PSYCHIATRIA ET NEUROLOGIA JAPONICA

Special Feature Article

The Characteristics and Predictors of Subjective and Objective Sleepiness in Obstructive Sleep Apnea

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Abstract

Obstructive sleep apnea (OSA) is an age-associated disorder and its prevalence is increasing in Japan. OSA affects daytime physical and mental functions due to sleep fragmentation and hypoxia caused by apnea and hypopnea during sleep. OSA is associated with the development of depression and increases suicide scores in PTSD, but treatment by continuous positive airway pressure (CPAP) reduces the depressive symptom scores. OSA causes cognitive impairment across a range of domains and is linked to car accidents and dementia; however, CPAP reduces the risk of car accidents. Drowsiness, fatigue, and non-restfulness are some of the most frequent symptoms of OSA. There are two main methods to assess sleepiness: the assessment of subjective sleepiness, e. g. the Epworth Sleepiness Scale (ESS), and assessment of objective sleepiness, e. g. the Multiple Sleep Latency Test (MSLT) and the Maintenance Wakefulness Test (MWT). The ESS is a self-administered questionnaire designed to assess sleepiness in all aspects of daily life; however, the relationship between ESS scores and the apnea hypopnea index (AHI), which represents the severity of OSA, is controversial. The MSLT score is based on the mean latency to fall asleep at 5 daytime sessions, but its relationship with the AHI is unclear. Furthermore, although CPAP can improve ESS and MSLT scores, some patients still have excessive daytime sleepiness.

According to previous studies that examined the relationship between sleepiness and EEG activity during sleep in OSA patients, the alpha waves and spindle waves are associated with subjective and objective sleepiness, respectively. Thus, it may be possible to estimate the degree of subjective or objective sleepiness in OSA by examining the physiological background of EEG activity during sleep rather than considering only the effects of subjective and objective sleepiness due to respiratory impairment variables of OSA.

Keywords: obstructive sleep apnea (OSA), Epworth Sleepiness Scale (ESS), Multiple Sleep Latency Test (MSLT), alpha waves, spindle waves

Introduction

Sleep-related breathing disorders are a group of conditions characterized by abnormal breathing during sleep, including central sleep apnea and obstructive sleep apnea as subclassifications. Obstructive sleep apnea (OSA) occurs in all age groups, but becomes more frequent with aging. The prevalence of OSA is high, estimated to be 34% in men and 17% in women in the United States, and is thought to have increased by about 30% between 1990 and 2010 12)22). The prevalence of OSA is similar in Japan, although there are differences in the body mass index (BMI), and is thought to be at least 10% 30). OSA causes repeated sleep fragmentation and hypoxia due to apnea or hypopnea during night-time sleep, which affects physical and mental functions during the day. The severity of OSA is classified according to the apnea hypopnea index (AHI), which is the number of hypopneas per hour of sleep. In this paper, we describe subjective and objective sleepiness, its characteristics, and predictors, based on the effects of OSA on psychiatric disorders.

I. Obstructive Sleep Apnea and Psychiatric Disorders (Mental Function)

OSA affects various mental and cognitive functions. Regarding the prevalence of OSA in various psychiatric disorders, Stubbs, B. et al. found that it was 15.4% (95% CI: 5.3 to 37.1%) in schizophrenia, 24.5% (95% CI: 10.6 to 47.1%) in bipolar disorder, and 36.3% (95% CI: 19.4 to 57.4%) in depression, being particularly common in those with depression 29). A one-level increase in

OSA severity was associated with a 1.8-fold adjusted odds of developing depression 21), and patients with OSA had a 2.18-fold hazard ratio for developing a depressive disorder within one year compared with non-OSA patients 6), suggesting a close association between OSA and the development of depression. An association with suicide has also been suggested, and it has been reported that OSA severity scores are associated with suicide scores in patients with post-traumatic stress disorder (PTSD) 13). On the other hand, continuous positive airway pressure (CPAP) therapy significantly improved the mental component score of the 36-Item Short Form Health Survey 15), and there was also a significant improvement in depression scores from the baseline for both depression and depressive states 23).

With regard to the effects on cognitive function, Stranks, E.K. et al. reported that OSA patients showed significant reductions in stated memory, unstated memory, constructed concepts, psychomotor speed, executive function, attention, processing speed, working memory, etc. 28). In a meta-analysis of the effects of sleep apnea on the cognitive function in cognitively normal elderly subjects, Cross, N. et al. reported that OSA patients had lower overall cognitive domains compared with controls (Figure 1) 9). In addition, Zhu, J. et al. reported in a systematic review that sleep apnea with excessive sleepiness was associated with functional impairment in three domains: (1) attention, (2) learning and memory, and (3) executive function, with excessive sleepiness being particularly associated with attention impairment and hypoxemia with executive dysfunction 40). This effect extends beyond daily life to social life, with Tregear, S. et al. reporting that OSA increases the rate ratio of traffic accidents by 2.427 times 31) and the odds ratio of occupational accidents by 2.18 times compared with controls 11). Therefore, OSA also has a serious social impact, as it causes loss of productivity and traffic and industrial accidents. On the other hand, the effect of OSA on the development of dementia has also been discussed, along with cognitive decline: having OSA increases the risk ratio of dementia and mild cognitive impairment (MCI) by 1.69-fold 40), and it has been shown that people with sleep-disordered breathing develop MCI about 10 years earlier and Alzheimer's disease about 5 years earlier than those without it. Thus, OSA is associated with various psychiatric and cognitive

disorders and is a cause of impaired functioning in daily and social life.

II. Obstructive Sleep Apnea and Sleepiness

1. Characteristics of sleepiness in obstructive sleep apnea

The main symptoms of OSA (Table) are excessive sleepiness, fatigue, and restlessness, which together account for 73 to 90% of patients, and excessive sleepiness is found in 15 to 50% of patients 12). Sleepiness in OSA is considered to be related to: (1) shallow sleep due to respiratory effort, (2) sleep fragmentation, and (3) intermittent hypoxemia 3) associated with respiratory events during sleep. There are two main methods to evaluate sleepiness: subjective and objective sleepiness.

2. Subjective sleepiness and obstructive sleep apnea

The Epworth Sleepiness Scale (ESS) is one of the most commonly used measures of subjective sleepiness, and the Pittsburgh Sleep Quality Index (PSQI) includes a sub-item of daytime functional impairment (C7). Twenty-four points is the maximum score, and 11 points or more is considered subjective sleepiness, being used in many clinical settings and studies. PSQI is a self-administered questionnaire that evaluates the state of sleep during the night by looking back over the past month. Seven components (sleep quality, sleep latency, sleep duration, sleep efficiency, night-time sleep disturbance, use of sleep medication, and daytime dysfunction) are evaluated based on 18 questions and scored. If the score exceeds 5 points on a 21-point scale, the patient is considered a poor sleeper 5). The sub-items of "Daytime Dysfunction" are scored in four levels from 0 to 3. There are reports that the total score of ESS is correlated with AHI, the severity of OSA, 19), and that AHI is significantly higher in the group with an ESS sleepiness greater than 10 than in the group with an ESS sleepiness less than or equal to 10 25). On the other hand, there are reports that AHI is not clearly related to the ESS score 26). Therefore, the reality is that the relationship between ESS and AHI is not consistent. Furthermore, meta-analyses have shown that the sensitivity and specificity of ESS for moderate OSA are 48 and 32%, and those for severe OSA are 58 and 60%, respectively 8), which are low values and should be considered with caution.

3. Objective sleepiness and obstructive sleep apnea

The Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT) are mainly

used to assess objective sleepiness. MSLT measures the time it takes to fall asleep using electroencephalography (EEG), with the subject instructed to fall asleep while lying in bed at rest. Four to five measurements are taken every two hours for approximately 20 minutes each, and the average is used as an index of objective sleepiness. The shorter the measurement, the greater the objective sleepiness 17). MWT, on the other hand, measures the time it takes to fall asleep in the same way as MSLT, with the subject seated in a slightly darkened room and instructed to maintain wakefulness; four measurements of approximately 40 minutes are taken every two hours, and the average sleep latency is calculated as an index of the ability to maintain wakefulness 17). In Japan, MSLT is covered by insurance, but MWT is not. Regarding this objective sleepiness, it has been reported that the mean onset latency of MSLT is inversely correlated with AHI and oxygen saturation less than 90% of the time (i.e., high objective sleepiness is related to high AHI and the length of time oxygen saturation is less than 90%) 16). On the other hand, AHI has been reported to explain only 11.0% of objective sleepiness 7). Depending on the severity of OSA, the MSLT mean sleep onset latency may not meet the diagnostic criteria for hypersomnia of 8 minutes 10). In addition, there is a report that the relationship between ESS and MSLT mean sleep onset latency remained negative after adjustment 16). There are reports of discrepancies between the results of the two 10), and it is possible that there are differences in objective sleepiness ratings between studies.

4. Treatment of obstructive sleep apnea and sleepiness

Treatment of OSA can be expected to improve subjective and objective sleepiness. A meta-analysis comparing CPAP treatment with control or conservative treatment for mild to moderate OSA found that although CPAP treatment did not change the mean onset latency of MSLT, it decreased ESS scores and increased the mean onset latency of MWT 18). In addition, it has been reported that wearing CPAP for more than 7 hours reduced the ESS score by approximately 70% and prolonged the mean latency to fall asleep by 30% in MSLT 35). Furthermore, a meta-analysis found that CPAP treatment significantly reduced the rate ratio of traffic accidents 32), suggesting that CPAP treatment for OSA contributes significantly to subjective and objective sleepiness, as well as to improvement in the quality of life and

social activities.

However, daytime sleepiness may persist even after appropriate CPAP treatment for OSA. The International Classification of Sleep Disorders, 3rd ed. (ICSD-3) defines OSA as "residual hypersomnia in patients with well-treated obstructive sleep apnea" under "hypersomnia due to physical illness" (Figure 2) 1). It is estimated to be present in approximately 6-14% of patients 2), and patients tend to complain of fatigue, indifference, depression, and anxiety 34). The mechanism of residual drowsiness may include irreversible neuropathy and monoaminergic dysfunction due to chronic hypoxia 33).

III. EEG during Sleep Related to Subjective and Objective Sleepiness

Considering the relationship of AHI with subjective and objective sleepiness and the problem of residual sleepiness, it is considered that AHI does not uniformly explain sleepiness. Therefore, we examined the physiological relationship of sleepiness caused by OSA from the perspective of sleep EEG.

First, EEG activity is divided into alpha waves (8-13 Hz), beta waves (14-30 Hz), gamma waves (30 Hz and up), delta waves (0.5-3 Hz), and theta waves (4-7 Hz) according to their frequency components and alpha waves are particularly common in resting, awake, and closed-eye conditions. As sleep progresses through stages 1, 2, 3, and 4, slow waves gradually shift to the center, with spindle waves (12-16 Hz) appearing in stage 2.

Involvement of EEG activity in subjective and objective sleepiness has been suggested by alpha waves and spindles. In relation to subjective sleepiness, it has been reported that patients with OSA have a lower spindle activity and frequency in Stages 2 and 3 compared with controls 36), but CPAP significantly increased spindle frequency 38). In addition, it has been reported that children with sleep-disordered breathing with subjective sleepiness show less spindle activity than those with sleep-disordered breathing without sleepiness 4). Spindle is the EEG activity observed during NREM sleep, which is formed in cortical and subcortical areas, and its rhythms are derived from a network of the thalamus, thalamic reticular nuclei, and neocortex. Considering that the sleep hormone is involved in the decreased responsiveness to external stimuli and formation of memory during sleep 27), a physiological relationship with subjective feelings of sleep and drowsiness is also suggested. On the other hand,

regarding objective sleepiness, it has been reported in EEG power analysis that alpha power during polysomnograhy (PSG) correlates with a prolonged latency to fall asleep in MSLT 24), and that alpha power decreases with CPAP intervention in patients with severe OSA 37). Therefore, it is suggested that sleep-disordered breathing variables may be associated with alpha waves and influence objective sleepiness. These results suggest that EEG activity during sleep may be related to the background of subjective and objective sleepiness in OSA, which cannot be explained by the severity of OSA alone.

Conclusion

This paper outlines the importance of OSA in affecting mental, cognitive, and social functioning, the limitations of assessing excessive daytime sleepiness, and the possibility of further assessing subjective and objective sleepiness using a physiological approach through EEG activity during sleep. As the number of patients with OSA is expected to increase in the future, assessment of sleepiness and daytime dysfunction will become more important, and we hope that further studies will be conducted.

There are no conflicts of interest to be disclosed in connection with this paper.

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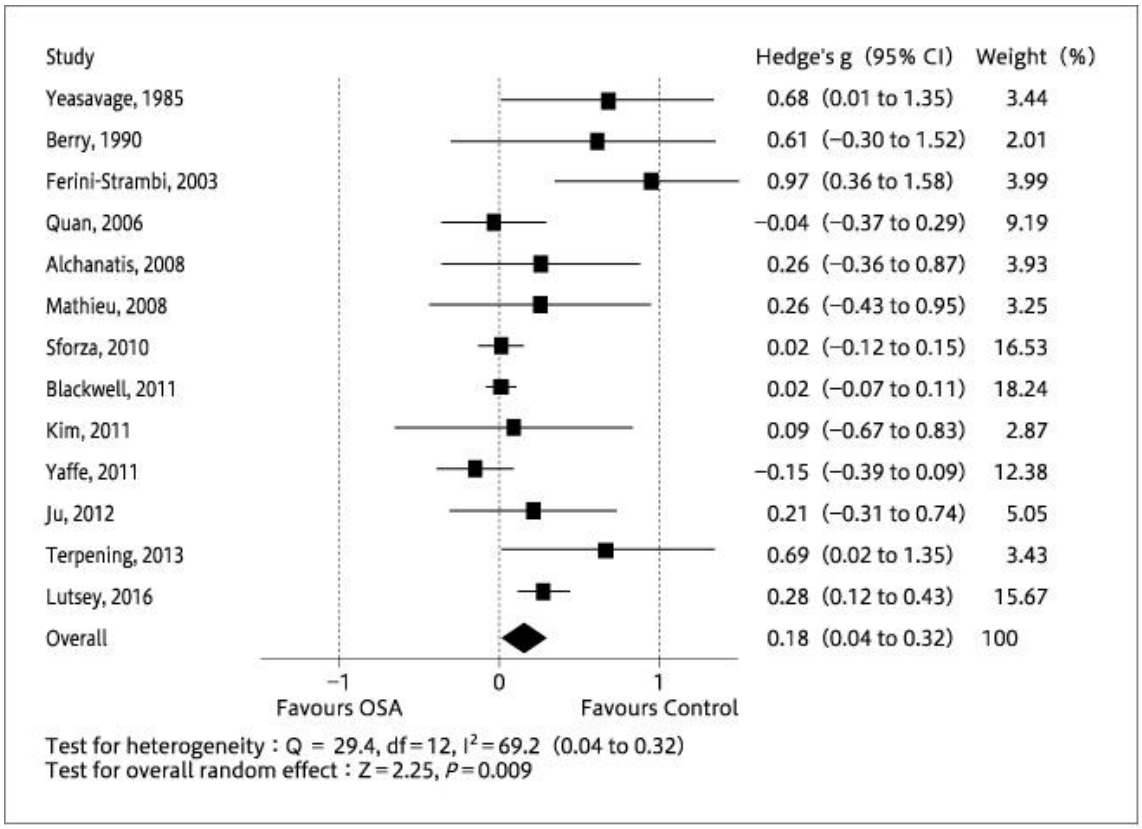

図 1　高齢者における閉塞性睡眠時無呼吸の認知機能への影響（across all cognitive domains）
（文献 9 より引用）

Figure 1 Effect of OSA on cognitive function in the elderly (across all cognitive domains).
(Adapted from Reference 9)

表　閉塞性睡眠時無呼吸の臨床症状・兆候と頻度

臨床症状・兆候	頻度（%）
過度の眠気・倦怠感・非休息感	73～90
夜間のいびき	50～60
睡眠中の呼吸停止，窒息，喘ぎの目撃	10～15
夜尿（1 夜に 2 回以上）	30
夜行性胃食道逆流	50～75
朝の頭痛	12～18

（文献 12 より改変）

Table Clinical Symptoms, Signs, and Frequency of OSA

Clinical Symptoms, Signs/Frequency (%)
Excessive sleepiness, fatigue, and restlessness 73-90
Night-time snoring 50-60
Respiratory arrest, choking, or wheezing witnessed during sleep 10-15
Nocturia (2 or more times per night) 30
Nocturnal gastroesophageal reflux 50-75
Morning headache 12-18
(Modified from Ref. 12)

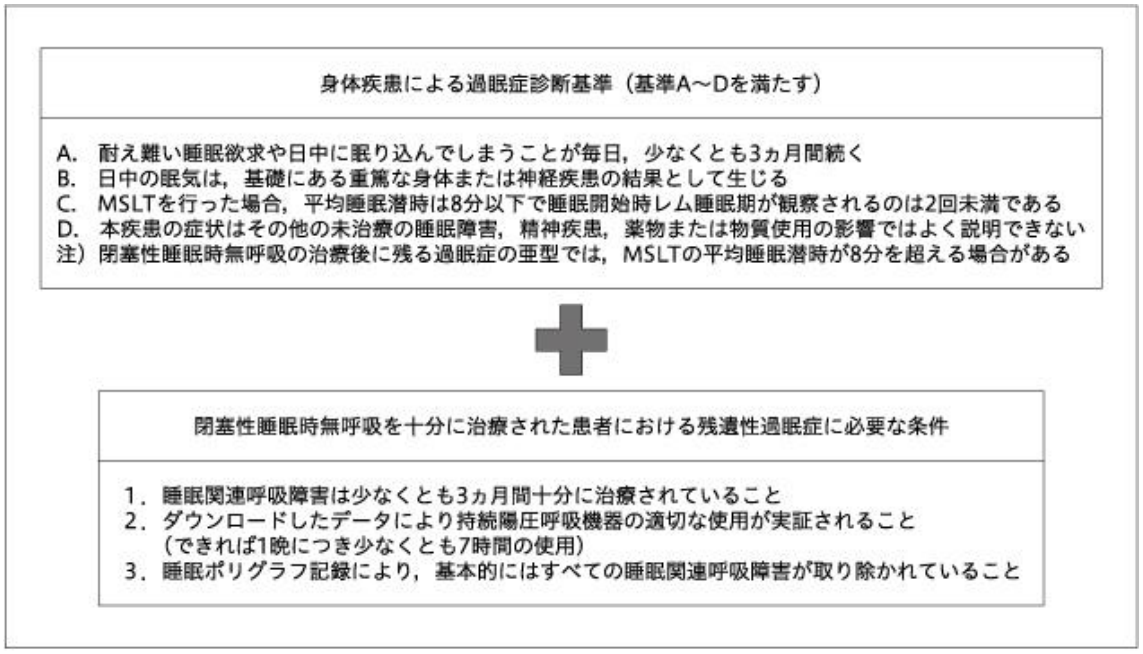

図 2　閉塞性睡眠時無呼吸を十分に治療された患者における残遺性過眠症の診断
（文献 1 より改変）

Figure 2 Diagnosis of residual hypersomnia in patients with well-treated OSA. (Modified from Ref. 1)

Diagnostic criteria for hypersomnia due to physical illness (criteria A-D are met)
A. Unbearable desire for sleep or falling asleep during the day every day for at least 3 months.
B. Daytime sleepiness is the result of underlying serious physical or neurological disease.
C. When MSLT is performed, the mean sleep latency is less than 8 minutes and the REM sleep phase at the onset of sleep is observed less than twice.
D. Symptoms of this disorder are not well-explained by other untreated sleep disorders, psychiatric disorders, or drug or substance use.
Note: In the subtype of hypersomnia that remains after treatment for OSA, the mean sleep latency of MSLT may exceed 8 minutes.

Requirements for residual hypersomnia in patients with well-treated OSA.

1. Sleep-related breathing disorders must have been adequately treated for at least 3 months.
2. The downloaded data demonstrate the proper use of continuous positive pressure breathing devices.
3. Polysomnographic recordings have essentially eliminated all sleep-related breathing disorders.