Reversibility of deficient sleep entrained growth hormone secretion in a boy with achondroplasia and obstructive sleep apnea

Steven J. Goldstein, Richard H. K. Wu, Michael J. Thorpy, Robert J. Shprintzen, Robert E. Marion and Paul Saenger

Department of Paediatrics, the Center for Cranio-Facial Disorders and the Sleep Wake Disorders Center of the Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, New York, USA

Abstract. Obstructive sleep apnea may lead to disordered sleep architecture and impair the physiologic slow wave sleep related growth hormone release. Obstructive sleep apnea occurs with craniofacial syndromes and in children with airway narrowing, pharyngeal hypoplasia, tonsillar adenoidal hypertrophy, micrognathia and achondroplasia. To examine the relationship between disordered sleep and growth hormone release we studied a 9 year old male with achondroplasia, growth failure (3 cm/year) and obstructive sleep apnea. Polysomnography data and a 20 min sampling for sleep entrained growth hormone showed before therapeutic tracheostomy numerous apneic episodes, absent slow wave sleep and abnormal low growth hormone secretion during sleep. Normalized slow wave sleep entrained growth hormone secretion after tracheostomy led to a sustained increase in growth rate. Normal growth rate (> 5 cm/year) continues 2 years after tracheostomy. We conclude that obstructive sleep apnea may impair sleep related growth hormone release. Obstructive sleep apnea may be a useful model for other diseases in which growth failure and sleep disturbances are linked.

Obstructive sleep apnea (OSA) is defined as the cessation of breathing lasting 10 sec or more with continuing respiratory effort, in the presence of upper airway obstruction; OSA syndrome is the occurrence of at least 30 apneas during 7 h of sleep (Guilleminault et al. 1976a). The syndrome can cause significant morbidity and mortality in children and adults. Symptomatology includes restless sleep with loud snoring, abnormal breathing with frequent periods of apnea, gasping for air, sleeping in unusual positions with abnormal body movements, enuresis, daytime somnolence, personality change, intellectual deterioration, and declining school performance in children (Guilleminault et al. 1976b). The causes of OSA include airway narrowing, pharyngeal hypoplasia, tonsillar and adenoidal hypertrophy, and micrognathia (Guilleminault et al. 1978). OSA is seen in many craniofacial syndromes, such as Treacher Collins and Stickler Syndrome, hemifacial microsomia, and the Robin sequence (Guilleminault et al. 1981; Shprintzen 1982). Short stature and poor weight gain have been described in children with OSA, as have a variety of sleep cycle disruptions (Brouillette et al. 1982).

A significant number of patients with craniofacial syndromes followed at the Center for Craniofacial Disorders at Montefiore Medical Center have had poor growth. Two patients with hemifacial microsomia who had OSA and growth failure grew rapidly after tracheostomy and resolution of sleep apnea. A boy decelerated in growth from the 75th percentile for height at age 2 to the 10th percentile at age 5. In the 2 years
after tracheostomy at age 5, he demonstrated significant growth acceleration; at age 7 his height was at the 50th percentile. The height of the other patient was at the 25th percentile at the time of tracheostomy, at 5½ years. At age 8, her height was plotted at the 75th percentile. She demonstrated a similar gain in weight. Because of the intimate association between slow wave sleep (SWS) and GH release, sleep disorders may cause disordered growth hormone secretion. When we observed that relief of OSA reversed growth failure, we were prompted to examine the relationship between sleep apnea, growth failure, and sleep entrained GH release, in a patient with achondroplasia, obstructive sleep apnea, and growth failure.

Material and Methods

Case report

This 9-year-old male was a 2470 g, 44 cm long product of a full term pregnancy, born by repeat caesarean section. Achondroplasia was diagnosed on day 5. He was subsequently hospitalized at 5 months of age for ventriculography for suspected hydrocephalus. The study, complicated by the development of alpha streptococcal ventriculitis, revealed slight ventricular dilatation consistent with communicating hydrocephalus.

Follow-up until age 4 8/12 revealed growth measurements consistently at 1 SD below the mean (all growth data analyses utilized growth charts developed especially for patients with achondroplasia) (Horton et al. 1978) unchanged ventricular dilatation, and moderate global developmental delay (Fig. 1). He was then lost to medical attention until age 8. He was referred to our services at age 8 4/12 because of marked growth failure (> 2 SD below the mean) and symptomatology consistent with severe OSA, including intellectual decline. Physical examination at that time revealed the classic stigmata of achondroplasia and marked somnolence with noisy respirations. Sexual development was Tanner 1. There was no evidence of progression of hydrocephalus. Developmental testing, limited by the patient's inability to fully understand instructions, was consistent with functioning at a 3 to 5 year level. There was no foreign body or soft tissue swelling visible on lateral neck radiography. Nasopharyngoscopy was performed with the patient upright and co-operative; Muller manoeuvre (deep inspiration with partial occlusion of the nares) demonstrated a small airway, with collapse of the lateral pharyngeal walls causing virtual total airway obstruction. Baseline endocrine and non-endocrine testing for growth failure was performed. Serum

![Graph](image-url)

**Fig. 1.**

Growth data of our study subject utilizing growth charts derived for patients with achondroplasia (see Horton et al. 1978).
Methods

The T4 electrolytes, liver function testing, BUN, creatinine, calcium, phosphorus and alkaline phosphatase were normal. Bone age and somatomedin-C were not done. At 08.00 h cortisol was 328 nmol/l; 21.00 h cortisol was 126 nmol/l (normal). TSH 2.8 mU/l (normal < 4); Free T4 was 30.9 pmol/l (normal). Polysomnography (PSG) was performed two days before tracheostomy at 8 8/12 years (pre tracheostomy study); the study was repeated 4.5 months later (post tracheostomy PSG).

Results

The pre-tracheostomy PSG revealed significant obstructive sleep apnea, with 105 apneic episodes per hour; there were no mixed or central apneas (Table 1). Significant hypopnea was present as well, with a high apnea/hypopnea index (total apneas and hypopneas divided by total study time), a widely used index of significant sleep apnea. Apnea was so frequent that there was no normal sleep architecture (i.e. no organized progression through the stages of sleep) (Fig. 2). The average duration of obstructive apnea was 20 seconds; the long apnea lasted 26 sec. During this study, sinus arrhythmia, bradytachycardia, and arterial oxygen desaturation were noted as well. There was a marked increase in time awake. Total overnight GH secretion and secretory peaks were diminished when compared to normal (Finkelstein et al. 1972) (Table 2).

Tracheostomy resulted in a dramatic normalization of the sleep pattern (Fig. 3), with normal sleep stage distribution (except for a decrease in percentage of REM sleep), a normal amount of SWS, and elimination of apnea. Percent wake time decreased by more than half. Arterial oxygen saturation during sleep normalized to 94%. Secretory episodes of GH and total overnight secretion of GH were comparable to age appropriate standards (Finkelstein et al. 1972). Growth velocity increased from 3 cm/year (growth rate > 2 SD below the mean), to 5.2 cm/year during the first 8 months after tracheostomy (normal for age in achondroplasia). This normalization of growth velocity (5.5 cm/year) has continued for the subsequent 21 months. Tracheostomy thus resulted in rapid reversal of the symptoms of OSA.

Table 1. Sleep apnea data (polysomnographic studies).

<table>
<thead>
<tr>
<th></th>
<th>Pre-tracheostomy study (8 8/12 years)</th>
<th>Post-tracheostomy study (9 0.5/12 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total recorded study time (min)</td>
<td>487</td>
<td>497</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>380</td>
<td>442</td>
</tr>
<tr>
<td>Total wake time (min)</td>
<td>107</td>
<td>55</td>
</tr>
<tr>
<td>Total obstructive apneas</td>
<td>659</td>
<td>0</td>
</tr>
<tr>
<td>Total central apneas</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total hypopneas (decrease in respiratory airflow)</td>
<td>62</td>
<td>0</td>
</tr>
<tr>
<td>Apnea/hypopnea index (apnea plus hypopneas per hour)</td>
<td>114.3</td>
<td>0</td>
</tr>
<tr>
<td>Lowest oxygen saturation (%)</td>
<td>78</td>
<td>94</td>
</tr>
<tr>
<td>EKG abnormalities</td>
<td>sinus arrhythmia</td>
<td>sinus arrhythmia</td>
</tr>
<tr>
<td></td>
<td>bradytachycardia</td>
<td></td>
</tr>
</tbody>
</table>
The totally disorganized sleep, with 105 apneas/hour, precluded generation of an adequate sleep histogram

Fig. 2.
Sleep entrained GH secretion during overnight polysomnography/pre-tracheostomy study.

Discussion
Severe sleep apnea as seen in our patient has been previously described in achondroplasia (Stokes et al. 1983). Upper airway obstruction secondary to abnormal angulation (anterior displacement) of the cranial base, causing anteroposterior shortening of the pharynx; hypotonia; brachycephaly; and mid-facial hypoplasia have been reported as causes (Shprintzen 1982; Stokes et al. 1983). Progressive hydrocephalus in achondroplasia may also lead to central and/or obstructive apnea (Stokes et al. 1983); there is no evidence for this in our patient.

While the GH secretory status in achondroplasia is incompletely clarified, normal GH responses to standardized L-DOPA and arginine testing have been reported (when subjects were compared to age matched controls) (Giordano et al. 1978). In a recent study, normal mononuclear

Table 2.
Results of polysomnography, growth hormone secretion and growth data.

<table>
<thead>
<tr>
<th>Age</th>
<th>Length (cm)</th>
<th>Weight (kg)</th>
<th>Obstructive apneas per hour</th>
<th>% Slow wave sleep</th>
<th>% Wake time</th>
<th>GH secretory episodes during sleep</th>
<th>Total GH secretion during sleep (µg)</th>
<th>Growth velocity (cm/year)</th>
<th>Observed period of growth (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-tracheostomy study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8  4/12</td>
<td>89.0</td>
<td>12.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8  8/12</td>
<td>90.0</td>
<td>13.4</td>
<td>105</td>
<td>none</td>
<td>28.1</td>
<td>1</td>
<td>24</td>
<td>3.0</td>
<td>4</td>
</tr>
<tr>
<td>Post-tracheostomy study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9  0.5/12</td>
<td>91.9</td>
<td>15.8</td>
<td></td>
<td>none</td>
<td>25.6</td>
<td>2</td>
<td>75</td>
<td>5.1</td>
<td>4.5</td>
</tr>
<tr>
<td>9  4.5/12</td>
<td>93.7</td>
<td>16.4</td>
<td></td>
<td>none</td>
<td>25.6</td>
<td>2</td>
<td>75</td>
<td>5.1</td>
<td>4.5</td>
</tr>
<tr>
<td>11  1/12</td>
<td>102.1</td>
<td>20.1</td>
<td></td>
<td>none</td>
<td>25.6</td>
<td>2</td>
<td>75</td>
<td>5.1</td>
<td>4.5</td>
</tr>
<tr>
<td>Normal for age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>none</td>
<td>15–24*</td>
<td>none</td>
<td>2–3**</td>
<td>54–122*</td>
<td>5***</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

compared cell receptor site numbers and affinity for somatomedin-C were reported for achondroplasia when compared to controls. Baseline somatomedin-C levels were normal (Rosenfeld & Hintz 1980).

Sleep entrainment of GH secretion is a well documented phenomenon. Growth hormone release is generally initiated 30 to 90 min after sleep onset, during SWS (stages 3 and 4 sleep). The first peak is generally the largest, with secretion of as much as 24–40% of the total 24-h GH output (Martin 1973). It is only during the first half of sleep that the majority of growth hormone peaks occur in SWS. Although peaks of GH do occur in other sleep stages, especially during the latter half of sleep, there is a disproportionately large percentage of SWS-related GH peaks when compared to the total time in SWS (Orr et al. 1977).

The degree of SWS disturbance in OSA appears to be variable in children. Frank et al. (1983) noted no abnormalities in sleep stage distribution in the 22 of 32 patients studied pre-operatively with PSG. In children with OSA 5–14 years of age, apneas were seen primarily in sleep stages 1 and 2, but persistent apnea delayed or precluded the progression to SWS. Guillemainault et al. (1976a) noted that older children with OSA had diminished or absent SWS with normal REM sleep and increased stage 2 sleep.

There have been few reports linking sleep disorders directly with hormonal deficiencies. Partial normalization of low sleep related LH release was reported in a 20-year-old hypogonadal male with sleep apnea two weeks after correction of the sleep abnormality by adenotonsillectomy (Mosko et al. 1980). Karacan et al. (1971) demonstrated a significant decrease in overnight GH secretion associated with SWS deprivation induced by auditory stimuli. In a study of 8 adult males with OSA (Miles et al. 1978) employing PSG and continuous blood withdrawal techniques, markedly abnormal sleep patterns and sleep entrained GH secretion were noted. All peaks were less than half of the normal value for adults; most were associated with stress or REM sleep. Two of the 3 patients with short episodes of SWS had measurable but minimal GH peaks. Wolfe & Money (1980) were able to directly correlate growth rates with sleep quality in psychosocial dwarfism and demonstrated dramatic reversibility of growth failure with environmental change. Environmental change resulted in catch-up growth, near normal sleep parameters and normalization of previously abnormal GH release by arginine provocation in 2 patients who underwent GH testing (Guilhaume et al. 1982).

While this patient did not undergo provocative
GH testing before or after tracheostomy, it is important to note that such testing might theoretically be normal in patients with deficient sleep entrained GH secretion. Such a discordance has been recently reported (Spiliotis et al. 1984) in patients with GH neurosecretory dysfunction, who had growth failure (growth rate < 4 cm/year), bone age delay, low somatomedin-C levels, and normal GH stimulation tests. These patients had partial GH deficiency, with 24 h GH levels intermediate between those of control and patients with true GH deficiency; overnight GH secretion was less than that of controls, although there were clear GH peaks.

The present study had several relative limitations which need to be addressed. The subject’s caloric intake was not specifically calculated, but food intake by recall was similar before and after tracheostomy. However, ease and duration of feeding was clearly improved with resolution of OSA. While we were unable to provide 24 h pre-study adaptation to the Sleep-Wake Disorders Unit, catheter and PSG monitor placement were completed several hours before bedtime, and a parent was present at bedside at all times. We were unable to extend the patient’s pretracheostomy observation period beyond 4 months. The observation period was terminated when the immediate need for surgical intervention became apparent after reviewing the initial PSG. Our interest focused on the patient’s sleep entrained GH release. Even though this patient did not have a full 24 h GH study; we compared his data to established normals for overnight GH secretion in children (Finkelstein et al. 1972).

In summary, we demonstrated a clear correlation between deficient overnight GH secretion and absent SWS secondary to OSA. Resumption of normal sleep patterns after tracheostomy normalized sleep entrained GH secretion and improved growth rate. Sleep related GH deficiency may contribute to the short stature seen in other craniofacial disorders in which OSA may be present, and may be a model for other states in which growth failure and sleep disturbances are linked.

Acknowledgments

Supported by grants from NIDR 1 RO3 DE 07419-01A1, GRC RR-53 and by a grant from Serono Laboratories, Inc.

References


Received July 1st, 1986.
Accepted May 21st, 1987.

Paul Saenger, M.D.,
Department of Pediatrics,
Montefiore Medical Center,
111 East 210th Street,
Bronx, NY 10467, USA.