Insomnia in patients with obstructive sleep apnea compared with controls.

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Abstract

The aim of this study was to investigate the incidence of insomnia in obstructive Sleep Apnea and Hypopnea Syndrome (OSAHS), as well as the impact of the comorbidity of insomnia and OSAHS on quality of life, sleep quality, and emotion. One hundred twenty-three patients with OSAHS, successively selected from May 2013 to December 2014, were assigned to the OSAHS group, and 52 age-matched subjects without OSAHS were assigned to the control group. The two groups were further divided by presence of insomnia, and the general characteristics, comorbidities, and quality of life were compared between the insomnia group and the non-insomnia group of patients with OSAHS. Hypertension (P=0.007), cerebral infarction (P=0.002), female sex (P=0.008), and senior age (P=0.002) were identified as risk factors for OSAHS with insomnia (P<0.05). The scores of the Pittsburgh Sleep Quality Index (P<0.001; 8.14 ± 3.20 *vs.* 5.19 ± 2.57) and the Depression Anxiety Stress Scale (P<0.05; 10.96 ± 5.25 vs. 9.09 ± 3.52) of patients with OSAHS and insomnia were higher than those of patients with OSAHS alone. The score of the healthy quality of life questionnaire (SF-12) was lower in patients with OSAHS and insomnia than in patients with OSAHS alone (P<0.001; SF-12 physiological score: 48.53 ± 3.68 vs. 54.25 ± 2.94; SF-12 mental score: 49.50 ± 3.40 vs. 53.19 ± 3.96). These results reveal that the incidence of insomnia in patients with OSAHS is significantly higher than in controls, cerebral infarction is a newly identified risk factor for insomnia in OSAHS patients, and OSAHS combined with insomnia significantly lowers quality of life compared with OSAHS alone.

Keywords: Obstructive sleep apnea and hypopnea syndrome, Insomnia, Comorbidity.

Introduction

Obstructive Sleep Apnea and Hypopnea Syndrome (OSAHS) is a very common disease characterized by repeated upper airway obstruction during sleep leading to recurrent apnea and hypopnea. OSAHS can cause damage to multiple organ systems, thereby seriously harming the health of patients with this disease. Insomnia manifests as difficulty falling asleep, sleep maintenance disorder, decreased sleep quality, early awakening, reduced total sleeping time, and daytime dysfunction.

Though OSAHS and insomnia are the two most common types of sleep disorders, the link between them remains in question. In 1973, Guilleminault et al. [1] attempted to explore the correlations between OSAHS and insomnia, but results were inconclusive. In 2001, Krakow et al. [2] performed retrospective statistics on the incidence of insomnia in OSAHS populations, showing incidence rates as high as 50%,

significantly higher than that in the general population. Since this study, many scholars have performed similar investigations. Alotair and Krell, for instance, found that the incidence of insomnia in OSAHS populations (22%-54.9%) was generally higher than that in non-OSAHS populations [3-8], and various studies have shown that the prevalence of insomnia in the general population is approximately 10%-30% [9-16].

While these studies indicate that the incidence of insomnia in patients with OSAHS is significantly higher than that in healthy individuals, understanding the factors influencing the prevalence of insomnia in these patients requires further study. Björnsdóttir identified hypertension, diabetes, and smoking history as risk factors for insomnia in patients with OSAHS [17]. However, it remains unknown whether cerebral infarction is a risk factor for the comorbidity of insomnia and OSAHS, whether the severity of OSAHS affects the probability of its comorbidity with insomnia [17,18], and whether comorbidity

with insomnia leads to differences in Epworth Sleepiness Scale (ESS) scores when compared with OSAHS alone [17,19,20]. To address these questions, this study aimed to screen for risk factors for insomnia in patients with OSAHS, to explore the quality of life of patients with both OSAHS and insomnia, and to provide new ideas and approaches for prevention and treatment of these patients.

Materials and Methods

General data collection

One hundred twenty-three patients with OSAHS, admitted as outpatients or inpatients to the Department of Neurology at the Second Affiliated Hospital of Nanchang University from May 2013 to December 2014, were successively selected and included 94 males and 29 females, with an average age of 51.01 ± 5.64 years (42-65 years). Meanwhile, 52 healthy volunteers were recruited for the control group during the same period, including 31 males and 21 females, with an average age of 50.83 ± 6.339 years (41-66 years). The individuals in the control group were recruited during their normal medical examinations as outpatients or inpatients of the Second Affiliated Hospital of Nanchang University. Patients with OSAHS, language comprehension and expression disorders, mental illness or family history of mental illness, or other severe or life-threatening complications were excluded from the control group. Complete medical history, polysomnography (PSG; 32-Lead Stellate Harmonie Video PSG System; Harmonie, Canada), and related test results were collected for all subjects.

The following inclusion and exclusion criteria were used: 1) Patients with OSAHS met the treatment guidelines of Chinese obstructive sleep apnea and hypopnea syndrome (revised edition, 2011) [21] and were diagnosed with OSAHS by PSG; 2) Patients with CPAP or surgical treatment, as well as those with neuropsychiatric disorders, physical illness, medication-caused secondary insomnia, obvious disorders in intelligence, language comprehension and expression disorders, mental illness or family history of mental illness, and presence of severe or life-threatening complications were excluded; and 3) The control group was age-matched and healthy.

All study subjects were aware of test contents and provided signatures giving informed consent. This clinical trial was approved by the ethics committee of our hospital. The assessments of all study scales were determined by experienced neurologists in our department who were trained with normalized language, and uniform standards were used for the evaluations.

Procedures and questionnaires

Name, age, sex, Body Mass Index (BMI), smoking history, alcohol abuse history, snoring history, night time sleep quality, previous history (hypertension, diabetes, cerebral infarction, restless legs syndrome, cardiovascular diseases, etc.), and family history of all subjects were recorded.

Insomnia

According to the Chinese diagnosis and treatment guidelines of adult insomnia in 2012 [22], patients with primary chronic insomnia (duration more than 6 months) were included and divided into group DIS (having difficulty falling asleep) and group DMS (having difficulty maintaining sleep) according to the types of insomnia. Difficulty falling asleep manifests as more than 30-minute falling asleep time, and sleep maintenance difficulties manifest as awakening at night ≥ 2 times.

Epworth sleepiness scale

The Epworth Sleepiness Scale (ESS) [23] is an easy self-assessment questionnaire for daytime sleepiness with good reliability and validity. ESS is composed of a total of 8 scenarios and has a total score of 24 points with higher scores indicating more severe lethargy.

Pittsburgh sleep quality index

The Pittsburgh Sleep Quality Index (PSQI) is used to assess the examinee's subjective sleep quality for the previous 1-month period. Chinese researchers have tested its reliability and validity concluding that it is suitable for Chinese people. The entire scale is composed of nine self-assessment items and five items assessed by others. The total score is 21 points with higher scores indicating poorer quality of sleep.

The self-assessed Depression Anxiety Stress Scales (DASS-21) [24] are used to test the severity of negative emotion symptoms, and are shown to have high stability, reliability, and validity. This measure is composed of three dimensions, namely depression, anxiety, and stress, and reflects the individual's recent negative emotional experiences (within approximately 1 week).

Healthy quality of life questionnaire (SF-12)

The SF-12 questionnaire [25] has good internal consistency and high validity within Chinese elderly populations, and it is widely used to evaluate quality of life. It is composed of the total physiological score (SF-12 PS) and the total mental score (SF-12 MS), with higher scores indicating positive subjective feelings and healthier physical and mental statuses.

National institutes of health stroke scale

The National Institutes of Health Stroke Scale (NIHSS) includes 11 items, namely consciousness, staring, vision, facial paralysis, upper limb movement, lower limb movement, ataxia, sensation, language, dysarthria, and neglect. Higher scores represent more severe neurological deficits. All study subjects were evaluated using this scale.

Statistical analysis

SPSS 19.0 statistical software was used in this study. Data were expressed as mean ± standard deviation, and normally distributed data were calculated as average values, standard

deviation, and P values, etc. and used for t-tests. Count data were used in the chi-square test, and the relationships of dichotomous results with certain impacting factors were assessed using binary logistic regression analysis, with the significance level set to $\alpha=0.05$ and $P<0.05$ considered statistically significant.

Results

General characteristics

There was no statistically significant difference in average age between patients with OSAHS and healthy subjects. The proportion of male patients with OSAHS was higher than that in healthy control group, and the difference was statistically significant ($P<0.05$, Table 1).

Because there was a statistically significant difference in the proportion of males and females between the two groups, general characteristics, such as BMI, apnea-hypopnea index

(AHI), individual history (smoking history, alcohol abuse history), and comorbidities (hypertension, diabetes, cerebral infarction, restless legs syndrome, etc.; Table 2) were analyzed separately by sex. We found statistically significant differences in BMI, AHI, smoking history, hypertension history, and cerebral infarction, but not in diabetes and restless legs syndrome, in males between the two groups. Statistically significant differences in BMI, AHI, and hypertension history, but not in smoking history, diabetes, cerebral infarction, and restless legs syndrome, were observed in females between the two groups.

Table 1. Analysis of age and gender between the two groups.

	Control group	OSAHS group	Test value	P
Cases	52	123		
Gender (M/F)	31/21	94/29	5.059	0.024
Age	50.83 ± 6.34	51.01 ± 5.64	-0.204	0.839

Table 2. General information in different genders between the two groups.

	M			F		
	Control group (n=31)	OSAHS group (n=94)	P	Control group (n=21)	OSAHS group (n=29)	P
BMI	25.45 ± 2.30	29.97 ± 8.32	0.003	22.29 ± 2.77	27.55 ± 5.92	<0.001
AHI	3.20 ± 1.16	33.55 ± 18.34	<0.001	2.69 ± 0.97	31.51 ± 4.32	<0.001
Smoking history	10	51	0.034	1	0	0.235
Hypertension	4	44	0.001	2	15	0.002
Diabetes	1	10	0.206	1	4	0.293
cerebral Infarction	1	17	0.041	1	7	0.065
Restless legs	0	4	0.243	1	0	0.235

The prevalence of insomnia in patients with OSAHS and controls

The incidence of insomnia was 56.91% (70/123) in the OSAHS group and 30.77% (16/52) in the control group, and the higher incidence of insomnia in the OSAHS group was statistically significant ($P<0.05$).

Table 3. Analysis of sleep quality between the 2 groups.

	OSAHS group (n=123)	Control group (n=52)	Test value	P
Insomnia	70	16	9.993	0.002
DIS	29	7	2.289	0.130
DMS	53	10	9.030	0.003

Patients with insomnia were then further divided into group DIS and group DMS. The incidence of DIS was higher in the OSAHS group than in the control group, but the difference was not statistically significant ($P>0.05$). The incidence of DMS

was higher in the OSAHS group than in the control group, and this difference was statistically significant ($P<0.05$, Table 3).

Associations with insomnia in patients with OSAHS and controls

Because more risk factors for insomnia were found in the OSAHS group, binary logistic regression analysis was used to analyze relevant factors individually. We found that sex, age, hypertension, and cerebral infarction were statistically associated with insomnia ($P<0.05$), while BMI, AHI, smoking history, diabetes, and restless legs syndrome showed no significant relationship with insomnia in patients with OSAHS ($P>0.05$). The statistically significant factors were then set as independent variables simultaneously for binary logistic regression analysis, and we found that cerebral infarction and sex maintained significant associations with insomnia (Table 4). Therefore, the effects of cerebral infarction and sex on insomnia in the OSAHS group were greater than those of age and hypertension.

Table 4. Relationships among different factors and insomnia in group OSAHS.

	Insomnia	
	P	OR (95%CI)
	0.008	3.833 (1.431-10.268)
	0.024[a]	3.412[a] (1.172-9.937)
Gender	0.002	1.119 (1.042-1.202)
Age	0.098[a]	1.067[a] (0.988-1.152)
BMI	0.412	1.020 (0.973-1.070)
AHI	0.447	1.415 (0.578-3.460)
	0.993	0.997 (0.483-2.057)
Smoking history	0.007	2.749 (1.310-5.769)
Hypertension	0.100[a]	1.992[a] (0.876-4.530)
	0.251	2.042 (0.603-6.911)
Diabetics	0.002	7.143 (2.001-25.492)
Cerebral infarction	0.019[a]	4.953[a] (1.295-18.947)
Restless leg	0.777	0.750 (0.102-5.505)

a: represented that gender, age, hypertension and cerebral infarction were set as the independent variables at the same time.

Table 5. Comparison of life qualities between the patients with OSAHS merged with insomnia and those simply suffering from OSAHS.

	Insomnia group	Non- insomnia group	t	P
ESS score	7.99 ± 4.85	6.79 ± 3.65	-1.499	0.136
PSQI score	8.14 ± 3.20	5.19 ± 2.57	-5.511	<0.001
NIHSS score	1.29 ± 2.18	0.25 ± 1.16	-3.15	0.002
DASS-21 score	10.96 ± 5.25	9.09 ± 3.52	-2.231	0.028
SF-12 PS	48.53 ± 3.68	54.25 ± 2.94	9.286	<0.001
SF-12 MS	49.50 ± 3.40	53.19 ± 3.96	5.548	<0.001

Note: NIHSS, NIH stroke score.

Characteristics of obstructive sleep apnea with and without insomnia

In the OSAHS group with insomnia, PSQI (P<0.001) and DASS-21 (P<0.05) scores were higher and SF-12 PS (P<0.001) and SF-12 MS (P<0.001) were lower than those of patients suffering from OSAHS without insomnia (Table 5). We observed lower qualities of physical and mental lives in patients with OSAHS and insomnia than in those with OSAHS alone. Patients with OSAHS and insomnia were more likely to experience anxiety, depression, and other negative emotions, but there was no significant difference in daytime sleepiness between the two groups.

Discussion

OSAHS and insomnia, both common sleep disorders, appear to be correlated based on reports from other countries. As described previously, many researchers believe that the incidence of insomnia in patients with OSAHS is significantly higher than in the general population. Gold found incidence rates of insomnia up to 59.9% in patients with OSAHS [18]; Hagen studied 100 patients at a sleep center and found 40% of patients with OSAHS suffered from moderate insomnia [26]. Overall, studies show that the incidence rate of insomnia in patients with OSAHS is in the range of 40%-60% [5,6,27-31], a conclusion that was further confirmed in our study. We found that the incidence of insomnia in the OSAHS group (56.91%) was significantly higher than that in the control group (30.77%).

Currently, there are few studies on the mechanisms of OSAHS-induced insomnia, which are hypothesized as follows: 1) OSAHS is prodromal to insomnia; 2) respiratory events, such as long-term nocturnal sleep apnea and hypoxia, may cause emotional movement disorder followed by increased times of awakening, the latter of which is the main symptom of insomnia [17]; 3) recurrent hypopnea may cause ease of awakening at night followed by sleep structural disorder and sleep maintenance disorder; 4) a variety of nocturnal respiratory events may activate the hypothalamic-pituitary-adrenal axis (HPA axis), thereby causing sleep fragmentation and insomnia. Respiratory events may also lead to autocrine activities, further activating the HPA axis and leading to the increase of HPA activities or metabolic abnormalities [32].

This study further divided insomnia into DIS and DMS for analysis and found that the more common type of insomnia in the OSAHS group was DMS. Similarly, Björnsdóttir found that the incidence of DMS in patients with OSAHS was 57.6% [17], while the incidence of DIS showed no difference compared with the control group. We hypothesize that further exploration of the mechanisms of OSAHS-induced insomnia would reveal that recurrent night-time hypopnea and nocturnal hypoxia cause awakenings at night followed by DMS, explaining the observed phenomenon that patients with OSAHS mainly exhibit DMS. In addition, our study had a higher proportion of males (76%) in the OSAHS group, and the main type of insomnia was DMS in males and DIS in females, similar to results described by Subramanian [33].

Views on the impact of the severity (AHI) of OSAHS on the probability of insomnia in these patients differ among scholars. Gold found that AHI was positively correlated with the appearance of DMS in OSAHS; specifically, higher AHI corresponded to greater probability of insomnia in patients with OSAHS [18]. However, Yang found that higher AHI corresponded to lower probability of insomnia in patients with OSAHS [34], and Krakow (2010) reported that the appearance of insomnia in the OSAHS population was independent of AHI [35]. Therefore, findings of the relationship between AHI and the incidence of insomnia in patients with OSAHS are inconsistent. In this study, we found that AHI had no

significant relationship with the appearance of insomnia in patients with OSAHS, consistent with Krakow's results.

This study is the first to show that cerebral infarction is a risk factor for insomnia in patients with OSAHS. Further analysis is needed to understand the possible mechanisms underlying this risk factor. For instance, many sleep-related anatomical sites in the brain, such as the frontal lobe bottom, brainstem ascending reticular activating system, midbrain tegmentum, and locus coeruleus, may be affected by cerebral infarction. Necrosis, edema, ischemia, hypoxia, and actions of related toxic substances in the above structures are likely to interfere with the sleep-awakening mechanism, thus leading to the occurrence of sleep disorders [36]. In addition, some scholars believe that the awakening-associated neurotransmitters such as serotonin (5-HT) and norepinephrine are important factors contributing to post-cerebral infarction sleep disorders. Because serotonergic and norepinephrine neurons are mainly located in the brainstem, the neural transduction pathways of norepinephrine and 5-HT are likely to be affected by lesions in these regions. 5-HT is an important neurotransmitter for REM sleep; therefore, it may play an important role in post-stroke sleep disorders [37]. Lastly, the incidence of post-cerebral infarction depression ranges from 20%-79%, and the degrees of depression and anxiety in patients with sleep disorders are significantly higher than in those without sleep disorders, indicating that depression and anxiety may influence post-cerebral infarction insomnia [38].

The comparison between the comorbidity group and the OSAHS alone group showed no significant difference in the average ESS score, contradicting Dubey's results showing that the comorbidity group had significantly higher ESS scores and daytime sleepiness [19], which was also confirmed by Björnsdóttir [17]. This difference may be related to the study population included in this study (Chinese population) and smaller sample size; however, Lichstein reported no significant difference in ESS between the above two groups [20], consistent with our results.

The results of this study show that the average DASS-21 score in the comorbidity group was significantly higher than that in the OSAHS alone group, indicating that the comorbidity of OSAHS and insomnia is more likely to cause anxiety, depression, or other negative emotions, consistent with Lichstein [20].

Finally, we found that the SF-12 PS and SF-12 MS scores in the comorbidity group were lower than in the OSAHS alone group, and the differences were statistically significant, indicating that the comorbidity of these conditions has negative impacts on both physical and mental health. Björnsdóttir also used the SF-12 questionnaire to compare the quality of life between the above two types of patients, and the results showed that the comorbidity group exhibited significantly reduced life quality [17] and suffered more from anxiety, depression, or other negative emotions. The latest study by Hayley in 2014 [39] also confirmed this conclusion by showing that the comorbidity of these two diseases resulted in poorer quality of life, consistent with the results of this study.

Limitations and Future Study

Presently, research about the correlation between OSAHS and insomnia remains scarce, and this study was the first to show that cerebral infarction is a risk factor for insomnia in patients with OSAHS. However, the total number of subjects in the control group in this study was 52, so the incidence of insomnia in the control group was not representative of the prevalence of insomnia in the general population, which should be expanded in future studies if allowed by the conditions.

Regarding the finding that patients with both OSAHS and insomnia had lower quality of life than those with OSAHS alone, we cannot make conclusions about causality as we did not discern whether insomnia caused poor quality of life in patients with OSAHS or poor quality of life was a risk factor for insomnia in OSAHS. LeBlanc et al. also mention this dilemma [16].

During the experiment, we used several assessments evaluated by subjects themselves or others. Though research has verified the reliability and validity of these scales, they do have some limitations. For example, the PSQI and ESS are self-assessment scales; therefore, some factors may interfere with results, including educational level, cognitive level, etc. If conditions permit, future studies will appropriately expand the sample size to reduce these confounding factors.

The present study preliminarily studied the correlations between OSAHS and insomnia, but treatment programs for the comorbidity of these two diseases were not investigated. In treating patients with both OSAHS and insomnia, consideration should be given to the respiratory inhibitory effects of various drugs when selecting drugs for insomnia [40,41]. Similarly, when using CPAP to treat OSAHS, we need to understand whether insomnia would reduce patient's compliance [5] or whether the discomfort from the CPAP treatment process might also increase the degree of insomnia. Therefore, patients suffering from these two diseases simultaneously should be considered for individualized treatment to achieve the best results.

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