ANALYSIS OF SLEEP- AND WAKE DISORDERS IN PRADER WILLI SYNDROME

N.L.E. Vandenbussche and J.H.M. de Groen
Centre for sleep- and wake disorders ‘Kempenhaeghe’, Heeze

INTRODUCTION

Prader Willi syndrome (PWS) is a complex genetic disorder with an incidence of one in 10,000 – 30,000 live births. Most patients (70 – 75%) carry a deletion in the paternally derived chromosome 15q11-q13 (Del 15), 25% have maternal uniparental disomy (UPD), and 2 – 5% show abnormal methylation of the imprinting center or balanced translocation. Clinical findings in PWS suggest an involvement of the hypothalamus – pituitary axis and include neonatal hypotonia, developmental delay, short stature, behavioral abnormalities, childhood-onset obesity, hypogonadisme and abnormal thermoregulation\(^1,2\). Excessive daytime sleepiness (EDS) during the day is common in PWS (2/3 of patients), but the pathogenesis of this symptom has not been fully clarified. Only in minority of cases, EDS can be explained by an underlying sleep disorder: sleep related breathing disorder (SRBD) or narcolepsy. We will discuss this in this article.

PATIENTS AND METHODS

All patients were referred to our outpatient clinic for sleep- and wake problems and had genetically confirmed diagnosis of PWS (n=5). The sleep history was taken from patients and their parents and parents were asked to fill out sleep logs during two weeks. All patients got full polysomnography, inclusive respiratory parameters, for one or two nights. Two patients got MSLT the day after the first registration night. Two patients got Human leukocyte antigen typing (HLA-typing)for DQB1*0602.

RESULTS

Patient 1
A 46 year old male with PWS was referred to our centre because of EDS, snoring and cataplectic attacks. Other characteristics were the marked weight gain, restlessness during sleep and obsessive compulsive behaviour such as skin-pinching and hair-pulling. The patient’s weight was 130 kg, height 161 cm, and calculated body mass index (BMI) 50.2 kg/m\(^2\). Physical examination revealed hypertension, blood pressure of 180/105 mmHg. He got polysomnography for two subsequent nights. The abnormalities we found were sleep onset REM sleep period (SOREMP) in both nights, apnea-hypopnea index (AHI) of 5.1 per hour but oxygen desaturation index (SaO\(_2\)-desat. index) of 28.2 per hour with respiratory effort related arousals (RERA’s). HLA-typing for DQB1*0602 was negative. We started a weight reducing diet. He lost 17 kg and his BMI decrease to 43.6, still very high, but not that high as before. With this treatment, the cataplectic attacks disappeared. Thus, the cataplexy appeared to be secondary to SRBD. EDS improved but did not disappear completely.
Patient 2
A 16 year old male with PWS was referred to our centre because of EDS, snoring in supine position and episodes of headache. His medical history was positive for complex partial epilepsy and behavioural problems with aggressive verbal behaviour. His epilepsy was treated by carbamazepine 300 mg per day (100 - 200 mg), it was only partially effective. The patient’s weight was 69 kg, height 167 cm, and BMI 24.8 kg/m² (p85-90). Physical examination showed a low position of the soft palate.

He got polysomnography for one night. We found apnea-hypopnea index (AHI) of 2 and RERA’s in supine position. We advised to avoid sleeping in supine position. With this treatment there was a decrease of snoring and of EDS.

Patient 3
A 35 year old male with PWS was referred to our centre because of EDS, snoring and cataplexy. The patient’s weight was 118.4 kg, height 164 cm, and BMI 44 kg/m².

He got polysomnography and multiple sleep latency test (MSLT). The sleep registration showed no abnormalities. On MSLT we found two REM sleep periods after 2 and 4 minutes and EDS. Patient refused blood analysis and lumbar punction.

We started venlafaxine 37.5 mg on trial, EDS and cataplexy disappeared completely with this treatment.

Patient 4
A 14 year old male with PWS was referred to our centre because of EDS. Parents described long daytime naps and episodes where the patient had fallen asleep in inappropriate circumstances, such as during meals and during a conversation. Further complaints were loud snoring, restlessness during sleep and morning headache. His medical history was positive for scoliosis. The patient’s weight was 51 kg, height 136 cm, and BMI 27.6 kg/m² (>p95 = 26).

He got polysomnography for one night. The abnormalities we found were decrease of Slow Wave Sleep (9%), AHI of 15 per hour, SaO₂-desat. index of 35 per hour and short periods of hyperventilation. We started Bilevel positive airway pressure (BiPAP). However, the complaints of EDS decreased, but they didn’t disappear. A polygraphic control with BiPAP (inspiratory pressure of 15 cm H₂O and expiratory pressure of 11 cm H₂O) showed an adequate suppression of the respiratory events with AHI of 2 per hour and SaO₂-desat. index of 10 per hour.

Patient 5
A 10 year old female with PWS was admitted to our centre because of snoring and apneas. No complaints of EDS. Parents described cataplectic attacks. These attacks were spontaneously decreased. Several years ago, she had it once a day, at this moment only once a month. Her medical history was positive for asthma and scoliosis. The patient her weight was 35 kg, height 151 cm, and BMI 15.4 kg/m² (p25).

She got polysomnography during one night and MSLT. There were no abnormalities found in the sleep registration. MSLT showed shortened sleep latency. HLA-typing for DQ-B1*0602 was negative.
**Table 1.** This table summarizes the 5 PWS patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>46</td>
<td>16</td>
<td>35</td>
<td>9</td>
<td>10</td>
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<tr>
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<td>Del 15</td>
<td>UPD</td>
<td>Del 15</td>
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<tr>
<td>BMI</td>
<td>50.2</td>
<td>24.8 (p85-90)</td>
<td>44</td>
<td>27.6 (&gt;p95=26)</td>
<td>15.4 (p25)</td>
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<td>EDS</td>
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<td></td>
<td>Cataplexy</td>
<td>Snoring</td>
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<td></td>
<td>PSG (2 nights)</td>
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<td>PSG + MSLT</td>
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<td>PSG + MSLT</td>
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<td>HLA-typing</td>
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<td>Investigations</td>
<td>2x SOREMP</td>
<td>RERA’s in supine position</td>
<td>2x REM sleep periods in MSLT</td>
<td>AHI 15</td>
<td>Moderate sleepiness (MSLT score between 5 and 8 min)</td>
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<tr>
<td></td>
<td>AHI 5.1</td>
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<td></td>
<td>SaO2-desat. index 35</td>
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<td>SaO2-desat. index 28.2</td>
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<td>Severe sleepiness (MSLT score ≤ 5 min)</td>
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<td>Narcolepsy</td>
<td>OSAS</td>
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<td></td>
<td>Cataplexy</td>
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M = male; F= female

**DISCUSSION AND CONCLUSIONS**

The following sleep disorders were found in our PWS patients: SRBD and narcolepsy. None of our patients had circadian rhythm disorder, restless legs syndrome or periodic limb movement disorder. Four of our five PWS patients complained of EDS, one of the patients did not complain of EDS but the MSLT showed a clear shortened sleep latency. Treatment of their SRBD or narcolepsy resulted in complete disappearance of the EDS in only one patient, in the others EDS improved only partially. This means that the underlying sleep disorder cannot be considered sufficient explanation for the EDS in PWS. These findings are consistent with previous studies, suggesting that EDS in PWS might be a consequence of a primary hypothalamic dysfunction.

Moreover, we found other discrepancies in our PWS-patients. The prevalence and the degree of SRBD is much lower in PWS than expected from the BMI. One possible explanation of these findings is that obesity in PWS is usually subcutaneous, quite different from visceral pattern of obesity involved in the pathogenesis of apneas in obese adult males. Another explanation is a reduced arousal- and cardiorespiratory response to hypoxia and hypercapnia in PWS patients.

In agreement with the literature we found SOREMP’s, REM sleep periods in MSLT and typical narcoleptic symptoms (cataplexy). These findings, together with the recent report of low cerebrospinal fluid hypocretin levels correlated with EDS, may lead to consider PWS sleep disturbances similar to narcolepsy. However, no association is found with HLA-DR-
Additionally, post-mortem research in PWS patients with narcolepsy-like symptoms, such as SOREMP and cataplexy, showed no significant difference in total number of hypocretin-containing neurons in the lateral hypothalamus compared to age-matched controls. Atypical is also that one of our patients had narcolepsy secondary to SRBD and another patient had cataplectic attacks decreasing during time. Further investigations are needed to clarify if increased REM pressure and EDS in PWS have a different pathogenesis from narcolepsy. Also, some of the narcolepsy-like symptoms in PWS could be a result of a primary hypothalamic dysfunction.

REFERENCES