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Research Article

How Frequently Is Obstructive Sleep Apnea Seen In Cluster Headaches?

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Summary

Objectives: After the importance of neuroanatomic structures had been proven of cluster headaches such as the hypothalamus; on the relationship between cluster headaches and sleep disorders started. Our purpose was to determine how frequently obstructive sleep apnea syndrome could be seen in cluster headache.
Materials and methods: The study included 18 cluster headache patients. All of them underwent polysomnograpic investigation.
Results: Six of the 18 patients [33.3%] had OSAS. The statistical analysis revealed that patients with OSAS were older than those without. There was a positive correlation between Respiratory Disturbance Index and Body Mass Index, and Respiratory Disturbance Index and age at the onset of the disease.
Conclusion: OSAS prevalence in this present study appeared to be higher in cluster headache patients than in the general population. Especially cluster headache patients with high Body Mass Index scores, older age and late onset of cluster headache should be assessed for sleep disorders in detail.

Key words: Cluster headache, Polysomnography, Sleep apnea, Comorbidity

Küme Başağrısında OSA Gerçekten O Kadar Sık Mı?

Özet

Giriş ve amaç: Uyku ve başağrısı arasındaki ilişki uzun süredir bilinmektedir. Küme başağrısı (KBA) patofizyolojisinde, uyku fizyolojisindeki önemi bilinen hipotalamusun rolü kanıtlandıktan sonra KBA ile uyku bozuklukları arasındaki ilişki ayrıntılı incelenmeye başlanmıştır. KBA'da obstruktif uyku apne sendromuna (OUAS) daha sık rastlandığı çalışmalarda gösterilmiştir. Bu çalışmada KBA hastalarında polisomnografi (PSG) incelemesi yapılarak, uykuda solunum bozukluklarının sıklığı araştırılmış ve OSAS sıklığını etkileyebilecek faktörler tartışılmıştır.
Yöntem: Çalışmaya toplam 18 KBA hastası dahil edildi ve hepsine tüm gece PSG incelemesi yapılarak uyku etkinliği, total uyku zamanı, minimal oksijen satürasyonu ve anormal solunum olayı indeksi (ASİ) değerlendirildi. ASİ değerinin 5'in üstünde olması OUAS olarak kabul edildi.
Bulgular: 18 hastanın 6'sında (%33.33) OUAS saptandı ve OUAS'lı hastalar anlamlı olarak ileri yaşta saptandı (p=0.049). PSG verileri ile korelasyon analizi yapıldığında ASİ değerleri ile sadece yaş (r=0.523, p=0.026) ve vücut kütle endeksi (VKİ) (r=0.630, p=0.005) arasında pozitif ilişki saptandı.
Sonuç: Bizim çalışmamızda da KBA'nda OUAS sıklığı genel popülasyondan yüksek saptanmıştır diğer çalışmalardaki gibi %80 gibi yüksek düzeylere ulaşmamıştır. Ayrıca KBA'da OUAS sıklığını artıran başka risk faktörleri de vardır ve bunlar daha önemli olabilir. Özellikle VKİ yüksek, ileri yaşta ve hastalık başlangıç yaşı ileri olan küme başağrısı hastaları, uyku bozuklukları açısından detaylı değerlendirilmelidir ve şüphelenilirse PSG incelemesi yapılmalıdır. Yaş ve VKİ daha önceki çalışmalarda da ilk 2 risk faktörü olarak tanımlanmıştır,

çalışmamız hastalık başlangıç yaşının ileri olmasının OUAS için 3. risk faktörü olduğunu ortaya çıkarmıştır.

Anahtar Kelimeler: Küme Başağrısı, Polisomnografi, Uyku apnesi, Komorbidite

INTRODUCTION

The association between sleep and headaches has been noticed for many years. While some headaches like migraine improve with sleep, some such as cluster headaches (CH) and hypnic headaches can be triggered by sleep. On the other hand, morning headaches or chronic headaches may develop in sleep disorders such as sleep apnea syndrome and insomnia.

Cluster headache is a rare primary headache which is more frequent in males and reported to have a prevalence of 0.1–1% [8]. The attacks are almost always unilateral, generally retroorbital and are characterized by very severe pain, discomfort, agitation and cranial autonomic symptoms and may last between 15 minutes and 3 hours. Episodic attacks comprising the great majority of the patients (80%) typically appear in clusters lasting from several weeks to several months. Between cluster periods, patients are totally asymptomatic. Headaches generally appear at the same hours of the day, and 50–60% of the patients develop headache attacks at night too. A minor percentage of the patients with CH (10%-20%) have a chronic form of the disease in which attacks continue without remission [11]. Periodic patterns, autonomic symptoms, circadian and circannual rhythmic features and comorbid neuroendocrinologic disorders especially the one in melatonin release led investigators to consider the possible role of hypothalamus in the pathogenesis, which was later proved by functional and anatomic imaging procedures [2,9,10].

After the hypothalamus had been proven to play a crucial role in both the physiology of sleep and pathophysiology of CH, detailed investigations on the relationship between these types of headaches and sleep disorder started. Earlier studies show that sleep apnea syndrome is seen more frequently in CH ranging from 31% to 80%[3,13,14]. Sleep apnea is defined as short term cessations of respiration during sleep. These cessations generally last 10 seconds or more and result in a decrease in blood oxygen level. Decreased oxygen and increased carbon dioxide levels in blood then stimulate the brain, and cause arousals which in turn result in excessive daytime sleepiness and attention and concentration difficulties[5].

Our purpose was to determine how high the frequency of OSAS in CH could be. In this study, the frequency of OSAS was examined in a group of patients with CH by polysomnographic (PSG) investigation and the factors that might affect the frequency of obstructive sleep apnea syndrome (OSAS) were discussed.

MATERIAL AND METHODS

Patients

The study was conducted in the neurology outpatient clinic of our university between July 2007 and February 2008, and included 18 patients (14 males, 4 females). They were chosen from among those who were presented to neurology outpatient clinics within a two year period up to the study and who accepted to participate in the study. All patients met the International Headache Society (IHS) criteria for the diagnosis of cluster headaches[4]. In the study duration, 5 patients with cluster headache were not accepted to participate in the study. The patients were examined for cardiac, pulmonary and hematologic disorders that could be associated with sleep disordered breathing and those having any such condition were excluded from the study. The local ethics committee approved the study and all patients gave their written informed consents after they had been informed clinically. Age, body

mass index (BMI), CH types, age at the onset of the disease, disease duration, the duration and the frequency of cluster periods, the frequency of headaches in clusters and nocturnal headache attacks, and response to standard treatment were evaluated. The sleep history of the patients was taken individually and then they were requested to complete an Epworth Sleepiness Scale (ESS). All patients underwent polysomnograpic investigation whether or not they had complaints related to sleep. Of the eighteen patients, fifteen were episodic CH patients and three were chronic CH patients (one patient with primary and the other two with secondary chronic). All patients underwent complete physical and neurologic examination and had cranial magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA).

The polysomnograpic investigation was carried out in 15 episodic CH patients; in 3 patients during both cluster period and out of cluster period, and in 12 patients out of cluster period. Standard treatment regimens were maintained during the study in all patients.

Polysomnography

Polysomnographic evaluation was performed on Embla A 10 (Flaga, Reyjavick, Iceland). Polysomnography (PSG) included electroencephalographic (EEG) leads (C3-A2, C4-A1, O1-A2 and O2-A1 of the 10-20 international electrode placement system), two electrooculographic (EOG) leads (right and left), chin and bilateral anterior tibialis surface electromyograms (EMGs), two electrocardiographic (ECG) leads, nasal and oral airflow, thoracic and abdominal excursion, and finger oximetry. PSG recordings were scored according to the standard criteria of Rechtschaffen and Kales as epochs of 30 seconds[15]. Apnea was defined as at least a 10 second cessation of airflow, and hypopnea was defined if there was at least 50 percent reduction in airflow relative to baseline, coupled with a desaturation of at least 4 percent or arousal and awakening. Respiratory Disturbance Index (RDI) was defined as apnea+hypopnea divided by the hours of sleep. RDI over five was considered as obstructive sleep apnea syndrome (OSAS).

Statistical Analysis:

For the statistical analysis Statistical Package for Social Sciences (SPSS 11.0) software was used. The frequency of OSAS in CH patients was determined. Non-parametric tests were used. The patients with OSAS were compared to the ones without OSAS in terms of age, BMI, age at the onset of the disease, disease duration with Mann-Whitney U test. Spearman's linear coefficient of correlation (r) was used to assess the dependence among the values of the variables. The significance level was established at a probability of 5% ($p<0.05$).

RESULTS

Fourteen patients were male and 4 were female CH patients included in the study. 13.80). In CH±Ages of the patients ranged between 22 and 67 (mean age 40.78 patients, age at the onset of the disease ranged from 14 and 63 years (mean age: 28.83±14.01 years) and the disease duration ranged from 2 to 28 years (mean duration 12.06±8.11 years). Neurological examinations of the patients were normal except 7 patients whom have slight unilateral blepharoptosis. In all patients, MRI and MRA were normal. On the day of PSG investigaiton 12 patients were not using any medication, 6 patients were using verapamil. The BMI values of the patients were between 20.30 and 35.90 (mean BMI 26.98±3.63). Twelve patients complained about nocturnal headaches and in 2 of these, headache attacks appeared only at night. Except for two patients, all patients responded to standard prophylaxis and attack treatments.

In PSG investigations total sleep durations were between 228.5 and 484.9 minutes

(mean duration 342.64±70.84 minutes), and sleep efficiencies ranged from 69.6 to 97.10% (mean efficiency 84.83±8.58 %). RDI was detected as 0–48.6 (mean 9.46±14.64), and MOS ranged from 73 to 96% (mean 87.44±6.71%) (Table 1). In six patients (33.3%), RDI was above 5, and in 2 patients RDI was below 5 during whole sleep except there were RDI increases only in supine positions. When six patients with RDI> 5 were compared with twelve patients with RDI≤5, it was found that age and BMI were higher in the RDI>5 group (mean age: 49.67±13.31 and 36.33±12.21 years, p:0.049; BMI mean 29.23±3.57 and 25.86 3.22 respectively) (Table 2). Furthermore, in correlation analysis between patient age, BMI, disease duration, age at onset of the disease, RDI and MOS; there was a positive correlation between RDI and BMI, and between RDI and age at onset of the disease (r=0.630, p=0.005 and r=0.523, p=0.026 respectively). There was a negative correlation between MOS and BMI (r=-0.762, p=0.000).

A headache attack was not observed during the polysomnographic investigation. There was no difference between the two PSG results of the three patients, which were obtained during the cluster period and out of cluster period. Among the patients with RDI value over 5, five had episodic CH in remission and one had chronic CH. For the patients with only nocturnal headaches, RDI values were not detected to be high. In five of the patients with high RDI values, there was a nocturnal headache history and none of them had a complaint of any of OSAS symptoms (snoring, apnea during sleep, daytime excessive sleepiness) or of some other sleep disorders. ESS values were detected to be between 0 and 11 (mean 6±4) for patients with RDI over 5 and between 2 and 11 (mean 5±3) for patients with RDI below 5.

Table 1. Demographic and polysomnographic features of cluster headache patients without OSAS.

Patient	Age	Gender	Age at onset of CH	CH type	ESS	BMI	RDI	MOS	Medication
1	33	M	26	Episodic	7	26,8	0,2	88	Verapamil
2	36	M	24	Primary chronic	9	22	0	95	No
3	27	F	17	Episodic	4	31,5	0,38	91	No
4	34	M	21	Episodic	5	26,23	0,41	94	No
5	31	M	22	Episodic	6	25,8	3,1	91	Verapamil
6	49	M	37	Episodic	3	20,3	0,4	96	Verapamil
7	28	M	21	Episodic	11	27,75	1,55	83	No
8	22	M	15	Episodic	4	23,2	0	93	No
9	40	F	14	Secondary chronic	5	24,3	0,3	93	Verapamil
10	67	F	55	Episodic	9	27	4,6	87	No
11	27	M	26	Episodic	4	30,4	2,8	74	Verapamil
12	42	M	21	Episodic	2	25	0	88	No

CH: Cluster Headache, ESS: Epworth Sleepiness Scale, BMI: Body Mass Index, RDI: Respiratory Disturbance Index, MOS: Minimal Oxygen Saturation, M: male, F: female

Table 2. Demographic and polysomnographic features of cluster headache patients with OSAS.

Patient	Age	Gender	Age at onset of CH	CH type	ESS	BMI	RDI	MOS	Medication
1	63	M	35	Episodic	8	29,4	19,2	79	No
2	34	M	30	Episodic	11	35,9	35,4	73	No
3	50	M	26	Episodic	7	27,5	18,3	89	No
4	53	M	49	Secondary chronic	0	29,7	48,6	84	Verapamil
5	64	F	63	Episodic	5	26	5,6	86	No
6	34	M	17	Episodic	3	26,9	29,4	90	No

CH: Cluster Headache, ESS: Epworth Sleepiness Scale, BMI: Body Mass Index, RDI: Respiratory Disturbance Index, MOS: Minimal Oxygen Saturation, M: male, F: female

Table 3: Comparison of age, age at the onset of the disease, body mass index (BMI), minimal oxygen saturation (MOS) in patients with Respiratory Disturbance Index (RDI)>5 or RDI ≤5.

	RDI>5	**RDI≤5**	**P**
Age	49.67 ±13.31	36.33 ±12.21	0.049
BMI	29.23 ±3.57	25.86 ±3.22	NS
MOS	83.50 ±6.47	89.42 ±6.14	0.049
Age at onset of the disease	36.67 ±16.69	24.92 ±11.24	NS

NS: Not significant

DISCUSSION

The frequency of sleep disordered breathing and of OSAS is not higher than that observed in the general population when all headache types are concerned[6]. In patients with OSAS, the frequency of a headache is not very different from that in the general population either[5]. The fact that the cluster headache is generally seen during sleep, and that treatment with oxygen is effective in acute attacks has suggested a potential relationship between CH and sleep disordered breathing[1,2,9]. After the importance of the neuroanatomic structures like hypothalamus in CH pathophysiology, which are also known to be important in sleep physiology, was confirmed, detailed investigations on the relationship between these types of headaches and sleep disorders started.

Sleep apnea in CH was first defined by Kudrow[7], and the following studies found OSAS to be more frequent in patients with CH than in the general population. Whereas the prevalence of OSAS was reported to be between 2% and 4% in general population[16], it was reported to greatly vary from 31% to 80% in patients with CH[1,3,12,13,14]. In our study, OSAS was found at a rate of 33% of the CH patients,

being at the lower end of this extensive range.

While evaluating OSAS frequency, it is important to investigate other factors especially age and BMI that might create a risk for OSAS in addition to CH. For instance, in some studies concerning CH, either BMI was not mentioned at all or its effects were not investigated sufficiently. In studies that detected OSAS in high rates like 80% in these patients, BMI was not mentioned[3]. Moreover, the ages of the patients in these studies were higher than those of our study group.

Nobre et al. indicated that CH increased the risk of OSAS, but in patients with low BMI and/or a younger age, this risk suddenly dropped down, and that detailed sleep investigations should be carried out only in patients with high BMI and aged over 40[14]. Our findings in the present study were consistent with theirs. In our study too, the mean age of the patients with OSAS was higher. Although statistically insignificant, mean BMI scores of the patients with OSAS tended to be higher. However, it was also found that RDI revealed a moderate positive correlation with BMI, and MOS had negative correlation with BMI in the correlation analysis. Another finding not mentioned in other studies was the positive correlation between RDI and age at the onset of the disease. With advanced aged, pathologic changes in the hypothalamic regions may lead to two different disorders such as CH and OSAS. All these findings suggest that OSAS frequency increases especially in patients with cluster headaches who are at an older age, in those with late age onset of the disease and whose BMI is high. It is also a striking finding that the patients with OSAS in the present study had short cluster periods and lower frequency of headache attacks; whereas in the patients with frequent and severe headache attacks, OSAS was not detected.

It is important to remember that even though the hypothalamus may play a role both in CH and OSAS, the underlying pathophysiologies may be different. The features of CH like periodicity and remissions are not among the characteristics of OSAS. If there were a direct relationship between CH and OSAS, one could expect that OSAS would be more frequent among chronic CH patients than episodic ones and should be related to the severity of the disease and treatment resistance. On the contrary, studies concerning OSAS and CH up to date revealed OSAS to be related to episodic disease more, however the severity of the disease and treatment resistance were not evaluated in this aspect. In our study, there was only one chronic case among the patients with OSAS and the frequency of OSAS was not related to the severity of CH. The two treatment resistant cases in our study, one with episodic and one with chronic CH did not have OSAS. Although it is not appropriate to make interpretations about a rare headache with a small sample size, we thought that these findings made this causal relationship less likely.

For most of the patients, increased BMI value and older age are much more important than having CH in the development of OSAS. CH patients with late onset are more susceptible to OSAS. It is difficult to define CH as an independent risk factor for OSAS by considering the studies with small sample sizes. Probably, CH and OSAS are two distinct entities in which similar neuroanatomic structures play a role, and thus appear simultaneously together with the presence of some risk factors.

CONCLUSION

The studies to date, as well as the present study, have shown that OSAS prevalence is higher in CH patients than in the general population. However, other risk factors increasing OSAS risk should not be ignored. Thus, it is probably not appropriate to consider CH as a great risk factor for the development of OSAS by just considering the studies reporting their

comorbidity as high as 80%, and evidence up to date is therefore insufficient to consider a causal relationship between these two conditions. A pathology related to hypothalamic region might contribute to the development of both diseases at the same time. So, especially CH patients with high BMI scores, older age and older age at the onset of cluster headaches should be assessed for sleep disorders in detail, and PSG investigation should be planned if sleep disorder is suspected. The treatment of CH patients having OSAS, especially the chronic ones, with CPAP may be helpful in enlightening the relationship between the two conditions. Thus, studies with wider sample sizes evaluating chronic and episodic CH patients both in cluster periods and in between headache periods and assessing other risk factors contributing to OSAS are needed to reveal the possible relationship between CH and OSAS.

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