Psychomotor Development in Infants with Prader-Willi Syndrome and Associations with Sleep-Related Breathing Disorders

DEDERIEKE A.M. FESTEN, MAAIKE WEVERS, AL W. DE WEERD, RENILDE A.S. VAN DEN BOSSCHE, HUGO J. DUIVENVOORDEN, BARTO J. OTTEN, JAN MAARTEN WIT, AND ANITA C.S. HOKKEN-KOELEGA

Dutch Growth Foundation [D.A.M.F., M.W., A.C.S.H.-K.], 3016AH Rotterdam, The Netherlands; Sleepcenter [A.W.W., R.A.S.B.], SEIN 8025BV Zwolle, The Netherlands; NIHES [H.J.D.], Erasmus University Medical Center, 3015GE Rotterdam, The Netherlands; Radboud University Hospital [B.J.O.], 6525GA Nijmegen, The Netherlands; Leiden University Medical Center [J.M.W.], 2333ZA Leiden, The Netherlands; Sophia Children's Hospital / Erasmus Medical Center [A.C.S.H.K.], 3015GJ Rotterdam, The Netherlands

ABSTRACT: Prader-Willi syndrome (PWS) is a neurogenetic disorder with hypotonia, psychomotor delay, obesity, short stature, and sleep-related breathing disorders. The aim of this study was to evaluate the association between psychomotor development and sleep-related breathing disorders in PWS infants. Bayley Scales of Infant Development were performed in 22 PWS infants, with a median (interquartile range, IQR) age of 1.8 (1.1–3.4) y, and a body mass index SD score (BMISDS) of -0.5 (-1.3 to 1.6). We evaluated psychomotor development in relation to results of polysomnography. Median (IQR) mental and motor development was 73.1% (64.3–79.6%) and 55.2% (46.5–63.1%) of normal children, respectively. All infants had sleep-related breathing disorders, mostly of central origin. The apnea hypopnea index was not associated with psychomotor development. Only four infants had obstructive sleep apnea syndrome (OSAS). They had a significantly delayed mental development of 65.5% (60.0–70.3%) of normal. They had a median BMISDS of 1.4 (0.1–1.6), which tended to be higher than in those without OSAS. Our data indicate that psychomotor development in PWS infants is not related to central sleep-related breathing disorders, but infants with OSAS have more severely delayed mental development, suggesting that PWS infants should be screened for OSAS. (*Pediatr Res* 62: 221–224, 2007)

PWS is characterized by a number of signs and symptoms, including muscular hypotonia, hypogonadism, psychomotor delay, obesity that may become extreme after the age of 2–4 y, and short stature. Children with PWS have an abnormal body composition with a relatively high body fat percentage and a low lean body mass. Even in infants, who are underweight, body fat percentage is high (1,2). Sleep-related breathing disorders (SRBD) may also occur (3). The underlying cause of the syndrome is a paternal deletion or a uniparental maternal disomy of chromosome 15q11-13 (4). In 1–5%, PWS is the result of an imprinting-center mutation (5), which causes genes in the 15q11-13 region of the paternally inherited chromosome to be silenced. Nowadays PWS is mostly diagnosed in infancy (6,7). This results in optimal management

opportunities with regard to diet, exercise, and education. As a result, most young PWS patients are currently not severely obese.

In healthy children, associations between sleep-disordered breathing and cognition, school performance and psychiatric and behavioral co-morbidities are well-known (8,9). In healthy infants, inverse associations between the snoring-related arousal index and standardized mental development assessment scores have been reported (10). In this study we examined whether there was an association between psychomotor development, and sleep-related breathing disorders in infants with PWS.

PATIENTS AND METHODS

Patients. All infants, included in the current analysis, participated in a randomized, controlled, growth hormone (GH) trial in children with genetically confirmed diagnosis of PWS. This trial investigated the effects of GH treatment *versus* no GH on growth, body composition, activity level, and psychosocial development. In April 2003, a polysomnography (PSG) study was started in addition to the original protocol, to evaluate the effects of GH on sleep-related breathing disorders. The inclusion criteria for infants in the PSG study were: 1) no upper respiratory tract infection during PSG, and 2) no previous GH treatment. We used standardized tests to assess psychomotor development. Data were related with results of PSG. Tests were performed before start of GH treatment. Twenty-two infants with PWS were eligible for the present analysis.

The study protocol was approved by the Medical Ethical Committees of Erasmus Medical Center, Rotterdam, The Netherlands, and the other participating centers.

Written informed consent was obtained from the parents.

Anthropometry. Below the age of 2.5 y, supine length was measured, and thereafter standing height. Height was measured with a Harpenden stadiometer. Weight was assessed on an accurate scale, and body mass index (BMI) (kg/m^2) was calculated. Height and BMI were converted into SDS (11) using Growth Analyser Version 3.0 (www.growthanalyser.org).

Psychomotor development. Psychomotor development was assessed at baseline and after 12 mo by the Bayley Scales of Infant Development–II, Dutch version (BSID-II) (12). BSID-II yields 2 scores: mental developmental age (in months) and motor developmental age (in months). The mental scale consists of items in relation to visual and auditory information processing, language development, memory, eye-hand coordination, imitation, and problem solving. The motor scale assesses fine and gross motor skills. All

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Correspondence: Dederieke A.M. Festen, M.D., Dutch Growth Foundation, Westzeedijk 106, 3016 AH Rotterdam, The Netherlands; email: d.festen@erasmusmc.nl

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Abbreviations: AHI, apnea hypopnea index; BSID-II, Bayley Scales of Infant Development; IQR, interquartile range; OSAS, obstructive sleep apnea syndrome; PSG, polysomnography; PWS, Prader-Willi syndrome; Sao_2 , oxygen saturation; SDS, standard deviation score

psychomotor tests were conducted by two psychologists. Reference data of healthy Dutch children were used to compare the results of our patients (12).

Polysomnography. Patients were admitted to the sleep center at 1700 h, accompanied by one parent. They underwent a complete overnight PSG. Recordings included EEG, electro-oculogram, one-channel derivation of ECG, and surface electromyography of the submental muscle and both anterior tibial muscles. Nasal-oral airflow was monitored by nasal pressure prongs fixed in the nose, respiratory effort by thoracoabdominal strain gauges and oxygen saturation (Sao₂) by pulse oximetry. All PSG studies were evaluated independently by two persons, both certified in PSG analysis. In case of major discrepancies between the two assessments, a third expert opinion was asked. The polygraphic records were scored according to standard criteria of Rechtschaffen and Kales (13). A period of apnea or hypopnea was defined as more than 90% (apnea) or 50% (hypopnea) reduction of airflow for at least three breaths. For hypopneas, the additional criterion was a reduction of oxygen saturation of at least 4%. Periods of apnea and hypopnea were counted over the period of sleep during the night and calculated as mean per hour of sleep (AHI). An AHI of more than 1 per hour is considered pathologic (14). Apneas were considered "obstructive" when absence of airflow occurred without a decrease in respiratory effort and "central," when thoracic movements were absent. Patients with an obstructive sleep apnea index of more than 1/h were considered to have obstructive sleep apnea syndrome (OSAS). Abnormal Sao₂ was defined as a Sao₂ below 92% or a decrease in Sao₂ of more than 4% compared with baseline values.

Data analysis. Data were expressed as median (IQR). We could not use standardized scores for psychomotor development, because PWS infants scored generally below the lowest range, in particular for the subscale of motor development. We therefore expressed these results as developmental age divided by chronological age, multiplied by 100, which reflects the percentage of expected development for that age. Differences between infants with and without OSAS were tested using independent sample *t* tests. Multiple regression analysis was used to calculate the associations between anthropometric parameters and psychomotor development. One-way ANOVA was used to test differences in respiratory parameters and psychomotor development between children with paternal deletion and those with uniparental maternal disomy. To calculate the magnitude of the difference in development between infants with or without OSAS, a Cohen's *d* was calculated, using the following formula (15):

$$d = \frac{(\bar{x}_{OSA=0} - \bar{x}_{OSA=1})}{\sqrt{\frac{sd^2 * (n-1)_{OSA=0} + sd^2 * (n-1)_{OSA=1}}{(n-1)_{OSA=0} + (n-1)_{OSA=1}}}}$$

Cohen's *d* of 0.20 was considered a minor, 0.50 a medium, and 0.80 a major difference. Statistical analysis was performed by the Statistical Package for Social Sciences (SPSS Version 11, SPSS Inc. Chicago, IL).

RESULTS

General clinical characteristics. Complete BSID-II tests and complete PSG were performed in 22 infants (15 boys) with PWS, who had a median (IQR) age 1.8 (1.1–3.4) y (Table 1). Most infants were not obese, the median BMI of the total group being –0.5 SDS (–1.3 to +1.6). Two of 22 infants (9%) had a BMI above +2 SDS. All infants had a genetically confirmed diagnosis of PWS. Nine patients had a paternal deletion, 10 had a uniparental maternal disomy. In three patients PWS was confirmed by methylation test, but the underlying genetic defect was not yet specified.

Psychomotor development and sleep-related breathing disorders. Median mental development in the total group was 73.1% of expected mental development for age and motor development was 55.2% of expected motor development. Both were significantly below normal (Table 1). All infants had a sleep-related breathing disorder (SRBD). Median (IQR) AHI was 6.1 (4.2–13.3)/h. Most apneas were identified as central apneas. Multiple regression analysis showed no association between mental or motor development and the severity of sleep-related breathing disorders. We did not find any

Table 1. Clinical characteristics, psychomotor development and respiratory parameters in infants with PWS

	Median	IQR
No.	22	
Sex	15 boys, 7 girls	
Age (y)	1.8	1.1–3.4
BMI (kg/m ²)	16.1	14.7–18.1
BMI (SDS)	–0.5	–1.3–1.6
Mental developmental ratio (%)	73.1	64.3–79.6
Motor developmental ratio (%)	55.2	46.5–63.1
AHI (per hour of sleep)	6.1	4.2–13.3
CAI (per hour of sleep)	5.2	2.6–7.9
OAI (per hour of sleep)	0.0	0.0–0.8
HI (per hour of sleep)	0.4	0.0–2.7
Duration longest apnea (s)	14.0	12.8–20.3

Data are expressed as median (IQR). Age mentioned in table corresponds with age at time of PSG. Median age during evaluation for psychomotor development was 1.6 (1.2–3.3 y).

Respiratory parameters are listed as indices (apneas/hour). AHI, apnea hypopnea index; CAI, central apnea index; OAI, obstructive apnea index; HI, hypopnea index.

difference between children with paternal deletion and maternal disomy with respect to psychomotor development or respiratory parameters.

Infants with obstructive sleep apnea syndrome. Four infants had obstructive sleep apnea syndrome (OSAS), defined as an obstructive sleep apnea index of more than 1/h. Motor development was not different between infants with and without OSAS. Mental development was however decreased in infants with OSAS [median (IQR) 65.5% (60.0–70.3%) of normal] compared with those without OSAS [74.9% (64.8–81.3%), *p* = 0.03] (Fig. 1, Table 2). The magnitude of the difference was 0.74 (Cohen's *d*), indicating a substantial difference. Infants with OSAS tended to be older and to have a higher BMI (median, 1.4 SDS) than infants without OSAS (median BMI, 0.6 SDS), although this did not reach statistical significance. Only one of the infants with OSAS was considered overweight, defined as a BMI above +2 SDS.

DISCUSSION

In PWS infants, mental and motor developments were both delayed compared with normal development for age. Sleep-related breathing disorders were common, in particular central sleep apnea. No associations between psychomotor development and any of the respiratory abnormalities were found. In the four infants with OSAS, we found a significantly lower mental development compared with infants without OSAS. Infants with OSAS tended to be older and tended to have a higher BMI than the remaining 18 children without OSAS. There was no significant difference in motor development between both groups.

Data concerning associations between psychomotor development and sleep-related breathing disorders in PWS infants are limited. In healthy infants, it was shown that the snoring-related arousal index was associated with the mental developmental index, measured by BSID (10). These data suggested that even mild symptoms of sleep-disordered breathing were associated with lower mental development scores in healthy

Figure 1. Mental development in infants with or without obstructive sleep apnea syndrome. The Y-axis represents mental development expressed as mental developmental age in children with ($n = 4$) and without ($n = 18$) obstructive sleep apnea. Mental development is significantly lower in infants with OSAS compared with those without. (* $p = 0.03$, independent t test for observations with unequal variances). Magnitude of the difference (Cohen's d) is 0.74, indicating a medium to large difference.

Table 2. Mental and motor development in infants with and without OSAS

	OSAS		No OSAS	
	Median	IQR	Median	IQR
No.	4		18	
Age	2.6	1.3–3.5	1.6	1.2–2.7
Gender	4 boys		11 boys/7 girls	
BMI (kg/m ²)	17.0	16.5–19.7	15.9	14.6–18.1
BMI (SDS)	1.4	0.1–1.6	0.6	–1.0–1.2
Mental development (%)	65.5	60.0–70.3	74.9*	64.8–81.3
Motor development (%)	50.1	45.2–61.8	56.2	47.9–63.3

Mental and motor development (%) is calculated by dividing developmental age, assessed by BSID II-NL by chronological age and multiply by 100 and represents the percentage of expected development for age. Mental development is significantly decreased in infants with OSA compared to infants without OSAS. OSAS is defined as obstructive sleep apnea index over 1/h. * $p < 0.05$.

children. In a study by Greenfield *et al.* (16), 5 of 29 normal children with OSAS, due to adenotonsillar hypertrophy, had a developmental delay, as subjectively reported by parents. After adenotonsillectomy, the developmental delay resolved in 3 of them.

To our knowledge, so far only one author has reported associations between neurobehavioral abnormalities and sleep-related breathing disorders in patients with PWS. In 13 patients (3 infants), aged 1.5–28 y, OSAS was prevalent and associated with a higher BMI, and some behavioral abnormalities. Unfortunately, they did not present data on the psychomotor development of the 3 infants (17).

In children, enlargement of adenoid or tonsils, in association with increased upper airway collapsibility, is by far the most common cause of OSAS (18). In addition, obesity may cause obstructive sleep-related breathing disorders, as has also been found in adults (19). In children and adults with PWS, both obesity and a small nasopharynx are thought to cause OSAS (3).

We used BMI SDS to define obesity in PWS infants. However, BMI underestimates the actual degree of obesity in individual with PWS, because of their abnormal body composition. As age-related reference data for body fat percentage, measured by dual energy x-ray absorptiometry (DXA) were not available for infants, we did not report DXA scans in the PWS infants.

Our results indicate that OSAS should be treated by adenoidectomy and/or tonsillectomy when adenoid and/or tonsils are enlarged. To optimize mental development in PWS infants, it is also important to introduce weight control, particularly when obesity is already present. If weight control or adenotonsillectomy do not relieve symptoms of OSAS, the use of nasal continuous positive airway pressure might be considered (20).

The mechanism underlying the negative association between OSAS and mental development is unknown. Beebe and Gozal (8) proposed a model, explaining the relation between OSAS, and lower cognition, and neurobehavioral abnormalities. According to this model, OSAS-related sleep disruption and intermittent hypoxia and hypercapnia may impair the restorative features of sleep and the cellular or chemical homeostasis in the brain, resulting in a prefrontal cortical dysfunction. The latter would lead to a dysfunction of the cognitive executive system, which is responsible for developing a future-oriented, organized and flexible approach to problem situations. This would result into adverse daytime effects, such as behavioral problems, in particular related to attention deficit/hyperactivity disorder, and difficulties with problem solving (21,22).

In our study, the infants with OSAS tended to be older and had a higher BMI than infants without OSAS. It cannot be excluded that the higher BMI in infants with OSAS also impaired their motor development. Motor development tended to be more impaired in infants with OSAS, although this did not reach statistical significance.

Remarkable is that the central apneas during sleep in infants with PWS are by far more common than obstructive sleep apneas. However, we found no associations between mental or motor development and central respiratory events during sleep. These results indicate that, although central respiratory abnormalities are more common in PWS, the obstructive events have more severe implications with regard to mental development in infants. Central apneas might reflect the hypothalamic dysfunction in PWS (23). In addition, it has previously been reported that the neurally differentiated embryonal carcinoma-cell derived factor (Necdin) gene, one of the protein-coding genes that are deficient in PWS, might be involved in the central SRBD in PWS (24).

To our knowledge, this is the first study in infants with PWS evaluating the association between psychomotor development

and sleep-related breathing disorders. Our results indicate that in PWS infants, as recently suggested for the normal population, mental development might be delayed in the presence of obstructive sleep apnea, suggesting that early treatment of OSAS in infancy should be considered.

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