 7.44) excluded hypoventilation.

Delorazepam was withdrawn and ITB reduced to 100 µg/d due to an improvement in spasticity. Pulse oximetry revealed a progressive ODI improvement. A second polysomnography (**Figure 1B**) documented a significant improvement of the breathing pattern. The patient was subsequently discharged with ITB at the dose of 100 µg/d, with no respiratory issues that demanded intervention. The child received her intrathecal baclofen therapy for a total of 7 months and 10 days, because at the end of the rehabilitation course it was no longer needed for spasticity. The child was ultimately able to walk independently, with ataxic tetraparesis and mild hypertonicity, and presented with dysarthria, specific neuropsychological and language impairments, and some behavioral issues. She had no residual respiratory issues demanding medical attention.

DISCUSSION

Patients with ABI receive complex pharmacological treatments that often potentiate the action of the centrally depressant neurotransmitter GABA, at least with two drug classes. They receive benzodiazepines, which are GABAa allosteric positive modulators, and can affect the mucociliary system, increasing bronchial secretions and sialorrhea. They receive baclofen, a GABAb receptor agonist, which is not directly depressant like benzodiazepines, but may also result in central depressant effects including hypotension, bradycardia, apnea or respiratory depression, and sedation.[2] A deeper understanding of the influence of different ABI comorbidities and drugs on facilitating sleep-disordered breathing during the neurological rehabilitation phase is needed, since adverse respiration effects may increase the risks of life threats, as well as respiratory infections, and decrease patients' quality of life.

In line with the previous literature, this case report suggests a causal relationship between a typical polysomnography pattern, benzodiazepines and baclofen, as the resolution of ABI comorbidities and drug tapering resulted in polysomnography normalization. It must be considered that, when the first polysomnography occurred, delorazepam had already been tapered, while ITB was still in a normal dosing range. Therefore, the neat amelioration in the polysomnography pattern may be attributed to the dramatic tapering of ITB to 100 µg/d, rather than to the withdrawal of a sub-therapeutic dose of delorazepam. Our routine use of baclofen demands dose to be increased up to when muscle hypertonicity can be reduced at least to "mild" (modified Ashworth scale, score 2). We then taper baclofen as long as the hypertonicity does not worsen, also due to the progressive neurological recovery, which in general occurs. Baclofen tapering is thus a standard procedure in our clinical practice, although its timing can vary from patient to patient. In the present case, we tapered baclofen because of the amelioration of the neurological condition and of spasticity. In support of a baclofen-induced polysomnography pattern, we could observe the same features reported by others in adults and young adults.[5–9] Although it is not completely possible to exclude the influence of GABAa agonists/positive modulators, it is reasonable to propose the present polysomnography pattern as typical of a dose-dependent adverse drug reaction to baclofen. The effects of baclofen on respiration are a dose-dependent adverse reaction, as consistently reported in the literature.[5,7–9] Baclofen effects may also be partially time-dependent, ie, GABAb receptors can display tolerance mechanisms. However, with baclofen concentrations as high as in the present case, and in the presence of a respiratory adverse effect, we considered that the risk of waiting for a spontaneous improvement due to tolerance was not justifiable. In general, we believe that respiratory effects are an adverse drug reaction to high baclofen doses, and the best medical option is to resolve the reaction by reducing baclofen doses. In cases where baclofen therapies are not tolerable, there are several therapeutic alternatives for spasticity, such as dantrolene or tizanidine, botulinum toxin, or selective dorsal rhizotomy. Noninvasive ventilation may also be an option to make baclofen tolerable, although it is not routinely used in rehabilitation.

One limitation of this case report is that we did not carry out an EEG recording within the polysomnography, which prevented us from clearly assigning the respiratory events to sleep periods. We however used a manually recorded sleep diary, in order to check whether sleep periods were detectable: in the present case we included around 90 minutes of presumed wake in the quantification, therefore a slight overestimation of desaturation episodes may have occurred. Broader clinical studies on baclofen and ITB should thus be conducted—that include EEG recordings—on patients not exposed to additional risk factors for central apnea induction, in order to confirm a marker role for this polysomnography pattern.

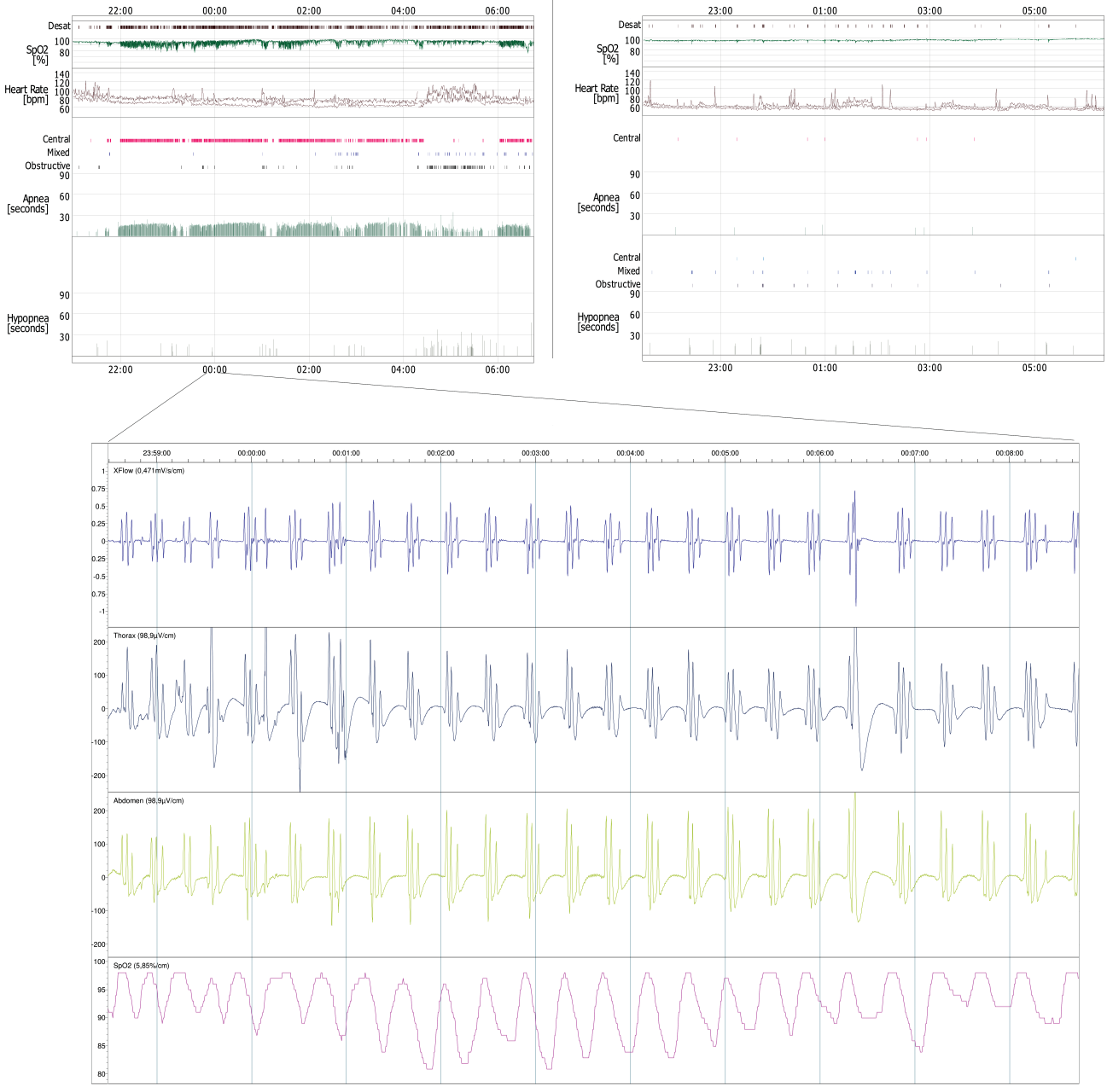
Figure 1—Results from two polysomnography tests.

A)

Respiration	Number	%	A or H/h	Supine	Non-Supine	Mean [seconds]	Longest [seconds]
Apnea	1009	93,9	102,8	1009	0	15,0	34,5
Obstructive	121	11,3	12,3	121	0	9,1	34,5
Central	834	77,7	85,0	834	0	16,0	28,7
Mixed	54	5,0	5,5	54	0	11,7	21,2
Hypopnea (All)	65	6,1	6,6	65	0	16,4	47,5
Obstructive	-	-	-	-	-	-	-
Central	-	-	-	-	-	-	-
Mixed	-	-	-	-	-	-	-
RDI				109,4	-		
Total	1074		109,4	1074	0	15,0	47,5

B)

Respiration	Number	%	A or H/h	Supine	Non-Supine	Mean [seconds]	Longest [seconds]
Apnea	7	16,7	0,8	7	0	11,5	14,3
Obstructive	0	0,0	0,0	0	0	0,0	0,0
Central	7	16,7	0,8	7	0	11,5	14,3
Mixed	0	0,0	0,0	0	0	0,0	0,0
Hypopnea (All)	35	83,3	4,0	35	0	15,8	25,5
Obstructive	13	31,0	1,5	13	-	14,3	21,9
Central	3	7,1	0,3	3	-	13,2	14,7
Mixed	19	45,2	2,2	19	-	17,2	25,5
RDI				4,8	-		
Total	42		4,8	42	0	15,0	25,5



The time between the first and second examination was 2 months and 15 days. **(A)** First polysomnography. The examination was performed while the patient received 0.01 mg/kg/d delorazepam and 650 µg/d ITB. The examination documented severe desaturations due to central apnea with an AHI of 109.4 events/h (11.3% obstructive apnea, 77.7% central apnea, 5% mixed apnea, 6.1% hypopnea). ODI was 92.6 events/h; the average saturation was 94.3%, with 75.4% minimum. The magnification highlights a breathing pattern consisting of short hyperpnoea phases (2–3 breaths) followed by central apnea, which recurred almost constantly through the whole night. As reported in the sleep diary, the patient was presumably awake between 4:30 AM and 6:00 AM, when the central breathing pattern was absent. **(B)** Second polysomnography. The examination was performed after delorazepam withdrawal and with an ITB dose of 100 µg/d. The examination showed an AHI of 4.8 events/h (16.7% obstructive apnea, 31% obstructive hypopnea, 7% central hypopnea, 45% mixed hypopnea). ODI was 6.1 events/h; the average saturation was 96.6%, with 89% minimum. No altered breathing pattern was observed. AHI = apnea-hypopnea index, ITB = intrathecally-administered baclofen, ODI = oxygen desaturation index, RDI = respiratory disturbance index.

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DISCLOSURE STATEMENT

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