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# Hypoventilation in patients with Prader-Willi syndrome across the pediatric age

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## Abstract

**Objectives:** Few data on alveolar hypoventilation in Prader-Willi syndrome (PWS) are available and the respiratory follow-up of these patients is not standardized. The objectives of this study were to evaluate the prevalence of alveolar hypoventilation in children with PWS and identify potential risk factors.

**Study Design:** This retrospective study included children with PWS recorded by polysomnography (PSG) with transcutaneous carbon dioxide pressure (PtcCO<sub>2</sub>) or end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) measurements, between 2007 and 2021, in a tertiary hospital center. The primary outcome was the presence of alveolar hypoventilation defined as partial pressure of carbon dioxide (pCO<sub>2</sub>) ≥ 50 mmHg during ≥2% of total sleep time (TST) or more than five consecutive minutes.

**Results:** Among the 57 included children (38 boys, median age 4.8 years, range 0.1–15.6, 60% treated with growth hormone [GH], 37% obese), 19 (33%) had moderate-to-severe obstructive sleep apnea syndrome (defined as obstructive apnea-hypopnea index ≥5/h) and 20 (35%) had hypoventilation. The median (range) pCO<sub>2</sub> max was 49 mmHg (38–69). Among the children with hypoventilation, 25% were asymptomatic. Median age and GH treatment were significantly higher in children with hypoventilation compared to those without. There was no significant difference in terms of sex, BMI, obstructive or central apnea-hypopnea index between both groups.

**Conclusion:** The frequency of alveolar hypoventilation in children and adolescents with PWS is of concern and may increase with age and GH treatment. A regular

**Abbreviations:** AI, arousal index; BMI, body mass index; CAI, central apnea index; CPAP, continuous positive airway pressure; CSAS, central sleep apnea syndrome; ETCO<sub>2</sub>, end-tidal CO<sub>2</sub>; GH, growth hormone; HNFC, high flow nasal cannula; NIV, noninvasive ventilation; NREM, non-rapid eye movement; NREM1, non-rapid eye movement stage 1; NREM2, non-rapid eye movement stage 2; NREM3, non-rapid eye movement stage 3; OAH1, obstructive apnea-hypopnea index; OAI, obstructive apnea index; OSAS, obstructive sleep apnea syndrome; pCO<sub>2</sub>, partial pressure of carbon dioxide; PG, polygraphy; PSG, polysomnography; PtcCO<sub>2</sub>, transcutaneous carbon dioxide pressure; PWS, Prader-Willi syndrome; RAI, respiratory arousals index; REM, rapid eye movement; SDB, sleep-disordered breathing; SpO<sub>2</sub>, pulse oxygen saturation; TST, total sleep time.

Patricia Franco and Laurianne Coutier have contributed equally to this work.

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screening by oximetry-capnography appears to be indicated whatever the sex, BMI, and rate of obstructive or central apneas.

#### KEYWORDS

alveolar hypoventilation; child, polysomnography; growth hormone; Prader-Willy syndrome; sleep-disordered breathing

## 1 | INTRODUCTION

Prader-Willi Syndrome (PWS) is a multisystemic genetic disorder mainly caused by the loss of paternal expression of several genes of the 15q11.q13 region, characterized by a hypothalamic dysfunction causing growth hormone (GH) insufficiency.<sup>1</sup> The phenotypic characteristics change throughout the age and include hypotonia and failure to thrive in the neonatal period, hyperphagia and obesity in childhood.<sup>2,3</sup>

Chronic respiratory failure, and more specifically sleep-disordered breathing (SDB), in PWS is well known.<sup>4,5</sup> Although obstructive sleep apnea syndrome (OSAS) is the main SDB described in PWS, with a prevalence between 53% and 80%,<sup>6,7</sup> central sleep apnea syndrome (CSAS) is also frequent and tends to disappear with age.<sup>8</sup> Alveolar hypoventilation has also been reported in PWS,<sup>9,10</sup> at a higher frequency in children with PWS and OSAS compared to non-syndromic control children with OSAS.<sup>11</sup> Importantly, in a review of 27 deceased PWS patients, a high morbidity and mortality related to hypoventilation was described.<sup>12</sup>

OSAS in PWS is known to be caused by pharyngeal hypotonia, facial dysmorphisms and tonsillar hyperplasia.<sup>13,14</sup> Conversely, the physiological mechanisms leading to CSAS and hypoventilation are still debated, and the age of onset remains unclear. Central chemoreceptor dysfunction, linked or not to the incomplete nervous system maturation observed in the neonatal period, associated with abnormal hypoxia arousal, has been shown to result in an absence of ventilatory response to hypercapnia.<sup>9,10</sup> Moreover, the restrictive syndrome secondary to muscle weakness and/or scoliosis can aggravate the respiratory failure phenomenon.<sup>14</sup>

The gold standard for diagnosing and evaluating SDB severity is polysomnography (PSG).<sup>15</sup> Its access however, remains limited and PSG studies in PWS are scarce. Other tools, such as polygraphy and oximetry-capnography are widely used but their lack of precision can lead to an underestimation of SDB severity.<sup>16</sup> To our knowledge, only one study used PSG to investigate hypoventilation in adolescents with PWS and found 18% of hypoventilation.<sup>17</sup> To increase the knowledge about PWS SDB frequency, PSG studies are needed.

Among the therapeutic options for PWS patients, GH is the main treatment. GH has beneficial effects on pulmonary function, obesity prevention and developmental outcomes.<sup>2,18,19</sup> According to a review however, 61% of deceased children with PWS under GH died before 3 years of age, with the highest risk of death during the first 9 months of treatment.<sup>20</sup> Nevertheless, this

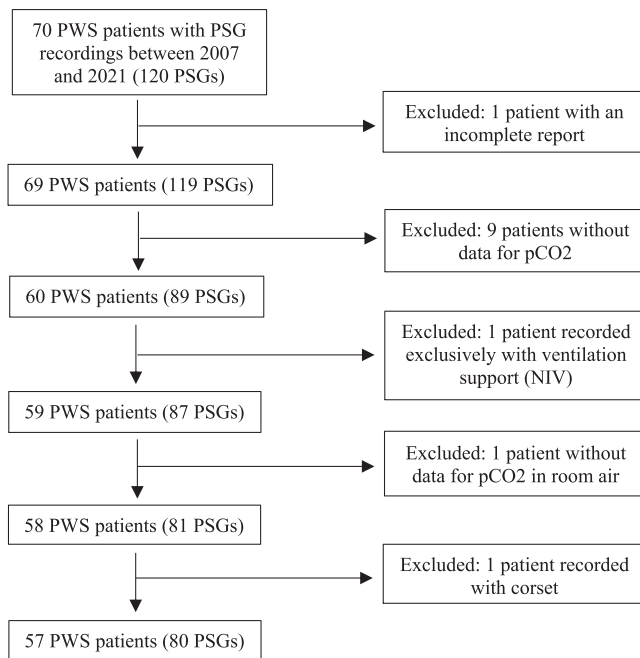
relationship between GH therapy and the occurrence of sudden death in PWS remains debatable,<sup>21,22</sup> especially since similar events have been observed in untreated children.<sup>20</sup> In this context, international and French guidelines now recommend performing a sleep evaluation in patients with PWS before starting GH and 3–6 months thereafter, and to maintain a regular clinical follow-up.<sup>1,3</sup> These guidelines however, lack precision in terms of sleep measurement technique and frequency of follow-up. Moreover, the effect of GH on SDB remains unclear. The main hypothesis is that GH has a beneficial impact on OSAS and hypoventilation by increasing muscle tonicity,<sup>3,18,19</sup> thus reducing apnea/hypopnea and increasing diaphragm strength, but this needs to be further investigated.

The primary objective of the study was to evaluate the frequency of hypoventilation during the sleep of children with PWS, from infants to adolescents, using PSG. The secondary objective was to determine the risk factors of hypoventilation. Our hypothesis was that if hypoventilation is linked to muscle weakness and/or a dysfunction in central chemoreceptors due to incomplete maturation of the central control of breathing, then hypoventilation would be more frequent during the first years of life and would improve under GH and with age.

## 2 | MATERIAL AND METHODS

### 2.1 | Study design

In this single-center retrospective study, all children aged <18 years with a genetically diagnosis of PWS, referred for a nocturnal PSG from December 2007 to January 2021 to the pediatric sleep unit of the Hôpital Femme Mère Enfant (Lyon, France) were included. Only the PSG performed in room air without any respiratory support during at least half of the night were analyzed. PSG with missing data or data obtained for less than 8 h regarding CO<sub>2</sub> transcutaneous pressure (PtcCO<sub>2</sub>) or end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) were excluded (Figure 1). As of 2013, the endocrinological management followed the international guidelines and was the same for each child in the cohort: GH before 2 years of life, sleep evaluation before GH initiation, systematic dietary measures with systematic dietary follow-up.<sup>23</sup> The study was approved by the hospital's ethics committee and the national data protection agency (*Commission Nationale de l'Informatique et des Libertés*, CNIL study number 22\_5867).



**FIGURE 1** Flow chart.

## 2.2 | Data collection

The following patients' characteristics were collected from their medical files: sex, age, height, weight, GH treatment, ENT history, respiratory support (i.e., high-flow nasal cannula [HFNC], continuous positive airway pressure [CPAP], or noninvasive ventilation [NIV]). Clinical signs of OSAS (i.e., snoring, sleep apneas, daytime tiredness, sleepiness, or agitation) was noted. Body mass index (BMI), and BMI Z-score<sup>24</sup> were retained for analysis: BMI Z-scores between 1.6 and 1.99 and BMI Z-score  $\geq 2$  were used to define respectively overweight and obesity.<sup>25</sup>

## 2.3 | Nocturnal PSG

All patients underwent nocturnal PSG in the sleep unit. One-night video-PSG in the sleep laboratory under nurse supervision was performed using the polysomnograph Morpheus (Medatec-Medical Data, Brussels, Belgium; Micromed). Eight electroencephalography bilateral channels were recorded and then referenced to the mastoids according to the 10–20 system (Fp1-A2, C3-A2, O1-A2, T3-A2, Fp2-A1, C4-A1, O2-A1, T4-A1). PSG measurements also included bilateral electrooculography (EOG, right and left), chin, tibia, and diaphragm electromyography (EMG), nasal cannula, oro-nasal thermistor, thoraco-abdominal belts, oximetry for pulse oxygen saturation (SpO<sub>2</sub>), one electrocardiogram, microphone, PtcCO<sub>2</sub> recording by SenTec system (SenTec Digital Monitor, Therwil, Switzerland) or ETCO<sub>2</sub> by Novamatrix system (Medical System, Wallingford, CT, USA). ETCO<sub>2</sub> was used in the older recordings since the technique changed over the years. Both PtcCO<sub>2</sub> and ETCO<sub>2</sub> measurements can

be used as surrogates of arterial pressure CO<sub>2</sub> for detecting hypoventilation during diagnostic studies.<sup>15</sup>

For PSG, the sleep was coded following the American Academy of Sleep Medicine recommendations 2012.<sup>15</sup> Total sleep time (TST), sleep efficacy (TST/duration of sleep\*100), sleep efficiency (TST/time in bed\*100), duration and % of sleep stages (non-rapid eye movement [NREM] including NREM1, NREM2, NREM3 stages, and rapid eye movement [REM]), NREM and REM latencies, arousal index (AI), and respiratory arousal index (RAI) were collected.

The respiratory events were scored in conformity with the pediatric AASM guidelines.<sup>15</sup> OAHl, CAI, mean SpO<sub>2</sub>, and time spent with SpO<sub>2</sub> values < 90% were collected. Indexes were expressed as the mean number of events per hour and each was calculated for the TST, NREM, and REM sleep. OAHl was defined as the sum of obstructive apnea index (OAI), obstructive hypopnea index (OHI), and mixed apnea index (MAI). OSAS was considered as mild if OAHl  $\geq 1$ –5/h, as moderate if OAHl  $\geq 5$ –10/h, or severe if OAHl  $\geq 10$ /h.<sup>1,16</sup> CSAS was considered significant if CAI is  $\geq 5$ /h.<sup>26</sup> Central hypopneas were not scored.

## 2.4 | Nocturnal carbon dioxide monitoring

The mean and maximum PtcCO<sub>2</sub> or ETCO<sub>2</sub>, along with the proportion of TST spent with PtcCO<sub>2</sub> or ETCO<sub>2</sub>  $\geq 50$  mmHg, were calculated. According to the European Respiratory Society 2021 statement, nocturnal hypercapnia, defined by a PtcCO<sub>2</sub>  $\geq 50$  mmHg during  $\geq 2\%$  of TST or more than five consecutive minutes, can be used as a criterion to initiate NIV if associated with nocturnal hypoventilation symptoms.<sup>27</sup> This definition, which was used to score hypoventilation as a primary outcome in this study, differs from that of the AASM, which considers hypoventilation if PtcCO<sub>2</sub> or ETCO<sub>2</sub>  $\geq 50$  mmHg for  $\geq 25\%$  of TST.<sup>15</sup> The latter was chosen as a secondary outcome in the study.

## 2.5 | Statistical analysis

Continuous variables were expressed as median (range) and dichotomous variables as number (%). All analyses were performed using R software (version 3.6.3, Vienna, Austria). Analyses were conducted using non-parametric tests. Children were divided in 3 groups according to age at PSG: group 1, from birth to 4 years of age; group 2, from  $\geq 4$  to 8 years of age; group 3, from  $\geq 8$  to 18 years of age. The first group was chosen because of an increased risk of sudden death in the first years of life. Then age groups were made by equal range. Groups  $\geq 8$  to 12 years and  $\geq 12$  to 18 years were merged because they contained few patients, since follow-up is less frequent through the years. They were also separated in 2 groups according to their OAHl, no/mild OSAS (OAHl < 5/h) and moderate-to-severe OSAS (OAHl  $\geq 5$ /h), and in 2 groups according to the presence of hypoventilation (hypoventilation vs no hypoventilation). Continuous variables were compared between groups using Wilcoxon test while

dichotomous or polychotomous variables were compared using  $\chi^2$  test. A *p*-value < 0.05 was initially considered statistically significant. Then, *p*-values were adjusted for multiple comparisons using Bonferroni correction; a *p*-value < .002 was considered statistically significant for comparisons of sleep characteristics between age groups and a *p*-value < .005 was considered statistically significant for comparisons performed between no/mild OSAS and moderate-to-severe OSAS groups and between hypoventilation and no-hypoventilation groups.

## 3 | RESULTS

### 3.1 | Patient characteristics

PSG data of 57 patients with PWS were included; there were 38 boys (67%) and 19 girls (33%). The median (range) age was 4.8 years (0.1–15.6). The characteristics of the total population and by age group at the time of their first PSG are presented in Table 1. As expected, GH therapy, ENT history, and OSAS symptoms were more frequent in the older age groups. The 4–8 years group comprised the highest percentage of children with obesity. Cataplexy was diagnosed in four patients (7%); two of them (50%) were later diagnosed with narcolepsy.

### 3.2 | Sleep characteristics

Overnight PSG in room air was performed for every patient. The median (range) sleep efficacy was 90% (71–98) and the median (range) sleep efficiency was 85% (68–94). The AI and RAI were low. OAH and CAI were more frequent during REM than NREM sleep. The median (range) OAH was 2.6/h (0–74.1) and the median (range) CAI was 0.2/h (0–5.9) and both decreased with age without significant difference after Bonferroni adjustment. The median (range) mean SpO<sub>2</sub> was 95.6% (90.1–99). The median (range) mean pCO<sub>2</sub> was 44 mmHg (36–50) and the median (range) maximum pCO<sub>2</sub> was 49 mmHg (38–69). The median (range) % of TST spent with PtcCO<sub>2</sub> or ETCO<sub>2</sub> ≥ 50 mmHg was 0% (0–85.6) whereas the mean (range) % of TST spent with PtcCO<sub>2</sub> or ETCO<sub>2</sub> ≥ 50 mmHg was 10% (0–85.6; Table 2). The median (range) capillary pCO<sub>2</sub> at awakening was 40 mmHg (33–60); the median (range) pH was 7.39 (7.3–7.45), and the median (range) bicarbonate concentration was 24 mmol/l (21–29).

### 3.3 | OSAS

A total of 19 patients (33%) had a moderate-to-severe OSAS, and 38 (67%) had no/mild OSAS. There was no significant difference in terms of sex, age, BMI Z-score, and treatment by GH between the two groups. Four patients (21%) in the moderate-to-severe group did not have any OSAS symptoms. Median OAH was significantly higher in the moderate-to-severe OSAS group while pCO<sub>2</sub> (PtcCO<sub>2</sub> or ETCO<sub>2</sub>)

max tended to be higher in this group. Median CAI did not differ significantly between the two groups (Table 3).

### 3.4 | Hypoventilation

pCO<sub>2</sub> was measured via PtcCO<sub>2</sub> for 32 patients (56%) and via ETCO<sub>2</sub> for 25 patients (44%). When using the AASM definition,<sup>15</sup> nine patients (16%), with a median age of 6.1 years old, had hypoventilation; their median pCO<sub>2</sub> max was 53.9 mmHg, and % of TST spent with pCO<sub>2</sub> > 50 mmHg was 59%. When using the criteria of PtcCO<sub>2</sub> or ETCO<sub>2</sub> ≥ 50 mmHg during ≥2% of TST or more than five consecutive minutes,<sup>27</sup> 20 patients (35%) had hypoventilation; among them, 5 (25%) did not have any clinical signs of SDB. Median (range) maximum pCO<sub>2</sub> was 54 mmHg (51–69) and the median (range) % of TST spent with PtcCO<sub>2</sub> or ETCO<sub>2</sub> ≥ 50 mmHg was 14% (1–85.6). The search for potential risk factors of hypoventilation was only conducted on the groups defined using the PtcCO<sub>2</sub> or ETCO<sub>2</sub> ≥ 50 mmHg during ≥2% of TST or more than five consecutive minutes criteria, because the number of patients with hypoventilation according to the AASM definition was too low. Patients with hypoventilation were significantly older (*p* = .006) and significantly more often treated by GH (*p* = .026) than patients without hypoventilation. After applying Bonferroni correction for multiple comparisons, no statistical difference remained. No significant difference in BMI Z-score, sex, median OAH, or median CAI was found between the two groups (Table 4). The frequency of hypoventilation was the highest in the 8–18 years group (64%). Treatment by GH was significantly more frequent with age ( $\chi^2 = 15.5$ ; *p* = .0004; Figure 2).

### 3.5 | Evolution of SDB with GH treatment (Figure S1)

A total of 18 patients (32%) had at least a second PSG recording. Considering all PSG data (*n* = 80), hypoventilation was significantly more frequent with age (*p* = .015) and GH treatment (*p* = .022) whereas BMI Z-score, sex, OAH, and CAI did not differ significantly between children with or without hypoventilation.

## 4 | DISCUSSION

This study was the first to use PSG to assess OSAS, CSAS, and hypoventilation from infancy to adolescence in a relatively large cohort of 57 patients with PWS. Moderate-to-severe OSAS was found in a third of the patients and was not always accompanied by clinical signs. Only two patients had CSAS on their first PSG. Hypoventilation was found in more than a third of the patients, 25% of whom did not show any symptom of SDB. Unexpectedly, hypoventilation was found to be more frequent with age and GH treatment. However, it is difficult to assess the part of GH therapy in the frequency of hypoventilation because of multifactorial bias.

**TABLE 1** Characteristics of children with Prader-Willi syndrome at the time of their first polysomnography.

	Total population n = 57	Age group		
		0–4 years (n = 25)	≥ 4–8 years (n = 18)	≥ 8–18 years (n = 14)
Median age, years (range)	4.8 (0.1–15.6)	1.6 (0.1–3.9)	6.3 (4.1–7.9)	10.9 (8.4–15.6)
Sex ratio M/F	2	3.2	0.6	6
Genetic mutation n (%)				
– Deletion in chromosome 15	24 (42)	12 (48)	8 (44)	4 (28.5)
– Uniparental disomy of chromosome 15	15 (26)	5 (20)	4 (22)	6 (43)
– Imprinting defect	1 (2)	0 (0)	1 (6)	0 (0)
– Unknown	17 (30)	8 (32)	5 (28)	4 (28.5)
Median BMI, Z-score (range)	0.9 (–2.6 to 10.4)	–0.5 (–2.6 to 9)	2.8 (–0.5 to 5.9)	1.5 (0.2–10.4)
Overweight, n (%)	3 (5)	2 (8)	1 (6)	0 (0)
Obese n (%)	21 (37)	3 (12)	12 (67)	6 (33)
Eating disorder n (%) (n = 56)	7 (13)	0 (0)	2 (11)	5 (28)
GH treatment, n (%)	34 (60)	8 (32)	13 (72)	13 (93)
Median age at GH initiation, years (range) (n = 56)	2 (0.4–13.9)	1.2 (0.4–2)	2.1 (0.6–7.5)	4.1 (1–13.9)
Tonsillar hypertrophy (Friedman score ≥ I), n (%) (n = 52)	24 (46)	8 (36) n = 22	11 (61)	5 (42) n = 12
History of ENT intervention (n = 56)				
– Orthodontic appliance	1 (2)	0 (0)	1 (6)	0 (0)
– Palate surgery	2 (4)	1 (4)	1 (6)	0 (0)
– Tonsillectomy	8 (14)	0 (0)	4 (22)	4 (29)
– Adenoidectomy	12 (21)	1 (4)	6 (33)	5 (36)
– Ear tube insertion	4 (7)	1 (4)	2 (11)	1 (7)
OSAS symptoms (n = 54)				
– Excessive sleepiness (n = 47)	14 (30)	3 (19) n = 16	3 (18) n = 17	8 (57)
– Snoring (n = 53)	31 (58)	13 (59) n = 22	9 (53) n = 17	9 (64)
– Apneas (n = 43)	10 (23)	5 (28) n = 18	3 (18) n = 17	2 (25) n = 8
– Tiredness (n = 46)	14 (30)	1 (7) n = 15	6 (35) n = 17	7 (50)
– Diurnal agitation (n = 43)	2 (5)	0 (0) n = 15	1 (6) n = 17	1 (9) n = 11
Respiratory support				
– HFNC	1 (2)	1 (4)	0 (0)	0 (0)
– CPAP	2 (4)	0 (0)	1 (6)	1 (7)
– NIV	3 (5)	3 (12)	0 (0)	0 (0)
Hypotonia (n = 30)	19 (63)	15 (79) n = 19	2 (40) n = 5	2 (33) n = 6
Cataplexy (n = 56)	4 (7)	0 (0) n = 24	2 (11)	2 (14)
Scoliosis (n = 56)	20 (34)	5 (17) n = 24	7 (39)	8 (57)
Hypothyroidism (n = 56)	9 (16)	1 (4)	7 (39)	1 (7)

Abbreviations: BMI, Body mass index; CPAP, continuous positive airway pressure; ENT, ear nose throat; F, female; GH, growth hormone; HFNC, high flow nasal cannula; M, male; NIV, noninvasive ventilation; OSAS, obstructive sleep apnea syndrome.

**TABLE 2** Sleep characteristics of children with Prader-Willi syndrome at the time of their first polysomnography.

	Total population n = 57	Age group			p-value
		0–4 years (n = 25)	≥ 4–8 years (n = 18)	≥ 8–18 years (n = 14)	
Median age, years (range)	4.8 (0.1–15.6)	1.6 (0.1–3.9)	6.3 (4.1–7.9)	10.9 (8.4–15.6)	
TST, minutes	514 (217–646)	517 (217–637)	534 (456–646)	502 (324–591)	0.245
Sleep efficacy, % (n = 56)	90 (71–98)	86 (71–98)	91 (77–96)	91 (74–95)	0.179
Sleep efficiency, % (n = 31)	85 (68–94)	n = 18 84 (68–92)	n = 7 89 (85–94)	n = 6 84 (71–90)	0.082
Arousal index, n/h	7.2 (0.5–65.4)	7.8 (0.6–65.4)	6.5 (0.5–23.7)	5.3 (2–15.2)	0.07
Respiratory arousal index, n/h	2 (0–43.9)	3.7 (0.1–43.9)	1.3 (0–18.3)	1.8 (0.2–5.8)	0.32
Proportion of sleep stage, % TST					
REM	21 (10–66)	24 (14–66)	20 (10–52)	18 (12–23)	0.007
NREM	79 (34–90)	76 (34–86)	80 (48–90)	82 (77–88)	0.007
NREM 1 (n = 56)	15 (2–41)	14 (2–32)	16 (6–35)	n = 13 14 (3–41)	0.38
NREM 2 (n = 56)	42 (11–66)	36 (11–57)	39 (16–55)	n = 13 49 (21–66)	0.003
NREM 3 (n = 56)	19 (0–38)	20 (0–38)	20 (0–27)	n = 13 18 (8–25)	0.27
Sleep stage latency, minutes					
REM latency (n = 56)	74 (0–244)	58 (0–171)	86 (11–244)	n = 13 89 (61–202)	0.007
NREM latency (n = 56)	15 (0–103)	19 (2–103)	16 (0–61)	n = 13 11 (5–25)	0.09
Respiratory indexes, n/h					
OAHl in TST	2.6 (0–74.1)	3.5 (1–74.1)	2.1 (0.1–69.7)	1.9 (0–6.3)	0.025
OAHl in REM (n = 54)	10 (0–109.2)	n = 22 12.2 (3.2–109.2)	8.9 (0.5–80.8)	7.3 (0–29.1)	0.117
OAHl in NREM (n = 51)	1.1 (0–82.7)	n = 22 1.3 (0–70.2)	n = 16 1 (0–82.7)	n = 13 0.3 (0–3.1)	0.09
CAI in TST	0.2 (0–5.9)	0.4 (0–4)	0.3 (0–5.9)	0.2 (0–1.5)	0.088
CAI in REM	0.5 (0–9.5)	0.6 (0–5.6)	0.7 (0–9.5)	0 (0–4.2)	0.35
CAI in NREM	0 (0–5.2)	0.1 (0–4.1)	0 (0–5.2)	0 (0–0.8)	0.11
Mean SpO <sub>2</sub>	95.6 (90.1–99)	96 (90.1–98.8)	95.5 (93–99)	95.6 (91.1–98)	0.85
SpO <sub>2</sub> < 90%, % TST	0.1 (0–22.2)	0.1 (0–22.2)	0.1 (0–8.8)	0.1 (0–22.1)	0.909
Mean pCO <sub>2</sub>	44 (36–50)	43 (36–50)	44 (41–49)	48 (44–49)	0.117
pCO <sub>2</sub> max	49 (38–69)	48 (38–62)	49 (41–69)	52 (45–61)	0.052
pCO <sub>2</sub> > 50 mmHg, % TST	0 (0–85.6)	0 (0–85.6)	0 (0–78)	2.2 (0–66.5)	0.149

Note. All data are expressed as median (range). A p-value < .05 was initially considered statistically significant. Then, p-values were adjusted for multiple comparisons using Bonferroni correction.

Abbreviations: Central apnea index (CAI), non-rapid eye movement (NREM), non-rapid eye movement stage 1 (NREM1), non-rapid eye movement stage 2 (NREM2), non-rapid eye movement stage 3 (NREM3), obstructive apnea-hypopnea index (OAHl), partial pressure of carbon dioxide (pCO<sub>2</sub>), pulse oxygen saturation (SpO<sub>2</sub>), rapid eye movement (REM), total sleep time (TST).

**TABLE 3** Characteristics of children with Prader-Willi syndrome according to the severity of OSAS.

	No/mild OSAS (n = 38)	Moderate-to-severe OSAS (n = 19)	Total (n = 57)	p-value
Sex male, n (%)	26 (68.4)	12 (63.2)	38 (66.7)	.769
Median age (range)	5.1 (0.1–15.6)	4.1 (0.2–14.1)	4.8 (0.1–15.6)	.286
Age group, n (%)				.543
– 0–4 years	16 (42.1)	9 (47.4)	25 (43.9)	
– ≥4–8 years	11 (28.9)	7 (36.8)	18 (31.6)	
– ≥8–18 years	11 (28.9)	3 (15.8)	14 (24.6)	
BMI Z-score	0.9 (-1.5 to 10.4)	0.9 (-2.6 to 8.4)	0.9 (-2.6 to 10.4)	.827
Obese, n (%)	14 (37)	7 (37)	21 (37)	
OSAS symptoms, n (%)	21 (55)	15 (79)	36 (63)	
OAHl	1.9 (0–4.2)	9.9 (5–74.1)	2.6 (0–74.1)	<.001
CAI	0.2 (0–5.9)	0.1 (0–4)	0.2 (0–5.9)	.514
pCO <sub>2</sub> > 50 mmHg, % TST	0 (0–85.6)	0.2 (0–60)	0 (0–85.6)	.118
pCO <sub>2</sub> max	n = 36/38 49 (38–69)	51 (43–62)	n = 55/57 49 (38–69)	.072
Hypoventilation, <sup>a</sup> n (%)	11 (28.9)	9 (47.4)	20 (35.1)	.280
CSAS, n (%)	2 (5.3)	0 (0)	2 (3.5)	.548
GH treatment, n (%)	25 (65.8)	9 (47.4)	34 (59.6)	.253

<sup>a</sup>Hypoventilation was defined as transcutaneous carbon dioxide pressure (PtcCO<sub>2</sub>) or end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) ≥ 50 mmHg during ≥2% of TST or more than five consecutive minutes.

Note. Data are expressed as n (%) or median (range). A p-value < .05 was initially considered statistically significant. Then, p-values were adjusted for multiple comparisons using Bonferroni correction.

Abbreviations: Body mass index (BMI), central apnea index (CAI), central sleep apnea syndrome (CSAS), growth hormone (GH), obstructive sleep apnea syndrome (OSAS), obstructive apnea-hypopnea index (OAHl), partial pressure of carbon dioxide (pCO<sub>2</sub>).

## 4.1 | OSAS

OSAS was not found to be significantly more frequent with age, GH treatment, BMI Z-score, hypoventilation, nor CSAS in children with PWS, consistent with previous studies. For instance, in a study of 88 patients with PWS, no correlation was found between OAHl, age and BMI Z-score.<sup>6</sup> Moreover, any significant change in SDB (OSAS or CSAS) after 2 years of GH therapy was found.<sup>28</sup> Furthermore, no significant differences were previously found in OAHl, CAI, oxygen desaturation index, and SpO<sub>2</sub> according to the age at treatment initiation.<sup>29</sup> This indicates that OSAS in children with PWS develops independently of age at GH treatment initiation, which is reassuring since GH treatment is now usually initiated between 3 and 12 months of age.<sup>2</sup> The literature concerning the evolution of SDB with age in children with PWS shows that CSAS predominates within the first 2 years of life while OSAS predominates later on.<sup>30</sup> These findings were not observed herein, likely due to the small number of infants included in the cohort, and thus the rare cases of CSAS recorded.

## 4.2 | Hypoventilation

The present study found hypoventilation in more than a third of children with PWS when using the criteria of PtcCO<sub>2</sub> or ETCO<sub>2</sub> ≥ 50 mmHg during ≥2% of TST or more than five consecutive minutes. This result is the first, to our knowledge, to be reported using this definition. The hypoventilation frequency observed using the AASM definition however,<sup>15</sup> was slightly higher than the 12.5% reported in a cohort of younger children (median age 2.3 years).<sup>11</sup> To date, the change in hypoventilation frequency according to age in children with PWS is not well documented. In a rather small cohort of 17 children with PWS (median age 11.6 years), no difference in age between patients with or without hypoventilation was reported.<sup>17</sup> This differs from the observation herein that hypoventilation was found to be more frequent with age. More importantly, the latter result is not in line with our initial hypothesis, underlining the fact that the incomplete maturation of the central control of breathing cannot solely explain the appearance of hypoventilation in these children. The mechanisms causing a possible worsening of hypoventilation



**TABLE 4** Characteristics of children with Prader-Willi syndrome according to the presence of hypoventilation.<sup>a</sup>

	Hypoventilation <sup>a</sup> group (n = 20)	No hypoventilation <sup>a</sup> group (n = 37)	Total (n = 57)	p-value
Sex, male, n (%)	12 (60)	26 (70.3)	38 (66.7)	.558
Median age (range)	7.6 (0.2–14.8)	3.4 (0.1–15.6)	4.8 (0.1–15.6)	.006
Age group, n (%)				.092
– 0–4 years	5 (25)	20 (54.1)	25 (43.9)	
– ≥4–8 years	6 (30)	12 (32.4)	18 (31.6)	
– ≥8–18 years	9 (45)	5 (13.5)	14 (24.6)	
BMI Z-score	0.9 (-1 to 8.4)	0.8 (-2.6 to 10.4)	0.9 (-2.6 to 10.4)	.380
Obese, n (%)	8 (40)	13 (35)	21 (37)	
OAH1	3.3 (0–74.1)	2.2 (0–56.4)	2.6 (0–74.1)	.452
CAI	0.2 (0–5.9)	0.3 (0–2.5)	0.2 (0–5.9)	.659
pCO <sub>2</sub> > 50 mmHg, % TST	14 (1–85.6)	0 (0–0.5)	0 (0–85.6)	<.001
pCO <sub>2</sub> max	n = 18 54 (51–69)	47 (38–55)	n = 55 49 (38–69)	<.001
OSAS symptoms, n (%)	15 (75)	21 (57)	36 (63)	
OSAS, n (%)				.235
– Severe	4 (20)	5 (13.5)	9 (15.8)	
– Moderate	5 (25)	5 (13.5)	10 (17.5)	
– Mild	5 (25)	19 (51.4)	24 (42.1)	
– No	6 (30)	8 (21.6)	14 (24.6)	
CSAS, n (%)	1 (5)	1 (2.7)	2 (3.5)	1.000
GH treatment, n (%)	16 (80)	18 (48.6)	34 (59.6)	.026

<sup>a</sup>Hypoventilation was defined as transcutaneous carbon dioxide pressure (PtcCO<sub>2</sub>) or end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) ≥ 50 mmHg during ≥2% of TST or more than five consecutive minutes.

Note. Data are expressed as n (%) or median (range). A p-value < .05 was initially considered statistically significant. Then, p-values were adjusted for multiple comparisons using Bonferroni correction.

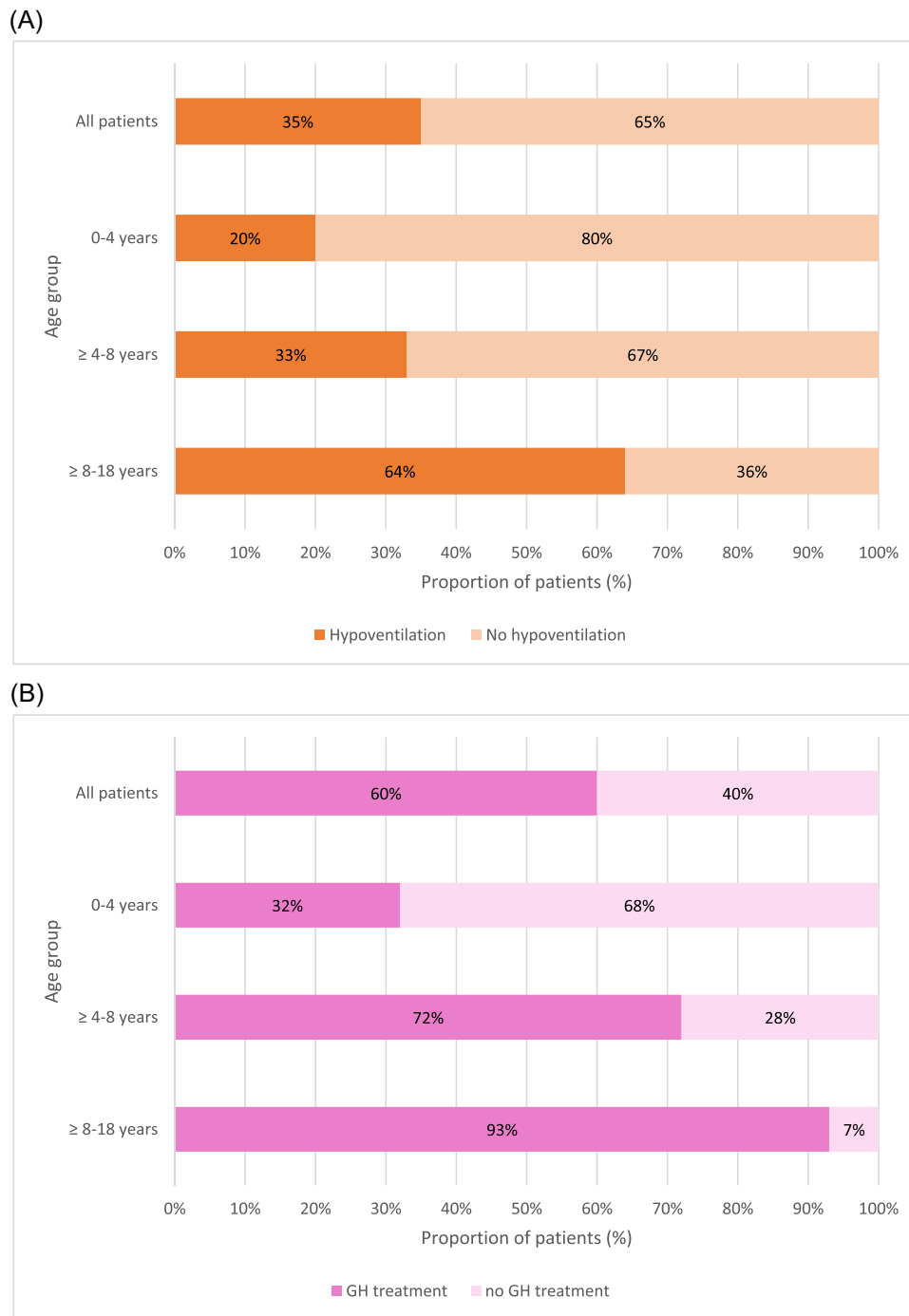
Abbreviations: Body mass index (BMI), central apnea index (CAI), central sleep apnea syndrome (CSAS), growth hormone (GH), obstructive sleep apnea syndrome (OSAS), obstructive apnea-hypopnea index (OAH1), partial pressure of carbon dioxide (pCO<sub>2</sub>).

with age thus remain unclear and require further investigation. There are strong arguments pointing towards the fact that the central control of breathing remains abnormal during adolescence and adulthood in PWS,<sup>31</sup> possibly due to a low sensitivity of central and peripheral chemoreceptors and related to a lack of neccin.<sup>32,33</sup>

In the present cohort, hypoventilation was also found to be more frequent in patients under GH treatment, also contradicting our initial hypothesis. Although the first months after GH initiation have been shown to represent a vulnerable time for the development of SDB<sup>20,22,34</sup> because of fluid retention caused by treatment,<sup>35</sup> data regarding GH impact on respiratory function after this initial period are scarce. In a randomized controlled study on children with PWS, an increase in percentage vital capacity and forced expiratory flow rate after GH intervention was demonstrated, highlighting the impact

of GH on muscle tonicity. The number and duration of hypopnea and apnea also tended to improve.<sup>19</sup> Since the median interval between the start of GH treatment and PSG recording herein was more than 3 years, it is unlikely that the at-risk fluid retention period would explain the higher frequency of hypoventilation observed under treatment; the beneficial effect of GH on muscle tonicity would be expected at that time. Given the retrospective design of the study, the link between hypoventilation and GH cannot be further established herein. It is very likely that age represents a confounding factor since the older the children are, the more likely they are to be under GH treatment.

Herein, the frequency of hypoventilation was not significantly different according to OAH1 nor CAI, suggesting that hypoventilation should be searched for independently of OSAS and CSAS, by a simple



**FIGURE 2** Hypoventilation (A) and GH treatment (B) in children with PWS at the time of their first PSG.

PtcCO<sub>2</sub> recording at home. It also implies that a PSG must always include a pCO<sub>2</sub> measure. Furthermore, hypoventilation was not found to be more frequent in patients with a higher BMI Z-score, a result that could be explained by the low prevalence of obesity in the present cohort. The distribution of obesity according to age was also surprising as the largest proportion of children with obesity was found in the 4–8 years group and not the older children. It is known that if PWS is not diagnosed during the neonatal period, obesity

tends to appear after the age of 3 and becomes more severe without GH.<sup>1</sup> We can thus hypothesize that the children from the present cohort benefited from good dietary follow-up, possibly explaining the reduced prevalence of obesity between the ages of 8 and 18.

To diagnose SDB in the context of PWS, French and international guidelines recommend to systematically perform a sleep evaluation before initiating GH treatment and to repeat it 3–6 months later, as well as once during late childhood/adolescence, and

if SDB symptoms are present.<sup>1,3</sup> The majority of studies reporting sleep monitoring in patients with PWS have focused on the GH initiation period, probably because of the fear of sudden death related to GH,<sup>21,22</sup> even if recent findings are reassuring concerning its use.<sup>20,36</sup> In view of the present results, which report the presence of hypoventilation on PSG at all ages, and even more so in older children, a vigilant and repeated monitoring of these patients during childhood and adolescence appears necessary. Moreover, given the relatively large proportion of asymptomatic patients in OSAS and hypoventilation groups herein, this monitoring should be performed regardless of the presence of SDB symptoms. The absence of SDB symptoms in patients with PWS who presented with OSAS or hypoventilation on PSG has previously been reported.<sup>17,37</sup> It thus appears primordial to include oximetry-capnography measurement in the follow-up of children with PWS. The latter however, should always be interpreted in accordance with SDB symptoms before considering other sleep recordings and/or implementing NIV.

### 4.3 | Study limitations

This study does have certain limitations, the first being its single-center and retrospective design preventing the longitudinal follow-up of a larger number of children with PWS. Moreover, the inclusion of children based on the requirement of having undergone a PSG with PtcCO<sub>2</sub> or ETCO<sub>2</sub> in room air induced a selection bias, preventing the generalizability of the present results to a larger and more severe population.

Furthermore, the retrospective data collection was performed over a period of transition in GH management, leading to a heterogeneity in terms of GH treatment initiation. This implies a heterogeneity in the ages at which the PSG were performed, possibly overestimating the hypoventilation frequency in older children, due to children having received GH treatment later than 2 years of age before the international guidelines were followed. The relationship between hypoventilation and GH also remains unclear because the number of patients in the cohort was insufficient to distinguish the respective effect of age and GH on hypoventilation.

Because of the relatively high number of comparisons conducted, Bonferroni correction was applied, resulting in no statistically significant differences after its application. Since the Bonferroni method represents a conservative approach, in our opinion, the impact of age on hypoventilation should nevertheless be further investigated.

## 5 | CONCLUSION

The present study found a high frequency of hypoventilation in a pediatric population of PWS. Although this observation concerned children of all ages, it was more frequent in the older ones, and in those under GH treatment. A regular screening by oximetry-capnography appears to be indicated in all children with PWS,

regardless of the presence of SDB symptoms or obesity. The longitudinal follow-up of a multi-center cohort is needed to better assess the impact of age and GH treatment on hypoventilation.

### AUTHOR CONTRIBUTIONS

**Catherine Chen:** Conceptualization; Methodology; Investigation; Data curation; Writing - original draft; Writing - review & editing; Project administration; Visualization; Formal analysis. **Iulia Ioan:** Methodology; Supervision; Validation; Writing - review & editing; Formal analysis. **Marine Thieux:** Writing - review & editing; Supervision; Validation; Formal analysis; Methodology. **Marc Nicolino:** Supervision; Validation; Data curation; Writing - review & editing. **Patricia Franco:** Conceptualization; Investigation; Formal analysis; Methodology; Data curation; Validation; Supervision; Writing - review & editing. **Laurianne Coutier:** Conceptualization; Investigation; Formal analysis; Methodology; Data curation; Validation; Supervision; Writing - review & editing.

### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

### DATA AVAILABILITY STATEMENT

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

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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