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Original Article

Investigation and Analysis of Sleep Status in Patients with Vascular Depression

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SUMMARY

Background: To investigate the sleep status of patients with vascular depression (VD) and analyze the characteristics of sleep by polysomnogram.
Methods: 50 VD patients, 30 patients with non-vascular depression (NVD) and 50 normal subjects were enrolled. All subjects were evaluated by the Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Scale (HAM-A), Pittsburgh Sleep Quality Index (PSQI) and Epworth sleepiness scale (ESS). All these patients were monitored by polysomnography (PSG).
Results: The PSQI scores of the VD patients didn't show difference compared with that of NVD, but both of them were significantly higher than the normal. The ESS scores of VD patients were significantly higher than other groups. The total sleep time (TST), sleep efficiency (SE) and sleep maintenance (SMT) in NVD patients and VD patients were poorer, and the waking time after sleep onset (WASO) and sleep latency (SL) were significantly longer. The N1/N2 ratio was longer, and the N3/REM ratio was shorter in NVD patients and VD patients. The HAMD score was negatively correlated with RL and positively with RD, RA and RI. The RL of VD patients was longer than the normal, and RD and RI were higher in VD patients, there was no difference in RA. The obstructivity and apnea-hypopnea index (AHI) significantly increased in VD patients.
Conclusion: The characteristic PSG findings of the NVD patients were shortening REM sleep latency and REM disinhibition. Characteristics of VD with PSG patients were sleep-related breathing disorders (SRBD) and daytime sleepiness, and disorders of 24-h sleep structure.

1. Introduction

Vascular depression (VD) is a late-life depression with severe harmfulness. VD was first proposed by Alexopoulos and Krishmn in 1997, which included late-onset depression (depression firstly developed in old age), depression with white matter lesions (WML), or cerebral infarction, depression with cardiovascular risk factors and cognitive impairment, and depression with poor sensitivity to antidepressants and electroconvulsive therapy.[1–5] VD is common in the elderly. It is characterized by easy fatigue, highlighted somatization, retardation of psychomotor, and lack of pleasure. With the aging of the population and the increase in the incidence of cardiovascular and cerebrovascular disease, the incidence of VD has also increased. Imaging studies have revealed that 94% of patients with late-onset severe depression had developed asymptomatic stroke. Therefore, late-onset depression is mostly VD.[6–9] Sleep disorders can be used as predictors of mental diseases, particularly for depression; and disordered sleep can often be used as a precursor and may be the only clinical symptom 10. Sleep disorders in NVD patients mainly manifest as sleep maintenance difficulty, early awakening and excessive sleep.[9–13] Since its pathogenesis is different from NVD, sleep disorders in VD patients have different characteristics. The Pittsburgh Sleep Quality Index (PSQI)[14] and Epworth sleepiness scale (ESS)[15] are the commonly used sleep assessment scales. In this study, the sleep quality of VD patients was investigated, and the sleep situations of VD patients at each stage were analyzed by polysomnography (PSG), in order to summarize the characteristics of sleep in VD patients, and diagnose and treat this disease early.

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2. Materials and Methods

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of our hospital. Written informed consent was obtained from all participants.

2.1. Subjects

2.1.1. Inclusion criteria

A total of 50 VD patients, who were admitted in our hospital from September 2012 to September 2015, were enrolled into this study. Inclusion criteria for VD patients[1]: patients who met the diagnostic criteria for depression in the Chinese Classification of Mental Disorders, Third Edition (CCMD-3), and had a Hamilton Depression Scale (HAMD) score ≥8 points[2]; patients who met the diagnostic criteria of vascular depression recommended by Alexopoulos et al. 1,2: depression occurs after the age of 65 years, patients have clinical and (or) laboratory evidence of cerebrovascular disease and vascular risk factors, and depression occur between 6 and 12 months after the occurrence of cerebrovascular events. In addition, 30 NVD patients, who were outpatients or inpatients during the same period, were enrolled into this study. These patients met criterion 1, but had no clinical and (or) laboratory evidence of cerebrovascular disease and vascular risk factors. The control group comprised of 50 healthy elderly people, who had a HAMD score of <8 points. Differences in terms of age, gender, education level and other socio demographic data between these three groups were not statistically significant ($P > 0.05$).

2.1.2. Exclusion criteria

Patients who had serious body disease, mental disease and other diseases that affect night time sleep were excluded. Patients who had head and body tremors, alcohol and drug abuse history, and developed symptoms of infection and fever within one week were excluded. Patients who had not taken sedative hypnotic drugs and psychoactive substances, or previously taken these drugs but had discontinued its administration for more than three days before detection were included into the study. Patients who had primary sleep disorders were excluded. Patients who could not cooperate with the examination were excluded.

2.2. Methods

2.2.1. Scale tests

The sleep status of patients was evaluated by two professionals using HAMD, Hamilton Anxiety Scale (HAMA), PSQI and ESS.

HAMD is the most commonly used scale for depression (24-item edition). A total score of >35 points indicates severe depression, a total score between 20 and 35 points surely indicates depression, a total score between 8 and 20 points indicates a certain possibility of depression, and a total score of <8 points indicates that the patient does not have depression symptoms. PSQI consists of 19 items, which can be divided into seven categories: subjective sleep quality, sleep time, sleep duration, sleep efficiency, sleep disorders, hypnotic drug use and daytime function. Subjects with a PSQI score <8 points were diagnosed “without sleep disorder”, while subjects with a PSQI score ≥8 points are diagnosed “with sleep disorder” 9. An ESS score of >6 points indicates sleepiness, an ESS score of >11 points indicates excessive sleepiness, and an ESS score of >16 points indicates dangerous sleepiness 10.

2.2.2. PSG monitoring

The patient's sleep situations were monitored using the PSG machine produced by Compumedic Siesta (Australia) for a duration of >7 h. Within 24 h before the examination, subjects were not allowed to take sedative drugs, or drink wine and tea. This monitoring was performed in the sleep apnea monitoring room. Polysomnography: Subjects were allowed to sleep for two nights in the sleep laboratory. One night was for adaptation, and the other night was for the PSG that was performed the whole night. The main indicators analyzed by the laboratory sleep monitoring system include the following aspects: (A) Sleep measurement and analysis, which includes the following[1]: sleep process, including total sleep time (TST), sleep latency (SL), sleep efficiency (SE), waking time after sleep onset (WASO) and sleep maintenance (SMT)[2]; sleep structure, including sleep stages (S1, S2, S3 and REM), sleep duration and percentages[3]; REM sleep indexes, including REM sleep latency (RL), REM activity (RA), REM intensity (RI) and REM density (RD), as well as the number of REM cycles. RL is the interval between the start times of S1 to the appearance of REM sleep. RT is the total time of all stages of REM sleep during the whole night sleep. RA, RI and RD: Each minute of REM sleep was divided into nine units and given a serial number ranging from 0 to 8, the time of rapid eye movement during each REM sleep period was calculated, the time was converted into the number of units, the number of units in all stages were summed up, and the result was RA. RI was the ratio of RA/TST. RD was the ratio of RA/REM sleep time.[2] Breath analysis: Breath airflow was transnasally detected, the abdominal and abdominal breathing motion was detected using a stretch gauge, and blood oxygen saturation was detected at the same time. Apnea and hypopnea were determined according to current international standards, apnea-hypopnea index (AHI) was calculated, and the presence of obstructive sleep apnea syndrome (OSAS) was analyzed.

2.3. Statistical methods

Data were expressed as mean ± standard deviation (±SD), and were evaluated using *t*-test and analysis of variance (ANOVA). Correlation analysis was conducted using Pearson's correlation. The statistical analysis of the experimental data was conducted using the Chinese version of statistical software SPSS 20. $P < .05$ was considered statistically significant.

3. Results

3.1. General information

(Table 1) The general information of the three groups of patients were comparison, and the differences in gender, handedness, marriage, age, education level and MMSE score were not statistically significant. Furthermore, the differences in HAMD and HAMA scores between VD patients and NVD patients were not statistically significant.

3.2. Comparison of PSQI and ESS scores among the three groups

(Table 2) PSQI and ESS scores in the VD and NVD groups were higher than in the normal group ($P < 0.05$), but the difference in PSQI scores between the VD and NVD groups was not statistically significant ($P=.2588$, $P > .05$). Furthermore, ESS scores were higher in the VD group than in the NVD group, and the difference was statistically significant ($P=.001$, $P < .05$).

3.3. Analysis of PSG characteristics among the three groups

(Table 3) TST, SE and SMT in the NVD patients and VD patients were shorter than in normal subjects, while WASO and SL in the VD and NVD groups were longer than in the normal group. Differences in the above indexes between VD patients and NVD patients were

Table 1
General information ($\bar{x}\pm s$).

Items	Vascular depression group (n = 50)	Non-vascular depression group (n = 30)	Normal group (n = 50)	p Value
Age (year)	68.91 ± 5.79	69.02 ± 4.83	69.32 ± 5.28	.8675
Gender (male/female)	27/23	16/14	26/24	.2366
BMI (kg/m 2)	22.20 ± 1.96	21.75 ± 1.92	22.41 ± 1.87	.3195
Education level (year)	9.07 ± 1.31	9.02 ± 1.19	8.73 ± 1.46	.8647
HAMD	21.13 ± 0.57	20.80 ± 0.74	6.12 ± 0.61	.2280
HAMA	16.71 ± 0.84	17.23 ± 0.91	7.01 ± 0.31	.2313
MMSE	24.70 ± 0.34	27.63 ± 0.57	27.79 ± 0.37	.0918

Table 2
Comparison of PSQI and ESS scores among the three groups (x±s).

	Vascular depression group (n = 50)	Non-vascular depression group (n = 30)	Normal group (n = 50)
PSQI (total points)	15.67 ± 1.32	16.01 ± 1.25	3.50 ± 0.79
ESS	9.45 ± 4.47	3.01 ± 3.76	2.69 ± 2.14

Table 3
PSG characteristics among the three groups.

	Vascular depression group (n = 50)	Non-vascular depression group (n = 30)	Normal group (n = 50)
Total sleep time (TST)	359.48 ± 69.21	346.57 ± 73.69	417.10 ± 59.21
Sleep efficiency (SE)	62.24 ± 2.86	60.31 ± 1.97	74.87 ± 2.31
Sleep maintenance rate (SMT) (%)	78.65 ± 17.21	80.74 ± 16.16	90.02 ± 9.63
Waking time after sleep onset (WASO)	94.24 ± 55.91	97.31 ± 46.25	61.35 ± 29.16
sleep latency (SL)	31.27 ± 24.36	33.18 ± 23.22	14.20 ± 20.38
Sleep proportion during different stages (%)			
N1	13.51 ± 9.87	12.66 ± 10.42	5.47 ± 3.39
N2	57.69 ± 15.34	58.82 ± 12.69	49.63 ± 11.21
N3	6.37 ± 1.13	7.21 ± 1.09	14.54 ± 2.18
REM sleep proportion (%)	11.53 ± 6.51	16.77 ± 6.28	20.52 ± 5.48
REM sleep latency	93.65 ± 14.92	55.24 ± 11.31	78.25 ± 12.46
REM density (%)	92.82 ± 26.71	124.94 ± 23.8	70.88 ± 20.52
REM activity	56.29 ± 29.56	89.40 ± 28.45	61.36 ± 28.17
REM intensity (%)	17.12 ± 8.46	24.15 ± 8.72	12.48 ± 7.51
REM cycles	8.21 ± 2.43?	7.65 ± 2.54	5.46 ± 2.61

not statistically significant. Furthermore, the N1/N2 ratio was longer, and the N3/REM ratio was shorter in NVD patients and VD patients, compared to normal subjects. The proportion of REM in VD patients was significantly lower than that in NVD patients. The RL of NVD patients was shorter than that of normal subjects, and the RA, RI and RD in the VD and NVD groups were higher than in the normal group. Furthermore, RL in VD patients was longer than in NVD patients and normal subjects, and RA in VD patients were less than that in NVD patients, but the difference in RA between VD patients and normal subjects was not statistically significant. Moreover, RD and RI in VD patients were less than that in NVD patients.

3.4. Correlation between PSG characteristics in the REM phase and HAMD in VD patients and NVD patients

The total HAMD score was negatively correlated with RL, but was positively correlated with RD, RA and RI. There was no significant correlation between the total HAMD score and changes in sleep structure.

Microarousal in VD patients increased, daytime sleepiness increased, the lowest and mean blood oxygen saturation significantly decreased, and obstructivity and AHI significantly increased, compared with normal subjects and NVD patients; and the differences were statistically significant ($P < .05$) (Table 4).

4. Discussion

Sleep disorder is one of the most common clinical symptoms of depression in the early stages. Previous studies have revealed that 90% of depression patients have complained insomnia, which may also be an early sign of a new depression attack.[9–12] The main symptoms of sleep disorders in depression patients are sleep maintenance difficulty, early awakening and excessive sleep; and its characteristics are not so obvious. The sleep electroencephalogram manifestations of depression patients mainly include the following: prolongation of SL, sleep maintenance disorder, reduction of slow wave sleep (SWS) and inhibitory disorder in REM sleep[13,16–18]. Among these, changes in REM sleep indexes have characteristics that mainly include shortened RL of REM sleep, increased duration of REM sleep, increased activity, density and strength of REM sleep, and increased cycles of REM sleep. Among these, RL shortening is a biomarker for characteristic changes in endogenous depression, and is related to relatively stronger negative cognitive and negative emotional experience and terminal insomnia, which reflect the severity of depression. With RL shortening as an indicator, the sensitivity of diagnosing major depressive disorders is 35−95%, and its specificity is 62−100%. RL shortening is the strongest and most characteristic form of sleep disorder in depression.[16–18] This study revealed that some aspects of sleep disorders were similar between NVD patients and VD patients, including prolonged SL, sleep maintenance disorder, reduction of SWS and sleep efficiency. These were consistent with the results of other studies.[19,20] Our further research revealed that the total score of HAMD in VD patients was negatively correlated with RL, and was positively correlated with RD, RA and RI. This study also revealed the following differences between sleep disorders induced by VD and NVD: RL in VD patients was longer than in NVD patients; RA, RD and RI in VD patients were less than those in NVD patients, that is, the increase in EEG bewaking at REM phase in VD patients was not as obvious as that on NVD patients. Compared with NVD

Table 4
The presence of obstructive sleep apnea syndrome (OSAS) among three groups.

	Vascular depression group (n = 50)	Non-vascular depression group (n = 30)	Normal group (n = 50)	p value
AHI (times/h)	16.78 ± 10.26	10.35 ± 8.79	3.78 ± 1.56	.0055
Microarousal index	39.41 ± 19.78	30.65 ± 11.79	18.69 ± 10.81	.0308
Oxygen desaturation index	24.58 ± 13.72	17.94 ± 10.53	8.07 ± 6.71	.0001

patients, the daytime sleepiness of VD patients was more obvious, the ESS scores and AHI of VD patients were higher, VD patients were more likely to develop SRBD (apnea or hypopnea occurs in the sleep stage), patients had more obvious disorders of 24-h sleep structure, and there was no significant correlation between the total score of HAMD and changes in sleep structure. For the reasons of the difference in PSG between these two groups, it is considered to include the following aspects[1]: VD patients have risk factors of cerebrovascular disease, and SRBD such as OSAS is one of the risk factors of cerebrovascular disease, which can cause daytime sleepiness, and also increase the disorder of sleep structure[2]; Although there was no significant difference in MMSE scores between VD patients and NVD patients, MCI patients are usually characterized by RL prolongation in PSG.[21,22] The nature of REM sleep remains unelucidated. Some scholars believe that REM sleep is a process to remove brain tissue metabolic wastes, while some scholars believe that this period is the process to prepare proteins and neurotransmitters that nerve cells need in the daytime.[23] We speculate that the activity and intensity of REM sleep may be related to cognitive function to a certain extent. The specific reasons need to be further studied.

Although we achieved interesting results, there were limitations in our study. We did not quantify the breath analysis of PSG in patients with sleep apnea. The size of studied population may also be a limitation. Although we made some observations on cognitive function, the results are not satisfactory. Considering these facts, further investigation is still a necessity in this area.

5. Conclusion

The characteristic PSG findings of the NVD patients was shortening REM sleep latency and REM disinhibition. Characteristics of VD with PSG patients were sleep-related breathing disorders (SRBD) and daytime sleepiness, and disorders of 24-h sleep structure.

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