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Obstructive sleep apnea characteristics in patients with well-controlled acromegaly and their compliance with positive airway pressure therapy

Mehmet Sezai TAŞBAKAN[1,*], Özen KAÇMAZ BAŞOĞLU[1], Ilgın YILDIRIM ŞİMŞİR[2], Füsun SAYGILI[2]

[1]Department of Chest Diseases, School of Medicine, Ege University, İzmir, Turkey

[2]Department of Endocrinology and Metabolic Diseases, School of Medicine, Ege University İzmir, Turkey

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Background/aim: Acromegaly is often associated with obstructive sleep apnea syndrome (OSAS) with a frequency between 40% and 80%. The aim of the present study was to evaluate the clinical and polysomnographic characteristics of acromegaly patients with sleep apnea symptoms and to identify positive airway pressure (PAP) adherence in acromegaly patients with OSAS diagnosis.

Materials and methods: Twenty-eight well-controlled acromegaly patients (17 males, mean age 48.7 ± 10.1 years) with sleep apnea symptoms were included in this prospective study. Demographic data, anthropometric measurements, and medical history were evaluated. Full-night in-laboratory polysomnography was performed.

Results: Polysomnography results showed that 25 patients (89.3%) had OSAS with a mean apnea-hypopnea index (AHI) of 37.7 ± 28.8/h. All 17 male patients were diagnosed with OSAS, whereas 8 female patients (72.7%) had OSAS (P = 0.05). Male patients also had more severe OSAS than females (AHI 48.3 ± 29.0 vs. 21.3 ± 20.1 events/h, respectively; P = 0.012). Twenty-two patients out of 28 were considered to be eligible candidates for PAP therapy. The PAP adherence rate was found to be 50% during follow-up.

Conclusion: Our results confirm OSAS as a common disorder in acromegaly patients as well as PAP therapy being required for a majority of patients. Therefore, all acromegaly patients should be assessed in terms of OSAS and be followed closely for the evaluation of PAP adherence.

Key words: Acromegaly, sleep apnea, positive airway pressure, adherence

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by the instability of the upper airway during sleep, resulting in reduction or elimination of airflow, oxygen desaturation, and sleep disruption. OSAS is a common disease that affects 3.9% of women and 8.8% of men between the ages of 30 and 70 (1).

Acromegaly is a rare disease characterized by an excessive secretion of growth hormone (GH) and insulin-like growth factor type 1 (IGF-1) (2). Both sexes are affected at equal rates and the prevalence rate is between 38 and 60 patients out of 1,000,000 people (3,4). Recent studies presented evidence supporting the association between sleep apnea and acromegaly (5–7).

The pathophysiology of nocturnal airway obstruction in acromegaly is not yet clearly defined but is predicted to be multifactorial. The persistent high levels of GH and IGF-1 in acromegaly can lead to anatomical changes, i.e. bone, cartilage, soft tissue, and multiple organ enlargements. The presence of macroglossia; hypertrophy of the laryngeal mucosa, aryepiglottic, and ventricular folds; and false vocal cords in active acromegaly result in the narrowing of the oropharynx and/or larynx, thus facilitating partial or complete obstruction during sleep. Despite a well-defined association between OSAS and acromegaly, there is a lack of studies assessing sleep apnea syndrome in acromegaly patients in all aspects, including adherence to therapy. Therefore, the aim of the present study was to evaluate the clinical and polysomnographic characteristics of acromegaly patients with sleep apnea symptoms and to identify positive airway pressure (PAP) adherence in acromegaly patients with OSAS diagnosis.

2. Materials and methods

2.1. Study population

We prospectively evaluated 30 consecutive acromegaly patients with presumed sleep-disordered breathing referred from the Department of Endocrinology and

* Correspondence: sezai72000@yahoo.com

Metabolic Diseases to the sleep laboratory of our university hospital between February 2012 and September 2014. Newly diagnosed and active acromegaly patients were not included in the study. All patients included in the study either had undergone pituitary surgery or had medical treatment (somatostatin analogs) prior their presentation to our clinic. Patients with IGF-1 values within the normal age- and sex-specific range and basal GH values below 1 ng/mL on any medication for acromegaly were considered to have well-controlled disease. Since all acromegaly patients met the well-controlled criteria, they were all considered as well-controlled acromegaly patients. Sleep medicine doctors (ÖKB and MST) reevaluated the patients admitted to the sleep laboratory in terms of OSAS and two patients with no specific OSAS symptoms/signs were excluded from the study. Thus, 28 patients with sleep apnea clinical symptoms (excessive daytime sleepiness, loud snoring, or witnessed apneas) were included the study. Demographic data (age, sex, smoking history, and alcohol and drug use), anthropometric measurements [height, weight, body mass index (BMI), and circumferences of neck, waist, and hip], sleep-related symptoms, and detailed medical history were evaluated. Subjective daytime sleepiness was assessed using the Turkish version of the Epworth sleepiness scale and scores higher than 10 were considered as excessive daytime sleepiness (8). Full-night in-laboratory polysomnography was performed for all patients. Full in-laboratory polysomnography and PAP titration were performed on two separate nights for patients who were candidates for PAP treatment. The local ethics committee approved the study and all subjects gave written informed consent.

2.2. Polysomnography

All patients underwent full overnight in-laboratory polysomnography. Electroencephalography electrodes were positioned according to the international 10–20 system. Polysomnography consisted of sleep monitorization of electroencephalography, electrooculography, electromyography, airflow, respiratory muscle effort, and measurements of electrocardiographic rhythm and blood oxygen saturation. A thoracoabdominal plethysmograph, oronasal temperature thermistor, and nasal cannula/pressure transducer system were used to identify apneas and hypopneas. A transcutaneous finger pulse oximeter was used to measure oxygen saturation. Sleep was recorded and scored according to the standard method (9). One of the criteria used in the definition of hypopnea is ≥50% signal drop, the other is ≥3% oxygen desaturation or associated arousal, and finally ≥90% of the event duration should meet the amplitude reduction criteria. The apnea-hypopnea index (AHI) is the sum of the number of apneas and hypopneas per hour of sleep. OSAS was defined as an AHI of ≥5 events/h with the presence of clinical symptoms, e.g., excessive daytime sleepiness, loud snoring, witnessed apneas, and nocturnal choking or AHI of ≥15 events/h without any OSAS symptoms (10).

2.3. PAP adherence

PAP therapy was suggested to all patients who had an AHI of ≥15 events/h. PAP devices were given after manual titration. The pressure of the PAP device controlling the patient's obstructive respiratory events (preferably AHI of <5 per hour) was selected for each patient following the titration study. The patients were contacted in the 1st, 3rd, and 6th months and then once a year for the evaluation of their adherence. Adherence to treatment was objectively assessed by the use of the built-in time counter on the device that recorded hours of device operation. The patients brought their PAP devices to the hospital to have their adherence data downloaded during the follow-up period. Patients were considered as adherent when using their PAP device for more than 4 h per night for 70% of the observed nights (11).

2.4. Statistical analysis

Statistical analysis was performed with SPSS 16.0 for Windows. Numerical variables were summarized as mean ± standard deviation. The significance of differences among groups was assessed by Mann–Whitney U test and analysis of categorical variables was examined by chi-square test. A value of $P < 0.05$ was considered significant for all statistical analysis.

3. Results

The study population of 28 patients (17 males, mean age 48.7 ± 10.1 years) had mean BMI of 32.4 ± 4.3 kg/m^2, neck circumference of 41.3 ± 4.0 cm, and waist circumference of 107.4 ± 11.2 cm. Obesity was observed in 19 patients (67.9%). Twenty patients (72.4%) had comorbidities. Hypertension (50.0%), diabetes mellitus (42.9%), hypothyroidism (25.0%), and dyslipidemia (17.9%) were the most frequent diseases. All patients were undergoing acromegaly-specific therapy (18 patients had transsphenoidal hypophysis surgery and 11 of them were under somatostatin analog therapy following surgery, while the remaining patients had not been operated on and were only treated with somatostatin analogs). All acromegaly patients met the well-controlled criteria. All 28 patients reported snoring whereas 20 (71.4%) had witnessed apnea and 13 (46.4%) had excessive daytime sleepiness. The mean Epworth sleepiness score was 10.7 ± 6.0 and 12 patients (42.9%) had a score of >10.

The mean elapsed time for the diagnosis of OSAS following the diagnosis of acromegaly was 5.3 ± 4.5 years. Polysomnography results showed that mean AHI was 37.7 ± 28.8/h, nadir SpO_2 (%) was 80.8 ± 8.5, and mean SpO_2 (%) was 92.7 ± 4.1. Twenty-five patients (89.3%) with an AHI of ≥5 events/h were diagnosed as OSAS. All

17 male patients were diagnosed with OSAS, whereas 8 female patients (72.7%) had OSAS (P = 0.05). Comparison of anthropometric and polysomnographic findings according to sex demonstrated that male patients had more severe OSAS than females (AHI 48.3 ± 29.0 vs. 21.3 ± 20.1 events/h, respectively; P = 0.012) (Table 1).

Out of 25 OSAS patients, 22 patients were considered to be eligible candidates for PAP therapy (AHI of ≥15 events/h). Three patients refused to use the PAP device and 19 of them accepted. Sixteen patients were given continuous positive airway pressure, 2 patients were given bilevel positive airway pressure, and one patient was treated with autoadjusting positive airway pressure device. No central apnea was observed in acromegaly patients during the PAP therapy. The patients were followed for an average follow-up period of 16.7 ± 11.2 months. PAP adherence rate was found as 57.9% in the 19 patients who accepted using the device. As 3 patients refused the therapy, the overall adherence rate was 50.0% among the 22 patients who were considered to be candidates for PAP therapy (Figure). Comparison of anthropometric, clinical, and polysomnographic findings according to PAP adherence demonstrated that PAP-adherent patients were younger than PAP-nonadherent patients (43.8 ± 10.3 vs. 52.6 ± 8.6 years, respectively, p = 0.044) and had more severe OSAS than PAP-nonadherent patients (59.6 ± 26.3 vs. 32.7 ± 20.1 events/h, respectively; P = 0.014) (Table 2).

4. Discussion

It is known that OSAS prevalence increases in patients with acromegaly and there are studies describing the association between sleep apnea and acromegaly (5–7). However, studies assessing sleep apnea syndrome in acromegaly patients in all aspects including adherence to therapy are limited. Therefore, in the present study, we aimed to evaluate the clinical and polysomnographic characteristics of acromegaly patients with sleep apnea symptoms and to identify PAP adherence in acromegaly patients diagnosed with OSAS. We observed a high frequency of OSAS (89.3%) in acromegaly patients although all of them were receiving specific therapy for acromegaly. Sleep apnea was more frequent and severe in male patients. Only half of the patients considered to be candidates for PAP therapy were adherent to the treatment. The present results confirm that OSAS is common in patients with acromegaly and provide evidence that the majority of the patients are candidates for PAP therapy. Accordingly, all acromegaly patients, especially males, should be investigated in terms of OSAS and they should be followed closely for the evaluation of PAP adherence.

The frequency of OSAS is high in patients with acromegaly. Hernández-Gordillo et al. performed polysomnography in 35 acromegaly patients and they found that 34 patients (97%) with AHI of ≥5 had OSAS (5). Vannucci et al. demonstrated that 14 out of 25 acromegaly

Table 1. Clinical and polysomnographic characteristics of male and female patients.*

	All patients (n = 28)	Male (n = 17)	Female (n = 11)	P-value
Age, years	48.7 ± 10.1	47.1 ± 10.1	51.2 ± 10.2	0.301
Body mass index, kg/m^2	32.4 ± 4.3	32.8 ± 4.5	31.9 ± 4.2	0.582
Neck circumference, cm	41.3 ± 4.0	43.6 ± 3.1	37.8 ± 2.4	<0.001
Epworth sleepiness score	10.1 ± 6.0	10.8 ± 6.6	9.0 ± 5.0	0.456
AHI, events/h	37.7 ± 28.8	48.3 ± 29.0	21.3 ± 20.1	0.012
Oxygen desaturation index, events/h	31.7 ± 29.2	43.6 ± 30.8	13.8 ± 14.0	0.002
Diagnosis OSAS, n (%)	25 (89.3)	17 (100.0)	8 (72.7)	0.050
N1 sleep, %	5.9 ± 3.3	7.0 ± 6.3	4.1 ± 2.5	0.103
N2 sleep, %	47.4 ± 18.0	51.2 ± 19.3	41.7 ± 14.8	0.175
N3 sleep, %	34.6 ± 20.9	31.8 ± 22.0	38.8 ± 19.2	0.399
REM sleep, %	12.1 ± 7.5	10.0 ± 5.5	15.5 ± 9.1	0.056
Nadir SpO_2, %	80.8 ± 8.5	78.1 ± 9.2	84.8 ± 5.5	0.040
Mean SpO_2, %	92.7 ± 4.1	91.1 ± 4.5	95.1 ± 1.7	0.003
Sleep time with SpO_2 <90%, %	10.3 ± 17.7	15.4 ± 21.0	2.4 ± 4.8	0.028

*Data are expressed as mean ± SD, unless otherwise stated.
AHI = Apnea hypopnea indexes ; N = nonrapid eye movement; REM = rapid eye movement; SpO_2 = oxygen saturation.

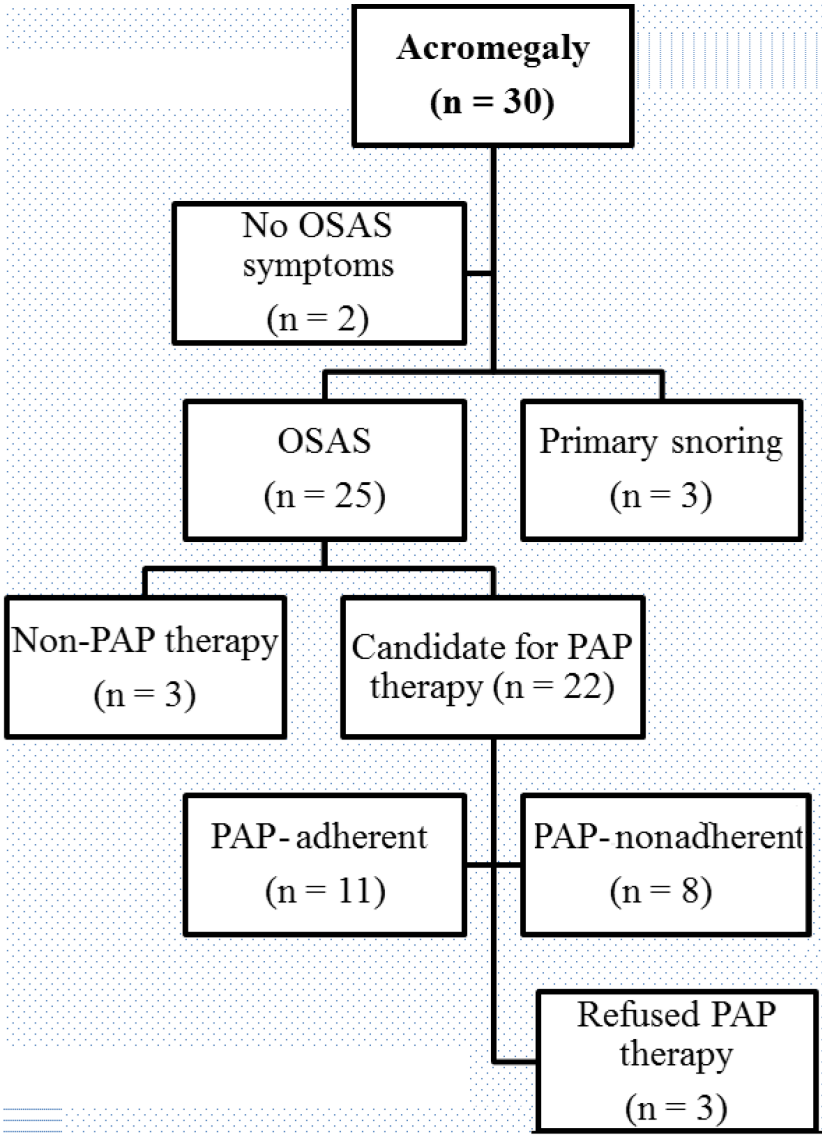

Figure. Flow chart of treatment options in acromegaly patients.

patients (56%) were diagnosed with OSAS (12). In our study, we also showed that 25 out of 28 (89.3%) patients were diagnosed with OSAS, and we concluded that OSAS is very common in acromegaly.

The relationship between activity of acromegaly and severity of OSAS is important and is being investigated in studies. Davi et al. assessed the frequency of OSAS in 18 active and 18 well-controlled acromegaly patients and found that OSAS frequency was 56% in the active group and 39% in the well-controlled group (13). In another study that investigated the OSAS rate in acromegaly patients, 66% of patients with active disease and 48% of patients in the well-controlled group had OSAS (7). Flavia et al. evaluated 24 patients with active acromegaly and found that 21 (87.5%) had OSAS (14). In a similar study, a high frequency of OSAS (87.5%) was detected in 24 active acromegaly patients (15). Anand et al. performed polysomnography at the time of diagnosis and 24 weeks after lanreotide autogel therapy in patients with acromegaly (16). However, AHI scores showed no significant difference after acromegaly treatment. In another study, a high frequency of OSAS (58.8%) was found in 17 acromegaly patients, and the incidence of OSAS was the same in somatostatin analog-treated and untreated patients (6). In the present study, it was observed that the frequency of OSAS was very high (89.3%) in acromegaly patients, although they were all well controlled in terms of acromegaly.

In a few studies, sex difference was evaluated in patients with OSAS and acromegaly. Male and female acromegaly patients were compared in a study and no

Table 2. Characteristics of PAP-adherent and PAP-nonadherent patients.*

	PAP-adherent (n = 11)	PAP-nonadherent (n = 11)	P-value
Age, years	43.8 ± 10.3	52.6 ± 8.6	0.044
Male, n (%)	9 (81.8)	6 (54.5)	0.181
Body mass index, kg/m^2	32.9 ± 5.0	32.2 ± 3.3	0.711
Loud snoring, n (%)	11 (100)	11 (100)	1.000
Witnessed apneas, n (%)	9 (81.8)	8 (72.7)	0.500
Excessive daytime sleepiness, n (%)	5 (45.5)	6 (54.5)	0.500
Epworth sleepiness score	10.5 ± 6.4	11.3 ± 6.1	0.763
Apnea hypopnea indexes, events/h	59.6 ± 26.3	32.7 ± 20.1	0.014
Duration of follow up, months	18.2 ± 12.4	14.3 ± 10.2	0.428

*Data are expressed as mean ± SD, unless otherwise stated.
PAP = Positive airway pressure.

significant differences were found in terms of frequency of apnea, severity of the disease, need for treatment, and Epworth sleepiness scale (5). In another study, female patients were found to have more severe OSAS (12). In contrast to this study, Davi et al. demonstrated that male sex was associated with OSAS in acromegaly patients (13). Similar to this study of Davi et al., all 17 male patients were diagnosed with OSAS whereas 8 female patients (72.7%) had OSAS in our study. In addition, it was demonstrated that male patients had more severe OSAS than females (AHI 48.3 ± 29.0 vs. 21.3 ± 20.1 events/h, respectively) and the difference was statistically significant. Therefore, it could be concluded that sleep apnea was more frequent and severe in male patients. Furthermore, 60.7% of acromegaly patients were male in our study, and this rate is similar to the OSAS patients without acromegaly. Women are more obese in the general OSAS population. However, we did not find any difference between the BMIs of female and male acromegaly patients with OSAS. The frequency of comorbidities is high in both acromegaly and OSAS patients. In a study from Japan, hypertension was detected in 25.0%, diabetes mellitus in 37.5%, and dyslipidemia in 45.0% of acromegaly patients (15). In our study, the frequency of hypertension, type 2 diabetes mellitus, hypothyroidism, and dyslipidemia were 50.0%, 42.9%, 25.0%, and 17.9%, respectively. It is concluded that hypothyroidism may be associated with hypophysis surgery. Additionally, obesity is an important risk factor in sleep apnea, as well as in most of these other diseases mentioned. We observed obesity in 19 patients (67.9%) and the mean BMI was 32.4 ± 4.3 kg/m^2. Both sleep-disordered breathing and acromegaly share common symptoms and prognostic features, namely high cardiovascular and respiratory mortality rates, high incidence of hypertension, and glucose-lipid dysmetabolism. Early diagnosis of sleep-disordered breathing in acromegaly patients may identify a group at higher cardiovascular risk. Despite the efficacy of PAP therapy in reversing sleep apnea, adherence to PAP devices is often suboptimal. In the studies using a cut-point of at least 4 h per night on at least 70% of nights to define PAP adherence, 29% to 83% of patients were adherent (17). In our previous study, the rate of PAP adherence in our sleep clinic was found as 85.1% in OSAS patients (18). To the best of our knowledge, this is the first study evaluating PAP adherence in acromegaly patients with OSAS. In our study, 22 patients were considered to be eligible candidates for PAP therapy. Three patients refused to use the PAP device whereas 19 of them accepted. During the follow-up period, it was observed that 11 patients were adherent to therapy, and the overall adherence rate was found as 50.0%. The PAP adherence rate of OSAS patients with acromegaly was found to be lower than that of OSAS patients without acromegaly in our sleep clinic. Consequently, this group of patients should be monitored closely to ensure PAP adherence and the adherence rate should be improved by education programs. Despite the low number of patients with OSAS and acromegaly in our study, it was demonstrated that PAP-adherent patients were younger and had more severe OSAS than nonadherent ones. To get more information about PAP adherence in acromegaly patients with OSAS, further studies with a larger sample size are required.

The present study has some limitations. First, all our patients were being treated with surgical procedures and/or medications. Therefore, we were unable to make a comparison between newly diagnosed (active) and well-controlled acromegaly patients and to assess the effect

of acromegaly treatment on OSAS severity. Another limitation could be the rather small sample size (28 patients). However, it is difficult to perform investigations with large numbers of subjects since acromegaly is a rare disease. The population of our study is similar to those of other acromegaly studies. Additionally, we did not include age-, BMI-, and sex-matched control subjects in the study. However, the aim of the present study was to evaluate sleep apnea syndrome in all aspects including adherence to PAP therapy in patients with acromegaly.

In conclusion, we observed that OSAS was very common (89.3%) in acromegaly patients although they were all treated in terms of acromegaly. Sleep apnea was more frequent and severe in male patients. In addition, most of the patients were considered to be treated with PAP devices but only half of them were adherent to the therapy. Therefore, all acromegaly patients, especially males, should be investigated in terms of OSAS and they should be followed closely for the evaluation of PAP adherence.

References

1. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 2013; 177: 1006-1014.
2. Ben-Sholmo A, Melmed S. Acromegaly. Endocrinol Metab Clin North Am 2008; 37: 101-122.
3. Alexander L, Appleton D, Hall R, Ross WM, Wilkinson R. Epidemiology of acromegaly in the Newcastle region. Clin Endocrinol 1980; 12: 71-79.
4. Bengtsson BA, Eden S, Ernst I, Oden A, Sjogren B. Epidemiology and long-term survival in acromegaly. Acta Med Scand 1988; 223: 327-335.
5. Hernández-Gordillo D, del Rocio Ortega-Gómez M, Galicia-Polo L, Castorena-Maldonado A, Vergara-López A, A, Guillén-González MÁ, Torre-Bouscoulet L. Sleep apnea in patients with acromegaly. Frequency, characterization and positive pressure titration. Open Respir Med J 2012; 6: 28-33.
6. Blanco Pérez JJ, Blanco-Ramos MA, Zamarrón Sanz C, Souto Fernández A, Mato Mato A, Lamela López J. Acromegaly and sleep apnea. Arch Bronconeumol 2004; 40: 355-359.
7. Roemmler J, Gutt B, Fischer R, Vay S, Wiesmeth A, Bidlingmaier M, Schopohl J, Angstwurm M. Elevated incidence of sleep apnoea in acromegaly-correlation to disease activity. Sleep Breath 2012; 16: 1247-1253.
8. Izci B, Ardic S, Firat H, Sahin A, Altinors M, Karacan I. Reliability and validity studies of the Turkish version of the Epworth sleepiness scale. Sleep Breath 2008; 12: 161-168.
9. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. The AASM Manual 2007 for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Westchester, IL, USA: American Academy of Sleep Medicine; 2007.
10. American Academy of Sleep Medicine. International Classification of Sleep Disorders. Diagnostic and Coding Manual (ICSD-2). 2nd ed. Westchester, IL, USA: American Academy of Sleep Medicine; 2005.
11. Kribbs NB, Pack AI, Kline LR, Smith PL, Schwartz AR, Schubert NM, Redline S, Henry JN, Getsy JE, Dinges DF. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. Am Rev Respir Dis 1993; 147: 887-895.
12. Vannucci L, Luciani P, Gagliardi E, Paiano S, Duranti R, Forti G, Peri Al. Assessment of sleep apnea syndrome in treated acromegalic patients and correlation of its severity with clinical and laboratory parameters. J Endocrinol Invest 2013; 36: 237-242.
13. Davi MV, Dalle Carbonare L, Giustina A, Ferrari M, Frigo A, Lo Cascio V, Francia G. Sleep apnoea syndrome is highly prevalent in acromegaly and only partially reversible after biochemical control of the disease. Eur J Endocrinol 2008; 159: 533-540.
14. Van Haute FR, Taboada GF, Corrêa LL, Lima GA, Fontes R, Riello AP, Dominici M, Gadelha MR. Prevalence of sleep apnea and metabolic abnormalities in patients with acromegaly and analysis of cephalometric parameters by magnetic resonance imaging. Eur J Endocrinol 2008; 158: 459-465.
15. Kashine S, Kishida K, Funahashi T, Shimomura I. Characteristics of sleep-disordered breathing in Japanese patients with acromegaly. Endocr J 2012; 59: 31-38.
16. Annamalai AK, Webb A, Kandasamy N, Elkhawad M, Moir S, Khan F, Maki-Petaja K, Gayton EL, Strey CH, O'Toole S et al. A comprehensive study of clinical, biochemical, radiological, vascular, cardiac, and sleep parameters in an unselected cohort of patients with acromegaly undergoing presurgical somatostatin receptor ligand therapy. J Clin Endocrinol Metab 2013; 98: 1040-1050.
17. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc 2008; 5: 173-178.
18. Arısoy A, Taşbakan MS, Başoğlu OK. The factors affecting positive airway pressure therapy compliance in patients with obstructive sleep apnea syndrome. In: Turkish Thoracic Society 19th Annual Congress, 6–10 April 2016, Antalya, Turkey, pp. 199-200 (in Turkish).