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ABSTRACT

Background: There is a high prevalence of obstructive sleep apnea (OSA) in children with Down syndrome (DS), sometimes associated with alveolar hypoventilation.

Objective: To compare transcutaneous partial pressure of carbon dioxid ($PtcCO_2$) and pulse oximetry (SpO_2) in children with DS and in control children with OSA.

Patients and methods: This retrospective case-control study involved children followed in Trousseau Hospital (Paris) Sleep Center. Polysomnography (PSG) recordings and clinical files of children with DS were reviewed to identify clinical signs of OSA and comorbidities associated with DS. Controls were children who presented with OSA of ENT origin without other comorbidities (exceptions: 2 overweight, 1 obese and 3 with well-controlled asthma). DS subjects and controls were matched for age and apnea hypopnea index.

Results: There were 28 children in each group. Mean $PtcCO_2$ during sleep was significantly higher in DS patients compared to controls (44 mmHg vs. 42 mmHg, $p = 0.001$). Five DS patients (21%) met the American Academy of Sleep medicine criteria for hypoventilation, compared to 1 (4%) in the control group. The mean $PtcO_2$ during sleep was significantly lower in DS patients (77 mmHg vs. 82 mmHg, $p = 0.003$).

Conclusions: This is the first study to compare nocturnal gas exchange in children with DS to a control group of children with similar OSA. Our data demonstrate that children with DS have increased $PtcCO_2$ regardless of the presence of OSA and its severity. This may be due to respiratory muscle hypotonia and/or ventilatory control alteration in DS patients.

INTRODUCTION

With an estimated prevalence ranging from 11.2 to 13.7 per 10,000 births [1,2], Down syndrome (DS), defined by an extra copy of chromosome 21, is the most common genetic disorder [3]. It is characterized by an ensemble of clinical features and comorbidities (e.g., heart defects, coeliac disease, hypothyroidism, epilepsy) [4,5]. Some clinical features, such as macroglossia, midfacial and mandibular hypoplasia, and obesity are responsible for a higher risk of obstructive sleep apnea (OSA) in children with DS compared to the general population [6,7].

Previous studies have demonstrated that the frequency of OSA is extremely high in DS patients with prevalence of 30 to 66% [8,9,10]. Approximately one-third of these patients have severe OSA (i.e., an apnea-hypopnea index (AHI) > 10 events/h) [7]. These findings led the American Academy of Pediatrics to recommend polysomnography (PSG) in all patients by the age of 4 years old [8], even in the absence of clinical signs of sleep disordered breathing (SDB). Treatment of OSA and hypoventilation in this population is important as it can prevent adverse effects on neurocognitive and behavioral development as well as on quality of life [9,10,11]. However, the management and evaluation of DS patients are challenging, mainly due to behavioral problems.

An altered autonomic cardiac regulation has previously been demonstrated in DS patients, indicating that they might suffer an overall dysfunction of the autonomic nervous system (ANS) [12]. The high prevalence of Hirschprung disease, where the enteric nervous system (derived from the ANS) is absent from the distal bowel, in this population supports this hypothesis [13,14]. However, the impact of an ANS dysfunction on ventilatory control in patients has not been studied so far, even though identifying an abnormal ventilatory response to hypoxia or

hypercapnia could help to better decipher the pathophysiology of sleep-related hypoventilation. To provide insight into nocturnal gas exchanges in DS patients, we compared transcutaneous partial pressure of carbon dioxide ($PtcCO_2$), transcutaneous partial pressure of oxygen ($PtcO_2$), and pulse oximetry (SpO_2) measurements during sleep in children with DS and in control children with similar OSA.

PATIENTS AND METHODS

Study design and patients

This retrospective study included children aged 0-18 years old, who underwent PSG recordings at the sleep unit of Trousseau Hospital (Paris, France), between September 2013 and January 2018.

DS patients with coexisting chronic respiratory insufficiency or associated comorbidities that could alter nocturnal gas exchanges (such as West syndrome or cyanotic heart disease) were excluded from the study. The control group was composed of otherwise healthy children referred to our sleep unit for clinical signs of OSA. Children with previous intervention for OSA (i.e., adenoidectomy and/or tonsillectomy, continuous positive airway pressure (CPAP), or non-invasive ventilation (NIV)) were excluded. Children from DS and control groups were matched for age and apnea-hypopnea index (AHI). The selection process for control subjects is detailed in the online supplement (E-text).

Clinical data for DS patients were recorded in the RespiRare® database, a database developed by the French Reference Center for Rare Lung Diseases. Data collection and storage were approved by the French national data protection authorities: "Commission Nationale de l'Informatique et des Libertés" and the "Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé" (CNIL N°908,324 and CCTIRS n°08.015 bis). Each patient and/or his or her legal representatives gave their informed consent prior to entering their data in the database. The data collected included medical and surgical history, medications, environmental data and familial history (smoke exposure, history of sleep disordered breathing).

For the children of both groups, night recordings were preceded by a sleep questionnaire (developed by Spruyt and Gozal, and translated into French by Nguyên et al.) to collect information on clinical signs of OSA [15,16]. Height, weight, and body mass index (BMI) were measured on the day of the PSG.

Polysomnography

The PSG recordings involved ventilatory polygraphy and monitoring of cardiorespiratory signals: respiratory flow using nasal cannula-pressure transducer, and microphone, respiratory efforts using thoracic and abdominal belts (piezoelectric strain gauges), and supra-sternal pressure transducer (CID102-108D, Cidelec^{TM,} Sainte Gemmes sur Loire, France), nocturnal gas exchange using pulse oximetry for SpO_2, and transcutaneous carbon dioxide and oxygen pressures for $PtcCO_2$ and $PtcO_2$ (Tina Combi M Radiometer, Copenhagen, Denmark), cardiac rate, and body movements and position. In addition to these parameters, electro-encephalographic (three derivations F2-A1, C4-A1, O2-A1), electro-oculographic, and chin electro-myographic recordings were performed to monitor sleep/wake states.

$PtcCO_2$ and $PtcO_2$ sensor temperature was set to 43.5°C under 6 months of age, 44°C between 6 months and 2 years of age, and 44.5°C after 2 years of age. Prior to application, the sensor was calibrated according to the manufacturer's recommendations. Over the sensor surface was placed an electrolyte solution, coupled to the skin via a highly gas permeable hydrophobic membrane. The transcutaneous electrode was placed on the forearm or anterolateral thigh. During the night, the site of the electrode was changed and the electrode calibrated every 2h. Daytime gas exchange measures were performed at installation; $PtcCO_2$ and $PtcO_2$ were recorded during 15

minutes after signal stabilization. For children younger than 2 years old, PSG recordings could also be performed during naps longer than 1 hour.

PSG recordings were scored according to the American Academy of Sleep Medicine (AASM) recommendations [17]. The AHI was calculated as the sum of all obstructive apneas and hypopneas with a ≥ 3% oxygen desaturation from pre-event baseline or when associated with an arousal, per hour of total sleep time (TST). OSA was mild for an AHI ≥ 1.5 and < 5, moderate for an AHI ≥ 5 and < 10 and severe when the AHI was ≥ 10. The desaturation index was defined as the number of drops ≥ 3% in oxygen saturation per hour of TST.

Outcome measures

Mean $PtcCO_2$ during sleep was the primary outcome measure. Secondary outcome measures were peak $PtcCO_2$, % of TST with $PtcCO_2$ > 50 mmHg, mean and minimum SpO_2, $PtcO_2$ during sleep.

Statistical analyses

Statistical analyses were performed using GraphPadPrism® software. Categorical variables are expressed using percentages. Data are presented as mean values ± standard deviation (SD) for normally distributed variables and median [IQR] or range otherwise. Between-group differences were tested using the Student's *t*-test for normally distributed variables and the Mann-Whitney test for not normally distributed continuous variables. Multiple comparisons were conducted using two-way ANOVA. Values of $p < 0.05$ were considered statistically significant. In the figures, significant differences are indicated as follows: *, $p < 0.05$; **, $p < 0.01$.

RESULTS

Population

Between September 2013 and January 2018, 52 PSG recordings were performed in 38 DS patients. For this study, we only analyzed the first recording for each patient. Ten patients were excluded from the study for the following reasons: two had pulmonary arterial hypertension (a condition that might alter $PtcO_2$ and SpO_2), two were diagnosed with concomitant West syndrome, one was treated using long-term oxygen therapy prior to the sleep recording, and one was initially misdiagnosed with DS and actually had trisomy 20. One recording was excluded because it was too short to be correctly analyzed, and nocturnal gas exchange recording was not available for three patients. The remaining 28 patients were then paired with control patients of similar age and AHI (see E text for more details). The study flow chart is presented in **Figure 1**.

The general characteristics of the study subjects are shown in **Table 1**. The sex ratio was the same in both groups, with a high prevalence of boys (19 boys versus 9 girls).

The most frequently reported clinical signs of OSA in the DS group were breathing difficulty during sleep (n=22, 79%), apnea (n=13, 46%), and snoring (n=13, 46%). Associated comorbidities were congenital non-cyanotic heart defects (n=13, 46%), well-controlled asthma (without exacerbation or recent short acting bronchodilator use in the last 4 weeks prior to inclusion, n=7, 25%), hypothyroidism (n=4, 14%), gastro-intestinal reflux (n=4, 14%), and epilepsy (n=2, 7%).

The control group children had been referred to the center for clinical signs of OSA. Twelve (43%) were previously diagnosed as having tonsillar hypertrophy and three (11%) were

overweighed or obese (BMIs of 26.8, 29.7, and 31 kg/m^2). Three patients were diagnosed as having well-controlled asthma.

Sleep study and nocturnal gas exchange

Among the 56 PSG recordings in both groups, 45 were performed during the night and 11 were performed during nap. Four DS patients with a nap study were paired with four controls with also a nap study. Three DS patients with nap time recordings were paired with controls recorded during nighttime. Median [IQR] artifact free recording time in the DS and control groups were 450 [197;516] and 488 [295;530] minutes, respectively. Sleep study and gas exchange results are presented in **Table 2**, and the results of nocturnal gas exchange are summarized in **Figure 2**. In both group, OSA was diagnosed as absent, mild, moderate, and severe in 4, 10, 6, and 8 children, respectively.

Nocturnal hypoventilation (defined as more than 25% of TST spent with a $PtcCO_2$ > 50 mmHg, according to the AASM definition) was detected in five DS patients (18%, 2 with mild OSA, 1 with moderate OSA, and 2 with severe OSA) and in one control lean child [17]. Detailed information on subjects with nocturnal hypoventilation is presented in **Table 3**. Mean $PtcCO_2$ was significantly higher in DS patients with hypoventilation compared to patients without hypoventilation, with a median [IQR] of 49 mmHg [48;50] vs. 44 mmHg [42.75;45.25], respectively (p=0.0008). There was no statistical difference for age (5.9 years old [2.8;10.55] vs. 4.4 years old [1.8;7.8], p = 0.37), BMI (16.8 kg/m^2 [16.25;21.50] vs. 16.5 kg/m^2 [15;19.85], p = 0.43), AHI (9 events/h [3.5;27.3] vs. 4.6 events/h [1.6;10], p = 0.25), mean $PtcO_2$ (78 mmHg [64;81] vs. 77 mmHg [72;82], p = 0.80) or mean SaO_2 (95.5% [94.25;96.75] vs. 96% [95;97], p = 0.78) between DS patients with or without hypoventilation.

There was no statistical difference in the number of central apnea (CA), micro-arousal index, sleep efficiency and percentage of REM and non REM sleep between the DS and the control group. The median CA number/h was 0, with a maximum of 2.5 and 1.8 in DS and control subjects, respectively. Data on CA, sleep architecture, and quality of sleep are presented as supplemental data (E-table 1).

Results of gas exchanges in both groups grouped by OSA severity are showed in E-table 2. In the mild OSA group, $PtcCO_2$ and % of TST with $PtcCO_2$ > 50 mmHg were higher in DS patients compared to controls ($PtcCO_2$: 45.5 vs. 42, respectively, $p<0.01$); with 2 (20%) patients meeting the AASM criteria for hypoventilation, and none in the control group. No between-group differences in $PtcCO_2$ characteristics were found for children with no, moderate, or severe OSA.

Awake daytime gas exchange

Results of awake daytime gas exchange analyses are presented in **Table 4.** These results, available for 19 DS patients and 17 controls, showed significantly higher $PtcCO_2$ values in the DS group despite similar $PtcO_2$ values.

DISCUSSION

The present study showed for the first time that, compared to controls, children with DS have lower SpO_2 and $PtcO_2$ associated with higher $PtcCO_2$ during sleep. Interestingly, we also found that DS patients had significantly higher $PtcCO_2$ during wakefulness.

Our study population included more boys than girls in the DS group (68%), which is in line with the sex ratio of this population [18]. The subnormal weights and heights reported here are also in agreement with a previous report [3]. In our study, the DS group had the same prevalence of non-cyanotic cardiopathy as described in the literature (46% here vs. 44%) [4]. The prevalence of other comorbidities, such as hypothyroidism, was slightly lower in our cohort (14% vs. 23.5%) than in a previous studies [5], which could have a negative impact on the prevalence of OSA.

The rate of severe OSA in our population (29%) was similar to that in previous studies [7]. Mean and maximum $PtcCO_2$ and % of TST with $PtcCO_2$ > 50 mmHg values were similar to those recently reported by Dudoignon et al. and Trucco et al. [19,20]. Nocturnal hypoventilation was present in 18% of DS children in our study, a frequency similar to that reported by Fan et al. of 22% in a cohort that included 144 PSG recordings of adults and children [21]. In terms of OSA severity our results are also in line with previous findings (14% vs. 22% without OSA, 34% vs. 36% with mild OSA, 21% vs. 21% with moderate OSA, and 29% vs. 24% with severe OSA) [21]. Wong et al. reported that mildly elevated $ETCO_2$ in the absence of OSA was frequent in DS patients [22]. With this study we confirm that, with equivalent OSA, DS patients have more hypoventilation than control otherwise healthy children, even in case of mild OSA. This finding could explain why in a previous analysis by Dudoignon et al., upper airway surgery failed to normalize gas exchanges in DS patients [19]. Indeed, surgery would not have any effect on

impaired ventilatory response to hypoventilation, whatever its etiology (hypotonia, altered ventilatory control, etc.).

Multiple studies have shown that DS patients have a deficit in muscular strength and motor skill development [23,24]. This hypotonia could also explain the prevalence of pharyngo-laryngomalacia in these patients, which is a well-known risk factor for OSA [25]. However, respiratory muscle strength has not yet been studied in DS, despite the fact that it could be an important factor contributing to nocturnal hypoventilation, independently from OSA, similarly to what is described in neuromuscular diseases [26].

A global ANS dysfunction has been suspected in DS patients, especially since studies have shown an altered cardiac autonomic modulation, with impaired heart rate variability, an index representing the sympathetic branch of the ANS [12]. Figueroa et al. showed that ANS dysfunction was independent from the presence of congenital cardiopathy [27]. Moreover, the high prevalence of Hirschprung disease in DS patients could be compared to that of Congenital Central Hypoventilation Syndrome (CCHS) patients, in whom ANS dysfunction has been well studied, and who have impaired ventilatory control and response to hypercapnia [13,14,28,29]. The higher $PtcCO_2$ levels during wakefulness found in our DS patients also corroborate the hypothesis of impaired ventilatory control, independently from SDB or OSA. The ANS must function correctly to enable adaptation of the ventilatory response to hypercapnia; lack of adaptation could lead to more severe hypoventilation. Once again, we would not expect this hypercapnia to be lifted by upper airway surgery alone.

Studying ventilatory control and hypoventilation in DS is of prime importance due to the negative impact of poor ventilatory control and blood gas exchange alterations on neurocognitive

development, and because of the DS children's predisposition to develop secondary pulmonary arterial hypertension [9,10,30,31]. Identification of characteristics that make patients good candidates for upper airway surgery, CPAP, and/or NIV is also mandatory to ensure good treatment compliance, particularly in this population where refusal of CPAP or NIV is frequent [10]. $PtcCO_2$ threshold for nocturnal ventilation have not been validated in children, and the question remains if these thresholds should be the same in DS than in other children, especially in light of our finding that DS subjects have higher baseline CO_2 levels even during wakefulness than controls.

Finally, we acknowledge that this single center, retrospective study was performed on a small number of subjects. Prospective, larger scale studies focusing on ANS functioning and respiratory muscle strength are mandatory to corroborate our results.

To conclude, we demonstrated a higher prevalence of hypoventilation in DS patients compared to their control counterparts (paired for age and AHI), which was independent of SDB severity and found even in patients with mild OSA. DS subjects also had higher $PtcCO_2$ levels during wakefulness than controls, which could indicate an altered response to hypercapnia; this could be secondary to decreased respiratory muscle strength and/or ANS dysfunction. Clarifying the etiology of hypoventilation in DS is particularly important as this will be necessary in order to establish recommendations for patients' management.

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