Growth and Biochemical Markers of Growth in Children With Snoring and Obstructive Sleep Apnea

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ABSTRACT. Objective. The pathophysiological mechanisms of growth impairment frequently associated with the obstructive sleep apnea syndrome (OSAS) in children are poorly defined. The main objective of this study was to evaluate whether nighttime upper airway obstruction attributable to adenotonsillar hypertrophy and subsequent surgical treatment affect the circulating concentrations of insulin-like growth factor-I (IGF-I) and IGF-binding protein 3 (IGFBP-3) along with other growth parameters in children.

Patients and Methods. We initially studied 70 children (mean age: 5.8 years; range: 2.4–10.5 years) admitted to a university hospital because of clinical symptoms of OSAS. Their sleep was monitored with a 6-channel computerized polygraph. Data on anthropometry and circulating concentrations of IGF-I and IGFBP-3 were generated and compared with corresponding characteristics in control children (N = 35). Thirty children with an obstructive apnea-hypopnea index (OAHI) of 1 or more were categorized as children with OSAS (mean OAHI: 5.4 [95% confidence interval for mean (CI): 3.8–6.9]), whereas 40 children with an OAHI of <1 were considered as primary snorers (PS) (mean OAHI 0.13 [95% CI: 0.05–0.21]). Nineteen children with OAHI >2 underwent adenotonsillectomy attributable to OSAS and were reassessed 6 months later together with 34 nonoperated children with OAHI <2.

Results. There were no initial differences in relative height and weight for height between the 3 groups of children. No differences were observed in peripheral IGF-I concentrations, but both OSAS and PS children had reduced peripheral IGFBP-3 levels. The operated children with initial OSAS experienced a highly significant reduction in their OAHI from 7.1 (95% CI: 5.1–9.1) to 0.37 (95% CI: 0.2–0.95). Weight-for-height, body mass index, body fat mass, and fat-free mass increased during the follow-up in the operated children with OSAS, whereas only fat-free mass and relative height increased in the PS children. Both the IGF-I and the IGFBP-3 concentrations increased significantly in the operated children, whereas no significant changes were seen in the PS children.

Conclusions. These observations indicate that growth hormone secretion is impaired in children with OSAS and PS. Respiratory improvement after adenotonsillectomy in children with OSAS results in weight gain and restored growth hormone secretion. Pediatrics 2002;109(4).

ABBREVIATIONS. OSAS, obstructive sleep apnea syndrome; GH, growth hormone; IGF-I, insulin-like growth factor-I; IGFBP-3, insulin-like growth factor-binding protein 3; PS, primary snorer; EMG, electromyogram; OAHI, obstructive sleep apnea-hypopnea index; SDS, standard deviation score; BMI, body mass index; SWS, slow-wave sleep.

Snoring is relatively common in children, with the prevalence of regular snoring about 10% in preschool-aged subjects.1–3 Obstructive sleep apnea syndrome (OSAS), a condition related to snoring, is estimated to affect 0.7% to 3.4% of all children according to epidemiologic surveys.1,2,4 Pediatric OSAS may occasionally lead to even life-threatening complications,5 but less serious complications, such as failure to thrive, are more commonly recognized. Retarded weight and height gain as complications of pediatric OSAS and “catch-up” growth after treatment have been well-documented.6–11 The prevalence of this phenomenon is unknown. The cause of poor growth is not known, although many different reasons have been implicated. Abnormal nocturnal growth hormone (GH) secretion has been suggested as one possible cause.5,9,12

Circulating concentrations of insulin-like growth factor-I (IGF-I) and IGF-binding protein 3 (IGFBP-3) are strongly related to diurnal GH secretion, reflecting mean daily GH levels, and seem to correlate well with physiologic changes in GH secretion.13,14 IGF-1 is perceived as the main mediator of the growth-promoting actions of GH,15 but its association with growth in children with OSAS has been poorly explored.

The purpose of this study was to examine the growth of children with symptoms of obstructive sleep disorder, verified as OSAS or primary snoring on overnight sleep monitoring. The main objective was to analyze the relationship between obstructive sleep disturbance and biochemical growth factors, as well as the effect of surgical treatment (adenotonsillectomy) on growth and growth factors.
Participants

The study population comprised children referred from primary health care to the Department of Otorhinolaryngology, Oulu University Hospital, during the period 1994–1997 for an assessment of their need for treatment because of nighttime snoring, apneas, or daytime breathing pauses for ≥60 seconds or secondary adenotonsillar hypertrophy. Children with known upper airway anomalies, any underlying disease predisposing to upper airway obstruction, asthma, or perennial allergy were excluded. The parents completed a detailed questionnaire regarding their child’s day and nighttime symptoms. After a review of the questionnaires, the children were invited for an ear, nose, and throat examination and a thorough update of patient history. If upper airway anomalies or abnormal facial morphology were recognized, the children were excluded. Previous adenotonsillectomy did not lead to exclusion. Seventy-eight children fulfilled the inclusion criteria. They had all symptoms suggestive of OSAS, were regular snorers and/or were observed to have apneas during sleep, and were scheduled for 2 visits 6 months apart.

Eight families (8 children) of the 78 children did not agree to take part in the assessments other than overnight sleep monitoring. Seventy children (40 boys), mean age 5.8 years, range 2.4 to 10.5 years, completed all the first-visit examinations and comprised the initial study group. At the follow-up study 6 months later, the same examinations were repeated. At this time, 6 children did not participate in the study. Four cases involved a protocol violation, and 1 case suffered from technical problems. In 6 cases, the laboratory or radiograph examinations could not be repeated. Thus, 53 children (27 boys), mean age 6.5 years, range 2.9 to 11.1 years, successfully completed the whole study protocol.

For the anthropometric and endocrinologic studies, 35 children (16 boys) with no health related complaints, mean age 6.45, range 1.5 to 10.2 years, recruited from child welfare clinics and schools, were used as control subjects.16,17

An assent from the children in addition to informed consent from the parents were obtained. The study protocol was approved by the Ethics Committee, Medical Faculty, University of Oulu. The study was conducted according to the Declaration of Helsinki.

Methods

Two visits were scheduled 6 months apart. Based on the results from the first visit, the children were recognized as OSAS children or primary snorers (PS). The children who were monitored to have abnormal sleep were treated surgically, whereas the others were observed without intervention. All the baseline measurements were repeated on the second visit to evaluate the effects of the interventional modalities on the measured parameters.

All children underwent overnight sleep monitoring in the Department of Otorhinolaryngology and a clinical examination for anthropometric measurements in the Department of Pediatrics on the following morning. Thereafter, the blood samples were drawn, and the radiographs for bone age assessment was taken.

The nocturnal sleep was monitored with a 6-channel computerized polygraph with leads for an oro-nasal thermistor, a thoracoabdominal strain gauge or the static charge sensitive mistor in the presence of continuous breathing efforts revealed by the thermodetector. The signal was defined as complete cessation of the oronasal airflow as detected by the thermistor in the presence of continuous breathing efforts revealed by the thoracoabdominal strain gauge or the static charge sensitive bed. Hypopnea was defined as a reduction of at least 50% in the thoracoabdominal strain gauge or the static charge sensitive mistor in the presence of continuous breathing efforts revealed by the oronasal airflow as detected by the thermodetector. A hypopnea was only scored if an obstructive or central component was identified into the obstructive apnea/hypopnea category. Central apnea was defined as cessation of the airflow in the absence of breathing efforts. Central apneas were not included into the criterion index. Intervals of periodic obstructive hypopneas with a <50% decrease in the oronasal signal amplitude linked to a pulse increase at the termination of the hypopneas were scored.

All the patients and controls were examined for anthropometric measurements. Height was measured to the nearest 1.0 mm with a Harpenden wall-mounted stadiometer (Holtain Limited, Crymtech, Dyfed, United Kingdom) and weight to the nearest 0.1 kg with an electronic scale. Relative height (standard deviation score, SDS) [height (cm) of mother + height (cm) of father)/2 - 171]/10.22 Target height deficit was target height minus relative height at the final evaluation. The data on parental height were collected by means of a questionnaire.17 The biceps, triceps, and subscapular skin folds were measured to the nearest 0.1 mm with a Harpenden skinfold caliper (John Bull, British Indicators Ltd, St Albans, Herts, United Kingdom).21 Body mass index (BMI) was calculated [weight (kg) divided by height squared (m²)]. Finnish age- and gender-matched references were used to assess the relative BMI in SDS.24 Body density was calculated from the combined skinfolds and subscapular skinfold thicknesses according to the method described by Parizkova.25 The percentage of body fat was calculated with the method described by Keys and Brozek.26 All the anthropometric measurements were performed 3 times, and the mean value was subsequently used. The stage of puberty was ascertained according to Tanner and Whitehouse.27 Radiologic bone age was assessed from radiographs of the left hand and wrist according to Tellegen.28

Blood samples were taken on the morning following sleep monitoring. Plasma IGF-I concentrations were analyzed with a radioimmunoassay using commercial reagents (Incstar Corporation, Stillwater, MN) with a sensitivity of 1.0 pg/mL. Serum IGFBP-3 concentrations were determined radioimmunoanalytically (Diagnostic Systems Laboratories Inc, Webster, TX) with a sensitivity of 30 pg/mL. The methods have intra-assay coefficients of variation <5%. Both samples from the same individual were analyzed in the same assay, to exclude the effect of interassay variation.

Within a fortnight after the first visit children with OAHI ≥2 (19 children) underwent tonsilllectomy and adenoidectomy, if not previously performed. Children with OAHI <2 were observed without intervention (34 children), including those with mild abnormal sleep monitoring (1-OAHI<2).

One child with an OAHI of 2.34 was included in the nonintervention group; because of ongoing speech therapy, the speech therapist suggested that surgical therapy should be avoided. The children served as their own controls. The results from the first and the second visits were analyzed within and between the groups.

Statistics

The data were processed using the SPSS for Windows software (SPSS Inc, Chicago, IL). Student's t test for 2 independent samples and paired samples was applied for normally distributed data. The nonparametric Mann-Whitney U test and Wilcoxon signed rank tests were used for data with skewed distribution. The Mann-Whitney U test was used for ordinal data. Regression analysis was applied when the dependent and independent variables were continuous, and the residuals ranged from −3 to 3 without obvious skewness.

RESULTS

First Visit

Thirty of the children studied had OSAS (OAHI ≥1), whereas 40 were considered as PSs (OAHI<1; Table 1). The relative height and weight for height did not differ between the groups (Table 2). The OSAS and PS children showed a similar trend toward a target height deficit compared with the controls. Mean relative height was lower in both groups than mean target height. The BMIs were similar in the 3 groups (Table 2). All the children studied were prepubertal, and the anthropometric data were therefore not presented according to sex.

<ref>http://pediatrics.aappublications.org/ by guest on October 3, 2017</ref>
Increased weight for height in the operated group (OAHI ≥ 50%) with pulse oxygen desaturation index of 4% increases at the end of periods (min/h).

Follow-up Visit

On the second visit, significant improvements could be seen in the respiratory parameters in the surgically treated group of 19 children (OAH ≤ 2; Table 4). In the nonsurgery group of 34 children (OAH < 2), no significant changes were observed. Weight for height and BMI had increased significantly in the operated group (P = .001 and P = .01, respectively). The increase in the weight for height in the operated group seemed to be primarily attributable to an increase of body fat (P = .02); because although the mean fat-free mass increased more in the operated group, the difference was not significant according to the linear regression model with age and intervention status as independent variables (B = 0.59; r² = 0.21; P = .08). Relative height increased significantly only in the nonsurgery group (P = .02). There were no significant changes in bone age between the 2 visits in either group.

The peripheral concentrations of IGF-I and IGFBP-3 were significantly higher in the operated children and IGFBP-3 concentrations in the circulating IGF-I and IGFBP-3 levels were inositive. The initially significant difference in IGFBP-3 levels between the operated children and the controls (P = .001) had disappeared at the second visit (Fig 2). Only in 2 cases (10%) out of 19 were the IGF-I and IGFBP-3 concentrations lower on the second visit in the operated group, whereas in the non-

<table>
<thead>
<tr>
<th>Variable</th>
<th>OSAS (n = 30)</th>
<th>P*</th>
<th>Snorers (n = 40)</th>
<th>P*</th>
<th>Controls (n = 35)</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>5.67 (4.93–6.30)</td>
<td>.40</td>
<td>6.04 (5.50–6.58)</td>
<td>.37</td>
<td>6.45 (5.63–7.27)</td>
<td>.15</td>
</tr>
<tr>
<td>Relative height (SDS)</td>
<td>.72</td>
<td>.13 (± 0.25–0.51)</td>
<td>.39</td>
<td>0.26 (0.03–0.69)</td>
<td>.60</td>
<td></td>
</tr>
<tr>
<td>Target height (SDS)</td>
<td>.46</td>
<td>0.25 (0.07–0.43)</td>
<td>.12</td>
<td>0.07 (0.08–0.21)</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Target height deficit (SDS)</td>
<td>.09 (± 0.40–0.23)</td>
<td>.92</td>
<td>–0.13 (± 0.44–0.17)</td>
<td>.05</td>
<td>0.29 (± 0.01–0.58)</td>
<td>.07</td>
</tr>
<tr>
<td>Weight-for-height (%)</td>
<td>101.9 (97.2–106.7)</td>
<td>.96</td>
<td>101.2 (98.2–104.2)</td>
<td>.74</td>
<td>100.3 (97.2–103.3)</td>
<td>.50</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.9 (15.2–16.7)</td>
<td>.92</td>
<td>15.7 (15.2–16.3)</td>
<td>.51</td>
<td>16.0 (15.5–16.5)</td>
<td>.86</td>
</tr>
<tr>
<td>Body fat mass (%)</td>
<td>18.1 (16.0–20.2)</td>
<td>.17</td>
<td>16.5 (15.4–17.7)</td>
<td>.95</td>
<td>16.6 (15.4–17.8)</td>
<td>.18</td>
</tr>
<tr>
<td>IGF-I (nmol/L)</td>
<td>11.02 (9.79–12.23)</td>
<td>.15</td>
<td>12.15 (11.14–13.16)</td>
<td>.19</td>
<td>11.11 (9.81–12.41)</td>
<td>.92</td>
</tr>
<tr>
<td>IGFBP-3 (μg/L)</td>
<td>2.65 (2.46–2.85)</td>
<td>.95</td>
<td>2.66 (2.49–2.83)</td>
<td>.001</td>
<td>3.47 (3.17–3.78)</td>
<td>.001</td>
</tr>
</tbody>
</table>

The values are given as mean values and their 95% confidence intervals. P1 indicates the statistical difference between the OSAS children and primary snorers, P2 the difference between the primary snorers and normal controls, and P3 the difference between the OSAS children and controls.
operated group the IGF-I and IGFBP-3 levels were lower at the second visit in 44% (15/34) and 29% (10/34) of the cases, respectively.

**DISCUSSION**

Improved growth, especially weight gain, after resolved OSAS was accompanied by a significant increase in the circulating IGF-I and IGFBP-3 concentrations. The pattern of growth improvement after surgical treatment of OSAS was consistent with earlier studies.6–11 A detailed analysis of the different body mass components showed that the weight increase after treatment of OSAS was attributable to an increased amount of fat rather than an increase in fat-free mass.

The possible role of abnormal GH secretion in the observed growth impairment in OSAS children has been addressed in a series of studies.5,2–11 Recently, Bar et al9 demonstrated a significant increase in weight and serum IGF-1 concentrations after surgical treatment of OSAS in 10 prepubertal children. In the present study, this was confirmed in 19 children operated on and assessed twice. Moreover, 34 children with similar symptoms without significant OSAS were observed without surgical intervention. At baseline, altogether 70 children with obstructive sleep disorder were assessed for overnight sleep monitoring, and their anthropometric data and growth factor concentrations were compared with those found in the control subjects.16,17

GH stimulates the synthesis of IGF-I in the liver and other target tissues.29 IGF-I is considered as the main mediator of the growth-promoting actions of GH,15 reflecting the daily mean GH levels, and it has been reported to correlate well with the physiologic changes in GH secretion.13 Among prepubertal children, IGF-I is not clearly sex-dependent.30 In this study, the children remained in prepuberty, when the peripheral IGF-I levels increase fairly slowly,30 so the increase in age over the relatively short time interval between the first and second measurements must have very modestly affected the circulating IGF-I concentrations, as shown by the insignificant increase observed in the nonoperated children. Accordingly, the significant increase in peripheral IGF-I levels observed in the operated children suggests that the alleviated airway obstruction resulted in increased GH secretion.

IGFBP-3, the GH-dependent major carrier protein of IGF-I, has also been shown to correlate significantly with nocturnal GH secretion, but not as strongly as in the case of IGF-I.14 Although IGFBP-3 probably exerts some functions of its own on cells, its major role is to prolong the half-life of IGF-1.31 The major advantage of IGFBP-3 determinations in diagnostics is its relative stability over time,14 and it may therefore be a more reliable indicator of GH secretion over a longer time span than IGF-I. It is also less dependent of age than IGF-I.31 In contrast to the findings of Bar et al,9 we observed that the IGFBP-3 concentrations increased significantly along with the IGF-I levels in the operated children on the follow-up, further strengthening the assumption of increased GH secretion secondary to the relief of airway obstruction. The changes in circulating IGF-I and IGFBP-3 concentrations in the follow-up study were consistent in the sense that the peripheral concentrations only decreased slightly in 2 operated individuals.

Our findings are consistent with the findings in adult OSAS patients, in whom it has been shown that successful treatment results in a significant increase in nocturnal GH secretion32 and peripheral IGF-I levels.33 GH is released in a pulsatile fashion, with the initial secretion probably synchronized with the onset of slow-wave sleep (SWS), with a strong correlation with δ-wave activity,24 within 90 to 120 minutes from the onset of sleep.29 In adults, there is convincing evidence of a consistent relationship be...
between SWS and increased GH secretion and decreased GH secretion with awakenings. In OSAS children, the sleep architecture is relatively well-preserved, and the distribution pattern of apneas over the night is different from the profile of GH secretion. One of the limitations of the methods used in this study was the lack of electroencephalogram, electro-oculogram, and chin EMG tracing, so the different sleep stages could not be differentiated, but changes in the proportion of SWS do not seem to be significant after treatment of OSAS.

Impaired GH secretion is probably not the only cause for the failure to thrive, because OSAS children may also be obese, but only the minority was overweight in this study. The children classified as having OSAS had a higher proportion of body fat, but only 2 children had a BMI over 20, 1 girl with OSAS (BMI: 21, OAHI: 11.8) and 1 boy who snored (BMI: 20.2), and both the OSAS and PS children had equal BMIs compared with the control group.

Increased appetite or reduced nighttime caloric expenditure could explain some of the increase in fat accumulation after the treatment of OSAS. However, these do not explain the observed changes in IGF-I and IGFBP-3 concentrations. The finding that relative height increased significantly only in the nonoperated group may be attributable to natural variation in growth rate, as these children had lower relative height at both visits than the OSAS children.

The fact that no significant differences could be observed initially in the anthropometric data or the circulating concentrations of IGF-I and IGFBP-3 between the children with OSAS and those with primary snoring might be explained by sleep abnormalities, which were also present in the children considered PSs. The children in this study had all symptoms suggestive of OSAS, although the majority were found to be PSs. This is consistent with the findings from other studies, where half or less of the children with such symptoms were actually confirmed to have OSAS. The criteria for OSAS, OAHI of 1 or higher, was based on normative data established by others and our own findings in a group of 30 normal children. Coincident desaturation with apnea/hypopnea was not a criterion for scoring in this study. The mean 4% desaturation index was significantly higher in the OSAS group than in the PS group, whereas the PS children had a significantly higher mean 4% desaturation index than the children in our normative data group. The PS children had also significantly more tachycardic episodes associated with prolonged partial obstructive hypventilation than the children in our normative data group, although significantly less than the children with OSAS. Some of the PSs could perhaps have been classified differently based on the hypventilation criterion, despite the lack of significant apneas and hypopneas. The significantly reduced IGFBP-3 concentrations in the PSs (as well as in the children with OSAS) seem to indicate some longer-term abnormality in GH secretion also in the PS group. The somewhat younger age of the PSs than the controls is hardly the explanation, because IGFBP-3 remained stable in the nonsurgical group during the follow-up. The fact that the snorers showed a similar target height deficit and retarded bone age as the children with OSAS further supports the idea of long-term abnormality in growth regulation also in the PSs.

The selection of an OAHI of 2 or higher as the criteria for surgery in the follow-up study was based on the criteria of abnormal OAHI. The clinical impact of mild OSAS is still unknown, which means that children with OAHI <2 might well be observed for a period of 6 months, whereas symptomatic children with more abnormal sleep monitoring results

### TABLE 4. Polysomnographic and Anthropometric Results on the 2 Visits in the Operated and Nonoperated Children Expressed as Means and Their 95% Confidence Intervals

<table>
<thead>
<tr>
<th></th>
<th>Operated (n = 19)</th>
<th>Nonoperated (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 1</td>
<td>Visit 2</td>
</tr>
<tr>
<td>Age (y)</td>
<td>5.56 (4.51–6.61)</td>
<td>6.25 (5.23–7.27)</td>
</tr>
<tr>
<td>Earlier adenoidectomy</td>
<td>74% (14/29)</td>
<td>.03</td>
</tr>
<tr>
<td>Total apnea index, &gt;10 s*</td>
<td>7.52 (5.36–9.69)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>OAHI &gt;10 s</td>
<td>7.10 (5.06–9.15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>OAHI &gt;5 s</td>
<td>8.83 (6.52–11.14)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>4% oxygen desaturation index</td>
<td>4.26 (3.53–7.99)</td>
<td>.01</td>
</tr>
<tr>
<td>10% oxygen desaturation index</td>
<td>0.18 (0.01–0.35)</td>
<td>.02</td>
</tr>
<tr>
<td>Hypopneic episodes (&lt;50%) with pulse increases at the end of periods (min/h)</td>
<td>1.52 (0.84–2.19)</td>
<td>.01</td>
</tr>
<tr>
<td>Relative height (SDS)</td>
<td>0.26 (–0.33–0.86)</td>
<td>.12</td>
</tr>
<tr>
<td>Weight-for-height (%)</td>
<td>101.3 (94.0–108.7)</td>
<td>.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.9 (14.8–17.0)</td>
<td>.01</td>
</tr>
<tr>
<td>Body fat mass (%)</td>
<td>17.9 (14.3–21.5)</td>
<td>.02</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>18.5 (15.5–21.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IGF-I (nmol/L)</td>
<td>11.25 (9.50–13.9)</td>
<td>.001</td>
</tr>
<tr>
<td>IGFBP-3 (µg/L)</td>
<td>2.66 (2.39–2.92)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

P1 indicates the difference between the two visits in the operated children, P2 the difference between the operated and nonoperated at the first visit, P3 the difference between the 2 visits in the nonoperated children, and P4 the difference between the operated and nonoperated children at the second visit.

* Total apnea index includes obstructive and central apneas.
could hardly be subjected to any follow-up or blinded study because of ethical reasons.

We found here that the circulating IGF-I and IGFBP-3 concentrations increased significantly in children with OSAS after surgical treatment, along with a significant increase in weight. These findings suggest decreased nocturnal GH secretion secondary to upper airway obstruction in children. The mechanisms of the initially impaired GH axis have to be elucidated in additional studies.

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