Severe central apnea secondary to cerebellar dysplasia in a child: look past Joubert syndrome

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ABSTRACT

We report the case of a 12 years old girl referred to our pediatric sleep unit with a history of central sleep apnea (CSA), associated to transient episodes of tachypnea on polysomnography recordings. The patient was otherwise healthy, with no personal or family medical history, and had normal physical and neuropsychological examination. Brain magnetic resonance imaging (MRI) showed signs of cerebellar vermis dysplasia, but without the classical features of the molar tooth sign. The rest of the workup (genetic tests, blood tests, cardiac investigations) was normal, except for an increased peripheral chemosensitivity to carbon dioxide (CO_2) and oxygen (O_2). The patient was successfully treated with bi-level positive airway pressure (bi-level PAP). This case highlights the importance of performing a brain MRI in case of CSA in order to study the cerebellum, beyond the brainstem area. Cerebellum malformations can be found even in the absence of any other neurological condition.

INTRODUCTION

Central sleep apnea (CSA) in children can be attributed to congenital malformations (Arnold-Chiari malformation or craniofacial abnormalities) or to genetic (congenital central hypoventilation syndrome, Down syndrome, etc.), neurological or endocrine conditions[1]. Although the ventilatory drive to breathe is mainly under brainstem structures control, cerebellar malformations are sometimes responsible for ventilatory drive impairment, resulting in CSA. In this case, the most frequent diagnosis is Joubert syndrome and related disorders (JSRD) with a sleep pattern of central apnea associated with episodes of tachypnea[3]. Joubert syndrome is characterized by a vermian dysplasia (with typical cleft in the superior vermis) associated with thickening and horizontalization of the superior cerebellar peduncles leading to the so-called "molar tooth" pattern seen on Magnetic Resonance Imaging (MRI)[2].

In this case report, we present a 12 years old girl with severe CSA and transient episodes of tachypnea associated with cerebellar dysplasia affecting the vermis. In this patient, neither the typical image of "molar tooth" sign nor any of the usual clinical features associated to JRDS were present. She was successfully treated with bi-level positive airway pressure (bi-level PAP) ventilation.

REPORT OF CASE

A 12 years old girl was referred to our pediatric sleep unit with a history of CSA. CSA had been diagnosed in another center at 7 years old, after the patient's parents witnessed apneas during sleep. There was no significant personal or family medical history, and the patient was not under any medication. She met all developmental milestones and followed a normal scholar education.

At the time of diagnosis, there was no daytime clinical sign, especially no symptoms of sleepiness (Epworth score of 2/24), but apneas witnessed by the parents during sleep and nocturia. Initial

polysomnography (PSG) showed a central apnea index (CAI) of 16/h and an obstructive sleep apnea hypopnea index of 6/h, with normal nocturnal gas exchanges. The patient was started on Continuous Positive Airway Pressure (CPAP) without any improvement, and then switched to bi-level PAP with good tolerance. Concurrent brain MRI was considered normal.

Upon her arrival in our department, physical examination was normal (height: 158 cm; weight: 56 kg; body mass index (BMI): 22.4 $kg.m^{-2}$, 1.42 Z-score). Awake respiratory rate at rest was of 16 breaths per minute and Oxygen (O_2) saturation in room air was 98%. Lung auscultation and neurological examination were both normal.

A general work-up was initiated in our center including the search for *PHOX2B* mutation which was negative. Cardiac investigations (echocardiography, electrocardiogram with 24-hours holter monitoring, tension holter monitoring) were normal, except for a sinus arrhythmia (with a total of 21 supraventricular extra-systoles/24h) which did not require any specific treatment. Arterialized capillary blood gas sampled at earlobe showed a PaO_2 of 93 mmHg and a $PaCO_2$ of 37 mmHg. Central carbon dioxide (CO_2) chemosensitivity was normal but there was an increased peripheral chemosensitivity to CO_2 and to O_2. The pulmonary function test showed moderate, significantly reversible bronchial obstruction. Blood tests, including thyroid function test, were normal.

Considering the absence of diagnosis, a new brain MRI was performed and showed cerebellar vermis dysplasia and hypoplasia without the characteristic appearance of midbrain “molar tooth” sign on axial images. Neither horizontalization nor thickening of the superior cerebellar peduncles were present (**Figure 1**). Following the diagnosis of cerebellar malformation, a neuropsychological assessment was found normal and the normal neurological examination was confirmed, without cerebellar or oculomotor apraxia.

New PSG were realized under different conditions (**Table 1**). All recordings were performed and scored according to the American Association for Sleep Medicine (AASM) recommendations and

scoring rules[4]. Acknowledging for the increased peripheral chemosensitivity, PSG were performed with or without bi-level PAP, in room air or with nasal O_2 therapy (**Figure 2**). The latter did not elicit a decrease in central apneas, and showed an increased periodic breathing cycle length compared with the recording in room air (70 vs 50 seconds, respectively). Whatever the ventilatory conditions, nocturnal gas exchanges remained within the normal range.

Bi-level PAP was pursued under S/T mode with dramatic efficacy on CSA (**Table 1**). Since the clinical tolerance was perfect, the machine parameters were not modified, and set as follows: inspiratory positive airway pressure of 11 cmH_2O, expiratory positive airway pressure of 4 cmH_2O, and breathing frequency of 14/min.

DISCUSSION

We describe a unique case of CSA associated with cerebellar vermis dysplasia in an otherwise healthy 12 years old girl showing no specific neurological condition.

The AASM defines CSA as the cessation of airflow associated to the absence of chest wall and/or abdominal movements for longer than 20 seconds or lasting more than 2 baseline respiratory cycles if associated to an arousal, an awakening or an O_2 desaturation of at least 3%[4]. CAI is considered to be pathological when equal or higher than 5/h[1]. In children, CSA has an estimated prevalence of 1 to 5%[1].

A brain MRI is systematically recommended to explore CSA, with a special interest for the brainstem area where the respiratory centers are located. However, attention should also be paid to the cerebellum which has been implicated in central chemoreception[5]. Unlike the brainstem area, the cerebellum does not contain central pattern generators. It encompasses deep cerebellar nuclei that are partly responsible for the response to stressed breathing and hypoxic or hypercapnic

challenges[5,6]. In particular, the fastigial nucleus has been reported to have a potential excitatory effect on breathing via the facilitation of respiratory responses mediated by carotid chemoreceptors[6].

Disordered breathing during sleep is an important feature of syndromes including cerebellar malformations, such as the Chiari type II malformation[6]. Malformations are frequently secondary to genetic diseases and often associated to other neurological dysfunctions of varying severity such as developmental delay, cerebellar ataxia, severe hypotonia, dysarthria or oculomotor apraxia[7,8]. JRDS are the most frequent genetic cerebellar diseases involving abnormal respiratory pattern and CSA. A pattern of episodes of tachypnea followed by central apnea is considered as a hallmark of JRDS[8].

Our patient did not have any clinical and radiological sign of JRDS, therefore, other cerebellar malformations, especially vermian malformations, should be systematically searched for to explain cases of severe CSA syndrome. Although considered typical of JRDS, episodes of transient tachypnea have been described in other rare cases of cerebellar vermis hypoplasia, but usually in association with hypoplastic brainstem in patients presenting other neurological symptoms.

In a recent literature review on CSA in children, McLaren and colleagues pointed out that individuals with high loop gain were prone to ventilatory instability and at risk of periodic breathing[1]. In our case with increased peripheral chemosensitivity, the O_2 therapy, which levels blood O_2 content, should have drastically reduced central respiratory events[9]. The absence of CSA improvement with O_2 therapy, alongside with the higher mean periodic breathing cycle length compared to the recording in room air, makes the high loop gain unlikely to be the sole responsible for CSA in our patient. However, as O_2 therapy is a possible therapeutic option for patients with periodic breathing, testing central and peripheral chemosensitivity should be considered when investigating CSA. The use of Acetazolamide is another therapeutic option in case of CSA

associated with hyperventilation. This treatment has been used in patients with Cheyne-stokes secondary to heart failure or in patients experiencing CSA at high altitude. Acetazolamide is a carboanhydrase inhibitor which interferes with kidney reuptake of bicarbonate, resulting in a metabolic acidosis. It is thought to stimulate chemosensitivity by inducing changes in tissue and systemic pH, and by decreasing peripheral chemoreceptors sensitivity to PaO_2, therefore stabilizing breathing control[10]. However, data on the use of Acetazolamide in children are very scarce, and limited to case reports. It could be considered as a second-line treatment in our patient, if poor tolerance to bi-level PAP therapy appears.

ABBREVIATIONS

AASM: American Association for Sleep Medicine

Bi-level PAP: Bi-level positive airway pressure

BMI: Body mass index

CAI: Central apnea index

CO_2: Carbon dioxide

CSA: Central sleep apnea

JSRD: Joubert syndrome and related disorders

MRI: Magnetic resonance imaging

O_2: Oxygen

PSG: Polysomnography

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Figure 1. Brain magnetic resonance imaging. Midline sagittal T2-weighted image showing vermian dysplasia.

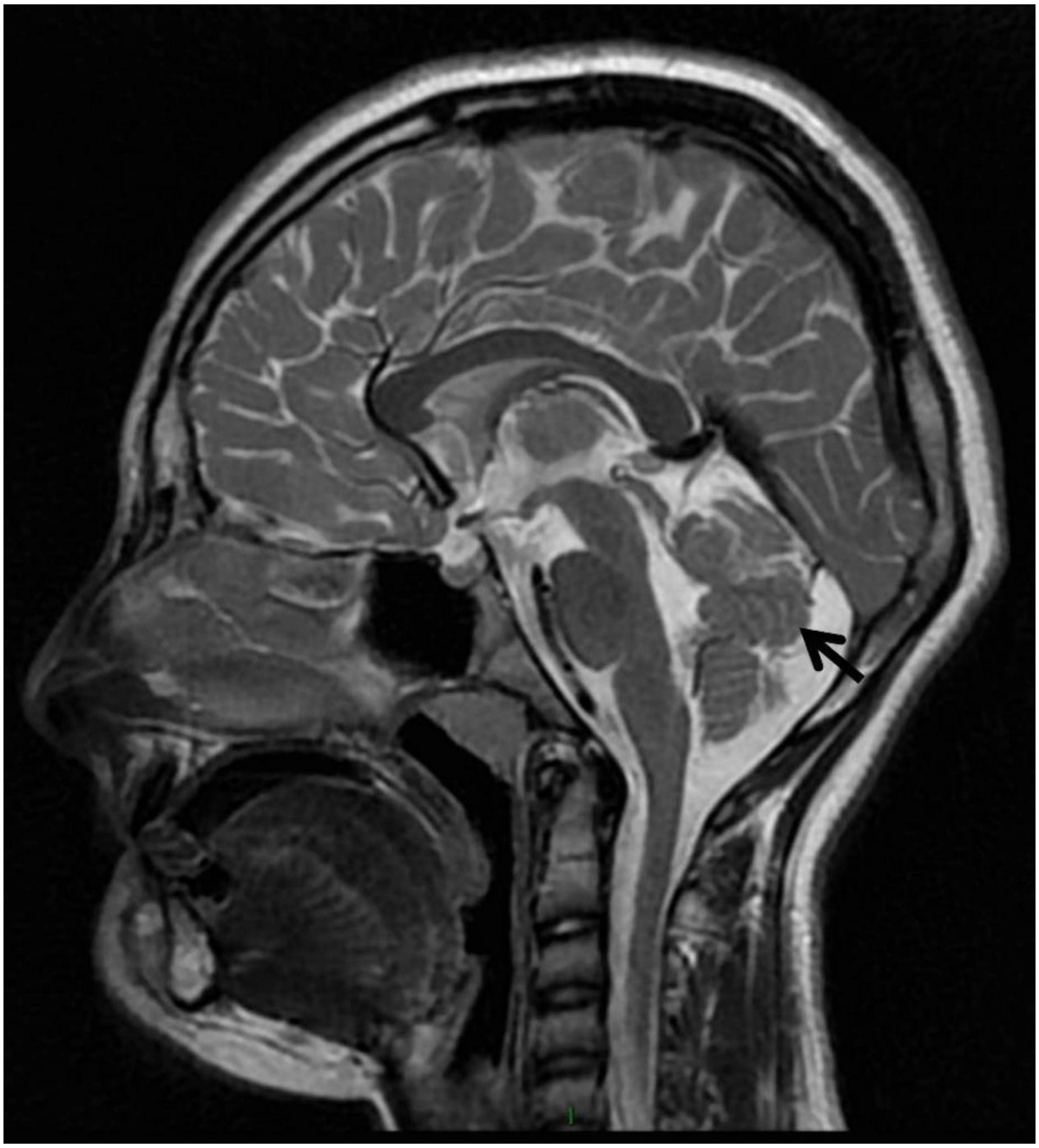

Figure 2. PSG recordings (A) Recording in room air and without bi-level PAP (B) Recording under oxygen therapy (1L/min) (C) Recording with bi-level PAP

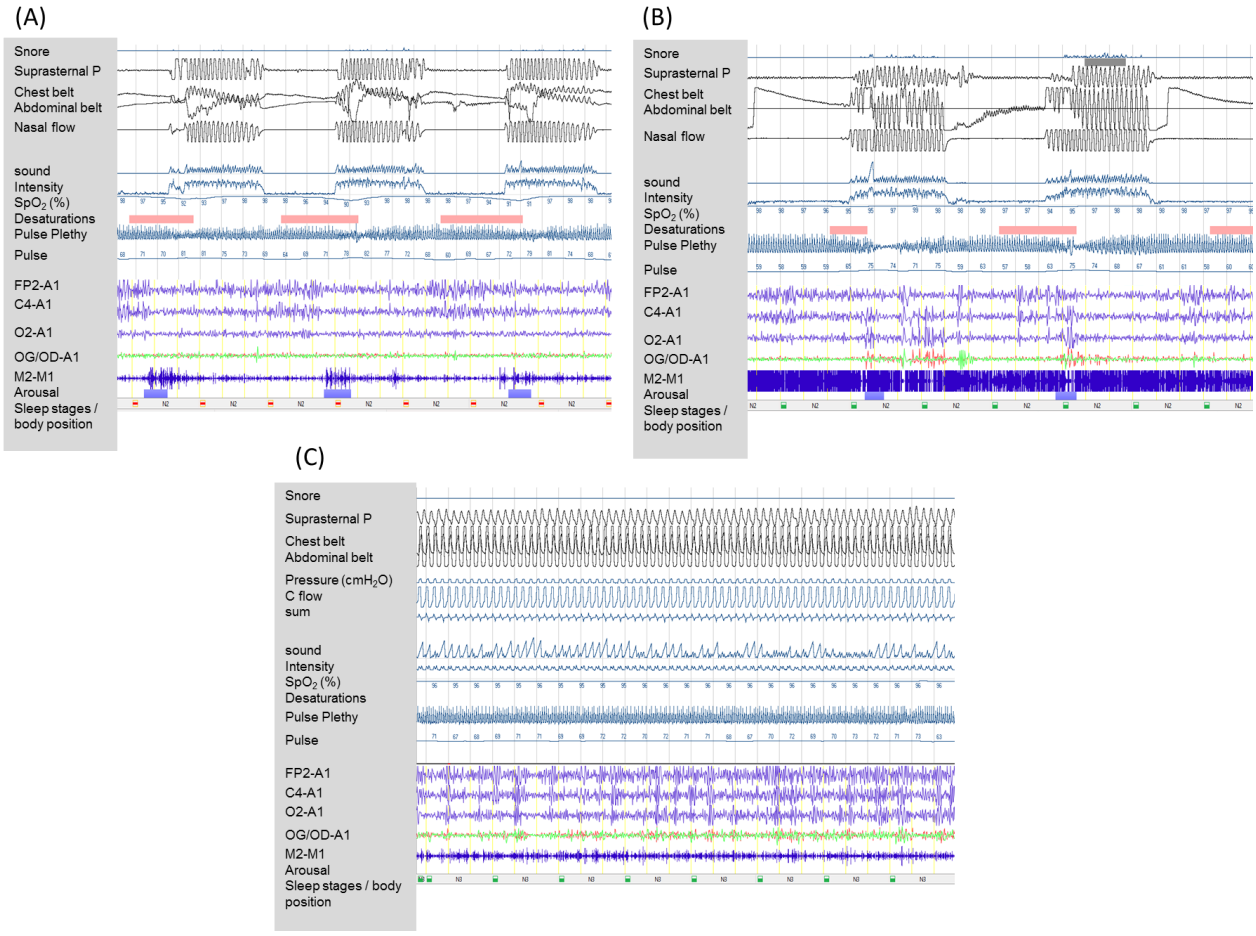

Table 1. PSG results

Sleep architecture	Room air	Oxygen therapy (1L/min)	Bi-level PAP
TST (min)	535	538	483
Sleep efficiency (%)	96	97	96
REM sleep (% TST)	21	18	21
N1 and N2 stages (% TST)	52	50	46
Micro arousal (h^{-1})	17	16	9
Respiratory characteristics and events			
Respiratory rate (min^{-1})	16	16	18
Respiratory cycle length (s)	3.7	3.7	3.3
Snore index (h^{-1})	215	192	130
AHI (h^{-1})	18	17	1.5
OAHI (h^{-1})	8	5	1.5
CAHI (h^{-1})	10	12	0
ODI (h^{-1})	12	9	4.5
Mean periodic breathing cycle length (s)	50	70	-
Mean apnea length (s)	22	30	0
Maximum apnea length (s)	46	72	0
Gas exchanges			
Mean SpO_2 (%)	97	98	96
SpO_2 nadir (%)	87	88	91
Mean $TcPCO_2$ (mmHg)	40	43	45
Max $TcPCO_2$ (mmHg)	44	47	49
$TcPCO_2$ > 50 mmHg (% of TST)	0	0	0

REM: rapid eye movement; Bi-level PAP: bi-level positive airway pressure; TST: total sleep time; AHI: apnea hypopnea index; OAHI: obstructive apnea hypopnea index; CAHI: central apnea hypopnea index; ODI: oxygen desaturation index; SpO_2: pulse oximetry; $TcPCO_2$: transcutaneous partial pressure of carbon dioxide