Sleep Apnea in Patients with Acromegaly. Frequency, Characterization and Positive Pressure Titration

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Abstract: *Objectives*: (1) to describe the frequency of sleep apnea in patients with acromegaly; (2) to identify the proportion of candidates for treatment with positive airway pressure; and, (3) to report our experience with the positive pressure titration process in acromegaly patients.

Methods: A cross-sectional study that included the acromegaly cohort at the *Centro Medico Nacional "20 de Noviembre"* in Mexico City (n=44). A standard polysomnography (PSG) was carried out for each patient. A second PSG was done for purposes of CPAP titration.

Results: A total of 35 patients were studied (80% of the cohort, 20 [57%] women). Polysomnography results showed that 34 subjects (97%, 95%CI 91-100%) had apnea hypopnea indexes (AHI) $\geq$ 5. No patient had central apnea. We identified 19 subjects with AHI $\geq$5 and Epworth $\geq$10, for a frequency of obstructive sleep apnea syndrome of 54% (95%CI 36-71%). A total of 31 patients (88%; 95%CI 77-99%) were deemed to be candidates for positive pressure treatment, but only 8 of them accepted CPAP. They required pressures that ranged from 10 to 18 cmH$_2$O.

Conclusions: Our results confirm a high prevalence of sleep apnea in patients with acromegaly, and provide evidence that the majority of those patients are candidates for treatment with positive pressure. Contrary to what has been reported, we identified no patients with central apnea.

Keywords: Acromegaly, sleep, sleep apnea, sleep-disordered breathing, growth hormone.

INTRODUCTION

Acromegaly is a disease characterized by an excessive secretion of growth hormone (GH) and insulin-like growth factor type 1 (IGF-1) [1]. Though the incidence of this illness is low (3-4 cases per million inhabitants per year) and there is a wide range of treatment modalities available, life expectancy is reduced by at least 10 years due, primarily, to mortality caused by cardiovascular factors [2].

Though information exists on the high frequency of SDB in patients with acromegaly, those disorders have been poorly characterized and little is known about the daytime symptoms of patients with acromegaly who experience SDB. Finally, there is no data on positive pressure titration as a therapeutic measure applied in acromegaly patients [3-6].

Therefore, the objectives of this study were, first, to describe the frequency of sleep apnea in a cohort of patients with acromegaly; second, to identify the proportion of

patients with acromegaly and sleep apnea that are candidates for treatment with positive pressure; and, third, to report our experience with the titration process of positive pressure in patients with this disease.

METHODS

This study was approved by the Science and Bioethics Committee of the *Instituto Nacional de Enfermedades Respiratorias* (code C04-09). Participants in the study signed an informed consent form. Data confidentiality was maintained at all times.

This is a cross-sectional study in which all patients of the acromegaly cohort at the *Centro Medico Nacional "20 de Noviembre"* in Mexico City were invited to participate. At the time the study was undertaken that cohort included 44 patients. The diagnosis of acromegaly was made according to the accepted international criteria [7-9].

Once patients had agreed to participate in the study, they filled in questionnaires on their habits and symptoms related to sleep, including a validated Spanish version of the Epworth Sleepiness Scale (ESS) [10]. Anthropometric measurements were made using an electronic scale (Tanita™, Japan, precision ±200g), and a stadimeter (SECA

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240™, Hamburg, Germany, precision ±0.2cm). Body mass index (BMI) was obtained through the following formula: BMI = (weight/high^2). Neck circumference was measured at the level of the cricoid cartilage using a non-extendible, polycarbonate tape measure. Blood pressure was measured using a mercury manometer after patients had remained at rest for 5 minutes. All measurements were made by a single researcher (DHG).

The polysomnography studies were conducted using a 16-channel Grass Instrument (model 15LT-PSGA, Gamma 4.1 version, West Warwick, Rhode Island, USA), or a 32-channel Alice Sleepware device (version 5, model 1018958, Respironics brand, Murrysville, Pennsylvania, USA). All studies were conducted in accordance with the American Academy of Sleep Medicine's recommendations (AASM, 2007) [11]. The montage utilized included electroencephalography derivations: frontal, central and right occipital (F4-M1, C4-M1, O2-M1), left and right electrooculograms (EOG), electromyograms (EMG) of the chin, EMGs of the tibialis anterior muscle to detect leg movements, and electrocardiogram channel obtained through a unipolar derivation. Airflow was measured simultaneously using an oronasal thermistor and a pressure transducer (Respironics Sleep Sense™ brand, Murrysville, Pennsylvania, USA), while respiratory movements of the thorax and abdomen were determined through inductance plethysmography (Respiband™; New York, USA, or bands, Pro tech™, Murrysville, Pennsylvania, USA). The state of oxygenation was measured by pulse oximetry (Massimo™ set Irvine, USA). The studies were assessed in 30-second epochs in order to identify sleep stages in accordance with the guidelines established by the AASM (2007) [11]. Apnea was considered to be obstructive when a decline in the thermal sensor's peak ≥90% from baseline for at least 10 seconds was observed, together with the presence of continuous or augmented respiratory movement throughout the event. Central apnea, meanwhile, was defined as a decline in the peak of the thermal sensor ≥90% from baseline for at least 10 seconds with an absence of respiratory movement during the entire event. Mixed apnea was diagnosed by a decline in the peak of the thermal sensor ≥90% from baseline for at least 10 seconds associated with an absence of inspiratory effort at the initial part of the event, followed by the resumption of that effort during the second part of the event. Hypopnea was identified on the basis of a reduction ≥30% in the signal from the pressure cannula with respect to baseline for a duration of at least 10 seconds, associated with desaturation ≥4% and when at least 90% of the time of the event satisfied the reduction criteria for the pressure signal.

Patients with severe apnea (apnea hypopnea index, AHI >30), as well as those with AHI between 5 and 30 with Epworth ≥10 points, and patients with AHI between 5 and 30 with Epworth below 10 points and high cardiovascular risk were judged to be candidates for CPAP treatment [12].

Statistical Analysis

Most of the variables showed asymmetrical distributions; therefore, data are presented as medians, interquartile intervals (IQI) and minimum and maximum values. The categorical variables were described as frequencies and percentages using 95% confidence intervals (95%CI). Associations were explored using Spearman's coefficient correlation, while group comparisons were carried out –as appropriate– using the Wilcoxon Rank-Sum Test or the X^2. Data analysis was conducted using a commercially available statistical package (Stata, release 9.2, StataCorp, College Station, TX, USA).

RESULTS

The original cohort consisted of 44 patients, but 9 declined to participate. Thus, 35 patients were studied (response rate 80%). No differences were found in age, gender, ESS or IGF-1 between responders (n=35) *vs* non-responders (n=9). Of these individuals, 20 were women (57%) and 15 were men (43%). Table **1** shows their general characteristics.

Table 1.　General Characteristics of the Patients

Parameter	Value
Age (years)*	51 (39 – 63) 13 – 85
Age at diagnosis (years)*	47 (35 – 52) (13 – 71)
Weight (Kg)	75 (68 – 88) 49 – 137
Height (m)*	1.62 (1.56 – 1.70) 1.43 – 1.82
BMI (Kg·m^{-2})*	29 (26 – 33) 22 – 46
NC (cm)*	38 (35 – 40) 32 – 50
Years since diagnosis of acromegaly*	4 (3 – 10) 0 – 30
Patients subjected to surgery[a] n (%)	28 (80)
Patients subjected to radiation therapy n (%)	14 (40)
Months receiving octreotide*	30 (20 – 36) 3 – 62
Controlled patients n (%)	28 (80)
Uncontrolled patients n (%)	7 (20)
Sleep-Related Symptoms	
Patients with snoring n (%)	31 (91)
Patients with insomnia n (%)	26 (76)
Patients with observed apneas n (%)	10 (30)
Hypertension[b] n (%)	20 (59)
Mallampati score*	2 (2 – 3) 1 - 4
Tonsillar grade[c] *	1 (1 – 2) 0 - 3
Daytime SpO$_2$%*	93 (92 – 95) 86 - 96
Epworth Scale score*	10 (6 – 15) 2 – 24
Epworth ≥10 n (%)	20 (59)

BMI: body mass index, NC: neck circumference, SpO$_2$%: oxygen saturation by pulse oximetry.
*Mean (interquartile Interval) min. – max.
[a]Surgery to resect the pituitary adenoma.
[b]Medical diagnosis of hypertension; or on antihypertensive treatment; or blood pressure greater than 140/90 mmHg.
[c]Grade 0: tonsillectomy; grade 1: tonsils were in the tonsillar fossa; grade 2: tonsils were visible behind the anterior pillars; grade 3: tonsils extended three-quarters of the way to the midline; grade 4: tonsils were completely obstructing the airway [25].

Table **2** shows the results of the polysomnography studies. In order for a test to be considered adequate for

interpretation, sleep efficiency had to reach at least the level of 80%. One patient was studied on two occasions because on the first sleep efficiency was below 80%. Sleep efficiency for the group as a whole showed a mean of 87% (IQI 82-92). In the majority of patients (97%; 95%CI 91-100), tests revealed an AHI considered "abnormal" (≥5 events/hour), and in 60% of patients, AHI was above the cutoff point for "severity" (≥30 events/hour). Nineteen patients (54%, 95%CI 36-71%) satisfied the usual criteria of obstructive sleep apnea syndrome (AHI ≥5 events/hour with and Epworth score ≥10). Alterations of sleep architecture were documented: the mean for slow-wave sleep was 16% (IQI 10-21), while that of REM sleep (R sleep) was 15% (IQI 13-18), with an average of 30 alerts per hour of sleep. Upon comparing men and women, no significant differences were found in the frequency of apnea, the severity of the disease, the need for treatment, the Epworth Sleepiness Scale, or any of the other variables evaluated (Table **3**).

Table 2. Results of Polysomnography Studies

Parameter	Value
Sleep efficiency (%)*	87 (82 – 92) 56 - 98
Latency to 1st stage of sleep (minutes)*	16 (12-21) 0 - 59
Latency to REM (minutes)*	89 (74 – 128) 50 - 339
N1 (%)*	14 (12 – 19) 3.2 - 52
N2 (%)*	51 (46 – 58) 37 - 71
N3 (%)*	16 (10 – 21) 0.6 - 31
NREM (%)*	85 (82 – 88) 72 - 92
REM (%)*	15 (13 -18) 9 - 27
Index of arousals*	30 (23 – 42) 8 - 82
Index of respiratory arousals*	16 (5 – 26) 0 - 66
Central apneas*	1 (0 – 5) 0 - 97
Mixed apneas*	0.2 (0 – 2.4) 0 - 60
Obstructive apneas*	54 (9 – 146) 1 - 637
Hypopneas*	169 (82 – 219) 0 - 327
Central apnea index (events/hr)*	0.1 (0- 0.7) 0.1 – 14.2
Obstructive apnea index (events/hr)*	9 (1.3 – 20) 0.1 – 84
AHI (events/hr)*	34 (22 – 57) 3.3 – 108
AHI <5 n (%)	1 (3)
AHI ≥5 and <15, n (%)	7 (20)
AHI ≥15 and <30, n (%)	6 (17)
AHI ≥30, n (%)	21 (60)
SpO$_2$ while laying awake*	93 (90 – 94) 82 – 96
Average SpO$_2$ during sleep*	90 (87 – 92) 62 – 95
REM SpO$_2$*	89 (86 – 92) 56 – 95
NREM SpO$_2$*	90 (87 – 92) 67 – 95
AHI ≥ 5 and Epworth ≥ 10, n (%)	19 (54)

REM: rapid eye-movement sleep, NREM: non-rapid eye-movement sleep, AHI: apnea-hypopnea index, SpO$_2$: percentage of saturation by pulse oxymetry.
*Mean (interquartile interval) min. – max.

Seven patients had "uncontrolled" acromegaly, though IGF-1 levels were not found to be associated with either the AHI or central apneas. The correlation between the IGF-1 levels and the index of central apneas was not significant (p = 0.98), nor did we find any difference between the controlled (n=28) *versus* the uncontrolled patients (n=7) with respect to sleep architecture or respiratory indexes.

All patients received octreotide for at least 3 months from the onset of treatment. The study did not demonstrate any associations between the duration of treatment and the severity of the apnea (r_s= 0.13), or between the degree of sleepiness and the activity of the acromegaly (r_s = 0.15) or the number of years since diagnosis (r_s = -0.11), or between AHI and the Epworth Scale (r_s = 0.03). A weak association between AHI and body mass index was found (r_s= 0.35, p= 0.03), but no association with neck circumference (r_s= 0.16, p=0.37) was documented. We also compared patients according to excessive daytime sleepiness (ESS ≥10 *vs* ESS <10) but found no significant differences in age, BMI, IGF-1, months of treatment with octreotide, or years since diagnosis.

Of the 35 patients studied, 31 were considered candidates for CPAP treatment (88%, 95%CI 77-99%). Those patients were classified as follows: (a) 9 (26%) with AHI ≥30 events/hour; (b) 19 (54%) with AHI between 5 and 30 events/hour and Epworth ≥10; and, (c) 3 (8%) with AHI between 5 and 30 events/hour with Epworth <10 and systemic arterial hypertension.

The 31 patients judged to be candidates for treatment with positive pressure were invited to undergo a second polysomnograph for pressure titration, but only 8 of them (26%) agreed to undergo the test. These results are shown in Table **4**. Three of these patients were titrated using both the CPAP and bi-level methods (patients 1, 2 and 6), but the latter showed no advantages over CPAP in terms of sleep architecture, residual AHI, tolerance, or gas exchange. One patient did not tolerate CPAP. Optimal CPAP pressures ranged from 12 to 18 cmH$_2$O.

DISCUSSION

The principal results of this study are as follows: (1) almost all patients (97%) presented abnormal AHI; (2) just over half of the patients (54%) had AHI ≥5 and Epworth ≥10; (3) 88% of patients were candidates for CPAP treatment; (4) contrary to reports by other authors, we did not identify patients with central apnea in our cohort; and, (5) CPAP treatment seems to be efficient in most patients with acromegaly; while the bi-level method does not appear to have advantages over CPAP.

The prevalence reported for sleep apnea in patients with acromegaly varies from 19 to 81%, depending on the methods and diagnosis criteria used [13]. Given that these figures differ from the prevalence of sleep apnea in the general population –2% and 4% for women and men, respectively–[14,15] it is suggested that acromegaly is a risk factor for the development of sleep apnea. In this study, the diagnostic method utilized was nocturnal polysomnography, which allowed researchers to identify (according to current staging standards), that 97% of patients with acromegaly have abnormal AHI, and that the prevalence of obstructive sleep apnea syndrome –defined as AHI ≥5 events/hour and

Table 3. **Comparison of Polysomnographic Findings Between Men and Women**

Parameter	Women (n= 20)	Men (n= 15)	*p* Value
AHI <5 n(%)	0	1 (7)	0.24
AHI ≥5 n(%)	20 (100)	14 (93)	0.25
AHI ≥5 y <15, n(%)	3 (15)	4 (27)	0.39
AHI ≥15 y <30, n(%)	4 (20)	2 (13)	0.60
AHI ≥30, n(%)	13 (65)	8 (53)	0.48
Habitual snorer, n(%)	20 (100)	12 (80)	0.03
Candidate for CPAP, n(%)	19 (95)	12 (80)	0.16
Epworth score*	10 (6 – 18) 2 - 22	10 (7 – 12) 2 - 24	0.54
Sleep Efficiency (%)*	86 (79 – 91) 62 - 95	88 (84 – 92) 57 - 98	0.30
Latency to 1st stage (min)*	18 (11 – 25) 4 - 59	16 (12 – 19) 0 - 25	0.31
Latency to REM (min)*	89 (84 – 128) 52 - 339	76 (67 – 128) 50 - 249	0.30
Stage 1 (%)*	15 (12 – 17) 5 - 28	13 (11 – 25) 3 - 52	0.94
Stage 2 (%)*	54 (46 – 59) 37 - 71	48 (47 – 56) 39 - 58	0.32
Stage 3 (%)*	16 (10 – 19) 8 - 31	16 (13 – 23) 1 - 26	0.66
REM (%)*	15 (13 – 19) 9 - 22	15 (13 – 18) 9 - 27	0.84
Index of arousals*	30 (24 – 38) 8 - 82	30 (16 – 59) 8 - 70	0.86
Index of respiratory arousals *	16 (5 – 22) 0 - 63	11 (5 – 53) 0 - 67	0.52
AHI (events/hour)*	33.4 (29 – 54.5) 11 - 108	39.4 (12 – 76) 3.3 – 87.5	0.96
Daytime SpO$_2$*	94 (92 – 95) 86 - 96	93 (92 – 95) 88 - 96	0.53
SpO$_2$ while laying awake*	92 (89 – 94) 82 - 95	93 (90 – 94) 90 - 96	0.37
Average SpO$_2$ during sleep*	90 (86 – 92) 62 - 95	90 (87 – 93) 70 - 95	0.89
REM SpO$_2$*	89 (86 – 91) 56 - 95	89 (84 – 93) 63 - 95	0.83
NREM SpO$_2$*	90 (86 – 92) 69 - 95	90 (88 – 93) 75 - 94	0.97

AHI: apnea-hypopnea index, CPAP: continuous positive airway pressure, REM: rapid eye-movement sleep, NREM: non-rapid eye-movement sleep, SpO$_2$: percentage of saturation by pulse oxymetry.
*Mean (Interquartile interval) min. – max.

Table 4. **Patients Titrated with CPAP**

Patient	Gender	Age	BMI	Epworth Scale Score	Average SpO$_2$ During Sleep	AHI	CPAP Pressure (cmH$_2$0)	Residual AHI with CPAP	Average SpO$_2$ with CPAP	Supplementary Oxygen
1	F	53	30	6	69	108	16	0	84	Yes
2	M	38	46	15	70	70	18		94	No
3	M	64	27	12	87	70	Did not tolerate	-	87	Yes
4	F	34	25	15	91	28	14	3	91	No
5	F	37	23	20	91	40	10		95	No
6	M	68	27	11	90	27	12	9	92	No
7	F	43	30	16	92	51	11		93	No
8	F	50	42	10	86	54	12	0	91	No

F: Female. M: Male. BMI: body mass index in Kg·m^{-2}. SpO$_2$: percentage of saturation by pulse oxymetry. AHI: total apnea hypopnea index.

Epworth ≥10– was 54%. To the best of our knowledge, this is the first report on the frequency of sleep apnea in patients with acromegaly to utilize the current scoring rules and recommendations, published by the American Academy of Sleep Medicine in 2007 [11].

Though we cannot affirm that an AHI ≥5 in patients with acromegaly is equally deleterious as in patients who do not suffer from this disease, intuitively we could consider that the high cardiovascular risk seen in patients with acromegaly might be due, at least in part, to their high frequency of sleep

apnea. Sleep apnea is considered an independent risk factor of cardiovascular morbidity; nonetheless, the mechanisms underlying this association are not well known [16-19]. There is evidence to suggest that the hypoxemia-reoxygenation phenomenon induces an *"oxidative"* state that has harmful consequences for endothelial functioning and the atherogenic process, in addition to inducing a systemic inflammatory condition. Other mechanisms that cause cardiovascular damage include high sympathetic activation, changes in intrathoracic pressure and the hypo-hypercapnia phenomenon [19]. The participation of these mechanisms in the development of cardiovascular diseases in patients with acromegaly remains to be clarified.

Another significant finding documented by this study is that 54% of patients suffer from obstructive sleep apnea syndrome (AHI ≥5 and Epworth ≥10). Clearly, all those patients are candidates for treatment. Upon adding other groups who meet the criteria for receiving treatment, it was possible to determine that 88% are candidates for CPAP, but additional studies are needed to evaluate the effect of CPAP on cardiovascular morbidity and mortality in patients with acromegaly. Another additional salient point to explore is whether the craniofacial abnormalities of such patients negatively affect long-term adherence to CPAP.

Other factors not associated with the craniofacial abnormalities may potentially explain the high frequency of sleep apnea observed in patients with acromegaly. For example, chronic exposure to high altitudes in untreated patients with obstructive sleep apnea aggravates hypoxemia and increases sleep-related breathing disturbances due to frequent central apneas/hypopneas [20]. This factor could lead to an overestimate of the prevalence of sleep apnea in our cohort, given that Mexico City is at 2240 meters above sea level. However, as shown in Table **2**, the AHI observed in our patients were due mainly to obstructive, not central, disturbances; moreover, they were acclimatized residents of Mexico City and previous data from our group (n=23) demonstrated that, in healthy people living at that altitude, the median of AHI was 3.3 events/hr and sleep architecture was similar to that described in other studies carried out at sea level [21]. Therefore, we do not believe that altitude is a significant element in the high frequency of sleep apnea observed in patients with acromegaly. Another potential confounder is obesity; however, only a weak association between AHI and body mass index was found, and no association with neck circumference was recognized; suggesting that the high frequency of sleep apnea observed in our patients could be predominantly a consequence of their craniofacial abnormalities, and not of obesity as is seen in the general population [22].

Previous studies have established an association between the number of central apneas and the activity of this disease (IGF-1 levels). However, we did not encounter this association in our patients, and in no case was the presence of central apneas above 50% of total AHI. Treatment with octreotide may explain this finding, as all patients had been taking that medication for at least 3 months, and earlier research has shown that this therapy reduces the severity of the illness, at the cost of diminishing the number of central apneas [23].

Finally, our study has limitations. First, all our patients were being treated with octreotide, which impedes us from speculating on the frequency of sleep apnea in patients who are virgins in terms of treatment. Second, we were unable to include control subjects matched for age and BMI, a fact that impedes any affirmation as to whether those potential confounders may be contributing to the high frequency of sleep apnea in patients with acromegaly. Third, the response rate to CPAP titration was low (25%), a fact that limits the external validity of the data obtained from the titration process using positive pressure; however, though we were unable to determine why so few patients accepted CPAP, we believe that factors other than medical reasons are involved; for instance, economic conditions had some effect because patients' had to purchase the CPAP device (it could not be provided by the study, nor is it covered by Mexico's national health system). Also, several patients were unwilling to undergo CPAP titration because they had many medical appointments in different hospitals. Nonetheless, our study did have the second-largest series in terms of the number of patients studied using the reference standards and following the current guidelines for staging. Moreover, it is the first report to explore the CPAP titration process in patients with acromegaly.

In conclusion, there is a high frequency of sleep apnea in patients with acromegaly (97%), the majority of whom (90%) are candidates for CPAP treatment. In contrast to what is consistently observed in the general population, we did not identify any difference in the frequency of sleep apnea between men and women; nor did we observe patients with acromegaly under treatment with octreotide who had central sleep apnea. Our results thus provide evidence that, regardless of disease activity, acromegaly patients must be examined routinely to detect sleep apnea. Additional studies are required to explore whether CPAP treatment reduces the cardiovascular morbidity and mortality seen in patients with acromegaly.

CONFLICT OF INTEREST

Declared none.

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