CLINICAL STUDY

Craniofacial abnormalities and their relevance for sleep apnoea syndrome aetiopathogenesis in acromegaly

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Abstract

Objective: To explain the effect of craniofacial relations on the development of the sleep apnoea syndrome (SAS) in acromegaly, and to elucidate how the activity of acromegaly affects the severity of SAS.

Design: Prospective observational study.

Methods: Cephalometry and sleep ventilation measurements were performed in 26 acromegalic men and in 96 men with SAS.

Results: SAS was found in 20 acromegalic men. Compared with non-acromegalic men with SAS, patients with acromegaly and SAS were found to have: enlargement of almost all linear dimensions; increased angle indicating mandibular protrusion; increased difference between maxillary and mandibular protrusion; articular angle decrease; soft palate lengthening; and pharyngeal airway space (PAS) enlargement in the palatal and uvular-tip planes. A comparison of acromegalic men with and without SAS revealed no significant difference in the craniofacial skeleton, although there was a narrowing of the minimal PAS (MinPAS) and of PAS in the uvular-tip plane in patients with SAS. SAS was more frequent in the patients with active acromegaly. MinPAS in the patients with active acromegaly was narrower than in those without disease activity.

Conclusion: Skeletal abnormalities in acromegalic men with SAS were different from those in SAS patients without acromegaly. Upper airway narrowing due to changes in pharyngeal soft tissues takes a more relevant share in the development of SAS in acromegalic men than skeletal anomalies.

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Introduction

Sleep apnoea syndrome (SAS) is a set of symptoms caused by repeated apnoea during sleep. Snoring, particularly intermittent snoring, excessive daytime sleepiness, early morning headache and cognitive impairment are the most important symptoms of SAS. Hypertension, cor pulmonale, ischaemic heart disease, impaired cardiac rhythm and coronary thrombosis are frequent complications of SAS (1).

Two studies revealed an increased prevalence of SAS in patients suffering from acromegaly (ACRO) (2, 3). There are two theories to account for a higher prevalence of SAS: one suggests the influence of abnormal levels of pituitary hormones and impaired respiratory control (4), the other emphasises (as a cause of SAS) anatomical changes in the upper airways, as seen in ACRO patients (5, 6).

Two findings support the functional pathophysiology of SAS: sleep apnoea is reported to be more common in active than in inactive ACRO (3, 7, 8); and growth hormone (GH) and insulin-like growth factor-I (IGF-I) levels in ACRO patients with predominantly central apnoea are higher than in those with obstructive apnoea (2). In the same study, Grunstein et al. (2) found no differences in the mean GH level or in GH pulsation between ACRO patients with and without sleep apnoea. These results detracted from the importance of GH for SAS development in ACRO.

Cephalometry, computed tomography, magnetic resonance and fluoroscopy are employed to help elucidate anatomical abnormalities of the upper airways in terms of their effect on the pathophysiology of SAS. Each of these methods is focused on different tissues. Cephalometry was chosen for this particular purpose as a way of measuring the shape and size of the orofacial skeleton, the size of the velum and the shape of the upper airways. The aim of the present study was to elucidate anatomical abnormalities in ACRO patients with confirmed SAS and to compare the results with those in non-ACRO patients with SAS.
Subjects and methods

Patients

Twenty-six men with ACRO, aged 51.3 ± 9.2 years (mean ± s.d., range 28–67 years) were examined. The diagnosis of ACRO had been confirmed on the basis of typical clinical features. The activity of ACRO was determined from a single measurement of serum IGF-I and average GH obtained from three blood samples taken from each patient at 0600, 0700 and 0800 h and after ingestion of 75 g glucose. Increased hormonal activity of ACRO was established by increased average GH levels higher than 2.5 μg/l, by the inability to suppress GH levels below 2 μg/l after the ingestion of 75 g glucose, and by the presence of serum IGF-I levels above the normal sex- and age-matched levels.

The duration of the disease activity was 16.7 ± 6.7 years (mean ± s.d., range 6–30 years). The onset of the disease was estimated according to patients’ subjective reports of the appearance of ACRO signs. The treatment of ACRO was initiated in 22 patients before sleep and cephalometric examination. Eighteen subjects had neurosurgery performed. Twelve patients underwent further post-operative treatment in either the form of conventional external irradiation or Leksell gamma knife application. Four were treated with irradiation alone. At the time of sleep examination, four active ACRO patients had not yet had any proper specific treatment for ACRO. Hormonal replacement therapy with hydrocortisone, levothyroxine and testosterone was used when needed. Three patients were successfully treated for bronchial obstruction.

The non-ACRO population consisted of 131 randomly selected males examined and diagnosed as having SAS. Patients suffering from bronchial obstruction, neuromuscular diseases, narcolepsy or endocrinological diseases were excluded. In the end, the non-ACRO SAS group comprised 96 men, aged 49.0 ± 9.4 years (mean ± s.d., range 22–69 years) with confirmed SAS.

Cephalometric measurements

The films were obtained under standard conditions during centric occlusion with the head fixed. The constant distance from the X-ray source to the median plane of the head was 2.2 m. The distance between the median plane of the head and the film was 0.24–0.36 m. The calculated magnification was 11–16%. The linear dimensions were corrected with regard to enlargement.

Figure 1 shows X-ray cephalometric points indicated on each film. The following angles evaluating the skeleton were measured: the maxillary and mandibular protrusion angles (SNA, SNB); the angle of sagittal maxillo–mandibular relations (ANB); the angle characterising the vertical maxillo–mandibular relations (ML/NL); the articular angle (S-AR-GO); and the gonion angle (AR-GO-ME). The following skeletal dimensions were measured: anterior and posterior facial height (N-GN, S-GO); the depth of the maxilla (PNS-A); the length of the mandibular body (GO-GN); the anterior and posterior height of the lower face (ANS-ME, GO-PNS); the depth of the upper face (BA-A); the basion supramentale distance (BA-B); the length of the anterior part of the cranial base (S-N); and the overall length of the cranial base (BA-N). Also measured were the following soft tissue parameters: the angle between the uvular axis and the nasal plane (ANS-PNS-UT) and the length of the soft palate (PNS-UT). The narrowest dimension of the PAS (MinPAS)
was identified (9–12). In the case of double contours, the midpoint between both sides was marked.

**Sleep ventilation examination**

All-night POLYMESAM monitoring records were used to confirm the diagnosis of SAS. POLYMESAM was an off-line monitoring system recording respiratory sounds, airflow, respiratory movements of the chest and the abdomen, oxygen saturation, heart rate and body position and lower extremity movements. The records were visually analysed. For statistical processing the following parameters were used: (i) Oxygen desaturation index (ODI) – mean number of oxygen saturation drops higher than 3% in any 1 h. (ii) Basal oxygen saturation (%). (iii) Average of lowest oxygen saturations. (iv) Respiratory disturbance index (RDI) – number of apnoeas and hypopnoeas per hour of sleep. SAS was diagnosed if an RDI of 10 or more was present.

**Somatometric examination**

Neck circumference, body weight and height were measured. From the last two the body mass index (BMI) (weight (kg)/height (m)²) was calculated.

**Endocrine measurements**

GH and IGF-I levels were determined by means of RIA using commercial kits (Immunotech, Marseille, France).

**Statistics**

The basic statistical characteristics were calculated from the measured values obtained. The differences between the mean values of the cephalometric parameters, sleep ventilation parameters, neck circumference and BMI were analysed by a two-tailed t-test or by the Mann–Whitney test wherever appropriate.

**Results**

Obstructive SAS was diagnosed in 20 ACRO patients (77%). The sleep ventilation parameters, neck circumference, BMI and age in the group of ACRO patients with confirmed SAS and in the SAS group are shown in Table 1. No differences were found between the group of ACRO patients with confirmed SAS and the group of patients with SAS without ACRO with respect to principal parameters indicating SAS intensity (ODI, RDI and the saturation decrease mean values).

The mean duration of active ACRO in the groups of ACRO patients with and without SAS was 16.9 ± 7.3

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**Table 1** Basic clinical characteristics of patients with ACRO and SAS and patients with SAS alone.

<table>
<thead>
<tr>
<th></th>
<th>ACRO with SAS (n = 20)</th>
<th>SAS (n = 96)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (S.D.)</td>
<td>Mean (S.D.)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.10 (7.65)</td>
<td>49.00 (9.39)</td>
<td>0.024*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.50 (4.54)</td>
<td>30.33 (5.35)</td>
<td>0.544</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>43.15 (2.30)</td>
<td>43.12 (3.05)</td>
<td>0.883</td>
</tr>
<tr>
<td>RDI</td>
<td>34.14 (22.06)</td>
<td>32.66 (18.28)</td>
<td>0.989</td>
</tr>
<tr>
<td>ODI</td>
<td>30.00 (24.88)</td>
<td>28.32 (20.81)</td>
<td>0.988</td>
</tr>
<tr>
<td>Average of lowest saturation</td>
<td>87.42 (6.25)</td>
<td>88.27 (4.74)</td>
<td>0.842</td>
</tr>
<tr>
<td>Basal saturation</td>
<td>93.58 (2.91)</td>
<td>94.81 (2.10)</td>
<td>0.039*</td>
</tr>
</tbody>
</table>

Average of lowest saturation – average of oxygen saturation decrease minima (%).

Basal saturation – basal oxygen saturation (%).

*P < 0.05 by Mann–Whitney test.

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**Table 2** Basic clinical characteristics of ACRO patients with and without SAS.

<table>
<thead>
<tr>
<th></th>
<th>ACRO with SAS (n = 20)</th>
<th>ACRO without SAS (n = 6)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean (S.D.)</td>
<td>Mean (S.D.)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.10 (7.65)</td>
<td>41.83 (7.68)</td>
<td>0.002**</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>29.50 (4.54)</td>
<td>31.36 (3.63)</td>
<td>0.369</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>43.15 (2.30)</td>
<td>43.33 (1.51)</td>
<td>0.761</td>
</tr>
<tr>
<td>RDI</td>
<td>34.14 (22.08)</td>
<td>6.20 (1.92)</td>
<td>0.001**</td>
</tr>
<tr>
<td>ODI</td>
<td>30.00 (24.88)</td>
<td>4.67 (2.42)</td>
<td>0.001**</td>
</tr>
<tr>
<td>Average of lowest saturation</td>
<td>87.42 (6.25)</td>
<td>89.33 (1.21)</td>
<td>0.824</td>
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<tr>
<td>Basal saturation</td>
<td>93.58 (2.91)</td>
<td>93.50 (1.64)</td>
<td>0.373</td>
</tr>
</tbody>
</table>

Average of lowest saturation – average of oxygen saturation decrease minima (%).

Basal saturation – basal oxygen saturation (%).

**P < 0.01 by Hest (t) or Mann–Whitney test (M).**
and $16.4 \pm 4.6$ (means $\pm$ S.D.) years respectively. A comparison of these groups (Table 2) revealed the anticipated difference in the values which determine the presence and severity of SAS (RDI, ODI). There was no difference between the BMI and circumference of the neck.

Fourteen ACRO patients had increased hormonal activity of ACRO. SAS was confirmed in 13 of them. The differences between the groups of patients with and without active ACRO are included in Table 3. A significant inter-group difference was found in those parameters which indicate the presence and degree of SAS. The ODI and RDI values were higher in the patients with active ACRO.

Table 3 Basic clinical characteristics of patients with active and inactive ACRO.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Active ($n = 14$)</th>
<th>Inactive ($n = 12$)</th>
<th>P value</th>
</tr>
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<tr>
<td>Age (years)</td>
<td>52.64</td>
<td>10.99</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>30.34</td>
<td>4.80</td>
<td></td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>43.79</td>
<td>2.42</td>
<td></td>
</tr>
<tr>
<td>RDI</td>
<td>42.13</td>
<td>21.56</td>
<td></td>
</tr>
<tr>
<td>ODI</td>
<td>35.08</td>
<td>26.88</td>
<td></td>
</tr>
<tr>
<td>Average of lowest saturation</td>
<td>86.15</td>
<td>7.16</td>
<td></td>
</tr>
<tr>
<td>Basal oxygen saturation</td>
<td>93.38</td>
<td>3.45</td>
<td></td>
</tr>
</tbody>
</table>

Average of lowest saturation – average of oxygen saturation decrease minima (%).
Basal saturation – basal oxygen saturation (%).

**P < 0.01 by t-test (f) or Mann–Whitney test (M).**

Table 4 represents the results of X-ray cephalometric measurements in ACRO patients with confirmed SAS and SAS subjects without ACRO. In comparison with non-ACRO patients with SAS and ACRO patients with SAS, the group of ACRO patients differs in the following ways: enlargement of practically all linear dimensions; increased angle indicating mandibular protrusion; increased difference between maxillary and mandibular protrusion; articular angle decrease; soft palate lengthening; and PAS enlargement in the palatal and uvular-tip planes.

No significant craniofacial skeletal differences were proved between ACRO patients with and without SAS (Table 5). Comparing ACRO patients with and without confirmed SAS, we discovered a statistically significant narrowing of MinPAS and PAS in the uvular-tip plane in patients with sleep apnoea.

Table 6 represents a comparison of the cephalometric parameters in patients with and without active ACRO. The groups of patients displayed no substantial differences in skeleton-rating cephalometric values. MinPAS in patients with hormonally active ACRO was narrower than in those with non-active involvement.

**Discussion**

Our study confirmed the frequent occurrence of SAS in our patients with ACRO. SAS was diagnosed in 77% of them, while the prevalence of SAS in the general population is between 1 and 10% (13).

No significant difference in BMI and circumference of the neck was found between patients with ACRO and SAS and patients with SAS alone. The difference of 5.1 years in the mean age of the patients of both groups does not detract at all from the relevance of the comparison. It should be pointed out that no differences were found in the principal parameters indicating SAS intensity (ODI, RDI, and the saturation decrease mean values). Whatever difference in the mean basal saturation that was found between men with ACRO and SAS and SAS patients without ACRO ($93.58$ and

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The cephalometric characteristics of ACRO patients with and without SAS were compared. Table 5 shows the mean and standard deviation of various cephalometric parameters. There are three studies rating cephalometric findings in ACRO (14–16). Kunzler & Farmand (15) explored the relationship between SAS intensity and the mandibular relations. The groups under study exhibited no difference in the position of the maxilla. We were able to find a similar difference between a group of men with ACRO and demonstrable SAS and a group with SAS but without ACRO. Hence, changes like these are typical of ACRO as such, although they do not appear to influence the development of SAS so long as we expect a similar SAS pathophysiology in patients with and without ACRO.

Hochban et al. (14) studied skeletal and pharyngeal parameters in a group of three women and nine men with ACRO and SAS and in two women and five men suffering from ACRO without SAS. Their findings of narrowed PAS in the tip of the uvula plane, and no differences in the sagittal position of the maxilla and the mandible in ACRO patients with SAS compared with ACRO patients without SAS, tally with our own.

Unlike that of Hochban and colleagues, our study found no evidence of a dolicho-facial appearance of ACRO patients with SAS or a narrowing of the PAS in the mandibular plane in this group of patients. Cephalometric findings in SAS patients were compared with the healthy population (9–12). From those studies, there are anatomical skeletal abnormalities predisposing to SAS: maxillary and mandibular retrognathism and cephalometric parameters in 25 ACRO patients unmatched for sex, and in 21 healthy men and women. In comparison with the control group, the group of patients was found to have a greater angle indicating mandibular protrusion, increased mandibular length, and a decreased angle of sagittal maxillo–mandibular relations. The groups under study exhibited no difference in the position of the maxilla. We were able to find a similar difference between a group of men with ACRO and demonstrable SAS and a group with SAS but without ACRO. Hence, changes like these are typical of ACRO as such, although they do not appear to influence the development of SAS so long as we expect a similar SAS pathophysiology in patients with and without ACRO.

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dorsocaudal rotation of the mandible; enlargement of the anterior and posterior facial height, and lower facial height; increased articular angle and lower part of the gonion angle; diminution of the length of the anterior cranial base; and narrowing of the depth of the bony framework of the nasopharynx.

The skeletal changes found in the patients with ACRO and demonstrable SAS were different in character from those in SAS patients without ACRO. The mandible was enlarged with signs of prognathism, decreased articular angle, increased depth of the upper part of the face and greater length of the anterior part of the base. Both ACRO and SAS patients exhibited increased facial height, with the changes even more prominent in the former. This is due to the fact that ACRO patients are noted for an enlargement of practically all linear dimensions. Put in a simplified way, elongated facial heights and shortened facial depth are typical of the skeletal configuration in SAS patients; in contrast, facial depth is increased in patients with ACRO.

According to literature sources (9, 10), the uvula is larger and the PAS is narrower in SAS patients than in the healthy population. In our group of patients with ACRO and SAS, the uvula was even larger than in the SAS group without ACRO. Patients with ACRO and SAS have the uvula located more vertically, probably due to its increased weight or flaccidity. This accounts for increased PAS (UL) breadth. Unlike SAS patients without ACRO, patients with ACRO and properly diagnosed SAS had the airway space wider not only in the uvular-tip plane but also in the nasal plane.

The groups of ACRO patients with and without SAS showed no difference in BMI or circumference of the neck, thus suggesting that the BMI (a tentative index of obesity) and circumference of the neck (a tentative index of neck configuration and fat deposition in the area), have no effect on the development of the SAS in ACRO patients as distinct from the non-ACRO population. A difference was found in the mean age value. As follows from Stradling & Crosby’s study (17), the growth of SAS intensity is very slow in those age categories, and the authors certainly do not regard age as the reason why patients with ACRO and SAS should have contracted the disease.

No significant craniofacial skeletal differences have been proved between ACRO patients with and without SAS, implying that the abnormal craniofacial relations should not be a major predisposition to SAS in the patients with ACRO. Some of the skeletal changes in patients with ACRO and SAS demonstrated by Hochban & Brandenburg (10) (e.g. dorsocaudal rotation of the mandible) were never found in our own, larger group made up solely of men with ACRO. The presence of a narrowed PAS and an enlarged uvula in ACRO patients with SAS as distinct from those without SAS shows that upper airway narrowing caused by changes in pharyngeal soft tissues has a role to play in the development of SAS in ACRO patients.

SAS was more frequent in the patients with hormonally active ACRO. The values of parameters which indicate the presence and degree of SAS (ODI and RDI) were significantly higher in the patients with active ACRO compared with those without active ACRO. These results seem to warrant the conclusion that hormonal activity of ACRO does have an effect on the development of SAS in ACRO patients.

The findings of PAS narrowing and an enlarged uvula in patients with the active form of ACRO compared with patients without such activity show the influence which the active adenoma exerts over the induction of changes in the upper respiratory tract soft tissues: that is, changes which constrict the lumen directly may subsequently predispose patients to the suction narrowing of the pharynx (18).

We conclude that the increased SAS frequency in ACRO is not due to bone changes, soft-tissue changes may contribute to SAS development, and adenoma activity is a major SAS aetiology factor in ACRO.

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