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□ ORIGINAL ARTICLE □

Characteristics of Japanese Patients with Complex Sleep Apnea Syndrome: A Retrospective Comparison with Obstructive Sleep Apnea Syndrome

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Abstract

Objective The prevalence of complex sleep apnea syndrome (CompSAS) among Asian patients with obstructive sleep apnea syndrome (OSAS) has not yet been reported. Distinguishing CompSAS from pure OSAS is difficult using only diagnostic polysomnography (PSG). We examined the prevalence of CompSAS in Japanese patients with OSAS and the possibility to distinguish CompSAS from pure OSAS by analyzing the severity of respiratory events based on either sleep body position or sleep stage using a diagnostic PSG.

Patients and Methods A retrospective chart review of 297 consecutive Japanese patients who were 15 years of age or older with a primary diagnosis of OSAS who were referred for CPAP titration (AHI≧20 events/hr).

Results Seventeen patients (5.7%) out of the 297 patients who had an obstructive apnea hypopnea index (AHI) of 20 or higher showed adverse increases in central apnea index (CAI) by the treatment with CPAP whereas obstructive apnea index (OAI) and mixed apnea index (MAI) were significantly decreased. In the results, the AHI on the PSG for CPAP titration reached only approximately half of the values on the diagnostic PSG. In these CompSAS patients, both the total CAI and the CAI in the supine position during NREM sleep on the diagnostic PSG were significantly higher than those in the OSAS group. The sleep body position did not so strongly affect the AHI, OAI and MAI in the CompSAS group. Multiple, stepwise, and logistic regression analyses revealed that the CAI in the supine position during NREM (p=0.026) was a significant variable to distinguish CompSAS from OSAS statistically although the variables were within the normal range.

Conclusion The prevalence of CompSAS in Japanese OSAS patients may be lower when compared with Caucasian patients. The increase of CAI in the supine position during NREM sleep on diagnostic PSG may be a characteristic feature in CompSAS.

Key words: complex sleep apnea syndrome, central sleep apnea, body position, non-REM sleep, obstructive sleep apnea syndrome

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Introduction

Sleep-related breathing disorders (SRBD) are common among the general population. The estimated prevalence of SRBD, as indicated by five or more episodes of apnea or hypopnea per hour of sleep, is 24 percent of middle-aged men and nine percent of middle-aged women (1). SRBD is increasingly recognized for its contribution to excessive daytime sleepiness, systemic hypertension, the risk of cardiovascular disease and stroke, and a high rate of automobile accidents (2, 3).

SRBD has two basic pathophysiological mechanisms: upper-airway obstruction which is the cause of obstructive

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sleep apnea syndrome (OSAS) and neural dysfunction of the ventilatory control which is the cause of central sleep apneas (CSA) and Cheyne-Stokes respiratory (CSR) pattern. The most common type of SRBD is OSAS. For example, a community-based study in Hong Kong using full polysomnography (PSG) demonstrated an estimated 4.1% prevalence of OSAS among middle-aged Chinese men (4). Most of the patients who have moderate-to-severe OSAS are treated with continuous positive airway pressure (CPAP) therapy. The therapeutic response to CPAP is usually complete, but some patients develop a high frequency of CSA and/or a disruptive CSR pattern after the application of CPAP (5). Gilmartin et al introduced complex sleep-disordered breathing as a new category (6), and Morgenthaler et al termed this type of sleep-disordered breathing "complex sleep apnea syndrome (CompSAS)" (7). The prevalence of CompSAS was previously reported to range from 13.1% to 15% (7, 8), but the prevalence among Asian people has not yet been reported. A review published by Gilman and Thomas proposed that CompSAS occurs predominantly during unstable sleep, e.g. in the cyclic alternating pattern (CAP) type during non-rapid eye movement (NREM) sleep (9). Regarding the pathogenesis of CPAP-induced CSA, it is presumed that CPAP may adversely affect sleep continuity due to discomfort or other factors, but it remains to be fully elucidated (10). It is very important to discriminate the CompSAS from pure OSAS because CPAP, a gold standard therapy for OSAS, is non-effective, therefore another treatment such as non-invasive positive pressure ventilation (NPPV) or adaptive servoventilation is needed for Comp SAS. Also, it has been demonstrated that there is a higher frequency of cardiac or cerebrovascular complications found in CompSAS groups in studies undertaken in the Mayo Clinic (7).

The change in respiratory events according to the sleep body position or sleep stage has been reported for OSAS and CSA-CSR, but there are few reports about CompSAS. The severity of events in OSAS is known to worsen in the supine body position during rapid eye movement (REM) sleep (6, 11), and the lateral position has been reported to attenuate the severity of CSA-CSR (12).

Distinguishing CompSAS from OSAS is difficult using diagnostic PSG, because the patients with CompSAS are generally similar to those with OSAS until CPAP is applied (7). While the treatment of OSAS is generally successful with CPAP therapy, CPAP is not effective for CompSAS (13). Non-invasive positive pressure ventilation or adaptive servoventilation are more effective than CPAP to treat CompSAS (14, 15). Thus to distinguish between CompSAS and OSAS using diagnostic PSG would be helpful in order to select the optimal therapy for CompSAS.

The two primary aims of this study were as follows: first, to investigate the prevalence of CompSAS in Japanese patients, and secondly, to differentiate the patients with CompSAS from OSAS using diagnostic PSG. As a result, we compared the severity of respiratory events according to either the sleep body position or sleep stage using diagnostic PSG in order to distinguish CompSAS patients from OSAS patients.

Patients and Methods

Patients

A retrospective review was undertaken based on the clinical records and PSG findings of 1,410 consecutive Japanese patients (1,130 men and 280 women) who were 15 years of age or older with a primary diagnosis of OSAS at Matsumoto Kyoritsu Hospital from August 2003 to July 2008. Three hundred eight patients of the 1,410 OSAS patients were referred for an in-laboratory CPAP titration polysomnographic study according to the Japanese medical insurance criteria. Six patients who had less than 110 minutes of total sleep time, four patients who could not tolerate CPAP, and one patient who needed oxygen inhalation during CPAP titration were excluded. As a result, we selected 297 patients, consisting of 249 males and 48 women for this study. All patients enrolled in this study were moderate to severe OSAS with AHI of 20 and more than 20 events/hr because CPAP therapy is not acceptable for OSAS patients with AHI of less than 20 events/hr based on the Japanese medical insurance criteria. During the analysis, all patients had 30 minutes or more of REM sleep period and slept more than 60 minutes in either the supine or non-supine sleep position. No split-night studies were included. The patient characteristics, include age, gender, body mass index (BMI), comorbidities were all obtained from the clinical records. The study protocol was approved by the institutional ethics committee of Matsumoto Kyoritsu Hospital and Shinshu University School of Medicine, and informed consent was obtained from all patients.

Polysomnography

All PSGs were performed using a digital polygraph (E-Series, Compumedics, Victoria, Australia) with a clinical technologist in attendance. Standard PSG montages were used as follows: Electroencephalography (EEG, C4-A2, C3-A1, O2-A1, O1-A2), left and right electrooclography (EOG), submental electromyography (EMG), a nasal cannula to measure nasal pressure and thermistor to monitor nasal and oral flow, left and right anterior tibialis movement sensors, respiratory effort by thoracoabdominal piezoelectric belts, electrocardiography (ECG), finger pulse oximetry, a neck microphone for recording snoring, a sensor on the thoracic belt to evaluate the body posture. Sleep stages and respiratory events were defined by the standard criteria (16, 17). Apnea was defined as the cessation of airflow for at least 10 seconds. Hypopnea was defined as a significant reduction in effort together with an arousal or with a decrease in oxyhemoglobin saturation of at least 3% (17). Central apneas were those unaccompanied by evidence of respiratory effort. Obstructive apneas were those with evidence of continuous respiratory effort. Mixed apneas were

Table 1. Patient Characteristics

	CompSAS (n=17)	OSAS (n=280)
Age, y	54.8 ± 15.9	58.6 ± 14.7
Men, n (%)	15 (88.2)	234 (83.6)
Body mass index, kg/m^2	28.8 ± 6.1	25.7 ± 3.9
Hypertension, n (%)	8 (47.1)	115 (40.1)
Diabetes mellitus, n (%)	2 (11.8)	41 (14.6)
Dyslipidemia, n (%)	1 (5.9)	70 (25.0)
Hyperuricemia, n (%)	2 (11.8)	26 (9.3)
Ischemic heart disease, n (%)	2 (11.8)	36 (12.6)
Cerebrovascular accident, n (%)	0 (0)	16 (5.7)

Data are presented as the means ± SD (standard deviation) or number (%).

those that began as central apneas but had respiratory effort with evidence of obstructive apnea later in the apneic interval. All studies were scored by polysomnographic technologists certified by Japanese Society of Sleep Research (JSSR), and reviewed by a certified physician of sleep medicine, JSSR.

Definition of sleep disordered breathing syndromes

We considered the patients to have OSAS if the sum of the obstructive apneas and hypopneas per hour of sleep was 15 or more with or without subjective symptoms, e.g. excessive daytime sleepiness. The patients were considered to have CompSAS if CPAP titration eliminated any events defining OSAS, but the residual central apnea index was five or more per hour. In CPAP titration, we applied automatic CPAP (AutoSet Spirit, ResMed, Sydney, Australia) which was programmed to a pressure range between four and 20 cmH_2O.

Statistics

The data analysis was done using a statistical software program (StatView version 5.0, SAS Institute Inc., North Cary, NC, U.S.A.). The variables that were compared between the CompSAS and OSAS groups included age, gender, BMI, comorbidities. Fisher's exact test was used to compare the two groups. The PSG features were compared for intergroup differences using the Mann-Whitney U-test and for intragroup differences using a Student paired t test. Multiple, stepwise, and logistic regression analyses were performed to identify which variables among central apnea index (CAI), obstructive apnea index (OAI), and mixed apnea index (MAI) in the supine or non-spine position during NREM or REM sleep can significantly discriminate CompSAS from OSAS. The value of $p<0.15$ was used first to identify candidate variables and then the variables were removed from the regression model if the p-value was more than 0.1. In all cases, a 2-sided p-value of 0.05 or less was considered to be statistically significant.

Results

Prevalence of complex sleep apnea syndrome

Seventeen patients (5.7%) had either an emergence or persistence of CSA out of the 297 patients who underwent a CPAP titration study for OSAS and who had an obstructive apnea hypopnea index (AHI) of 20 or higher. According to gender, 15 (6.0%) of 249 OSAS men, and 2 (4.2%) of 48 OSAS women were considered as CompSAS.

Baseline characteristics and comorbidities

The demographic and clinical findings of the patients in the CompSAS (n=17) and the OSAS group (n=280) are summarized in Table 1. There were no significant differences in age and sex between the CompSAS group and OSAS group, and the CompSAS patients had a slightly higher BMI than the OSAS patients. There was no significant difference for comorbidities between the two groups.

Comparison of PSG for diagnosis and CPAP titration between CompSAS and OSAS

There was no statistical difference between the CompSAS group and the OSAS group for AHI, CAI, OAI, MAI, 3% oxygen desaturation index (3%ODI), cumulative percentage of sleep time with SpO_2 below 90% (CT90), sleep architecture and arousal index on the diagnostic PSG (Table 2). The patients with OSAS showed decreases of CAI, OAI, and MAI below 5 events/hour and a marked decrease in AHI, 3%ODI, CT90 and arousal index and significant increases in slow-wave sleep (SWS) and REM sleep by the treatment with CPAP on the PSG for CPAP titration. On the other hand, the patients with CompSAS showed significant decreases in AHI, OAI, MAI, 3%ODI and CT90, and OAI and MAI decreased to below 5 events/hour. But, the CAI was adversely increased above 5 events/hour by the treatment with CPAP. Considering the results, the improvement re-

Table 2. Polysomnographic Features (Respiratory Parameters)

	CompSAS (n=17)		OSAS (n=280)	
	Diagnostic PSG	CPAP titration	Diagnostic PSG	CPAP titration
AHI, events/h	55.7 ± 24.2	24.0 ± 8.2 **††	48.5 ± 20.2	9.0 ±8.2 ††
CAI, events/h	1.7 ± 2.5	9.4 ± 3.5 **††	0.9 ± 1.8	0.5 ±0.8 ††
OAI, events/h	27.4 ± 19.3	2.7 ± 3.7 ††	26.8 ± 21.5	1.7 ± 3.7 ††
MAI, events/h	7.1 ± 11.8	2.6 ± 4.1*†	4.3 ± 8.8	0.3 ± 0.7 ††
3% ODI, events/h	51.0 ± 22.9	24.4 ± 14.8 ** ††	40.3 ± 22.1	7.9 ± 8.3 ††
CT90, %TST	9.7 ± 10.8	1.6 ± 2.6 ††	12.0 ± 17.4	0.9 ± 4.7 ††
SWS, %TST	9.8 ± 7.2	11.8 ± 7.8	8.3 ± 9.0	12.2 ± 10.6 ††
REM sleep, %TST	11.7 ± 6.6	16.4 ± 8.6 †	13.1 ± 6.2	18.1 ± 7.0 ††
Arousal index, events/h	48.2 ± 19.2	26.0 ± 11.3 ††	47.3 ± 21.3	22.9 ± 11.6 ††

Data are presented as the means ± SD. CompSAS; complex sleep apnea syndrome, PSG; polysomnography, CPAP; continuous positive airway pressure, AHI: apnea hypopnea index; CAI: central apnea index; OAI: obstructive apnea index; MAI: mixed apnea index; ODI: oxygen desaturation index; CT90: cumulative percentage of sleep time with SpO_2 below 90%; TST: total sleep time; SWS: slow-wave sleep; REM: rapid eye movement.

*p<0.05 and **p<0.01 vs OSAS. †p<0.05 and ††p<0.01 vs. diagnostic PSG.

sponse to the treatment with CPAP was poor and AHI on the PSG for CPAP titration reached only approximately half of the values on diagnostic PSG, and the values of AHI, CAI, MAI and 3%ODI on the PSG for CPAP titration were significantly higher than those in OSAS group. Also, the CPAP titration resulted in no significant increases in SWS in the CompSAS group, although REM sleep was increased and arousal index was significantly decreased.

Comparison of diagnostic PSG according to the sleep body position or sleep stage between the CompSAS and OSAS groups

The AHI in the non-supine position during NREM sleep was significantly higher in the CompSAS group than in the OSAS group (Table 3). Both the total CAI and the CAI in the supine position during NREM sleep were significantly higher in the CompSAS group than those in the OSAS group. Regardless of the sleep body position or sleep stage, no difference was observed between the two groups regarding the average OAI and MAI.

In the OSAS group, the AHI, OAI and MAI in the supine position were significantly higher than those in the non-supine position, and the MAI during NREM sleep were significantly higher than those during REM sleep. On the other hand, in the CompSAS group, the sleep body position did not so strongly affect the AHI, OAI and MAI, and both the total CAI and the CAI in the supine position were significantly higher during NREM sleep than those during REM sleep.

Multiple, stepwise, and logistic regression analyses showed that the CAI in the supine position during NREM (p=0.026) was a significant and independent variable to distinguish the CompSAS from the OSAS patients statistically although the CAI was within normal range and the difference between the values in both groups was very small.

Discussion

In our retrospective study, we found that 5.7% of the Japanese moderate to severe OSAS patients had CompSAS. Morgenthalar et al reported the prevalence of CompSAS to be 15%; namely 34 of 223 patients who had SRDB, including OSAS and CSA (7). They considered the patients to have OSAS if the sum of the obstructive apneas and hypopneas per hour was five or greater, or if the patient complained of sleepiness and the number of respiratory-related arousals per hour was 10 or greater. Lehman et al reported the prevalence of CompSAS to be 13.1%; 13 of 99 OSAS patients (8), but they did not clearly define their criteria for OSAS. As a result, the CompSAS patient populations tended to differ for each report, and therefore it is not possible to accurately compare the prevalence of CompSAS. Our findings did suggest, however, that the prevalence of CompSAS in Japanese OSAS patients may be lower when compared with the prevalence of CompSAS in Australian or American OSAS patients.

There was no significant difference in age between CompSAS and pure OSAS in this study which was the same as in previous reports. Many previous reports suggested that the proportion of men is greater in CompSAS,

Table 3. Polysomnographic Features (Respiratory Parameters by Sleep Stage and Sleep Body Position)

	CompSAS (n=17)		OSAS (n=280)	
	NREM	REM	NREM	REM
AHI, events/h				
Total	51.4 ± 24.0	43.4 ± 25.3	51.2 ± 20.5	44.3 ± 18.3
Supine	57.8 ± 27.3	45.4 ± 31.3	51.3 ± 20.5 ‡‡	47.8 ± 21.6 ‡‡
Non-supine	47.4 ± 23.3 *	35.4 ± 26.3	33.2 ± 25.1	35.4 ± 22.4
CAI, events/h				
Total	1.6 ± 2.3 *	0.1 ± 0.5 †	0.7 ± 1.6	0.7 ± 1.9
Supine	2.5 ± 3.1 *	0.4 ± 1.5 †	0.9 ± 2.3	0.7 ± 3.4
Non-supine	0.9 ± 1.6	0.1 ± 0.3	0.6 ± 1.9	0.6 ± 2.3
OAI, events/h				
Total	25.7 ± 19.4	21.9 ± 16.5	24.9 ± 22.1	27.4 ± 18.9
Supine	31.1 ± 25.7	23.3 ± 20.3	29.1 ± 23.3 ‡‡	32.4 ± 21.4 ‡‡
Non-supine	24.3 ± 17.5	17.7 ± 18.6	16.3 ± 21.6	18.7 ± 20.3
MAI, events/h				
Total	6.3 ± 9.8	2.0 ± 4.0	4.0 ± 8.8	2.7 ± 6.6
Supine	7.6 ± 9.6	2.4 ± 3.9	4.7 ± 9.8 ‡	3.1 ± 7.6 †
Non-supine	5.2 ± 10.4	2.0 ± 5.4	2.8 ± 8.1	1.9 ± 5.7

Data are presented as the means ± SD. REM: rapid eye movement; NREM: non-rapid eye movement; AHI: apnea hypopnea index; CAI: central apnea index; OAI: obstructive apnea index; MAI: mixed apnea index. *$p<0.05$ vs OSAS. †$p<0.05$ vs. NREM. ‡$p<0.05$ and ‡‡$p<0.01$ vs. non-supine position.

but in this present study there was no significant difference in the sex between the CompSAS and OSAS groups. Regarding the BMI, in some previous reports (7, 8), no differences in BMI between the CompSAS and OSAS groups, but Pusalavidyasagar et al demonstrated that the BMI in CompSAS was lower when compared with OSAS patients (13). In the present study, adversely, the CompSAS patients showed a tendency toward a higher BMI when compared with OSAS group. A racial difference is thought to be one of the reasons for the differences between our findings and those of other studies regarding the prevalence of CompSAS, age and gender difference because the differences in obesity and craniofacial anatomy have been demonstrated to be risk factors for OSAS between Far-East Asian and white man patients with OSAS (18).

Many previous reports have demonstrated no difference in AHI between CompSAS and OSAS. The present study showed similar results. Allam et al reported that the majority of the apnea-hypopnea events in the CompSAS occurr in NREM sleep and are more frequent in the supine sleep position (15). Thomas et al also reported the respiratory disturbance index (RDI) during REM sleep in the patients with CompSAS to be lower than that of the patients with REM-dominant OSAS (19). In the present study, the AHI in the supine sleep position in OSAS groups was significantly greater than those in the non-supine sleep position, however, in the CompSAS group, the sleep body position did not markedly affect the AHI, OAI and MAI. The AHI in both the CompSAS and OSAS showed a tendency to be greater in NREM sleep, but there were no significant differences. It is well known that obstructive apneas tend to increase in the supine position in OSAS patients. Moreover, obstructive apnea is usually worse in REM sleep than in NREM sleep, but the OAI in REM sleep is not always larger than that in NREM sleep (6, 20). Siddiqui et al reported a higher NREM AHI than REM AHI found in up to one-half of all patients with OSAS (21). Therefore, the characteristic features of AHI, OAI and MAI in the CompSAS by the sleep body position and NREM or REM sleep may be not specific and could not discriminate CompSAS from OSAS.

Regarding CAI, some reports have suggested CompSAS patients to have a significantly higher CAI than OSAS patients (8, 13), while other reports have suggested that no significant difference exists in CAI during the total sleep period or NREM sleep between CompSAS and OSAS (7). In the present study, the CompSAS group showed a significantly higher total CAI in NREM sleep, especially in the supine position compared with the OSAS group. Multiple, stepwise, and logistic regression analyses showed that the CAI in the supine position during NREM was a significant and independent variable to distinguish the CompSAS from the OSAS patients statistically although the CAI was within the normal range and the difference between the values in both groups was very small. In one review, the dysregulation of CO_2 homeostasis is stated to be the dominant pathophysiological mechanism of complex sleep-disordered breathing (6). Central apnea may occur by the Hering-Breuer reflex when the lung is enlarged by CPAP. However, the mechanism by which CPAP administration provokes central sleep apneas in CompSAS patients still remains unclear. It is only our speculation that the patients with CompSAS have two pathological statuses of obstructive apnea and central apnea and the central apnea is hidden by obstructive apnea, and then will become remarkably dominant when the obstructive apnea is removed by the treatment with CPAP. Some anatomical and physiological differences may possibly exist between CompSAS and OSAS patients, and therefore further studies are needed to clarify this point.

This study has several limitations. First, it was a retrospective design and data availability regarding comorbidities was limited. Secondly, the number of patients in our study was small. CPAP therapy is acceptable for OSAS patients who have an AHI of 20 and more than 20 events/hr based on the Japanese medical insurance criteria. Therefore, the OSAS patients whose AHI was less than 20 events/hr did not undergo CPAP titration. As the result, the sample size was small numbers to perform statistical analysis.

In conclusion, CompSAS is not rare among Japanese moderate to severe OSAS patients, however, the prevalence is lower when compared with Caucasian patients. CompSAS showed a characteristic feature of an increased central apnea index, especially in the supine position when compared with OSAS group, which may be a suggestive variable to distinguish the CompSAS from the OSAS patients.

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