

Effects of Growth Hormone Therapy on Sleep-Disordered Breathing and Metabolic Parameters in Patients with Prader–Willi Syndrome According to Genetic Subtype

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Abstract

Objective

Prader–Willi syndrome (PWS) is frequently associated with sleep-disordered breathing, and the respiratory effects of recombinant human growth hormone (rhGH) therapy are debated. This study assessed the anthropometric, metabolic, and polysomnographic outcomes of rhGH therapy in children with PWS and investigated whether these outcomes varied according to molecular subtype.

Methods

This retrospective cohort study included 66 children with genetically confirmed PWS who received rhGH therapy for a minimum of 12 months. Patients were classified as having either a paternal 15q11–q13 deletion or maternal uniparental disomy (mUPD); deletion cases were further categorized as type I, type II, or atypical. Anthropometric and metabolic parameters were measured at baseline and after 12 months. Polysomnography was conducted prior to treatment and repeated after 3–6 months. Longitudinal polysomnographic analyses included 39 patients with a baseline apnea–hypopnea index (AHI) less than 5 events per hour who did not require additional respiratory intervention.

Results

The median age at initiation of treatment was 3.53 years, with 32 patients (49%) identified as female. Forty-five patients (68.3%) exhibited a paternal deletion. After 12 months, the height standard deviation score increased significantly ($P < 0.001$), while weight and body mass index standard deviation scores did not change significantly. Glucose and lipid parameters remained stable. In the longitudinal polysomnographic analysis, both total AHI and obstructive AHI increased significantly during the first 3–6 months of treatment, primarily among patients with deletions rather than those with mUPD. Within the deletion group, patients with type II deletions demonstrated significant increases in both total and obstructive AHI, whereas no significant longitudinal deterioration was observed in patients with type I deletions.

Conclusion

After one year of rhGH therapy, linear growth improved without adversely affecting short-term metabolic outcomes in children with PWS. However, early obstructive respiratory events increased, particularly among patients with type II deletions. These findings indicate that molecular subtype may influence the respiratory response to rhGH and support the need for close polysomnographic monitoring during the initial six months of treatment.

What is Known

- Growth hormone therapy improves growth and body composition in children with Prader–Willi syndrome.
- Sleep-disordered breathing may worsen initially during rhGH therapy, necessitating polysomnography.

What is New

- One-year growth hormone therapy significantly improved height SDS without increasing BMI-SDS.
- Early changes in total and obstructive apnea–hypopnea indices varied by deletion subtype, with significant increases in patients with type 2 deletions.

Introduction

Prader–Willi syndrome (PWS) is a rare genetic disorder caused by abnormal imprinting, affecting approximately 1 in 20,000 to 30,000 live births. It is marked by hypothalamic dysfunction with hormone deficiencies, abnormal body composition, developmental delays, and hyperphagia, which can lead to obesity (1). It results from the absence of expression of paternally inherited genes within chromosome 15q11–q13, most commonly caused by paternal deletions (~65–70%) or maternal uniparental disomy (mUPD) (~20–30%). Imprinting defects account for fewer than 5% of cases (2). There are 2 types of 15q11–q13 deletions: Type I, which involves the proximal 15q breakpoint (BP1) and a distal 15q breakpoint (BP3), or Type II, which involves a smaller deletion with a second proximal breakpoint (BP2) and a distal BP3 (3). These molecular subtypes result in the same clinical diagnosis; However, some studies indicate they are linked to variations in behavioral, cognitive, and metabolic characteristics (4)

Recombinant human growth hormone (rhGH) therapy is the current standard treatment for children with PWS. It promotes increased linear growth and lean muscle mass, reduces total body fat, and can influence cognitive performance (5). Although its efficacy and overall safety have been well established, PWS is a rare disorder and most available studies have been limited by relatively small and genetically heterogeneous cohorts. Therefore, findings from relatively large, well-characterized single-center cohorts remain valuable to further characterize the anthropometric, metabolic, and respiratory effects of rhGH therapy (6).

Children with PWS also frequently experience sleep-related breathing disorders (SRDB), including central sleep apnea (CSA), obstructive sleep apnea (OSA), and nocturnal hypoventilation (7, 8). Consequently, polysomnography (PSG) is advised both before starting and after beginning rhGH therapy. In the literature, Conflicting data exist regarding the effect of GH treatment on polysomnography (PSG) results in PWS. Some evidence indicates that GH therapy may temporarily worsen SRDB (9). It is proposed that GH contributes to adenotonsillar hypertrophy, increased fluid retention, and soft-tissue edema factors driven by abnormal renin activity—that collectively lead to upper airway obstruction (10, 11, 12). However,

whether the respiratory effects of rhGH differ according to the underlying molecular subtype has not been systematically investigated.

Therefore, we aimed to evaluate the anthropometric, metabolic, and polysomnographic effects of one year of rhGH therapy in a relatively large, single-center cohort of genetically well-characterized children with PWS. In addition, we investigated whether treatment responses and polysomnographic outcomes, differed according to the underlying molecular subtype.

Materials and methods

Patients and Study Design

This retrospective cohort study reviewed the medical records of 149 genetically confirmed patients with PWS who were evaluated at the Pediatric Endocrinology Department of Gülhane Training and Research Hospital from January 2017 to December 2025. Among these, 66 patients who had received rhGH therapy for at least 12 months and had complete baseline and follow-up clinical data were included in the study. All treatments were performed in accordance with the latest international consensus guidelines for the diagnosis and management of PWS (13). Patients were categorized according to molecular subtype (deletion and mUPD), and the deletion group was further classified into Type I and Type II deletions. Data on anthropometric, biochemical, and metabolic parameters were recorded before the start of rhGH treatment, 3–6 months after treatment initiation, and again at follow-up visits 12 months later. All patients underwent baseline polysomnographic (PSG) evaluation before initiation of rhGH therapy. For longitudinal PSG analyses, only patients with a baseline apnea–hypopnea index (AHI) < 5 events/hour who did not require additional medical or surgical intervention during follow-up and who underwent repeat PSG were included. Consequently, longitudinal PSG analyses were performed in 39 patients to evaluate changes in sleep parameters following rhGH therapy.

Study design

Genetic analysis

Peripheral blood samples for genotypic subtyping and diagnosis of PWS were obtained from 149 patients. Genomic DNA was extracted with the PureLink Genomic DNA Mini Kit (Invitrogen, Carlsbad, California, USA) according to the manufacturer's guidelines. To confirm PWS diagnosis, DNA methylation analysis was used as the initial diagnostic step. The methylation status of the 15q11-q13 region was assessed via methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) (14). For PWS diagnosis, we employed MS-MLPA ME028 kits from MRC-Holland (Amsterdam, The Netherlands), adhering to their instructions. The fragments were separated using the 3130xl Genetic Analyzer (Applied Biosystems, Tokyo, Japan) and analyzed with Coffalyser software (MRC-Holland). If methylation patterns suggested PWS, additional molecular tests were conducted to identify the exact genetic cause. These included high-resolution karyotyping, FISH (Fluorescence In Situ Hybridization), single nucleotide

polymorphism (SNP) microarray, to perform deletion and UPD subtyping. SNP microarray analysis was conducted with the Infinium Global Screening Array and Cytogenetics-24 v1.0 BeadChip following the manufacturer's instructions (Illumina, San Diego, California, USA). The Infinium Global Screening Array contains approximately 7 million genome-wide probes and is utilized for analyzing chromosome structure, copy number variations, and segregation. Image retrieval was conducted with an iScan System (Illumina), and molecular karyotype analysis used GenomeStudio software (Illumina). For patients without deletions, DNA polymorphism analysis was conducted to differentiate UPD from imprinting defects. Imprinting defects were diagnosed after mUPD was ruled out.

Growth Hormone Therapy

Before initiating rhGH therapy, patients underwent anthropometric measurements, biochemical tests, and polysomnography to screen for SRDB. The treatment began at 0.5 mg/m²/day and was increased to 1.0 mg/m²/day based on clinical response and serum IGF-1 levels. Serum IGF-1 was checked every three months, with doses adjusted to keep IGF-1 levels below + 2 SDS.

Anthropometric Assessment

Anthropometric measurements were obtained every three months during follow-up by trained healthcare professionals using standardized techniques. In children over 2 years old, body weight was recorded using a calibrated digital scale, while standing height was measured with a Harpenden stadiometer (Holtain Ltd., Crosswell, UK). Recumbent length was measured in children younger than 2 years. Body mass index (BMI) was determined by dividing weight by height squared (kg/m²). Height SDS, weight SDS, and BMI SDS were calculated using the Turkish national reference standards (Neyzi et al.) with Endo-C software (15).

Biochemical Assessment

Venous blood samples were obtained after an overnight fast and analyzed at Gülhane Training and Research Hospital's Biochemistry Laboratory. Tests included fasting plasma glucose, fasting insulin, HbA1c, total cholesterol, triglycerides, HDL-C, LDL-C, and serum IGF-1. Insulin resistance was assessed using the HOMA-IR formula: fasting insulin (μU/mL) × fasting glucose (mg/dL) / 405. Serum IGF-1 levels were converted to age- and sex-specific SDS values using validated reference data.

Polysomnographic Assessment

Polysomnographic studies were conducted to evaluate SRDB. PSG recordings were performed in the Sleep Laboratory of Gülhane Training and Research Hospital. PSG recordings were performed using the Compumedics Greal 4K amplifier system in accordance with standard montage guidelines. Recordings included electroencephalography [EEG; F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1], electrooculography (EOG), chin electromyography (EMG), anterior tibial EMG, electrocardiography (ECG), oronasal thermistor, nasal airflow cannula, thoracic and abdominal respiratory effort bands, pulse oximetry, and body position channels.

Respiratory events were scored following the pediatric criteria in the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events (Version 3). Apneas were detected when airflow, measured via the oronasal thermal sensor, decreased by at least 90% from baseline for at least two breaths. These apneas were classified as obstructive, central, or mixed depending on whether inspiratory effort was present or absent. A central apnea was scored when the reduction in airflow was accompanied by absent inspiratory effort throughout the event and either persisted for at least 20 seconds or lasted for at least two missed breaths in association with an oxygen desaturation of $\geq 3\%$, an EEG arousal, or bradycardia in infants. Hypopneas were identified when the nasal pressure signal dropped by at least 30% from baseline for at least two breaths and was linked to either a minimum 3% oxygen desaturation or an EEG arousal.

The apnea–hypopnea index (AHI) was determined by dividing the total number of apneas—covering obstructive, central, and mixed types—and hypopneas by total sleep time in hours, resulting in a value expressed as events per hour of sleep. Sleep apnea–hypopnea severity was categorized based on the apnea–hypopnea index (AHI): normal (< 1 event/h), mild (1 to < 5 events/h), moderate (5 to < 10 events/h), and severe (≥ 10 events/h). These classifications align with standard pediatric sleep medicine criteria. An AHI greater than 1 event per hour was deemed sufficient for diagnosing sleep apnea (16). Mild sleep apnea was characterized by an AHI of 1–5 events per hour, and patients with this level of severity typically began GH therapy (17). Patients with an AHI > 5 events/hour were evaluated by pediatric pulmonology and otolaryngology specialists, and GH therapy was initiated after appropriate medical and/or surgical treatment. Follow-up polysomnography (PSG) studies were repeated within 3–6 months.

Ethics

The Institutional Ethics Committee of Gülhane Training and Research Hospital approved the study protocol. The research was carried out following the Declaration of Helsinki. Since it was a retrospective study, the ethics committee waived the need for written informed consent.

Statistical Analyses

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed via the Shapiro–Wilk test, complemented by visual inspection of histograms and Q–Q plots. Data are presented as mean $\pm$ SD for normally distributed variables and as median with interquartile range (25th–75th percentile) for non-normal data. Categorical variables are shown as frequencies and percentages. Comparisons between independent groups employed the Student's t test or the Mann–Whitney U test, depending on data distribution. Within-group comparisons utilized either the paired Student's t test or the Wilcoxon signed-rank test. Categorical variable comparisons were made using the χ^2 test or Fisher's exact test as suitable. All tests were two-sided, with a significance threshold set at $P < 0.05$.

Results

Patient characteristics

The median age at treatment initiation was 3.53 (2.00–6.45) years, and 32 patients (49%) were female. A paternal 15q11–q13 deletion was identified in 45 patients (68.3%), whereas 21 patients (31.7%) had mUPD. Among patients with deletions, 16 (35.5%) had type I deletions, 19 (42.3%) had type II deletions, and 10 (22.2%) had atypical deletions (Table 1).

Table 1
Baseline demographic and clinical characteristics of the study population

Characteristic	Overall (n = 66)
Age at GH initiation, years	3.53 (2.00–6.45)
Female sex, n (%)	32 (49.0)
Male sex, n (%)	34 (51.0)
Deletion, n (%)	45 (68.3)
• Type deletion, n (%)	16 (35.5)
• Type 2 deletion, n (%)	19 (42.3)
• Atypical deletion, n (%)	10 (22.2)
Maternal uniparental disomy, n (%)	21 (31.7)
<i>Note.</i> Values are presented as median (25–75 p) or n (%). Atypical deletions were included in the overall deletion group but excluded from deletion subtype analyses.	

Growth and metabolic outcomes

After one year of rhGH therapy, height SDS increased significantly compared with baseline ($p < 0.001$). However, changes in weight SDS and BMI SDS were not statistically significant ($p = 0.070$ and $p = 0.751$, respectively).

Metabolic parameters, including fasting glucose, HbA1c, triglycerides, LDL cholesterol, HDL cholesterol, total cholesterol, and IGF-1 SDS, remained unchanged after one year of treatment (all $p > 0.05$). Although HOMA-IR values increased during follow-up, the change did not reach statistical significance ($p = 0.054$). Detailed anthropometric and biochemical outcomes are summarized in Table 2.

Table 2

Changes in anthropometric and metabolic parameters after one year of recombinant human growth hormone therapy

Variable	Baseline (n = 66)	12 months (n = 66)	P value
Height SDS	-1.75 ± 1.18	-0.98 ± 1.31	< 0.001
Weight SDS	-0.27 ± 2.01	0.38 ± 1.93	0.070
BMI SDS	1.26 ± 1.66	1.07 ± 1.78	0.751
Fasting glucose (mg/dL)	78.1 ± 12.8	79.8 ± 15.2	0.210
HOMA-IR	1.17 (0.55–1.78)	1.36 (0.81–2.38)	0.054
HbA1c (%)	5.34 ± 0.41	5.41 ± 0.37	0.572
Triglycerides (mg/dL)	78.0 ± 33.1	68.4 ± 21.3	0.070
LDL-C (mg/dL)	105.7 ± 33.2	106.0 ± 30.5	0.860
HDL-C (mg/dL)	50.8 ± 14.8	60.7 ± 10.7	0.086
Total cholesterol (mg/dL)	169.4 ± 39.9	176.0 ± 37.4	0.253
IGF-1 SDS	0.44 ± 2.37	1.10 ± 1.69	0.158
Continuous variables are presented as mean ± standard deviation (SD) or median (25–75 P), as appropriate. Paired comparisons were performed using the paired <i>t</i> test for normally distributed variables and the Wilcoxon signed-rank test for non-normally distributed variables			

Outcomes according to genetic subtype

Baseline age and sex distributions were comparable between patients with deletions and those with mUPD. After one year of rhGH therapy, no significant between-group differences were observed in changes in height SDS, weight SDS, or biochemical parameters. However, at the end of follow-up, BMI SDS was significantly higher in patients with mUPD than in those with deletions (1.65 ± 1.12 vs. 0.65 ± 1.83 , $p = 0.047$). In the first year of GH treatment, a significant increase in height SDS was observed in both genetic subgroups (mUPD [-1.80 ± 0.96 vs -0.88 ± 0.95], $p < 0.001$; deletion [-1.61 ± 1.28 vs -0.98 ± 1.20], $p = 0.023$). No significant changes were observed in BMI SDS or metabolic variables in either subgroup.

Among patients with deletions, baseline anthropometric characteristics did not differ between the type I and type II deletion subgroups. Height SDS increased significantly after one year of treatment in the type I deletion group (1.08 ± 1.60 vs. 0.42 ± 1.20 , $p = 0.037$), whereas HDL cholesterol increased significantly in the type II deletion group (50.00 ± 16.42 vs. 57.66 ± 11.53 , $p = 0.032$). No other anthropometric or biochemical variables changed significantly during follow-up.

Polysomnographic outcomes

Overall, 39 patients (59%) had an AHI < 5 events/h, including 5 (7.5%) with an AHI < 1 event/h, whereas 27 patients (41%) had an AHI ≥ 5 events/h. The median AHI was 4.20 (2.50–8.50) events/h.

Among patients with a baseline AHI < 5 events/hour, total AHI increased significantly from baseline to the 3-6-month assessment (2.66 [2.10–3.80] vs. 2.80 [2.00–11.70] events/hour, $p = 0.011$). Obstructive AHI also increased significantly, whereas central AHI and ODI remained unchanged. In patients with baseline and 3-6-month AHI values < 5 events/h, total AHI did not differ significantly from baseline at the 12-month evaluation ($p = 0.609$).

Baseline AHI values were similar between the deletion and mUPD groups (Table 3). Analysis by deletion subtype showed that baseline obstructive AHI was significantly higher in patients with type I deletions than in those with type II deletions (1.47 ± 0.54 vs. 0.26 ± 0.20 , $p = 0.001$). In the deletion subgroup, total AHI increased significantly during the first 3–6 months of rhGH therapy ($p = 0.021$), whereas no significant change was observed in the mUPD subgroup ($p = 0.172$) (Table 4).

Table 3
Baseline polysomnographic findings according to genetic subtype

Variable	Overall (n = 66)	Deletion (n = 45)	mUPD (n = 21)	P value
Total AHI	4.20 (2.50–8.50)	3.80 (2.55–7.15)	3.90 (2.40–9.40)	0.810
Obstructive AHI	1.32 (0.48–5.86)	1.18 (0.46–6.21)	1.57 (0.54–2.65)	0.729
Central AHI	2.44 (0.62–4.67)	2.25 (0.68–4.34)	2.99 (0.82–4.00)	0.715
ODI	4 (1.35–10.2)	5.05 (2.10–10.10)	3.30 (1.40–10.30)	0.631
Note. AHI, apnea–hypopnea index; ODI, oxygen desaturation index; mUPD, maternal uniparental disomy.				
Values are presented as median ((25–75 P), or number (%), as appropriate. Comparisons between deletion and maternal uniparental disomy (mUPD) groups were performed using the Mann–Whitney <i>U</i> test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables.				

Table 4

Longitudinal polysomnographic changes after recombinant human growth hormone therapy in patients with baseline AHI < 5 events/hour

Variable	Baseline	3–6 months	P value
Total AHI (n = 39)	2.66 (2.10–3.80)	2.80 (2.00–11.70)	0.011
Obstructive AHI	0.59 (0.26–1.57)	2.06 (0.73–4.71)	0.013
Central AHI	2.44 (0.62–4.67)	1.62 (0.34–3.23)	0.141
ODI	4.00 (1.30–10.30)	4.20 (2.40–9.45)	0.556
mUDP (n = 13)			
Total AHI	2.55(2.40–3.70)	2.80(2.00-12.1)	0.172
Obstructive AHI	1.37 (0.54–1.57)	2.44(0.43–9.37)	0.263
Central AHI	1.10 (0.43–3.12)	1.13(0.0-2.08)	1.000
ODI	1.60(0.70–3.30)	2.50(1.45–3.80)	0.278
Deletion (n = 26)			
Total AHI	2.80 (2.10–3.95)	5.20 (2.10-12.85)	0.021
Obstructive AHI	0.59 (0.22–1.43)	2.15 (0.17–8.05)	0.004
Central AHI	2.07 (0.50–3.11)	1.38 (0.15–3.03)	0.124
ODI	2.45(0.85–6.92)	3.35 (2.17–6.82)	0.472
Values are presented as median (25–75 p). Baseline and follow-up polysomnographic parameters were compared using the Wilcoxon signed-rank test.			

In patients with baseline and 3-6-month AHI values < 5 events/h, AHI did not differ significantly from baseline at the 12-month evaluation in the deletion subgroup ($p = 0.168$).

During the first 3–6 months of rhGH therapy, patients with type II deletions showed significant increases in both total AHI ($p = 0.035$) and obstructive AHI, whereas no significant longitudinal changes were observed in patients with type I deletions (Table 5).

Table 5

Longitudinal polysomnographic changes according to deletion subtype in patients with baseline AHI < 5 events/hour

Variable	Type 1 deletion (n = 12)			Type 2 deletion (n = 10)		
	Baseline	3–6 months	P value	Baseline	3–6 months	P value
Total AHI (events/h)	3.30 (2.35–3.80)	2.60 (2.10–11.15)	0.154	2.00 (0.35–4.20)	7.15 (3.00–28.00)	0.035
Obstructive AHI (events/h)	1.59 (0.94–1.99)	2.71 (0.62–7.19)	0.093	0.18 (0.08–0.47)	2.15 (0.85–20.43)	0.036
Central AHI (events/h)	2.07 (1.50–2.40)	1.14 (0.24–2.44)	0.161	2.36 (0.24–3.65)	1.30 (0.07–3.38)	0.674
Values are presented as median (25-75p). Baseline and 3–6-month polysomnographic parameters were compared within each deletion subtype using the Wilcoxon signed-rank test. Analyses were restricted to patients with genetically confirmed type 1 or type 2 deletions who had complete paired polysomnographic evaluations at both time points.						

Discussion

The primary finding of this study was the early deterioration of obstructive sleep apnea in patients with PWS, which appeared even at the initial stages of rhGH therapy, despite no negative impact on metabolic parameters like lipid profile and carbohydrate metabolism. This deterioration in sleep disordered breathing was more pronounced among patients with deletions when subgroups were analyzed by genetic subtype. Notably, within the deletion subgroup, patients with the smaller Type II deletion exhibited a more marked increase in both the development and severity of apnea following growth hormone therapy. To our knowledge, this is among the first studies to evaluate longitudinal polysomnographic outcomes after rhGH therapy by molecular subtype.

The positive impacts of rhGH on linear growth, body composition, muscle strength, and psychomotor development in children with PWS are well established and form the basis of current treatment recommendations (18, 19). In prepubertal children with PWS, rhGH therapy has been linked to increased insulin resistance, with some cases of impaired glucose tolerance emerging after roughly two years of treatment (20). Analysis of data from the KIGS study revealed that hyperglycemia and type 2 diabetes mellitus (T2DM) were infrequent among those receiving rhGH treatment for PWS (21). In contrast, other longitudinal studies and recent systematic reviews have suggested that abnormalities in glucose homeostasis are more strongly related to age, obesity, and the natural course of PWS than to rhGH treatment itself (22, 23). As aligned with these reports, our study found no adverse effects on glucose metabolism or lipid profile after a year of growth hormone therapy. (24). We suggest that short-term rhGH therapy is metabolically safe when patients are appropriately monitored.

Treatment with rhGH has been shown to enhance respiratory function in some PWS individuals, mainly by improving body composition and muscle strength, potentially reducing obstructive breathing issues. Nonetheless, the evidence remains inconclusive (23, 25). Some studies indicate that the early phase of rhGH therapy may worsen SRBD (26, 27). This may be attributed to rhGH-induced increases in IGF1, which may contribute to adenotonsillar hypertrophy (26). Regardless of rhGH treatment, SRBD, including both CSA and OSA, is well documented to occur frequently in individuals with PWS. OSA in patients with PWS can be attributed to various factors, including obesity, narrowing of the upper airways, adenoid and/or tonsillar hypertrophy, hypotonia of the respiratory muscles, reduced saliva production, and scoliosis. In contrast, CSA is thought to result primarily from hypothalamic dysfunction (28). Furthermore, the protective ventilatory and cardiovascular responses to hypoxia and hypercapnia are impaired in PWS (29). Collectively, these abnormalities may adversely affect the physical health, psychological well-being, and social functioning in individuals with PWS (26, 27, 30, 31). Several studies have reported no detrimental effect of rhGH therapy on SRDB. One study found that although rhGH therapy improved BMI z-scores, it did not influence the presence or severity of SRDB. (32). Similarly, no deterioration in SRDB was reported over a 6-month period of rhGH treatment (33). Tan et al. (30) reported that respiratory parameters remained largely unchanged in children with PWS receiving rhGH treatment. Schaefer et al. (31) observed a decrease in the severity of respiratory events after rhGH treatment in children with PWS. On the other hand, Khayat et al. (32) indicated that rhGH therapy might exacerbate OSA in individuals with PWS, particularly in those with adenotonsillar hypertrophy. Pavone et al. (33) observed that certain patients starting rhGH therapy may need upper-airway surgery or non-invasive ventilation. According to Lecka-Ambroziak et al. (6) rhGH treatment may affect the severity of SRDB in children with PWS. Furthermore, the risk of mortality appears to be increased in children with PWS undergoing rhGH therapy, particularly during the first nine months of treatment (34). Moreover, the severity of OSA does not appear to correlate with age or obesity in PWS patients (35). These differences could stem from various factors, such as variations in study populations and the methods employed to evaluate SRDB. Additionally, the impact of rhGH therapy on sleep patterns is probably affected by elements like the dosage, treatment length, pre-existing conditions, and individual differences in response to therapy (26). Furthermore, most studies have not reported the distribution of genetic subtypes within their patient cohorts. Our study suggests that differences in the distribution of genetic subtypes may contribute to the variability in outcomes reported across studies.

Emerging evidence indicates that responses to rhGH treatment may differ by molecular subtype. While earlier research generally shows similar growth responses between deletion and mUPD, differences by genotype have been noted in metabolic outcomes, particularly insulin resistance and IGF-1 fluctuations (36). For example, Zhou et al. (37) reported greater insulin resistance and higher IGF-1 levels in patients with deletions, despite similar growth improvements compared with those with mUPD, suggesting differential biological responses to rhGH by genotype (38). Similarly, Mahmoud et al. (35) demonstrated that molecular subtype influences several phenotypic characteristics in PWS, although overall growth responses remain largely comparable across genotypes. In contrast, we did not observe significant genotype-related differences in anthropometric or metabolic responses after one year of treatment. This

discrepancy could be due to differences in study populations, follow-up periods, treatment protocols, or sample sizes. Notably, our findings contribute to existing research by indicating that genotype-based variability may also affect respiratory responses to rhGH therapy.

The relationship between genotype and phenotype in Prader–Willi syndrome has been thoroughly studied (39, 40). However, few studies have explored whether the molecular defect influences respiratory outcomes or modifies the response to rhGH therapy (26, 5). Many studies have shown that the deletion subtype contributes to phenotypic variability; type I deletions are generally associated with more pronounced cognitive impairment, behavioral problems, and compulsive traits than type II deletions (41). More recently, Clinical observations of individuals with the 15q11.2 BP1–BP2 microdeletion, also known as Burnside–Butler syndrome, have further highlighted the functional significance of genes located within this interval (42). In total, these findings suggest that genes located between BP1 and BP2 may influence multiple biological pathways beyond neurodevelopment and contribute to differences in respiratory regulation, upper respiratory anatomy, or susceptibility to sleep disturbances (43, 44). Nevertheless, direct evidence to support this hypothesis is still scarce. Biologically, genetic differences among deletion subtypes may influence lymphoid tissue growth, upper airway structure, or craniofacial development, thereby impacting the risk of upper airway obstruction during rhGH therapy. Since adenoid hypertrophy has been proposed as one of the primary mechanisms by which rhGH may worsen OSA, patients with type I deletions may have a lower tendency for lymphoid tissue proliferation and adenoidal growth compared to those with type II deletions. This hypothesis is supported, at least in part, by previous reports showing that genes located in the BP1–BP2 interval are involved in immune regulation and that deletions in this region are associated with recurrent infections, immune responses, and altered lymphoid tissue development (45).

A key finding of our research is that respiratory impairment during rhGH treatment varies across molecular subtypes. While anthropometric growth and metabolic responses were largely comparable between patients with deletions and those with mUPD, worsening of obstructive sleep apnea was particularly observed in patients with deletions and was especially pronounced in those with type II deletions. Interestingly, previous studies evaluating respiratory outcomes after rhGH treatment have rarely considered molecular subtype as a potential modifier. This deficiency might partly account for the inconsistent results in the literature on rhGH's impact on sleep disorders, since genetically diverse patient groups may respond differently to the treatment even if they share similar clinical features. Although these observations offer a plausible biological explanation for our findings, the underlying mechanisms remain speculative and should be explored in future mechanistic and translational research. Our findings enhance current knowledge of genotype–phenotype interactions in PWS by indicating that molecular subtype may affect not only neurobehavioral and metabolic features but also respiratory responses during rhGH therapy. If confirmed in larger prospective studies, molecular stratification could play a crucial role in risk assessment prior to rhGH treatment, enabling early identification of patients who may need more intensive polysomnographic monitoring.

Several limitations of this study need to be considered. As noted, our study lacks a control group that received no rhGH. Second, in this retrospective study, when patients were stratified by genetic subtype, the sample size within each group became substantially smaller. In particular, when analyzing polysomnographic data, patients who required positive airway pressure therapy during follow-up had to be excluded. Consequently, the polysomnographic findings at the end of the first year could not be directly compared with the baseline data.

Our research ultimately validated the necessity of specific molecular diagnosis for every patient with PWS. This practice is crucial not only for enhanced genetic counseling but also for gaining deeper insight into the potential future phenotype.

Given that PWS involves a large genomic region, it is not surprising that different genetic subtypes exhibit distinct clinical phenotypes. Larger, well-designed studies are essential to further characterize these genotype–phenotype differences. Our findings also demonstrate that genetic subtyping in patients with PWS is important for anticipating the clinical course during recombinant human growth hormone (rhGH) therapy and may help guide patient monitoring. Based on our results, we recommend that follow-up polysomnography during the first six months of rhGH treatment not be overlooked, particularly in patients with type II deletions.

Declarations

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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Author Contribution

Author contributions Onur Akin: Conceptualization, Methodology, Investigation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Project Administration, and Supervision. Esra Yazarlı: Methodology, Investigation, Data Collection, Data Curation, Formal Analysis, Visualization, Writing – Original Draft, and Writing – Review & Editing. Nursel Kara Ulu: Investigation, Data Collection, and Writing – Review & Editing. Birce Sunman: Investigation, Data Collection, Polysomnographic Assessment, and Writing – Review & Editing. Dicle Canoruç Emet: Investigation, Data Collection, and Writing – Review & Editing. Emre Özer: Investigation, Data Collection, and Writing – Review & Editing. Gönül Yardımcı: Investigation, Data Collection, and Writing – Review & Editing. Mehmet Koçer: Investigation, Data Collection, Polysomnographic Assessment, and Writing – Review & Editing. Volkan Tekin: Investigation, Data Collection, Polysomnographic Assessment, and Writing – Review & Editing. Sevinç Odabaşı Güneş: Conceptualization, Methodology, Supervision, and Writing – Review & Editing. Deniz Torun: Investigation, Genetic Data Interpretation, Data Collection, and Writing – Review & Editing. Sinan Yetkin: Investigation, Data Collection, Polysomnographic Assessment, Supervision, and Writing – Review & Editing. All authors read and approved the final manuscript and agree to be accountable for the work.

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Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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