CLINICAL SCIENCE

OBSTRUCTIVE SLEEP APNEA IN ISCHEMIC STROKE PATIENTS

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OBJECTIVE: To investigate the prevalence of obstructive sleep apnea in patients with ischemic stroke and to evaluate the effectiveness of nasal continuous positive airway pressure treatment.
METHODS: Overnight polysomnography was performed by a computerized system in 19 subjects with ischemic stroke. Patients with an apnea-hypopnea index ≥ 5 were considered to have obstructive sleep apnea. The appropriate level of continuous positive airway pressure for each patient was determined during an all-night continuous positive airway pressure determination study. Attended continuous positive airway pressure titration was performed with a continuous positive airway pressure auto-titrating device.
RESULTS: Obstructive sleep apnea prevalence among patients with ischemic stroke was 73.7%. The minimum SaO_2 was significantly lower, and the percent of total sleep time in the wake stage and stage 1 sleep was significantly longer in patients with obstructive sleep apnea. In two patients with severe obstructive sleep apnea, we observed a decrease in the apnea-hypopnea index, an increase in mean wake time, mean SaO_2, and minimum SaO_2, and alterations in sleep structures with continuous positive airway pressure treatment.
CONCLUSION: As the diagnosis and treatment of obstructive sleep apnea is of particular importance in secondary stroke prevention, we suggest that the clinical assessment of obstructive sleep apnea be part of the evaluation of stroke patients in rehabilitation units, and early treatment should be started.

KEYWORDS: Stroke; Sleep apnea; Continuous positive airway pressure.

INTRODUCTION

Stroke is an important cause of mortality and a major cause of disability among adults, leading to considerable economic and social problems. The most effective means of diminishing stroke-related burden is by reducing the incidence of first-time and recurrent stroke. Therefore, recognizing and treating modifiable risk factors are of particular importance. Besides the well-known modifiable risk factors, such as hypertension, diabetes mellitus, heart disease, smoking, excessive alcohol use, and hypercholesterolemia,[1] obstructive sleep apnea (OSA) is emerging as an important risk factor.[2]

Obstructive sleep apnea syndrome (OSAS), characterized by repeated episodes of upper airways obstruction during sleep that lead to significant hypoxemia, is a prevalent disorder particularly among middle-aged men, though its existence in women is increasingly recognized. Epidemiological studies estimate that 2 to 5% of the population meets the minimal diagnostic criteria (snoring, witnessed apnea and excessive daytime sleepiness), and two community-based studies have found that about 2% of women and 4% of men were affected by OSAS.[3] We recently reported a female patient for whom severe OSAS was the cause of fibromyalgia syndrome, which was totally resolved with the treatment of OSAS.[4] OSAS is characterized by periods of breathing cessation (apnea) and periods of

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reduced breathing (hypopnea). Both types of events have similar pathophysiology and are generally considered equal with respect to their impact on patients. There are several methods of quantifying the severity of the disorder, such as measuring the number of apneas and hypopneas per hour of sleep (the apnea-hypopnea index, AHI), the severity of oxygen desaturation during sleep, or the severity of the most commonly associated symptom, daytime sleepiness.[3,5] OSAS is also associated with increased risk of stroke and other cardiovascular diseases. There are various mechanisms that contribute the increased risk of stroke and other cardiovascular diseases, such as increased sympathetic activity, endothelial dysfunction, elevated fibrinogen levels, increased in vivo platelet activation during sleep, alteration of in vitro platelet aggregability, hypercoagulability, and decreased cerebral blood flow in sleep apnea (SA) patients.[6-11] The increased carotid wall thickness observed in patients with severe sleep apnea may also increase the risk of stroke.[12] Therefore, the treatment of OSA is important since it might prevent these consequences of the disease. The accepted and highly effective treatment of OSA is nasal continuous positive airway pressure (CPAP).[2] It is reported that stroke patients with OSA can also be effectively treated with CPAP.[13,14]

This study aimed to investigate the OSA prevalence in ischemic stroke patients and to evaluate the effectiveness of the CPAP treatment in this group.

METHODS

Patients

Among 55 stroke patients hospitalized for rehabilitation, 25 patients with ischemic stroke at the subacute and chronic stages were selected. Exclusion criterion disqualified patients with previous diagnoses of sleep disordered-breathing, current CPAP treatment, unstable comorbidities (cardiac or respiratory failure), or ventilatory dependence. As a result, the study was completed with 19 patients (13 men, 6 women) with ischemic stroke who were able to give informed consent. The study was approved by the local ethics committee. Stroke was diagnosed according to the World Health Organization criteria,[15] and cerebral lesion was confirmed by computerized tomography or magnetic resonance imaging in all patients. A detailed history was taken before examinations, including previous transient ischemic attacks (TIA) or strokes, concomitant diseases that are among modifiable risk factors of stroke (hypertension, ischemic cardiovascular diseases (CVD), diabetes, and hypercholesterolemia), former or current smoking history, alcohol consumption, and complaints of habitual snoring, excessive daytime sleepiness, and witnessed apneas before stroke. Habitual snoring, excessive daytime sleepiness, and witnessed apneas were considered clinical signs of OSA. Snoring was considered habitual if it was reported to occur often or always. Daytime sleepiness was evaluated using the Epworth Sleepiness Scale (ESS) with scores > 10 regarded as excessive.[16] The patients' heights and weights were measured, and body mass index (BMI) was calculated in kg/m^2. An overnight polysomnography was performed in all patients. Patients diagnosed with moderate to severe OSA were further evaluated for CPAP treatment.

Sleep study

Overnight polysomnography (PSG) was performed in all patients by a computerized system (Somnostar alpha; Sensormedics, USA) that included the following variables: electrooculogram (2 channels), electroencephalogram (4 channels), electromyogram of submental muscles (2 channels), electromyogram of the anterior tibialis muscles of both legs (2 channels), and electrocardiogram and airflow (with an oro-nasal thermistor). Chest and abdominal efforts (2 channels) were recorded using inductive plethysmography, and arterial oxyhemoglobin saturation (SaO_2: 1 channel) was recorded by pulse oximetry with a finger probe. The recordings were conducted at a paper speed of 10 mm/s, and sleep stages were scored according to the standard criteria of Rechtschaffen and Kales.[17] Arousals were scored according to accepted definitions,[18] and the arousal index (ARI) was calculated as the number of arousals per hour of sleep. Apnea was defined as a complete cessation of airflow ≥ 10 s. Hypopnea was defined as a reduction of > 50% in either: one of the three respiratory signals, the airflow signal, or either respiratory or abdominal signals of respiratory inductance plethysmography, with an associated fall of ≥ 3 % in oxygen saturation or an arousal.[19] Each apnea and hypopnea was classified as obstructive, central, or mixed, based on the presence or absence of respiratory effort.[2] It is also recommended that mixed apnea be included as a part of OSA. The diagnosis criteria for central sleep apnea syndrome is five or more central apneas per hour of sleep.[20] The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. Patients with AHI ≥ 5 were considered to have OSA. Patients with AHI 5 to 15 were diagnosed as mild, 15-30 were moderate and greater than 30 were severe OSA.[19] Patients with OSA were compared to patients without OSA. Patients with sleep disorders other than OSA, such as upper airway resistance syndrome, periodic leg movement syndrome, or narcolepsy, were excluded. Patients with moderate to severe OSA were further evaluated for CPAP treatment. The therapy and possible side

effects were explained to the patients, and in patients who agreed to use CPAP treatment, the appropriate level of CPAP for each patient was determined during an all-night CPAP pressure determination study. A polysomnographic study was performed with the same setup as the diagnostic study, except that nasal CPAP was applied during sleep. Attended CPAP titration was performed with the CPAP auto-titrating device (AutoSet; Resmed, Sydney, Australia) on the second night of the study in our hospital. Patients were prescribed the use of the CPAP device (Vector Plus CPAP devices; Hoffrichter, Germany) that automatically turned on when the mask was removed. We measured compliance by the mean rate of CPAP use (hours per day). Acceptable duration was considered ≥ 4 h/night.

Statistical analysis

A computer-based statistics program (SPSS version 11.5) was used to evaluate the study data. The differences between groups were assessed using the Fisher exact test for categorical variables and Mann-Whitney U test for the ordinal variables. The results are expressed as mean ± SD. The significance level was set at $p < 0.05$.

RESULTS

Obstructive sleep apnea was diagnosed in 14 of the 19 stroke patients (73.7%), of whom eight had mild (mean AHI: 9.6 ± 3.5), two had moderate (mean AHI: 20.6 ± 1.0), and four had severe (mean AHI: 83.1 ± 41.9) OSA. The mean AHI of OSA (+) patients was 32.2 ± 39.3; the mean AHI of OSA (-) patients was 2.0 ± 0.9. The mean total counts of apneas-hypopneas were 121.8 ± 120.6 in the OSA (+) group (central 7.8 ± 8.6, mixed 9.3 ± 19.4, obstructive 104.6 ± 108.7) and 10.8 ± 4.9 in the OSA (-) group (central 1.4 ± 1.1, mixed 0, obstructive 9.4 ± 5.8). The mean central apnea counts did not differ statistically between groups with AHI ≥ 5 and < 5 (Table 1). There were no statistically significant differences between the OSA (+) and OSA (-) stroke patients in mean ages, mean time elapsed from the

Table 1 - Characteristics and polysomnography data of stroke patients with and without obstructive sleep apnea (OSA)

	OSA (n=14)	No OSA (n=5)	*p*
Age (years)	63.3±12.8	55.8±14.7	NS*
Male gender (%)	8 (57.1)	5 (100)	NS
Time after stroke onset (months)	11.4±15.7	18.1±19.2	NS
Body Mass Index (kg/m^2)	25.8±3.6	25.4±5.9	NS
Total apnea-hypopnea count (mean± SD) (range)	121.8 ± 120.6 (28-382)	10.8 ± 4.9 (6-19)	P=0.001
Obstructive	104.6 ± 108.7 (16-373)	9.4 ± 5.8 (3-19)	P=0.002
Mixed	9.3 ± 19.4 (0-70)	0 (0)	P=0.014
Central	7.8 ± 8.6 (0-30)	1.4 ± 1.1 (0-3)	NS
Prior history of TIA or stroke (%)	6 (42.9)	None	NS
Concomitant diseases** (%)	10 (71.4)	4 (80)	NS
Smoking history (%)	6 (42.9)	5 (100)	p=0.045
Alcohol history (%)	1 (7.1)	1 (20)	NS
Habitual snoring (%)	9 (64.3)	1 (20)	NS
Excessive daytime sleepiness or witnessed apneas (%)	10 (71.4)	2 (40)	NS
Mean sleep period time (minutes)	401.4±42.1	391.5±43.0	NS
Total sleep time (minutes)	268.2±64.2	331.7±30.0	NS
Sleep efficiency (%)	63.6±16.3	78±6.6	NS
Arousal index	12.2 ±8.9	10.2±4.4	NS
Mean SaO_2*** (%)	90.2±2.4	92.2±1.9	NS
Mean wake SaO_2 (%)	94.1±2.5	94±1.8	NS
Minimum SaO_2 (%)	78.5±7.9	88.2±3.1	p=0.005
Percent of total sleep time in Stage Wake (%)	32.5±16.6	14.8±7.4	p=0.014
Percent of total sleep time in Stage 1 (%)	14.1±10.8	6.9±3.7	p=0.044
Percent of total sleep time in Stage 2 (%)	53.6±15.4	58.7±13.2	NS
Percent of total sleep time in Stage 3 (%)	5.2±3.2	5.9±4.9	NS
Percent of total sleep time in Stage 4 (%)	14.4±15.3	13.4±11.9	NS
Percent of total sleep time in Stage REM (%)	12.6±7.2	15.1±10.5	NS

* NS: Not significant; ** Concomitant diseases: Hypertension, ischemic cardiovascular diseases, diabetes or hypercholesterolemia; *** SaO_2: Oxygen saturation

onset of stroke, and BMI (Table 1). There were also no statistically significant differences between OSA (+) and OSA (-) patients in mean sleep period time, total sleep time, sleep efficiency, arousal index, mean SaO_2, and mean wake SaO_2. There were also no statistically significant differences in the percent of total sleep time in stage 2, stage 3, stage 4 non-rapid eye movement (NREM), and stage rapid eye movement (REM) sleep. Minimum SaO_2 was significantly lower in OSA (+) than in OSA (-) patients, while the percent of total sleep time in the wake stage and stage 1 NREM sleep were significantly longer in OSA (+) than in OSA (-) patients. Among OSA (+) patients, eight were (57.1%) male, six had (42.9%) a prior history of TIA or CVA, ten had (71.4%) concomitant diseases, six (42.9%) were former or current smokers, one (7.1%) was a former alcohol user, nine defined habitual snoring (64.3%) and ten (71.4%) had other clinical signs (excessive daytime sleepiness or witnessed apneas). Among the five OSA (-) patients, all were males, all were former or current smokers, four had (80%) concomitant diseases, two (40%) had clinical signs of OSA, one (20%) was a former alcohol user, one (20%) defined habitual snoring and none had a prior history of TIA or CVA,. Among all these parameters, only the frequency of former or current smoking history was higher in OSA (-) patients (χ^2= 4.93, p=0.045), but this is likely a misleading result due to the small study population. The characteristics and PSG data of the patients with and without OSA are given in Table 1.

Treatment with CPAP

Only two patients with severe OSA (ages 86 and 65 years; AHI of 144.1 and 62.3) agreed to use the CPAP treatment. The polysomnography data of these patients before and after the CPAP treatment are given in Table 2.

Table 2 - Polysomnography data of patients before and after continuous positive airway pressure treatment

		Before CPAP	After CPAP
Total Apnea-Hypopnea Count	*Patient 1*	347	5
	Patient 2	382	121
Apnea-Hypopnea Index	*Patient 1*	144.1	1.0
	Patient 2	62.3	31.6
Arousal Index	*Patient 1*	10	10.2
	Patient 2	33.4	16.4
Mean wake SaO_2* (%)	*Patient 1*	88	96
	Patient 2	91	94
Mean SaO_2 (%)	*Patient 1*	85	94
	Patient 2	86	90
Minimum SaO_2 (%)	*Patient 1*	71	84
	Patient 2	59	83
Sleep efficiency (%)	*Patient 1*	32	71
	Patient 2	77	59
Percent of total sleep time in Stage Wake (%)	*Patient 1*	67.2	26.7
	Patient 2	22.6	39.4
Percent of total sleep time in Stage 1 (%)	*Patient 1*	40.8	7.7
	Patient 2	10.6	3.9
Percent of total sleep time in Stage 2 (%)	*Patient 1*	59.2	60.0
	Patient 2	55.2	50.7
Percent of total sleep time in Stage 3 (%)	*Patient 1*	0	5.8
	Patient 2	5.6	9.1
Percent of total sleep time in Stage 4 (%)	*Patient 1*	-	7.2
	Patient 2	14.0	2.8
Percent of total sleep time in Stage REM (%)	*Patient 1*	-	19.3
	Patient 2	14.7	33.5

* SaO_2: Oxygen saturation

DISCUSSION

In this study, OSA was diagnosed in 73.7% of stroke patients. The minimum SaO_2 was significantly lower in patients with OSA than without OSA, and the percentages of total sleep time in wake stage and stage 1 NREM sleep were significantly longer.

The OSA frequency of 73.7% in these ischemic stroke patients was exceedingly high when compared with its prevalence of 2% in women and 4% in men in the middle-aged population. This frequency was also above the range of 12.5-23% reported for the control groups of previously published studies in stroke or TIA patients.[21-23] When compared with the previously reported frequencies (36.7-79%) of SA in stroke or TIA patients,[7,13,21-31] our result is closer to the upper limit. The discrepancy between the reported frequencies may have resulted from differences in the intervals between the onset of stroke and sleep recordings, stroke subtypes, sleep study methods, and sleep apnea definitions between these studies.. Most of these studies evaluated the SA prevalence in acute stroke or TIA syndromes, some of these studies included both ischemic and hemorrhagic types, and most of them used AHI > 10 for diagnosis of SA instead of > 5. Additionally, not all of these studies used in-laboratory comprehensive PSG recordings, which is the accepted test for diagnosing and determining the severity and treatment of OSA.[32] Therefore, it can be assumed that some mild SA patients might have been overlooked in previous work, and the SA prevalence may be higher, especially in the acute stages of stroke or TIA. Another possible explanation for why our result is closer to the upper limit of reported frequencies though all our

patients were in subaute or chronic stages of ischemic stroke, the sensitive detection methods and lower diagnostic criteria may have identified more mild cases of OSA.

Central apneas are also observed in patients with stroke. Central periodic breathing (CPB) most frequently results from congestive heart failure and is characterized by cyclic fluctuations in breathing drive, such as hyperpneas alternating with apneas or hypopneas in a gradual waxing and waning fashion. CPB may also develop in stroke patients without cardiopulmonary disease and disturbed consciousness.[30] Obstructive sleep apneas predominate in the acute phases of stroke, whereas central apneas are associated with an altered state of consciousness, brain edema, and brainstem localization of ischemia. During recovery after stroke, the incidence of central apneas diminishes, whereas obstructive apneas remain at a similar level.[31] Hermann et al. reported that 58% of 31 first-ever stroke patients had sleep-disordered breathing; 9.7% of these presented as CPB, and all others presented as OSA.[30] Rola et al. evaluated 55 patients with ischemic stroke and 15 patients with TIA for sleep related breathing disorders (SRBD), and they found that SRBD were present in 36 patients (65.4%) with stroke and ten patients (66.6%) with TIA. Obstructive apneas were the most frequent apnea-related episodes in both stroke and TIA patients (77.6 ± 12.6% and 80.5 ± 13.6, respectively). Central apneas amounted to 13.2 ± 9.6% of stroke patients and 10.5 ± 8.6% of TIA patients.[31] Likewise, obstructive events were the predominating type, and central apnea-hypopneas constituted only 6.4% of the total apnea-hypopnea count in sleep apnea patients in our study group; none of the patients in this study group satisfied the criteria of central apnea syndrome.

In our study, all patients were ischemic stroke patients, and the mean time elapsed from the stroke onset was 11 months (minimum 6 weeks), representing the stable phase of stroke. The results of this study confirm the study of Szücs et al., who reported that SA frequency and severity were unchanged three months later in most ischemic stroke patients, while greatly improved in hemorrhagic stroke patients. Moreover, the study presumed that hemorrhagic strokes lead more often to central apneas. In contrast, OSA itself is a probable risk factor for ischemic stroke.[27]

In our patients with OSA, the minimum SaO_2 was significantly lower, and the percent of total sleep time in the wake stage and stage 1 NREM sleep were significantly longer, as expected. Apnea-related episodes lower the SaO_2 during sleep, and OSA patients spent more time in the wake and transition stages between awake and sleep during the night due to apneas and arousals. Sleep efficiency was also decreased in OSA patients, though we did not demonstrate a statistically significant difference. The other statistically significant variable was the smoking history; however, surprisingly, the frequency of smoking history was higher in OSA (-) patients than OSA (+) patients, although this was likely a misleading result due to the small study population. Although not statistically significant, the presence of habitual snoring and other clinical signs of OSA were also higher in OSA patients in accordance with the literature.[2,21,24,29] Although we could not demonstrate any statistically significant differences in these variables, this was likely a result of our small sample size. However, since the in-laboratory comprehensive PSG recordings technique used in this study was detailed, not readily available, and expensive, we had to conduct our study with a limited number of patients. These factors also contributed to the absence of an appropriate control group from the population, which was a limitation of our study. Since the history of habitual snoring and other clinical signs of OSA were present before stroke, we can presume that OSA might be a preceding risk factor for stroke, in accordance with the opinion that OSA constitutes a significant risk for cardiovascular diseases including stroke.[2,7-12]

Whether OSA is a cause or consequence of stroke, its management is of particular importance in secondary stroke prevention.[13] It was shown that stroke patients with OSA can also be effectively treated with CPAP.[13,14] A reversal of the blood coagulability, increase in oxygen saturation, increase in cerebral blood flow response to hypoxia, reduction in mean nocturnal blood pressure, and improvements in sleep structures are observed with CPAP therapy.[9,10,14,33] In our study, only two patients with severe OSA agreed to use the CPAP treatment. Although it is impossible to draw a conclusion about the effectiveness of CPAP with two patients, we wished to share the results of these patients. A decrease in AHI, increases in mean wake time, mean SaO_2, and minimum SaO_2, and alterations in sleep structures were observed with the CPAP treatment. In one of the patients, sleep efficiency was obviously increased, and the percentage of total sleep time in the wake stage and stage 1 NREM sleep were decreased with the CPAP treatment. Before the CPAP treatment, the patient spent nearly no time in stage 3/4 NREM sleep (deep sleep) and REM sleep. After the CPAP treatment, the patient began sleeping for longer periods at the deep sleep and REM sleep stages. These changes in sleep structure were consistent with the study that reported that CPAP significantly reduced stage 1/2 NREM sleep and markedly increased stage 3/4 NREM and REM sleep on the first night of treatment.[34] The CPAP treatment was well tolerated, and home treatment was continued in this patient. However, in the other patient, the percent of total sleep time in stage 1, stage 2, and deep sleep decreased, while the percent of total sleep time in the wake stage and REM sleep

increased. This second patient also experienced decreased sleep efficiency and did not continue the CPAP treatment at home due to the discomfort caused by the device. The obvious improvement in one of the patients confirms the effectiveness and usefulness of CPAP therapy[13,14] in stroke patients with OSA.

To conclude, the OSA prevalence was fairly high in our small sample of ischemic stroke patients. As the diagnosis and treatment of OSA is of particular importance in secondary stroke prevention, we suggest that the clinical assessment of OSA be a part of the evaluation of stroke patients in rehabilitation units. Since CPAP is an effective treatment of OSA and provides clinical improvements in compliant stroke patients, early treatment should be started.

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