Prevalence of sleep apnea and metabolic abnormalities in patients with acromegaly and analysis of cephalometric parameters by magnetic resonance imaging

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Abstract

Objectives: To determine the prevalence of sleep apnea (SA) and SA syndrome (SAS) in patients with acromegaly and correlate SA with clinical, laboratory, and cephalometric parameters.

Design and methods: Prospective and cross-sectional study of 24 patients with active acromegaly evaluated by clinical and laboratory (GH, IGF-I) parameters, polysomnography and magnetic resonance imaging (MRI) of the pharynx.

Results: Out of 24 patients, 21 had SA (87.5%), of which 20 (95.3%) had the predominant obstructive type. Median age of these 21 patients was 54 years (range 23–75) and median estimated disease duration was 60 months (range 24–300). The frequency in SA patients of impaired glucose tolerance, diabetes mellitus (DM), and hypertension was 19, 33.3, and 71.4% respectively. Goiter was found in 10 patients (47.6%) and obesity in 18 (90%). Median GH level was 14 μg/l (1.4–198) and median %IGF-I (percentage above the upper limit of normal range of IGF-I) was 181% (K31.6 to 571.2). The prevalence of SAS was 52.4%. Apnea–hypopnea index (AHI) correlated significantly with age, waist circumference, body mass index, and hypopharynx area. The AHI was significantly higher in patients with hypertension and DM.

Conclusions: The prevalence of SA and SAS in acromegaly was similar to the one previously described in other series. Age was a significant risk factor, and hypertension and DM were significantly associated complications of SA. Obesity was also significantly related to SA, as a risk factor, a complication or both. Overall, cephalometric parameters by MRI did not correlate with SA.

Introduction

Patients with acromegaly have a 1.6- to 3.3-fold increase in mortality rate and a 10-year reduction in their lifespan (1, 2). Respiratory disorders account for up to 25% of causes of death, second only to cardiovascular events that contribute to 60% of mortality (2–5). The most typical respiratory complication in acromegaly is sleep apnea (SA) that has only been recognized as part of the clinical spectrum of acromegaly within the last 15 years (6–10).

SA is defined in adults as the presence of five or more episodes of apnea or hypopnea, lasting at least 10 seconds for each hour of nocturnal sleep (apnea–hypopnea index, AHI), whereas SA syndrome (SAS) is characterized by the association of SA and daytime sleepiness (11, 12). Based on pathophysiological criteria, two types of SA are recognized, a central and an obstructive type. In the obstructive type of SA (OSA), the prevailing form in acromegaly, changes of soft, cartilaginous, and bony tissues at the level of craniofacial, pharyngeal, and laryngeal structures may lead to obstruction of the airflow through the airways (2, 13). Despite the impression that OSA in acromegaly is secondary to changes in the upper airway, there has been no documentation of the relationship between hormonal profile, cephalometric parameters, and sleep disorders. Additionally, the overall prevalence of hypertension, metabolic syndrome, and disturbances in glucose metabolism in patients with OSA and acromegaly is unclear. To address these issues, we have performed a prospective study in 24 patients with active acromegaly. All of them underwent clinical and laboratory evaluation and polysomnography (PSG) to identify SA. To evaluate cephalometric parameters, 22 patients also underwent magnetic resonance imaging (MRI) of the pharynx.
Patients and methods

Study population

The study group consisted of patients with active acromegaly recruited from the outpatient endocrinology clinic of the Hospital Universitário Clementino Fraga Filho, HUCFF, of the Universidade Federal do Rio de Janeiro, UFRJ, over a 12-month period. Inclusion criteria were age > 18 and active acromegaly. Despite previous treatment (dopaminergic agonists, surgery, or radiotherapy), all patients had evidence of active disease based on: 1) symptoms and signs of acromegaly; 2) increased upper limit of normal range of insulin-like growth factor (IGF) type I (IGF-I), %IGF-I and growth hormone (GH) levels; and 3) a lack of suppression of GH below 1 µg/l after the oral administration of 75 g glucose.

All subjects entered the study after written informed consent according to a protocol approved by the Ethics Committee of the Hospital Universitário Clementino Fraga Filho (HUCFF). Reasons for ineligibility included previous use of octreotide long acting release (LAR), the presence of comorbidities, or untreated endocrinopathies that could influence the prevalence of SA (e.g., hypothyroidism, muscular dystrophies) and contraindications for MRI (metallic clips, pacemakers, and implantable defibrillators).

Clinical parameters

Besides documentation of age, sex, and estimated disease duration (time between the beginning of signs and symptoms, and the time of inclusion in the study), the following parameters were also evaluated: 1) daytime sleepiness (evaluated by the Epworth Sleepiness Scale and defined by an Epworth score >10) (14); 2) hypertension; 3) diabetes mellitus (DM); 4) glucose intolerance; 5) insulin resistance (measured by the homeostatic model assessment-insulin resistance, HOMA-IR); 6) body mass index (BMI); 7) waist circumference (WC); and 8) goiter (defined as an increase in thyroid gland volume of at least one half-time normal on palpation and/or ultrasonography).

Hormone assays

Serum GH levels were determined by a chemiluminescence immunometric assay (Diagnostic Products Corporation – DPC, Los Angeles, CA, USA), with the IMMULITE 1000 analyzer, specifically directed for the 22 kDa isoform. Intra- and inter-assay coefficients of variation (CV) for a low point of the standard curve were 6.5 and 6.2% respectively. The sensitivity of the method was 0.01 µg/l (0.026 mU/l). Plasma IGF-I concentrations were measured by an IRMA (Diagnostic Systems Laboratories – DSL, Inc., Webster, TX, USA). The intra-assay CV values were 3.4, 3.0, and 1.5%, whereas the inter-assay CV values were 8.2, 1.5, and 3.7% for a low, medium, and high point of the standard curve respectively. The sensitivity of the method was 0.80 µg/l.


All serum samples were collected in the early morning after an 8-h fasting period.

Cephalometric measurements

Pharynx MRI was performed using either a Philips 1.5T Gyroscan (Philips Medical Systems, Best, Holland) or a Siemens 0.2T Magnetom Open Viva (Siemens Medical Systems, Erlangen, Germany). Images were processed using a Philips EasyVision 4.4 Workstation (Philips Medical Systems). Patients preferably underwent MR scanning at the Philips 1.5T. Only claustrophobic patients (n = 3) were examined at the Siemens 0.2T Magnetom Open Viva. All examinations were done with patients awake in the supine position, with the head and neck extended in a neutral position. Head position during scanning was maintained using head and chin straps. Except when the patient’s facial features precluded their use, we used head coils, otherwise we employed either a synergy torso coil (n = 2) or a cervical spine coil (n = 2). In order to avoid motion artifacts, patients were instructed not to move or to swallow, and to keep their mouth slightly closed, breathing quietly.

We obtained images in three orthogonal planes: axial, coronal, and sagittal with 4 mm thick slices and a 10% increment. The sagittal plane images were obtained using T1-weighted sequence, with a rectangular field of view (FOV), 280/1.1 (RFOV 90%), and both coronal and axial images were obtained using T2-weighted sequence, with rectangular FOVs, 280/1.4 (RFOV 90%) and 220/0.9 (RFOV 80%) respectively.

Image acquisition in the axial plane was done from the sphenoid body through the upper larynx, strictly parallel to the hard palate, and the coronal and sagittal planes were perpendicular to the hard palate and parallel to the cervical spine.

All data were transferred to the workstation and the measurements were made by the same certified radiologist.

The following cephalometric measurements were made using electronic cursors at the workstation: soft palate length and width, tongue thickness in two different planes, and cross-sectional air-filled areas of the nasopharynx, oropharynx, and hypopharynx. The first four measures were obtained in the median sagittal image. The cross-sectional areas were measured in the axial images, using the following anatomical landmarks:
the inferior borders of the nasopharynx, oropharynx, and hypopharynx were defined as the lowest extent of the hard palate; as the tip of the uvula; and as the air space, just above the superior tip of the epiglottis, respectively (Fig. 1). There are no established normal ranges for all these measurements, except for the length of the soft palate, for which the reference value is $34 \pm 6$ mm (15).

**Sleep study**

Complete overnight PSG using the Meditron System was performed between 2100 and 0600 h. Four-channel electroencephalography (C4/A1, C3/A2, O1/A2, and O2/A1), electro-oculography and chin electromyography were performed using standard methods. Oronasal airflow was recorded by a thermistor, and thoracic and abdominal respiratory efforts were measured by impedance plethysmography. Oxygen saturation was measured by finger pulse oximetry (Moria 1001), and electrocardiography was performed from standard leads. Body position was monitored by a position sensor. Sleep data were staged according to standard criteria (16), and arousals were scored according to the American Sleep Disorders Association criteria (12).

The respiratory events were scored in accordance with the American Academy of Sleep Medicine Task Force recommendations (11). The AHI was calculated as the number of all respiratory events per hour of sleep. An AHI < 5 was defined as normal. Sleep-related breathing events were considered mild when AHI was between 5 and 15 events per hour, moderate when it was between 15 and 30 events per hour, and severe when it was more than 30 events per hour.

**Statistical analysis**

The data are shown as median (range). Comparisons of AHI between two different groups were tested by Mann–Whitney’s test. The Spearman rank correlation coefficient ($r_s$) was used to assess the relation between AHI and numerical variables. $P$ values < 0.05 were considered statistically significant.

Figure 1 Sagittal plane imaging of pharynx by magnetic resonance imaging. HPH, hypopharynx area; OPH, oropharynx area; NPH, nasopharynx area; SPW, soft palate width; SPL, soft palate length; TT, tongue thickness; and MTD, mento-tongue distance.

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Results

Demographics

In total, 24 patients met study entry criteria and were recruited, but only 21 patients with SA were evaluated. The median age of the twelve females was 54.5 (range 34–75) years, and for the male patients it was 44 (range 23–74) years. Eleven patients had undergone previous treatment for acromegaly (nine had previous transsphenoidal surgery, one of whom received additional radiotherapy, and two had primary therapy with dopaminergic agonists). None of the patients had ever used octreotide LAR previously. At the time of study inclusion, there was 1 patient with microadenoma, 18 with macroadenomas, and 2 with an empty sella. Five patients had hypogonadic deficiency and the other five patients had corticotrophin deficiency, but all were on adequate hormonal replacement. Nine patients were hypogonadic, of whom two male patients received hormone replacement. None of the post-menopausal women were being treated with hormonal replacement.

The median BMI was 29.4 kg/m² (23.9–50.8), with a 90% prevalence of obesity. The median WC was 96 (80–124). The median insulin resistance index evaluated by HOMA-IR method was 4 (1.2–33). Seven (33.3%) patients had previously been diagnosed with DM and four (19%) with glucose intolerance. At study entry, 15 (71.4%) patients had arterial hypertension and 9 (47.6%) patients had goiter.

Prevalence of SA

The prevalence of SA was 87.5% (21/24), of which 95.3% (20/21) had predominantly OSA. The only patient with predominantly central SA had a Cheyne–Stokes respiratory pattern associated with congestive heart failure. The prevalence of SAS was 52.4% (11/21).

SA was mild in 6 (28.5%), moderate in 3 (14.3%), and severe in 12 (57.2%) patients.

Clinical and laboratory patients’ profile

Table 1 describes the characteristics of the study group.

Cephalometrics parameters on pharynx MRI of the study sample

Table 2 describes cephalometric parameters of the study group.

We found that 63.1% of the patients (12/19) had enlarged soft palates (reference value: 34 ± 6 mm) (15).

Correlation analysis between AHI and other parameters

Correlation analyses between AHI and numeric parameters (clinical, laboratory parameters, and cephalometric indices) showed that there was a positive correlation between AHI and age \( r_s = 0.71 \) \( P < 0.001 \) \( n = 21 \), BMI \( r_s = 0.50 \) \( P = 0.026 \) \( n = 20 \), WC \( r_s = 0.71 \) \( P = 0.001 \) \( n = 19 \), and hypopharynx area \( r_s = 0.463 \) \( P = 0.03 \) \( n = 19 \).

Analyses between AHI and qualitative variables showed that AHI was significantly higher in patients with DM and hypertension in comparison with patients without these conditions, as evidenced in Table 3.

Discussion

In this series of patients with active acromegaly, we found an SA prevalence of 87.5% and an SAS prevalence of 75%, confirming previous reports from others studies (6, 17, 18). Only one patient (4.7%) had the central form of SA that was related to a severe left ventricular dysfunction and Cheyne–Stokes breathing episodes at PSG. Although it has previously been described that patients with the central form of SA have significantly higher GH and IGF-I levels than those with obstructive disease (6), in this patient GH and IGF-I levels were lower than the respective maximum levels of the group.

Also, we confirmed previous reports that suggested OSA to be the most prevalent form of sleep-disordered

<table>
<thead>
<tr>
<th>Table 1 Characteristics of the patients.</th>
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<tbody>
<tr>
<td>Characteristics</td>
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<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Estimated disease duration (months)</td>
</tr>
<tr>
<td>Epworth (score)</td>
</tr>
<tr>
<td>HOMA-IR</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>WC (cm)</td>
</tr>
<tr>
<td>GH (µg/l)</td>
</tr>
<tr>
<td>%IGF-I (µg/l)</td>
</tr>
<tr>
<td>IGF-I (µg/l)</td>
</tr>
<tr>
<td>AH1 (episodes/h)</td>
</tr>
</tbody>
</table>

BMI, body mass index; HOMA-IR, homeostatic model assessment-insulin resistance; WC, waist circumference; GH, growth hormone; IGF-I, insulin-like growth factor type I; %IGF-I, upper limit of normal range of IGF-I; AHI, apnea–hypopnea index.

<table>
<thead>
<tr>
<th>Table 2 Cephalometric parameters of the patients.</th>
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</thead>
<tbody>
<tr>
<td>Total patients ((n=22)) Median (range)</td>
</tr>
<tr>
<td>Nasopharynx area</td>
</tr>
<tr>
<td>Oropharynx area</td>
</tr>
<tr>
<td>Hypopharynx area</td>
</tr>
<tr>
<td>Soft palate width</td>
</tr>
<tr>
<td>Soft palate length</td>
</tr>
<tr>
<td>Tongue thickness</td>
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<td>Mento-tongue distance</td>
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</table>
breathing in acromegaly (95.3%, n = 21) (2, 6, 19). Several anatomical skeletal abnormalities that predispose to OSA, such as dorso-caudal rotation of the mandible, increase in facial height, and narrowing of the depth of the bony framework of the nasopharynx, have been identified in patients with acromegaly (20–22). Other studies suggested that upper airway narrowing caused by changes in pharyngeal soft tissues may play a more relevant role in the development of OSA in acromegalic patients than skeletal anomalies (19, 22, 23). In addition to adenoid, uvular, and tonsilar hypertrophy, macroglossia also narrows pharyngeal airway space (18).

MRI, compared with other imaging techniques, has the advantage of more precise delineation of soft tissue and determination of length and thickness of soft palate and tongue (18), which is why this method was adopted in our study. Active acromegalic patients have increased tongue volumes by MRI (18). Additionally, when compared with non-obstructive SA controls, patients with OSA had a higher length and area of soft palate; tongues that were not only more inferiorly positioned but also had more tongue tissue at the hypopharyngeal level; and pharyngeal airway spaces that had significantly reduced anteroposterior dimensions at the nasopharyngeal, oropharyngeal, and hypopharyngeal levels (24). Of all the cephalometric parameters evaluated, the sole with a well-characterized reference value is soft palate (15) that proved to be enlarged in 63.1% of patients (12/19). Unexpectedly, hypopharynx area was positively correlated with AHI (r = 0.463, P = 0.03; n = 19). This finding may be explained by the fact that, whereas MRI provides a static image, the area of the hypopharynx is highly variable depending on factors, such as respiratory movements, patient arousal, and tongue position.

We found that AHI also correlated significantly with age, BMI, and WC, supporting the hypothesis that factors independent of disease activity might influence SA in patients with acromegaly. Some studies have described the BMI-independent effect of age in SA prevalence, showing an approximate doubling of AHI every 10 years, probably due to age-related weakening of the upper airway musculature (25).

We observed a slight but not significant predominance of the female gender with higher median age when compared with the male population (54.5 years versus 44 years). This finding lends support to the influence of age on the prevalence of SA, as well as to the detrimental effects of menopause on nocturnal breathing. Interestingly, none of the post-menopausal women were being treated with hormonal replacement.

Although GH and IGF-I levels did not correlate with AHI, the increased prevalence of SA in this population suggests a relationship between acromegaly activity and SA. Despite the lack of definitive documentation, it is generally accepted that improvement of OSA is mediated through a decrease in upper airway obstruction, either by reduction of upper airway soft tissue bulk, and collapsibility, or by improvement of upper airway muscle function (18). Additionally, octreotide might have direct effects on respiratory control and upper airways that are unrelated to its action on the pituitary (18, 19, 26–28).

The prevalence of patients with disturbances of glucose metabolism was 52.3%, of which 19% had glucose intolerance and 33.3% had diabetes (29–31). We also found that AHI was significantly higher in diabetic patients (P = 0.03). In patients with SA, nocturnal awakenings are associated with pulsatile cortisol release and autonomic activation, with ensuing increase in catecholamine release and hypothalamic–pituitary–adrenal (HPA) axis activation. HPA axis activation with increased cortisolemia may be a risk factor for the development of the metabolic syndrome in untreated OSA patients (32). This interaction may result in a vicious cycle whereby sleep deprivation itself is associated with HPA axis hyperactivity and glucose intolerance (32), exacerbating the metabolic syndrome (33) and SA.

In our group, AHI did correlate significantly with WC (r = 0.71, P = 0.001; n = 19), supporting the hypothesis that SA exerts a detrimental influence on the metabolic syndrome and vice versa. Obesity has been associated with SA patients, mainly in the obstructive type, and is considered a major risk factor for SA development. This relationship between obesity and OSA is thought to be secondary to variations in neck circumference related to the degree of fat deposition in the neck (34). In fact, upper airway soft tissue structures increase in size with increasing obesity (35). Upper airway MRI has shown excess fat deposition in the soft palate, tongue, and surrounding collapsible segments of the pharynx in patients with OSA compared with weight-matched controls (36). In this study, the prevalence of obesity was 90%, and AHI correlated significantly with BMI (r = 0.50, P = 0.026; n = 20), confirming that obesity can be an aggravating factor for OSA (18, 35).

### Table 3: Comparison of the AHI and hypertension, goiter, diabetes mellitus, and sex in patients with or without these conditions.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Category</th>
<th>Median AHI</th>
<th>Range</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>No</td>
<td>6</td>
<td>10.5</td>
<td>1–79</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>15</td>
<td>36</td>
<td>4–71</td>
</tr>
<tr>
<td>Goiter</td>
<td>No</td>
<td>11</td>
<td>32</td>
<td>1–71</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>10</td>
<td>18</td>
<td>6–79</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>No/OGI</td>
<td>14</td>
<td>16</td>
<td>1–71</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>9</td>
<td>25</td>
<td>1–79</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>12</td>
<td>27.5</td>
<td>1–71</td>
</tr>
</tbody>
</table>

Statistical significance was determined by Mann–Whitney’s test. OGI, oral glucose intolerance; AHI, apnea–hypopnea index.
Hypertension was present in 71.4% of our population, whereas in other series it varies from 18 to 60% among patients with acromegaly (37). Perhaps, the higher prevalence in our group can be explained by the tight and reciprocal association of the two disorders (hypertension and OSA) (38). Some authors correlated the severity of SA, quantified by the AHI, with blood pressure, and found that increasing apnea severity closely correlates with an increase in systolic and diastolic blood pressure, even after adjustment for confounding factors such as age, gender, and BMI (38, 39). Recent studies have shown that most patients with SA and hypertension become normotensive after CPAP therapy (40, 41). Accordingly, in our patients, we observed that AHI was significantly higher ($P=0.049$) in hypertensive patients than in normotensive ones, suggesting that SA either predisposes to or aggravates hypertension.

The hypothesis that the coexistence of goiter may aggravate OSA was not confirmed by our study; we found no correlation between goiter and AHI. Aggravation of SA was not confirmed by our study; we observed that AHI was significantly higher ($P=0.049$) in hypertensive patients than in normotensive ones, suggesting that SA either predisposes to or aggravates hypertension.

In conclusion, we found that OSA is extremely prevalent in patients with acromegaly, which confirms previous reports. Additionally, we observed that hypertension is more common in patients with OSA and acromegaly than in hypertensive patients alone. It follows that hypertension is almost always present in patients with acromegaly, which confirms our previous reports. Additionally, we observed that AHI was significantly higher ($P=0.049$) in hypertensive patients than in normotensive ones, suggesting that SA either predisposes to or aggravates hypertension.

Based on these findings, we suggest that all patients with active acromegaly should be routinely screen for OSA.

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