ORIGINAL ARTICLES

Acromegaly and Sleep Apnea

J.J. Blanco Pérez,[a] M.A. Blanco-Ramos,[b] C. Zamarrón Sanz,[c] A. Souto Fernández,[a] A. Mato Mato,[d] and J. Lamela López[a]

[a]Servicio de Neumología, Complexo Hospitalario Ourense, Ourense, Spain.
[b]Unidad de Investigación, Complexo Hospitalario Ourense, Ourense, Spain.
[c]Servicio de Neumología, Hospital Clínico Universitario, Santiago de Compostela, A Coruña, Spain.
[d]Servicio de Endocrinología, Complexo Hospitalario Ourense, Ourense, Spain.

OBJECTIVE: Acromegaly is often associated with sleep apnea-hypopnea syndrome (SAHS). The purpose of this study was to understand the prevalence of SAHS in patients with acromegaly and define the characteristics of acromegalic patients with and without SAHS.

PATIENTS AND METHODS: The study enrolled 17 patients (11 women and 6 men) residing in the province of Ourense, Spain, who were diagnosed with acromegaly. All patients underwent overnight polysomnography in a sleep laboratory. In addition, growth hormone and insulin-like growth factor 1 levels were assessed. Sixteen of the patients underwent cephalometric study.

RESULTS: The average age of the patients was 58 years (95% confidence interval [CI], 52-63). The average body mass index was 31 (95% CI, 29-34) and average neck circumference was 41 (95% CI, 39-43). Ten patients (58.8%) had an apnea-hypopnea index (AHI) greater than 10. Nine had obstructive apnea and one had central apnea. Seven (5 with an AHI>10 and 2 with an AHI<10) reported excessive daytime sleepiness with Epworth scores greater than 10 (41.2%). Five patients (29.4%) were diagnosed with SAHS (AHI>10 and Epworth>10). No correlation was found between an AHI greater than 10 and hormonal activity (*P*=.082). The mean growth hormone level for patients with an AHI greater than 10 was 4.8 (95% CI, 0.5-9) and the mean for those with an AHI less than 10 was 12 (95% CI, 2-27). Fifty percent of the patients were treated with a somatostatin analog and half of those treated exhibited apnea (*P*=.302). No cephalometric differences related to the presence of apneas were found.

CONCLUSIONS: We found a high prevalence of sleep apneas (58.8%) and SAHS (29.4%), and central apneas were rare. We found no correlation between hormone activity level and the presence of SAHS. The incidence of SAHS was the same in somatostatin analog treated and untreated patients. Cephalometric variables did not distinguish between acromegalic patients with and without SAHS.

Key words: *Sleep apnea-hypopnea syndrome. Cephalometry. Acromegaly.*

Acromegalia y apnea del sueño

OBJETIVO: La acromegalia se relaciona frecuentemente con el síndrome de apnea-hipopnea del sueño (SAHS). El propósito de este trabajo es conocer la prevalencia del SAHS en los pacientes con acromegalia y definir las características de esta población con y sin SAHS.

PACIENTES Y MÉTODOS: Se estudió a 17 pacientes diagnosticados de acromegalia en la provincia de Ourense (11 mujeres y 6 varones). A todos ellos se les realizó polisomnografía nocturna diagnóstica en el laboratorio del sueño, además de una determinación de hormona de crecimiento y de factor 1 de crecimiento insulina-*like,* y a 16 se les efectuó un estudio cefalométrico.

RESULTADOS: La edad media de los pacientes era de 58 años (intervalo de confianza [IC] del 95%, 52-63). La media del índice de masa corporal era de 31 (IC del 95%, 29-34) y la del perímetro del cuello, de 41 (IC del 95%, 39-43). Diez pacientes (58,8%) tenían un índice de apnea-hipopnea (IAH) mayor de 10; 9 presentaban apnea obstructiva y 1, central. Del total de pacientes, 7 (5 con IAH > 10 y 2 con IAH < 10) presentaban somnolencia diurna excesiva, con un índice de Epworth superior a 10 (41,2%). Presentaban SAHS (IAH > 10 y Epworth > 10) 5 pacientes (29,4%). No se encontró relación entre un IAH mayor de 10 y actividad hormonal (p = 0,082). Los sujetos con IAH mayor de 10 presentaban un valor medio de hormona de crecimiento de 4,8 (IC del 95%, 0,5-9) y en aquellos con IAH menor de 10 dicho valor era de 12 (IC del 95%, 2-27). Estaban tratados con análogos de la somatostatina el 50% de los pacientes, de los cuales la mitad presentaba apnea (p = 0,302). El estudio completo de las cefalometrías no evidenció diferencia en relación con la presencia de apneas.

CONCLUSIONES: Encontramos una alta prevalencia de apnea del sueño (58,8%) y de síndrome de apnea del sueño (29,4%), y fue una rareza la presencia de apneas centrales. No encontramos relación entre actividad hormonal y la presencia de SAHS. Los pacientes tratados con análogos de la somatostatina presentaban la misma incidencia de SAHS que los no tratados. Ningún parámetro de cefalometría resultó discriminador.

Palabras clave: *Síndrome de apnea-hipopnea del sueño. Cefalometría. Acromegalia.*

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Correspondence: Dr. J.J. Blanco Pérez.
Servicio de Neumología. Complexo Hospitalario Ourense.
C/ Ramón Puga, 52-56. 32005 Ourense. España.
E-mail: xosej@tiscali.es

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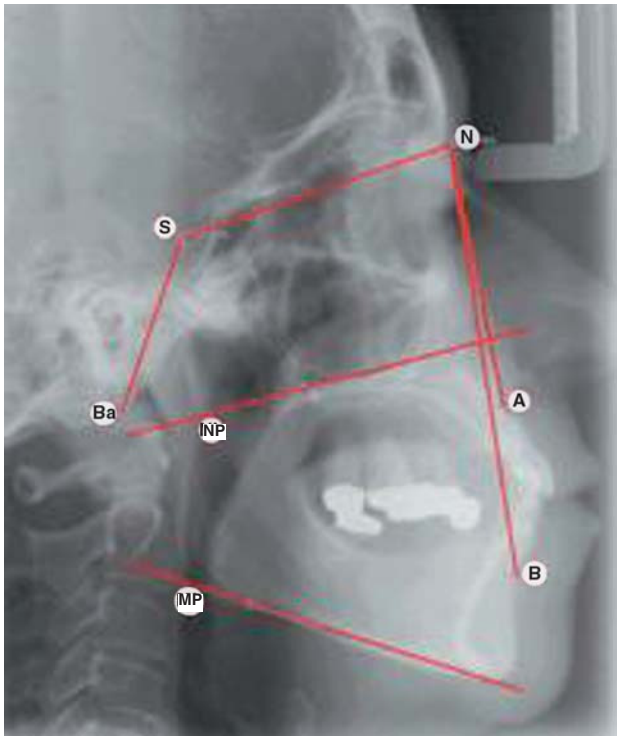

Figure. Cephalometry measures were carried out with cephalometric landmarks and angles NS-Ba, SNA, SNB, NP-NSP, MP-NSP, and MP-NP. NS-Ba indicates the angle formed between sella turcica, nasion, and apex of anterior margin of foramen magnum; NP, nasal plane; MP, mandibular plane; NSP, nasospinale plane; SNA, angle formed between the sella turcica, nasion and point A (subspinale) of superior maxilla; SNB, angle formed between sella turcica, nasion, and supramental point (anterior margin of foramen magnum).

Introduction

Sleep apnea syndrome is a common disorder that affects 2% of adult women and 4% of adult men. It is associated with symptoms such as excessive daytime sleepiness, headaches, and personality changes and is accompanied by cardiovascular complications. An apnea-hypopnea index (AHI) greater than 5 is found in 24% of men and 9% of women between the ages of 30 and 60 who do not have daytime sleepiness.[1] One Spanish study showed that 19% of men and 15% of women have an AHI greater than 5 and the prevalence of sleep apnea-hypopnea syndrome (SAHS, AHI>10 including daytime sleepiness) was found in 3.5% of men and 3% of women.[2]

Acromegaly, on the other hand, is a rare disease that affects both sexes at equal rates and has a prevalence rate between 38 and 60 cases out of 1 000 000 population.[3,4] Acromegaly is the result of an excess of the growth hormone somatotropin caused by hypophysis adenoma in adults. This excess of growth hormone leads to an insidious development of rough facial features, bone growth and soft tissue swelling.[5] A large number of publications have described the association between sleep apnea and acromegaly.[6-9] The majority of patients with acromegaly and sleep apnea suffer from obstructive sleep apneas, with central apneas constituting 34% of the examinations of the disease.[8] A correlation has been established between craniofacial changes and the presence and severity of apneas.[10,11]

The connection between acromegalic activity and sleep apnea has been a source of disagreement among many authors, with some observing a correlation between the two diseases[6,7,9] and some finding none.[8] On the other hand, various studies report a favorable response in sleep apnea with somatostatin analog treatment.[11,12] The aim of our study, in addition to establishing the prevalence of sleep apnea among our acromegaly patients, was to determine the relationship between apnea and hormonal treatment and cephalometric variables.

Patients and Methods

Seventeen patients who had been diagnosed with acromegaly since 1982 and were being followed by the Department of Endocrinology at the Complexo Hospitalario Ourense, Spain, underwent overnight polysomnography. Four patients who suffered from severe SAHS and were being treated with continuous positive airway pressure (CPAP), withdrew treatment one week before the sleep study. One patient who had been diagnosed with SAHS before being diagnosed with acromegaly was excluded from the study. Three patients died before the conclusion of the study; 1 from a pulmonary embolism following a fractured femur and 2 from stroke.

Polysomnographic Study

Sleep was monitored with a two-channel electro-encephalogram (EEG) (C4.A1, C3-A2), an electrooculogram, and a submental electromyogram. Oronasal airflow was recorded using a thermistor sensor, thoracic and abdominal movements using mercury strain gauge bands, and oxygen saturation in arterial blood using a pulse oximeter (Ohmeda Biox 3740). An electrocardiogram and limb movements were monitored. The presence of apneas and hypopneas was determined by the manual analysis of all reports and sleep phases. Apnea was defined as a cessation in airflow longer than 10 seconds, obstructive apnea if respiratory effort was recorded by the bands and central apnea if respiratory effort ceased. Hypopnea was defined as an oxygen desaturation equal to or greater than 3% and/or arousal was defined using the American Sleep Disorders Association's criteria.[13] All patients were evaluated for daytime sleepiness using the Epworth scale. SAHS was diagnosed when the AHI and Epworth score were greater than 10.

Hormone Activity

Although true acromegaly remission requires secretion control over a period of 24 hours, we do not consider the disease to be managed when there is an abnormal growth hormone response to a glucose stimulus or basal concentrations of insulin-like growth factor 1 (IGF-1) and a growth hormone level greater than 2 ng/mL and/or IGF-1 greater than 389 ng/mL, as reflected in growth hormone production.[8] Growth hormone levels were assessed in all patients through chemiluminescent enzyme immunoassay with a noncompetitive

TABLE I
Anthropometric and Hormonal Characteristics of Patients With and Without Sleep Apnea*

	With Apnea (n=10)	Without Apnea (n=7)	*P*
Man-to-woman ratio	5:6	4:2	.402
Average age, years	51 (95% CI, 43-60)	61 (95% CI, 54-68)	.088
BMI, kg/m^2	33 (95% CI, 29-36)	30 (95% CI, 24-36)	.475
NC, cm	43 (95% CI, 41-45)	40 (95% CI, 36-43)	.109
GH, ng/mL	4.84 (95% CI, 0-27.9)	12.9 (95% CI, 0.5-9.1)	.088
IGF-1, ng/mL	322 (95% CI, 184-460)	577.6 (95% CI, 253-901)	.252
Peak, ng/mL	16.4 (95% CI, 9.2-23.6)	43.6 (95% CI, 4.4-82.8)	.315
Active acromegaly	2 (20%)	3 (42.9%)	.314
Epworth >10	5 (50%)	2 (28.6%)	.354
Analog treatment	4 (40%)	4 (66.7%)	.302
Surgery	9 (90%)	4 (66.7%)	.304

*Apnea indicates apnea-hypopnea index >10; NC, neck circumference; GH, growth hormone; CI, confidence interval, IGF-1 insulin-like growth factor-1; BMI, body mass index; Peak, maximum level during acromegaly.

double antibody (Immulite®). IGF-1 was assessed by immunoradiometric assay performed after ethanol extraction.

Cephalometry

Sixteen patients underwent lateral cranial teleradiography while standing using a Siemens Ortoceph cephalometer where, following the technique of Riley et al,[15] the plane that intersects the porion and orbitale is parallel to the floor. The bones and soft-tissue were measured and digitized with an Epson GT-12000 at 600 dpi (0.00423 mm/point). The measures were calculated with software specializing in digital linear and angular measures. Reliability of the measurements was confirmed with standard reference points by the Official Measures Laboratory of Galicia[16] (Figure).

Statistical Analysis

Data collection was carried out with the EpiInfo 2002 software program and statistical analysis was performed with SPSS 10.0. Comparative analysis between classifying variables was performed as defined by exact Fisher tests. Comparison of the means of independent groups was performed with the Mann-Whitney U test. The level of significance was 0.05.

Results

The study included all patients diagnosed with acromegaly at Complexo Hospitaliario Ourense after 1982 who were being treated by the Department of Endocrinology. The Ourense province of Spain has a population of approximately 350 000 and the rate of acromegaly is 45 per 1 000 000 population.[3,4] Of the 11 women and 6 men studied, the average age was 58 (95% confidence interval [CI], 52-63), average body mass index (BMI) was 31.8 kg/m^2 (95% CI, 29-34), and average neck circumference (NC) was 41 cm (95% CI, 39-43). The only variable that was significantly related to the presence of apneas was neck circumference (*P*=.02); no differences in the rate of apneas were found to be related to sex or age. The mean AHI was 25 (95% CI, 10-39), with a median of 13. The AHI was greater than 10 in 10 out of 17 patients (58.8%) of whom 9 had obstructive-type apnea and 1 had central apnea. Five patients (29.4%) had excessive daytime sleepiness (>10 on the Epworth scale). Hormone activity level was above 2 ng/mL in 5 patients (29.4%) with an average of 7.70 (range, 2.4-13). No correlation was found between an AHI greater than 10 and hormone activity reflected by mean growth hormone concentration, given that subjects with AHIs less than 10 had a mean somatotropin level of 12 (95% CI, 2-27) and those with an AHI greater than 10 had a mean somatotropin level of 4.8 (95% CI, 0.5-9). In fact, only 2 patients with an AHI greater than 10 showed disease activity. Fifty percent of the patients were treated with a somatostatin analog and half of those exhibited apnea (*P*=.302) (Table 1). No significant correlation was found between daytime sleepiness and hormone activity (*P*=.280), number of arousals (*P*=.471), or presence of apnea (*P*=.421) (Table 2).

As shown in Table 3, no significant correlations were found between bony and soft tissue measurements and the presence of SAHS. This finding was confirmed in both groups.

Discussion

It was Pierre Marie who first wrote about acromegaly as a clinical entity in 1876, according to Grunstein,[17] who notes that F. Roxburgh and A.J. Collis described the presence of excessive daytime sleepiness in acromegaly cases only 10 years later and that W.F. Chappell and J. A. Booth observed upper airway obstruction associated with this disease. However, it was not until the 1970's when Laroche et al[18] described the association between sleep apnea and acromegaly. Mortality from cardiovascular

TABLE 2
Polysomnographic Study Characteristics and Epworth Scale*

	With Apnea(n =10)	Without Apnea (n=7)	*P*
Light sleep, stages 1&2	79% (95% CI, 70-87)	67% (95% CI, 56-77)	.109
Deep sleep, stages 3&4	7% (95% CI, 3-12)	15% (95% CI, 6-24)	.109
REM Sleep	12% (95% CI, 7-17)	15% (95% CI, 11-19)	.536
Arousals	133 (95% CI, 81-185)	55 (95% CI, 34-77)	.01
AHI	41 (95% CI, 22-60)	3 (95% CI, 0-6)	.0001
CT90	9 (95% CI, 2-17)	0 (95% CI, 0-6)	.014
Epworth >10	5 (31%)	2 (12%)	.423

*AHI indicates apnea-hypopnea index; CI, confidence interval; CT90, percentage of time SaO_2<90%; REM, rapid eye movement.

TABLE 3
Cephalometric Variables of Patients With and Without Sleep Apnea*

	With Apnea (n=10)	Without Apnea (n=7)	*P*
NS-Ba angle	127.9 (5.5)	129.9 (7.4)	.336
SNA angle	82.9 (4.1)	78.8 (3.6)	.189
SNB angle	82.5 (6.1)	77.9 (3.3)	.189
NP-NSP	8.2 (4.7)	5.5 (7)	.463
MP-NSP	35 (11.1)	37.6 (8)	.867
MP-NP	26.8 (10)	32 (14)	.536
Stella angle	121.4 (6.7)	126.7 (7.6)	.152
Articular angle	145 (12.5)	144.6 (9)	.955
Gonion angle	129.2 (8.7)	126.5 (6.5)	.613
Sn-Go-Gn	395.7 (10.4)	397.9 (7.9)	.779
Facial axis	90.9 (7)	85.1 (8.4)	.189
Facial depth	92 (5.9)	89.9 (1.6)	.573
Maxillary depth	91.6 (3.5)	89.7 (3.5)	.573
Mandibular plane	26.4 (10.5)	24.8 (6.2)	.662
Mandibular arch	33.1 (10.9)	30.7 (5.4)	.491
Soft palate depth	39 (4.7)	38.9 (4.6)	.536
Functional depth of pharynx	32.9 (4.5)	32.6 (4.4)	.955

*Data are given as means (SD). SNA indicates the angle formed between the sella turcica, nasion and point A (subspinale) of superior maxilla; SNB, angle formed between sella turcica, nasion and supramental point (anterior margin of foramen magnum); NS-Ba, angle formed between sella turcica, nasion, and apex of anterior margin of foramen magnum; Sn-Go-Gn, angle formed between nasospinale, gonion and gnathion; NP, nasal plane; MP, mandibular plane; NSP, nasospinale plane.

disease among untreated or partially treated acromegaly patients is approximately double the rate of healthy individuals and sleep apnea has been named as a possible cause.[19]

The prevalence of acromegaly is estimated at between 38 and 60 cases per 1 000 000 population. Therefore, we consider our study sample of 17 patients to be representative of persons with the disease in our geographic area. SAHS, as defined by an AHI greater than 10 accompanied by daytime sleepiness (Epworth >10), was found in 29.4% of the patients in our sample, and the percentage of all cases with sleep apnea, regardless of symptoms, was 58%. These figures are somewhat higher than those from the largest study conducted to date: Rosenow et al,[20] who studied 54 patients with treated acromegaly, found that 21 (39%) had sleep apnea. They used the MESAN-IV to carry out sleep studies and based SAHS diagnosis on more than 10 desaturation events per hour. Grunstein et al,[8] in a study of 53 patients with acromegaly, found the highest prevalence of apnea of any study to date. Without specifying the degree of daytime sleepiness, those authors observed that 60% of unselected patients with acromegaly and 93% of patients who were suspected of having SAHS had apneic events during sleep, and they associated the presence of sleep apnea with advanced age but not with obesity. Although our patients with acromegaly and SAHS tended to be older, heavier, and had a larger mean neck circumference than did the patients without SAHS, the differences were not significant. The average BMI of the patients of Grunstein et al with SAHS and acromegaly was similar to that of the patients diagnosed with obstructive sleep apnea in our study sample (mean, 32 kg/m^2). We found less difference between genders: the male-to-female ratio for patients with both SAHS and acromegaly was 1:1, whereas the male-to-female ratio is 10:1 for SAHS patients without acromegaly in our practice.

The first apnea and acromegaly studies found that macroglossia was a significant etiological factor in the

narrowing of the hypopharynx, although endoscopic studies performed during apneic episodes were not conslusive.[21] More recently, authors have given a greater importance to craniofacial changes and have observed that a greater amount of vertical or dolichofacial growth leads to mandibular hypoplasia, retroposition of the tongue, and obstruction. This would explain why not all patients with acromegaly have apneic events during sleep.[12] In our study, no notable bone differences were found between the group with apnea and the group without apnea. While computed tomography was carried out on all patients, the results are currently undergoing analysis and it remains to be seen what can be interpreted from that data.

Central apneas were rare in our group, in contrast with the findings of Grunstein et al[8] in which a high rate (34%) of central apnea was found. They suggested that the high rate was the result of abnormal respiratory control demonstrated by a low $PaCO_2$ while awake and a high ventilatory response within the central apnea group, a pattern observed when the inhibitory effects of somatostatin are not effective.

Hormonal treatment of acromegaly, on the other hand, has been found to have a positive effect on SAHS. In 1986, Chason et al[22] found a decrease of 50% in the number apneas in one patient after 6 days of treatment with the somatostatin analog octreotide. Grunstein et al,[17] in a study of 10 patients (4 with central apnea and 6 with obstructive apnea) found that all showed improvement after 6 months of octreotide treatment. In a more recent study, 14 patients (8 with AHI>5) showed improved AHIs, growth hormone levels, and IGF-1 levels after 6 months of octreotide treatment.[13] Improvement was seen in cephalometric indices such as the mandibular-to-hyoid and the vallecula-to-tongue distances, and a relationship between the reduction of both growth hormone levels and AHI were noted. The authors concluded by recommending the use of octreotide before surgery based on the difficulty of CPAP following transsphenoidal surgery.

Our study, which was not prospective in nature, found no relationship between hormonal activity and AHI, or somatostatin analog treatment and AHI. In fact, 5 patients (4 who were undergoing CPAP treatment at the beginning of the study) required continued CPAP treatment over the course of the study. Our data demonstrated no relationship between excessive daytime sleepiness and hormonal activity, although such a relationship was reported by Rosenow et al.[20] Nor did we see a relationship between hormonal activity and the presence of apnea and number of arousals. The stage of acromegaly progression at the time of diagnosis may be an important factor in the onset of SAHS, but it is not a variable that can be determined by our analyzing data from our small and homogenous sample. All patients diagnosed with SAHS had been prescribed CPAP treatment by an endocrinologist before presenting with obvious symptoms of the disease. This is a common practice that is based on the high prevalence of sleep apnea in acromegaly patients, its clinical importance when it occurs, and the improved prognosis that early CPAP treatment offers patients. For these reasons, we believe that it is appropriate to perform a polygraphic or polysomnographic study on all patients with acromegaly.

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