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USING CLINICAL DATA TO PREDICT SLEEP HYPOXEMIA IN PATIENTS WITH ACROMEGALY

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ABSTRACT - Hypoxemia secondary to sleep apnea is commonly seen in patients with acromegaly, and this alteration apparently leads to considerable morbidity and mortality among such patients. With the objective of identifying hypoxemia based on clinical data, we conducted a cross-sectional study of 34 patients with acromegaly, all of whom were submitted to nocturnal oximetry and evaluation of snoring, as well as to the determination of body mass index (BMI) and neck circumference. In addition, daytime sleepiness was evaluated using the Epworth sleepiness scale (ESS). In this study, sleep hypoxemia was defined as five or more episodes of desaturation per hour. The sensitivity and specificity of the various parameters in predicting such hypoxemia were, respectively, as follows: snoring (92.9% and 35%); BMI >28.5 kg/m^2 (71.4% and 60%); neck circumference >44 cm (28.6% and 95%); ESS score >10 (42.9% and 70%). For patients with a neck circumference of more than 44 cm, the probability of sleep hypoxemia was found to increase from 41% (pre-test) to 80% (post-test). For patients with a neck circumference of less than 44 cm, positivity for two or three of the other parameters (snoring, ESS score >10 and BMI >28.5 kg/m^2) increased the post-test probability to 62%, whereas positivity for only one (or none) reduced post-test probability to 8%. We can conclude that the clinical parameters evaluated allowed us to predict, with considerable accuracy, whether or not sleep hypoxemia would occur in patients with acromegaly.

KEY WORDS: sleep apnea, acromegaly, hypoxemia.

Utilização de achados clínicos para predizer hipoxemia durante o sono em pacientes com acromegalia

RESUMO - A hipoxemia secundária a apnéia do sono é comumente encontrada na acromegalia e parece ser a alteração sobre a qual se estabelece considerável morbi-mortalidade. Com o objetivo de reconhecer sua presença a partir de dados clínicos foram estudados transversalmente 34 pacientes, os quais foram submetidos a oximetria noturna, medida do índice de massa corporal (IMC), circunferência do pescoço, sonolência pela escala de Epworth e avaliados quanto a presença de roncos. A sensibilidade e especificidade para predizer hipoxemia, mais de 5 episódios de dessaturação por hora, foram respectivamente: IMC >28,5 Kg/m^2 (71,4% e 60%); circunferência do pescoço >44 cm (28,6% e 95%); Epworth >10 pontos (42,9% e 70%); roncos (92,9% e 35%). Se presente circunferência do pescoço maior que 44 cm, a probabilidade de hipoxemia aumenta de 41% (pré-teste) para 80% (pós-teste). Se ausente este dado, a presença de dois ou três dos demais (ronco, Epworth >10, IMC >28,5 Kg/m^2) eleva a probabilidade pós-teste para 62%, enquanto a presença de no máximo um deles é capaz de reduzir para 8%. Conclui-se que os achados clínicos avaliados permitem com alta probabilidade predizer ou não hipoxemia durante o sono na acromegalia.

PALAVRAS-CHAVE: apnéia do sono, acromegalia, hipoxemia.

Acromegaly is frequently accompanied by respiratory sleep disorders[1-4]. These disorders, in turn, have repercussions for quality of life by impairing the performance of daily activities, as well as implying a risk of cardiovascular disease[5], and certainly play a major role in increasing morbidity and mortality among patients with acromegaly[6]. A factor subjacent to respiratory disorders during sleep, especially to sleep apnea syndrome, is hypoxemia. Sleep hypoxemia is transitional and recurrent, inducing fragmented sleep presenting multiple micro-awakenings and reducing the duration of the deepest sleep stages. The patient then presents non restorative sleep, complaining of excessive daytime sleepiness and of impaired cognitive activities. However, within this context, hypoxemia appears to be the alteration upon which car-

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diovascular disease is established[7]. It is well known that, disease control based solely on the normalized hormonal levels of a patient with acromegaly is insufficient in terms of eliminating apnea and the ensuing hypoxemia, despite reducing their degree. Sleep apnea can persist even in patients considered cured[4]. In most cases, it becomes necessary for the patient to undergo treatment specifically targeting the sleep apnea. One must often resort to the use of continuous positive airway pressure (CPAP), which can reduce the number of hospitalizations for pulmonary and cardiovascular diseases[8], thereby substantially altering prognostics for patients with sleep apnea. Snoring, higher body mass index (BMI), greater neck circumference and daytime sleepiness are all clinical findings commonly associated with sleep apnea and consequently, hypoxemia[9]. Measuring these parameters is a simple, seamless procedure in routine clinical assessments.

The role that these indicators, whether in isolation or in conjunction, play in predicting sleep disorders has not been defined within the context of acromegaly. In the present study, we sought to assess the power of these clinical findings in the estimation of sleep hypoxemia in patients with acromegaly.

METHOD

Patients – We conducted a cross-sectional study of 34 outpatients treated on the endocrinology ward of the University Hospital of Brasília. The diagnosis of acromegaly was established based on clinical characteristics and biochemical findings: unsuppressed growth hormone (GH) serum levels of less than 1 ng/mL during the standard test for oral tolerance to glucoses; and levels of insulin-like growth factor 1 that are considered high for age and gender. Patients displaying uncontrolled hypopituitarism were excluded from the study.

The patient sample comprised 17 males and 17 females. The mean age was 49±12.5 years (range, 24-67 years). The mean time since the diagnosis of acromegaly was 7.2±5.2 years (range, 7 months-25.1 years). With the exception of two subjects (5.9%), who were included prior to the treatment for acromegaly, all patients had been subjected to the following therapeutic approaches prior to the study outset: 13 (38.2%) had undergone surgery, radiotherapy and octreotide administration; 8 (23.5%) had undergone surgery and had received octreotide; 7 (20.6%) had received primary treatment with octreotide; 3 (8.8%) had been treated with surgery only; and 1 (2.9%) had undergone surgery and radiotherapy but had not received octreotide.

For all patients, the following anthropometrical parameters were assessed: weight; height; BMI (defined as weight in kilograms divided by height in meters squared); and circumference of the neck measured at the level of the cricothyroid membrane (with the patient in the orthostatic position).

After a brief explanation, patients provided simple yes or no answers to the questions "Do you frequently snore?" and "Do you feel drowsy during the day?" The Epworth sleepiness scale (ESS) questionnaire[10], which aims to determine the degree of daytime sleepiness, was then administered. This is an easy, self-administered questionnaire that gathers information on the chance that the patient will doze off or actually fall asleep during eight everyday situations and demonstrates a good correlation with the multiple sleep latency test, the gold standard for measuring sleepiness[11]. The scale ranges from 0 to 24, the latter being the highest level of sleepiness. A cut-off value of 10 points has been suggested to identify patients who display excessive sleepiness during waking periods. Scores higher than this value virtually always indicate pathological sleepiness[10].

Oximetry – To measure oxygen saturation by pulse oximetry (SpO_2) during sleep, we used a pulse oximeter (model 3100; Nonin Medical, Minneapolis, MN, USA) connected to the index finger on the dominant hand. The duration of the time in bed was recorded and was considered acceptable if of at least five hours. The instrument registers a value every four seconds. The all-night record was analyzed using the nvision program, version 5.1e (Nonin). A drop in SpO_2 was defined as a decrease of at least 4% for a period of at least 8 seconds. This criterion was also applied to the 90-100% interval of SpO_2 values. The SpO_2 drop index is determined through dividing the total number of desaturation episodes by the total time in hours. When presenting five or more episodes per hour, the patient was classified as having significant sleep hypoxemia, since this value presents satisfactory sensitivity and specificity[12] for diagnosing respiratorysleep disorders, especially for patients with normal SpO_2 levels during waking.

Data analysis – Values corresponding to neck circumference, BMI and ESS score were evaluated using receiver operating characteristic (ROC) curves in order to establish the best cut-off point, defined as that which best identified sleep hypoxemia. Therefore, these variables were rendered dichotomous in order to simplify the clinical analysis.

Data related to snoring, ESS score and BMI, as well as neck circumference above the cut-off point, were evaluated in isolation and collectively in terms of predicting sleep hypoxemia. The collective analysis was performed based on one, two, three or even four risk factors present in the same patient. New ROC curves were created in order to determine the best number of indicators present.

The frequency of true-positive (TP), true-negative (TN), false-positive (FP) and false-negative (FN) results was ascertained. Sensitivity (TP/TP+FN), specificity (TN/TN+FP), the positive likelihood ratio (LR+=sensitivity/1–specificity) and the negative likelihood ratio (LR–=1–sensitivity/specificity) were then calculated. The LR+ refers to the presence of the clinical finding in question, whereas the LR– refers to its absence. The probability of sleep hypoxemia in acromegaly was assumed to be the prevalence found in our sample compared with the post-test probability (P_{post}) of each finding being present or absent. First, the P_{post} was obtained by converting the pre-test probability (P_{pre}) into the pre-test odds (O_{pre}): $P_{pre}/(1–Ppre)$. Subsequently, the O_{pre} was multiplied by the LR+ or LR– to obtain the post-test odds (O_{post}). Finally, the O_{post} was converted back into the post-test probability: $O_{post}/(1+O_{post})$.

In the statistical analysis, the chi-square test was used to compare proportions. The Student's t-test was used to compare mean SpO_2 values between the two groups of patients (those with and those without hypoxemia). Correlations between quantitative variables were expressed using the Spearman coefficient, given that the rate of desaturation episodes per hour does not present normal distribution on the Kolmogorov-Smirnov test. For the ROC curve, the area under the curve (AUC) was expressed together with a 95% confidence interval (95% CI). Values of $p<0.05$ were considered statistically significant. The statistical program used was the Statistical Package for Social Sciences, version 13.0 for Windows.

Ethics – The study was approved by the Research Ethics Committee of the University of Brasília. All participating patients gave written informed consent.

RESULTS

The prevalence of sleep hypoxemia was 41% of the 34 patients studied. This percentage corresponds to 14 subjects with a SpO_2 drop rate greater than five episodes per hour. Of the 14 patients presenting sleep hypoxemia, 9 (64.3%) were male, and 5 (35.7%) were female. The distribution was equal for both genders (p=0.16). The mean SpO_2 during waking was 94.9±1.1%, which is within the normal range, for the entire sample. There was no difference between the group of patients with sleep hypoxemia and the group of those without (94.8±1.3% and 94.9±0.9%, respectively, p=0.71).

The cut-off point for quantitative variables was defined through evaluation of the ROC curve. The ROC curve related to BMI as a predictor of sleep hypoxemia presented an AUC of 0.634 (95% CI: 0.447-0.821; p=0.18) and indicated 28.5 kg/m^2 to be the best cut-off point. In the neck circumference ROC, the AUC was 0.691 (95% CI: 0.508-0.875; p=0.06), and the best cut-off point was shown to be 44 cm. The ROC-determined cut-off value for the ESS score was 10, and the AUC was 0.525 (95% CI: 0.323-0.727; p=0.80).

As shown in Table 1, snoring, BMI higher than 28.5 kg/m^2, neck circumference greater than 44 cm and ESS score higher than 10 were found to differ in proportion between the two groups of patients (those with and those without hypoxemia). However, this difference was not statistically significant.

Table 2 displays the sensitivity, specificity, LR+, LR–, P_{pre} and P_{post} for each variable, the last based on presence or absence. As a predictor of sleep hypoxemia, snoring was found to be highly sensitive (92.9%). When present in isolation, snoring increased the probability of hypoxemia from 41% to 50%. However, when absent, it reduced the probability of hypoxemia to a mere 12%. As shown in Table 2 a neck circumference greater than 44 cm presented high speci-

Table 1. Clinical findings in patients with and without sleep hypoxemia.

	Sleep hypoxemia		p
	Yes	No	
ESS score >10	42.9%	30.0%	0.44
Snoring	92.9%	65.0%	0.06
BMI >28.5 kg/m^2	71.4%	40.0%	0.07
Neck circumference >44 cm	28.6%	5.0%	0.06

ESS, Epworth sleepiness scale; BMI, body mass index.

Table 2. Diagnostic accuracy of clinical findings to predict sleep hypoxemia in acromegaly.

	Sensitivity	Specificity	LR+	LR–	Ppre	Ppos (present)	Ppos (absent)
ESS score >10	42.9%	70%	1.43	0.81	41%	50%	36%
Snoring	92.9%	35%	1.42	0.20	41%	50%	12%
BMI >28.5 kg/m^2	71.4%	60%	1.79	0.48	41%	56%	25%
Two or three of the findings above*	92.8%	60%	2.32	0.12	41%	62%	8%
Neck circumference >44 cm	28.6%	95%	5.71	0.75	41%	80%	34%

ESS, Epworth sleepiness scale; BMI, body mass index. LR+, positive likelihood ratio; LR–, negative likelihood ratio; Ppre, pre-test probability; Ppos, post-test probability. *Provided the circumference of the neck is ≤44 cm.

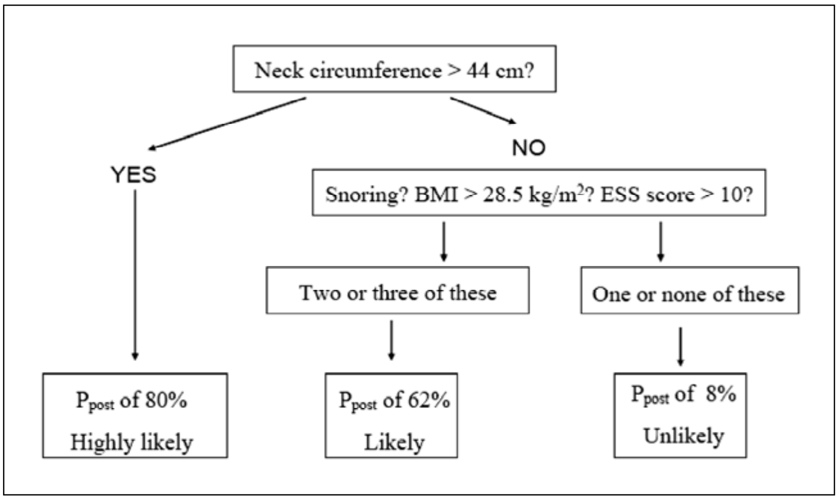

Figure. Algorithm for diagnosing sleep hypoxemia in patients with acromegaly, based on the clinical findings of neck circumference, snoring, body mass index (BMI) and Epworth sleepiness scale (ESS) score, ultimately resulting in the determination of post-test probability (P_{post}).

ficity (95%). In isolation, this variable increased the probability of hypoxemia from 41% to 80%, despite the fact that its absence was considered a variable of low-relevance, since it reduced the probability from 41% to 34%. A score higher than 10 on the ESS and a BMI higher than 28.5 kg/m^2 presented sensitivities and specificities that were intermediate in relation to the values obtained for the variables listed above. Therefore, in isolation, these two variables do not significantly alter P_{post}.

A collective analysis of these clinical findings, in terms of how many are present or absent, was also performed in order to determine the values related to the parameters studied for each variable in isolation. Therefore, if we exclude neck circumference greater than 44 cm, the presence of two or three of the remaining variables increases the probability of sleep hypoxemia from 41% to 62%, whereas the absence of all three or the presence of only one is capable of reducing the P_{post} to only 8%. This cut-off point (the presence of at least two variables) was also determined by the ROC curve, with an AUC of 0.730 (95% CI: 0.558–0.903; p=0.02). When neck circumference greater than 44 cm was added to the analysis, the cut-off point identified via the ROC curve remained the same, i.e., the presence of two or more findings. The AUC was 0.757 (95% CI: 0.595–0.920; p=0.01). At the cut-off point identified, sensitivity and specificity, as well as, consequently, P_{post}, were the same as those found in the analysis from which neck circumference had been omitted. Therefore, there was no advantage in using the four parameters in conjunction, since a 44-cm neck circumference, in isolation, increased the P_{post} to a much greater degree.

Clinical investigation becomes more efficient if two divergent tracks are followed, as suggested in Figure. On the first track, a neck circumference greater than 44 cm makes sleep hypoxemia highly likely. The absence of this finding puts us on the second track, on which the three other clinical variables studied are assessed. Should at least two be present, hypoxemia is likely. Conversely, if only one (or none) of these variables are present, hypoxemia becomes unlikely.

No significant linear correlation was found between any one of the quantitative clinical variables, with the exception of BMI, and the SpO_2 hourly drop rate: neck circumference (r=0.31; p=0.07); ESS (r=0.15; p=0.38); BMI (r=0.36; p=0.03). When the frequency of the ESS scores equal to or greater than 10 or less than 10 were compared with the answer to the yes/no question regarding daytime sleepiness, a significant difference was observed (p<0.01). All 11 patients who answered "no", claiming to have experienced no daytime sleepiness, scored less than 10 on the ESS. At the opposite end of the spectrum, all 12 patients who scored higher than 10 on the ESS had answered "yes" to the daytime sleepiness question. Nevertheless, the remaining 11 patients answered "yes" and scored less than 10 on the ESS.

The proportion of each clinical variable was also analyzed in function of treatment with octreotide or with radiotherapy. None of these variables presented any statistically significant proportional difference related to the type of treatment. Comparing patients submitted to octreotide therapy with those not receiving octreotide, respectively, we obtained the following results: snoring in 79% and 67% (p=0.53); a neck circumference greater than 44 cm in 14% and 17% (p=0.88); a BMI higher than 28.5 kg/m2 in 50% and 67% (p=0.45); an ESS score of 10 or more in 36%

and 33% (p=0.91). Comparing those who received radiotherapy with those who did not, respectively, the following was observed: snoring in 71% and 80% (p=0.56); a neck circumference greater than 44 cm in 21% and 10% (p=0.35); a BMI higher than 28.5 kg/m^2 in 71% and 40% (p=0.07); an ESS score of 10 or more in 43% and 50% (p=0.44).

DISCUSSION

In our sample, the prevalence of sleep hypoxemia was 41%. This value is within the range of values reported by other authors for the prevalence of sleep apnea in patients with acromegaly, assuming that such patients had not been submitted to prior triage for suspicion of this profile: 39%[1], 58.8%[2], 60%[3]. Using the criterion of five SpO_2 drop episodes per hour created the potential for a small portion of patients with mild apnea to go undetected. Therefore, if one thinks of sleep apnea rather than severe hypoxemia, the value of 41% might represent an underestimation. However, within this context, the principal factor implicated in the morbidity and mortality seems to be hypoxemia, which justifies its choice as a clinical reference. In the present study, not one patient presented low SpO_2 during waking. In addition, mean SpO_2 during waking did not differ between the two groups (those with and those without sleep hypoxemia). This suggests that the hypoxemia observed during sleep results from the respiratory sleep disorder itself and not from the subjacent lung disease. Of the clinical findings studied, snoring displayed the highest sensitivity and lowest specificity for the detection of sleep hypoxemia: 92.9% and 35%, respectively. Therefore, the absence of snoring reduced the P_{post} considerably, although its presence did not increase P_{post} to any significant degree.

Snoring results from the vibration of the soft tissue in the upper airways and is invariably accompanied by increased airway resistance. In extreme cases, snoring is predictive of interrupted airflow (apnea), which in turn results in hypoxemia. In most cases, however, apnea does not occur. Increased airway resistance can then cause an increase in respiratory effort, accompanied by micro-awakenings and resulting in fragmented sleep. This profile is characteristic of increased upper airway resistance syndrome. Patients with this syndrome also present daytime sleepiness similar to that seen in patients with sleep apnea but without hypoxemia[13].

This syndrome seems to occupy a place intermediate between normality and sleep apnea. Snoring, which indicates early alteration, appears as a sensitive finding, albeit not very specific for sleep hypoxemia, because this hypoxemia usually happens in the context of sleep apnea.

Daytime sleepiness is another symptom commonly seen in patients with respiratory sleep disorders. In our sample, the best cut-off point identified for ESS score (10 points) coincides with the level recommended and employed by other authors[2,10]. We found that this criterion presented 42.9% sensitivity and 70% specificity, although it was not found to correlate linearly with the rate of SpO_2 drops per hour. In another study, it was also observed that the degree of daytime sleepiness correlates more with the apnea frequency rate than with the severity of sleep hypoxemia[14]. Fragmented sleep, however, appears to be the principal determinant of daytime sleepiness, suggesting that tolerance to the various levels of hypoxemia during sleep varies from person to person.

Although daytime sleepiness has been linked to the presence of sleep apnea in patients with acromegaly[2,15], some authors suggest that such sleepiness is linked to the direct effect of GH, which reduces the quantity of REM sleep[16], or even to the effects of radiotherapy[17]. In the current study, the degree of sleepiness, as determined through the use of the ESS, did not differ between patients who received radiotherapy and those who did not; nor did it differ between those treated with octreotide and those who were not. It is possible that these explanations are at least partially related to different conceptual approaches to sleepiness. The ESS assesses sleepiness by determining the probability of falling asleep at a given moment and in specific situations. This does not necessarily correspond to the sensation of weariness or fatigue[14].

The simple question of whether there is or is not sleepiness, which is included in various clinical reports, can be answered in different ways depending on the perception of the patient or examiner. Compared with the ESS, the answer in terms of a yes or a no presented a high number of FP results, which led us to consider this question inappropriate for the clinical assessment of patients with acromegaly.

Obesity plays an important pathogenic role in the development of sleep apnea and therefore in that of hypoxemia. When the individual is not obese, there must be another kind of abnormalities, like in craniofacial structure, to produce sleep apnea[18]. The BMI and the neck circumference are clinical parameters commonly used to evaluate the degree of obesity. Therefore, these parameters are useful in the clinical evaluation of respiratory sleep disorders.

Patients with sleep apnea tend to present higher BMI and greater neck circumference, both proportional to the apnea/hypopnea index or to the SpO_2 drop per hour index. When matched for BMI and age, patients with apnea present greater neck circumferences, indicating that greater neck circumference is a more powerful indicator of sleep apnea than is BMI[19]. The neck circumference parameter demonstrates an even stronger correlation with sleep hypoxemia than do radiologically-determined craniofacial alterations[20] or other clinical characteristics[21].

In agreement with the findings of these studies, the data we obtained display a 5.71 LR+ for a neck circumference greater than 44 cm. In isolation, the presence of this finding makes sleep hypoxemia highly likely. However, the sensitivity is low (only 28.6%). For patients without acromegaly, other authors[22] have proposed a 40-cm cut-off point, with which a sensitivity of 60.6% and a specificity of 93.4% were obtained.

In patients with acromegaly, Rosenow et al.[1] demonstrated a significant difference in sleep hypoxemia using a 41-cm cut-off point, although the authors did not determine whether this would be the best discriminatory value based on the various sensitivities and specificities. It is likely that the ideal discriminatory value differs between and among dissimilar populations. It is equally probable that patients with acromegaly present values that are higher than those observed in other patients.

We conclude that the recognition of clinical aspects relative to neck circumference, BMI, ESS score and snoring provides important information, allowing the probability of sleep hypoxemia in patients with acromegaly to be determined with a high degree of reliability.

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REFERENCES

1. Rosenow F, Reuter S, Deuss U, et al. Sleep apnoea in treated acromegaly: relative frequency and predisposing factors. Clin Endocrinol 1996; 45:563-569.
2. Blanco Perez JJ, Blanco-Ramos MA, Zamarron SC, et al. Acromegaly and sleep apnea. Arch Bronconeumol 2004;40:355-359.
3. Grunstein RR, Ho KY, Sullivan CE. Sleep apnea in acromegaly. Ann Intern Med 1991;115:526-532.
4. Grunstein RR, Ho KY, Sullivan CE. Effect of octreotide, a somatostatin analog, on sleep apnea in patients with acromegaly. Ann Intern Med 1994;121:478-483.
5. Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. Am J Respir Crit Care Med 2002;166:159-165.
6. Wright AD, Hill DM, Lowy C, Fraser TR. Mortality in acromegaly. Q J Med 1970;39:1-16.
7. Kraiczi H, Caidahl K, Samuelsson A, Peker Y, Hedner J. Impairment of vascular endothelial function and left filling: association with the severity of apnea-induced hypoxemia during sleep. Chest 2001;119:1085-1091.
8. Peker Y, Hedner J, Johansson A, Bende M. Reduced hospitalization with cardiovascular and pulmonary disease in obstructive sleep apnea patients on nasal CPAP treatment. Sleep 1997;20:645-653.
9. Flemons WW, Whitelaw WA, Brant R, Remmers JE. Likelihood ratios for a sleep apnea clinical prediction rule. Am J Respir Crit Care Med 1994;150:1279-1285.
10. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-545.
11. Richardson GS, Carskadon MA, Flagg W, et al. Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. Eletroencephalogr Clin Neurophysiol 1978;45:621-627.
12. Chiner E, Signes-Costa J, Arriero JM, et al. Nocturnal oximetry for the diagnosis of the sleep apnoea hypopnoea syndrome: a method to reduce the number of polysomnographies? Thorax 1999;54:968-971.
13. Guilleminault C, Do KY, Chowdhuri S, et al. Sleep and daytime sleepiness in upper airway resistance syndrome compared to obstructive sleep apnoea syndrome. Eur Respir J 2001;17:838-847.
14. Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth sleepiness scale. Chest 1993;103:30-36.
15. Pekkarinen T, Partinen M, Pelkonen R, Iivanainen M. Sleep apnoea and daytime sleepiness in acromegaly: relationship to endocrinological factors. Clin Endocrinol 1987;27:649-654.
16. Astrom C, Christensen L, Gjerris F, Trojaborg W. Sleep in acromegaly before and after treatment with adenomectomy. Neuroendocrinology 1991;53:328-331.
17. Faithfull S. Patients' experiences following cranial radiotherapy: a study of the somnolence syndrome. J Adv Nurs 1991;16:939-946.
18. Ferguson KA, Ono T, Lowe AA, Ryan CF, Fleetham JA. The relationship between obesity and craniofacial structure in obstructive sleep apnea. Chest 1995;108:375-381.
19. Hoffstein V, Mateika S. Differences in abdominal and neck circumferences in patients wit and without obstructive sleep apnoea. Eur Respir J 1992;5:377-381.
20. Davies RJ, Stradling JR. The relationship between neck circumference, radiographic pharyngeal anatomy, and the obstructive sleep apnoea syndrome. Eur Respir J 1990;3:509-514.
21. Davies RJ, Ali NJ, Stradling JR. Neck circumference and other clinical features in the diagnosis of the obstructive sleep apnoea syndrome. Thorax 1992;47:101-105.
22. Kushida CA, Efron B, Guilleminault C. A predictive morphometric model for the obstructive sleep apnea syndrome. Ann Intern Med 1997;127:581-587.