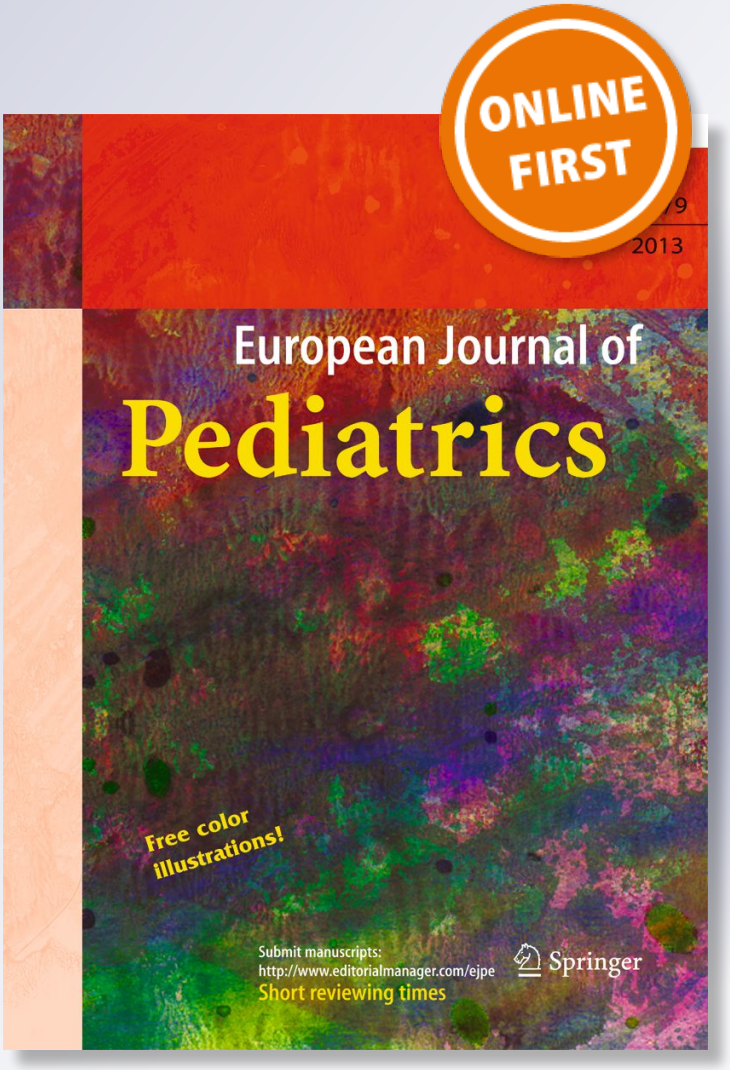
Severe obstructive sleep disorders in Prader-Willi syndrome patients in southern Italy

Angelo Canora, Adriana Franzese, Enza Mozzillo, Valentina Fattorusso, Marialuisa Bocchino & Alessandro Sanduzzi

European Journal of Pediatrics

ISSN 0340-6199

Eur J Pediatr
DOI 10.1007/s00431-017-3083-9



Springer

European Journal of Pediatrics
https://doi.org/10.1007/s00431-017-3083-9

SHORT COMMUNICATION

Severe obstructive sleep disorders in Prader-Willi syndrome patients in southern Italy

Angelo Canora[1] · Adriana Franzese[2] · Enza Mozzillo[2] · Valentina Fattorusso[2] · Marialuisa Bocchino[1] · Alessandro Sanduzzi[1]

Received: 31 October 2017 / Revised: 23 December 2017 / Accepted: 28 December 2017

Abstract

Sleep-related disordered breathing (SDB) is very common in paediatric patients affected by Prader-Willi Syndrome (PWS). However, data addressing SBD patterns and their management are lacking. The aim of the present study was to analyse SDB features in 14 PWS patients (age range, 8 months-17 years). Polygraphic registration (PG) during a 12-h nocturnal sleep was performed in all patients. Obstructive and central apnoea indices and oxygen saturation (SpO_2) were recorded along with demographic and clinical data. Obstructive sleep apnoea (OSA) was diagnosed in 13/14 patients (92.9%); the mean obstructive apnoea-hypopnea index (OAHI) was 7.6 ± 4.2 events/h with a mean central apnoea index (CAI) of 0.7 ± 1.04 events/h. Time spent with SpO_2 < 90% was of 0.02% [range 0–23%], with a mean oxygen desaturation index of 12.1 ± 6.9 events/h. No correlation was found between OAHI and body mass index (mean BMI 28 ± 9.8 kg/m^2 and BMI *z*-score 2.7 ± 1.7).

Conclusion: OSA was the predominant sleep-related disorder in our PWS patients, not associated with age or obesity, and appeared more severe than previously reported. Further studies addressing the underlying mechanisms are necessary in larger study populations to better design the most appropriate clinical approach.

What is Known:
• *Sleep-related patterns and their management are very limited in patients with Prader-Willi syndrome.*

What is New:
• *Severe obstructive sleep apnoea is the most frequent sleep-related disorder in our case series.*

Keywords Prader-Willi syndrome · Sleep · Obstructive sleep apnoea

Abbreviation

BMI	Body mass index
CAI	Central apnoea index
CSA	Central sleep apnoea
GH	Growth hormone
OAHI	Obstructive apnoea-hypopnea index
OSA	Obstructive sleep apnoea
PG	Polygraphic registration

Communicated by Peter de Winter

✉ Angelo Canora
a.canora@hotmail.it

Adriana Franzese
franzese@unina.it

Enza Mozzillo
enzamozzillo@gmail.com

Valentina Fattorusso
vfattorusso1@gmail.com

Marialuisa Bocchino
marialuisa.bocchino@unina.it

Alessandro Sanduzzi
sanduzzi@unina.it

[1] Section of Respiratory Disease, Department of Clinical Medicine and Surgery, Monaldi Hospital, University "Federico II" Naples, Via Leonardo Bianchi, 80131 Naples, Italy

[2] Departments of Translational and Medical Sciences, University "Federico II" Naples, Naples, Italy

Published online: 09 January 2018

PWS Prader-Willi syndrome
SDB Sleep-disordered breathing
SpO_2 Oxygen saturation

Introduction

Prader-Willi syndrome (PWS) is a multisystemic complex genetic disorder caused by lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region. It occurs in 1/10000–1:30,000 live births. About two-thirds of patients (65–75%) have a de novo paternally inherited chromosome deletion, 20–30% have maternal uniparental disomy and 1–3% have defects in the genomic imprinting centre. PWS infants are characterized by severe hypotonia, poor feeding leading to failure to thrive and hypogonadism. In later infancy and early childhood, they develop hyperphagia related to hypothalamic dysfunction and, consequently, morbid obesity; also, short stature, intellectual disabilities and behavioural problems are parts of the clinical picture.

High prevalence of sleep-disordered breathing (SDB) is reported among children with PWS, including obstructive sleep apnoea (OSA), central sleep apnoea (CSA) and hypoventilation syndromes. SDB are investigated by overnight polygraphic registration (PG) during a 12-h night. SDB reported in PWS children also include excessive daytime sleepiness, altered sleep architecture, and abnormal arousal and cardiorespiratory response to hypoxia and hypercapnia. In addition to hypothalamic dysfunction, other factors such as developmental brain abnormalities, craniofacial dysmorphia, hypotonia, obesity and chest wall deformities can contribute to the presence and severity of sleep-disordered breathing in PWS [1].

Traditionally, OSA of PWS patients has been associated with coexisting obesity and narrowing of the upper airways and respiratory muscle hypotonia. Furthermore, a high number of PWS patients have CSA and associated significant oxygen desaturations. CSA are reported to be more common in PWS infants. The etiology of CSA in PWS infants seems to be multifactorial; contributing mechanisms include hypotonia, brainstem immaturity and hypothalamic dysfunction. Abnormal chemosensitivity to CO_2 and O_2 may also contribute to hypoxia induced by respiratory depression [3].

The benefits of growth hormone (GH) therapy on improving lean muscle mass and its likely positive impact in hypotonia has led to increase therapeutic use of GH in PWS infants [4]. It is well known that PWS children have to be studied by PG before GH therapy and then periodically, especially in the presence of significant changes in weight, prior to and following adenotonsillectomy and before spinal or craniofacial surgery. Some authors also suggest to repeat PG 3–6 months after start of GH therapy in PWS patients previously diagnosed and treated for OSA [7].

The aim of this study is to describe the prevalence and severity of SDB in a group of paediatric patients with PWS.

Materials and methods

Study population and data collection

We enrolled 14 PWS patients (genetic diagnosis correctly performed; 11 males; 8 months–17 years; 6 obese) who performed overnight PG between September 2014 and November 2015. Collected data included sex, age, height and weight at the time of the PG. It was also recorded if patients were on GH therapy, if they had not yet started such therapy or if they had done it in the past. Body mass index (BMI) was calculated as weight (kg) / height $(m)^2$. BMI *z*-scores were calculated according to age- and sex-specific growth curves of the World Health Organization [8]. Obesity is defined as BMI > 90th percentiles (based on specific reference populations) or as BMI *z*-score > 2 [2].

PG All PG have been performed by trained physicians. Patients underwent standard overnight PG using a VitalNight (AirLiquide Medical System, Rangendigen, Germany) data acquisition and analysis system. PG measurements included chest wall and abdominal movements recorded by belts, nasal airflow using a nasal air pressure transducer, oxygen saturation (SpO_2) and cardiac rate. Respiratory data included number and indices of obstructive apnoeas, obstructive hypopneas, central apnoeas and mixed apnoeas. All events were scored according to the American Academy of Sleep Medicine scoring guidelines [5]. Parents/caregivers were trained to complete a sleep log to describe when subjects fall asleep and when they are awake.

PG technical definitions:

(1) Obstructive apnoea, when airflow drops more than 90% from baseline for at least 90% of the entire respiratory event with chest and/or abdominal movements during the entire event, during at least two baseline breaths;
(2) Obstructive hypopnea, when airflow drops at least 50% from baseline during at least two baseline breaths, with drop in SpO_2 with a minimum of 3%;
(3) Central apnoea, when it happens, a complete stop of airflow with an absence of respiratory and abdominal effort during a minimum of 20 s or at least two baseline breaths, with a minimum of 3% decrease of SpO_2;
(4) Mixed apnoea, when airflow drops more than 90% from baseline for at least 90% of one entire respiratory event, during a minimum of two baseline breaths, with absent inspiratory effort in the initial portion of the event, followed by resumption of inspiratory effort before the end of the event.

PG indexes

OSA severity was graded according to accepted clinical criteria.

Obstructive apnoea-hypopnea index (OAHI) reflects the number of obstructive apnoeas, mixed apnoeas and obstructive hypopneas per hour during sleep. OAHI index of ≤ 1 events/h and CAI of ≤ 1.0 events/h have been classified as normal PG values, OAHI > 1.5 of < 5 events/h indicated mild OSA, OAHI > 5 of < 10 events/h indicated moderate OSA and OAHI of ≥ 10 events/h indicated severe OSA.

Oxygen desaturation index (ODI) is the number of desaturation events per hour. Desaturation means a drop of basal oxyhemoglobinic saturation of at least of 3%.

Results

SDB was diagnosed in 13/14 patients (92.9%), 3 mild OSA (21.4%), 6 moderate OSA (42.9%) and 4 severe OSA (28.6%), while only 1 patient was negative for sleep apnoea (7.1%). The mean OAHI was 7.6 ± 4.2/h (range 0.7–15.1/h) while mean CAI was 0.7 ± 1.04/h (range 0–3.9/h). Three patients > 2 years old presented sporadic central events (CAI > 1 < 5) but their PG presented prevalent obstructive pattern. The mean ODI was 12.1 ± 6.9/h (range 0.9–27/h). The median value of mean SpO_2 was 95% (range 90–99%). The mean percentage of time spent with SpO_2 < 90% was 0.02% (range 0–23%). Only one patient had nocturnal respiratory failure. Five patients were never treated with GH, four patients were on GH treatment and five patients have been previously treated with GH.

It seems that GH therapy does not impact SDB, for example, patient number 3 presents severe SDB even if treatment with GH is ongoing since 4 years; on the other hand, patient number 13 treated with GH in the past presents normal OAHI. Data are presented in Table 1.

Discussion

The actual prevalence of SDB in patients with PWS is difficult to define due to the small number of patients reported in literature, the variable selection of inclusion criteria, the wide age ranges and the lack of multicentre studies. In the largest report to date, including 88 adult and paediatric PWS patients followed in three Italian and French centres, Pavone et al. reported that patients exhibited high prevalence of SDB but not associated with obesity [6]. Cohen et al. by focusing only on 44 paediatric PWS cases compared SDB in children over and below 2 years of age and found that OSA was more prevalent than CSA in patients aging > 2 years [3]. Conversely, CSA with associated oxygen desaturations was more prevalent in < 2-year-old children and supplemental oxygen was efficacious to treat [3].

In agreement with the previous observations [6], our study confirms the high prevalence of SDB in PWS paediatric patients with no correlation with BMI (the Pearson test, $p = 0.33$) but is in contrast with Cohen's data which show correlation between SDB and obesity [3]. In addition, we found that all patients affected by SDB had a predominant obstructive

Table 1 The prevalence and severity of SDB in a group of paediatric patients

Patient number	Age (years)	Sex	BMI *z*-score	GH therapy	OAHI nv ≤ 1	CAI nv ≤ 1	ODI	Mean SpO_2	T90% nv ≤ 10
1	4.4	M	1.72	C	2.9	1.6	6.3	96%	0
2	17.5	M	2.22	P	8.4	0.2	9.7	93%	0
3	5.2	M	4.42	C	11.6	0	17.1	90%	23%
4	2.8	M	1.41	N	2.4	0.4	4.8	99%	0
5	1.7	M	n.v.	N	15.1	0.1	27	96%	0
6	12.7	M	5.59	P	6.7	0.6	10	95%	0
7	14.3	M	2.3	P	7.9	3.9	10.9	97%	0
8	11.2	M	0.81	C	8.4	1.4	11.4	95%	0
9	0.6	M	n.v.	N	12.9	0	20.3	95%	0
10	1.8	M	n.v.	N	6.3	0.3	16.6	96%	0
11	3.0	F	4.26	C	7.8	0	10.8	96%	0
12	5.9	F	3.12	P	11.8	0.3	17.6	93%	8%
13	17.5	M	0.69	P	0.7	0.2	0.9	97%	0
14	1.5	F	n.v.	N	4	0.5	6.5	96%	0
Mean ± SD	7.1 ± 6,1		2.6 ± 1,6		7.6 ± 4.2	0.6 ± 1	12.1 ± 6.9	95 ± 0.02	

M male, *F* female, *BMI* body mass index, *OAHI* apnoea-hypopnea index, *CAI* central apnoea index, *ODI* oxygen desaturation index, *SpO_2* oxygen saturation, *T90%* percentage of time spent with SpO_2 < 90%, *n.v.* not valid, *C* on course, *P* in the past, *N* never, *nv* normal values

respiratory pattern, according to Pavone et al. [6], without age-related differences. Our study population also exhibited a more severe sleep disorders. In contrast, mean OAHI was of 9.6 ± 5.27 among patients, < 2 years old, and 6.86 ± 3.76 among those aging > 2 years. Similarly, mean ODI values were 17.6 ± 8.6 in patients, < 2 years old, and 9.95 ± 5.11 in patients aging > 2 years. Conversely, both OAHI and ODI values were reported to be lower in previous literature observations [3, 6]. To date, unlike Pavone et al. that showed an increasing OAHI from childhood to adulthood [6], mean OAHI higher were higher in patients aging ≤ 2 years in our case series. Finally, we did not find considerable CAI events in agreement with Pavone's data [6] while Cohen et al. described a relevant CAI phenomenon significantly correlated with low age (less than 2 years) [3].

Conversely to Pavone and Cohen, our study involved both patients already in GH therapy and patients GH treatment-naïve. We did not find any correlation between GH therapy and sleep respiratory disorders but the limited number of cases could be a limitation about this data.

Our study has several limitations. First, the number of cases are limited and the age range is very wide. Second, we did not have polysomnographic recordings so we are not able to stage accurately sleep stage and hypopneas linked to arousal. Third, we had information about sleep quality only thanks to sleep log completed by parents/caregivers as well as information on the prevalence of nocturnal hypoventilation were not available.

In conclusion, OSA is the predominant sleep-related disorder in our PWS patient with the lack of association with obesity suggesting that hypotonia and/or facial dysmorphic features might play a pivotal role in SDB. As up to now, there are still few available data addressing the mechanisms of SDB in PWS patients; further data are necessary in larger study populations to better define clinical and instrumental features of SDB in PWS patients and to find the most appropriate therapy and follow-up strategies.

Authors' contributions All coauthors attended the initial meeting and participated in the discussion of topics and in the design of the consensus paper. AC wrote the initial draft of the manuscript which was then circulated to all coauthors. Comments and annotations of all coauthors were included in subsequent drafts. The final version of the manuscript was approved by all coauthors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statement of informed consent The participants/their caregivers gave informed consent.

References

1. Angulo MA, Butler MG, Cataletto ME (2015) Prader-Willi syndrome: a review of clinical, genetic, and endocrine findings. J Endocrinol Investig 38(12):1249–1263. https://doi.org/10.1007/s40618-015-0312-9
2. Butler MG, Sturich J, Lee J, Myers SE, Whitman BY, Gold JA, Kimonis V, Scheimann A, Terrazas N, Driscoll DJ (2011) Growth standards of infants with Prader-Willi syndrome. Pediatrics 127(4):687–695. https://doi.org/10.1542/peds.2010-2736
3. Cohen M, Hamilton J, Narang I (2014) Clinically important age-related differences in sleep related disordered breathing in infants and children with Prader-Willi Sydrome. PLoS One 9(6):e101012. https://doi.org/10.1371/journal.pone.0101012
4. Grugni G, Sartorio A, Crinò A (2016) Growth hormone therapy for Prader–Willi syndrome: challenges and solutions. Ther Clin Risk Manag 12:873–881. https://doi.org/10.2147/TCRM.S70068
5. Iber C, Ancoli-Israel S, Chesson A, Quan SF, for the American Academy (2007) The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. American Academy of Sleep Medicine, Winchester
6. Pavone M, Caldarelli V, Khirani S, Colella M, Ramirez A, Aubertin G, Crinò A, Brioude F, Gastaud F, Beydon N, Boulé M, Giovannini-Chami L, Cutrera R, Fauroux B (2015) Sleep disordered breathing in patients with Prader-Willi syndrome: a multicenter study. Pediatr Pulmonol 50(12):1354–1359. https://doi.org/10.1002/ppul.23177
7. Sedky K, Bennett DS, Pumariega A (2014) Prader-Willi syndrome and obstructive sleep apnea: co-occurrence in the pediatric population. J Clin Sleep Med 10(4):403–409. https://doi.org/10.5664/jcsm.3616
8. The WHO Child Growth Standard, the WHO website. Available: http://www.who.int/childgrowth/standards/en/