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- Birgül TUHANIOĞLU[1]
- Sanem Okşan ERKAN[1]
- Zehra DINIZ[2]
- Orhan GÖRGÜLÜ[1]
- Gökhan KURAN[1]

RESEARCH

RELATIONSHIP BETWEEN SEVERITY OF OBSTRUCTIVE SLEEP APNEA AND AGE AND INFLAMMATORY MEDIATORS IN GERIATRIC PATIENTS

Abstract

Introduction: There is a high prevalence of obstructive sleep apnea in the age group of ≥65 years. The neutrophil-lymphocyte ratio (NLR) and mean platelet volume (MPV) are used as systemic inflammatory markers. In this study, it was aimed to investigate the association between polysomnography data and inflammatory mediators as well as the association between age and severity of obstructive sleep apnea in patients ≥ 65 years.

Metarials and Method: This study included 154 patients with obstructive sleep apnea symptoms. Patients were divided into two groups: patients ≥65 years (study group) and those<65 years (control group). Polysomnography was performed in all patients. Neutrophil levels, lymphocyte counts, mean platelet volume and other hematological parameters were analyzed.

Results: There was no statistically significant difference between age groups in terms of body mass index (BMI), apnea-hypopnea index (AHI) and inflammatory mediator values ($p>0.05$). The severity of obstructive sleep apnea was not significantly different between patients in both groups ($p>0.05$). Mean platelet volume of patients with moderate apnea-hypopnea index in both groups was found to be significantly lower than that of those with severe apnea-hypopnea index ($p<0.05$).

Conclusion: According to the study results, the severity of obstructive sleep apnea and inflammatory mediator did not correlate with age.

Key Words: Sleep apnea syndrome; Geriatrics; Polysomnography

Correspondance

Birgül TUHANIOĞLU
Adana Numune Research and Training Hospital,
Otolaryngology Clinic
ADANA

Phone: 05434842329
e-mail: birgultuhanioglu@mynet.com

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[1] Adana Numune Research and Training Hospital,
Otolaryngology Clinic
ADANA
[2] Adana Ceyhan State Hospital,
Chest Diseases Clinic
ADANA

ARAŞTIRMA

GERİATRİ YAŞ GRUBUNDAKİ HASTALARDA OBSTRÜKTİF UYKU APNESİ ŞİDDETİ İLE YAŞ VE İNFLAMATUAR MEDİATÖRLER ARASINDAKİ İLİŞKİ

Öz

Giriş: 65 yaş üstü grupta obstrüktif uyku apnesi oranı yüksektir. Nötrofil-lenfosit oranı ve mean platelet volümü sistemik inflamatuar marker olarak kullanılmaktadır. Bu çalışmada, 65 yaş üstü hastalarda polisomnografi verileri ile inflamatuar mediatörler arasındaki ilişki; yaş ve obstrüktif sleep apne şiddeti ilişkisi de irdelenerek araştırılmıştır.

Gereç ve Yöntem: Bu çalışma obstrüktif uyku apnesi semptomları olan 154 hastayı içermektedir. Hastalar 65 yaş ve üstü (çalışma grubu) ve 65 yaş altı (kontrol grubu) olmak üzere iki gruba ayrıldı. Tüm hastalara polisomnografi yapıldı ve obstrüktif sleep apne şiddetine göre hafif, orta, ağır olarak ayrıldı. Nötrofil sayısı, lenfosit sayısı , mean platelet volüm ve diğer hematolojik parametreler analiz edildi.

Bulgular: Gruplar arasında vücut kitle indexi, apne-hipopne indexi ve inflamatuar mediatör değerleri açısından, istatistiksel olarak farklılık izlenmedi($p>0.05$). Obstrüktif sleep apne şiddeti her iki grupta anlamlı derecede farklı bulunmadı ($p>0.05$). Her iki grupta mean platelet volüm, orta şiddetli obstrüktif sleep apne hastalarında ağır şiddetli obstrüktif sleep apne hastalarına göre anlamlı derecede düşüktü ($p<0.05$).

Sonuç: Araştırma sonuçlarına göre, obstrüktif sleep apne şiddeti ve inflamatuar mediatörler yaşla korele değildir.

Anahtar Sözcükler: Uyku apnesi sendromu; Geriatri; Polisomnografi

INTRODUCTION

In recent years, there has been an increase in the elderly population in Turkey and in the world. Although the proportion of the elderly population in Turkey (≥65 years) was 5.682.003 persons (7.5%) in 2012, this proportion has increased to 6.651.503 persons (8.3%) in 2016. Sleep disorders are common in the geriatric population, but the most important and life-threatening sleep disorder is obstructive sleep apnea (OSA) (1). OSA syndrome is a sleep-related respiratory disorder that presents with recurrent apnea and hypopnea episodes due to intermittent upper airway obstruction. Systemic and pulmonary pressure changes as well as nocturnal oxygen desaturation and hypercapnia are observed (2).

There are arguments that sleep disorders are independent of age (3,4). However, with an increase in age, important physiological and histological changes occur in the body. The airway becomes narrow depending on changes in the supporting connective tissue. Early airway closure due to altered elastin collagen ratio is observed. Residual volume and functional residual capacity increase in the lungs, leading to decreased vital capacity and inspiratory reserve volume (5). For these reasons, hypoxia and hypercapnia may be more common in the elderly population than in the younger population. But the basic mechanism is in fact not completely understood.

New systemic inflammatory markers including the neutrophil-lymphocyte ratio (NLR) and mean platelet volume (MPV) values that are already included in complete blood count (CBC) testing have been used to detect systemic inflammation levels in the human body. CBC is inexpensive, is easy and provides rapid results. NLR evaluates two important mediators of inflammation: neutrophils and lymphocytes, therefore their ratio gives more precise information about inflammation. Neutrophils act in most inflammatory processes by secreting mediators, while lymphocytes play roles in inflammation, such as inflammation regulation (6,7). There are studies that emphasize that there is a positive association between NLR and apnea-hypopnea index (AHI) (8). MPV is an indicator of platelet activation, and it has been reported to increase in patients with OSA. MPV shows us platelet size and larger platelets have greater thrombotic potential (9).

The incidence of systemic diseases, particularly diabetes mellitus, hypertension, and cardiovascular diseases, increases in the geriatric group. Previously, inflammatory mediators have been investigated in many systemic disease and OSA groups (2). The association of these mediators with age and OSA is not clear in the literature. In this study, we aimed to investigate the association between polysomnographic data and inflammatory mediators as well as the association between age and severity of OSA in patients with>65 years.

MATERIALS AND METHOD

Study population

The study has been carried out with institutional ethics committee clearance (2017/64). This study included 154 patients admitted to ENT clinic between January 2015 and September 2016 with complaints of snoring, congestion, and daytime sleepiness and had the indication of polysomnography. Patients were divided into two groups: patients ≥65 years (study group) and those<65 years (control group). After detailed ear, nose, and throat examination, polysomnography was performed in all patients. According to the polysomnography results, the severity of OSA was rated as mild, moderate, and severe. A total of 16 patients, 8 in the control group and 8 in the study group, were excluded because of AHI<5. BMI, AHI, NLR, MPV and Epworth sleepiness scale (ESS) were noted in all patients. In addition, systemic examination of the patients was performed and existing additional diseases were questioned.

Patients with sleep disorders, such as central sleep apnea, upper airway resistance syndrome, and narcolepsy; those with hematologic disorders; those with systemic diseases, such as diabetes mellitus (DM), hypertension, and cardiovascular diseases; and those receiving medical treatment, such as anticoagulants, anti-inflammatory, and systemic corticosteroids,were not included in the study.

Polysomnography

Devices of the ComMedics E and Somte series were used for the polysomnographic measures in our study. Apnea was defined as a cessation of airflow that lasts for at least 10 second, and hypopnea was defined as an airflow reduction of at least 50% for 10 second plus 3% decrease in oxygen saturation, and development of arousal that lasted ≥10 second. AHI is defined as the total number of episodes of apnea and hypopnea per hour of sleep. A decrease in capillary O_2 saturation by ≥3% is referred to as desaturation. OSAS was classified according to the AHI as mild (5≤AHI<15), moderate (15≤AHI<30), and severe (30≤AHI) (10).

Biochemical measurements

Blood samples were collected from the antecubital vein at 8–10 AM after a fasting period of approximately 12 h. WBC counts, neutrophil levels, lymphocyte counts, MPV, and other hematological parameters were analyzed using an XN-1000 (Sysmex) Hematology Analyzer. NLR was calculated for each patient.

Statistical analysis

Data obtained in this study were analyzed using the IBM SPSS Statistics Version 20 package program.

Shapiro Wilk's test was used because of the unit numbers while investigating the normal distribution of variables. While interpreting the results, the level of significance was considered to be 0.05. In the case of p <0,05, it is stated that the variables do not come from the normal distribution, whereas in the case of p> 0,05, the variables come from the normal distribution.

Mann Whitney U and Kruskal Wallis-H Tests were used while analysing the variance between the groups, because the variables were not from normal distribution.

In the case of significant differences in the Kruskal Wallis-H test, the groups that differed with the Post-Hoc Multiple Comparison Test were identified.

Chi-square analysis was applied when relations between groups of nominal variables were examined. Fisher's Exact Test was used when the expected values in the cells of 2x2 tables did not have sufficient volume and Pearson Chi-Square analysis was applied with the help of Monte Carlo Simulation in R × C tables. While interpreting the results, the level of significance was considered to be 0.05; it was determined that there was a significant association if p<0.05, whereas there was no significant association if p>0.05.

RESULTS

The age of the patients in the study group was between 65 and 82 (mean age, 71.20; 52.3% male) years and that of the patients in the control group was between 27 and 63 (mean age, 45.26; 81.4% male) years. In total, 11.43% of the patients in the control group and 9.52% of those in the study group were excluded from the study as their AHI was <5. The severity of OSA in both of study and control population were divided into three groups by the AHI score: mild OSAS (study 11.9%, control 17.14%), moderate OSAS (study 20.24%, control 22.86%), and severe OSAS (study 58.33%, control 48.57%) groups. The severity of OSA was not significantly different between patients in both groups (p>0.05) (Table 1).

There was no statistically significant difference between two age groups in terms of BMI, AHI and NLR values (p>0.05). O_2 saturation values were found to be significantly lower in patients in the study group than in those in the control group (p<0.05). The ESS score was significantly higher in the study group than the control group (p<0.05) (Table 2).

Table 1. Chi-square test results for the association between groups and demographic information.

Variable		Groups						Chi-square test	
		<65 years		≥65 years		Total			
		n	%	n	%	n	%	Chi-square	p
Gender	Female	13	18.57	40	47.62	53	34.42	14.273	0.001
	Male	57	81.43	44	52.38	101	65.58		
	Total	100.0	100	84	100	154	100		
Severity of OSA (AHI)	<5	8	11.43	8	9.52	16	10.39	1.664	0.645
	5≤AHI<15, mild	12	17.14	10	11.9	22	14.29		
	15≤AHI<30, moderate	16	22.86	17	20.24	33	21.43		
	30≤AHI, severe	34	48.57	49	58.33	83	53.9		
	Total	100.0	100	84	100	154	100.0		

Table 2. Mann–Whitney U test results for differences between groups by values.

Vaiable								Mann–Whitney U Test		
		n	Mean	Median	Min	Max	sd	Mean Rank	z	p
BMI	<65 years	62	31.87	30.95	23	46.8	5.51	73.05	−1.13	0.258
	≥65 years	76	34.62	31.95	24	175	16.67	81.21		
	Total	138	33.37	31.2	23	175	12.9			
AHI	<65 years	62	36.13	29.3	0.9	107.4	27.81	71.5	−1.524	0.128
	≥65 years	76	43.59	40.75	0.8	128.5	30.39	82.5		
	Total	138	40.2	32.2	0.8	128.5	29.38			
O_2 SAT	<65 years	62	91.09	92	76	99	3.65	87.79	−2.628	0.009
	≥65 years	76	88.19	90	57	95	7.53	68.92		
	Total	138	89.51	91	57	99	6.23			
ESS	<65 years	62	4.51	4	0	13	3.58	65.54	−3.055	0.002
	≥65 years	76	6.54	6	0	18	4.08	87.46		
	Total	138	5.62	6	0	18	3.98			
MPV	<65 years	62	9.38	9.5	6.23	12	1.56	84.25	−1.715	0.086
	≥65 years	76	9.06	8.36	6.15	14.5	1.93	71.88		
	Total	138	9.2	9.09	6.15	14.5	1.78			
NLR	<65 years	62	2.21	1.89	0.78	7.2	1.22	79.94	−0.621	0.535
	≥65 years	76	2,17	1.87	0.84	7.62	1.22	75.46		
	Total	138	2.19	1.88	0.78	7.62	1.22			

In both groups, BMI of those with severe AHI was significantly higher than that of those with mild and moderate AHI ($p<0.05$). In both groups, O_2 SAT values were also significantly lower in patients with severe OSA than in those with mild or moderate OSA ($p<0.05$). The ESS score of patients with mild and moderate AHI was significantly lower than that of those with severe AHI in both groups ($p<0.05$).

Table 3. Kruskal–Wallis H test results between AHI and other values in ≥65 years group.

Variable			AHI						Kruskal Wallis H test		
			n	Mean	Median	Min	Max	ss	Mean rank	H	p
≥65 years	AGE	Mild	10	71.2	67	66	82	6.46	34.15		
		Moderate	17	72.88	72	66	82	4.97	47.26		
		Severe	49	70.41	69	65	82	4.12	36.35	3.572	0.168
		Total	76	71.07	70	65	82	4.71			
	BMI	Mild	10	29.93	30.25	25.8	33.6	2.57	24.95		
		Moderate	17	30.65	29.1	24	44.5	5.45	26.76		
		Severe	49	38.01	34.5	25.8	175	20.95	45.34	13.271	0.001
		Total	76	35.3	32.95	24	175	17.37			1-3 2-3
	O_2 SAT	Mild	10	91.3	92	86	94	2.63	51.9		
		Moderate	17	91.82	92	88	93	1.42	55.71		
		Severe	49	85.41	88	57	94	8.74	29.8	21.814	0.001
		Total	76	87.62	90	57	94	7.69			3-1 3-2
	ESS	Mild	10	4.9	6	0	10	2.92	28.1		
		Moderate	17	5.06	4	0	12	3.73	28.24		
		Severe	49	7.84	8	0	18	4	44.18	9.249	0.01
		Total	76	6.83	6	0	18	4.01			2-3
	MPV	Mild	10	9.4	8.3	6.34	14.5	2.71	38.5		
		Moderate	17	8.1	7.9	6.15	11.7	1.43	27.12		
		Severe	49	9.43	9.48	6.32	14.3	1.94	42.45	6.085	0.048
		Total	76	9.13	8.54	6.15	14.5	2.01			2-3
	NLR	Mild	10	2.23	2	1.14	4.44	1.2	40.05		
		Moderate	17	2.53	2	0.86	5.06	1.35	44.62		
		Severe	49	2.08	1.82	0.84	7.62	1.26	36.06	1.952	0.377
		Total	76	2.2	1.91	0.84	7.62	1.27			

Table 4. Kruskal–Wallis H test results between AHI and other values in <65 years group.

Variable			AHI						Kruskal Wallis H test		
			n	Mean	Median	Min	Max	ss	Mean Rank	H	p
<65 years	AGE	Mild	12	45.75	49.5	30	59	10.92	31.54	1.047	0.593
		Moderate	16	43.5	41.5	28	61	8.91	27.69		
		Severe	34	46.85	46.5	27	63	10.18	33.28		
		Total	62	45.77	45.5	27	63	9.95			
	BMI	Mild	12	28.89	28.2	24.6	35.7	3.43	20.38	7.216	0.027
		Moderate	16	31.47	30.8	25.4	40.5	4.41	29.53		
		Severe	34	33.95	32.45	24.3	46.8	6.09	36.35		
		Total	62	32.33	31.1	24.3	46.8	5.56			1-3
	O_2 SAT	Mild	12	92.75	92	91	95	1.22	43.33	14.83	0.001
		Moderate	16	92.06	92.5	87	95	2.29	39.31		
		Severe	34	89.29	89.5	76	99	4.17	23.65		
		Total	62	90.68	91.5	76	99	3.66			3-2 3-1
	ESS	Mild	12	2.17	1	0	8	2.92	16.88	20.066	0.001
		Moderate	16	3.44	3	0	10	2.61	23.25		
		Severe	34	6.5	6	0	13	2.94	40.54		
		Total	62	4.87	4.5	0	13	3.37			1-3 2-3
	MPV	Mild	12	9.15	9.15	7.06	11	1.3	29.17	6.773	0.034
		Moderate	16	8.49	7.98	6.23	12	1.84	22.56		
		Severe	34	9.78	10.15	7.13	11.9	1.51	36.53		
		Total	62	9.33	9.43	6.23	12	1.63			2-3
	NLR	Mild	12	2.29	2.01	0.78	7.2	1.66	30.29	0.467	0.792
		Moderate	16	1.94	1.88	1.06	2.74	0.43	29.44		
		Severe	34	2.47	1.93	0.98	5.4	1.35	32.9		
		Total	62	2.3	1.92	0.78	7.2	1.25			

When we evaluated the association between MPV and AHI, MPV of patients with moderate AHI in both groups was found to be significantly lower than that of those with severe AHI ($p<0.05$) (Table 3 and 4).

DISCUSSION

Obstructive sleep apnea is a multisystem disease in terms of its clinical symptoms and etiology. It requires joint evaluation by many branches. Nasal

obstruction, oropharyngeal entry obstruction, retrognathia, micrognathia, and inflammation are important factors in the pathophysiology of OSA. Polysomnography (PSG) is the gold standard test in the investigation of OSAS (1,11). According to the polysomnographic data, OSA is divided into the three groups with the AHI score as mild, moderate and severe.

There is no routine laboratory test that helps the diagnosis and eveluates the severity of OSAS. NLR and MPV are important mediators of the diagnostic value in inflammation. In similar studies, it has been reported that NLR and MPV increase with the severity of OSA (11-13). Hypoxia periods that occur during the night are believed to activate inflammatory pathways. But there is no enough information about the details of inflammation in OSA patients yet (11).

In their study, Yenigün et al. reported that an increase in NLR is correlated with the severity of OSA, and after 3 months of CPAP therapy, a decrease in this ratio is observed (8). Elimination of the hypoxic condition through CPAP therapy may lead to this decrease. Over time, studies showing NLR as an important indicator of inflammation in both cardiac and non-cardiac pathologies have been reported (14-16). Altıntaş et al. reported that NLR significantly increased in patients with severe OSA, but there were no differences among patients with mild and moderate OSA and healthy patients (17). Similarly, Oyama et al. reported that NLR increased in patients with severe OSA and this value decreased after 3 months of CPAP therapy (18). However, there are contradictory views. Korkmaz et al. studied CRP, ESR, and NLR in patients with OSA, and they reported that an increase in the severity of OSA is not correlated with these values (19). In our study, we found that NLR did not have a significant difference in patients with mild, moderate, and severe OSA in both groups.

In studies investigating the association between OSA and inflammation, MPV, a platelet activator indicator has been reported in the literature. In the study conducted by Akyol et al., it was pointed out that MPV is an increasing mediator also in OSA beside cardiovascular diseases (20). In apnea episodes that occur during night, platelets become active because of the secretion of epinephrine and norepinephrine with increased sympathetic activity associated with hypoxia (21). Similarly, in the study conducted by Varol et al., MPV were reported to be elevated in severe OSA (9). Present study may support the results of this study; MPV of patients with moderate OSA in both groups was found to be significantly lower than that of those with severe OSA.

There are studies that suggest that OSA frequency increases with age in geriatric patients (22). In our study, we found that the severity of OSA seems higher in an elderly population, but this result was not statistically significant. Of polysomnographic data, O_2 saturation values were found to be significantly lower in patients in the older group than in those in the control group. The ESS score was also significantly higher in the study group than the control group. Furthermore, O_2 SAT values were significantly lower and the ESS score was also higher in patients with severe OSA in both groups, The severity of OSA seems more likely to be due to comorbid conditions, such as hypothyroidism, DM, and cardiovascular diseases, and conditions such as weight gain; decreased pharyngeal muscle response against negative pressure, leading to increased upper airway collapse; or decreased airway width due to pharyngeal fat deposition (4, 22). In both of our groups, BMI of those with severe OSA was significantly higher than that of those with mild and moderate OSA. We used such comorbid conditions as exclusion criteria to strengthen the accuracy of the association between age and the severity of OSA.

In summary, we found that the severity of OSA was not associated with aging. We also found that NLR was not found to be significance as an inflammatory mediator in patients with

OSA. MPV also did not change with increasing age, but MPV increased as the severity of OSA increased. To our knowledge, this is one of the first study try to clarify the relationship between OSAS, age and inflammatory markers in geriatric patients.

The most important limitations of our study were that it was not prospective and a single-centered study. This study, which we conducted with a limited number of patients in our clinic, may only be a prediction of the general population. Secondly, new prospective studies need to be performed in the future to check whether there is a change in inflammatory markers in the blood of these patients after CPAP therapy. In future, there is a need for multi-centered, randomized, prospective, controlled studies with more patients.

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