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The clinical and polysomnographic features in complex sleep apnea syndrome

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Aim: Complex sleep apnea syndrome (CompSAS) is characterized by the onset of central apneas or a Cheyne-Stokes breathing pattern in some patients with obstructive sleep apnea syndrome (OSAS) who were treated with continuous positive airway pressure (CPAP). The etiology of CompSAS is unclear, but derangement of respiratory control has been proposed. We sought to compare clinical and polysomnography (PSG) features of patients with CompSAS and OSAS.

Materials and methods: Records of PSG were evaluated in a total of 270 patients, retrospectively. CPAP titration was prescribed in patients with an apnea-hypopnea index (AHI) of ≥15. Patients who developed a central AHI of ≥5 following titration PSG were diagnosed with CompSAS.

Results: There were 71 patients with OSAS and 12 with CompSAS. The mean ages and body mass indexes (BMIs) were similar between the 2 groups. The incidences of diagnostic AHI, congestive heart failure (CHF), and chronic renal failure (CRF) were higher in patients with CompSAS. The average and minimum oxygen saturation levels were lower in patients with CompSAS and those with diagnostic PSGs.

Conclusion: According to our results, lower oxygen saturation may cause instability of respiratory control in these patients and may be responsible for the pathophysiology of CompSAS.

Key words: Central sleep apnea, Cheyne-Stokes breathing, complex sleep apnea syndrome, continuous positive airway pressure, obstructive sleep apnea, congestive heart failure

Kompleks uyku apne sendromunun klinik ve polisomnografik özellikleri

Amaç: Kompleks Uyku Apne Sendromu (CompSAS) sürekli pozitif havayolu basınç (CPAP) tedavisi alan obstrüktif uyku apne sendromlu (OSAS) bazı hastalarda, CPAP sonrası santral apnelerin veya Cheyne-Stokes solunum paterninin meydana gelmesi ile karakterizedir. Hastalığın nedenleri tam bilinmemektedir, solunum kontrol mekanizmalarındaki bozukluğun sorumlu olduğu ileri sürülmektedir. Bu çalışmada amacımız OSAS ve CompSAS'lı olguların klinik ve polisomnografik özelliklerinin karşılaştırılmasıdır.

Yöntem ve gereç: Toplam 270 olgunun polisomnografi kayıtları retrospektif olarak değerlendirildi. Apne Hipopne İndeksi (AHİ) ≥15 olan olgulara CPAP titrasyonu uygulandı. Titrasyon polisomnografisinde (PSG) santral AHİ ≥5 olan olgular CompSAS kabul edildi.

Bulgular: OSAS'lı 71 olgu, CompSAS'lı 12 olgu mevcuttu. Yaş ortalaması ve beden kitle indeksi gruplar arasında benzerdi. Tanısal AHİ, konjestif kalp yetmezliği, kronik böbrek yetmezliği insidansı CompSAS'lı grupta daha yüksekti. Tanısal polisomnografik değerlendirmede ortalama ve minimum oksijen saturasyon düzeyleri CompSAS grubunda anlamlı düzeyde düşüktü.

Sonuç: Sonuçlarımıza göre düşük oksijen saturasyon değerlerinin, CompSAS'lı hastalarda solunum kontrolünde bozukluğa yol açabileceği ve bunun da patofizyolojide rol oynayabileceği düşünülmüştür.

Anahtar sözcükler: Santral uyku apne, Cheyne-Stokes solunumu, kompleks uyku apne sendromu, sürekli pozitif havayolu basıncı, obstrüktif uyku apne, konjestif kalp yetmezliği

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Introduction

Obstructive sleep apnea syndrome (OSAS) encompasses the majority of sleep related breathing disorders. This syndrome is a commonly seen disorder, affecting 4% of men and 2% of women (1). The disorder is characterized by periods of breathing cessation (apnea) and periods of reduced breathing (hypopnea) during sleep (2). Although central sleep apnea (CSA) is more frequently seen in some clinical settings such as congestive heart failure (CHF) and chronic renal failure (CRF), CSA is found in less than 5% of patients who have been admitted to sleep disorder centers (3). A new category of sleep-disordered breathing has recently emerged. Some patients with OSAS develop problematic central apneas or a Cheyne-Stokes pattern with acute application of continuous positive airway pressure (CPAP), herein called complex sleep apnea syndrome (CompSAS) (4-7). CompSAS is a different form of sleep apnea. Clinical features of patients with CompSAS are similar to those of OSAS, while the breathing patterns resemble those of CSA. Morgenthaler et al. estimated that the prevalence of CompSAS would be 15% while the incidences of CSA and OSAS were 0.4% and 84%, respectively (6). In cases of CompSAS, CPAP suppresses obstructive apneas, but apnea hypopnea index (AHI) is higher due to central apneas, which is called residual AHI.

In this study, we aimed to assess the prevalence of CompSAS and compare clinical and polysomnographic features of patients with CompSAS and OSAS.

Materials and methods

We performed a retrospective review of patients in our sleep disorders center (Gazi University, Faculty of Medicine, Ankara, Turkey). OSAS patients had been examined by using polysomnography (PSG). An AHI of ≥ 5/h was accepted as an inclusion criterion for this sleep study. In this study, polysomnographic and clinical records were evaluated in a total of 270 patients. All patients underwent PSG for suspected OSAS. CPAP titration was prescribed for patients with AHI of ≥15. CPAP titration was performed using an automated CPAP device. The lower and the upper limit of pressure provided by the device were set at 4 cmH_2O, and 20 cmH_2O, respectively. Only 83 patients underwent CPAP titration. Patients who had a central AHI of ≥5 following titration PSG were diagnosed with CompSAS. Patient characteristics, including age, gender, body mass index (BMI), and concomitant diseases, were recorded. Comorbidity data were either obtained from the case notes or reported by patients at the time of the sleep study.

Sleep Study

Overnight PSG was performed in all patients by using a computerized system (Somnostar alpha; Sensormedics, USA), which included the following examinations: electrooculography (2 channels), electroencephalography (4 channels), electromyogram of submental muscles (2 channels), electromyogram of the anterior tibialis muscle of both legs (2 channels), an electrocardiogram, and airflowmeter (with an oro-nasal transducer). Chest and abdominal efforts (2 channels) were recorded using inductive plethysmography and arterial oxyhemoglobin saturation (SaO_2: 1 channel) by pulse oximetry with a finger probe. Sleep stages were scored according to the standard criteria of Rechtschaffen and Kales (8). Arousals were scored according to the accepted criteria of the American Sleep Disorders Association (ASDA) (9). In our study, we assessed nasal airflow with a pressure transducer. Based on the ASDA criteria for measurements, definitions, and severity ratings established for the Sleep Related Breathing Disorders Task Force Report (2), apnea is defined as the cessation of airflow for ≥10 s and hypopnea as a recognizable, transient reduction, but not a complete cessation of breathing for ≥10 s . A >50% decrease in the amplitude of a validated measure of breathing or a reduction of <50% in the amplitude associated with either an oxygen desaturation of ≥3% or an arousal should be present. Obstructive apneas and hypopneas are typically distinguished from central apneas-hypopneas by the detection of respiratory efforts during the episode. AHI was defined as the number of apneas and hypopneas per hour of sleep. Patients with an AHI of ≥5 were considered to have OSAS; patients who developed a central AHI of ≥5 titration PSG were diagnosed with CompSAS. All subjects underwent all-night PSG. Apart from OSAS patients with upper airway resistance syndrome (UARS), central sleep

apnea syndrome (CSAS), narcolepsy, and those having other factors that could promote the occurrence of central sleep apnea as sleep instability, periodic limb movements (PLMs) and drugs were excluded from the study.

Statistical analysis

CompSAS and OSAS groups were compared in terms of demographic variables, concomitant diseases, and characteristics of diagnostic and titration PSG. The significance of differences within groups was analyzed by using Student's t test and categorical data with chi-square (χ^2) and Fisher's exact probability test. Arithmetic means and standard deviation (x ± SD) were calculated for all values.

All statistical analyses were carried out by using statistical software (SPSS, version 11.0 for Windows; SPSS, Chicago, IL, USA). Differences were considered significant at $P < 0.05$.

Results

A total of 270 patients' records were evaluated. Of the 83 patients who had a CPAP titration study performed with OSAS, 12 (14.4%) had a central AHI of ≥5. The demographic and clinical data of patients with CompSAS and OSAS are presented in Table 1. The distribution of mean ages, BMIs, and genders of patients were similar between the groups (P values of 0.155, 0.405, and 0.758, respectively). CompSAS patients were less prone to somnolence than patients with OSAS (Epworth Sleepiness Score 8.09 ± 5.3 in CompSAS vs. 11.7 ± 5.3 in OSAS, P = 0.041).

The findings of the diagnostic PSG are shown in Table 2. The average AHI in both groups was within the severe range of OSAS, but patients with CompSAS had more severe sleep-disordered breathing (37.7 ± 32.3 and 57.1 ± 35.2, respectively), and the difference was statistically significant (P = 0.026). There was no difference between the 2 groups with regard to percentage ratio of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep stages, sleep efficiency, and arousal index (ARI). Awake oxygen saturation (SpO_2) was similar between the 2 groups; however, the average SpO_2 and minimum SpO_2 were lower in patients with CompSAS than in patients with OSAS (87.1 ± 4.2 vs. 89.3 ± 4.6 and 68.9 ± 11.3 vs. 76.2 ± 9.9, respectively) and there were statistically significant differences between them (P = 0.027 and P = 0.017, respectively). In the CompSAS group, significantly more severe oxygen desaturation (SpO_2 < 90%) was seen during the night when compared with the OSAS group (60.05 ± 37.8 vs. 38.5 ± 35.2, P = 0.042). In the CompSAS group, central (0.82 ± 1.35 vs. 0.22 ± 1.12, P < 0.001), obstructive (26.2 ± 18.5 vs. 21.7 ± 19.3, P = 0.019), and mixed apnea index (8.3 ± 11.9 vs. 5.2 ± 9.2, P < 0.001) were significantly higher when compared with the OSAS group.

The findings of titration PSG are shown in Table 3. CPAP suppressed obstructive apneas, but residual AHI, mostly from central apneas, remained higher in patients with CompSAS (9.8 ± 5.8 vs. 3.1 ± 4.7 in OSAS, P < 0.001). Central apneas were much more frequently seen in patients with CompSAS (27.3 ± 18.7 in CompSAS, 2.4 ± 2.6 in OSAS, P < 0.001). Similarly, the duration of central apneas was longer in

Table 1. Demographic and clinical data of patients with CompSAS and OSAS.

Characteristics	CompSAS (n = 12)	OSAS (n = 71)	P-value
Mean age (year) (n ± SD)	55.8 ± 10.6*	51.2 ± 10.2	0.155
Sex (male) (%)	69.2	72.5	0.758
BMI (kg/m²) (n ± SD)	31.5 ± 6.2	30 ± 5.5	0.405
ESS (n ± SD)	8.09 ± 5.3	11.7 ± 5.3	0.041

BMI=body mass index , ESS=Epworth sleepiness score

* Mean ± standard deviation

Table 2. Diagnostic polysomnographic findings.

Variables	CompSAS (n = 12)	OSAS (n = 71)	P-value
Stage 1 (%)	18.9 ± 9.7	14.9 ± 11.1	0.064
Stage 2 (%)	50.6 ± 8.3	48 ± 9.1	0.262
Stage 3 (%)	4.6 ± 3.1	6.1 ± 4	0.135
Stage 4 (%)	8.1 ± 7.9	10.3 ± 6.9	0.226
REM (%)	17.5 ± 5.6	20.6 ± 7.4	0.120
Sleep efficiency (%)	71.3 ± 17.6	74.3 ± 13.3	0.604
ARI events/h	25.6 ± 16.8	21.9 ± 18.7	0.224
AHI events/h	57.1 ± 35.2	37.7 ± 32.3	0.026
Awake O_2 sat (%)	94.1 ± 2.08	94.8 ± 1.5	0.297
Average O_2 sat (%)	87.1 ± 4.2	89.3 ± 4.6	0.027
Minimum O_2 sat (%)	68.9 ± 11.3	76.2 ± 9.9	0.017
Desaturation (%)*	60.05 ± 37.8	38.5 ± 35.2	0.042
CAI, events/h	0.82 ± 1.35	0.22 ± 1.12	< 0.001
OAI, events/h	26.2 ± 18.5	21.7 ± 19.3	0.019
MAI, events/h	8.3 ± 11.9	5.2 ± 9.2	< 0.001

REM=rapid eye movement sleep, ARI=arousal index, AHI=apnea hpopnea index, sat= saturation,
* Sleep time of SpO_2 < 90%, CAI= central apnea index, OAI= obstructive apnea index, MAI= mixed apnea index, sleep stages are given as % of total sleep time

patients with CompSAS (15.5 ± 1.8 vs. 9.3 ± 6.8, P < 0.001). CPAP titration was prescribed for 83 cases; there were no differences in the requirements for CPAP pressures between CompSAS and OSAS (8.4 ± 1.4 and 8.8 ± 1.5, respectively, P = 0.380).

When CompSAS and OSAS patients were compared in terms of concomitant diseases, the difference was significant as for CHF and CRF ratio (16.6% in CompSAS, 2.43% in OSAS for CHF, P = 0.048 and 8.3% in CompSAS, 0% in OSAS for CRF, P = 0.047) (Table 4).

Discussion

CompSAS is a distinct clinical entity different from OSAS. Though accepted as a speculative claim, this

Table 3. Titration polysomnographic findings.

Variables	CompSAS (n = 12)	OSAS (n = 71)	P-value
Residual AHI	9.8 ± 5.8	3.1 ± 4.7	<0.001
Number of cases with CA (n ± SD)	27.3 ± 18.7	2.4 ± 2.6	<0.001
Duration of CA (s)	15.5 ± 1.8	9.3 ± 6.8	<0.001
CPAP pressure (cmH2O)	8.4 ± 1.4	8.8 ± 1.5	0.380

CA=Central apnea
CPAP = Continuous Positive Airway Pressure

Table 4. The incidences of concomitant diseases in patients with CompSAS and OSAS.

Incidences (%)	CompSAS (n = 12)	OSAS (n = 71)	P-value
CHF	16.6	2.4	0.048
CRF	8.3	0	0.047
HT	58.3	44.5	0.386
CAD	16.6	13.4	0.670
CVD	0	0.4	1.000

CHF=congestive heart failure, CRF=chronic renal failure, HT= hypertension, CAD=coronary artery disease, CVD=cerebrovascular disease

syndrome has been attempted to be explained by some physiologic mechanisms (10). Two mechanisms are mostly emphasized. One of them is hypocapnia, and resultant central apneas, the other, is impaired respiratory control occurring as a result of increased chemosensitivity of the respiratory center. In respiratory control, chemoreceptor inputs play key roles. Hypercapnia and hypoxemia are the most important stimulators of the respiratory center. The response of the respiratory center to oxygen (O_2) and carbon dioxide (CO_2) is different. In other words, chemosensitivity differs from person to person. Higher chemosensitivity leads to impairment of respiratory stability. Very small scale variations in chemical stimuli in these individuals induce exaggerated responses. For example, in patients with a higher chemosensitivity, even milder increases in CO_2 or minor decreases in O_2 levels lead to enhanced respiratory response and impaired respiratory control (3). In the presence of a highly responsive chemoreceptor, arterial CO_2 ($PaCO_2$) decreases below apneic levels (i.e. below the hypocapnia-induced apneic threshold) and apnea occurs. Sleep unmasks a highly sensitive hypocapnia-induced apneic threshold (11). In patients with OSAS, variations in blood gas concentrations (especially hypoxia) because of recurrent nocturnal apneas increase chemoreceptor sensitivity with a resultant higher ventilatory response (12). In patients with complex sleep apnea syndrome, deranged cardiovascular stability has been reported (5). In cardiac failure patients with central apneas, it has been demonstrated that oxygen therapy corrected desaturation and decreased the number of nocturnal sympathetic discharges and central apneas (13). Consequently, oxygen level plays an important role in respiratory and cardiovascular control and hypoxia offsets this regulation mechanism. In our study, the average SpO_2 and minimum SpO_2 values were lower in patients with CompSAS when compared with patients with OSAS and also oxygen desaturation was more severe in the CompSAS group than in the OSAS group. Based on the information in our study, it has been suggested that hypoxia might be one of the pathophysiological mechanisms playing a role in the development of CompSAS.

Furthermore, reflex inhibition might play a role in the central control of respiration. Some inhibitor signals originating from the upper respiratory tract have a role in the pathogenesis of central apnea (5,11).

Stability of breathing in individuals with low threshold for arousal is also disturbed. Arousal gives rise to hyperventilation and PCO_2 below the apneic threshold results in central apnea. The breathing process has a stable course during slow wave sleep stages due to the elevation of the arousal threshold. This mechanism may explain why central respiratory events tend to occur during lighter stages of sleep.

In this retrospective study, the prevalence of CompSAS was 14.4%, which is consistent with the only reported prevalence of 15% in the literature (6).

Morgenthaler et al. showed that patients with CompSAS had a lower diagnostic AHI in CSA, but it was higher in patients with OSAS (6). Our results revealed that patients with CompSAS had more severe

sleep-disordered breathing than patients with OSAS. As seen in Table 2 in the CompSAS group, central and mixed apnea index were significantly higher when compared with the OSAS group, in diagnostic PSG. Post-titration residual apneas in the CompSAS group might be these baseline central and mixed apneas. Even if AHI was higher and oxygen saturations were lower in the CompSAS group, Epworth scores were found to be significantly lower. In other words, somnolence was lower in this group. These data were in contrast to the expected findings.

The majority of patients with CompSAS are male. It has been shown that males have a higher incidence of disrupted and lighter sleep than females. This mechanism may explain why CompSAS is more frequently seen in the male population. It is reported that BMI is lower in CompSAS cases than in OSAS cases (5). In our study, no possible difference between OSAS and CompSAS groups as for gender and BMI was found because of the scarcity of cases.

Lehman et al. reported that a history of ischemic heart disease or heart failure was more prevalent amongst patients with CSA (14). In our study, when the incidences of CHF and CRF were compared in both groups, in the CompSAS group higher incidences of these diseases were found (16.6% vs. 2.4%, P = 0.048 for CHF, 8.3% vs. 0%, P = 0.047 for CRF). Because of the scarce number of cases in this group, the clinical significance of these data may be debatable.

There is a controversy regarding the optimal treatment of CompSAS. However, adaptive servo ventilation (ASV) is the most popular and emphasized method in the treatment of CompSAS. In the literature, numerous publications have indicated that central apneas and Cheyne-Stokes syndrome could be improved with CPAP therapy (15), while others have suggested that CPAP therapy had no effect on central apneas or, on the contrary, it even worsened this condition (16). In a study, the outcomes of long-term (49-452 days, median: 195 days) CPAP treatment of 13 patients with CompSAS were evaluated and 7 patients with AHIs <10 and 6 patients with AHIs >10 were observed. The study suggested that 50% of the cases responded to CPAP (4). Moreover, other studies were carried out to compare the effects of noninvasive positive pressure ventilation (NPPV) and ASV with those of CPAP in CompSAS and they demonstrated that NPPV and ASV had improved AHI and ARI more than CPAP, but the effect of ASV was superior to that of NPPV (17). Another study showed that sleep-related breathing problems in patients with CSA, CSA/Cheyne-Stokes respiration (CSR) and CompSAS could not easily be controlled with CPAP. In the cases in which the method of ASV was used, a dramatic improvement in sleep-disordered breathing and sleep architecture was observed (18). In addition to CPAP, various therapeutic options have been studied including oxygen supplementation, pharmacotherapy (theophylline, acetazolamide), and minimizing hypocapnia by using a nonvented mask, usage of the lowest pressure, enhanced expiratory rebreathing space, and controlled increases in CO_2 concentrations in the inhaled air (11,19). For all of our patients, CPAP was prescribed. There were no differences in the requirements for CPAP pressures between the 2 groups. Subjective improvement was evaluated by telephone questioning. All of the patients reported improvement in sleep quality and/or daytime sleepiness. When the response to CPAP therapy was evaluated, in cases with mostly mixed apneas the response to treatment was apparently inadequate (11). In our results, when diagnostic PSG registries of our cases were analyzed, the number of mixed apneas was less than the number of obstructive apneas. This fact could be accounted for the improved response of our cases to CPAP therapy. We later obtained objective follow-up data to define treatment responses more efficiently. Recently one of the mechanisms proposed for the treatment response has been that in most patients with CompSAS with long-term CPAP treatment the response of the respiratory center to chemical stimuli is reset, leading to normalization of the respiratory pattern, and resolution of central apneas (12).

Conclusion

The results of our study revealed that the rate of CHF was significantly higher, the average and minimum values of oxygen saturation were lower, and more severe oxygen desaturation was observed in the diagnostic PSG group with CompSAS. Disturbances in the mechanisms of respiratory and/or

cardiovascular control may be responsible for the pathophysiology of CompSAS according to our results. Further research is needed to understand its pathophysiology in detail. Identifying the clinical profile of patients with CompSAS might be helpful in understanding the pathophysiology of this syndrome and in discovering management strategies.

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