Prevalence of Sleep-Disordered Breathing in Patients With Acute Ischemic Stroke: Influence of Onset Time of Stroke

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Objective: To analyze the prevalence of sleep-disordered breathing in patients with acute ischemic stroke and the influence of the characteristics of the stroke and time of onset.

Patients and Methods: Polysomnography was performed with an Autoset Portable Plus II in 139 patients within 72 hours of the onset of symptoms. Standard polysomnographic data, signs and symptoms related with sleep apnea-hypopnea syndrome (SAHS) prior to ischemic stroke, vascular risk factors, and characteristics and onset time (day/night) of ischemic stroke were recorded. The polysomnographic data were compared with results published for subjects of a similar age in the general population.

Results: The mean age was 73.6 (SD 11.1) years (59% of the patients were men). Prior to the stroke, 64.7% of the patients snored, 21.6% presented repetitive sleep apneas, and 35.6% had daytime sleepiness. The mean apnea-hypopnea index (AHI) was 29.1 (17.9) episodes/hour, the obstructive component of which was 20.1 (15.7) episodes/hour. Five patients presented Cheyne-Stokes breathing. The AHI (for all cut-points from 5 to 50), chronic snoring, and daytime sleepiness were significantly greater than those published for the general population. The stroke characteristics showed no significant differences between daytime and nighttime onset. Nighttime stroke (60.4%) was associated with a significantly higher AHI (33.3 compared to 24.7 episodes/hour) mainly because of obstructive apneas. Nighttime stroke was also associated with a greater nighttime desaturation and a greater probability of SAHS symptoms prior to stroke (odds ratio 2.62). In contrast, there were no differences in vascular risk factors between daytime and nighttime stroke onset.

Conclusion: The prevalences of sleep-disordered breathing with clinical signs and symptoms of SAHS were high in this population of patients with acute ischemic stroke. Patients with nighttime stroke had more obstructive sleep-disordered breathing and a higher clinical probability of obstructive SAHS before stroke. These findings support the hypothesis that obstructive SAHS is a risk factor for ischemic stroke, particularly for strokes presenting at night.

Key words: Prevalence. Sleep apnea-hypopnea syndrome. Nighttime stroke. Ischemic stroke.

Prevalencia de trastornos respiratorios durante el sueño en pacientes con ictus isquémico agudo. Influencia del momento de aparición del ictus

Objetivo: Analizar la prevalencia de trastornos respiratorios durante el sueño en pacientes con accidente cerebrovascular isquémico agudo (ACVI) y la influencia de las características y el momento de aparición del ictus.

Pacientes y métodos: Se realizó una poligrafía respiratoria (Autoset Portable Plus II) en 139 pacientes con ACVI en las primeras 72 h desde el inicio de los síntomas. Se recogieron los datos poligráficos habituales, síntomas y signos relacionados con el síndrome de apnea-hipopneas del sueño (SAHS) previos al ACVI, factores de riesgo vascular y características y momento de aparición (diurno/nocturno) del ACVI. Los resultados poligráficos se compararon con los publicados para individuos de edad semejante de la población general.

Resultados: La edad media (± desviación estándar) fue de 73.6 ± 11.1 años (el 59% eran varones). Antes del ictus, el 64.7% de los pacientes eranroncadores, el 21.6% presentaba apneas nocturnas repetidas y el 35.6%, somnolencia diurna. El índice medio de apneas-hipopneas fue de 29.1 ± 17.9, con un índice de apneas obstructivas de 20.1 ± 15.7. Cinco pacientes presentaron patrón de Cheyne-Stokes. El índice de apneas-hipopneas (para todos los puntos de corte estudiados; de 5 a 50), la roncopatía crónica y la hipersomnia diurna fueron significativamente mayores que los encontrados en población general. No hubo diferencias significativas según las características del ACVI. Los ACVI nocturnos (60.4%) mostraron de forma significativa un mayor índice de apneas-hipopneas (33.3 frente a 24.7) a cargo fundamentalmente de las apneas de carácter obstructivo, así como una mayor desaturación nocturna y una mayor probabilidad clínica de presencia de SAHS previos al ictus (odds ratio de 2.62). No hubo, sin embargo, diferencias con respecto a los factores de riesgo vascular estudiados.

Conclusión: En nuestra serie hubo una alta prevalencia de trastornos respiratorios durante el sueño y de clínica relacionada con SAHS en pacientes con ACVI agudo. Los ictus nocturnos presentaron un mayor número de trastornos respiratorios del sueño de carácter obstructivo y una mayor probabilidad clínica de SAHS previo. Nuestro estudio apoya la hipótesis de un SAHS obstructivo previo al ictus que podría funcionar como factor de riesgo, sobre todo en las formas de aparición nocturna.

Introduction

There is growing evidence that sleep apnea-hypopnea syndrome (SAHS) is an independent risk factor for hypertension1,2 and other cardiovascular diseases,3,4 but its association with cerebrovascular diseases is more controversial.5 Ever since Partinen and Palomaki6 established a possible association between chronic snoring and ischemic stroke in 1985, unexpectedly high prevalences of both chronic snoring and SAHS have been reported in such patients, predominantly in case-controlled studies.7-13 A recent large cross-sectional study of a general population showed a positive linear relationship between the number of nighttime respiratory events and the probability of suffering ischemic stroke,4 though a number of factors may have affected the reliability of the results. These include lack of agreement on the definition of SAHS, confounding variables such as age, hypertension or other risk factors common to both pathologies, and differences in the timing of the diagnostic study with respect to the onset of the cerebrovascular event.

It is even less clear whether SAHS is a risk factor for stroke or whether stroke causes SAHS. The importance of the type of respiratory event is also unclear. The site, severity, or time of onset of stroke may also affect the type of respiratory event. The findings of some studies suggest that SAHS occurs before stroke and so can be considered a risk factor for stroke. For example, patients who suffer a stroke are more likely to have been snorers,7 the severity and type of stroke does not influence the frequency of nighttime respiratory events,10,11 and there is a high proportion of obstructive episodes with few central-type events in either the acute or stable phases of stroke.12 Other studies report predominance of obstructive episodes but with numerous central apneas and many patients who experience Cheyne-Stokes breathing. Both types of event might be caused by the stroke itself.13 The most plausible explanation for these discrepancies would be the presence of both mechanisms (SAHS as a risk factor and a consequence of stroke) with weighting based on the number and type of apneas. It is also known that half of strokes occur at night and that their causes are unknown.14

The objective of the present study was to analyze the prevalence of different types of sleep-disordered breathing during the acute phase of stroke and the influence of the characteristics and time of onset of the stroke on respiratory events.

Patients and Methods

All patients admitted to our hospital in 2002 for acute ischemic stroke were enrolled in the study. Patients with a substantial decrease in the level of consciousness (Glasgow coma score <8), those in critical condition, those with underlying terminal diseases or in need of urgent admission to the intensive care unit, those with nighttime respiratory or heart failure, or those who regularly took mood-altering drugs (such as benzodiazepines and their derivatives) were excluded from the study. Patients who refused to give informed consent to perform the necessary polysomnography study and those whose onset of symptoms was more than 72 hours before admission to our hospital were also excluded. A neurologist diagnosed stroke by evaluations of the neurological deficit and computed tomography scans performed within hours of the patient’s admission to our emergency department and some days later. For all patients, we recorded the type of stroke (transient ischemic attacks or documented cerebrovascular accident), extent (lacunar or non-lacunar) and site (right hemisphere, left hemisphere, vertebrabasilar, or undetermined) according to widely accepted diagnostic criteria.15 We also recorded whether the patient had suffered prior stroke and the timing of onset of symptoms ("1" if stroke occurred during sleep or on waking; "0" if it occurred during the rest of the day). The clinical outcome and severity of the stroke at the time of admission were assessed with extensively validated scales. The Barthel Index, which ranges from 0 to 100, provided an assessment of the patient’s degree of autonomy in activities of daily living, with a score of 100 indicating that the patient is completely autonomous. The Canadian scale was used to assess the severity of stroke on a scale ranging from 0 (most severe) to 10 (least severe) and the Glasgow coma scale to assess level of consciousness of the patient, with increasing consciousness reflected by a score ranging from 3 to 15. We collected information on the following vascular risk factors: smoking habit, hypertension (as defined by the criteria of the World Health Organization16 or antihypertensive agents taken), hypercholesterolemia (>250 mg/dL), diabetes mellitus, atrial fibrillation, ischemic heart disease, and fibrinogen concentration (mg/dL) in peripheral blood. The clinical characteristics relevant to SAHS prior to stroke were gathered with a questionnaire that offered the patients a series of alternatives for each question. The patients were questioned on chronic snoring (every night, usually/most nights, sporadically/few nights, never, or don’t know); nighttime apneas (frequency: every night, usually/most nights, sporadically/few nights, never, or don’t know; repetition: many episodes in the same night, few episodes in the same night, don’t know), daytime sleepiness assessed with the Epworth scale validated in Spanish,17 and anthropometric and general variables (age, sex, body mass index in kg/m², and neck circumference in centimeters). Snoring was considered to be clinically significant if it appeared every night or most nights. Clinically significant apneas were those witnessed every night or most nights or those repeatedly witnessed on the same night. A patient was considered to have a high clinical probability of suffering SAHS if he or she presented 2 of the main symptoms of the syndrome, namely, chronic snoring, witness of repeated apneas, or clearly pathological daytime sleepiness (Epworth Score >12).18

All patients finally enrolled underwent polysomnography with an Autoset Portable Plus II (ResMed, Sydney, Australia) within 72 hours of the onset of symptoms. In diagnostic mode, the Autoset apparatus can record different respiratory variables and heart rate with continuous positive airway pressure. We measured nasal flow with a nasal
Statistical Analysis

The SPSS 9.0 package for Windows (SPSS, Chicago, IL, US) was used for the statistical analysis. For quantitative variables, the mean (SD) value was calculated, whereas qualitative variables were presented as absolute values and percentages. Means were compared with the Student t-test if the variables were normally distributed (according to the Kolgomorov-Smirnov test), otherwise the Mann-Whitney U test was applied. The χ² test was applied to qualitative variables. The results of prevalence of sleep-disordered breathing and symptoms related to SAHS in patients with acute stroke were compared with results published for the general population with adjustment for age by the z test for comparison of 2 proportions. Risk was determined by odds ratios with 95% confidence intervals. For all tests, a P value less than .05 was considered statistically significant.

Results

Of the 164 patients who were admitted with diagnosis of acute stroke in 2002, 3 were excluded from the study due to daytime respiratory or heart failure, 3 due to chronic use of benzodiazepines, 6 due to extreme severity of the stroke or short-term underlying terminal diseases, and 5 because they were admitted directly to the intensive care unit. In addition, 4 patients were excluded because they died within 24 hours of admission, 4 because the onset of symptoms occurred more than 72 hours before admission, and 1 because he refused to give informed consent to perform the polysomnography study. Thus 139 patients were finally enrolled in the study (59% men) with a mean age of 73.6 (11.1) years (range: 38-87 years). The time between onset of symptoms and the polysomnography study was 1.4 (0.8) days. The study population presented the following cardiovascular risk factors: 81 patients (58.3%) had hypertension, 27 (19.4%) atrial fibrillation, 43 (31%) diabetes mellitus, 17 (12.2%) ischemic heart disease, 29 (21%) hypercholesterolemia, 78 (56.1%) were smokers or ex-smokers, and the mean concentration of fibrinogen in peripheral blood was 326 (91) mg/dL. Thirty-two patients (23%) suffered at least 1 stroke prior to entry in the study. Table 1 shows the characteristics of the strokes suffered by the patients and their clinical effects. Table 2 shows the prevalence of signs and symptoms related to SAHS and the results for the polysomnographic variables. Eight patients had a negative result from the Autoset polysomnography study despite having a high clinical suspicion of SAHS, so they underwent full polysomnography. In 3 patients, the results of this study were normal. A further 3 patients presented a syndrome of increased upper airway resistance, 1 presented signs and symptoms compatible with narcolepsy, and the remaining patient had SAHS (AHI=23). Stroke occurred during sleep or...
with an hour of waking in 60.4% of the patients.

The figure compares the prevalence of sleep disordered breathing defined by AHI cut-points between 5 and 50 episodes/hour and clinical findings related to SAHS with a study in the general population after adjustment for age (individuals between 71 and 100 years old).²⁰

Neither clinical signs of SAHS prior to stroke nor the polysomnographic variables did not vary significantly by site (P=.89) or extent (P=.3) of stroke. However, AHI values tended to be higher for patients with documented cerebrovascular accidents than for those with transient ischemic attacks. This difference approached statistical significance (AHI of 31.9 [19] for documented cerebrovascular accidents versus 26.3 [15.6] for transient ischemic attacks; P=.06). Likewise, differences between documented cerebrovascular accidents and transient ischemic attacks approached significance for the central apnea index (2.9 [2.2] versus 1.9 [2.2]; P=.09) and nighttime desaturation (percentage of recorded time with hemoglobin saturation below 90%: 10.4 [17] versus 5.8 [18.1]; P=.1).

Patients who presented with stroke during sleep or in the first hour after waking had a significantly higher AHI compared to those with daytime stroke (33.3 [19.4] versus 24.7 [17.9]; P=.01) due largely to the obstructive component (obstructive apnea index: 23.3 [16.4] versus 16.9 [18.2]; P=.02). This difference was particularly significant in the subgroup of patients with AHI greater than 30 (n=68; mean AHI: 47.3 [9.9] versus 34.1 [12.2]; P=.007) with an obstructive apnea index of 38.1 [11.7] versus 25.5 [13.9] (P=.009). These patients also showed longer nighttime desaturation. Moreover, prior to stroke, patients with nighttime onset of stroke tended to be snorers, and had greater daytime sleepiness, a higher body mass index, and a larger neck circumference. These patients therefore had a significantly higher clinical probability of suffering

<table>
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<tr>
<th>Parameter</th>
<th>Nighttime stroke (n=82)</th>
<th>Daytime stroke (n=57)</th>
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<td>74.1 (10.7)</td>
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</tr>
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<td>BMI, kg/m²</td>
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<td>7.9 (4.3)</td>
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<td>Neck circumference, cm</td>
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<td>30 (36.6%)</td>
<td>19 (33.4%)</td>
<td>NS</td>
</tr>
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<td>Chronic snoring</td>
<td>35 (67.1%)</td>
<td>35 (61.4%)</td>
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<tr>
<td>RWA</td>
<td>20 (24.4%)</td>
<td>10 (17.5%)</td>
<td>NS</td>
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<td>T90</td>
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<td>5.2 (15.3)</td>
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<td>HCP-SAHS</td>
<td>42 (51.2%)</td>
<td>13 (22.8%)</td>
<td>.004</td>
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</table>

*BMI indicates body mass index; AHI, apnea-hypopnea index; HI, hypopnea index; T90, percentage of recorded time with hemoglobin saturation below 90%; HCP-SAHS, criteria of sleep apnea-hypopnea syndrome prior to stroke. Mean (SD).

Figure. Prevalence of nighttime respiratory episodes and clinical symptoms related to sleep apnea-hypopnea in patients who have suffered acute ischemic cerebrovascular accident. Comparison with general elderly population.

CS indicates chronic snoring; DS, daytime sleepiness (Epworth Score >10 points); AHI, apnea-hypopnea index; SAHS-10, sleep apnea-hypopnea syndrome defined as AHI >10 and an Epworth Score >10; SAHS-20, sleep apnea-hypopnea syndrome defined as AHI >20 and an Epworth Score >10.
SAHS before the neurological episode (odds ratio: 2.62; 95% confidence interval: 1.23-5.58; P=.01) according to our definition of “high suspicion of SAHS” in this study. There were, however, no differences in vascular risk factors (including hypertension), strokes prior to the current episode, or severity or clinical outcome of the stroke.

Discussion

We found a greater prevalence of various types of sleep-disordered breathing and SAHS in patients with acute stroke than in the age-matched general population. Patients who suffered the cerebrovascular event during sleep or the first hour after waking had obstructive respiratory events more often and a greater percentage of clinical signs and symptoms indicative of SAHS, suggesting that obstructive SAHS is present before the appearance of stroke.

Several case-controlled studies have assessed the relationship between chronic snoring and ischemic stroke, though their findings have been contradictory.6-13 When confounding variables such as age, hypertension, or body mass index are taken into account (odds ratio between 1 and 2) the relationship between chronic snoring and ischemic stroke is weaker but remains significant. But when chronic snoring was added to the presence of other main symptoms of SAHS, such as witnessed apneas or pathological daytime sleepiness, a stronger relationship was seen.21 Studies show greater agreement regarding the increase in number of pathological respiratory episodes during sleep (normally assessed by AHI and measurements of nighttime desaturation) in patients with acute stroke compared to the age-matched general population.22 Our results also confirmed this association, particularly as the mean age of our patients was actually slightly lower than that of the general population used for comparison. In the published studies, the frequency of these events varies greatly according to the study characteristics, the diagnostic device used, and the time elapsed between stroke onset and the diagnostic polysomnography. Further variation arises because of differences in the patient characteristics. The type of respiratory event (obstructive or central) is more controversial. Central apneas or Cheyne-Stokes breathing could be the result of the hemodynamic abnormalities due to the acute stroke itself in patients with no relevant heart disease. Prior SAHS could therefore lead to more obstructive apneas. Some authors suggest that the increase in obstructive apneas is due to loss in pharyngeal muscle tone in patients with stroke.19 Thus the stroke itself becomes a cause of this type of respiratory episode. Nevertheless, the high clinical probability of SAHS before stroke and the larger number patients with stroke onset during the night (when cerebral gasometric and hemodynamic abnormalities are most pronounced) would point to prior obstructive SAHS. Hui et al12 found that 49% of the stroke patients had an AHI over 20 and 31% had an AHI over 30% in the first 24 hours after stroke, with a clear predominance of obstructive apneas—the central apnea index was only 5 (7.6) out of a total AHI of 32.3 (17.6). In contrast, Parra et al13 reported 28% of a total of 161 patients with stroke had an AHI over 30, also with a predominance of obstructive episodes, but more central apneas than obstructive apneas (central apnea index of 5.6 [10.1] versus obstructive apnea index of 4.5 [8.4]) and a high proportion of patients with Cheyne-Stokes breathing (26.1%). Our results agree more closely with those of Hui et al12; that is, our patients have few central-type events and the Cheyne-Stokes breathing pattern occurs infrequently though it is more common at certain AHI values. This could be influenced by the difficulty of separating central apneas from Cheyne-Stokes breathing and the different diagnostic devices used.

Several studies seem to show that both AHI and the measures of nighttime desaturation are unrelated to the type, extent, severity, or site of the stroke.10,11,13 The conclusions that can be drawn from these studies may be limited because patients with less severe strokes (normally transient ischemic attacks) were included in the study but those with the most severe strokes were excluded. Our study, despite similar limitations, did show a non-significant tendency for patients with more severe stroke (documented cerebrovascular accident with worse neurological indices) to have a larger AHI as a function of both the number of obstructive episodes and greater nighttime desaturation. No differences were found for extent or location of the stroke.

A more detailed examination of our results reveals a significantly higher prevalence and greater severity of nighttime respiratory episodes in patients with onset of stroke at night or within an hour of waking, regardless of the severity or site of the stroke. The results for the influence of timing of stroke onset in the circadian cycle on the frequency and severity of the sleep disordered breathing are contradictory.14,22 Stroke is known to occur more often during sleep or early in the morning, but no satisfactory explanation has emerged.14,23 Many of these patients presented clinical signs and symptoms highly indicative of prior obstructive SAHS. Although separate analysis of each one of the symptoms related to SAHS showed no statistically significant differences between daytime and nighttime onset, all these symptoms appeared more often in patients with nighttime onset of stroke. However, no noteworthy differences were seen for cardiovascular risk factors, severity or clinical outcome of the stroke, or prior strokes. These differences were particularly pronounced in the subgroup of patients with AHI's over 30, supporting the hypothesis that patients with nighttime onset of stroke are more likely to suffer undiagnosed obstructive SAHS before the cerebrovascular event. Thus obstructive SAHS can be considered a risk factor or trigger for stroke.24 Netzer et al24 demonstrated substantial hemodynamic abnormalities in the medial cerebral
artery during episodes of obstructive apnea or hypopnea with resultant oxygen desaturation. Such abnormalities occurred less often with central apneas. These findings might help explain why the prevalence of nighttime strokes is higher with increased AHI.

We performed respiratory polysomnography with the Autoset Portable Plus II, a device that has been extensively validated in the literature for different AHI cut-points and has produced excellent results for populations with a high pretest prevalence of SAHS, 25-30 such as in our population of patients with ischemic strokes. Full polysomnography still remains the test of reference for diagnosing SAHS. Our use of the Autoset device may limit the interpretation of the findings of the present study, particularly as it only has 1 thoracoabdominal belt for the identification of central apneas. Special care was nevertheless taken to repeat tests in which the patient claimed to have slept less than 3 hours in an attempt to reduce the error due to lack of objective measurement of sleep. Moreover, patients with negative respiratory polysomnographic results but clinical signs and symptoms highly indicative of SAHS were referred to another clinic for a full polysomnography study. We also recognize that the present study has no control group that would allow risk measurements to be established. Instead, we compare prevalence of events in our population with the general elderly Spanish population (71-100 years of age) described by Durán el al 20 to correct as far as possible for the known increase in respiratory disorders with age. We conclude that there is a high prevalence of mainly obstructive sleep-disordered breathing and clinical signs and symptoms related to SAHS in our stroke patients, particularly when the onset of stroke is at night. These patients show clinical signs and symptoms more indicative of prior SAHS, but the prevalence of other cardiovascular risk factors is not greater, suggesting that obstructive SAHS is present before the onset of stroke and that obstructive SAHS can be considered as a risk factor for stroke. We believe that active screening for clinical signs and symptoms indicative of SAHS by detailed and specific questioning is necessary in patients who have suffered a stroke.

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