Original article

Sleep cycling alternating pattern (CAP) expression is associated with hypersomnia and GH secretory pattern in Prader–Willi syndrome

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Abstract

Background and purpose: Hypersomnia, sleep-disordered breathing and narcoleptic traits such as rapid eye movement (REM) sleep onset periods (SOREMPs) have been reported in Prader–Willi syndrome (PWS). In a group of young adult patients with genetically confirmed PWS we evaluated sleep and breathing polysomnographically, including cycling alternating pattern (CAP), and we analyzed the potential interacting role of sleep variables, sleep-related breathing abnormalities, hypersomnia, severity of illness variables and growth hormone (GH) secretory pattern.

Patients and methods: Eleven males and 7 females (mean age: 27.5 ± 5.5 years) were submitted to a full night of complete polysomnography and the multiple sleep latency test (MSLT). GH secretory pattern was evaluated by a standard GH-releasing hormone plus arginine test. Sixteen non-obese healthy subjects without sleep disturbances were recruited as controls.

Results: Compared to controls PWS patients showed reduced mean MSLT score ($P < 0.001$), reduced mean latency of sleep ($P = 0.03$), increased REM sleep periods ($P = 0.01$), and increased mean CAP rate/non-rapid eye movement (NREM) ($P < 0.001$). Only four PWS patients had apnea/hypopnea index (AHI) ≥ 10. Conversely, significant nocturnal oxygen desaturation was frequent (83% of patients) and independent from apneas or hypopneas. In the PWS group, CAP rate/NREM showed a significant negative correlation with MSLT score ($P = 0.02$) independently from arousals, respiratory disturbance variables, severity of illness measured by Holm's score or body mass index (BMI). PWS patients with CAP expression characterized by higher proportion of A1 subtypes presented less severe GH deficiency ($P = 0.01$).

Conclusions: Our study suggests a relationship between hypersomnia and CAP rate, and between CAP expression and GH secretory pattern in PWS, possibly reflecting underlying central dysfunctions.
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Keywords: Prader–Willi syndrome; Cycling alternating pattern; Hypersomnia; GH deficiency; Apnea/hypopnea index; Multiple sleep latency test

1. Introduction

Prader–Willi syndrome (PWS) is a complex genetic disorder with an estimated incidence of one in 10,000–30,000 live births [1]. Most PWS patients (70–75%) carry a deletion in the paternally derived chromosome 15q11–q13, 25% have maternal uniparental disomy, and 2–5% show abnormal methylation of the imprinting center or a balanced translocation [2–6]. Clinical findings in PWS suggest an involvement of the hypothalamus–pituitary axis [7] and include hypogonadism, marked obesity, short stature, mental retardation, hypotonia and

impaired growth hormone (GH) secretory pattern [1,8–10]. Hypersomnia during the day is common in PWS (2/3 of patients), but the pathogenesis of this symptom has not been fully clarified [11–13]. Obstructive and central sleep apneas, abnormal ventilatory responses to hypoxia and hypercapnia, sleep-related alveolar hypoventilation may be present [14–17], but they can be considered sufficient explanations for hypersomnia in only a minority of cases [18–21].

Classical sleep analysis and scoring according to Rechtschaffen and Kales, which reflect the macrostructure pattern of sleep did not show specific findings in PWS [18,22]. The occurrence of increased number of rapid eye movement (REM) episodes and REM sleep onset periods (SOREMPs), together with the findings of reduced cerebrospinal fluid hypocretin levels, suggested a possible relationship with narcolepsy and a possible involvement of a central dysfunction in the genesis of hypersomnia [23–25]. Transient electroencephalographic (EEG) phenomena lasting less than the scoring epoch and cycling alternating pattern (CAP) [26–28], describing what is known as the microstructure of sleep, have not been studied in PWS. In particular, CAP analysis could add important information as the percentage of CAP to total NREM sleep (CAP rate/NREM), reflecting arousal instability and appearing as a valid indicator of sleep quality, may be related to daytime sleepiness [29–32].

In a group of young adult PWS patients we evaluated sleep, including CAP, and we analyzed the potential interacting role of sleep variables, sleep-disordered breathing, hypersomnia, severity of illness variables and GH secretory pattern.

2. Patients and methods

Eighteen PWS patients (7 females and 11 males) aged 18.1–40.1 years (mean age: 27.5±5.5 years) were recruited for the study (Table 1). The entire study protocol was approved by the local ethical committee, and written informed consent was obtained from parents and, when applicable, from patients. Cytogenetic studies were performed in all patients and severity of illness was determined by Holm's diagnostic criteria [33]. This scoring system comprises both major and minor criteria. Major criteria are weighted at one point each and include neonatal and infantile central hypotonia, feeding problems in infancy with poor weight gain, excessive or rapid weight gain after 12 months but before six years of age, characteristic facial features, hypogonadism, mild to moderate mental retardation, hyperphagia, cytogenetic/molecular abnormality of the PWS chromosome region. Minor criteria are weighted at one half-point and include decreased fetal movement or infantile lethargy, characteristic behavior problems, daytime hypersomnolence or sleep apnea, short stature for genetic background, hypopigmentation, acromicria, narrow hands with straight ulnar borders, eye abnormalities, thick viscous saliva, speech articulation defects and skin picking. In adulthood a total score of 8 is necessary for the diagnosis, and major criteria must comprise five or more points of the total score. We defined as obese those patients with a body mass index (BMI: kg/m²) higher than 30 in males and 28.6 in females [34]. All PWS subjects in our study were markedly obese (mean BMI: 47.9±8.6) and had typical clinical features with

Table 1
Clinical and laboratory data of PWS patients

Prader–Willi patients	Sex	Age (years)	BMI	WHR	ESS	Holm's score	Karyotype	GH peak (ng/ml)
MA	M	18.1	37.8	0.85	8	11.5	Del 15	16.4
MI	M	22.3	43.5	0.96	18	10.5	Del 15	8.8
CL	M	29.2	40.0	1.02	11	12.0	Del 15	12.9
ZE	F	26.0	38.9	0.79	4	11.5	Del 15	7.3
PE	M	23.0	44.5	1.02	8	11.5	Del 15	5.0
GS	M	27.1	69.0	0.72	14	12.0	Del 15	3.8
SV	M	28.9	42.1	0.98	16	11.5	Del 15	3.0
SS	F	31.2	60.3	0.86	9	11.5	Del 15	3.4
BM	F	33.4	50.8	0.86	9	10.5	Del 15	9.1
PA	F	25.9	46.8	0.95	13	11.5	UPD	2.5
BA	F	21.2	44.2	0.92	12	11.5	Del 15	6.2
SR	F	32.0	46.3	0.91	10	10.0	Del 15	12.8
RD	M	19.6	50.5	1.03	11	11.5	Del 15	6.3
GS	M	28.9	42.5	0.83	12	11.0	Del 15	3.8
CG	M	28.3	53.1	0.91	13	12.0	Del 15	7.5
BM	F	33.1	63.0	0.98	7	11.5	Del 15	4.0
BP	M	40.1	42.0	0.94	15	11.5	Del 15	4.4
BF	M	27.1	46.8	0.92	11	11.0	Del 15	10.6
Mean ±SD		27.5±5.5	47.9±8.6	0.93±0.1	11.2±3.4	11.2±0.7		7.1±3.9

GH secretion is expressed as peak response to GHRH + arginine. Holm's score according to Consensus Diagnostic Criteria (Holm et al., 1993). UPD, uniparental maternal disomy of chromosome 15; Del 15, deletion of the proximal long arm of chromosome 15 (15q11–q13); BMI, body mass index (kg/m²); WHR, waist/hip ratio; ESS, Epworth sleepiness scale.

Holm's score equal to or higher than 10. No PWS patient was undergoing hormonal replacement, with the exception of case 13, with diabetes mellitus and treated with insulin. Patients together with parental help completed the Epworth Sleepiness Scale (ESS) to measure sleep propensity. All patients underwent an adaptation night and then a full-night polysomnography (PSG) in the sleep laboratory in a quiet room with video monitoring, and a multiple sleep latency test (MSLT) the day after PSG. Patients were allowed to maintain their usual sleep habits and schedule. Therapy with benzodiazepines and neuroleptics taken by two and four patients, respectively, was discontinued 1 week before PSG. The following parameters were recorded: electroencephalogram (EEG) using C3–A2, C4–A1, O2–A1, O1–A2 derivations integrated by bipolar montages Fp2–F4, F4–C4, C4–P4, P4–02; Fp1–F3, F3–C3, C3–P3, P3–01; Fz–Cz, Cz–Pz of the 10–20 international placement system; electro-oculogram (EOG) (bipolar montage: right ocular cantus–left ocular cantus); electrocardiogram (EKG); respiratory effort by thoracic and abdominal strain gauges, nasal air-flow by nasal cannula, snoring nose by a microphone, arterial oxyhaemoglobin (SaO$_2$) using a pulse oximeter with finger probe; electromyogram (EMG) at submental and tibialis anterior muscles. Subjects were not allowed to sleep during the daytime prior to polysomnographic examination. MSLT was performed the day after nocturnal PSG at 10:00, 12:00, 14:00, 16:00 h. Sleep latency was measured from the time lights were switched off until the onset of stage 1 sleep of at least one-min duration, or the onset of either stage 2 or REM sleep. The early onset of REM sleep was indicated by the occurrence of REM sleep within 20 min of sleep onset. Caretakers made sure that patients did not fall asleep between MSLT naps. Conventional sleep analysis, arousals, and CAP analysis were performed independently by two evaluators experienced in sleep staging according to Rechtschaffen and Kales' criteria, American Sleep Disorders Association (ASDA) rules for arousal classification [29], and on the basis of the guidelines defined by Terzano and colleagues for CAP scoring [35,36]. Considering the age of our patients, respiratory patterns were scored and interpreted according to the available criteria for adults. Abnormal breathing events during sleep were defined according to the criteria of complete cessation of airflow lasting at least 10 s with ventilatory effort maintained (obstructive apnea) or interrupted (central apnea), or a discernible reduction in respiratory airflow accompanied by a decrease of 4% or more in oxyhemoglobin saturation (hypopneas). When characteristics of both central and obstructive apnea were present, we considered it mixed apnea. Apnea/hypopnea index (AHI) was calculated as number of all apneas and hypopneas/hours of sleep.

Sixteen non-obese healthy subjects without sleep disturbances (8 males, 8 females, mean age: 25.2±7.3 years, range 20–32 years, mean BMI: 23.1±4.5) were recruited as controls.

All PWS subjects (Table 1) underwent a standard GH-releasing hormone (GHRH) plus arginine (ARG) test after an overnight fast. According to the literature [37], we considered a GH peak response to GHRH + ARG lower than 9 and 16.5 ng/ml for severe and partial GH deficiency (GHD), respectively. Most patients showed severe GHD (72%) and five subjects had a partial GHD (28%).

Statistical analysis of polysomnography variables between groups was performed by means of unpaired Student *t*-test. In order to analyze the relationships among variables, Pearson correlation tests were computed. A commercially available statistical software package (StatView, SAS Institute, Inc.™) was used for statistics.

3. Results

Main nocturnal polysomnographic measures are reported in Tables 2 and 3. Compared to controls, PWS group presented reduced mean sleep latency ($P = 0.03$), increased REM sleep periods ($P = 0.01$) and REM sleep following wake after sleep onset (WASO) in four patients. Prolonged periods of oxygen desaturation, most of them occurring during REM sleep and independent from apneas or hypopneas, were found in 15 patients. REM abnormalities were independent of the presence of oxygen desaturations. Only four PWS patients had AHI $\geq$ 10, while two patients presented AHI between 5 and 10, and 12 patients had AHI $\leq$ 5.

Table 2
Main nocturnal polysomnographic measures in Prader–Willi patients and control group

	Prader–Willi (18 patients)	Control group (16 subjects)
TST (min)	374.5±67.8	412±113.4
SE (%)	85.5±8.6	87.2±13.3
Sleep latency (min)	9.8±4.5[a]	13.3±4.5[a]
REM latency (min)	114.0±60.1	93.5±47.2
WASO (%)	11.3±6.2	12.8±8.3
NREM I (%)	10.7±5.4	11.5±9.2
NREM II (%)	39.4±9.9	35.4±18.2
NREM III–IV (%)	23.0±10.3	28.2±15.8
REM (%)	15.3±5.3	18.2±8.2
REM periods for each sleep (*n*)	6.8±3.8[b]	3.1±4.4[b]
REM periods after WASO (*n*)	7 in 4 patients	0
Arousal index (*n*/h)	22.5±10.2	18.9±8.4
MSLT (min)	7.2±2.9[c]	15.3±7.2[c]

Values expressed as mean±SD. TST, total sleep time; WASO, wake after sleep onset; SE, sleep efficiency = TST/time in bed; Arousal index, number of arousals/hours of sleep; MSLT, multiple sleep latency test. Unpaired *t*-test: [a]$p = 0.03$, [b]$p = 0.01$, [c]$p < 0.001$.

Table 3
Respiratory disturbance variables in Prader-Willi patients and control group

	Prader-Willi (4 patients with AHI ≥ 10)		Prader-Willi (14 patients with AHI < 10)		Prader-Willi (Total: 18 patients)		Control group (16 subjects)	
AHI	17.0 ± 6.2 (range: 14.1–21.3)		2.5 ± 2.3 (range: 0–6.6)		5.9 ± 6.8[a] (range: 0–21.3)		1.1 ± 2.5[a] (range: 0–5.2)	
Basal SaO_2 (%)	90.3 ± 4.9		92.3 ± 5.6		91.3 ± 9.3[b]		98.5 ± 2.0[b]	
Time spent in SaO_2 < 90% (% TST)	47.1 ± 14.7		13.9 ± 15.6		22.4 ± 21.1[c]		2.6 ± 3.1[c]	
Average minimum SaO_2 during desaturations (%)	82.8 ± 6.5		85.5 ± 3.5		83.8 ± 7.3[d]		90.5 ± 5.0[d]	
Lowest SaO_2(%)	72.3 ± 5.1		78.2 ± 8.2		75.6 ± 9.2[e]		88.2 ± 5.1[e]	
	NREM	REM	NREM	REM	NREM	REM	NREM	REM
Obstructive sleep apneas index	7.4 ± 4.3	12.4 ± 4.2	0.1 ± 0.5	2.5 ± 1.2	1.7 ± 0.5	4.7 ± 6.2	0.1 ± 0.5	0.3 ± 0.8
Mixed sleep apnea index	2.1 ± 2.2	3.2 ± 2.8	0.2 ± 0.8	1.5 ± 1.2	1.2 ± 0.8	2.3 ± 3.3	0.1 ± 0.8	0.3 ± 0.3
Central sleep apnea index	2.5 ± 2.5	3.1 ± 2.1	1.6 ± 2.1	1.2 ± 1.4	1.8 ± 3.5	2.0 ± 2.4	0	0
Hypopnea index	9.6 ± 5.2	10.4 ± 6.9	0.2 ± 0.3	2.1 ± 1.9	2.5 ± 2.7	2.9 ± 2.1	0.8 ± 2.7	0.9 ± 1.1

Values expressed as mean ± SD. AHI, apnea/hypopnea index; TST, total sleep time. Indexes are calculated as number of episodes of corresponding sleep-disordered breathing/hours of sleep. Unpaired t-test: [a]$p = 0.01$, [b]$p = 0.005$, [c]$p = 0.001$, [d]$p = 0.004$, [e]$p < 0.001$.

Obstructive apneas and hypopneas were predominant compared to central apneas and appeared slightly more frequent in REM sleep (not statistically significant). Two groups, PWS patients with AHI ≥ 10 and with AHI < 10, were considered for further analysis. This cut-off was chosen in order to obtain homogeneous groups of patients with and without significant sleep disruption or CAP increase due to apneas. Mean CAP rate/NREM in both PWS groups resulted significantly higher compared to controls ($P < 0.01$), due to a significant increase of CAP sequence duration and an increase of CAP cycles in each CAP sequence (Table 4). CAP subtype scoring was then performed excluding CAP sequences clearly concomitant with apnea/hypopneas, in order to focus this analysis primarily on CAP not induced by detectable stimuli [38,39]. Mean percentage of subtypes A1, A2 and A3 of CAP referred to total A phases (not related to apneas or other detectable stimuli) was 65.2±10.2, 23.6±5.7, 10.2±3.2%, not significantly different from controls (59.8±9.5, 26.6±6.2, 11.2±5.2%, respectively). Within CAP, 1% of subtypes A1, 52% of subtypes A2 and 91% of subtypes A3 met

ASDA criteria for arousals. No patient had periodic limb movements during sleep concomitant with or independent of CAP sequences. No constant relationship between CAP sequences and snoring could be established.

Subjective excessive daytime sleepiness was reported at ESS in most patients and confirmed by MSLT scores (Tables 1 and 2). Severe sleepiness (MSLT score ≤ 5) and moderate sleepiness (MSLT score between 5 and 8 min) was present in three patients and eight patients, respectively. Only three patients had an MSLT score > 10. SOREMPs were recorded in three patients. However, no patient presented the typical narcoleptic symptoms such as cataplexy, sleep paralysis or hypnagogic hallucinations.

MSLT score correlated with AHI ($r = -0.63$; $P = 0.002$) and CAP rate/NREM ($r = -0.60$; $P = 0.003$), while CAP rate/NREM showed a mild correlation with AHI ($r = 0.46$; $P = 0.03$) and arousal index ($r = 0.47$; $P = 0.03$). Excluding patients with AHI ≥ 10, a moderate negative correlation was maintained only between MSLT score and CAP rate/NREM

Table 4
CAP (cycling alternating pattern) parameters in Prader–Willi patients and control group

	Prader–Willi (4 patients with AHI ≥ 10)	Prader–Willi (14 patients with AHI < 10)	Prader–Willi (total: 18 patients)	Control group (16 subjects)
No. of CAP sequences for each sleep	18.7 ± 6.7	15.1 ± 6.4	15.5 ± 7.1	14.3 ± 6.8
Duration of CAP sequences (min)	7.6 ± 2.2	6.2 ± 2.5	6.9 ± 2.9[a]	4.7 ± 3.2[a]
No. of CAP cycles in each CAP sequence	12.2 ± 4.5	13.1 ± 4.1	12.8 ± 4.7[b]	7.8 ± 6.2[b]
CAP rate/NREM (%)	48.6 ± 8.1	36.5 ± 8.3[c]	40.3 ± 8.5[d]	28.5 ± 4.3[c,d]

Values expressed as mean ± SD. Unpaired t-test: [a]$p = 0.04$, [b]$p = 0.01$, [c]$p = 0.002$, [d]$p < 0.001$.
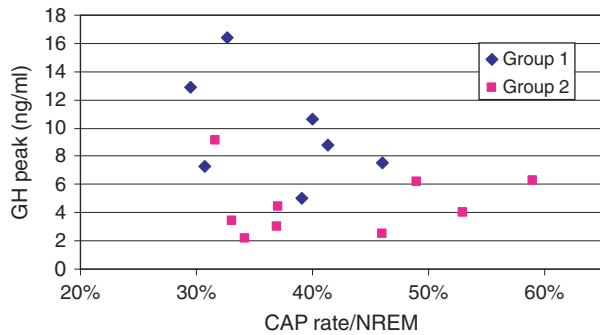
Fig. 1. Scattergram of GH secretion (expressed as peak response to GHRH + arginine) and CAP rate (CAP sequences during apneas/hypopneas excluded), according to proportion of phase A subtypes of CAP. Group 1: percentage of A1 subtypes of CAP referred to total A phases ≥ 60%. Group 2: percentage of A1 subtypes of CAP referred to total A phases < 60%.(For interpretation of the reference to colour in this legend, the reader is referred to the web version of this article)

($r = -0.56$; $P = 0.02$). MSLT score and CAP rate did not show significant correlations with the other sleep respiratory disturbance variables, sleep efficiency, age, BMI or Holm's score. AHI was lower in females than males (3.1 ± 4.2 and 7.1 ± 7.5, respectively), but this difference was not statistically significant. None of the respiratory disturbance variables during sleep correlated with sleep efficiency, arousal index, BMI, waist/hip ratio, Holm's score, GH secretory pattern or age.

CAP rate/NREM was lower in females than males (26.2 ± 7.5 and $30.9 \pm 12.2\%$, respectively, not statistically significant). Correlation with genetic pattern could not be made due to the small sample size of subjects with uniparental maternal disomy. Excluding patients with AHI ≥ 10, interesting associations seem to emerge between CAP expression and GH secretion, as shown in Fig. 1: CAP rate/NREM showed a mild negative correlation with GH peak response ($r = -0.53$; $P = 0.04$) and, more interesting, seven patients with A1 subtypes (60% referred to total A phases, considered the normal value in young adults [26], clearly presented less severe GHD compared to nine patients with A1 subtypes < 60% (GH peak response equal to 9.7 ± 3.8 and 4.5 ± 2.2 ng/ml, respectively; $P = 0.01$). Mean age was not statistically different in these two groups (26.7 ± 5.0 and 25.8 ± 3.9 years, respectively).

4. Discussion

This is the largest study reporting sleep analysis in young adult PWS patients, and the first study analyzing CAP. Previous reports included children, whose degree of somnolence, sleep pattern and respiratory disorders differ from adult patients [12,17,18,22]. The majority of our PWS patients presented excessive daytime sleepiness, but this could be explained by the occurrence of sleep apneas and consequent sleep disruption only in about 22% (4/18) of cases. These findings are consistent

with previous studies reporting hypersomnia in most patients but a prevalence of obstructive sleep apnea syndrome much lower than expected in PWS, both in children and adults [12,13,18,22]. One possible explanation of these findings is that obesity in PWS is usually subcutaneous, different from the visceral pattern involved in the pathogenesis of apneas in adult males with essential obesity. However, marked obesity and consequent chronic hypoventilation may explain the occurrence of prolonged periods of oxygen desaturation not related to apneas or hypopneas found in our PWS patients, in accordance with previous studies [14,17,18]. Interestingly, despite the fact most patients presented an increased risk of arousals, primarily due to apneas and nocturnal oxygen desaturation episodes, sleep efficiency and arousal index did not significantly differ from controls. This may be explained by the demonstration of reduced arousal and cardiorespiratory response to hypoxia and hypercapnia in PWS patients [14–16].

In our study, sleep parameters obtained from conventional sleep analysis did not show alterations clearly related to hypersomnia. In agreement with the literature [18,22,25], we found REM sleep periods after WASO and SOREMPs at MSLT in about one-fifth of patients. These findings, together with the recent report of low cerebrospinal fluid hypocretin levels correlated with hypersomnia [23], may lead to consideration of PWS sleep disturbances as similar to narcolepsy. Nevertheless, no patient presented typical narcoleptic symptoms and further investigations are needed to clarify if increased REM pressure and hypersomnia in PWS have a different pathogenesis from narcolepsy.

In the group of patients devoid of significant apneas that could be considered a sufficient explanation for sleep disruption and daytime sleepiness, we found an interesting association, not previously reported, between hypersomnia and CAP rate. Even if subtypes A2 and A3 of CAP are partially covered under the classification of arousals, in this group of patients arousal index was not correlated with CAP rate or MSLT score, and sleep efficiency was in normal range. Nevertheless, CAP is considered to reflect arousal instability in higher duration range than individual micro-arousals, may be a valid indicator of poor sleep and may be related to daytime sleepiness [29–32]. However, a direct cause–effect relationship between high CAP rate and hypersomnia is not demonstrated in our preliminary study and needs to be confirmed by further investigation with a larger number of patients. Considering that the influence of all respiratory disturbance variables during sleep, periodic limb movements, age and BMI have been excluded, the occurrence of some stimulus not detectable with standard recordings and responsible for CAP increase cannot be excluded. However, this possible relationship between CAP and hypersomnia is intriguing and may lead to some consideration. CAP is supposed to be the expression of a basic

arousal modulator oscillating between greater (phase A) and lesser (phase B) arousal levels. Moreover, A1 subtypes, characterized by predominant high-voltage slow waves, contribute to the build-up and maintenance of EEG synchronization during NREM sleep, while A2 and A3 subtypes, characterized by larger amount of low-amplitude fast rhythms, may be related to the onset and consolidation of REM sleep [26]. There is evidence that CAP components corresponding to EEG synchrony represent the cortical expression of cortical–subcortical interactions mediated by thalamocortical pathways, while the high-frequency component of CAP appears to be the expression of the activity of the same structures involved in the generation of alpha waves, comprising pyramidal neurons in layer IV and V within the cerebral cortex, with surface-parallel intracortical neurons involved in its spread [40–42]. Altered CAP expression, similar to REM abnormalities and central apneas as suggested in the literature [22,25], may reflect a primary dysfunction of central nervous system, and the hypothalamus may play an important role [7]. In accordance with this hypothesis is the relationship between CAP and GH secretion found in our study. Patients with more severe GHD have a higher CAP rate and a pattern of CAP characterized by lower proportion of A1 subtypes, independently from age, sex or BMI. This suggests that a subgroup of patients with more severe central dysfunctions might be defined. Further studies considering potential interacting role of other factors, age, sex, genetic pattern and cerebrospinal fluid hypocretin level are needed to confirm our data and to corroborate the hypothesis of common central dysfunctions responsible for hypersomnia, endocrine and CAP alterations in PWS.

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