Prevalence of Complex Sleep Apnea Among Japanese Patients with Sleep Apnea Syndrome

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Sleep apnea syndrome (SAS) is basically divided into two types: obstructive and central SAS. Recently, the concept of complex SAS has been advocated. Complex SAS is defined as SAS that initially manifests as primarily obstructive SAS, but is characterized by the frequent central apneas after the removal of upper airway obstruction. To determine the prevalence and clinical significance of complex SAS among Japanese patients with SAS, 1,312 patients with SAS were enrolled in this study. Diagnosis of central SAS was made based on diagnostic polysomnography, and differentiation of obstructive SAS from complex SAS was made from polysomnographic findings for treatment with continuous positive airway pressure, which resolved upper airway obstruction. As a result, obstructive SAS was found in 1,232 of 1,312 patients with SAS (93.9%) and central SAS was found in 14 patients (1.1%). The overall prevalence of complex SAS was 5.0% (n = 66). The prevalence of complex SAS among 1,218 male and 94 female patients with SAS were 5.3% and 1.1%, respectively. Patients with complex SAS had significantly higher apnea/hypopnea indices than patients with either obstructive or central SAS, but were similar in both mean age and average body mass index to obstructive SAS patients. There were no significant between-group differences in numbers of patients with clinical complications including hypertension, cardiac diseases, or cerebrovascular diseases. In conclusion, the prevalence of complex SAS in Japanese SAS patients is 5.0%, which is lower than previously reported prevalence of complex SAS in the USA and Australia. ——— obstructive sleep apnea syndrome; central sleep apnea syndrome; hypertension; cardiac disease; cerebrovascular disease.

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The recognition of sleep apnea syndrome (SAS) as a common and serious public health problem has become widespread, and the prevalence of SAS in the Japanese male working population has increased during the past decade, being recently estimated at 22.3% (Hida 1998, Nakayama-Ashida et al. 2008). SAS has conventionally been divided into two categories: obstructive sleep apnea syndrome (OSAS) and central sleep apnea syndrome (CSAS) including Cheyne–Stokes respiration. Pure obstructive sleep apnea (OSA) events are caused by the reduction or cessation of respiration because of narrowing or occlusion of the upper airway during sleep. Pure central sleep apnea (CSA) events or Cheyne–Stokes respiration are thought to be induced by chemosensitivity to hypoxia or hypercapnia. Currently, a large majority of patients with SAS are diagnosed with OSAS. Continuous positive airway pressure (CPAP) application is the first-line noninvasive treatment for OSAS, and can almost completely suppress obstructive respiratory events. However, it has long been noted in sleep-disorder clinics that some patients presenting with predominately obstructive apneas at baseline experience accompanying CSA events after tracheostomy or application of CPAP (Guilleminault and Cummiskey 1982, Onal et al. 1982, Thomas et al. 2004).

Sleep apnea initially manifests as primarily an obstructive components, but the presentation of frequent central components or a predominant Cheyne–Stokes respiration pattern after the removal of upper airway obstruction has been defined as complex sleep apnea syndrome (CompSAS) (Gilmartin et al. 2005, Morigenthaler et al. 2006). The reported prevalence of CompSAS among patients with SAS in the USA and Australia ranged from 13.1% to 20.4% (Morigenthaler et al. 2006, Pusalavidyasagar et al. 2006, Lehman et al. 2007). However, there may be genomic, environmental, or cultural differences between Caucasian and Japanese patients with SAS both in upstream pathophysiological risk factors such as obesity or neurological respiratory control dysfunction, and downstream clinical events such as cardiovascular or cerebrovascular consequences (Villaneuva et al. 2005). The purpose of this study was therefore to retrospectively determine the prevalence of CompSAS and the clinical significance of the condition among Japanese patients with SAS.

**Methods**

**Study Subjects**

A retrospective study was performed in two sleep-disorder centers. Japanese subject patients who were 20 years or older were newly examined for SAS, diagnosed by clinical symptoms, and attended overnight polysomnography (PSG). None of the patients had been previously treated with CPAP. Patients were diagnosed with SAS if the sum of the apnea and hypopnea events per hour [apnea hypopnea index (AHI)] was 5 or more at diagnostic PSG. Patients were diagnosed with pure CSAS if the number of CSA events per hour [central apnea index (CAI)] was 5 or more and at least 50% of the total apneic events were CSA at diagnostic PSG (Shin et al. 1999). Patients with more than 5 events per hour of both obstructive AHI and CAI, and with percentages of CSA and/or Cheyne–Stokes respiration events less than 50% at diagnostic PSG, were defined as showing mixed breathing patterns. Standard CPAP titration was performed manually during attended overnight in-laboratory sleep within 1 month of the diagnostic PSG night on the patients having an AHI of 20 or more based on the criteria stipulated by Japanese health insurance. Standard CPAP titrations were performed except for those with CSAS, indications for surgeries or oral appliances, and those pretreated with auto-adjusted CPAP. Patients were considered to have pure OSAS if obstructive AHI included 5 or more events per hour at diagnostic PSG, and if CPAP titration was successful in decreasing total AHI to less than 5 events per hour (Pusalavidyasagar et al. 2006). Patients were considered to have CompSAS if CPAP titration eliminated events defined as part of OSAS but for whom the residual CAI was 5 or more per hour or the Cheyne–Stokes respiration pattern became prominent and disruptive (Morigenthaler et al. 2006). Among patients with mixed breathing patterns, those in whom both obstructive AHI and CAI decreased to less than 5 events per hour at the titration were defined as [diagnosis(+) titration(−)].

Clinical complications including hypertension, cardiac diseases, and cerebrovascular diseases were investigated based on medical chart reviews. Cardiac diseases included left and right ventricular hypertrophy, chronic
Prevalence of Complex Sleep Apnea Among Japanese Patients with Sleep Apnea Syndrome

heart failure, mitral regurgitation, pulmonary stenosis, atrial fibrillation, and ischemic heart diseases (i.e., angina pectoris and myocardial infarction). Cerebrovascular diseases included stroke, subarachnoid hemorrhage, and cerebral infarction. The Institutional Review Boards of our institutes approved this study after reviews by the respective Ethics Committees.

**Polysomnography and titration**

Overnight sleep studies, diagnostic PSG, and manual CPAP titration were carried out as published previously (Suzuki et al. 2005). Briefly, we simultaneously performed electroencephalography (EEG, C4/A1, C3/A2), electrooculography (EOG), submental electromyography (EMG), and electrocardiography (ECG) using surface electrodes, and measured air flow at the nose and mouth using a thermistor, respiratory movements of the rib cage and abdomen by inductive plethysmography, and percutaneous arterial oxygen saturation (SpO2) using a finger pulse oximeter. Apneas were identified as a near-flat airflow (< 10% of baseline; baseline amplitude was identified during the closest preceding period of regular breathing with stable oxygen saturation) for at least 10 sec. Hypopneas were identified as airflow or thoracoabdominal excursions of approximately < 70% of baseline for at least 10 sec, associated with either an oxygen desaturation of > 3% or an arousal.

On titration nights, technologists provided instructions on the use and adjustment of the CPAP apparatus, nasal mask adjustment, symptoms indicating an incorrect CPAP setting, and modes of hands-on intervention. The technologists increased CPAP pressure during sleep in a stepwise fashion (step size: 0.2–1.0 cm H2O) to abolish respiratory events and associated arousals. The CPAP apparatus used for titration was a REMStar Pro fixed-type CPAP machine (Respironics; Pittsburgh, PA).

**Statistical Analyses**

All descriptive statistical data are presented as mean ± standard deviation. Descriptive statistical data were calculated for each variable. Variables were evaluated by the one-way factorial ANOVA test and the Yates Chi-squared test. A p value less than 0.05 was considered to indicate statistical significance. Statistical comparisons were performed using the Statistical Package for Social Sciences (SPSS) for Windows, version 11.01 (SPSS Inc.; Chicago, IL).

**RESULTS**

In all, 3,694 patients were diagnosed with SAS at diagnostic PSG. Consecutive CPAP titration was performed on patients with AHI of 20 or more except for those with CSAS, indications for surgeries or oral appliances, and those pretreated with auto-adjusted CPAP. The total study population consisted of 1312 Japanese patients with SAS (1,217 male and 95 female). Schematic results of the study are outlined in Fig. 1. Fourteen patients exhibited pure CSAS, and 50 exhibited a mixed breathing pattern at diagnostic PSG. Sixty-six patients were diagnosed with CompSAS and 1,232

![Fig. 1. Composition of the study population](image)

SAS, sleep apnea syndrome; CSAS, central SAS; OSAS, obstructive SAS; CompSAS, complex SAS.

* [diagnosis(+) titration(−)], patients who showed mixed breathing patterns at diagnostic polysomnography and whose apnea/hypopnea indices at titration decreased to less than 5 events per hour.
with pure OSAS from the results of CPAP titration PSG. The overall prevalence of CompSAS was 5.0% (66 in 1,312 patients). The percentage of CompSAS as a proportion of all patients with mixed breathing patterns was 28.0% (14 in 50 patients). In all, 21.2% of patients with CompSAS had a mixed breathing pattern on their diagnostic PSGs (14 in 66 patients), compared with only 2.9% of patients with pure OSAS had a mixed breathing pattern (36 in 1,232 patients).

The anthropometric and polysomnographic characteristics of the patients with CompSAS, OSAS, and CSAS are shown in Table 1. The prevalence of CompSAS among males and females with SAS was 5.3% (65 in 1218 patients) and 1.1% (1 in 94 patients), respectively. There were no significant differences in age among the three groups; however, there were significant differences in AHI values (F = 17.0, p < 0.01, ANOVA), and patients with CompSAS had a slightly but significantly higher value of AHI than patients with either OSAS or CSAS (p < 0.01, post-hoc). There were also significant differences in body mass index (BMI) among the groups (F = 6.2, p < 0.01, ANOVA). The patients with CSAS showed a significantly lower value of BMI than those with CompSAS or OSAS (p < 0.01, post-hoc), whereas there were no significant differences in BMI between patients with CompSAS and those with OSAS.

We then compared levels of clinical complications, such as hypertension, cardiac diseases, and cerebrovascular diseases, in the CompSAS, OSAS, and CSAS groups (Table 2). There was a tendency for higher levels of each complication in the CompSAS group compared with the OSAS group, but none of the between-group differences were statistically significant (hypertension, p = 0.09; cardiac diseases, p = 0.06; cerebrovascular diseases, p = 0.69).

**DISCUSSION**

This is the first attempt to determine the prevalence of CompSAS among Japanese patients

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**Table 1. Anthropometric and polysomnographic characteristics of the CompSAS, OSAS, CSAS, and [diagnosis(+) titration(−)] groups.**

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Age</th>
<th>Males</th>
<th>BMI (kg/m²)</th>
<th>AHI (events/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1,312</td>
<td>46.9 ± 12.4</td>
<td>1,218 (92.8%)</td>
<td>28.2 ± 5.1</td>
<td>48.6 ± 24.6</td>
</tr>
<tr>
<td>CompSAS</td>
<td>66</td>
<td>43.7 ± 12.1</td>
<td>65 (98.5%)</td>
<td>30.1 ± 6.7</td>
<td>58.7 ± 25.9</td>
</tr>
<tr>
<td>OSAS</td>
<td>1,196</td>
<td>47.0 ± 12.2</td>
<td>1,103 (92.2%)</td>
<td>28.4 ± 7.8</td>
<td>49.3 ± 23.9</td>
</tr>
<tr>
<td>CSAS</td>
<td>14</td>
<td>40.8 ± 18.6</td>
<td>13 (92.9%)</td>
<td>22.3 ± 2.7</td>
<td>18.1 ± 13.4</td>
</tr>
<tr>
<td>[diagnosis(+) titration(−)]</td>
<td>36 (2.7%)</td>
<td>54.6 ± 12.8</td>
<td>36 (100%)</td>
<td>28.3 ± 3.7</td>
<td>58.7 ± 19.4</td>
</tr>
</tbody>
</table>

Data are presented as mean ± s.d. or number (%). BMI, body mass index; AHI, apnea/hypopnea index; CompSAS, complex SAS; OSAS, obstructive SAS; CSAS, central SAS; [diagnosis(+) titration(−)], patients who showed mixed breathing patterns at diagnostic polysomnography and whose apnea/hypopnea indices at titration decreased to less than 5 events per hour. * p < 0.05 between CompSAS and OSAS groups; † p < 0.05 between CompSAS and CSAS groups; § p < 0.05 between OSAS and CSAS groups.

**Table 2. Comparisons of clinical complications in the CompSAS, OSAS, and CSAS groups.**

<table>
<thead>
<tr>
<th></th>
<th>HTN</th>
<th>Cardiac Diseases</th>
<th>Cerebrovascular diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CompSAS</td>
<td>66</td>
<td>30 (44.5%)</td>
<td>9 (13.6%)</td>
</tr>
<tr>
<td>OSAS</td>
<td>1,196</td>
<td>502 (42.0%)</td>
<td>89 (7.4%)</td>
</tr>
<tr>
<td>CSAS</td>
<td>14</td>
<td>1 (7.1%)</td>
<td>3 (21.4%)</td>
</tr>
</tbody>
</table>

HTN, hypertension. Data are presented as the number of patients (%). There was no significant difference in clinical complications among the three groups.
Prevalence of Complex Sleep Apnea Among Japanese Patients with Sleep Apnea Syndrome

353

Clinicians and researchers should be aware of ‘central apneas in disguise’ (i.e., CompSAS), because such discrimination has clinical implications given that the diagnosis of pure OSAS cannot be achieved by diagnostic PSG but after the removal of upper airway obstruction.

SAS has two possible underlying causes: anatomically vulnerable airway and neurologically unstable breathing control. Central and obstructive features may co-exist in individuals with SAS. OSAS patients may demonstrate periodic breathing patterns, in which reduced and oscillating motor tone to the upper airway induces central apnea (Khoo et al. 1991), and CSAS patients may demonstrate intermittent obstructive apnea at the nadir of the respiratory cycle (Badr et al. 1995). CSA events may also originate from unstable breathing control arising from the sleep–awake transition, as well as from cardiac or neurogenic causes (Naughton et al. 1993). Periodic breathing patterns in patients with heart failure have been considered to be induced by instability of chemical control during sleep (Arzt et al. 2003, Dempsey et al. 2004). Unstable plant gain and controller gain cause a reduction in arterial CO₂ (PaCO₂) to a level below the apneic threshold, thereby resulting in central apnea. CompSAS is essentially chemoreflex-dependent or modulated sleep apnea. The more active the chemoreflex, the more likely that complex breathing patterns will emerge.

There was no significant difference in clinical complications between OSAS and CompSAS groups in the present study. This might reflect the fact that the study was performed in two sleep-disorder centers located in central Tokyo, being convenient facilities for the working population. The higher frequency of cardiac or cerebrovascular complications found in CompSAS groups in studies undertaken in the Mayo Clinic and Adelaide Institute might have contributed to the differences in the reported prevalence of CompSAS between these earlier studies and our own (Morgenthaler 2006, Pusalavidyasagar 2006, Lehman 2007).

Moreover, differences in titration protocol (i.e., overnight titration in this study and a split-night PSG in the Mayo Clinic and Adelaide Institute) might also reflect between-study discrepancies. Generally, SAS patients use the CPAP apparatus for the first time on titration night unless pretreated with an auto-adjusted CPAP instrument. Consequently, a certain number of patients cannot sleep well in a CPAP titration setting because of inconvenience and intolerance of the device, especially in the first few hours after titration starts. It may be that CSA events occur at arousals under such conditions. Dernaika et al. reported that most CSA events disappeared after continued CPAP use (2007). Patients with complex breathing patterns with the exception of pure CSAS could be categorized into CPAP-emergent CSA and CPAP-persistent CSA (Lehman 2007). CPAP-emergent CSA is defined as CompSAS in which CSA events emerge during CPAP titration, but with these events being so acute and transient that they disappear through continued CPAP use. In contrast, CPAP-persistent CSA is defined as CompSAS in which CSA events persist despite continued CPAP follow-up. What proportion of patients with CompSAS have CPAP-persistent CSAS is uncertain, but the work of Dernaika et al. suggests it may be only a small fraction. The majority of CSA events in patients with CPAP-emergent CSA could be a different manifestation of obstructive apnea, which represents instability of the respiratory drive at sleep–awake transitions, as described above. The other possible mechanism might be a maladaptive response to CPAP in which patients take larger than normal breaths producing “post-hyperpnea pauses”. Some of these pauses might be prominent enough to meet the criteria for CSA.

In the present study, only 28.0% of patients with mixed breathing patterns were diagnosed as CompSAS cases at diagnostic PSG, indicating that the diagnosis of CompSAS can usually be made after CPAP titration. It was difficult to diagnose CompSAS by event-based scoring in diagnostic PSG. In the future, however, it will be important to diagnose most CompSAS cases from the diagnostic PSG (Thomas et al. 2007).

There are several limitations to this study. First, we were unable to perform second titrations.
on all patients with CompSAS to distinguish CPAP-persistent from CAP-emergent CSAS. Second, there exist potential limitations in the retrospective chart review in determining the presence or absence of the accuracy of data related to comorbidities. Echocardiography and/or Holter electrocardiography would have provided better estimations of cardiac complications.

In conclusion, the overall prevalence of CompSAS was 5.0% among 1,312 Japanese patients with SAS, suggesting that the prevalence of CompSAS in Japanese SAS patients is lower than that in the USA and Australia. Thinking in a time series fashion considering all of the oscillatory pattern variants (periodic or episodic), cyclic time variants (short or long), and rhythmicity variants (rhythmic or arrhythmic) might be important in the recognition of CompSAS. Further prospective research is needed to determine whether CompSAS is associated with cardiac or neurogenic diseases and how central components of the condition are mediated by neurologically unstable breathing control in patients with the disorder.

References