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The assessment of headache and sleep quality in patients with chronic obstructive pulmonary disease

Fettah Eren [1], Bengu Ozkan Bakdik [2], Aysegul Demir [3]

[1] Selcuk University, School of Medicine, Department of Neurology, Konya, Turkey
[2] University of Health Sciences Turkey, Konya City Hospital, Chest Diseases Clinic, Konya, 42700, Turkey
[3] University of Health Sciences Turkey, Konya City Hospital, Neurology Clinic, Konya, Turkey

ORCID ID of the author(s)

FE: 0000-0001-6834-0827
BOB: 0000-0001-9195-8561
AD: 0000-0002-5444-9837

Corresponding Author
Fettah Eren
Selcuk University, School of Medicine, Department of Neurology, 42700, Konya, Turkey
E-mail: dreren42@hotmail.com

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Approval was obtained from the Clinical Research Ethics Committee at Selcuk University (Number: 2021/109).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: It is known that sleep disorders and headaches are related. However, there are only very few studies examining this correlation in chronic obstructive pulmonary disease (COPD). The aim of this study was to evaluate the association between sleep disorders, headaches, and hypoxia in COPD patients.
Methods: This study was designed as a prospective case-control study with 120 COPD and 83 controls patients of similar age/gender. International classification of headache disorders - version 3 (ICHD III) was used for the diagnosis of headache. Pain intensity was calculated using the visual analog scale (VAS). For the effect of headache, headache activities of daily living index (HADLI) questionnaire was applied. Pulmonary function tests were performed with a PC-based spirometry device. Blood pressure and blood oxygen saturation were measured by fingertip pulse oximetry. Sleep quality was assessed using the Pittsburgh sleep quality index (PSQI). Dyspnea severity was graded according to the modified medical research council (mMRC) scale.
Results: Headache was detected in 54 patients (45%) with COPD. The most common type of headache was tension type (66.7%). Patients with headache had higher diastolic blood pressure, severity of dyspnea score, and lower forced expiratory volüme-1 (FEV1), forced vital capacity (FVC) (P = 0.037, P = 0.001, P = 0.001, P = 0.001 respectively). Sleep disturbance was quite common in COPD patients (79.2%). PSQI score was higher in patients with headache (P = 0.006). Patients with poor sleep quality had higher pain severity (P = 0.006). Female gender, high diastolic blood pressure and low forced expiratory volume-1 second (FEV1) increased the risk of headache (P = 0.004, P = 0.02, P = 0.032, respectively).
Conclusion: Headache is a complex symptom in patients with COPD and associated with higher diastolic blood pressure and pulmonary dysfunction. These parameters should be evaluated in COPD patients with headache.

Keywords: COPD, Headache, Sleep quality, Hypoxia, Pulmonary functions

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Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease characterized by restriction of airflow during breathing [1]. It is the third most common non-communicable disease, and its incidence is approximately 10% in the population over 40 years old [2]. It is the 5th most common cause of morbidity worldwide [3]. The most important risk factor of the disease is smoking [2]. In spirometry-based studies, the prevalence of COPD was found to be 26% in smokers and 8% in non-smokers [4].

Forced expiratory volume in 1 second (FEV1) can be used to determine the severity of the disease in COPD. FEV1 relative to normal ≥ 80% is called as mild COPD, 50-80% moderate, 30-50% severe and < 30% very severe [3, 5]. Low FEV1 is a risk factor for cardiovascular and cerebrovascular diseases. This impairment in respiratory functions disrupts cerebral and muscular perfusion, leading to fatigue, headache and sleep quality impairment [6, 7].

Sleep disturbances are closely correlated with many chronic diseases. Pittsburgh sleep quality index (PSQI) disturbances are detected in approximately 70% of COPD patients [8]. However, the correlation between them has not been fully revealed. Besides many factors in chronic diseases, headache also negatively affects sleep functions. Headache is most commonly associated with insomnia, obstructive sleep apnea syndrome (OSAS) and restless legs syndrome/periodic limb movement disorder among sleep disorders [9]. The mechanism of the relationship between hypoxia, hypercapnia and sleep disturbance in diseases that cause respiratory dysfunction has not been fully elucidated, but it has been observed that all these factors affect each other [7, 9].

Sleep-related headache is a known fact in both the clinical practice and literature review. However, there are few studies evaluating the relationship between sleep disorders and the headache character associated with chronic hypoxia in COPD patients. Therefore, we aimed to examine sleep disorders, headache characteristics and their relationship with pulmonary function tests (PFT) in COPD patients.

Materials and methods

Field of study and ethical approval

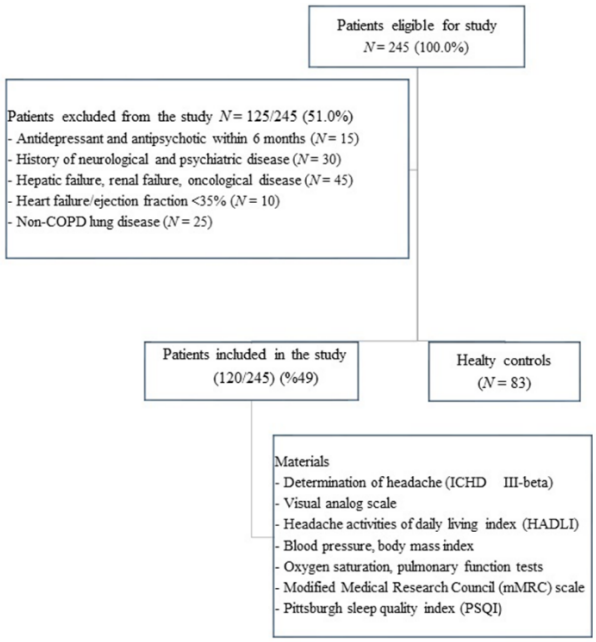
COPD patients who applied to the pulmonary outpatient department were included in the study and all patients were also evaluated in the neurology outpatient clinic. The study was planned as a case-control prospective study. The ethical approval was obtained from Selcuk University clinical research ethics committee.

Participants and sociodemographic characteristics

Sample size was calculated using the G-power program. In the two-way analysis of variety, it was calculated that a minimum of 120 patients and 80 controls were required for medium effect size. 120 COPD (40-85 years of age, because there is a consensus that COPD cannot be diagnosed < 40 years age) patients and 83 healthy controls were included in the study. The Declaration of Helsinki and good clinical practice guidelines were adhered throughout the study. The objective of the study was explained to the patients participating. Consent form prepared for the study was given to each participant. Participants who had not read and not signed this form were not included in this study.

Diseases and conditions that could affect the study results were excluded. Exclusion criteria were treatment with antidepressants and antipsychotics within 6 months, history of neurological and psychiatric disease (epilepsy, stroke, schizophrenia, depression), hepatic, chronic renal or heart failure, oncological disease and non-COPD lung disease (Figure 1). Patients' age, gender, educational and financial status, living environment, number of children, smoking and alcohol use were questioned. The period of COPD and the treatments applied (beta agonist, corticosteroid, theophylline, home non-invasive mechanical ventilation and oxygen use) were examined. Body weight and height of the patients were measured. Body mass index (BMI) was calculated with [weight (kg) / height^2 (m^2)].

Figure 1: Patient selection and study design



Determination of headache and its subtypes

The same neurologist performed detailed neurological evaluation and examination. Patients with normal neurological examination results were included in the study to exclude secondary headache. Brain magnetic resonance imaging (MRI) was requested for patients who were suspected of having cranial pathology in their neurological examination. Patients without cranial pathology included in the study, other patients were excluded. The patient and control group were asked whether they had a headache in the last 3 months. ICHD III-beta version was used for the diagnosis of headache [10]. Pain type, frequency, duration (when using analgesic, without analgesic use), localization, accompanying factors (nausea and/or vomiting, photophobia-phonophobia, sensory symptoms) and presence of aura were questioned. Pain type was grouped as migraine (with or without aura), tension-type headache (TTH), trigeminal autonomic cephalalgia and other headaches. Pain intensity was calculated using the visual analogue scale (VAS) (without the use of analgesics). Pain severity was graded from 0 to 10. The higher the numerical value of the VAS result, the higher the pain intensity was considered [11]. Pain intensity was divided into two groups as over 5, 5 and less. In order to evaluate the effect of headache in daily life, the headache activities of daily living

index (HADLI) questionnaire was applied. This questionnaire composed of 7 questions, each scored between from 1 to 10 (1: it does not affect at all, 10: it affects completely) [12]. The total score ranges between 7-70.

Pulmonary function and determination of subgroups

A detailed pulmonary examination was performed by the same pulmonologist. Pulmonary function tests were performed with a PC-based spirometry device (Spirobank Office; Medical International Research (MIR); Rome; Italy) while the patients were sitting in a comfortable and upright position. Patients were asked to close their lips tightly with a disposable mouthpiece for spirometry. Patients were asked to inhale and exhale at maximum. This measurement was repeated 3 times and the best value was obtained. With this test, FEV1, forced vital capacity (FVC) and FEV/FVC values were obtained [13]. Patients based on FEV 1 value divided into 4 groups as ≥ 80, 50-79, 30-49 and < 30 [5].

The severity of dyspnea is rated according to the Modified Medical Research Council (mMRC) scale [14]. This scale has degrees from 0 to 4 and the increase in the degree indicates that the severity of dyspnea increases. Grade 0-2 was named as mild, 3-4 severe dyspnea. Blood oxygen saturation was measured with a fingertip pulse-oximeter (Nonin, Digital pulse oxi-meter, USA).

Blood pressure measurement

After the patients rested for 15 minutes, measurements were made 3 times in sitting position and the arithmetic mean was obtained. The cuff size suitable for the arm circumference of each patient was selected. It is measured with a mercury sphygmomanometer. The first and fifth Korotkoff sounds were determined as systolic blood pressure (SBP) and diastolic blood pressure (DBP) [15].

Evaluation of sleep quality

Sleep quality was assessed by using the Pittsburgh sleep quality index (PSQI) [16]. This questionnaire consists of 19 questions and 7 subgroups with 0-3 grades. Subgroups included questions about sleep duration, quality, latency and efficiency, sleep disturbance, daytime dysfunction and use of drugs for insomnia. The total score ranges between 0-21. Higher scores indicate worse sleep quality. If the score is above 5, it indicates that the sleep quality is clinically poor [17].

Statistical analysis

For data analysis, SPSS 16.0 Package Software (Statistical Package for the Social Sciences Inc.; Armonk, NY, USA) analysis program was used. Normality analysis was performed with Kolmogorov-Smirnov test. Data were expressed as number (n), percentage (%), and mean (standard deviation). Independent sample T, Kruskal Wallis, and Mann Whitney U tests were used for comparison of the means. Nonparametric data were compared with $\chi 2$ or Fisher's exact test. The correlation between numerical data was evaluated using Spearman's Correlation test. R-value = 0.26-0.49: poor and 0.50-0.69: considered to be moderate correlation. A logistic regression analysis was used to predict the factors affecting of headache. Results were evaluated at a 95% confidence interval and a significance level of $P < 0.05$.

Results

The average age in our study was 63.38 (11.49), there were 120 COPD patients (range 40-85 years old) and the number of male patients was higher (n = 97, 80.8%). There were 83 healthy volunteers of similar age group and gender ($P > 0.05$). Smoking was higher in COPD patients (79.2%, mean (SD): 23.29 (17.91) pcs/day), whereas the use of alcohol was lower (n = 4, 3.3%). Mean BMI was 26.59 (5.04), and blood pressures were 126.75 (18.71) mmHg and 78.11 (12.62) mmHg for systolic and diastolic, respectively. The mean duration of COPD was 7.19 (4.82) years. 112 (93.3%) patients were receiving inhaled B2 agonists, 98 (81.7%) inhaled anticholinergics, 63 (52.5%) inhaled glucocorticoids, and 43 (35.8%) patients were receiving sustained-release theophylline. 30 (25%) patients were using home oxygen and 4 (3.3%) patients were using non-invasive mechanical ventilation. 16 (13.3%) of the patients had a history of COPD in the first degree, 21 (17.5%) in the second- and third-degree relatives.

For the relationship between the treatments used by COPD patients and headache, there was no correlation between the use of inhaled b2 agonists, glucocorticoids, theophylline, and home oxygen and the frequency of headache ($P = 0.729$, $P = 0.362$, $P = 0,168$, $P = 0.836$, respectively). The frequency of headache was higher in patients using inhaled anticholinergics ($x^2 = 10.707$, $P = 0.001$). The frequency of headache in COPD patients was 45% (n = 54). 18 (33.3%) patients with headache were female and 36 (66.7%) were male. Of the headaches, 11 (20.4%) had migraine, 36 (66.7%) had TTH, 3 (5.6%) of them had trigeminal autonomic type headache. Aura was detected in three patients. While VAS score of the patients was 5.38 (1.77), it was 6.25 (1.31) in healthy controls ($P > 0.05$). Headache prevalence was higher in COPD patients ($P = 0.036$). Headache characteristics in patient and control groups were summarized in (Table 1). The diastolic blood pressure of COPD patients with headache was higher ($P = 0.037$). FEV1, FVC values were lower and mMRC scores were higher in patients with headache ($P < 0.001$, $P = 0.001$, $P < 0.001$, respectively). Especially, sleep latency, sleep duration, sleep disturbance and sleep medication use scores were higher ($P = 0.007$, $P = 0.001$, $P = 0.002$, $P = 0.004$, respectively). Total PSQI scores of patients with headache were higher ($P = 0.006$). In the study, sociodemographic characteristics, blood pressure, PFTs and sleep quality of COPD patients with and without headache summarized in (Table 2).

Table 1: Headache characteristics in patients with chronic obstructive pulmonary disease (COPD) and healthy control group

Parameters	Headache in COPD (n = 54)		Headache in healthy group (n = 27)		X^2 *P*-value
	n	%	n	%	
Increased with cough					
Yes	14	25.9	3	11.1	2.382
No	40	74.1	24	88.9	0.155
Duration					
Less than 4 hours	35	64.8	11	40.7	4.262
4 to 24 hours	11	20.4	9	33.3	0.119
More than 24 hours	8	14.8	7	25.9	
Physical activity					
Increase	17	31.5	12	44.4	3.154
Decrease	15	27.8	3	11.1	0.207
No difference	22	40.7	12	44.4	
Localization					
Unilateral	13	24.1	14	51.9	6.250
Bilateral	41	75.9	13	48.1	0.023
Pain character					
Throbbing pain	22	40.7	23	85.2	15.68
Dull head pain	31	57.4	3	11.1	0.001
Accompanying symptoms					
Nausea and/or vomiting					
Yes	23	42.6	17	63	2.988
No	31	57.4	10	37	0.102
Photo-phonophobia					
Yes	14	25.9	19	70.4	14.727
No	40	74.1	8	29.6	0.001
Visual					
Yes	9	16.7	5	18.5	0.043
No	45	83.3	22	81.5	1.00
Sensorial					
Yes	7	13.0	5	18.5	0.440
No	47	87	22	81.5	0.522
Visual analog scale					
Mild	30	55.6	9	33.3	3.560
Severe	24	44.4	18	66.7	0.065
Headache type					
Migraine	11	20.4	8	29.6	2.423
Tension	36	66.7	14	51.9	0.850
Trigeminal-autonomic	3	5.6	1	3.7	
Other	4	7.4	4	14.8	

COPD: Chronic obstructive pulmonary disease, n: Number

Table 2: Characteristics in patients with chronic obstructive pulmonary disease (COPD) according to headache (n = 120). Data are mean (SD) unless otherwise indicated

Parameters	COPD with headaches (n = 54)	COPD without headaches (n = 66)	*P*-value
Age, years	62.57 (12.06)	64.04 (11.06)	0.488
Disease duration, year	8.01 (4.78)	6.51 (4.78)	0.084
Blood pressure			
Systole (mmHg)	129.72 (19.28)	124.31 (18.01)	0.192
Diastole (mmHg)	81.18 (12.19)	75.60 (12.51)	0.037
Body mass index	26.11 (4.86)	26.98 (5.18)	0.300
mMRC	2.81 (0.84)	1.93 (1.10)	0.001
FEV_1 (%)	46.64 (16.49)	59.50 (20.51)	0.001
FVC (%)	62.59 (17.54)	74.48 (20.11)	0.001
FEV_1 / FVC ratio	74.26 (14.31)	78.82 (14.57)	0.088
Oxygen saturation	88.92 (5.13)	90.25 (5.43)	0.115
PSQI (total)	12.29 (5.98)	9.16 (5.11)	0.006

COPD: Chronic obstructive pulmonary disease, n: Number, mMRC: Modified medical research council, FEV: Forced expiratory volume, FVC: Forced vital capacity, PSQI: Pittsburgh sleep quality index

The number of COPD patients with sleep quality score above 5 was 95 (79.2%), and the frequency of headache in these patients was 48.4% (n = 46). PSQI total score was 10.57 (5.72) in COPD patients, and 7.89 (4.25) in healthy controls (P = 0.001). Especially in COPD patients, sleep duration was shorter, sleep efficiency and daytime functions were more impaired (P = 0.008, P < 0.001, P < 0.001, respectively). Patients with poor sleep quality had higher headache severity (P = 0.006) and dyspnea severity score (mMRC) was higher in these patients (P = 0.018). Demographic characteristics of COPD patients with sleep quality disorder (PSQI > 5) and without sleep quality disorder (PSQI ≤ 5) were summarized in (Table 3).

Table 3: Characteristics of the patients with chronic obstructive pulmonary disease (COPD) according to sleep quality (N = 120). Data are mean *(*SD) unless otherwise indicated

Parameters	COPD with poor sleep quality (n = 95)	COPD with good sleep quality (n = 25)	*P*-value
Age, years	63.61 (11.65)	62.52 (11.06)	0.667
Gender, female-male (%)	22 (%23.3)-73 (%76.8)	1 (%4)-24 (%96)	0.042
Disease duration, year	7.34 (4.99)	6.60 (4.15)	0.543
Blood pressure			
Systole (mmHg)	126.89 (18.62)	126.20 (19.43)	0.877
Diastole (mmHg)	78.46 (11.99)	76.80 (14.99)	0.776
Body mass index	26.51 (5.09)	26.88 (4.92)	0.745
mMRC	2.46 (1.03)	1.84 (1.14)	0.018
FEV_1 (%)	51.86 (18.99)	60.76 (21.58)	0.069
FVC (%)	67.56 (19.96)	75.08 (19.73)	0.122
FEV_1 / FVC ratio	76.06 (14.46)	79.47 (14.99)	0.240
Oxygen saturation	89.25 (5.23)	91.20 (5.45)	0.078
Headache (%)	46 (%48.4)	8 (%32)	0.178
Painful day/month	8.17 (6.18)	9.50 (8.50)	0.858
Pain frequency/month	7.39 (5.72)	9.87 (8.33)	0.296
Visual analog scale	5.65 (1.74)	3.87 (1.12)	0.006
Restricted Activities	31.23 (17.24)	20.00 (9.87)	0.106

COPD: Chronic obstructive pulmonary disease, n: Number, mMRC: Modified medical research council, FEV: Forced expiratory volume, FVC: Forced vital capacity

In COPD patients with headache, as FEV1, FVC, and FEV1 / FVC decreased, sleep quality deteriorated according to Spearman correlation test (P < 0.001, P < 0.001, P = 0.001 r = -0.463, r = -0.426, r = -0.310, respectively). Sleep quality was deteriorated as the mMRC score increased and blood oxygen saturation decreased (P < 0.001, P < 0.001, r = -0.366, r = 0.515, respectively). As the severity of headache increased, sleep quality deteriorated (P < 0.001, r = 0.468) and activities were restricted due to headache scores increased (P < 0.001, r = 600).

Logistic regression model was created with age, gender, blood pressure, mMRC, FEV1, FVC, PSQI to predict headache in patients with COPD. The model achieved a good fit (Hosmer-lemeshow = 0.236, Nagelkerke R^2 = 0.294). Gender, diastolic blood pressure, and FEV1 had an effect on headache. Female gender increased the risk of headache by 5.243 times (P = 0.004). Headache risk increased 0.96 times (P = 0.02) when FEV1 decreased by one unit, and 0.37 times increased when diastolic blood pressure increased by one unit (P = 0.032).

Discussion

Headaches include primary headaches as well as secondary headaches in the second part according to the international classification of headache disorders - version 3 (ICHD-3 beta). This part especially includes the section where the causality relationship with headaches is established. In addition, headache subgroups that are not included in this section, whose causality relationship is not fully confirmed or that are likely to be developed, have been placed in the appendix section [10]. In ICHD-3 beta, section number 10 includes headaches attributed to homeostasis disorder. It has been revealed that headache experienced in this category is not uncommon and its lifetime prevalence is 22% (95% confidence interval, 19-25%) [18]. Headache attributed to hypoxia and/or hypercapnia forms part 10.1, which is the subsection of this section. This subsection includes high-altitude headache (10.1.1), headache attributed to flights (10.1.2), diving headache (10.1.3), and sleep apnea headache (10.1.4) [10]. However, COPD, a major disease with secondary effects of hypoxia and hypercapnia, is not included in this subsection, even in this ICHD-3 beta classification. Therefore, a study was planned to examine the relationship between respiratory functions and headache in COPD.

Although the pathophysiology of the disease remains unclear, cerebral edema that occurs with restriction of intracranial compliance induced by hypoxia, cerebral blood flow and increased venous pressure are blamed among the possible mechanisms [19, 20]. Therefore, placebo double-blind sham controlled magnetic resonance spectroscopy study revealed that hypoxia in migraine is an individual triggering risk factor in patients. According to the sham group, hypoxia caused an increase in the amount of lactate around the occipital cortex and cerebral arteries [21]. Although hypoxia and/or hypercapnia-related headache is classified in ICHD-3, a large-scale epidemiological study conducted in Norway showed no difference between oxygen desaturation and lowest oxygen saturation in patients with and without headache in sleep apnea. Similar headaches were detected in the sleep apnea severity subgroups (mild-moderate-severe) in the same study [22]. However, a limited number of uncontrolled studies have shown that continuous positive airway pressure (CPAP) support reduces the frequency of primary and secondary headaches in patients with sleep apnea syndrome [23, 24]. COPD is a disease that is characterized by inflammation and obstruction of the lung and causes significant morbidity and mortality worldwide. It is also a common serious public health problem [1-4]. The fact that the disease is quite prevalent also brings many accompanying diseases. It has been determined that the frequency of headache in COPD patients is 31.9%. TTH has been seen most frequently (22/38, 57.8%). Headache is particularly high in male COPD patients (female, male 7/31). In this study, a clear relationship between impairment in pulmonary function tests and the presence of headache could not be determined [25]. In our study, the frequency of headache in COPD patients was 45%, and similarly, the most common headache was TTH (36/54, 66.7%). Similar to literature, headache was more prevalent in men (66.7%). Diastolic blood pressure was higher in COPD patients with headache. In addition, the severity of dyspnea, low FEV1 and FVC were found to be associated with headache. Bilateral headache without photo-phonophobia and dull pain type was in the foreground in the patients. However, there was less pain intensity, although headache was more common in COPD patients. These results support the induction of hypoxia in COPD patients with possible mechanisms mentioned earlier (hypoxia-hypercapnia). This situation demonstrates that respiratory functions with impaired obstructive pattern are correlated with headache in COPD patients.

Sleep disorders can accompany many chronic diseases and are also related to the course and severity of the disease. There is also a close correlation between headache and sleep disorders [25]. Cerebral structural abnormalities should be kept in the foreground in headaches that are more pronounced in the morning and persist even if their intensity decreases during the day. Sleep apnea should be considered especially in these pains. This condition is not specific for symptoms and should also suggest other sleep disorders, cervicogenic headaches, analgesic overuse, migraine, and psychiatric disorders [25, 26]. Sleep disturbance is one of the most common symptoms in COPD patients. In the evaluations made using the PSQI scale, it was found that approximately 70% of COPD patients had sleep quality disorders [8]. In another study, this rate was calculated as 73% (final score average = 7.27) [27]. It has been determined that patients with obstructive pulmonary diseases and sleep apnea syndrome have worse sleep quality and this condition is associated with disease severity [28-30]. In our study, sleep quality disturbance was present in 79.2% of COPD patients and this rate is similar to other studies in literature. Sleep disturbance increased as the severity of dyspnea increased in COPD patients. Sleep quality disturbance was higher in COPD patients with headache. FEV1, FVC, FEV1 / FVC, and oxygen saturations were lower in patients with sleep disturbance (but these values were not statistically significant). In addition, headache was severe in patients with sleep quality disturbances. Especially in female COPD patients, sleep quality was worse. In patients with headache, sleep latency was prolonged, sleep duration was decreased, sleep disturbance was severe, and these patients were using more sleeping drugs.

Limitations

Blood gas (arterial and/or venous) analysis was not performed for the evaluation of hypoxia. Headache (diagnosed by patients' answers) is a subjective condition. Polysomnography was not performed for the evaluation of sleep disorder. The relationship between headache and brain neuroradiological imaging has not been evaluated.

Conclusions

Although there is hypoxia and hypercapnia related headache section in the ICHD-3 beta classification, it is observed that there is no COPD-related headache in the subsection of this group. However, COPD is a very common disease that causes severe disability. In 45% of patients (especially TTH), headache is more frequent than in the normal population. Female gender, high diastolic blood pressure and low forced expiratory volume-1 second (FEV1) increase the risk of headache. Sleep disturbances are quite common in these patients (79.2%). Sleep disturbance is associated with severity of dyspnea and headache. Coexistence of sleep quality disorder and headache is common. For this reason, COPD patients are followed closely, especially in terms of headache and sleep disturbance. Perhaps with larger-scale studies, it will find a place for itself in the subgroup of headaches induced by hypoxia and hypercapnia in the ICHD classification.

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