NOTE

Sleep-Disordered Breathing in Acromegalics —Relation of Hormonal Levels and Quantitative Sleep Study by Means of Bedside Oximeter—

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Abstract. Sleep-disordered breathing (SDB) is common in patients with growth hormone (GH) secreting pituitary adenomas. Since long-term untreated SDB aggravates systemic conditions (hypertension and arrhythmia etc.), the therapeutic outcome of SDB is important in reducing morbidity and mortality rates. But the results of a quantitative analysis of the lowered GH and IGF-1 levels in SDB in a relatively large number of patients are not detailed. Ten consecutive acromegalic patients were studied with a bedside oximeter. Preoperatively they were divided into two groups based on the presence (SDB group = 6 patients) or absence (non-SDB group = 4 patients) of clinical symptoms of SDB such as habitual snoring, excessive daytime somnolence and nocturnal apneic episodes. The serum IGF-1 averaged 931.7 ng/ml in SDB group and 898.3 ng/ml in non-SDB group. The oxygen desaturation index (ODI) (the number of oxygen desaturations exceeding 4% from the base line) was 29.1 ± 15.4 in the SDB group and 2.5 ± 1.8 in the non-SDB group (P = 0.01). Other oximeter parameters such as the percent of the time spent at O₂ saturation < 90% and the mean and the lowest O₂ saturations closely correlated with the degree of the clinical symptoms. A postoperative sleep study was conducted in 5 patients in the preoperative SDB group, 4 months or more after the surgery. The serum GH and IGF-1 levels normalized in 3 patients but remained slightly high in 2. ODI became 9.1 ± 5.6, which was significantly lower than the preoperative value (P = 0.026). One patient had a complete clinical resolution. The other 4 obtained slight to moderate improvement clinically and oximetrically despite normalized or decreased hormonal levels. This study clarified that the response of SDB to lowering of the GH level varies from one patient to another and persisting SDB despite the normalization of the hormonal levels suggests the involvement of other factors in the production of SDB.

Key words: Growth hormone, Sleep apnea, Acromegaly, Sleep study (Endocrine Journal 46: 585-590, 1999)

Sleep apnea (SA) is common in acromegalic patients and its prevalence is estimated to be 17-60% in all acromegalic patients [1-3]. Furthermore increased mortality of acromegaly is believed to be mainly due to the high prevalence of cardiovascular, metabolic and respiratory complications such as hypertension, diabetes mellitus and sleep apnea [1, 3]. Untreated SA becomes a factor aggravating systemic conditions such as hypertension and arrhythmia [1]. Therefore, the effect and outcome of treatment for SA has a serious effect on overall mortality and morbidity rates in acromegalics, but there have been few detailed studies on the relationship between the hormonal levels and SA and the effect of the treatment on SA in a relatively a large number of patients. The aim of this study is to clarify the relation of preoperative GH and IGF-1 levels and their effect on SA in acromegaly and to evaluate the long-term outcome of SA after treatment.

Formal polysomnography is the gold standard for the diagnosis of SA [4]. The currently accepted
definition of SA is apnea and hypopnea events in at least 30 apneic episodes/night, each lasting a minimum 10 seconds. The definition was proposed by Guilleminault et al. in 1978 [5]. The cost and inconvenience of the polysomnography, however, have made an alternative diagnostic method desirable. The oximeter has become an accepted substitute for the polysomnograph [4, 6]. With this new method, the most important parameter is the oxygen desaturation index (ODI), defined as the number/hour of oxygen desaturation exceeding 4% from the baseline. This criterion has been considered useful in order to diagnose patients with SA [4, 6]. In this report we therefore use the expression, sleep disordered breathing (SDB) instead of SA.

**Methods**

We studied 10 consecutive patients with acromegaly who were scheduled for transsphenoidal adenomectomy. The patients were 9 men and 1 woman with average age of 49.3 years (36-59). Baseline GH and IGF-1 levels were measured both pre-and post-operatively by radioimmunometric assay. A postoperative long-term baseline GH level lower than 3 ng/ml was considered to be normal [7]. Nocturnal disordered breathing was preoperatively evaluated by means of a pulse oximeter (Pulsox-5, Minolta, Tokyo, Japan) in all patients at least twice during hospitalization. Computer calculated oximetry parameters such as the oxygen desaturation index (ODI), which was defined as the number of oxygen desaturations exceeding 4% from the baseline, and the percent of time spent at O₂ saturation <90% (CT₉₀). The ODI >15 times/hour or more is likely that there is SDB. CT₉₀ <1% excludes clinically significant SAS [4, 5]. Clinical symptoms suggesting SDB, such as hypersomnolence, heavy snoring and apnea witnessed by others were carefully evaluated. The same evaluation was carried out in 6 patients 6 to 44 months after the surgery.

**Statistics**

All values were expressed as the mean+/−SD. Statistical analysis was performed using paired t test, Wilcoxon signed rank test or Mann Whitney rank sum test. Difference between groups was considered when P value was <0.05.

**Results**

Individual clinical features including serum hormonal levels and results of nocturnal oximetry are shown in Tables 1 and 2. The patients were divided...
into two groups, SDB (cases 1–6) and non-SDB (cases 7–10) groups based on the presence or absence of the clinical symptoms and signs suggesting SDB. Subjective complaints related to sleep disorder such as excessive daytime somnolence, easy fatigability and inactivity were noted in cases 3 and 5. Objective findings such as snoring and nocturnal hypopnea or apnea episodes were witnessed in cases 1 to 6. We classified cases 1 to 6 into the SDB group and the cases 7 to 10 into the non-SDB group.

**Preoperative study**

**Endocrinological analysis**

Serum GH and IGF-1 levels were 74.5+/−72.2 ng/ml (mean +/−SD) and 931.7+/−220.6 ng/ml in the SDB group and 33.3+/−21.0 ng/ml and 898.3+/−171.0 ng/ml in the non-SDB group, respectively. No statistically significant difference was noted between the two groups in the serum GH or IGF-1 levels.

**Sleep study**

The ODI, CT90, N-Sao2 and L-Sao2 were 29.1+/−19.4%, 9.6+/−11.4%, 89.8+/−2.9% and 65.5+/−20.6% in the SDB group and 2.5+/−1.8, 0.25+/−0.5%, 95.2+/−2.8% and 84.3+/−2.6% in the non-SDB group, respectively. No statistically significant difference was noted between the two groups in the serum GH or IGF-1 levels.

**Postoperative study**

The sleep study was conducted in 6 patients (5 in the SDB group and 1 in the non-SDB group), 24 months (6–44) after the surgery. The study was not performed in the remaining 4 patients, because two patients lived in a remote place and the other 2 had minimum or no complaints related to SDB preoperatively and were reluctant to undergo the sleep study. Postoperative data analysis was limited to 5 patients in the preoperative SDB group (cases 1, 3, 4, 5, 6).

**Endocrine analysis**

Serum GH and IGF-1 levels in the 5 patients decreased to 4.3+/−5.4 ng/ml and 379.4+/−286.1 ng/ml, respectively. The postoperative decrease in both GH level and IGF-1 was statistically significant (P=0.0431 and 0.024, respectively), compared with preoperative value in the SDB group. Cases 3 needed the replacement of thyroid and adrenocortical hormones in addition to local irradiation with 54 Gy. Bromocriptine 5 mg was used in cases 3 and 6. But the drug was discontinued a year later in case 3, who

### Table 2. Postoperative clinical features and sleep study in 5 patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>BMI Kg/m²</th>
<th>GH ng/ml</th>
<th>IGF-1 ng/ml</th>
<th>Snoring</th>
<th>EDS</th>
<th>Apnea</th>
<th>Time of sleep study months after surgery</th>
<th>ODI %</th>
<th>CT90 %</th>
<th>N-Sao2 %</th>
<th>L-Sao2 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24.7</td>
<td>0.8</td>
<td>230</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>31</td>
<td>13.7</td>
<td>5.8</td>
<td>89.0</td>
<td>72.5</td>
</tr>
<tr>
<td>3</td>
<td>23.0</td>
<td>7.5</td>
<td>784</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>44</td>
<td>14.1</td>
<td>6.9</td>
<td>88.5</td>
<td>57.0</td>
</tr>
<tr>
<td>4</td>
<td>20.3</td>
<td>0.92</td>
<td>152</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>6</td>
<td>11.6</td>
<td>1.2</td>
<td>91.9</td>
<td>83.3</td>
</tr>
<tr>
<td>5</td>
<td>24.5</td>
<td>0.14</td>
<td>154</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>11</td>
<td>2.6</td>
<td>0</td>
<td>93.3</td>
<td>88.3</td>
</tr>
<tr>
<td>6</td>
<td>27.1</td>
<td>12.3</td>
<td>577</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>34</td>
<td>3.6</td>
<td>0.5</td>
<td>91.1</td>
<td>77.7</td>
</tr>
</tbody>
</table>

**SS= sleep study**

Table 3. Pre-and post-operative hormonal levels and results of sleep study.

<table>
<thead>
<tr>
<th></th>
<th>GH (ng/ml)</th>
<th>IGF-1 ng/ml</th>
<th>ODI (%)</th>
<th>CT90 (%)</th>
<th>N-Sao2 (%)</th>
<th>L-Sao2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDB + N=6</td>
<td>74.5+/−72.2</td>
<td>931.7+/−220.6</td>
<td>29.1+/−15.4</td>
<td>9.6+/−11.4</td>
<td>89.8+/−2.9</td>
<td>65.5+/−20.6</td>
</tr>
<tr>
<td>SDB − N=4</td>
<td>33.3+/−21.0</td>
<td>898.3+/−171.0</td>
<td>2.5+/−1.8</td>
<td>0.25+/−0.5</td>
<td>95.2+/−2.8</td>
<td>84.3+/−2.6</td>
</tr>
<tr>
<td>Postop.</td>
<td>N=5</td>
<td>4.3+/−5.4</td>
<td>379.4+/−286.1</td>
<td>9.1+/−5.6</td>
<td>2.9+/−3.2</td>
<td>90.8+/−2.0</td>
</tr>
</tbody>
</table>

The sleep study was conducted in 6 patients (5 in the SDB group and 1 in the non-SDB group), 24 months (6–44) after the surgery. The study was not performed in the remaining 4 patients, because two patients lived in a remote place and the other 2 had minimum or no complaints related to SDB preoperatively and were reluctant to undergo the sleep study. Postoperative data analysis was limited to 5 patients in the preoperative SDB group (cases 1, 3, 4, 5, 6).
complained of persistent daytime sleepiness which was suspected of being a side effect of the drug. The other patients were free of adjuvant therapy for tumor control and chronic hormone replacement.

**Sleep study**

Clinically in case 5 the complaints related to SDB disappeared a few weeks after the surgery. In the remaining 4 patients the symptoms did not disappear but had improved slightly a few months after the surgery. The average and standard deviation of ODI, CT90, N-SaO2 and L-SaO2 were 9.1+/-5.6, 2.9+/-3.2%, 90.8+/-2.0%, 75.8+/-12.0% (Tables 2, 3). The postoperative decrease in ODI was statistically significant (P=0.026). The other parameters also improved but were not statistically significant (P=0.063 in CT90, P=0.225 in N-SaO2 & L-SaO2).

**Representative case (case 5)**

The results for oxymetric study in a representative acromegalic are shown in Fig. 1. The patient was a 59-year-old man. Serum GH and IGF-1 levels were 29.8 ng/ml 1107 ng/ml, respectively. He was not obese (24.9 kg/m² = BMI). Preoperative nocturnal oxymetry study revealed that ODI, CT90, N-SaO2 and L-SaO2 were 18.1, 1.0%, 92.2% and 84%, respectively (Fig. 1 upper). Eleven months after the successful adenectomy, the profile of SaO2 was normalized (Tables 2, 3, Fig. 1 lower).

**Discussion**

**Preoperative evaluation**

The prevalence of SDB in acromegaly was 17% in one study and 60% in another [1-3, 8]. This wide range seemed to depend on the strict or liberal definition adopted by the reporters. It might be based on the criteria based on a polysomnography study or an interview concerning clinical symptoms alone. In our consecutive 10 patients, a history interview of both patients and their families revealed 60% SDB. Clinical symptoms such as excessive daytime sleepiness, habitual snoring and hypopneic and apneic episodes during sleep closely corresponded to the oximetric ODI, which was 29.1 in our study. The other oximetric parameters supported the presence or absence of SDB, as well.

**Outcome of patients with SDB after surgery**

The surgical outcome in the treatment of GH secreting adenomas was relatively clearly defined. But the outcome for sleep apnea has been vague. Reports on a large number of operated patients rarely referred to outcome of the symptoms [7, 9]. Results for this symptom has been reported in only a relatively small number of acromegalic patients. Barnes reported 7 patients with sleep apnea in 372 reviewed cases [10]. In the 6 treated patients, 3 had complete resolution. The sleep study was not conducted in their report. Pekkarinen described the operative results of 5 acromegalic patients with sleep apnea [11]. Improvement was observed in only one
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Patient. Recently Piper reported 4 patients in a sleep study, with complete resolution in one case and improvement in the remaining 3 patients [8]. In our study one patient had complete disappearance of the SDB and the remaining 4 patients had improved clinically and oximetrically. The improvement was initially noticed in the first 1 to 2 months. A sufficient decrease in postoperative GH and IGF-1 levels seemed to induce a slight to moderate improvement or complete disappearance of the symptoms. The resolution of the symptoms seemed to parallel the soft tissue changes in the hands and feet [1, 8]. The better results in recent articles including ours are probably due to more refined microsurgical techniques and the development of such as bromocriptine. Since in the majority of the patients the clinical symptoms did not disappear completely but improved, the effect of the treatment was not all or none. An objective and quantitative evaluation method is important in assessing the degree of SDB. The oximeter seems to be a convenient substitute for the polysomnograph.

Relation of GH and IGF-1 levels to SDB before and after the surgery

In our preoperative data no remarkable difference was noted in the SDB and non-SDB groups in the GH and IGF-1 levels. In addition it appears that the preoperative hormonal levels did not relate to the severity of the symptoms and signs of SDB. Grunstein et al. reported the same results as ours, whereas Rosenow et al. reported the proportional relationship of the hormonal levels and the severity of SDB [1, 2]. But in our study the patients had clinical improvement after lowering the GH and IGF-1 levels to various degrees. Since the normalization of hormonal levels did not induce disappearance of the symptoms in all patients, our data have indicated that there are a number of causes of SDB. They may be of central origin or peripheral origin, such as systemic conditions and/or upper air-way obstructive process, all of which may or may not be directly related to acromegaly. Therefore, although the extent of involvement of a high GH level itself to produce SDB in acromegaly differs from one patient to another, it is one important factor in producing or aggravating SDB in every patient. From the viewpoint of treating SDB in acromegaly, normalization of the serum GH level is essential.

We used bromocriptine postoperatively to reduce the GH level in two patients. Since this drug has an adverse effect in causing nasal congestion in 3%, which may aggravate SDB. Although our patients were free of such complaints, we need to pay a particular attention to the side effect when we use this drug on acromegalics with critical SDB [12].

Finally, the importance of treatment of SDB cannot be overemphasized in order to decrease the morbidity and mortality rates in acromegaly. A major cause of death in acromegaly is cardiac complications which are aggravated by chronic nocturnal hypoxia, frequently seen in this condition [1]. It is clinically important that we should consider the diagnosis of sleep apnea in treating all patients with acromegaly.

References


