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Research Article / Araştırma Makalesi

Long Term Mortality in Hospitalized Chronic Obstructive Pulmonary Disease Exacerbation: A Comparison of Multiple Indices

Hastanede Kronik Obstruktif Akciğer Hastalığı Ataklarında Uzun Dönem Mortalite: Çoklu İndekslerin Karşılaştırılması

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Abstract

The aim of this study is to identify the factors affecting mortality in patients with chronic obstructive pulmonary disease (COPD) hospitalized with exacerbation. A COPD cohort study was designed. Demographic data, the reason of mortality, Charlson co-morbidity index (CCI), COPD comorbidity index (COTE), age, dyspnea, airway obstruction (ADO) index, modified ADO index and dyspnea, airway obstruction, smoking, exacerbation (DOSE) index, and their relationship with mortality were investigated. One hundred and forty COPD patients hospitalized with exacerbation were included in the study. Eighty-seven (62.15%) of the patients were alive and 53 (37.85%) of them were deceased. The number of patients with CCI ≥ 7 was none in living patients and 11 (20.8%) in the deceased group (p<0.001). The percentage of treatment compliant patients during stable conditions was lower in the deceased group (p<0.001). ADO and COTE indices were significantly higher in the deceased group. There was no difference in modified ADO and DOSE scores between the groups. Multivariate analysis showed that lung cancer, CCI 7, hypoxemia (PaO2 <60 mmHg), and longer admission to the intensive care unit were independently associated with 3.4, 4.4, 2.1, and 3.0-fold mortality, respectively (p <0.05). Additionally, COTE ≥ 4 and noncompliance to regular COPD treatment were found to be associated with shorter survival in Kaplan Meier analysis (p<0.05). In conclusion, comorbidities and most notably lung cancer was associated with mortality in COPD. Also, high CCI and COTE index were risk factors for increased mortality.

Keywords: COPD, mortality, ADO, DOSE, COTE, CCI

Özet

Bu çalışmada amaç kronik obstrüktif akciğer hastalığı (KOAH) alevlenmesi ile hastaneye yatırılan olan hastalarda mortaliteyi etkileyen faktörleri belirlemektir. Bir KOAH kohort çalışması tasarlanmıştır. Demografik veriler, mortalite nedeni, Charlson komorbidite indeksi (CCI), KOAH komorbidite indeksi (COTE), yaş, dispne, hava yolu tıkanma (ADO) indeksi, modifiye ADO indeksi ve dispne, hava yolu tıkanması, sigara, alevlenme (DOSE) indeksi ve bunların mortalite ile ilişkisi araştırıldı. Çalışmaya KOAH alevlenmesi ile yatan 140 KOAH hastası dahil edildi. Hastaların 87'si (%62.15) hayatta iken 53'ü (%37.85) ölmüştü. Yaşayan hastalarda CCI ≥ 7 olan hasta yokken, ölen grupta 11 (%20.8) kişide CCI ≥ 7 idi (p <0.001). Stabil durumda tedaviye uyumlu hasta yüzdesi ölen grupta daha düşüktü (p <0.001). Değiştirilmiş ADO indeks yüzdesi ölen grupta daha düşüktü (p <0.001). Ölen grupta ADO ve COTE indeksleri anlamlı olarak daha yüksekti. Gruplar arasında modifiye ADO ve DOSE skorlarında fark yoktu. Çok değişkenli analiz, akciğer kanseri, CCI ≥ 7, hipoksemi (PaO2 <60 mmHg) ve yoğun bakım ünitesine daha uzun başvuru almasının sırasıyla 3.4, 4.4, 2.1 ve 3.0 kat mortalite ile bağımsız olarak ilişkili olduğunu gösterdi (p < 0.05). Ek olarak, Kaplan Meier analizinde COTE ≥ 4 ve düzenli KOAH tedavisine uyumsuzluğun daha kısa sağkalım ile ilişkili olduğu bulunmuştur (p <0.05). Sonuç olarak, komorbiditeler ve en belirgin olarak akciğer kanseri, KOAH'da mortalite ile ilişkili bulunmuştur. Aynı zamanda yüksek CCI ve COTE indeksleri de mortalite ile ilişkilidir.

Anahtar Kelimeler: KOAH, mortalite, ADO, DOSE, COTE, CCI

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1. Introduction

Chronic obstructive pulmonary disease (COPD) causes 3.2 million deaths worldwide comprising the third leading cause of death in 2017 and becomes in 2030 the third leading cause of death worldwide (1, 2). Systemic manifestations correlate with increased risk of mortality in COPD and may be considered surrogates of disease severity. There are several clinical surrogates such as airflow obstruction, age, dyspnea, malnutrition, exercise capacity, hypoxemia, lung hyperinflation and exacerbations that have long been evaluated for mortality prediction (3-5). Comorbidities are known as the major contributors in morbidity and mortality in COPD (6). The most prevalent comorbidities include anxiety/depression, heart failure, ischemic heart disease, pulmonary hypertension, metabolic syndrome, diabetes, osteoporosis, and gastroesophageal reflux disease (7).

Charlson comorbidity index (CCI) was introduced for classifying comorbidities as a valid method of estimating risk of death from comorbid conditions (8). Recently, Divo et al. described comorbidities strongly correlated with mortality in COPD patients named as 'COPD comorbidity (COTE) index' to form 'comorbidome' in COPD (9).

In recent years, several composite indices have been introduced to establish a multidimensional risk assessment of mortality. BODE (Body mass index, Obstruction, Dyspnea, Exercise capacity), ADO (Age, Dyspnea, Obstruction), DOSE (Dyspnea, Obstruction, Smoking, Exacerbation), and the several variants including BODEX (Body mass index, Obstruction, Dyspnea, Severe exacerbation) and CODEX (Comorbidity, Obstruction, Dyspnea, Severe exacerbation) indices are known in the studies (10, 11). This study was aimed to define the clinical prognostic markers and indices of exacerbated COPD patients for short and long term mortality.

2. Material and Methods

Subjects and Study Design

This is a retrospective COPD cohort study. A total of 753 patients were screened who were hospitalized under the diagnosis of COPD at the Department of Pulmonary Disease in Gazi University, School of Medicine between January 2000 and May 2011. Information of the patients was obtained through the patients' records and the electronic database of the hospital. The complete information was obtained in 324 COPD patients out of 753 scanned patient files. The patients with incomplete record and who were suspected of asthma were excluded from the study. Death status could be achieved in 168 of 324 patients whose files were obtained. The relatives of the patients who died were asked about the date and reasons of death verbally. Death information confirmed from hospital registration system. Considering the death dates of the patients and the years of COPD diagnosis, their lifespan with the disease were determined. Of the patients whose survival information was obtained, 140 of them who were treated at hospital due to exacerbation were included in the study.

Demographic data of the patients on admission period when they were included in the study (index date), dyspnea levels, smoking history, prebronchodilator pulmonary function tests (PFTs), comorbidities, the medication for COPD and comorbidities, long-term oxygen treatment (LTOT), the use of noninvasive mechanical ventilator (NIMV) at home and the the use of nebulizer were recorded from hospital records.

The technical steps in the use of the inhaler device could not be obtained. The patients and/or their relatives who were contacted through telephone were asked whether they were using inhaler medicine, whether they complied with the recommended period and dose, and whether they skipped any dose. The patients who used LTOT and NIMV were also

asked whether they complied with the recommended period and frequency.

The presence of comorbidities proven by patient's self-declaration or by medical records was obtained from the patients' reports and medical examination results. CCI and COTE were retrospectively calculated in the groups.

The number of exacerbations requiring antibiotic treatment and/or oral corticosteroid that they underwent the previous year, and the numbers of stays at hospital and intensive care unit for these reasons were recorded. The reasons for exacerbation at the patients' present hospitalization, arterial blood gas measured at room air at the moment of admission, the duration of hospital stay and the need for intubation and the intensive care unit admission were recorded. ADO, modified ADO, DOSE scorings were retrospectively calculated.

The effects of all the parameters on mortality and survival were assessed with the univariate, multivariate logistic regression model, Kaplan Meier and Cox regression model. The study was approved by the Gazi University School of Medicine, Institutional Review Board (Approval number: 248/2011).

Diagnosis, Definitions and Evaluation Tools

The diagnosis of COPD was established according to the Global Initiative for Obstructive Lung Disease (GOLD) Guideline in a stable condition (12). Accordingly, a forced expiratory volume in one second/forced vital capacity (FEV1/FVC) < 0.7 and a compatible medical history were required for the diagnosis (12).

PFTs were performed with Sensor Medics Vmax20 Spirometer in sitting position while wearing a noseclip. Three full inspiration and forced expiration maneuvers were performed according to the European Respiratory Society (ERS) Criteria. The recorded values were taken from the best of three forced expiratory measurements (13).

COPD exacerbation was defined as an increase of symptoms beyond the normal daily variability which need a treatment change. Exacerbations that need to be treated with oral corticosteroids and/or antibiotics were defined as moderate exacerbations. Two or more moderate exacerbations per year were defined as frequent exacerbation (14). Dyspnea was evaluated with modified Medical Research Council (mMRC) at the index admission (15). Infectious exacerbations were defined by Anthonisen's Criteria. According to this definition, the patient has to have at least one of the following three symptoms; increased dyspnea, increased sputum production and purulent sputum (14). Type I exacerbation (severe) is characterized by all of the three symptoms; Type II (moderate) is characterized by two of the three symptoms; Type III (mild) is characterized by only one of the three symptoms and at least one of symptoms related with upper airway infectious symptoms (14).

Lung conditions, such as pneumonia, pulmonary embolism, bronchiectasis and lung carcinoma, were defined by radiological findings and an appropriate clinical picture. Bronchiectasis was only recorded if there was a radiologically considerable amount of bronchiectatic lung area (16). CCI is an automatized method designed to determine for analytic purposes. In this method, the patients were classified in such a way as to take 1, 2, 3 and 6 points and the total score of the patients' combordities in this scale were categorized. With increased level of the comorbidity index, there were stepwise increases in the cumulative mortality attributable to comorbid disease (8).

COTE has been defined as a COPD specific index based on comorbidities that increase the risk of mortality. Similar to the CCI, a scale value points in the range of one to six point was assigned to each selected comorbidity in proportion to its Hazard Ratio (HR) (1-1.5=1, >1.5-2=2, and >2=6 points with an exception other cancers, which were assigned two points). A total score of 4 was chosen as a cut point as a predictor of increased mortality (9).

'Compliant patients' were defined as the patients who used the recommended dose of medicine during the recommended period and they did not skip any dose. 'Noncompliant patients' were defined as the patients who skipped doses or never used any medicine. The use of LTOT 16 hours or more a day was described as 'regular usage' and the use of LTOT less than 16 hours a day or when pushed for it was described as 'irregular usage'. The use of NIMV at least two hours three times a day was defined as 'regular usage' and the use of NIMV less than two hours a day or when pushed for it was defined as 'irregular usage'.

ADO index is calculated with the parameters of age, dyspnea (mMRC) and airway obstruction (FEV1) (17). Accordingly, patients take scores between 0 and 2, depending on the level of obstruction; between 0 and 3, depending on the degree of dyspnea; and between 0 and 5, depending on the age. Modified ADO index is calculated with the parameters of age, (mMRC) and airway obstruction (FEV1), too. Total score varies between 0 to 11. Unlike ADO index, however, patients take scores between 0 and 4, depending on the level of obstruction and between 0 and 7, depending on the age in modified ADO index. There is no difference between the scoring of both indices according to the degree of dyspnea. The total score varies between 0 and 14. Though the exact limits are not determined for both indices, the increased score points to the worsened prognosis (18). DOSE scoring is a scoring system that helps predict the important results such as COPD patients' hospitalization, respiratory insufficiency and exacerbation. Dyspnea (mMRC) is calculated by using the parameters of airway obstruction (FEV1), smoking and the number of exacerbations (19). Patients take scores between 0 and 3, depending on the degree of dyspnea; between 0 and 2, depending on the level of obstruction; between 0 and 1, depending on smoking, and between 0 and 2, depending on the number of annual exacerbations. The patients whose scores are equal to and higher than 5 bear high risks in terms of hospitalization and respiratory insufficiency (19).

Statistical Analysis

Analysis of the data was made with SPSS for Windows 15 package programme. The risk factors had statistically significant effects on distinguishing the surviving group and the dying group was analyzed with Univariate Logistic Regression Analysis, Pearson's Chi-Square or Fisher's Chi-Square Test. Multivariate Logistic Regression Analysis was researched with Bacward LR Test. The rate of odds for each variable and 95% confidence interval were calculated. Furthermore, the importance of the difference from the aspect of median values between the groups was analyzed with the Mann-Whitney U Test. Lifespan analysis was made with univariate Kaplan Meier, log-rank test. Lifespan analysis was made with the multivariate Cox regression analysis. The rate of hazard for each variable and 95% confidence interval were calculated. The results for $p<0.05$ were accepted as statistically significant.

3. Results

One hundred and forty hospitalized COPD patients with exacerbation in the ten-year period were examined in the study. It was found that 87 of them were alive, while 53 were dead. The etiology of deaths and the proportion of in-hospital or ex-hospital mortality were demonstrated in Figure 1. Thirty one patients (58.5%) died due to COPD while 10 patients (18.9%) died due to lung carcinoma.

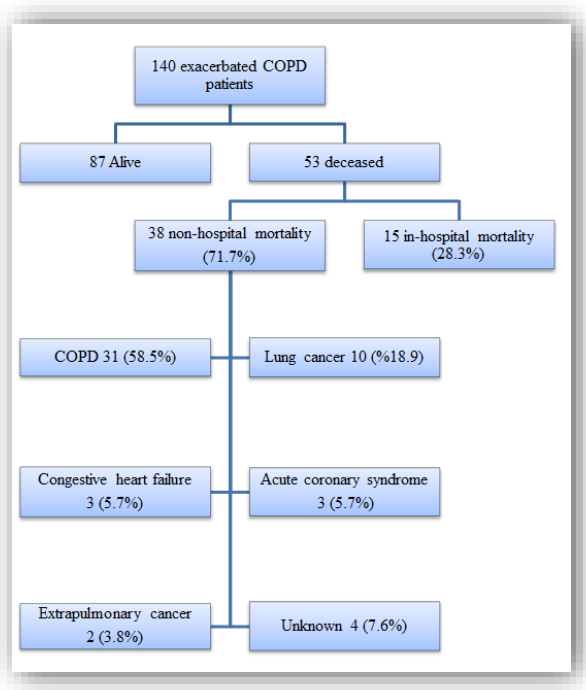


Figure 1. Distribution of death causes of 140 hospitalized COPD exacerbation patients.

CORD: *Chronic obstructive pulmonary diseaze*

Demographic data of both groups were analyzed (Table 1). None of the parameters had statistically significant effect on mortality with the univariate logistic regression analysis (p >0.05). Data on PTFs at index admission, were available in 81 (96.4%) of the alive patients and in 35 (79.5%) of the deceased patients. There was no statistically significant difference between the groups (p>0.05).

Comorbities were shown in Table 2. None of the alive patients had CCI ≥ 7. However, in deceased group, 11 (20.8%) patients had CCI ≥ 7. According to the univariate logistic regression analysis, the presence of lung cancer and high CCI increases mortality 3.4 and 4.4 times higher, respectively (p<0.001). The COTE index was significantly higher in deceased patients (p<0.001). The univariate analysis showed that high COTE score increases mortality 1.1 times higher (p=0.012).

Table 1. Demographic features of patients.

Variable	Alive (n=87)	Deceased (n=53)	p	OR (95% CI)
Age (years) (Mean ±SD)	68.7±8.7	71.2±9.4	0.122	1.555 (0.663-5.561)
Female n(%)	14 (16.1)	8 (15.1)	-	1.000[a]
Male n(%)	73 (83.9)	45 (84.9)	0.875	1.029 (0.728-1.454)
BMI (kg/m^2) (Mean±SD)	25.8±6.2	26.1±9.3	0.833	0.211 (0.936-2.498)
Smoking n(%)	73 (84.8)	48 (90.5)	0.337	0.585 (0.196-1.746)
Cigarettes pack/year (Median)(min-max)	50 (1-200)	59 (8-180)	0.311	1.005 (0.996-1.014)
Smoking status n(%)				
Never smoker	8 (9.3)	2 (3.8)	-	1.000[a]
Active smoker	19 (21.8)	8 (15.1)	0.229	2.800 (0.523-14.992)
Ex-smoker	51 (58.6)	36 (67.9)	0.216	2.776 (0.550-14.004)
Passive smoker	9 (10.3)	7 (13.2)	0.410	2.333 (0.310-17.545)
mMRC (Median)(min-max)	4 (1-12)	4 (2-4)		

OR: *Odds Ratio,* ***CI:*** *Confidence Interval,* ***BMI:*** *Body Mass Index,* ***mMRC:*** *modified Medical Research Council*
[a] *Reference category*
Odds ratios were calculated by univariate logistic regression analyses.

Table 2. Comorbidities in patients

Variables	Alive(n=87) n(%)	Deceased(n=53) n(%)	p	OR (95% CI)
Hypertension	53 (60.9)	29 (54.7)	0.485	1.290 (0.6686-2.576)
Hyperlipidemia	6 (7.0)	8 (15.1)	0.122	1.493 (0.804-2.773)
Arrhythmia	21 (24.1)	19 (35.9)	0.177	0.569 (0.7250-1.200)
ASHD	27 (31.2)	21 (39.6)	0.299	0.558 (0.336-1.400)
Congestive Heart Failure	27 (31.2)	20 (37.7)	0.415	1.123 (0.842-1.499)
Diabetes mellitus	23 (26.4)	18 (34.0)	0.343	1.152 (0.333-1.467)
Metabolic Syndrome	9 (9.4)	8 (11.1)	0.712	1.208 (0.442-3.303)
Chronic Kidney Disease	1 (1.0)	2 (2.8)	0.577	2.714 (0.241-30.531)
Sleep Disorders	3 (3.4)	4 (7.5)	0.280	1.621 (0.094-2.036)
Bronchiectasis	**26 (29.9)**	**7 (13.3)**	**0.024**	**2.801 (1.118-7.015)**
Malignancy	**9 (10.3)**	**20 (37.7)**	**<0.001**	**2.264 (1.299-3.948)**
Lung Carcinoma	**4 (4.6)**	**16 (30.2)**	**<0.001**	**3.458 (1.428-8.376)**
Non-Lung Carcinoma	5 (5.7)	4 (7.5)	0.674	1.127 (0.619-2.051)
CCI (Mean±SD)	**2.68±1.20**	**4.37±2.61**	**0.000**	**4.417(1.044-2.330)**
CCI			**<0.001**	**4.173 (1.246-9.455)**
≤3	68 (78.2)	24 (45.3)		
4-6	19 (21.8)	18 (34.0)		
≥7	-	11 (20.8)		
COTE index (Mean±SD)	**2.75±2.86**	**4.82±3.70**	**0.012**	**1.108(1.022-1.200)**
Number of Comorbidity	3 (0-8)	4 (0-9)	0.221	1.100 (0.915-2.291)

OR: *Odds Ratio,* ***CI:*** *Confidence Interval,* ***ASHD:*** *Atherosclerotic heart disease.* ***CCI:*** *Charlson comorbidity index,* ***COTE:*** *COPD comorbidity index.*
Odds ratios were calculated by univariate logistic regression analyses.

In stable condition 30.6% of the alive patients and 56% of the deceased patients were noncompliant to the inhaler medication. According to the univariate logistic regression analysis, noncompliance to medication and the use of short-acting anticholinergic was related with higher mortality (p<0.001). There were no effects of the comorbidity treatment drugs on mortality.

LTOT was prescribed for 47 (54.0%) of the alive patients and for 31 (58.5%) of the deceased ones. Home NIMW treatment was prescribed 12 (13.8%) of the alive patients and to 12 (22.6%) of the deceased ones. NIMW did not have a statistically significant effect on mortality (p>0.05). Irregular use of LTOT was related with higher mortality (p<0.05).

The median number of exacerbations in the previous year was one in the alive group, while it was two in the group of deceased patients (Table 3). Eighteen point three percent of the alive patients were followed in intensive care unit and so were 39.6% of the deceased ones. The difference was statistically significant (p=0.013). Intubation was present in 6 (6.9%) of the alive patients and in 12 (22.7%) of the deceased ones. The difference was statistically significant (p=0.015).

Table 3. Exacerbation features of patients in previous year.

Variables	Alive(n=87) n%	Deceased(n=53) n%	p	OR (95% CI)
Number of exacerbation (Mean±SD)	1.83 ±1.17	1.83 ±0.99	0.989	0.013 (-0.380 -0.348)
Number of exacerbation (Median) (min-max)	1 (1-4)	2 (1-5)	0.035	2.031 (2.021-2.577)
Patients who requires ICU	16 (18.3)	21 (39.6)	0.013	2.539 (2.059-2.849)
Patients who requires intubation	6 (6.9)	12 (22.7)	0.015	2.485 (2.035-2.515)
Exacerbation Frequency				
One	41 (47.1)	25 (47.2)	-	1.000 [a]
≥2	34 (39.1)	22 (41.5)	0.993	0.881 (-0.331 -0.385)

OR: *Odds Ratio,* ***CI:*** *Confidence Interval,* ***ICU:*** *Intensive care units,*
[a] *Reference category, Odds ratios were calculated by univariate logistic regression analyses*

Table 4 was contains the data about the exacerbation in index admission. While high C-reactive protein (CRP) (p=0.002), and erythrocyte sedimentation rate (ESR) (p=0.006) were risk factors, high PaO2 was protective for mortality (p=0.029). Intubation also increased the risk of mortality (p=0.020).

Table 5 contains the data about the ADO, modified ADO and DOSE indices for the index admission. High ADO index was a risk factor for increased mortality (p=0.026). Modified ADO index and DOSE index had no effect on mortality (p>0.05).

Table 4. Clinical features of exacerbation in index admission

Variables	Alive (n=87)	Deceased (n=53)	p	OR (95% CI)
ETBEH days (Median) (min-max)	10 (2-60)	10 (1-30)	0.012	0.951 (0.810-0.993)
Length of hospitalization (Median) (min-max)	11 (3-32)	11 (2-45)	0.180	0.986 (0.010-1.856)
Exacerbation type n (%)				
Anthonisen Type 1	39 (44.3)	35 (66.0)	0.241	1.705 (0.699-4.158)
Anthonisen Type 2	30 (34.1)	8 (15.1)	0,223	0.507 (0.170-1.511)
Anthonisen Type 3	19 (21.6)	10 (18.9)	-	1.000[a]
PaO_2 (mmHg) (Mean±SD)	62.1±11.6	57.2±16.6	**0.029**	**0.375 (0.353-0.998)**
$PaCO_2$ (mmHg) (Mean±SD)	41.9±11.5	43.9±10.9	0.317	1.017 (0.975-1.050)
	(n=74)	**(n=42)**		
CRP (mg/L) (Mean±SD)	14.7±18.1	35.0±42.6	**0.002**	1.025 (1.009-1.042)
	(n=74)	**(n=43)**		
ESR (mm/saat) (Mean±SD)	27.2±22.1	42.9±35.5	**0.006**	1.020 (1.006-1.034)
Intubated patients n (%)	6 (6.9)	12 (22.7)	**0.020**	1.201(1.018-1.214)

OR: *Odds Ratio,* ***CI:*** *Confidence Interval,* ***ETBEH:*** *Elapsed time between exacerbation and hospitalisation,* ***CRP:*** *C-Reactive Protein,* ***ESR:*** *Erythrocyte sedimentation rate.*
[a] *Reference category*
Odds ratios were calculated by univariate logistic regression analyses

Tablo 5. ADO, Modified ADO and DOSE indices distribution among the patients.

Variables	Alive(n=84) n%	Deceased(n=44) n%	p	OR (95% CI)
ADO index				
4-6	44 (75.9)	14 (24.1)	-	1.000[a]
≥7	40 (57.1)	30 (42.9)	**0.026**	**1.328(1.034-1.704)**
Modified ADO index				
≤ 9	30(68.2)	14 (31.8)		1.000[a]
≥ 10	53 (63.9)	30 (36.1)	0.626	1.068 (0.824-1.383)
DOSE index				
≤3	35 (41.7)	13 (31.9)	-	1.000[a]
4-6	45 (53.6)	27 (61.4)	0.276	1.543 (0.707-3.366)
≥7	4 (4.8)	3 (6.8)	0.427	1.929 (0.382-9.738)

OR: *Odds Ratio,* ***CI:*** *Confidence Interval,* ***ADO:*** *Age, Dyspnea, Obstruction* ***DOSE:*** *Dyspnea, Obstruction, Smoking, Exacerbation*
[a] *Reference category*
Odds ratios were calculated by univariate logistic regression analyses

Multivariate Logistic Regression Analysis for Mortality

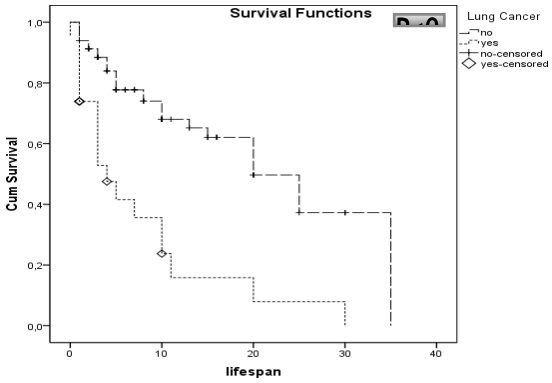
Multivariate logistic regression analysis showed that the patients developed lung cancer increased mortality independently by 2.58 times (p=0.011, CI [0.084-0.636]); PaO2 < 60 mmHg increased mortality independently by 2.17 times (p=0.031, CI [0.001-0.012]); CCI ≥ 7 increased mortality independently by 1.06 times (p=0.041, CI [0.011-0.310]); and ICU admission more than 14 days increased mortality independently by 3.09 times (p=0.002, CI [0.074-0.338]).

Survival Analysis

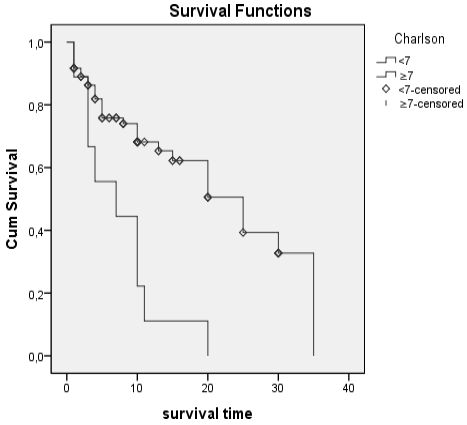
The mean period of follow-up in whole cohort was 79.3±69.9 months. The lifespan of the survivors was 86.4±72.6 months, while it was 67.6±64.2 months in who did not survive. The death rate in the index admission was 2.5%. The 6 and 12-month mortality rate was 5%. The 24-month mortality was 12%; the 60-month mortality was 28%; and the 120-month mortality rate was 44%.

Kaplan Meier Analysis

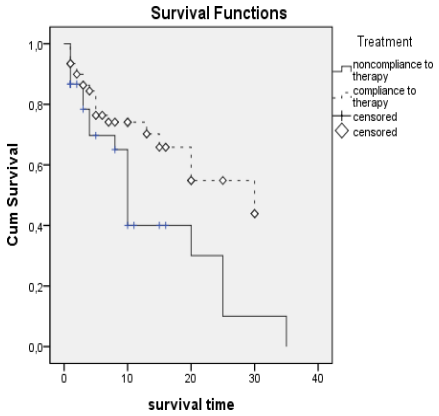
Kaplan Meier survival analysis results are demonstrated in Table 6. Age and sex did not affect the survival. Patients with COPD who develop lung cancer have two times shorter survival than those without lung cancer. COTE≥4 was associated with significantly decreased survival. The average survival with COPD of those who received a regular treatment and who had no criteria of respiratory insufficiency (PaO2≥60 mmHg) was statistically longer than the that of the patients who did not use a regular inhaler treatment and who had criteria of respiratory insufficiency (p=0.025, p=0.024, respectively) (Figure 2).



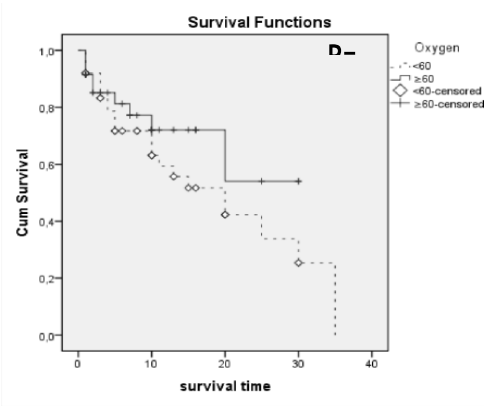
(A)+Lung cancer (p<0.001)



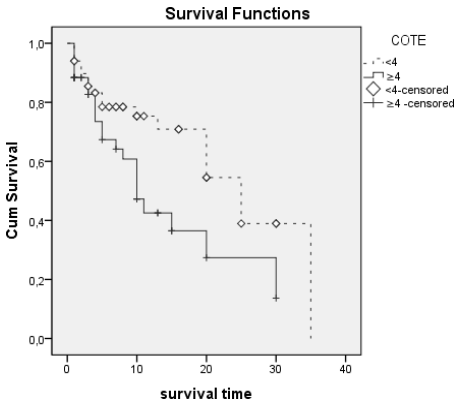
(B) Charlson Comorbidity Scores (p=0.001)



(C) Noncompliance to treatment (p=0.025)



D) Low arterial partial oxygen level (p=0.024)



(E) COTE index (p<0.001)

Figure 2. Kaplan Meire Analysis showed (A) lung cancer (p<0.001), (B) Charlson comorbidity index (p=0.001), (C) noncompliance to treatment (p=0.025), (D) low arterial partial oxygen level (p=0.024) and (E) COTE (p<0.001) were related with survival.

Table 6. The life span of variables that are analyzed by univariate (Kaplan Meier)

Variables	Lifespan (month) (Mean±SD)	Lifespan (month) (Median) (min-max)	p
Age group			
≤60 years (n=21)	57.71 ±40.80	60 (0-132)	0.124
>60 years (n=119)	83.19±73.38	60 (0-372)	
Gender			
Female (n=22)	98.72±83.05	84 (0-288)	0.158
Male (n=118)	75.76±67.03	60 (0-372)	
Lung cancer			
No (n=120)	86.0±72.6	66 (0-372)	**<0.001**
Yes (n=20)	39.6±29.1	36 (0-96)	
CCI			
0-3 (n=92)	82.56 +78.18	48 (0-372)	0.192
4-6 (n=37)	82.37+78.18	48 (0-324)	
≥7 (n=11)	42.54±27.02	36 (12-96)	
Compliance to medication			
No (n=54)	64.44+63.89	48 (0-324)	**0.025**
Yes (n=81)	92.14+72.93	72 (0-372)	
PaO_2			
≥60 mmHg (n=58)	85.03+71.97	72 (0-372)	**0.024**
<60 mmHg (n=68)	82.76+71.19	60 (0-324)	
CRP			
0-6 mg/L (n=38)	84.31±74.15	60 (0-252)	0.666
>6 mg/L (n=65)	78.27±64.76	60 (0-324)	
ADO index			
≤6 (n=58)	73.03±63.54	66 (0-372)	0.124
≥7 (n=70)	92,05±75.61	66 (0-324)	
COTE index			
<4 (n=50)	11.22±9.25	9 (1-35)	**0.019**
≥4 (n=43)	7.84±7.29	5 (1-30)	

CCI: *Charlson Comorbidity index,* ***CRP:*** *C-reactive protein,* ***ADO:*** *Age, Dyspnea, Obstruction Index,* ***COTE****: COPD comorbidity index*

4. Discussion

In this retrospective cohort study in which an average 6.5-year-long term follow-up was conducted, the factors affecting the long- and short-term mortality after COPD exacerbation were analyzed with multiple statistical methods. While the six-month mortality was 5%, the five-year mortality was 28%. While the reason was COPD in 58.5% of the deaths, it was lung cancer in 18.9%. The best predictor of mortality was lung cancer, while high CCI (≥7) and COTE (≥4) co-morbidity scores, non compliance to treatment, low PaO2 (<60 mmHg) value and long stay in ICU (≥ 14 days) were among the other independent risk factors.

Hospitalization for severe exacerbations represents a major predictor of mortality (5). Short-term mortality due to severe COPD exacerbation varied from 2.5% and 15% to 24% due to different settings. ICU admission remarkably increased the risk of mortality (20-22). Medium and long-term survival decreased after severe exacerbations. In Canada, a cohort study included 73,106 patients hospitalized for COPD exacerbation, showed a mortality rate of 50% and 75% at 3.6 and 7.7 years, respectively (23). The strongest mortality predictors were non-respiratory organ system dysfunction and severity of the underlying respiratory function (22). Mortality reports from Turkey were scarce, revealing 17.8% in 5 years in outpatient setting and 39% in 3 years following exacerbations (24).

The cause of death in COPD varied in severity of different diseases. In the mild-to-moderate diseases, cardiovascular reasons and the lung cancer are the leading cause of death; however, respiratory failure is the most common reason (25). The recent landmark studies showed that non-respiratory reasons of death are greater than respiratory reasons. The main non-respiratory reasons were cancer and cardiovascular diseases (26, 27). Our cohort consisted of severe COPD cases with severe exacerbation. The mean FEV1 was approximately 40%, and the information about the etiology of mortality originated from verbal autopsy. Therefore, we did not exactly know whether the consideration of respiratory death in 58% of the patients was misclassified or not. The second most attributed reason was lung cancer, which was not surprising in that population. Lung cancer was the most powerful predictor of the mortality according to several statistical methods.

Several prognostic parameters such as age, sex, body mass index (BMI), smoking, functional status, comorbidities, exacerbations, respiratory physiology, and biomarkers were studied in stable and exacerbation settings. Some studies found that older age was a poor prognostic marker in exacerbation setting, while others were contrasting with these results (8, 13, 16, 19). Low BMI (<20 kg/m2) and more specifically low fat free mass index were also found to be independently related with poor prognosis in large patient cohorts (15). In our study age, BMI, smoking, dyspnea levels, spirometric values and the number of the previous exacerbations were not associated with mortality; therefore, the multidimensional indices (ADO, modified ADO and DOSE) did not reveal any statistical significance. This may be best explained by the uniformity of patients' demography and the severity of the disease described by FEV1 or dyspnea level in a single center setting.

Our study was composed of exacerbated patients and the major impacts in prognosis were the presence of lung carcinoma, low PaO2 in index admission, and the presence of previous ICU admission, high CCI and COTE scores and nonadherence to therapy. Although cardiovascular diseases were the most frequent comorbidities in the whole cohort, lung carcinoma was more frequent in decent patients (28). CCI was related with mortality in COPD patients (29). The mean CCI was 2 times more in decent patients in our cohort. The score ≥7 was found to be associated with mortality in our cohort. More recently COTE was introduced as a COPD specific comorbidity score and was found to be related with increased mortality (9).

Although this study showed several remarkable issues, this was a retrospective and single center study with potential selection bias. The comorbidity evaluation and compliance to regular COPD treatment was based on self-reporting and patient records. The proactive approach was not applied for systematic evaluation. The mortality record was completed in the relatively small number of the entire cohort and related to the patient's called. This the limited factor for this research. Also, since the study is a retrospective study, there may be error in the assessment of infectious exacerbations and in determining the exacerbation severity.

In conclusion, the current results showed that the short and long term mortality in COPD was related with comorbidities in particular with lung carcinoma and respiratory insufficiency indicated by hypoxemia. Also, high CCI and COTE indices were a risk factor for increased mortality.

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Research Article / Araştırma Makalesi

The Effectiveness of Home Based Pulmonary Rehabilitation in Elderly Patients with COVID 19 Infection

COVID 19 Geçirmiş Geriatrik Hastalarda Ev Temelli Pulmoner Rehabilitasyonun Etkinliği

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Abstract

While Coronavirus disease-2019 (COVID-19) affects the whole world, most affected group is geriatric individuals. There is a need for strategies for geriatric individuals returning to society and their social life. The aim of this study is to investigate the effect of an 8-week home-based Pulmonary Rehabilitation program on quality of life, depression, anxiety and functional capacity in geriatric individuals with COVID-19. Twenty-five patients were included in this prospective study. Patients over 65 years of age with COVID-19 were evaluated. Physical capacity with the 6-minute walking test (6MWT), dyspnea status with the Medical Research Council Dyspnea Scale, quality of life with the Short Form-36 (SF-36), depression and anxiety with the Hospital Anxiety and Depression Scale were evaluated. The mean age of the patients included in the study was 68.9 ± 6.4 years. 56% of the patients were men and 44% were women. When pre-treatment and post-treatment values were compared, a significant improvement was found in the 6MWT, dyspnea scores, SF-36 and all subgroups, anxiety and depression scores ($p < 0.05$). This study shows that the home-based Pulmonary Rehabilitation program is an effective method on parameters such as quality of life, depression and physical capacity in geriatric individuals with COVID-19. Prospective large-scale studies are needed to validate our current results.

Keywords: Covid-19; pulmonary rehabilitation; quality of life

Özet

Coronavirüs hastalığı-2019 (COVID-19) tüm dünyayı etkilerken en çok etkilenen grup geriatrik bireylerdir. Geriatrik bireylerin topluma ve sosyal yaşamlarına dönmeleri için bazı stratejilere ihtiyaç vardır. Bu çalışmanın amacı, COVID-19'lu geriatrik bireylerde 8 haftalık ev temelli Pulmoner Rehabilitasyon programının yaşam kalitesi, depresyon, anksiyete ve fonksiyonel kapasite üzerine etkisini araştırmaktır. Bu prospektif çalışmaya 25 hasta dahil edildi. COVID-19 geçirmiş 65 yaş üstü hastalar değerlendirildi. Fiziksel kapasite 6 dakikalık yürüme testi (6DYT) ile, dispne durumlar Medical Research Council Dispne Skalası ile, yaşam kalitesi Kısa Form-36 (KF-36) ile, depresyon ve anksiyete durumları ise Hastane Anksiyete ve Depresyon Ölçeği ile değerlendirildi. Çalışmaya dahil edilen hastaların ortalama yaşı 68.9 ± 6.4 idi. Hastaların% 56'sı erkek,% 44'ü kadındı. Tedavi öncesi ve tedavi sonrası değerler karşılaştırıldığında 6DYT, dispne skorları, SF-36, anksiyete ve depresyon skorlarında anlamlı iyileşme saptandı ($p < 0.05$). Bu çalışma, ev tabanlı Pulmoner Rehabilitasyon programının COVID-19'lu geriatrik bireylerde yaşam kalitesi, depresyon ve fiziksel kapasite gibi parametreler üzerinde etkili bir yöntem olduğunu göstermektedir. Mevcut sonuçlarımızı doğrulamak için ileriye dönük büyük örneklem büyüklüğüne sahip çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Covid-19; pulmoner rehabilitasyon; yaşam kalitesi

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1. Introduction

Coronavirus Disease 2019 (COVID-19) is an infectious disease that was identified in Wuhan, China in late December 2019. This disease has affected many countries and millions of people with high infectiousness rates (1). Although many people with COVID-19 undergo the disease mildly and without complications, approximately 5% of patients are admitted to Intensive Care Units (2). COVID-19 mainly affects the respiratory system; however, it can also cause physical, psychological, and systemic involvements. Although COVID-19 is a threat to the general population, it is also known to affect the elderly more in particular (3). It is considered to be more mortal in people with underlying diabetes, hypertension, cardiovascular disease and cerebrovascular disease (4, 5). It is already known that elderly and people with comorbidities have higher morbidity and mortality; however, there are not enough data on how the return to the society and integration of the survivors will be. It is considered that supportive rehabilitation programs can be used during this period.

The purpose of Pulmonary Rehabilitation (PR) is to reduce the physical and psychological symptoms of individuals with pulmonary disease-related disabilities, improve their quality of life, and ensure that they return to the highest functional capacity possible (6,7). Most PR programs are performed under the supervision of a healthcare professional. Home-based PR has been proposed as an alternative to hospital-based programs.

PR is important as COVID-19 is a respiratory infection. Many experts recommend PR programs to improve respiratory, physical and psychological impairments in COVID-19 patients (8, 9) While COVID-19 continues to affect the whole world, online exercise programs and home-based exercise programs are becoming more preferable as access to health resources can be restricted (10). There are not adequate data on the effectiveness of PR in patients with COVID-19. In this study, our purpose is to examine the effect of home-based PR program on quality of life, depression, anxiety, functional capacity in geriatric patients with past COVID-19.

2. Patients and Methods

Geriatric patients with COVID-19 infection who were admitted to our clinic PR Unit were included in this study. The criteria for being included in the study were as follows; 1) Being diagnosed with COVID-19, 2) being 65 years of age or older, 3) having a mini-mental status score of >21, 4) not having any other chronic respiratory disease (such as COPD), 5) not having moderate or severe heart disease, 6) not having a condition that would prevent participating in the rehabilitation program (psychiatric, neurological). Before the study was initiated, approval was obtained from the local ethics committee (approval number 2021/08), and the study was conducted according to the Helsinki Declaration. Written informed consent was obtained from all participants included in the study.

Participants

At first, 36 patients were included in the present study. A total of 11 patients did not meet the inclusion criteria. Six patients did not meet the inclusion criteria, 5 patients did not give consent to participate in the study.

Assesment

The socio-demographic and clinical data of the patients were obtained from patient files. The clinical data of the patients before and after the treatment were recorded from patient files. The patients were taken to an 8-week home-based PR program. All patients were given detailed information on the PR Program, and informed consent forms were obtained. Weekly phone calls were made to increase the exercise compliance of the patients. Physical examinations and clinical evaluation scales of all patients were done by the same doctor before and after the rehabilitation program (in the 8thweek).

Evaluation of Physical Capacity

The exercise capacity measurement of the patients was done with a 6-Minute Walking Test (6MWT). Patients, who rested for 10 minutes before the test, walked on a specially marked 20-meter corridor. At the end of 6 minutes, the distance was recorded in meters (11).

Evaluation of Dyspnea Status

The dyspnea status was recorded from patient files and were then evaluated with medical research council dyspnea scale (MRC) measured scores.The MRC is a scale in which patients choose the expression that best describes their dyspnea levels, out of five statements on dyspnea status. High scores in MRC show higher dyspnea perception (12).

Evaluation of Depression and Anxiety Status

Hospital Anxiety and Depression Scale (HADS) scores, which are used to evaluatethe anxiety and depression levels of patients, were recorded from patient files. HADS consists of a total of 14 items, each of which is scored in the range of 0-3 points. High scores show the presence of more severe anxiety and depression (13).

Evaluation of Quality of Life

Quality of life was evaluated with Short Form-36 (SF-36). The SF-36 consists of 8 different sub-scales, which are; physical function, social function, pain, restriction due to emotional problems, mental health, general health perception, energy/fatigue and physical problems (14). Each subscale is scored between 0 and 100, and the height of the score shows better quality of life.

PR Program

Participants underwent a home-based respiratory rehabilitation program 3 days a week for 8 weeks in addition to clinical treatment and recommendations related to COVID-19. Before the respiratory rehabilitation program started, patients were informed about general precautions, such as exercise habits and smoking. All patients were given a standard exercise program by the same doctor. Also, all patients were given a brochure and video recording containing the exercise program by the same doctor. The same doctor made weekly phone calls for 8 weeks to provide standardization and identify problems. Exercise program consisted of pursed lip breathing, bending forward posture, diaphragmatic breathing (abdominal breathing), relaxation exercises, upper extremity-shoulder girdle exercises, and endurance exercises.

In pursed lip respiration, the patient breathes from his/her mouth for a few seconds, and then gradually exhales from his/her mouth in whispering position. S/he then sits in forward-leaning posture (a forward tilt position of 20-45 degrees according to the vertical axis), and in this way, does pursed lip respiration.

In the diaphragmatic breathing technique, the patient lying in the supine position puts the dominant hand on the upper-middle of the abdomen andnon-dominant hand on the anterior-upper of chest area.S/he then breathes through the nose, gradually exhales with pursed lip respiration. During this procedure, while the hand on the chest does not move as much as possible, the diaphragm is moved to the abdomen as loose as possible. During inspiration, the patient feels that the abdomen rises despite the motionless status of the rib cage. The patients were told about the exercise program consisting of breathing muscles exercises, upper extremity-shoulder girdle exercises and endurance (resistant aerobic) exercises. They were also told to do gravity resistance exercises with 1-2kg weights for upper extremity-shoulder girdle muscles (subclavius, pectoralis major and minor, serratus anterior, trapezius upper and lower part, latissimus dorsi, sternocleidomastoid muscles) to be performed 3 times a week.

Statistical analysis

When the findings of the study were evaluated, the Statistical Package for Social Sciences (SPSS, Inc.; Chicago, IL, USA) for Windows 15.0 Program was used for statistical analyses. Clinical parameters were evaluated twice, before and after the treatment. “One Samples T test” was used to

calculate group averages, and "Paired Sample T Test" was used to compare pre- and post-treatment data. The data was expressed as mean ± standard deviation from the average data. Statistical significance level was considered to be $p < 0.05$.

3. Results

The mean age of the 25 patients who were included in the study was 68.9±6.4 years. Among the patients, 14 were male and 11 were female; the sociodemographic data are shown in Table 1.

When the pre- and post-treatment values were compared, significant improvements were detected in anxiety and depression scores, 6MWT, dyspnea, SF-36 and all sub-groups ($p<0.05$). Pre- and post-treatment values are shown in Table 2.

Table 1. Sociodemographic data of the patients

Age (years) (Mean±SD †)	68.9 ± 6.4
Body Mass Index (kg/cm^2)	26.8 ± 3.9
Marital Status	
Married (n/%)	16/ 64
Single (n/%)	9/ 36
Gender	
Male (n/%)	14/56
Female (n/%)	11/44
Smoking	
Yes (n/%)	3/12
No (n/%)	22/88
Comorbidity	
Hypertension (n/%)	11/44
Diabetes Mellitus (n/%)	8/32
Osteoporosis (n/%)	6/24

†: Standard Deviation

Table 2. Comparison of pre- and post-treatment values

	Pre-treatment Mean ± SD	Post-treatment Mean ± SD	P
MRC †	3.1 ± 0.9	1.9 ± 0.3	< 0.001
6MWT ‡	112.7 ± 61.0	183.3 ± 72.1	< 0.001
SF-36 §-physical health	58.4 ± 6.2	72.6 ± 5.9	< 0.001
SF-36 §-social function	56.0 ± 4.2	74.2 ± 3.8	<0.001
SF-36 §-pain	59.2 ± 6.4	78.7 ± 5.8	< 0.001
SF-36 §-emotionel function	59.5 ± 3.3	72.7 ± 7.2	< 0.001
SF-36 §-mental health	61.7 ± 6.8	76.5 ± 7.9	< 0.001
SF-36 §-energy	62.8 ± 4.3	79.2 ± 3.6	< 0.001
SF-36 §-general health status	63.2 ± 6.4	73.9 ± 5.7	<0.001
Anxiety score	54.7 ± 7.3	43.4± 7.9	<0.001
Depression score	55.8 ± 5.2	41.5 ± 9.2	<0.001

†: Medical Research Council Dyspnea Scale, ‡: 6 Minute Walking Test, §:Short Form-36

4. Discussion

According to our present data, this study is the first to show the effectiveness of the home-based exercise program in geriatric individuals who underwent COVID-19. We found significant improvements in physical capacity, anxiety, depression, dyspnea and quality of life scores with the 8-week home-based PR program.

It is not clear whether permanent lung and/or physical damage will prevail in people with COVID-19 pneumonia. However, in those who are particularly elderly and who need intensive care hospitalization, limitations may occur in terms of respiratory functions and gas exchange (15). It is considered that this disorder in respiratory function may be because of some residual fibrotic lesions (16). In this context, many people who have COVID-19 will need PR programs.

PR programs are used as part of the treatment programs in many respiratory system diseases, especially in Chronic Obstructive Pulmonary Disease (COPD). There are no adequate data on PR practices in people who have COVID-19. Liu et al. applied a hospital-based PR program for 6 weeks in geriatric individuals with COVID-19. At the end of 6 weeks, they found significant improvements in pulmonary functions and physical capacities of their patients (17). Similarly, in our study, we also found significant improvements in physical capacity. Long-term inactivity and muscle pain are the most important problems in people with COVID-19. Similarly, the most important factors that limit physical capacity in COPD patients were shown to be muscle fatigue rather than dyspnea (18). In cases of immobilization such as bed rest in the skeletal muscle, motor loss, decrease in muscle mass, and in physical capacity occur (19). Reidy et al. (20) found that even a decrease in the number of daily steps in geriatric individuals was associated with muscle strength. Isolation, quarantine and subsequent muscle pains in people with COVID-19 might be the factors reducing muscle strength. Replacing this decreased muscle strength is very important for increasing physical capacity and ensuring quality of life. The present study showed that physical capacity and quality of life increased with home-based PR program. The effect of PR on increased physical capacity and improvements in quality of life is related to the changes in gas exchange, ventilation, cardiovascular function, and skeletal muscles.

The COVID-19 pandemic continues to have effects both in psychological and physical terms. As with SARS and MERS viruses, viral infections and subsequent quarantine period may result in depression and anxiety disorder (21). Covid-19 patients who have psychiatric comorbidities have longer hospitalization periods and difficulty in healthcare services with increased medical costs (22). The positive effect of PR programs on anxiety and depression scores is known (23, 24). In our study, anxiety and depression scores decreased at significant levels with PR. Similarly, Liu et al. found significant decreases with PR in depression and anxiety scores (17). This improvement is very important for people to return to normal lives and for their motivations.

Although most PR applications are performed under the supervision of a healthcare professional in a hospital setting, home-based exercise programs are used less frequently (25). Difficulty in accessing PR programs is an important factor in less use of this intervention (26). As the COVID-19 pandemic continues in full speed, we believe that it may be more possible to spread home-based exercise programs and PR programs. Although no economic analyses have been done so far, it is clear that home-based PR programs will be cheaper than hospital-based PR programs. As the number of people affected by the pandemic increases, we believe that home-based PR programs might be more appropriate to relieve the demand for healthcare and related costs.

There are some limitations in this study. The number of patients was relatively small, and there were no long-term follow-ups. In addition, the clinical characteristics of the patients, such as disease severity, were not questioned. Long-term follow-up studies with larger number of patients are needed in future studies.

As a conclusion, home-based PR programs have positive effects on physical capacity, quality of life, anxiety, and depression in elderly individuals with COVID-19.

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Research Article / Araştırma Makalesi

Unipolar Depresyon ve Bipolar Duygu Durum Bozukluğunda Serum Magnezyum Düzeylerinin Değerlendirilmesi: Retrospektif Bir Çalışma

Evaluation of Serum Magnesium Levels in Unipolar Depression and Bipolar Affective Disorder: A Retrospective Study

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Özet

Magnezyum sinir sisteminin işleyişinde önemli rolü olan bir elementtir. Bu çalışmada unipolar depresyon ve bipolar duygudurum bozukluğu tanısı olan hastalarda serum magnezyum düzeylerinin araştırılması amaçlanmıştır. Psikiyatri polikliniğine başvurusu olan hastaların kayıtları retrospektif olarak taranarak, serum magnezyum düzeyleri bakılmış olan 49 depresif bozukluk ve 21 bipolar duygu durum bozukluğu olan hasta çalışma grubu olarak, herhangi bir psikiyatrik hastalığı bulunmayan 50 kişi ise kontrol grubu olarak toplandı. Hem unipolar depresyonu olan hastalarda hem de bipolar duygu durum bozukluğu olanlarda kontrol grubuna kıyasla daha yüksek serum magnezyum düzeyleri saptandı. Unipolar depresyon ve bipolar duygu durum bozukluğu arasında ise anlamlı farklılık saptanmadı. Unipolar depresyon ve bipolar duygu durum bozukluğunda serum magnezyum düzeylerinin yüksek bulunması, magnezyumun bu hastalıkların patofizyolojisinde önemli olabileceğini göstermekte olup, potansiyel bir biyomarker olabileceğine işaret etmektedir.

Anahtar Kelimeler: Depresyon; bipolar bozukluk; magnezyum; duygu durum bozukluğu

Abstract

Magnesium is an element that plays an important role in the functioning of the nervous system. The aim of this study was to investigate serum magnesium levels in patients with unipolar depression and bipolar disorder. The records of the patients who applied to the psychiatry outpatient clinic were retrospectively reviewed. Forty-nine patients with depressive disorder and 21 patients with bipolar mood disorders and 50 subjects without any psychiatric disorder that serum magnesium levels were studied previously were involved in the study. Both patients with unipolar depression and bipolar mood disorder had higher serum magnesium levels than the control group. There was no significant difference between unipolar depression and bipolar disorder. High serum magnesium levels in unipolar depression and bipolar mood disorder show that magnesium may be important in the pathophysiology of these diseases, indicating that it may be a potential biomarker.

Keywords: Depression; bipolar disorder; magnesium; mood disorders

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1. Giriş

Elektrolitler, duygu durum bozukluklarının patofizyolojisinde yer alan monoaminlerin metabolizmasında önemli rol oynarlar (1). Magnezyum en fazla bulunan ikinci hücre içi katyon olup yüzlerce enzimin de kofaktörüdür (2). Ayrıca hücre döngüsünde, karbonhidrat, protein, yağ ve nükleik asit metabolizmasında yer alır, hücre memran geçirgenliğinden ve hücre göçünden kısmen sorumlu olup, DNA, RNA ve glutatyon sentezi, ATP üretimi ve kullanımı, nöromusküler iletim, kemik mineralizasyonu, kan glukoz kontrolü ve kan basıncı düzenlenmesinde görev alır (3). Magnezyumun özellikle santral sinir sistemi için de önemli görevleri bulunmaktadır. Adrenerjik ve serotonerjik reseptörlerin normal işlevlerini gösterebilmeleri için gerekli olan tirozin ve triptofan hidroksilazın kofaktörüdür. Ek olarak 5-HT-1a serotonin reseptör transmisyonunda direkt etkisi olduğu da bildirilmiştir (4,5). Magnezyum santral sinir sisteminde N-metil D-aspartat (NMDA) reseptör kanallarını bloke eder (6). Ekstrasellüler magnezyum düşüklüğü NMDA dizinhibisyonuna bağlı olarak, santral hipereksitebiliteyi artırır (7) ve aynı zamanda magnezyum, NMDA reseptör kompleksinin alt ünitesi olan GluN2B ekspresyonunu da artırır (3). Magnezyum iyonları nöronal NMDA kanallarındaki kalsiyum iyonlarını regüle eder ve bu da nöronal nitrik oksit üretimini düzenlemeye yardımcı olur. Düşük magnezyum konsantrasyonu olması durumunda nöron içine kalsiyum akışı artar ve patolojik miktarlarda nitrik oksit üretimi olur. Post sinaptik bölgedeki artmış nitrik oksit üretimi ise presinaptik uçlara yayılarak depresyon gibi çeşitli patolojik durumlara yol açabilir (8). Magnezyum prefrontal kortekste BDNF ekpresyonunu artırır, ek olarak hipokampal ateşlemeyi baskılar ve prefrontal kortekste protein kinaz c yolağını düzenler (9). Bütün bu fonksiyonlar depresyon patofizyolojisinde önemli mekanizmalardır. Magnezyumun antienflamatuar yanıtta ve uyku üzerinde de etkili olduğu bildirilmektedir (10).

Hipokampüsteki düşük magnezyum düzeyleri ve kalsiyum ve glutamat düzeylerindeki artışın duygu durum bozukluklarının gelişmesine yol açtığı düşünülmektedir (9). Üstelik rutin klinik uygulamalarda da magnezyum oldukça kolay ölçülebilmektedir (11).

Santral sinir sistemindeki önemli görevleri olması ve kandan kolaylıkla ölçülebilmesi sebebiyle de magnezyum ile psikiyatrik hastalıkların ilişkisi araştırmacıların ilgisini çeken bir konu olmuştur. Yapılan çalışmaların bir kısmında magnezyumun diyetle kısıtlı alımının depresyonla ilişkili olduğu gösterilmiştir (12,13) Hatta depresyonda tedaviye magnezyum eklemenin olumlu katkısı olduğunu bildiren çalışmalar da mevcuttur (14,15). Ancak hala duygu durum bozukluklarında magnezyum düzeyinde düşüş mü yoksa artış mı olduğu konusu net değildir. Bazı çalışmalar düşük magnezyum düzeyinin depresyon için potansiyel bir marker olduğunu söylerken (11) bazıları da unipolar depresyon ve bipolar duygu durum bozukluğunda magnezyum düzeyinde artış olduğunu (16,17) belirtmiştir. Bazıları ise kanıtların tutarsız olduğunu, daha fazla prospektif çalışmaya ihtiyaç olduğunu savunmaktadır (18).

Bu çalışma ile unipolar depresyon ve bipolar duygu durum bozukluğu olan hastaların serum magnezyum düzeylerinin değerlendirilmesi ve kontrol grubu ile karşılaştırılarak bu hastalıklarda magnezyum düzeyinin nasıl etkilendiğinin belirlenmesi amaçlanmıştır.

2. Gereç ve Yöntemler

Çalışma için önce Üniversite Tıp Fakültesi Araştırma ve Uygulama hastanesi psikiyatri bölümüne 2015 ve 2019 yılları arasında başvuran hastaların verileri retrospektif olarak tarandı. İçlerinde unipolar depresyon ve bipolar duygu durum bozukluğu tanıları olanlar ve serum magnezyum düzeyi bakılmış olan hastalar çalışma grubunu oluşturdu. Sinirlilik şikayeti ve uyum sorunları nedeniyle polikliniğimize başvurmuş, yapılan muayenesinde psikiyatrik bir hastalığının olmadığına karar verilmiş ve kan tetkikleri istenmiş hastalar taranarak kontrol grubu oluşturuldu. Çalışma grubunda unipolar depresyon tanısı almış 49 (32 kadın, 17 erkek) hasta ve bipolar duygu durum bozukluğu olan 21 hasta (11 kadın, 10 erkek) bulunmaktaydı. Kontrol grubunda ise 50 kişi (32 kadın, 18 erkek) bulunmaktaydı. Depresif veya bipolar duygu durum bozukluğuna ek olarak başka psikiyatrik hastalığı olanlar, psikoaktif madde (alkol ve madde) kullanımı olanlar ve ciddi bedensel hastalığı olanlar çalışmadan dışlandı.

Çalışma için aynı hastanenin etik kurulundan onay alınmıştır (etik kurul karar numarası:2017-KAEK-189_2019.11.27_03).

İstatistiksel analiz

Tüm veriler SPSS (Statistical Package for the Social Sciences) versiyon 15 programı ile analiz edildi. Kategorik veriler ki-kare testi kullanılarak analiz edildi ve sayı olarak ifade edildi. Sürekli veriler için ortalama ve standart sapma değerleri verildi. Unipolar depresyon, bipolar duygu durum bozukluğu ve kontrol grubu arasında serum magnezyum düzeylerinin karşılaştırması parametrik test varsayımları karşılanmadığından Kruskal Wallis testi kullanılarak yapıldı. Anlamlılık düzeyi için $p<0.05$ kabul edildi. Anlamlı farklılık saptandığı durumda farkın hangi gruptan kaynaklandığını tespit etmek için ikili gruplar arasında Mann- Whitney U testi uygulandı. Bonferroni düzeltmesi yapılarak yeni anlamlılık düzeyi 0.017 olarak belirlendi.

3. Bulgular

Unipolar depresyon grubunun yaş ortalaması 42,10±13,76, bipolar bozukluk grubunun 43,57±11,27, kontrol grubunun ise 41,64±11,05 idi. Gruplar arasında yaş ve cinsiyet bakımından anlamlı fark yoktu(yaş için p=0,907, cinsiyet için p=0,745). Çalışma grubunda diabetes mellitus tanısı olan 7 kişi, hipertansiyon olan 6 kişi bulunurken, kontrol grubunda diabet tanısı olan 3 kişi, hipertansiyon tanısı olan 5 kişi bulunmaktaydı.

Serum magnezyum düzeyleri (mg/dl) bakımından gruplar karşılaştırıldığında ise gruplar arası anlamlı farklılık saptandı (tablo-1, şekil-1). Farklılığın hangi gruptan kaynaklandığını belirlemek için gruplar ikili olarak karşılaştırıldı (tablo-2).

Unipolar depresyon ve kontrol grubu karşılaştırıldığında (tablo-2); yeni p değeri olan 0,017'ye göre aralarında anlamlı fark bulundu (p=0,003), bipolar bozukluk ve kontrol grubu karşılaştırıldığında da yine aralarında anlamlı fark saptandı (p=0,014). Ancak depresif bozukluk ve bipolar bozukluğun ikili karşılaştırması sonucu istatistiksel olarak anlamlı fark bulunmadı (p=0,788).

Tablo1. Hastalık grubuna göre magnezyum düzeylerinin karşılaştırılması

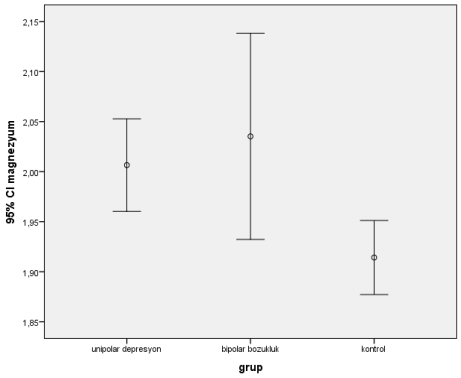
	Unipolar Depresyon (N= 49)	BAB (N= 21)	Kontrol (N= 50)	x^2	p
	Sıra Ortalaması				
Mg düzeyi (mg/dl)	68,79	70,74	48,08	10,98	0,004
	Medyan				
	2,01	2,0	1,91		

x^2: Kruskal Wallis test
Mg (mg/dl): Serum magnezyum düzeyi
BAB: Bipolar duygu durum bozukluğu

Tablo 2. Grupların magnezyum düzeyleri (mg/dl) bakımından birbiri ile karşılaştırılması

	Mean rank	U	p
Depresyon-Kontrol	58,71 41,46	798,0	0,003*
BAB-Kontrol	45,24 32,12	331,0	0,014*
Depresyon-BAB	35,07 36,50	493,5	0,788

**: p<0,017*



Şekil 1. Gruplar arasında serum magnezyum düzeylerinin karşılaştırılması

4. Tartışma ve Sonuç

Bu çalışmada unipolar depresyon ve bipolar duygu durum bozukluğu olan hastaların serum magnezyum düzeyleri kontrol grubuna göre anlamlı olarak daha yüksek saptanmıştır. Unipolar depresyon ve bipolar bozukluk gruplarının birbiri ile karşılaştırılması sonucunda ise iki grup arasında anlamlı fark saptanmamıştır. Literatür incelendiğinde depresyonda serum magnezyum düzeyleriyle ilgili çelişkili sonuçların yer aldığı görülmektedir. Deb ve arkadaşları 30 depresif hastayla yaptıkları çalışmada depresif bozukluğu olan grupta anlamlı olarak daha düşük serum magnezyum düzeyleri saptamışlardır (8). You ve arkadaşlarının yaptıkları metaanalizde de depresif hastalarda serum magnezyum düzeyleri kontrollerden daha düşük bulunmuştur. Ayrıca metaanalize dâhil edilen çalışmalardan iki tanesi analiz dışı bırakıldığında ise bulunan anlamlılığın kaybolduğu saptanmıştır. Bununla birlikte plazma ve serebrospinal sıvıdaki magnezyum düzeyleri değerlendirildiğinde ise fark bulunmamıştır (11). Üstelik dâhil edilen çalışmaların çoğunun da eski tarihli olmasının da göz önünde bulundurulması gerektiğini söyleyen yazarlar, bu nedenlerle bulunan sonuçların dikkatli yorumlanması gerektiğini vurgulamışlardır. Başka bir çalışmada ise burada sunulan çalışmayla uyumlu olarak, ilaç kullanmayan depresif bozukluk hastalarının kan magnezyum düzeyleri sağlıklı kontrollerden daha yüksek bulunmuştur (1). Bir diğerinde ise ilaç tedavisi almayan 20 depresif bozukluk hastasıyla yapılan çalışma sonucunda mevcut çalışmayla uyumlu olarak yüksek serum magnezyum düzeyleri saptanmıştır (19).

Bugüne kadar bipolar duygu durum bozukluğunda serum magnezyum düzeyini değerlendiren fazla çalışma bulunmamakla birlikte, burada sunulan çalışma sonuçlarıyla uyumlu olarak Siwek ve arkadaşları da bipolar duygu durum bozukluğu olan hastalarda; manik, hipomanik veya depresif epizodda olmasından bağımsız olarak serum magnezyum düzeylerini sağlıklı kontrollere kıyasla daha yüksek olarak bulmuşlardır (20). Aynı zamanda magnezyum düzeyleri ile manik veya hipomanik epizod süreleri ve geçen yılki alevlenme sayısı arasında pozitif yönde anlamlı ilişki saptamışlardır. Yine mevcut çalışmayı destekler nitelikte Imada ve ark.nın 34 bipolar 37 depresif bozukluk hastasıyla yaptıkları çalışmalarında da her iki grupta kontrol grubuna kıyasla daha yüksek serum magnezyum değerleri saptanmıştır (21). Ayrıca bu çalışmada magnezyum düzeyleri ile hastalığın aktif fazı veya remisyon fazında olması arasında ilişki de saptanmamıştır. Yazarlar magnezyum düzeylerinin hastalığın fazı veya şiddetinden etkilenmemesinden dolayı serum magnezyum düzeyinin patofizyolojiyi gösteren potansiyel bir marker olabileceğini iddia etmişlerdir. Burada sunulan çalışmada ise retrospektif olarak tasarlanmış olması sebebiyle hastalık şiddeti ve fazına dair mevcut bilgi olmadığından böyle bir değerlendirme yapılamamıştır. Yüksek magnezyum düzeyinin vücudun patofizyolojiyle

karşılaşmasına verdiği bir savunma tepkisi olabileceği düşünülmektedir. Şöyle ki magnezyumun antidepresan etkinliği olduğu, vücutta azalmasının nöronlarda NMDA blokajını engellediği ve hipereksitabiliteyi artırdığı bilinmektedir (7,22). Belki de organizmanın magnezyum düzeyini artırmak suretiyle, oluşan bu hipereksitabl durumu geri çevirmeye çalıştığı speküle edilebilir. Bu konuda yapılacak prospektif çalışmalarla bu yorumların araştırılmasına ihtiyaç olduğu düşünülmektedir.

Literatür incelemesi sonucunda depresif ve bipolar duygu durum bozukluklarında serum magnezyum düzeyinde bir etkilenme olduğu gösterilmekle birlikte artış mı yoksa azalma mı olduğu konusunda görüş birliğinin olmadığı anlaşılmaktadır. Muhtemelen farklı sonuçlar üzerinde örneklem sayısındaki farklılıklar ve dâhil edilen hastaların özellikleri, uygulanan dışlama kriterleri etkili olmuş olabilir. Burada sunulan çalışmada depresif bozukluk hasta sayısı diğer bazı çalışmalarla kıyaslandığında daha fazla olmakla birlikte bipolar bozukluk hastası daha az sayıda kalmıştır. Bu da çalışmanın bir kısıtlılığını oluşturmaktadır. Verilerin retrospektif olarak elde edilmiş olması, hastalıkların süresi, şiddeti, başlangıç yaşı, geçirilen atak sayısı gibi bilgilerin kaydedilmemiş olması sebebiyle daha detaylı analizler yapılamamış olması da çalışmanın bir başka kısıtlılığı olarak söylenebilir. Ayrıca çalışmadaki hastaların çoğunluğu psikotrop ilaç kullanan hastalardan oluşmaktaydı. Bu nedenle ilaç kullanımının etkisi dışlanamamıştır. Her ne kadar psikotrop ilaç kullanımının magnezyum düzeylerini etkilemediğini söyleyen çalışmalar olsa da (21,23) ileride yapılacak çalışmalarda bu durumun göz önünde bulundurulması faydalı olacaktır. Çalışmanın kısıtlılıklarından bir tanesi de majör kronik hastalık tanısı olanlar çalışmaya dâhil edilmemiş olsa da diabetes mellitus, menopoz gibi magnezyum düzeyini etkileyen hastalıkların çalışmada dikkate alınmamasıdır.

Sonuç olarak bu çalışmada hem unipolar depresyon hem de bipolar duygu durum bozukluğu olan hastalarda kontrollere kıyasla daha yüksek serum magnezyum düzeyleri saptanmıştır. Bu sonuçlar serum magnezyum düzeylerinin bu hastalıklar için potansiyel bir biyomarker olabileceğine dair kanıtlar sunsa da ileride yapılacak daha geniş serili ve diğer hastalık gruplarının da dâhil edildiği, kısıtlılıkların minimuma indirildiği prospektif çalışmalarla sonuçların desteklenmesinin literatüre olumlu katkısının olacağı düşünülmektedir.

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Research Article / Araştırma Makalesi

Vitamin D Receptor Contents and Receptor Expression Rates of CD4+ and CD8+ T Lymphocytes in Renal Transplant Recipients

Böbrek Nakli Alıcılarında CD4+ Ve CD8+ T Lenfositlerin Vitamin D Reseptör İçerikleri ve Reseptör Ekspresyon Hızları

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Abstract

This study aims to evaluate the vitamin D receptor (VDR) expression and intracellular amounts of VDRs in CD4+ and CD8+ lymphocytes of renal transplant (RT) recipients with chronic allograft dysfunction (CAD). A total of 43 patients (Group 1:RT patients=29 patients, 15 patients CAD proven by renal biopsy (Group 1a), 14 patients stable renal function (Group 1b), Group 2:Control group=14 healthy individuals) have been enrolled in this study. 25-hydroxycholecalciferol, 1.25 dihydroxycholecalciferol levels were measured. The number of cells expressing VDR among the CD4+ and CD8+ type T lymphocytes of the subjects was determined as % of those cell groups. The mean VDR molecule contents per cell have been measured and expressed as mean fluorescence intensities (MFI). No difference was found between Group 1 and Group 2 in terms of their 25-hydroxycholecalciferol, 1.25 dihydroxycholecalciferol levels, and the percentages of the cells expressing VDR in CD4+ and CD8+ cells ($p>0.05$). CD4+/VDR(MFI) and CD8+/VDR(MFI) values were higher in RT patients than healthy subjects ($p<0.001$). When the RT patient subgroups compared, there were no statistically significant differences regarding CD4+/VDR(%), CD8+/VDR(%), CD4+/VDR(MFI) and CD8+/VDR(MFI) values ($p>0.05$). This study showed VDR in T lymphocytes of patients who had RT did not change, but the VDR content in the cells increased due to reasons independent of serum 25-hydroxycholecalciferol and 1.25 dihydroxycholecalciferol levels.

Keywords: CD4+ lymphocytes, CD8+ lymphocytes, 25(OH)D3, 1.25(OH)2D3, Vitamin D receptor, Renal transplantation

Özet

Bu çalışma, kronik allogreft disfonksiyonu (KAD) olan böbrek nakli (BN) alıcılarının CD4+ ve CD8+ lenfositlerinde D vitamini reseptörü (VDR) ekspresyonunu ve hücre içi VDR miktarlarını değerlendirmeyi amaçlamaktadır.Toplam 43 hasta (Grup 1:BN hastaları=29 hasta, böbrek biyopsisi ile KAD kanıtlanmış 15 hasta (Grup 1a), böbrek fonksiyonu stabil 14 hasta (Grup 1b), Grup 2:Kontrol grubu=14 sağlıklı birey) bu çalışmaya dahil edilmiştir. 25-hidroksikolekalsiferol, 1.25 dihidroksikolekalsiferol seviyeleri ölçüldü. Deneklerin CD4+ ve CD8+ tip T lenfositleri arasında VDR eksprese eden hücre sayısı, bu hücre gruplarının %'si olarak belirlendi. Hücre başına ortalama VDR molekülü içeriği ölçülmüş ve ortalama floresan yoğunlukları (MFI) olarak ifade edilmiştir. Grup 1 ve Grup 2 arasında 25-hidroksikolekalsiferol, 1.25 dihidroksikolekalsiferol düzeyleri ve CD4+ ve CD8+ hücrelerinde VDR eksprese eden hücrelerin yüzdeleri açısından fark bulunmadı ($p>0.05$). BN hastalarında CD4+/VDR(MFI) ve CD8+/VDR(MFI) değerleri sağlıklı kişilere göre daha yüksekti ($p<0,001$). BN hasta alt grupları karşılaştırıldığında, CD4+/VDR(%), CD8+/VDR(%), CD4+/VDR(MFI) ve CD8+/VDR(MFI) değerleri açısından istatistiksel olarak anlamlı fark yoktu ($p>0.05$).Bu çalışma, BN uygulanan hastaların T lenfositlerinde VDR'nin değişmediğini, ancak hücrelerdeki VDR içeriğinin serum 25-hidroksikolekalsiferol ve 1.25 dihidroksikolekalsiferol düzeylerinden bağımsız nedenlerle arttığını gösterdi.

Anahtar Kelimeler: CD4+ lenfositler, CD8+ lenfositler, 25(OH)D3, 1.25(OH)2D3, Vitamin D reseptörü, Böbrek nakli

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1. Introduction

Renal transplantation (RT) is the most prominent treatment method for patients developing stage 5 chronic renal disease. Acute/chronic rejections are the main immunological problems that occur after RT.

Active vitamin D level in RT recipients is associated with kidney allograft function. Vitamin D and its analogs, reduce intraglomerular hypertension and proteinuria, limit glomerular and tubulointerstitial damage (1). Vitamin D may also reduce renal fibrosis by inhibiting mesangial cell proliferation, podocyte loss, and prevent podocyte hypertrophy (2). It is suggested to prevent profibrotic cytokine synthesis and renal inflammation (3,4).

Vitamin D receptor (VDR) belongs to the nuclear hormone receptor family and is bound to chromosomal DNA in the nucleus and is found in the cytoplasm. Vitamin D receptors are found in antigen-presenting cells as well as in various immune cells such as T and B lymphocytes, monocytes, macrophages, and mast cells. Active vitamin D prevents the differentiation of dendritic cells and causes their apoptosis (5). It is involved in immune tolerance by preventing antigen presentation to T lymphocytes and thereby the differentiation of antigen-specific T lymphocytes (5). It also inhibits Thelper1 (Th1) differentiation by inhibiting interleukin-12 (6). Vitamin D also inhibits the release of interleukin-2, interleukin -3, interferon-gamma and, tumour necrosis factor α (TNF-a) from the Th1 cells and exhibits anti-inflammatory and anti-rejection activity by stimulating the release of anti-inflammatory cytokines. Correlation between transforming growth factor beta 1 (TGF-beta1) expression and interstitial fibrosis and glomerulosclerosis and its relationship with the development of chronic allograft dysfunction (CAD) has also been shown (7). Active vitamin D analogs have been shown to inhibit the expression of proinflammatory cytokines by inhibiting the nuclear factor kappa B (NF-KB) pathway (4).

CAD is characterized by progressive kidney dysfunction which is manifested by slowly and continuously increasing serum creatinine and proteinuria and frequently, hypertension. The etiopathogenesis of CAD is still uncertain and no definitive therapy and special preventive methods have been established yet (7). The etiology of CAD includes immunological factors such as previous acute rejections, subclinical rejection, antibody-mediated chronic rejection, human leucocyte antigen incompatibility, inadequate immunosuppression, or non-immunological factors associated with viral infections, hyperlipidemia, hypertension, nephrotoxic effects of calcineurin inhibitors (8). Definitive diagnosis requires a biopsy for the exclusion of other factors such as acute rejection, recurrent glomerulonephritis, drug toxicity, and infections.

This study aims to compare serum $25(OH)D_3$ and $1.25(OH)_2D_3$ levels and CD4+ and CD8+ lymphocyte VDR levels in RT patients with healthy people and to evaluate their relationship with some demographic and clinical parameters.

2. Material and Methods

A total of 43 people were enrolled in the study, including 29 RT patients older than 18 years of age who received an RT at Akdeniz University, Faculty of Medicine, Prof. Dr. Tuncer Karpuzoglu Transplantation Center, with a posttransplant period longer than 6 months (Group 1) and age and gender-matched healthy control subjects without any known chronic or acute diseases (Group 2: n=14). RT recipients were divided into two subgroups: patients with chronic allograft dysfunction (Group 1_a:n=15 patients) and patients with stable renal function (Group 1_b:n=14 patients). All demographics such as age, gender, body mass index (BMI), etiology of CKD, duration, and type of dialysis, type of donor, number of rejections and their treatment, immunosuppressive drug use, and clinical,

laboratory results were obtained from the patient files. Glomerular filtration rate (GFR) level was calculated by using the CKD-EPI formula. BMI was calculated by dividing body weight (kg) by the square of the height in meters.

Patients with a pathological diagnosis of chronic allograft dysfunction were included in the study. The diagnosis of CAD was based on the BANFF-2013 classification (9). Patients who have been diagnosed with acute rejection, infection, primary disease, recurrence/glomerulonephritis, etc. were excluded from the study. Furthermore, although the pathological diagnosis was CAD, patients using vitamin D and its metabolites, patients with parathyroidectomy/idiopathic hypoparathyroidism, those with active malignancy were also not included in the study. Those with an active infection, chronic liver disease, non-CKD calcium-phosphorus metabolism disease, and those who did not accept biopsy were excluded from the study. Biopsy results were evaluated by the same expert pathologist in the pathology department of our center. Local ethics committee from XXX University clinical research ethics committee (date/number: 31.07.2013/86) approval was received for the study. The study was performed by the Helsinki 2013 Brasil version. Written informed consent to participate in the study was obtained from the participants.

Blood samples were collected from all healthy participants and RT recipients included in the study and the sera were separated by centrifugation at 3000 rpm for 5 minutes to be kept at -80 C°. Lymphocytes were isolated from the blood cells and the number of cells expressing VDR was given as VDR(%).Determination of the percentage of peripheral lymphocytes expressing VDR was made by flow cytometry. Subsequently, the VDR content in the VDR carrier cells was measured and reported as VDR(MFI) (mean fluorescence intensity).

Based on the Kidney Disease Outcomes Quality Initiative guidelines, levels of $25(OH)D_3$ lower than 5 ng/ml were considered as severe; 5-15 ng/ml as mild vitamin D deficiency and 15-29 mg/ml as vitamin D deficiency. Levels higher than 30 mg/ml were considered as normal and levels higher than 150 mg/ml as vitamin D intoxication.(10) $1.25(OH)_2D_3$ and $25(OH)D_3$ levels were tested to measure the serum vitamin D activity.

Serum creatinine was measured using the Jaffe method; BUN, calcium, phosphorus, albumin were all measured using the enzymatic colorimetric method; Serum intact parathyroid hormone (iPTH) and $25(OH)D_3$ analysis was performed using the electrochemiluminescence immunoassay method using a Cobas 8000 autoanalyzer (Roche Diagnostics, Mannheim, Germany) in the central biochemistry laboratory of our hospital.

Serum 1.25 $(OH)_2D_3$ Analysis

Serum $1.25(OH)_2D_3$ Analysis was carried out using a solid-phase sandwich ELISA method using Cusabio branded kit (Cusabio, Human-1.25- Dihydroxy vitamin D3 (DHVD3), Cat. No: CSB-E05120H). The amounts of $1.25(OH)_2D_3$ in serum samples were calculated from the curve plotted using standards. The results are given in pg / mL.

Statistical analysis

"Statistical Package for Social Sciences (SPSS) v.18.0" package program was used for statistical analysis. The continuous variables were expressed as arithmetic mean ± standard deviation (x ± SD). For numerical parameters with normal distribution properties, unpaired student t-test was used for comparison of two independent groups, while one-way analysis of variance (ANOVA) and Scheffe test as a post-doc test were used for comparison of three independent groups; categorical parameters were compared with the chi-square test. Correlations between vitamin D and VDR levels in various cells were determined by

Pearson correlation analysis. $p<0.05$ was considered statistically significant.

3. Results

There were no statistically significant differences in age, gender, and BMI values between RT recipients and the healthy control groups, as well as RT subgroups 1a and 1b ($p> 0.05$) (Table 1). There was no significant difference between RT patients with and without CAD in terms of dialysis duration, donor types, number of previous acute rejections, age at transplantation date and transplantation vintage, immunosuppressive drug protocols, mismatch numbers, diabetes mellitus and preemptive transplant rate ($p>0.05$) (Table 2).

Table 1. Basic demographics, clinical and laboratory data of patients.

Parameter	Subgroup 1a(CAD+) n=15	Subgroup 1b(CAD-) n=14	Group 2 (HG) n=14	p
Age[t]	45.67±11.67	41.29± 12.89	37.64± 9.43	0.298
BMI[+]	24.80±4.66	24.86±4.02	25±3.23	0.991
BUN	33.20±14.76	13.79±3.79	13.79±4.90	**<0.001***
Creatinine	2.25±0.78	0.88±0.18	0.72±0.19	**<0.001***
GFR	33.75±12.88	93.43±16.0	99.97±13.17	**<0.001***
Calcium	9.09±0.78	10.0±0.65	9.44±0.32	**0.004***
Phosphorus	3.62±1.0	3.41±0.92	3.64±0.58	0.740
Albumin	3.58±0.62	4.35±0.44	4.58±0.25	**<0.001***
iPTH	167.10±164.24	73.38±46.67	49.20±20.55	**0.001***
$25(OH)D_3$	18.98±8.16	23.04±12.58	22.77±11.08	0.593
$1.25(OH)_2D_3$	15.70±9.44	16.50±11.82	12.21±6.73	0.544
CD4+/VDR(%)	65.46±20.0	70.24±9.52	64.01±13.52	0.468
CD8+/VDR(%)	66.83±16.36	72.29±82.9	63.84±12.71	0.224
CD4+/VDR(MFI)	1091.40±331.82	810.86±203.88	627.0±72.0	**<0.001***
CD8+/VDR(MFI)	1013.53±281.14	770.64±183.79	595.43±52.06	**<0.001***

[t]*Kruskal Wallis test;* [+] *One-way analysis of variance (ANOVA)*

Abbreviations: CAD: Chronic allograph dysfunction, HG; Healthy group Tx: Transplantation, CKD: chronic kidney disease, BUN: Blood urea nitrogen, iPTH:intact parathyroid hormone, BMI: body mass index, MFI: MFI: Mean Fluorescence Intensity,GFR: glomerular filtration rate, CD8+/VDR(%): Percentage of VDR-expressing CD8+ lymphocytes, CD4+/VDR(%): Percentage of VDR-expressing CD4+ lymphocytes, CD8+/VDR(MFI): Vitamin D receptor amount in CD8+ lymphocytes, CD4+/VDR(MFI): Vitamin D receptor amount in CD4+ lymphocyte

Table 2. Demographic and clinical characteristics of patients with and without chronic allograft dysfunction

	Subgroup 1a (CAD positive)	Subgroup 1b (CAD negative)	p
Gender[#]			0.858
Women (n,%)	7 (46.7%)	7 (50.0%)	
Men (n,%)	8 (53.3%)	7 (50.0%)	
Etiology of CKD			
Hypertension	13.3%	35.7%	
Of unknown primary cause	26.7%	14.3%	
Urological	33.3%	21.4%	
Other	26.7%	28.6%	

Relatives[#]			0.858
First degree (n,%)	8 (53.3%)	7 (50.0%)	
Fourth degree (n,%)	7 (46.7%)	7 (50.0%)	
Dialysis modality[$]			0.999
Preemptive (n,%)	5 (33.3%)	5 (35.7%)	
HD-PD (n,%)	10 (66.7%)	9 (64.3%)	
Medication[$]			0.999
TAC (n,%)	11 (73.3%)	10 (71.4%)	
Cyclosporin-A(n,%)	4 (26.7%)	4 (28.6%)	
Tx type[$]			0.999
Live (n,%)	12 (80%)	12 (85.7%)	
Cadaver (n,%)	3 (20%)	2 (14.3%)	
Acute rejection episode during follow-up[$]			0.330
No (n,%)	11 (73.3%)	13 (92.9%)	
Yes (n = 16)	4 (26.7%)	1 (7.1%)	
Donor age[+] **(year)**	46.47±11.35	42.36±10.49	0.321
Tx age [ι] **(year)**	43.07±11.86	39.07±12.74	0.484
Tx duration [ι] **(month)**	32.67±18.01	28.21±9.22	0.662
Dialysis duration [ι] **(month)**	20.90±17.12	25.78±27.06	0.902
Number of Missmatches[ι]	3.83±1.64	3.82±2.18	0.682

[#] The chi-square value in the Pearson chi-square test; [$] Fisher's exact test (this test has no test statistic value); [ι] The z value in the Mann-Whitney U test; [+] The t value in the Student t test.

Abbreviations: CAD: Chronic allograph dysfunction, Tx: Transplantation, CKD: chronic kidney disease.

In RT patients with CAD, BUN and creatinine values, eGFR, iPTH, albumin, and calcium were found to be significantly different than patients without CAD ($p < 0.05$). There were no significant differences in $25(OH)D_3$ and $1.25(OH)_2D_3$ and CD4+/VDR(%), CD8+/ VDR(%), CD4+/VDR(MFI), CD8+/VDR(MFI) levels between these two groups ($p > 0.05$) (Table 3).

CD4+/VDR(MFI), CD8+/VDR(MFI) values of patients with CAD were significantly higher, and GFR and albumin values were lower than normal healthy subjects ($p < 0.05$). There were no statistically significant differences between the groups in terms of CD8+/VDR(%), CD4+/ VDR(%).

CD4+/VDR(MFI) and CD8+/VDR(MFI) values of patients with stable renal function without CAD were higher than healthy controls ($p < 0.05$). However, there was no statistically significant difference between the groups in terms of BUN and creatinine, eGFR, albumin, calcium, and iPTH levels (Table 3).

Table 3. Intergroup paired comparisons

	With and without CAD	With CAD and HG	Without CAD and HG
BUN [ι]	**<0.001***	**<0.001***	0.999
Creatinine [ι]	**<0.001***	**<0.001***	0.394
GFR[+]	**<0.001***	**<0.001***	0.443
Calcium [ι]	**0.004***	0.058	0.999
Albumin [ι]	**0.004***	**<0.001***	0.602
iPTH [ι]	0.128	**0.001***	0.312

CD8+VDR(MFI)ᵗ	0.177	**<0.001***	**0.014***
CD4+/VDR(MFI)ᵗ	0.156	**<0.001***	**0.018***
CD8+VDR(%)	0.743	0.520	0.471
CD4+/VDR(%)	0.556	0.494	0.176

*ᵗBonferroni-Dun Test; ⁺ Tukey's post-hoc test; * p<0.05*

Abbreviations: CAD: Chronic allograph dysfunction, HG; Healthy group Tx: Transplantation, CKD: chronic kidney disease, BUN: Blood urea nitrogen, iPTH:intact parathyroid hormone, BMI: body mass index, MFI: MFI: Mean Fluorescence Intensity,GFR: glomerular filtration rate, CD8+/VDR(%): Percentage of VDR-expressing CD8+ lymphocytes, CD4+/VDR(%): Percentage of VDR-expressing CD4+ lymphocytes, CD8+/VDR(MFI): Vitamin D receptor amount in CD8+ lymphocytes, CD4+/VDR(MFI): Vitamin D receptor amount in CD4+ lymphocytes

When 29 RT patients were evaluated as a single group, $25(OH)D_3$, $1.25(OH)_2D_3$, CD4 +/VDR(%) and CD8+/VDR(%) levelswere not different than healthy control group (p> 0.05), while CD4+/VDR(MFI) and CD8+/VDR(MFI) values were higher in RT recipients (p <0.05) (Table 4).

In the CAD group, $25(OH)D_3$ levels indicated a mild deficiency in 26.6%, deficiency in 66.6%, and were within normal limits in 6.6% of participants. In the group of patients without CAD, 21.42% had a mild deficiency, 64.2% had a deficiency, 14.2% were normal, while in the healthy controls 28.6% had a mild deficiency, 50% had a deficiency and 21.4% were normal. There was no statistically significant difference in $25(OH)D_3$, $1.25(OH)_2D_3$ levels between all three groups (p> 0.05).

Table 4. Comparison of $25(OH)D_3$, $1.25(OH)_2D_3$ and VDR in renal transplant recipients and healthy group

	Renal transplant recipients	Healthy group	p
$25(OH)D_3$ᵗ	20.94±10.54	22.77±11.08	0.392
$1.25(OH)_2D_3$ᵗ	16.08±10.47	12.21±6.73	0.271
CD8+/VDR % ᵗ	67.77±15.75	64.01±13.52	0.228
CD8+/VDR(MFI) ᵗ	896.28±265.44	595.43±52.06	**<0.001***
CD4+/VDR(%)ᵗ	69.47±13.17	63.84±12.71	0.108
CD4+/VDR(MFI)ᵗ	955.97±307.74	627.0±72.01	**<0.001***

*ᵗ z statistic in the Mann-Whitney U test; * p<0.05*

*Abbreviations: **CD8+/VDR(%):** Percentage of VDR-expressing CD8+ lymphocytes, **CD4+/VDR(%):** Percentage of VDR-expressing CD4+ lymphocytes, **CD8+/VDR(MFI):** Vitamin D receptor amount in CD8+ lymphocytes, **CD4+/VDR(MFI):** Vitamin D receptor amount in CD4+ lymphocytes*

When the correlation of GFR with $25(OH)D_3$, $1.25(OH)_2D_3$ and VDR was evaluated with Spearman correlation test, there was a significant negative correlation with CD4+/VDR (MFI), CD8+/VDR(MFI) values in RT patients and the healthy group (p <0.05). In patients with CAD, there was a positive correlation between C4+/VDR(%) and CD8+/VDR(%) values and eGFR (p <0.05). In patients without CAD, there was no correlation between eGFR and$25(OH)D_3$, $1.25(OH)_2D_3$, and VDR values (p> 0.05) (Table 5).

Table 5. Correlation of glomerular filtration rate with $25(OH)D_3$, $1.25(OH)_2D_3$and VDR

	$25(OH)D_3$	$1.25(OH)_2D_3$	CD8+/VDR %	CD8+ VDR(MFI)	CD4+/VDR %	CD4+/VDR (MFI)
Whole group n=43						
r	.075	-.034	.039	**-.587****	.079	**-.604****
p	.631	.828	.805	**.000**	.615	**.000**
Group 1 (CAD positive) n=15						
r	.222	-.265	**-.754****	.064	**-.737****	.059
p	.427	.340	**.001**	.820	**.002**	.834
Group 2 (CAD negative) n=14						
r	.192	.285	-.029	.108	.117	.166
p	.511	.324	.922	.713	.690	.572
Group 3 (healthy group) n=14						
r	-.440	.279	.000	**-.612***	.057	**-.667****
p	.115	.333	1,000	**.020**	.846	**.009**

*All analyzes were made using Spearman Correlation Test. ** p<0.01; *p<0.05*

Abbreviatios: CAD: Chronic allograph dysfunction, ***CD8+/VDR(%):*** *Percentage of VDR-expressing CD8+ lymphocytes,* ***CD4+/VDR(%):*** *Percentage of VDR-expressing CD4+ lymphocytes,* ***CD8+/VDR(MFI):*** *Vitamin D receptor amount in CD8+ lymphocytes,* ***CD4+/VDR(MFI):*** *Vitamin D receptor amount in CD4+ lymphocytes*

In terms of the correlation of the percentage of VDR expressing CD4+ and CD8+ T lymphocytes with demographic, clinical, and laboratory parameters were evaluated; CD8+/ VDR(%) was negatively correlated with BMI and positively correlated with donor age ($p < 0.05$). CD4+/VDR(%) had a significant negative correlation with BMI ($p < 0.05$) (Table 6). CD4+/VDR(MFI) and CD8+/VDR(MFI) values had a positive correlation with BUN, creatinine, and iPTH and a negative correlation with eGFR and albumin ($p < 0.05$). VDR did not show any difference in gender, kinship, dialysis, and transplantation types between groups ($p > 0.05$). The percentage of CD4+/VDR(%) was significantly higher in patients using cyclosporin-based immunosuppressive drugs compared to those using tacrolimus-based immunosuppressive drug regimens ($p < 0.05$).

In patients with CAD, there was no statistically significant correlation between vitamin $25(OH)D_3$ levels and VDR values, but there was a negative correlation between $1.25(OH)_2D_3$ levels and CD8+/VDR(MFI) and CD4+/VDR(MFI) values and it was statistically significant ($p < 0.05$). No significant correlation was found between $25(OH)D_3$ and $1.25(OH)_2D_3$ levels and VDR values in patients without CAD and in the healthy group ($p > 0.05$).

Table 6. Analysis for the correlation of vitamin D receptor percentage with demographics, clinical and laboratory data.

	CD8+/VDR%	Age	BMI	Tx Age	Tx Duration	Dialysis Duration	Number of Missmatch	Donor age	Leukocyte	Lymphocyte	Bun	Creatinine	GFR	Calcium	Phosphorus	Alb	iPTH
CD8+/VDR%	-.956**	-	-	-	.202	-.179	-.169	.447*	-.125	.177	-.065	.019	.039	.018	-.070	-.091	.081
r		.128	.330*	.142													
p	.000	0.412	0.03	0.462	0.294	0.464	0.441	0.015	0.426	0.257	0.679	0.905	0.805	0.910	0.658	0.564	.606
n	43	43	43	29	29	19	23	29	43	43	43	43	43	43	43	43	43
CD4+/VDR%		-	-397**	-	.180	-.141	-.081	.352	-.167	.156	-.091	.029	.079	.073	-.087	-.086	.061
r		.167		.198													
p	.	0.286	0.008	0.303	0.350	0.565	0.712	0.061	0.284	0.316	0.561	0.853	0.615	0.640	0.579	0.585	.695
n		43	43	29	29	19	23	29	43	43	43	43	43	43	43	43	43

Abbreviations: *CAD: Chronic allograph dysfunction, HG; Healthy group Tx: Transplantation, CKD: chronic kidney disease, BUN: Blood urea nitrogen, iPTH:intact parathyroid hormone, BMI: body mass index, MFI: MFI: Mean Fluorescence Intensity,GFR: glomerular filtration rate, CD8+/VDR(%): Percentage of VDR-expressing CD8+ lymphocytes, CD4+/VDR(%): Percentage of VDR-expressing CD4+ lymphocytes, CD8+/VDR(MFI): Vitamin D receptor amount in CD8+ lymphocytes, CD4+/VDR(MFI): Vitamin D receptor amount in CD4+ lymphocytes*

4. Discussion

In this study, we compared $25(OH)D_3$, $1.25(OH)_2D_3$ levels, CD4+, CD8+ T lymphocyte VDR expressing rates, and the number of VDR per cell in RT recipients with healthy control subjects and investigated their possible relationship with CAD.

A high rate of $25(OH)D_3$ deficiency was found in RT recipients. That result was similar to previous studies and no difference was observed between the healthy group, indicating a high prevalence of vitamin D deficiency in both patients and healthy individuals (11). There was no significant difference between groups with and without CAD regarding their $25(OH)D_3$, $1.25(OH)_2D_3$, and VDR values in T lymphocytes.

The treatment of many factors such as optimal blood pressure control, metabolic acidosis, renal osteodystrophy, and anemia, which slow the progression of CKD in RT recipients whose chronic kidney disease is confirmed by definition, is not that precise.(12) One of the treatable factors is vitamin D deficiency. The current KDIGO guidelines recommend that RT recipients be evaluated and treated for bone and mineral metabolism disorders as in CKD patients not receiving RT (13). Patients having a transplant generally do not receive vitamin D supplements. Wals et al. reported that 800 IU / day of vitamin D given to RT recipients have hardly increased serum $25(OH)D_3$ level (14). In the study of Courbebaisse et al. the monthly treatment of 100.000 IU vitamin D is recommended for adult RT recipients (4). Wissing et al. reported that treatment with 25.000 U/month of vitamin D given to RT recipients could not improve serum vitamin D levels (15). These studies suggest that the need for vitamin D in RT recipients may be higher than the amount recommended by the general guideline.

The role of vitamin D in acute and chronic allograft rejection has been demonstrated by many studies. Vitamin D deficiency triggers chronic inflammatory processes through various mechanisms (oxidative stress, DNA damage, endothelial dysfunction, increased proinflammatory cytokines, decreased antiinflammatory cytokines, etc.). It was demonstrated that vitamin D treatment slows GFR loss and improves graft function in patients with chronic allograft dysfunction who take vitamin D (1,16). This effect is probably due to the inhibition of profibrotic and proinflammatory pathways by vitamin D (6,17).

Sezer et al. reported that patients with low vitamin D before RT had higher creatinine and proteinuria levels in the first posttransplant year (18). Tanacı et al. reported that osteoporotic RT recipients had less rejection after calcitriol treatment (19). In the study of Uyar et al. the evaluation of 3-year data of 59 patients using calcitriol and 52 patients not using calcitriol for osteoporosis after RT have revealed that creatinine and iPTH levels of patients using calcitriol were significantly lower (20). Wesseling-Perry et al. did not find a relationship between $25(OH)D_3$ level and 2-year graft function in 68 pediatric RT patients with stable graft function (21). Animal studies have shown that $1.25(OH)_2D_3$ prolongs the life of the allograft and is effective in maintaining renal graft function with low-dose cyclosporin A (22). In our study, there was no statistically significant difference between the vitamin levels of RT recipients with and without CAD and also the healthy group of participants.

In this study, CD4+/VDR(MFI) and CD8+/VDR(MFI) levels showing the amount of VDR per cell in all the immune cell types assessed in the RT group were found to be statistically and significantly higher compared with the healthy group. These high levels could be similarly determined in CD4+/VDR (MFI) and CD8+/VDR (MFI) values in patients with CAD. Cell percentages expressing VDR in the RT group and subgroups did not differ from healthy subjects. These results suggested that the VDR amount increased significantly, although the number of cells with VDR expression in the immune system cells of the patients who underwent RT did not change.

Vitamin D resistance occurs in CKD as there is a disruption in the transcription of VDR-regulated genes and the VDR expression of tissues. Uremic plasma suppresses the enzyme 1-alpha hydroxylase and blocks their VDR's and the sensitivity of VDR to vitamin D decreases (23). Activation of VDR by's reduces the activation of dendritic cells and interleukin-2 transcription, preventing antigen presentation to T lymphocytes and antigenic stimulation. Additionally, fibroblast growth factor 23, which rises in the early stages of CKD, inhibits active vitamin D synthesis by suppressing the enzyme 1-alpha hydroxylase (24). Calcineurin inhibitors in RT patients additionally may cause downregulation of VDRs, leading to vitamin D resistance (25). In the subgroup with CAD, the number of receptors may have increased due to the decreased sensitivity of VDR to vitamin D. However, in the subgroup without CAD, the mean VDR count, MFI, was higher, although not statistically significant, compared with the normal healthy group. As a result, in response to the immunosuppressive effects of immunosuppressive drugs, vitamin D may be tried to be used more effectively by increasing the VDR count to maintain immune activation. However, when VDR exceeds a certain cut-off value, immune activation starts, and the question "May this be the onset of graft rejection?" come to mind. Is VDRactivation in immune cells undesirable in transplantation? We do not know. Perhaps VDR'smay needs to be suppressed. This hypothesis needs to be elucidated.

In the study by Lee.C et al., VDR's were suppressed when calcineurin inhibitors were used in animals that had RT (26). In the study by Grenet et al., when using

cyclosporin-A in RT rats, calcium-binding protein (calbindin) and VDR were decreased (27). In our study, patients using cyclosporin-A had significantly higher CD4+/VDR(%) than those using tacrolimus, but there was no difference between VDR amounts. The reason for this is not clearly understood.

The fact that there was a negative significant correlation between GFR, therefore, the level of uremia and CD4+/VDR(MFI) and CD8+/VDR(MFI) in Group 1, including all patients who underwent RT indicated that uremic toxins have suppressed VDR activity. A positive significant correlation was determined between CD4+/VDR(%) and CD8+/VDR(%) values and GFR only in the patients with CAD in terms of the cell percentages demonstrating VDR expression in the immune cells.

In the present study, no correlation was found between the VDR amount in the immune cells and $25(OH)D_3$ and $1.25(OH)_2D_3$ levels. When all patients with RT were included, a positive correlation was found between the VDR activities determined by CD4+/VDR(MFI), CD8+/VDR(MFI) and BUN, creatinine, and iPTH; on the other hand, a negative correlation was found between CD4+/VDR(MFI), CD8+/VDR(MFI) and GFR, albumin. Those findings have suggested that the uremic environment has decreased the VDR activity in CD4+ and CD8+ lymphocytes. A negative significant correlation was found at both CD4+/VDR(MFI), CD8+/VDR(MFI), and $1.25(OH)_2D_3$ levels only in the subgroup with CAD. Although the mechanism of regulation of VDR expression is not fully elucidated, this mechanism depends on calcitriol synthesis and metabolism. The regulation of VDR expression is specific to cell type and has been demonstrated in different cell lines that include both transcription and posttranscription mechanisms (28,29). Changes in serum calcium and phosphorus levels cause differences in VDR expression in the target tissue (30,31). iPTH plays a role in the regulation of VDR expression (30,32).

In this study, a negative correlation was found between CD4+/VDR(%) and CD8+/VDR(%) and BMI. A positive correlation was found between CD8+/VDR(%) and the age of transplant. In patients with CAD, there was a significant positive correlation between CD4+/VDR(%), CD8+/VDR(%)values, and GFR. Since vitamin D is a fat-soluble vitamin, it may have been sequestered in the fat tissue. In the study by Wortsman et al., there was an inverse correlation between BMI and $25(OH)D_3$ levels, but in our study, CD4+/VDR(%) and CD8+/VDR(%) and BMI were negatively correlated (33).

This study has several limitations. The first limitation is the cross-sectional design of the study and the relatively low number of patients. The second is the seasonal variability affecting vitamin D levels was not evaluated.

5. Conclusion

As a sum up, through our findings, we have seen that vitamin D deficiency is frequently observed in RT patients. There was no difference in vitamin D levels, VDR expression rates, and VDR contents per cell among RT patients with chronic allograft dysfunction and those with normal renal function. The effect of vitamin D supplementation on immune functions and long-term graft functions should be evaluated with randomized controlled studies in RT recipients.

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Research Article / Araştırma Makalesi

Acil Servise Başvuran Hastalardaki Sesamoid Kemiklerin ve Aksesuar Kemikçiklerin Ayak ve Ayak Bileğindeki Görülme Sıklığının Belirlenmesi

Determination of Frequency of Sesamoid Bones and Accessory Ossicles in Foot and Ankle in Patients Admitted to Emergency Service

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Özet

Aksesuar kemikçikler ve sesamoid kemikler, ayakta çeşitli hastalıklara neden olan ve kırıkları taklit eden kemikleşmesini tamamlamış kemik yapılardır. Radyografilerde tesadüfen keşfedilirler ve çoğu zaman gözden kaçırılarak yanlış teşhislere yol açarlar. Bu nedenle, acil servise ayak ve ayak bileği şikâyeti ile başvuran hastaların radyografi görüntülerinde aksesuar kemikçik ve sesamoid kemiklerin görülme sıklığının belirlenmesi amaçlandı. Acil Servisi başvuran hastalara ait anteroposterior, oblik ve lateral ayak grafileri (506) retrospektif olarak değerlendirildi. Aksesuar kemikçiklerin ve sesamoid kemiklerin varlığı, prevalansı, bir arada bulunuşu ve dağılımı cinsiyete ve ekstremite tarafına göre detaylı olarak analiz edildi. 506 ayak grafisinde, %18.4 oranında aksesuar kemikçik, % 86.4 oranında sesamoid kemik tespit edildi. En yaygın aksesuar kemikçikler; os naviculare accessorium (%11.5), os peroneum (%3.6), os trigonum (% 1.8), os supranaviculare (%0.4), os vesalianum (%0.2), os supratalare (%0.2), os subfibulare (% 0.6) ve os calcaneus secundarius (%0.2)'tur. Radyografilerin %86.4'ünde halluks sesamoid gözlemlendi. Halluks'un interfalangeal sesamoid kemiği, radyografilerin %2'sinde görüldü. Metatarsofalangeal sesamoid kemik insidansı MTP II'de % 2, MTP IV'te % 0.4 ve MTP V'te % 6.7 olarak bulundu. Çalışmanın sonuçları literatürde belirtilen aralıklarda olmasına rağmen, çalışma grubunun farklı populasyon ve yaş gruplarından oluşması ve sadece acil servise başvuran hastaların dahil edilmesi nedeni ile diğer literatür raporlardan önemli ölçüde farklı göstermektedir.

Anahtar Kelimeler: Aksesuar kemikçikler; Anatomi; Acil servis; Sesamoid kemikler.

Abstract

Accessory ossicles and sesamoid bones are bone structures that have completed ossification that mimic fractures and cause various diseases in the foot. They are discovered by chance on radiographs and are often overlooked, and lead to misdiagnosis. For this reason, it was aimed to determine the frequency of the accessory ossicles and sesamoid bones in the radiographic images of the patients who were admitted to the emergency department with foot and ankle complaints. Anteroposterior, oblique and lateral foot radiographs of patients (506) admitted to the Emergency Service were evaluated retrospectively. The presence, prevalence, coexistence and distribution of accessory ossicles and sesamoid bones were analyzed in detail according to gender and extremity sides. In 506 foot radiographs, accessory ossicles were detected in 18.4% and sesamoid bones in 86.4%. The most common accessory ossicles were accessory navicular (11.5%), os peroneum (3.6%), os trigonum (1.8%), os supranaviculare (0.4%), os vesalianum (0.2%), os supratalare (0.2%), os subfibulare (%0.6) ve os calcaneus secundarius (%0.2). We observed hallux sesamoid in 86.4% of radiographs. Interphalangeal sesamoid bone of the hallux was seen in 2% of radiographs. Incidences of MTP I were found as 2% in the MTP II, 0.4% MTP IV and 6.7% MTP V. In conclusion, although the results of the study are within the ranges stated in the literature, they differ significantly from other literature reports because the study group consisted of different population and age groups and only patients who applied to the emergency department were included.

Keywords: Accessory ossicles; Anatomy; Emergency service; Sesamoid bones.

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1. Giriş

Ayak aksesuar kemikçikleri ve sesamoid kemikler, ayak ve ayak bileği yakınında bulunan kortikasyonunu tamamlamış kemik yapılardır. Gelişimsel kemik varyasyonları olarak da tanımlanabilirler. Sıklıkla doğuştan olmakla birlikte bazen de travma kaynaklı olabilirler (1,2).

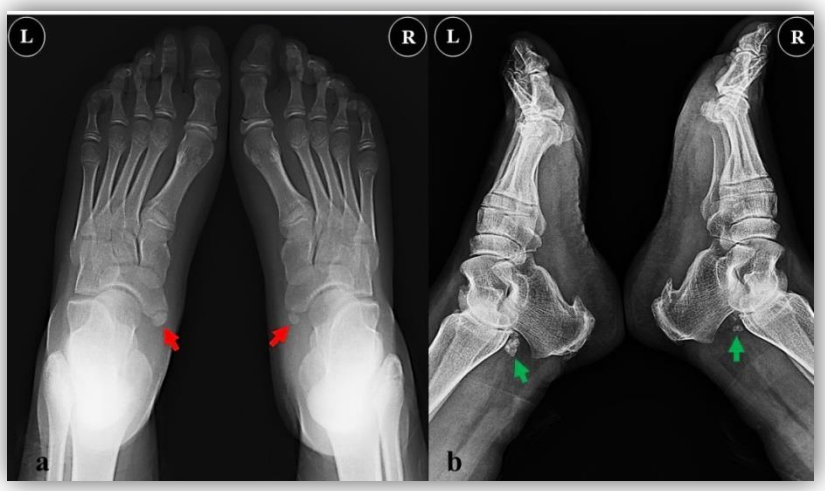
Aksesuar kemikçikler, genellikle avülsiyon kırıkları ile karıştırılırlar ve radyografilerde tesadüfen keşfedilirler. Çoğu zamanda gözden kaçırılarak yanlış teşhislere yol açarlar. Ayrıca semptomlara yol açarak altta yatan patolojiye katkıda bulunabilir veya bunları şiddetlendirebilirler. Örneğin, ağrılı kırıkların bir sonucu olarak bu kemikler enfekte olabilir veya yerinden çıkabilirler. Hatta bağ dokusu hastalıklarına bile neden olabilirler (3–5).

Sesamoid kemikler ise, kendi ossifikasyon merkezlerinden gelişen 5–10 mm çaplı yuvarlak veya oval şekilli kemiklerdir. Kısmen veya tamamen bir tendonun içerisinde gömülü olarak bulunurlar. Sürtünmenin azaltılmasında ve çekme açısının değiştirilmesinde aktif rol oynayarak tendonların zarar görmesini engellerler. Anatomik olarak, birinci metatarsofalangeal eklemin normal bir parçası olarak kabul edilir ve nadiren diğer ayak eklemlerinde görülürler (4,6).

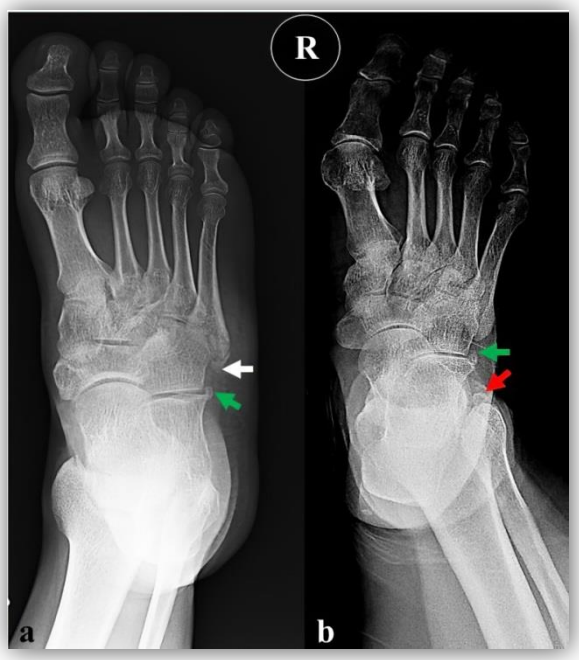
Aksesuar kemikçikler ve sesamoid kemikler, ayakta çeşitli hastalıklara neden olur ve ayak kemiklerinin kırılmasını taklit eder. Bu yüzden gereksiz ortopedik konsültasyonları ve yanlış tanıları azaltmak için bu kemiklerin anatomik yerleşimleri ve klinik önemleri iyi bilinmelidir (1,2,7,8). Bu çalışmada, herhangi bir ayak ve ayak bileği şikâyeti ile acil servise başvuran hastaların aksesuar kemikçiklerinin ve sesamoid kemiklerinin cinsiyete, görülme frekansına, bir arada bulunmalarına ve ekstremite tarafına göre radyografi görüntüleri üzerinde retrospektif bir şekilde incelenmesi amaçlandı.

2. Materyal ve Metot

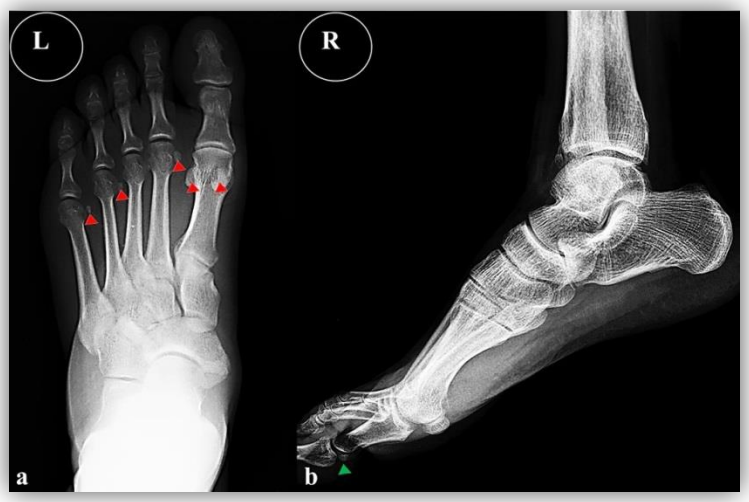
Bu çalışma, aksesuar kemikçiklerin ve sesamoid kemiklerin insidansını belirlemek amacıyla 2018-2021 tarihleri arasında AFSU Sağlık Uygulama ve Araştırma Merkezi Acil Servisine ayak ve ayak bileği şikâyeti ile başvuran 506 hastanın (287 erkek, 219 kadın, yaş aralığı 1-79 yaş) radyografileri görüntülerini üzerinde gerçekleştirildi. 506 hastanın anteroposterior, oblik ve lateral ayak grafileri her iki ayakta aksesuar kemikçiklerin (Şekil 1 ve 2) ve sesamoid kemiklerin (Şekil 3) varlığı, prevalansı, bir arada bulunuşu ve dağılımı açısından retrospektif olarak incelendi. Kemik yapısında anormal durumu olanlar (tümör, kist, kanama vb.), travma veya dejeneratif bozukluk kaynaklı kemik yapısının bütünlüğünde bozulma olanlar, radyolojik görüntüleri net olmayanlar ve ampütasyona uğrayanların görüntüleri çalışmaya dahil edilmedi.



Şekil 1. (a) *Os naviculare accessorium kırmızı okla gösterilmektedir.* ***(b)*** *Os trigonum yeşil okla gösterilmektedir.*



Şekil 2. (a) *Os peroneum yeşil okla, os vesalianum beyaz okla gösterilmektedir.* ***(b)*** *Os peroneum yeşil okla, os subfibulare kırmızı okla gösterilmektedir.*



Şekil 3. (a) *Metatarsofalangeal sesamoid kemikleri kırmızı ok başları ile gösterilmektedir.* ***(b)*** *Birinci proksimal interfalangeal eklem sesamoid kemiği yeşil ok başı ile gösterilmektedir.*

Çalışma için AFSU Klinik Araştırmalar Etik Kurulu'ndan onay alındıktan sonra (Onay tarihi: 05.02.2021 ve Karar No: 2021-97), ayak ve ayak bileği radyografileri deneyimli üç araştırmacı (AB; Anatomist, EA; Anatomist, AE; Acil Tıp Uzmanı) tarafından interpacs programı kullanılarak bağımsız olarak değerlendirildi. Değerlendirme sonucunda ortaya çıkan anlaşmazlıklar, radyografilerin yeniden değerlendirildiği ve nihai bir kararın verildiği bir fikir birliği toplantısında tartışıldı. Tespit edilen sesamoid kemiklerin (metatarsofalangeal (MTP), interfalangeal (IP) ve distal interfalangeal (DIP) eklemlerde) ve aksesuar kemiklerin (Calcaneus secundarium, os trigonum, os peroneum, os vesalianum, os supranaviculare, os supratalare, os naviculare accessorium ve

os subfibulare) ekstremite tarafına göre lokalizasyonları ve tipleri istatistiksel analizlerin yapılabilmesi için kaydedildi.
Verilerin istatistiksel analizi SPSS 20.0 paket programı (SPSS, Chicago, Illinois) ile yapıldı. Aksesuar kemikçiklerin ve sesamoid kemiklerin, cinsiyete, ekstremite tarafına ve dekatlar şeklinde ayrılan yaş gruplarına göre görülme sıklığı Ki-kare testi ile değerlendirildi. Kategorik veriler frekans ve yüzdeler olarak ifade edildi. Sonuçlar %95 güven aralığında değerlendirilerek, $p < 0.05$ olan veriler istatistiksel olarak anlamlı kabul edildi.

3. Bulgular

Çalışmamızda 262'si sağ, 244'ü sol olmak üzere 506 olgunun ayak radyografi görüntüleri değerlendirildi ve 506 olgunun 93'ünde aksesuar kemikçikler tespit edildi. Çalışmamızda ayak bileği ve ayak bölgesinde en sık görülen aksesuar kemikçik aksesuar naviküler kemikçikti ve 116 olguda belirlendi. Ayrıca 18 olguda os peroneum, 9 olguda os trigonum, 3 olguda os fibulare, 2 olguda os supranaviculare, birer olguda os vesalianum, os supratalare ve calcaneus secundarium tespit edildi. Aksesuar kemikçikler tüm kadın olguların %8.1'inde ve tüm erkek olguların %10.2'sinde görüldü. Aksesuar kemikçiklerin cinsiyete, ekstremite tarafına ve yaş gruplarına göre dağılımı Tablo 1'de gösterilmiştir.
Sesamoid kemikler 506 olgunun %86.4'ünde (437) mevcuttu. 437 olguda tespit edilen sesamoid kemiklerin dağılımı alt kısmında bulunduğu MTP'ye göre; MTP I (halluks sesamoidleri)'de 437 olgu, MTP V'te 34 olgu, MTP II'de 10 olgu ve MTP IV'te 2 olgu şeklindeydi. 56 olguda MTP I sesamoid kemiklerine eşlik eden sesamoid kemik belirlendi. 12 olguda bipartit medial halluks sesamoidleri gözlemlendi. Ayrıca birinci proksimal interfalangeal eklemlerinde sesamoid kemik 10 olguda görülürken, radyografilerin hiçbirinde ikinci, üçüncü, dördüncü ve beşinci ayak parmaklarının proksimal ve distal interfalangeal eklemlerinde sesamoid kemikler görülmedi. Ayak bölgesinin sesamoid kemikleri Tablo 1'de detaylandırılmıştır.
Ekstremite tarafı, cinsiyet ve yaş gruplarına göre aksesuar kemikçiklerin ve sesamoid kemiklerin varlığı veya yokluğundaki farklılıklar istatistiksel olarak analiz edildi. Ekstremite tarafına (sağ ve sol) göre aksesuar kemikçik ve sesamoid kemik görülme sıklığında anlamlı farklılık yoktu. Erkek ve kadın olgularda aksesuar kemikçiklerin ve sesamoid kemiklerin cinsiyetlere göre prevalansı genel olarak benzer iken, sadece birinci proksimal interfalangeal eklemde sesamoid kemikler kadınlarda erkeklere oranla istatistiksel olarak daha fazla görüldü ($p<0.05$). Aksesuar kemikçik ve sesamoid kemiklerin yaş gruplarına göre dağılımı değerlendirildiğinde, 1-10 yaş grubunda MTP I sesamoid kemiklerinin yokluğunun ($p<0.001$), 11-20 yaş grubunda aksesuar navicula kemikçiklerinin ($p<0.05$) ve 51-60 yaş grubunda ise MTP V sesamoid kemiklerinin varlığının ($p<0.001$) diğer yaş gruplarına göre istatistiksel olarak anlamlı derece daha fazla olduğu bulundu (Tablo 1).

4. Tartışma

Farklı aksesuar kemikçikler ve sesamoid kemikler, bipartisyonlar ve birliktelikler dahil olmak üzere ayak bileği ve ayakta birçok iskelet varyasyonu bulunabilir (3,9). Çoğu aksesuar kemikçik ve sesamoid kemik herhangi bir şikâyete yol açmaz ve asemptomatik olarak kalır. Genellikle travma veya aşırı kullanım sonrası rutin radyolojik incelemelerde tespit edilerek dejeneratif değişikliklere veya ağrıya neden olurlar. Kırılabilir veya uyarabilirler ya da hareket aralığını kısıtlayabilirler (10–13). Literatürde, ayak ve ayak bileğindeki aksesuar kemikçiklerin görülme oranı genel popülasyonda %18-36.6 oranlarında değişkenlik gösterirken (2,3,10), bizim çalışmamızda aksesuar kemikçiklerin görülme sıklığı %18.4'tür.

Literatürde yapılan radyografi çalışmalarında os naviculare accessorium, os trigonum ve os perenoum prevelansı en yüksek olan aksesuar kemikçikler olarak bildirilmiştir. Fakat bu kemikçiklerin görülme sıklıkları farklı çalışmalarda değişkenlik göstermektedir (1,3,6,13–15).

Tablo 1. Sesamoid Kemikler ve Aksesuar Kemikçikler'in cinsiyet, ekstremite tarafı ve yaş gruplarına göre dağılımı

Sesamoid Kemikler ve Aksesuar Kemikçikler		Tüm Olgular 506 (%)	Cinsiyet			Taraf			Yaş grupları								
			Erkek 287 (%)	Kadın 219 (%)	p değeri	Sağ 262 (%)	Sol 244 (%)	p değeri	1-10 88 (%)	11-20 77 (%)	21-30 57 (%)	31-40 77 (%)	41-50 71 (%)	51-60 73 (%)	61-70 49 (%)	71-80 13 (%)	p değeri
Sesamoid Kemikler	MTP I	437 (86.4)	247 (86)	190 (86.8)	.821	228 (87)	209 (85.7)	.654	20 (22.7)	77 (100)	57 (100)	77 (100)	71 (100)	73 (100)	49 (100)	13 (100)	.000
	MTP II	10 (2)	6 (2.1)	4 (1.8)	.833	5 (1.9)	5 (2)	.909	-	-	1 (1.8)	3 (3.9)	2 (2.8)	4 (5.5)	-	-	.147
	MTP IV	2 (0.4)	1 (0.3)	1 (0.5)	.848	1 (0.4)	1 (0.4)	.960	-	-	-	1 (1.3)	1 (1.4)	-	-	-	.676
	MTP V	34 (6.7)	16 (5.6)	18 (8.2)	.289	18 (6.9)	16 (6.6)	.888	-	2 (2.6)	4 (7)	5 (6.5)	3 (4.2)	15 (20.5)	3 (6.1)	2 (15.4)	.000
	IP	10 (2)	2 (0.7)	8 (3.7)	.018	5 (1.9)	5 (2)	.909	-	-	-	4 (5.2)	2 (2.8)	2 (2.7)	2 (4.1)	-	.165
Aksesuar Kemikçikler	Calcaneus secundarium	1 (0.2)	-	1 (0.5)	.252	-	1 (0.4)	.300	-	-	-	-	1 (1.4)	-	-	-	.524
	Os trigonum	9 (1.8)	4 (1.4)	5 (2.3)	.453	7 (2.7)	2 (0.8)	.115	-	4 (5.2)	-	1 (1.3)	2 (2.8)	2 (2.7)	-	-	.201
	Os peroneum	18 (3.6)	10 (3.5)	8 (3.7)	.919	10 (3.8)	8 (3.3)	.744	1 (1.1)	1 (1.3)	1 (1.8)	4 (5.2)	5 (7)	4 (5.5)	1 (2)	1 (7.7)	.331
	Os vesalianum	1 (0.2)	1 (0.3)	-	.382	-	1 (0.4)	.300	-	-	-	1 (1.3)	-	-	-	-	.589
	Os supratalare	1 (0.2)	1 (0.3)	-	.382	1 (0.4)	-	.334	-	1 (1.3)	-	-	-	-	-	-	.589
	Os supranaviculare	2 (0.4)	1 (0.3)	1 (0.5)	.848	-	2 (0.8)	.142	-	-	1 (1.8)	-	-	1 (1.4)	-	-	.554
	Os naviculare accessorium	58 (11.5)	34 (11.8)	24 (11)	.756	28 (10.7)	30 (12.3)	.570	4 (4.5)	2 (2.6)	6 (10.5)	15 (19.5)	14 (19.7)	7 (9.6)	9 (18.4)	1 (7.7)	.002
	Os subfibulare	3 (0.6)	1 (0.3)	2 (0.9)	.412	1 (0.4)	2 (0.8)	.521	-	-	-	1 (1.3)	-	2 (2.7)	-	-	.302

Os naviculare accessorium, musculus (m) tibialis posterior'un tendonu içinde ve/veya os naviculare'ye yapışmasına yakın bir yerde bulunur (2,3,10,11,16). Görülme insidansı %4-21 arasında değişkenlik göstermektedir (2). Os peroneum, articulatio (art) calcaneocuboidea'nın bitişiğinde, m. peroneus longus tendonu içerisine gömülü yuvarlak veya oval şekilli bir sesamoid kemiktir. Semptomatik hale gelebilir, lateral ayak ağrısı ve ağrılı os peroneum sendromu olarak da bilinen hassasiyet olarak kendini gösterir (17,18). Kolaylıkla bir avülsiyon kırığı olarak yanlış yorumlanabilir ve prevalansı %3- 26 arasındadır (3,11). Os trigonum, ayak bölgesinde talusun arka tarafında bulunan üçgen veya oval şeklinde görülen en büyük aksesuar kemikçiklerden biridir. Kemik ve talus arasında bir senkondroz vardır (4,6,16). %1-25 arasında değişkenlik gösteren bir prevalansa sahiptir. Arka ayak bileği ağrısı ve şişlik olarak kendini gösteririr. Çoğu zaman tekrarlayan plantar fleksiyonla ilişkili posterior impingement sendromuna neden olabilir (19,20).

Os naviculare accessorium, os peroneum ve os trigonum'un görülme sıklığı, Coskun ve ark.'ın (1) Türk populasyonundan 984 olgu ile yaptıkları çalışmalarında sırasıyla %11.7, %4.7 ve %2.3 oranında iken, Longo ve ark.'ın (8) İtalyan porpulasyonundan 505 halluk vaguslu kadın olgu ile yaptıkları çalışmalarında sırasıyla %6.7, %7.9 ve %6.7 oranında, Koo ve ark.'ın (21) Kore populasyonundan 257 artrit hastaları ile yaptıkları çalışmalarında sırasıyla %31.1, %19.4 ve %5.8 oranında tespit edilmiştir. Bizim çalışmamızda ise, bu aksesuar kemikçiklerin görülme oranları sırasıyla, %11.5, %3.6 ve %1.8 belirlenmiş olup, literatürle uyumlu olarak os naviculare accessorium en sık görülen aksesuar kemikçiklerden biri olmuştur.

Os vesalianum, os supratalare, os supranaviculare, os calcaneus secundarius ve os subfibulare gibi aksesuar kemikçiklerinin prevelansı çok yüksek olmamasına rağmen, radyografi ve MR görüntülerinde tespit edilen diğer aksesuar kemikçikler arasında yer almaktadır. Bu kemikçikler ayak grafilerinde çoğunlukla başka bir aksesuar kemik varlığında belirlenirken, nadiren tek olarak bulunurlar (3,9,10). Os vesalianum, m. peroneus brevis tendonu içinde, os metatarsale V'in tabanına yakın konumlanmış küçük bir aksesuar kemikçiktir. Tahmini prevalansı %0.1-1 olan çok nadir bir aksesuar kemiktir. Bireylerin yaklaşık %0.1-1'inde görülebilir ve os metatarsale V'in epifizinden ayırt edilebilir. Nadiren semptomlara neden olur (19,22). Os supratalare, tipik olarak caput ve collum tali arasında dorsal yüzde bulunur ve caput tali'nin üzerinde distal olarak görülebilir. Eski, birleşmemiş bir avülsiyon kırığı ile kolayca karıştırılabilir. Ancak lateral grafilerde görülebilir. Tahmini prevalansı %2'dir ve nadir rastlantısal bir iskelet varyasyonudur (3,4,15). Os supranaviculare, corpus navicula'nın dorsal yüzünün proksimal'inde yer alır. Genellikle asemptomatiktir ancak travma bağlamında os navicula veya caput tali'nin avülsiyon kırığı olarak yanlış teşhis edilebilir. Nadiren semptomatik hale gelebilir. Bu durumda ise cerrahi rezeksiyon gerektiren dorsal ayak ağrısına neden olabilir. Tahmini prevalans yaklaşık %1 ile 3.5'tir (16). Os calcaneus secundarius, calcaneus, os cubeideum, os navicula ve caput tali'nin arasındaki aralıkta yer alır. Daha çok üçgen olmasına rağmen yuvarlak olabilir. Ayakta nadir görülen bir aksesuar kemikçiktir. Klinik önemi yoktur ve tesadüfen rutin radyografilerde bulunabilir. Tahmini prevalansı %0.6-7'dir(3). Os subfibulare, lateral malleollus'un ucunun altında, yuvarlak veya virgül şeklinde bulunan bir aksesuar kemiktir. Tahmini prevelansı %2.1 olarak belirtilmiştir (9,13).

Literatür çalışmalarında görülme sıklığı daha az olan aksesuar kemikçikler; Coskun ve ark.'ın (1) çalışmalarında os supranaviculare (%1.6), os vesalianum (%0.4), os supratalare (%0.2) ve os subfibulare (%0.2), Longo ve ark.'ın (8) çalışmalarında os supranaviculare (%1.2), os vesalianum (%8.5), ve os supratalare (%2.6), Koo ve ark.'ın (21) çalışmalarında os vesalianum (%4.2), os subfibulare (%0.3) ve os calcaneus secundarius (%0.3) olarak bildirilmiştir. Bizim çalışmamızda ise os supranaviculare (%0.4), os vesalianum (%0.2), os supratalare (%0.2), os subfibulare (%0.6) ve os calcaneus secundarius (%0.2) sıklığı daha az olan

aksesuar kemikçikler olarak bulunmuştur. Genel olarak çalışmamız sonucunda tespit edilen aksesuar kemikçiklerin görülme sıklıkları literatürde belirtilen sınırlar içerisinde yer almaktadır. Fakat literatür çalışmaları arasındaki farklılıkları; ırklar arasındaki farklılıklar, çalışma gruplarının çeşitliliği (belirli hastalık sahibi/sağlıklı bireyler) veya belirli bir cinsiyet grubu etrafında kümeleşmesinden kaynaklanmaktadır.

Ayrıca bu çalışmada sesamoid kemiklerin görülme sıklığının da gösterilmesi amaçlanmıştır. Yetişkin insan iskeletindeki sesamoid kemiklerin sayısı bireyler arasında büyük farklılıklar gösterebilir. Bu kemikçiklerin insan iskeletindeki patogenezinin nedeni ve kesin sayısı bilinmemektedir (6,23,24).

Halluks sesamoidleri, alt ekstremiteyi etkileyen darbe yüklerinin dağıtılmasında kritik bir rol oynar ve patolojik durumlarında spor ve aktivitelerden önemli ölçüde uzaklaşmaya neden olabilir (25). Halluks sesamoidlerinin doğuştan yokluğu nadir bir varyasyondur. İskeletin normal bir parçası olarak kabul edilir. Fakat 10 yaş altı çocukların radyografilerinde görülmesi çok zordur (1,6,8). Longo ve ark.'ın (8) çalışmalarında (%80) ve bizim çalışmamız (%86.4) haricinde tüm literatür çalışmalarında halluks sesamoidleri tüm olgularda görülmüştür. Bu durum Longo ve ark. ve bizim çalışma grubumuzda kemik gelişimini tamamlayamamış olguların (15 yaşın altı bireyler) bulunmasından kaynaklanmaktadır.

Ayak bölgesinde bulunan diğer sesamoid kemikler nadiren görülürler. Medial tarafta lateral tarafa göre çok daha yaygın olmakla birlikte her zaman MTP sesamoid kemikleri ikinci ve beşinci parmaklarda diğer parmaklara göre daha baskındır (1,23). İkinci, üçüncü, dördüncü ve beşinci MTP sesamoid kemiklerinin görülme sıklığı Kiter ve ark.'nın (6) çalışmalarında sırasıyla %2.8, %0.5, %1 ve %15.1 oranında, Coşkun ve ark.'nın (1) çalışmalarında sırasıyla %0.4, %0.2, %0.1 ve %4.3 oranında, Longo ve ark.'ın (8) çalışmalarında sırasıyla %3, %1.2, %1.8 ve %19.2 oranında ve Koo ve ark.'ın (21) çalışmalarında sırasıyla %6.1, %0.6, %2.3 ve %27.3 oranında belirlendiği bildirilmiştir. Bizim çalışmamızda ise ikinci, dördüncü ve beşinci MTP sesamoid kemiklerinin görülme oranları sırasıyla, %0.4, %2, %2 olarak tespit edildi. Ayrıca Kiter ve ark. çalışmasında, beşinci MTP sesamoid kemiği istatistiksel olarak erkeklerde daha fazla tespit edilmiş iken, Çoşkun ve ark. (1)çalışmasında erkekler ve kadınlar arasında önemli bir fark görülmemiştir. Bizim çalışmamızda ise Kiter ve ark. çalışmasının aksine beşinci MTP sesamoid kemik kadınlarda istatistiksel olarak daha fazla bulunmuştur.

Literatürde bazı çalışmalarda halüsal interfalangeal sesamoidin çok nadiren görüldüğünü ve klinik olarak da çoğunlukla zararsız olan bu sesamoid kemiğin zaman zaman gösterdiği semptomlarının anatomik, biyomekanik ve klinik patolojinin gelişimi ile ilişkili olduğunu bildirilmiştir. Hallukal IP sesamoid, ilk MTP ve hallukal IP eklemlerinin biyomekanik fonksiyonları üzerinde zararlı bir etkiye sahiptir. IP sesamoidler eklemde plantar ağrılı kallozitelere neden olabilir veya çıkık bir eklemde hapsolabilir (26,27). Dharap ve ark.(28) %3.9 oranında, Bizzaro (29) %5 oranında, Jahss (30) %13 oranında, Coşkun ve ark. (1) ise %2 oranında bulmuşlardır. Bu oran bizim çalışmamızda da Coşkun ve ark. çalışması ile uyumlu olarak %2 oranında tespit edilmiştir.

5. Sonuç

Sonuç olarak, yapılan bu çalışma acil servise başvuran hastaların ayak aksesuar kemikçikleri ve sesamoid kemiklerin görülme sıklığını yaş gruplarına göre ayrıntılı bir şekilde inceleyen rapor olarak karşımıza çıkmaktadır. Çalışmanın sonuçları literatürde belirtilen aralıklarda olmasına rağmen, çalışma grubunun farklı populasyon ve yaş gruplarından oluşması ve sadece acil servise başvuran hastaların dahil edilmesi nedeni ile diğer literatür raporlardan önemli ölçüde farklı göstermektedir. Bu farklılıklara rağmen, acil servise ayak ve ayak bileği şikâyeti ile başvuran hastalardaki aksesuar kemikçik ve sesamoid kemik sıklıkları belirlenmiştir. İnanıyoruz ki bu çalışmamız sıklıkla gözden

kaçan aksesuar kemikçik ve sesamoid kemik bozukluklarının tanı ve tedavisinde klinisyenlere özellikle de acil hekimlerine yardımcı olabilecek anatomik veriler sağlar.

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Research Article / Araştırma Makalesi

Factors Affecting the Duration of Disease in Chronic Urticarial; Single Center Experience

Kronik U rtikerde Hastalık Su resini Etkileyen Fakto rler: Tek Merkez Deneyimi

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Abstract

Chronic urticaria (CU) is characterized by recurrent itchy blisters, angioedema, or both for more than six weeks. We evaluated patients' clinical and demographic characteristics, laboratory results, and factors affecting the disease's duration followed up with the diagnosis of chronic urticaria in our clinic. In our study 101 patients who applied to our outpatient clinic between March and December 2020 were included in the study. Demographic features, comorbid illness of patients, skin prick test results, phadiatop, Total IgE, anti-TPO, vitamin B12, vitamin D, ferritin, complete blood count, autologous serum skin test, urticaria activity score over seven days (UAS7) were examined from hospital records retrospectively. Correlations between variables and their effects on the duration of the disease were statistically investigated. It was observed that the duration of the disease was longer in chronic urticaria patients with anti-TPO positivity (p=0.019). As a result of the multiple regression analysis, it had been determined that the UAS7 value had 2,989 folding effects on the duration of the disease. A positive correlation between the duration of the disease and the UAS7 (r=0,277; p=0,005) was determined. The patients in the study defined as a longer disease duration in the patients with angioedema (p=0,005), dermatographism (p=0,012) and gender of female (p=0,031) Anti-TPO positivity, concomitant angioedema, dermatographism, and higher UAS7 scores predicts that their chronic urticaria will last longer.

Keywords: Chronic urticaria, disease duration, anti-TPO, ASST, Urticaria activity score (UAS7), dermatographism

Özet

Kronik ürtiker (KÜ), altı haftadan uzun süredir tekrarlayan kaşıntılı büller, anjiyoödem veya her ikisi ile karakterizedir. Kliniğimizde kronik ürtiker tanısı ile takip edilen hastaların klinik ve demografik özelliklerini, laboratuvar sonuçlarını ve hastalık süresini etkileyen faktörleri değerlendirdik. Çalışmaya Mart-Aralık 2020 tarihleri arasında polikliniğimize başvuran 101 hasta dahil edildi. Hastaların demografik özellikleri, komorbid hastalıkları, deri prik testi sonuçları, phadiatop, Total IgE, anti-TPO, vitamin B12, vitamin D, ferritin, tam kan sayımı, otolog serum deri testi(ASST), haftalık ürtiker aktivite skoru (UAS7) hastane kayıtlarından geriye dönük incelendi. Değişkenler arasındaki ilişkiler ve bunların hastalık süresine etkileri istatistiksel olarak araştırıldı. Anti-TPO pozitifliği olan kronik ürtikerli hastalarda hastalık süresinin daha uzun olduğu görüldü (p=0.019). Yapılan multiple regresyon analizinde UAS7 değerinin hastalık süresi üzerinde 2,989 kat etkisi olduğu tespit edilmiştir. Hastalık süresi ile UAS7 (r=0,277; p=0,005) arasında pozitif korelasyon saptandı. Anjiyoödem (p=0,005), dermatografizm (p=0,012) ve kadın cinsiyeti (p=0,031) olan hastalarda daha uzun hastalık süresi olduğu saptandı. Anti-TPO pozitifliği, eşlik eden anjiyoödem, dermatografizm ve daha yüksek UAS7 skorları, kronik ürtikerlerinin daha uzun süreceğini öngörmektedir.

Anahtar Kelimeler: Kronik ürtiker, hastalık süresi, anti-TPO, Otolog serum deri tetsti (ASST), Ürtiker aktivite skoru (UAS7), dermatografizm

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1. Introduction

Chronic urticaria (CU) lasts more than six weeks, characterized by recurrent itchy blisters, angioedema, or both, divided into two main groups as chronic spontaneous urticaria and chronic inducible urticaria. Chronic spontaneous urticaria (CSU) accounts for about 80% of chronic urticaria and occurs without a specific cause. Prevalence of CSU is 0.5% to 1% (1). Chronic inducible urticaria subgroups are; cholinergic urticaria, symptomatic dermatographism, aquagenic urticaria, cold urticaria, hot urticaria, late pressure urticaria, and vibration urticaria. Although the etiology of the disease is not known clearly, two main mechanisms related to the pathogenesis of the disease are considered. The first is the irregularity or defect of the intracellular signaling pathways of basophil and mast cells. In contrast, the second is the development of autoantibodies against the Fc part of Ig E or Fc Epsilon RI alpha (FcRIα) in both basophil and mast cells (2). It has been reported that the rate of physical urticaria association (most common symptomatic dermatographism and late pressure urticaria) is between 10-50%(3).

Second-generation H1 anti-histamine drugs are the first line of treatment. The regular dosage of second-generation H1-antihistamines could be increased up to 4 times if symptoms are not resolved or improved within the first 2-4 weeks of treatment. If there is still insufficient improvement after 2-4 weeks, omalizumab can be added to the treatment (1). Omalizumab is a recombinant DNA-derived humanized monoclonal antibody that binds to the IgE molecule and blocks the interaction between free IgE with IgE receptors (4, 5). This leads to a down regulation of high-affinity IgE receptor expression on inflammatory cells (6). Remission occurs in 30% to 50% of adult patients within 1-3 years after the onset of symptoms (7). 11 % of patients with CU symptoms continue longer than five years. In severe cases, the disease may take a longer time (8). Several studies have shown a positive association between autoimmune thyroid disease and CSU in adult patients, and a higher prevalence of serum IgG autoantibodies have been noted for thyroid peroxidase (TPO) and thyroglobulin (TG) (9-13).

We planned to investigate the clinical and demographic characteristics of patients, lab results, and factors affecting the duration of the disease followed up with the diagnosis of chronic urticaria in our clinic.

2. Methods

In our study one hundred one patients who applied to our outpatient clinic between March and December 2020 were included in the study. Informed consent was taken from all of the patients. Demographic features, comorbid illness of patients and results of skin prick test, phadiatop (Phadia, Uppsala, Sweden) Total IgE, anti-TPO (Immunoassay), vitamin B12, vitamin D, ferritin, complete blood count, autologous serum skin test, urticaria activity score were taken from hospital records retrospectively. After obtaining informed consent, skin prick tests and autologous serum test was done patients who do not use anti-histamine medication. Patients under 18 and over 65 years of age, history of malignancy, pregnant and breastfeeding women, and patients who received immunosuppressive therapy were excluded from the study. All of them were followed up; their remission period of CU was determined and reported as disease duration.

Ethics Ethical approval was obtained in the local ethics committee (2.Oct.2020 104/27), and the study followed Good Clinical Practice guidelines and the Declaration of Helsinki.

Skin Prick test: In the last 10 days, a skin prick test was performed for those who did not take anti-histamine or steroid drugs and those who did not have an acute infection. Pregnant women with chronic spontaneous urticaria were excluded. Mixtures of mites and molds, cat, dog, cockroaches, grass, cereals, tree pollen, weed mixture antigens were used in skin prick tests (ALK, Allergo). It was evaluated 15 minutes after the skin prick test was performed. The two longest diameters that cut each other perpendicularly were measured. If the result is more than 3

mm compared to the negative control, the test was accepted as positive (14).

Autologous serum skin test (ASST): 5cc Venous blood (5cc) taken from patients was allowed to coagulate at the temperature room for 30 minutes. Serum was separated by centrifugation at 500g in 15 minutes by creating a 45degree angle with insulin or tuberculin injector; 0.05 ml serum was administered intradermally. As a negative control (same dose), sterile saline was applied in the same way. Thirty minutes after the injection, the diameter of the erythematous papule was measured. 1.5 mm larger than negative control was accepted as positive. An autologous serum test is often used to show circulating antibodies that cause urticaria (15).

Dermatographism: Linear urticarial plaque developed five minutes after stroking the skin on the patient's forearm or the upper back with a wooden stick is called dermatographism.

Urticaria activity score (UAS7): It is used to evaluate the severity of urticaria. It includes the number of swelling and itching severity daily for seven days. UAS7 means ≤6 well controlled, 7-15 mild, 16-27 medium, 28-42 severe diseases (16).

Phadiatop: It's a screening test for atopy, including multi-allergen IgE E, and correlates with skin test results (17).

Statistics: SPSS (Statistical Package for the Social Sciences) 23.0-package program was used for the statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, continuous measurements as mean and standard deviation (median and minimum-maximum where necessary). The suitability of the variables to normal distribution was examined using the Shapiro-Wilk Tests. Independent student's test was performed in paired groups for parameters showing normal distribution, and Mann Whitney u test was analyzed for parameters not showing normal distribution. A multiple regression model was used to determine the relationship between disease duration and other parameters. A value of $p < 0.05$ was considered to be significant in statistical analysis.

3. Results

In our study, 70.3 % of patients were female, % 56.4 of patients didn't have any allergic disease in their family, 59.4 % (n=60) of patients had dermatographism (a subgroup of physical urticaria). The mean age was 39; mean disease duration was 39.5 months. 20.79 % (n=21) of patients had skin prick test positivity, almost mite sensitivity, 24.8 %patients had positive phadiatop value, and 43.6 % patients had comorbid as an allergic disease. Acute exacerbation with non-steroidal anti-inflammatory drugs was seen in 37.6% of patients. 50.5% of patients with chronic urticarial had angioedema. No smoking history was had in 68.3 % of patients. Any patient was not well controlled (UAS7 means ≤6). 9 patients had mild (UAS7means 7-15), seven patients had medium (UAS7 means 16-27) disease, and 85 patients had severe (UAS7 means 28-42) disease. 43,6 % of patients received omalizumab treatment because of inadequate treatment with anti-histamine drugs despite the four-fold increase. Demographic characteristics, skin test results, laboratory values, disease-related findings of the patients were shown in tables 1 and 2.

Table 1. Demographic features of patients

	Frequency (n)	Percent (%)
Gender		
Female	71	70.3
Male	30	29.7
Smoking		
No	69	68,3
Yes	32	31,7
Angioedema		
No	50	49,5
Yes	51	50,5

***NSAİD usage**		
Exacerbation (-)	63	62,4
Exacerbation (+)	38	37,6
Allergic disease		
No	57	56,4
Yes	44	43,6
Dermatographism		
No	41	40,6
Yes	60	59,4
Family History for allergic disease		
No	57	56,4
Yes	44	43,6
Autologous serum skin test (ASST)		
Negative	61	60,4
Positive	40	39,6
Skin Prick Test		
Negative	38	27,63
Positive	21	20,79
Dermographism	23	22,77
None	19	18,81
Phadiatop		
Negative	73	72,3
Positive	25	24,8
Unknown	3	3
Treatment		
Anti-histamine drugs	57	56,4
Anti-histamine drugs + omalızumab	44	43,6

**NSAİD: non-steroidal anti-inflammatory drug*

Table 2. Mean and median values of variables

	Mean ± ss	Median (min-max)
Age	39,0±12,8	39 (20-65)
Disease duration (month)	39,5±37,4	25 (2-132)
Urticaria activity score (UAS7)	33,2±8,86	35 (7-42)
Eosinophil count (µ/l)	207±156,5	150 (100-800)
IgE E level (IU/ml)	252,6±294,5	122 (6-1418)
Anti-Tpo kU/L	52,4±216,5	0,9 (0,25-1637)
Lymphocyte (µ/l)	2199±632,3	2200 (900-3700)
Neutrophil/lymphocyte (NLO)	2,77±3,96	2,24(0,95-40,5)
D vitamin	17,8±7,2	16,7 (6-34)
Ferritin µg/L	38,6±50,4	24,5(2,2-374)
Vitamin B12	194,3±100,5	165,5(68-585)

Antı-TPO level compared with variables below and above nine because our reference value for anti-TPO is 0-9 kU/L. It was observed that the duration of the disease was longer in chronic urticaria patients with anti-TPO values above 9 kU/ L (n=20 19.8%) compared to those below 9 kU /L (n=81) (p=0,019). It was observed that the frequency of hypothyroidism increased in values above normal (p=0.024). As a comorbid disease, eleven patients had hypothyroidism, and one patient had hyperthyroidism. According to anti-TPO values, there was no statistical differences in gender, age, smoking history, concomitant angioedema, dermatographism, family history of allergic disease, treatment groups (anti-histamine, anti-histamine + omalizumab), phadiatop, T IgE, allergen-specific IgE E, UAS7 variables

As a result of the multiple regression analysis, it has been determined that the UAS7 value has 2,989 folding effects on the duration of the disease (Table 3). In addition to this, a positive correlation between the duration of the disease and the UAS7 (r=0,277; p=0,005) was determined. There was a weak inverse

correlation between UAS7 values and vitamin B12 values (r=0,203) of the patients (p<0,05).

Table 3. Effect of variables on disease duration

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% ınterval	Confidence
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	-115,838	125,156		-,926	,367	-378,780	147,104
UAS	2,989	1,401	,665	2,133	**,047**	,046	5,932
IGE	,004	,032	,036	,137	,892	-,062	,071
D vitamin	-,184	1,168	-,036	-,158	,876	-2,638	2,270
ASST	-1,897	18,596	-,027	-,102	,920	-40,965	37,172
Eosinophil	,006	,048	,027	,124	,902	-,094	,106
Neutrophil	,039	,025	1,382	1,565	,135	-,013	,090
Lymphocyte	,036	,038	,652	,936	,362	-,045	,116
NLO*	-17,707	23,055	-,517	-,768	,452	-66,143	30,729
Leukocyte	-,026	,016	-1,378	-1,604	,126	-,060	,008
Ferritin	,195	,275	,169	,710	,487	-,383	,773
B12	,115	,070	,371	1,639	,119	-,032	,263
Anti-TPO	-,051	,062	-,184	-,821	,422	-,182	,080
Gender	-25,132	20,931	-,337	-1,201	,245	-69,105	18,841
Age	,070	,700	,029	,099	,922	-1,402	1,541
Smoking	12,789	18,814	,172	,680	,505	-26,737	52,315
Angioedema	8,724	19,180	,126	,455	,655	-31,571	49,018
NSAID usage	-15,488	20,595	-,220	-,752	,462	-58,756	27,781
Family allergic hystory	20,122	17,251	,286	1,166	,259	-16,121	56,365
SPT positivity	-17,292	15,183	-,254	-1,139	,270	-49,191	14,606

**Neutrophil to lymphocyte ratio*
Model 1:R=0.680; R^2 =0,462; Adjusted R=0,195; F=1,473;p=0,035 (Multiple regression analysis)

There was no significant difference between the patient's ASST results (negative or positive) and gender, age, smoking history, concomitant angioedema, dermatographism, family history of allergic disease, treatment groups (anti-histamine, anti-histamine + omalizumab), phadiatop, allergen-specific IgE E, T IgE, UAS7 and disease duration of chronic urticaria. When all variables were evaluated statistically according to treatment groups, no significant results were obtained.

The patients in the our study determined as a longer disease duration in the patients with angioedema (p=0,005), dermatographism (p=0,012) and gender of female (p=0,031) (Table 4). No significant result was found when other variables of the study were compared with the duration of the illness of CU.

Table 4. Variables affecting the duration of the disease

		Disease duration	
		Mean ±ss Median (min-max)	P value
Gender	Female	44,7±40,9 36(3-132)	**0,031**
	Male	27,1±23,9 24(2-72)	
Angioedema	No	29,1±30,5 19(2-120)	**0,005**

Dermatographism	Yes	49,6±41,0 36(3-132)	**0,012**
	No	28,2±33,4 12(2-120)	
	Yes	47,2±38,3 38(3-132)	

4. Discussion

Chronic urticaria has been reported in association with numerous variables, but CSU's underlying pathology, remission time and associated factors is still unclear. CSU is more common in women, but the relationship between the severity of the disease and gender is unknown (18). The literature found a significant positive correlation between the female gender and the time to remission (19). Like other studies, 70.3 % of female patients were included in our research. Unlikely it was found that female patients had a longer disease duration (p=0,031). It may be due to the high UAS7 levels of the patients included in our study. In multiple regression analysis, it has been determined that the UAS7 value has a 2,989 folding effect on the duration of the disease. Prospective studies have shown that disease severity correlates with disease duration; that is, the more severe disease tends to last longer (20).

Previous studies were reported Comorbidity between inducible urticaria and dermatographism might also be associated with long CU duration (18, 20). In our study, 59.4 % of our patients had dermatographism. The long duration of illness was found to be statistically significant in patients with dermographism (p=0,012).

In the literature 15 of 17 (88%) and 11 of 15 (73%) studies found higher IgG anti-TPO and IgG anti-TG levels, respectively, in patients with CSU vs. controls. Only six of 29 (21%) studies did not report significantly higher rates of IgG anti-thyroid antibodies in patients with CU than controls (6). A recent meta-analysis and a study with data on 12,778 patients and 10,714 controls were determined that patients with CSU compared to control subjects had significantly higher levels of anti-thyroid peroxidase (anti-TPO) antibodies (21). Levels of IgG-anti-TPO are more often elevated in CSU than those of other thyroid antibodies. The frequency of hypothyroidism and Hashimoto's thyroiditis are higher than hyperthyroidism and Graves' disease. Thyroid dysfunction is more common in females than in male patients with CSU (22). In our study, 11 patients had hypothyroidism (9 Female, 2 Male), and one female patient had hyperthyroidism. In our study, patients' mean anti-TPO level was 52,4±216,5 kU/L, and it was observed that the duration of the disease was longer in chronic urticaria patients with anti-TPO values above 9 kU/L (n=20 19.8 %) compared to those below 9 kU /L (p=0,019). Like our study, Nordyke et al. verified that anti-TPO antibodies had more correlation with thyroid dysfunction than other thyroid antibodies (23). Previous studies showed that thyroid disease might worsen urticaria through activation of the complement system (24). C4a levels decrease when thyroid disease is treated, resulting in remission of CU (25). Thus, while it is assumed that thyroid disease and CU may coexist due to the patient's predisposition to autoimmunity, thyroid disease may additionally exacerbate urticaria, longer CU duration through direct mechanisms resulting in complement activation.

There was no significant difference between the patient's ASST results (negative or positive) and all other variables, including disease duration of chronic urticaria. Similar results have been obtained in studies from our country. They found no significant difference in age, gender, atopy, allergic disease, and thyroid autoantibody between ASST negative and positive patients (26, 27).

Mete et al. reported lower vitamin B12 levels in 33 patients with chronic urticaria than healthy controls (28). In another study, B12 levels were determined lower in patients with CSU than in the general population (29). In our study, patients' vitamin B12 and vitamin

D mean values were 194,3±100,5 and 17,8±7,2, respectively. These values were below the normal reference values. Like our study; reduced low vitamin D level was detected in patients with chronic urticaria (30). In addition to reduced low B12, we found that a weak inverse correlation between UAS7 values and B12 values (r=0,203) of the patients (p<0,05). The absence of a control group is limited to our study.

Greaves M et al. found that Atopy with CU was more common in children (58%) than in adults (23%) (31). Our atopy test results for adults were; 20.79 % and %24.8 for positivity of skin prick test and phadiatop, respectively.

In different published studies, it has been reported that urticaria accompanied by angioedema may also be linked to a longer duration of the disease, and the onset of remission is delayed (18). Approximately 40 to 50% of CU patients have concomitant angioedema (32). Similarly, 50.5% of patients had urticaria concomitant angioedema. These patients had longer disease duration than those without angioedema (p=0,005).

While the remission rate at one year in children might be higher (33), it is about 30 to 50% for adult CU patients who do not have an identified triggering factor or underlying disorder (21). We found that 26,73 % of patients were in remission in one year and 39,6% of patients in two years. In our study mean of illness duration was 39.5±37,4. The low remission rate may be due to triggering factors such as NSAİD, dermatographism and anti-TPO level, concomitant angioedema. Also, our patients have high UAS7 at the time of admission to our clinic. Drugs such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and beta-lactams are well-known triggers for CU (34). NSAIDs may exacerbate skin lesions in up to 25 to 50% of patients with CU (35). Similar to the literature in our study NSAİD's exacerbate urticarial lesions in %37.6 of patients with chronic urticaria.

5. Conclusion

It is crucial to determine the variables that will determine the duration of the disease in chronic urticaria. It has been determined that the UAS7 value has 2,989 folding effects on the duration of the disease. Anti-TPO positivity, concomitant angioedema, dermatographism, and higher UAS7 scores predicts that their chronic urticaria will last longer.

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Research Article / Araştırma Makalesi

Immediate Type Systemic Hypersensitivity Reactions After the Inactivated SARS-CoV-2 Vaccine in Healthcare Workers

Sağlık Çalışanlarında İnaktive SARS-CoV-2 Aşısı Sonrası Gelişen Ani Tip Sistemik Aşırı Duyarlılık Reaksiyonları

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Abstract

The vaccines developed for Coronavirus disease 2019 (COVID-19) not only brought hope to the struggle against the pandemic but also raised questions about hypersensitivity reactions that might occur. Although some studies regarding these concerns with mRNA COVID-19 vaccines have been published, these data on inactivated Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccine are not available. The objective of this study was to determine the safety of the inactivated SARS-CoV-2 vaccine manufactured by Sinovac by evaluating the reported systemic immediate hypersensitivity reactions (IHRs) after the administration of the vaccine to healthcare workers (HCWs). This was a retrospective analysis of inactivated SARS-CoV-2 vaccine recipients in all HCWs vaccinated at our center. Relevant data of all patients who received the vaccine were collected from the electronic medical records available at our center's database. A statistical analysis of subjects who reported acute adverse reactions was conducted. Of the 3354 HCWs vaccinated with the first dose (female 59.9%, pre-existing allergic disorder 2.4%), four acute adverse reactions (0.12%) met the definition of a systemic IHRs were reported, and only one was confirmed to be anaphylaxis. One out of these four cases received her second dose through graded administration. For the second dose, no systemic reaction was reported in our study population. Inactivated SARS-CoV-2 vaccine appears to be well tolerated in HCWs without any pre-existing allergic disorders.

Keywords: Allergy; coronavac; covid-19; hypersensitivity; Turkey; vaccine

Özet

Koronavirüs hastalığı 2019 (COVID-19) için geliştirilen aşılar, pandemi ile mücadelede umut ışığı sağlarken bir yandan da oluşabilecek aşırı duyarlılık reaksiyonları hakkında soru işaretlerini de beraberinde getirmiştir. Yeni mRNA COVID-19 aşıları ile ilgili bu endişelere ilişkin bazı çalışmalar yayınlanmış olsa da inaktive Şiddetli Akut Solunum Yolu Sendromu Koronavirüs 2 (SARS-CoV-2) aşıları ile ilgili veriler yaygın değildir. Bu çalışmanın amacı, aşının sağlık çalışanlarına uygulanmasından sonra bildirilen sistemik ani aşırı duyarlılık reaksiyonlarını (ADR'ler) değerlendirerek Sinovac tarafından üretilen inaktive SARS-CoV-2 aşısının güvenliğini belirlemektir. Merkezimizde inaktive SARS-CoV-2 aşısı ile aşılanan tüm sağlık çalışanlarını retrospektif olarak inceledik. Aşı yapılan tüm hastaların ilgili verileri merkezimizin veri tabanında bulunan elektronik tıbbi kayıtlardan toplanmıştır. Akut advers reaksiyonlar bildiren deneklerin istatistiksel bir analizi yapılmıştır. İlk dozla aşılanan 3354 sağlık çalışanından (kadın %59,9, önceden var olan alerjik durum %2,4), sistemik ani tip aşırı duyarlılık reaksiyonu tanımını karşılayan dört akut advers reaksiyon (%0,12) bildirilmiştir. Sadece birinin anafilaksi olduğu doğrulanmıştır. Bu dört vakadan biri ikinci dozunu dereceli uygulama yoluyla almıştır. İkinci doz için, çalışma popülasyonumuzda herhangi bir sistemik reaksiyon bildirilmemiştir. İnaktive edilmiş SARS-CoV-2 aşısı, önceden herhangi bir alerjik hastalığı olmayan sağlık çalışanlarında iyi tolere edilmiş gibi görünmektedir.

Anahtar Kelimeler: Alerji; aşı; aşırı duyarlılık; coronavac; covid-19; Türkiye;

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1. Introduction

The pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a global public health concern which already took over two million lives and continues to threaten every individual on the planet earth. As of January 31, 2021, Turkey reported 2,477,463 confirmed cases of coronavirus disease-2019 (COVID-19) and 25,993 deaths (1). Vaccination, a miracle of modern medicine, has become the best chance to control this pandemic. After extensive study and work of devoted scientists, humanity now has numerous vaccines against the COVID-19. However, several questions arise regarding their safety. One of these questions focuses on the allergic potential of these vaccines. Although hypersensitivity reactions due to vaccines are not uncommon, systemic severe allergic reactions like anaphylaxis are rare (2, 3). A vaccine safety datalink study reported an incidence rate of 1.31 (95% confidence interval, 0.90-1.84) The anaphylaxis cases per million doses and found that majority of these cases had pre-existing atopic diseases (4). Due to a possible hypersensitivity reaction, The Centers for Diseases Control and Prevention advised observation of all patients for at least 15 minutes and monitorization of patients with allergy history at least 30 minutes after vaccination (5). After the authorities' approval, two COVID-19 mRNA vaccines from Pfizer-BioNTech and Moderna have been used in several countries. Although the results of phase III trials showed that these vaccines were relatively safe after the initiation of the COVID-19 vaccination program, there were some reports of allergic reactions in the United Kingdom and the United States of America (6, 7). Most of these reactions were mainly attributed to the polyethylene glycol (PEG) component of these vaccines (8, 9).

CoronaVac, the vaccine developed by Sinovac Life Sciences (Beijing, China), is an inactivated SARS-CoV-2 vaccine created from African green monkey kidney cells and contains aluminum hydroxide as an adjuvant. Inactivation of SARS-CoV-2 is achieved with β-propiolactone (10). After the promising results of this vaccine in phase 1/2 clinical trials, the Turkish Ministry of Health permitted this vaccine's applicationon14 January 2021 to be used in two specified doses at one-month intervals (10). The first group selected for vaccination included healthcare workers (HCWs). Because CoronaVac clinical trials excluded patients with known allergies, the question regarding the safety of applying this vaccine to allergic individuals remains unanswered (10-12). People with prior allergies may fear these side effects and step back for vaccination, which may result in a failure to reach the goal of aluminum. In our retrospective study, we evaluated the frequency of systemic immediate hypersensitivity reactions (IHRs) developed within the first two hours of the first and second doses of CoronaVac administration in 3354 HCWs. We aimed to determine its safety in individuals with a previous history of allergies or allergic reactions.

2. Material and methods

Study Design and Population

We performed a retrospective evaluation of CoronaVac administration to 3354 HCWs between 18 and 65 years of age. The study included 80 HCWs with pre-existing allergic diseases and 3274 HCWs without a pre-existing allergic disease. All were vaccinated with CoronaVac 600 SU/0.5mL at Eskisehir City Hospital. The data were collected from the hospital's electronic database and were recorded in terms of their demographic characteristics, past laboratory results, and post-vaccination symptoms. A systemic IHR after vaccination was defined according to World Health Organization and related literature, and anaphylaxis was defined according to World Allergy Organization (13-15). Local reactions such as erythema and itching at the injection site were not included in this study. The clinical symptoms of each case were retrospectively evaluated according to the Brighton Collaboration case definition (BCCD) level (16). History of pre-existing allergic disease was confirmed by an allergy specialist for patients who had a positive skin prick test result (wheal > 6mm) or a significant allergen-specific immunoglobulin

E (IgE) result (>3.5kUa/L) or a history of an associated hypersensitivity reaction after the administration of a drug.

The study was approved by the Ethics Committee of the Faculty of Medicine at Eskisehir Osmangazi University (Decision No. 19, dated 09.02.2021).

Vaccination Procedure

All HCWs were voluntarily vaccinated via the intramuscular route in the area reserved for them in the hospital according to the recommendations of the Turkish Ministry of Health Vaccine Application Guidelines which included allocation of a separate area for vaccination, preparation of experienced staff, and an emergency response team, and observation of individuals with allergies for at least one hour after administration.

Statistical Analysis

In our study, qualitative variables were defined with absolute frequencies and percentages. The definition of quantitative variables was made using mean, standard deviation (SD). Categorical data are given as a percentage (%). Shapiro Wilk's test was used to investigate the compatibility of the data for normal distribution. In the comparison of groups that do not conform to normal distribution, the Mann-Whitney U test was used for cases with two groups. IBM SPSS Statistics 21.0 program was used in the application of the analyses.

3. Results

Between 14 January 2021 and 18 January 2021, 3254 and 80 non-allergic and allergic HCWs received their first doses of the vaccine. Within one month following the first dose, the second dose was administered to 3187 and 76 non-allergic and allergic HCWs, respectively. Demographic characteristics of the study group and the number of systemic reactions seen after the two doses of the vaccine are shown in Figure 1. Eighty of these patients had pre-existing allergic disorders diagnosed by an allergy specialist prior to the vaccination. The distribution of these disorders was as follows; allergic rhinitis (n=32), chronic urticaria (n=13), drug allergy to antibiotics (n=9), HSR to non-steroid anti-inflammatory drugs (n=7), miscellaneous drug allergy (n=5), latex allergy (n=6), allergic contact dermatitis (n=3), allergic asthma (n=3), venom allergy (n=2). According to our database, a total of 4 systemic IHRs were reported and of these four patients, three had pre-existing allergic disorders. Characteristics of these cases are summarized in Table 1.

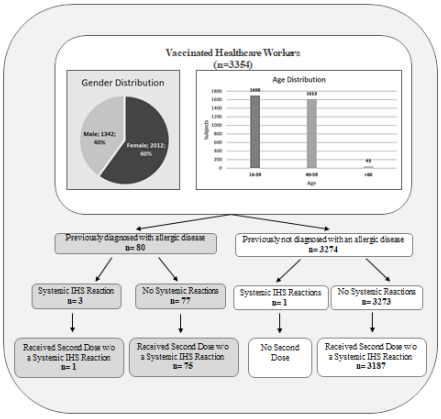

Figure 1. Characteristics of vaccinated healthcare workers and number of immediate hypersensitivity reactions

Figure Legend 1. *This flow chart demonstrates the characteristics of the vaccinated healthcare workers. All 3354 patients received the first dose and 3263 received the second of the inactivated SARS-CoV-2 vaccine manufactured by Sinovac Life Sciences at the same health institution. Of all, 80 were patients with a previous history of allergist-diagnosed allergies. Of these 80 patients, 3 reported a systemic immediate hypersensitivity reaction. Only 75 out of 77 allergic patients and 3187 out of 3273 non-allergic patients who safely tolerated the first dose of the vaccine were vaccinated with the second dose.*
(w/o; Without, IHRs; Immediate Hypersensitivity Reactions)

Table 1. Characteristics of cases of early adverse reactions following the first dose of CoronaVac administration (n=4)*

No.	Age (yrs.)	Sex	History		Onset (mins)	Signs and symptoms, Treatment Setting and Outcome	BDDC Level¶
			Allergic Disorders†	Previous Anaphy. †			
1	28	F	Chronic Urticaria	No	60	Itchy hives and tachycardia. Symptoms disappeared without treatment. Discharged home. Did not receive 2nd dose.	3
2	40	F	Allergic Contact Dermatitis, to Latex and Nickel	No	10	Generalized hives and respiratory distress. Recovered in 3 hours at level 1 ICU. Discharged home. Did not receive 2nd dose.	1
3	29	F	Muscle Relaxants	No	10	Urticaria and tachycardia. Recovered in 3 hours at level 1 ICU, discharged home. The second dose was administrated.	3
4	39	M	No	No	15	Generalized hives and a sensation of throat Treated at level 1 ICU and recovered in 2 hours. Discharged home. Did not receive 2nd dose.	2

Anaphy. = Anaphylaxis; ICU = intensive care unit; F = female; M = male; No. = number; Yrs = Years

** The production of this table was inspired by publications in the literature to provide visual integrity (6, 7).*

† Was accepted positive if the previous history of allergies or anaphylaxis were documented or confirmed by an allergist.

¶ To determine degrees of medical certainty, the Brighton Collaboration case definition (BDDC) uses combinations of symptoms. The highest degree of diagnostic confidence that a recorded case is actually a case of anaphylaxis is defined by Brighton level 1. Levels 2 and 3 are successively lower levels of diagnostic certainty. [15]

The first patient (a 28-year-old female) was under evaluation for slightly elevated basal serum tryptase levels (10.2 ng/ml) and had chronic urticaria. She was under regular antihistamine treatment at the time of vaccination. After 1 hour of the administration, the patient reported itchy hives over her chest area and tachycardia, which resolved in a short time without any intervention. Her tryptase level during this reaction was 11.2 ng/ml. This patient did not want to have the second dose of the vaccine.

The second patient (a 40-year-old female) was diagnosed with allergic contact dermatitis due to latex and nickel allergy, confirmed by a patch test. Ten minutes after the administration, she developed generalized hives and reported respiratory distress 10 minutes after the administration. Her examination revealed urticaria and rhonchi on osculation. She was immediately admitted to a level 1 intensive care unit (ICU) where she received 45.5 mg of intravenous diphenhydramine and 80 mg of methylprednisolone. No tryptase or any other blood study was performed. She was recovered within 3 hours and discharged home after 10 hours. This patient did not want to have the second dose of the vaccine.

The third patient (a 29-year-old female) was with a history of allergy to several muscle relaxants. Ten minutes after the administration, she developed urticaria and tachycardia. She was immediately admitted to the level 1 ICU and where she received 45.5 mg of intravenous diphenhydramine and 80 mg of methylprednisolone without further progression of symptoms. She was recovered in 3 hours. No blood sample was sent for tryptase level. The second dose of the vaccine was administered in graded doses under observation, and she tolerated it well without any symptoms. The protocol for graded administration is presented in Table 2.

Table 2. Protocol for graded administration of second dose of CoronaVac [21, 27]

Step*	Dose and Concentration
1	0.05 mL of 1:10 vaccine dilution**
2	0.05 mL of full-strength vaccine
3	0.1 mL of full-strength vaccine
4	0.15 mL of full-strength vaccine
5	0.2 mL of full-strength vaccine

The fourth patient (39-year-old male) was the only case in our study group who was not diagnosed with an allergic disorder prior to the vaccination. He reported generalized hives and a sensation of throat closure after 15 minutes of the administration. His physical examination revealed urticaria. The patient was admitted to the level 1 ICU where he received 45.5 mg of intravenous diphenhydramine and 80 mg of methylprednisolone. His symptoms resolved in two hours, and he was discharged home. This patient did not wish to have the second dose of the vaccine.

4. Discussion and conclusion

In our study population, we found the frequency of patients who reported a systemic IHRs as 0.12% (n=4) for the first dose and zero for the second dose. However, only one met the criteria of anaphylaxis (13). Out of these reactions, two were observed in patients with a pre-existing allergic disorder, and only one of them gave consent for the second dose of the vaccine. This study provides evidence about using the inactivated SARS-CoV-2 vaccine produced by Sinovac Life Sciences (CoronaVac) in HCWs without pre-existing allergic disorders. Although CoronaVac was well tolerated in most of the patients, there are still many questions that need to be answered regarding reported allergic reactions.

Thanks to vaccination, one of the most valuable public health interventions, significant reductions have been observed in the spread and mortality of infectious diseases (3, 14). As with any other drug, allergic reactions can also be observed with vaccines but fortunately, most of them are not severe (17). Nevertheless, nowadays, when the whole world is preparing and even started vaccination programs with unprecedented intensity, allergic reaction to vaccines has come to the attention. Although only 21 vaccine-related adverse events were reported after administration of 1,893,360 doses of Pfizer-BioNTech COVID-19 vaccine, this finding of the possible allergic potential of COVID-19 mRNA vaccines has given ground to discussions (6). Some researchers suggested that PEG, an excipient in mRNA vaccines, may have a role in allergic reactions (8, 9). While there is no hard evidence proving PEG as the cause of reported allergic reactions, these discussions do not apply to CoronaVac because this vaccine does not contain PEG. The adjuvant in CoronaVac, aluminum hydroxide, is one of the most frequently used adjuvants in vaccines which is known to induce contact allergy and nodules at the injection site (2, 3). Because there is no aluminum hydroxide-related IHRs reported to date, we don't suspect the history of metal allergy as the cause for the anaphylaxis reported in our second patient (No 2.).

Published studies regarding the safety and tolerability of CoronaVac are limited. Two phase 1/2 clinical trials done in China included a total of 923 patients who received a sum of 1838 doses and reported only two hypersensitivity reactions which only one was considered (a manifestation of urticaria) to be related to the vaccination (10, 12). As a result, the authors concluded that CoronaVac was well tolerated in adults aged 18 years and older. Since these studies included only healthy adults and excluded patients with known allergies, it may not be appropriate to compare their results with our study, which included 80 patients with pre-existing allergic disorders. A patient with a history of an allergic disorder may experience anxiety before vaccination and therefore may be unwilling to be vaccinated. In the literature, there are several studies and practice parameters advising not to exclude these patients from vaccination (2, 18-22). A study that included 478 children with asthma who were vaccinated with the live attenuated influenza vaccine reported that the vaccine was well tolerated (22). A phase 1 study that evaluated the safety of the smallpox vaccine in patients with atopic eczema and allergic rhinitis showed a good safety profile (23). In our study, a total of 32 patients with allergic rhinitis and 3 with allergic asthma were safely vaccinated with CoronaVac without reporting an IHR. More interestingly, there were six patients with allergist-diagnosed latex allergy in our cohort, and most of them tolerated the vaccine. Although the current Turkish package insert of CoronaVac does not indicate natural rubber latex in its tip caps on the

prefilled syringe, in the vaccine vial stopper, and the needle cover, it is known that many vaccines contain dry natural rubber (DNR) latex (24). A review of more than 167,233 Vaccine Adverse Event Reporting System (VAERS) notifications reported only 28 patients that developed a possible allergic adverse event after receiving a DNR containing vaccine (18). The authors of this study concluded that vaccines that contain DNR are associated with minimal risk of IHRs. Unfortunately, our sample size is too small to come to such a conclusion. Still, we consider our finding valuable because our study is the first to evaluate the administration of CoronaVac to patients with latex allergy.

As the whole world prepares for massive vaccination, allergists will play essential roles in not only supporting the allergic patients to receive the vaccine but also in training the clinical staff conducting the vaccines about the management of anaphylaxis. A striking result of our study was to see that epinephrine administration was not considered to any of the patients that experienced systemic reactions. This may be due to the quick and good response of our patients to steroids, antihistamines, and inhale salbutamol. Nevertheless, we believe it would not be wrong to administer it to the second and fourth patients (No.2 and No 4.). Anaphylaxis is an acute, potentially life-threatening hypersensitivity reaction. While epinephrine is a vital therapy for recovering from anaphylaxis, a recent review that evaluated several studies have stated that it is underused (25). In a such time, when everyone is a candidate for COVID-19 vaccination, a possible challenge lies in avoiding overdiagnosing anaphylaxis as Greenhawt et al. mentioned in their editorial (26). A patient in our study reported cold and pale skin shortly after the injection which are characteristic symptoms for vasovagal reactions. We suggest that all the clinical staff working in vaccination should know the differences between an IHR and a vasovagal reaction in order to correctly classify the acute adverse reactions (2). Therefore, we consider that allergists' expertise will be needed even more in the days to come.

Our study had several limitations and some strengths. Firstly, the insufficient sample size for statistical measurement prevented us from suggesting any precise clinical implication. Since immediate reactions to vaccines, including COVID vaccines is rare, this sample size may be inadequate to draw significant conclusions. Secondly, our study group included only HCWs, which is quite a heterogeneous group in regard to disorders. This limitation is a result of the emergency use authorization giving HCWs prioritization in the vaccination program. Interestingly not all HCWs who safely tolerated the first dose were vaccinated with the second dose We lack the data on why these HCWs did not receive their second doses. Thirdly, the lack of tryptase analysis for all reported acute reactions made it difficult for us to interpret them. Also, since our study group was HCWs, a population not easily impressed by late or mild local reactions, we had to limit our study to systemic reactions developed in the first two hours. Lastly, when considering the typical prevalence of allergic diseases in our country (7%-%20), it could have been expected that in a population of over 3000 people, there should have been at least 200 patients with known allergies. This resulted from our intention to make our database more reliable since we only accepted an individual as allergic if proven by an allergist; this may have impacted our sample size. The strengths of this study are that, to the best of our knowledge, this is the largest study documenting the tolerability of CoronaVac in a cohort that includes allergic patients and the first report documenting the safe administration of the second dose of CoronaVac through a graded dosing protocol. At the time in Turkey, the only available COVID-19 vaccine other than CoronaVac was the Pfizer-BioNTech vaccine. However, due to some concerns, our patient had she did not wish to be vaccinated with this vaccine. Therefore, we chose to vaccinate her with CoronaVac for the second time. Our graded dosing protocol has been adapted from the practice parameter about adverse reactions to vaccines which was published in 2012 (21). In a recent report, a similar protocol was safely used on two patients who experienced an IHR with the first dose of the Moderna COVID-19 vaccine (27).

In our study, we evaluated the frequency of systemic IHRs after the first dose of CoronaVac administration to a total of 3274 non-allergic and 80 allergic HCWs. The second dose of the vaccine was administered to 3187 and 76 non-allergic and allergic HCWs, respectively. Our results suggest that CoronaVac was well tolerated in HCWs without pre-existing allergic disorders. The results of this research provide the first comprehensive assessment of the idea that patients with known allergies may be vaccinated by educated staff who are equipped to manage anaphylaxis. Further research would be helpful to determine the safety of CoronaVac administration in allergic patients.

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Authors' contributions

A.U. and P.Ç. contributed to the design and implementation of the research, the analysis of the results, and the writing of the manuscript

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Research Article / Araştırma Makalesi

Spine Surgery During the COVID 19 Pandemic: One Trauma Center Experience in Central Anatolia

COVID 19 Salgını Sırasında Omurga Cerrahisi Orta Anadolu da Bir Travma Merkezi Deneyimi

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Abstract

The COVID-19 has affected all aspects of public health. In order to preserve valuable medical resources, most health care systems have halted elective and non-essential surgeries. Spine surgery is no exception in this period. However, defining essential and non-essential surgeries, the management of patients and due screening process has made a clear algorithm a must. The patients operated for various spinal surgeries during a 9-month period at an only reference trauma and spinal surgery performing secondary step state hospital in Central Anatolia were evaluated. During this time period, a guideline in discriminating essential surgeries, handling the pre and post-operative course based on previous publications and recommendations was formed. During this period 70 spinal surgeries were performed. The patients were categorized into 2 groups; 1- no to low risk and 2- high risk to definite group. Each group of patients underwent distinct process during their hospital stay in order to minimize the risk of contamination. No patient operated on was diagnosed with COVID-19 during their hospital stay or 10 days following their discharge. The COVID-19 pandemic is an ongoing process. Numerous centers have shared their experiences while still fighting the contagion. This paper aimed to share an experience of a single trauma hospital of a city serving a population more than 250,000. Numerous more studies based on evidence based medicine are needed to frame a golden standard approach for surgical candidates during the pandemic.

Keywords: COVID-19, pandemic, essential, elective, spine surgery

Özet

COVID-19 pandemisi halk sağlığını tüm yönleriyle etkiledi. Kısıtlı sağlık kaynakları korumak amacıyla çoğu sağlık sistemi seçmeli ve zorunlu olmayan ameliyatları durdurdu. Omurga cerrahisi de bu süreçte etkilendi. Fakat acil ve elektif ameliyatların tanımlanması, yapılması planlanan ameliyatlar öncesi, sırası ve sonrasında alınması gereken önlemlerin geliştirilmesi ve net bir algoritma yaratılması zorunlu hale getirmiştir. Bu çalışmada 9 aylık süreçte İç Anadolu'da bir şehrin tek travma ve omurga cerrahisi yapan ikinci basamak bir devlet hastanesinde omurga ameliyatı yapılan hastalar değerlendirildi. Bu süreçte daha önceki yayınlara ve önerilere dayalı olarak, acil ve elektif ameliyatların ayırt edilmesi, ameliyat öncesi ve sonrası sürecin ele alınması konusunda bir kılavuz oluşturulmuştur.Bu dönemde 70 omurga cerrahisi yapıldı. Hastalar COVID-19 açısından 1- düşük riskli ve 2- yüksek riskli olarak iki gruba ayrıldı. Kontaminasyon riskini en aza indirmek için her hasta grubuna hastanede kaldıkları süre boyunca gerekli tedbirler uygulandı. Ameliyat öncesi hazırlık döneminde, acil veya elektif ve risk grubuna göre önlemler alınarak paylaşıldı. Ameliyat edilen hiçbir hastaya hastanede kaldıkları süre boyunca veya taburcu olduktan 10 gün sonra COVID-19 teşhisi konmadı. COVID-19 pandemisi devam eden bir süreçtir. Çok sayıda merkez salgınla mücadele ederken deneyimlerini paylaştı. Bu makale, 250.000'den fazla nüfusa hizmet veren bir şehrin tek bir travma hastanesi deneyimini paylaşmayı amaçlamıştır. Pandemi sırasında cerrahi adayları için altın standart bir yaklaşımı belirlemek için kanıta dayalı tıp üzerine temellendirilen çok sayıda çalışmaya ihtiyaç vardır. Bu vaka serisi ile gelecekte yapılacak olan algoritmalar için kanıt sunulmuştur.

Anahtar Kelimeler: COVID-19, pandemi, esansiyel, elektif , omurga cerrahisi

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1. Introduction

On March 11th, 2020 the General Director of the World Health Organization (WHO), Dr. Tedros Adhanom Ghebreyesus announced the pandemic breakout of Coronavirus Disease 2019 (COVID-19) (4). COVID-19 caused by the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is primarily transmitted through aerosols and causes pulmonary infection in humans. In his briefing, he summarized that this virus broke out from Wuhan, China and has logarithmically increased in the last two weeks and the worst is yet to come. There are many take home messages from the briefing. The world, in all considerations has changed ever since from economics to politics, from sports to the health system. But his summary in four key areas can be applied to all fields and spine surgery is not exempt from it;

"First, prepare and be ready.
Second, detect, protect and treat.
Third, reduce transmission.
Fourth, innovate and learn."

The first case of COVID-19 in Turkey was recorded on 11 March and as of December 18, 2020 there are almost two million people diagnosed with COVID-19 in Turkey alone, making it the 6th country with most cases. Since March, strategies to contain the pandemic have involved the health system, politics and public coordination. In terms of the health system, it has shifted towards more urgent related treatments and COVID-19 diagnosis, treatment and follow-up. With the advice of the Coronavirus Scientific Advisory Board of the Ministry of Health in Turkey, on March 17th, 2020, just 6 days after the WHO briefing, all non essential and non urgent surgical interventions were halted (no. 14500235-403.99) (10). Thus similar questions boggled the minds of all spine surgeons; patient selection criteria, when and how to operate and the postoperative period. In this paper, a 9-month experience from the only spine surgery performing state hospital in a city is shared considering the diagnosis, inclusion criteria, anesthesiology and surgical management, and follow-up at the hospital until discharge with possible recommendations.

2. Methods

The study was performed in agreement with the ethical standards specified in the Declaration of Helsinki and was accepted by the Research Ethics Committee of Çankırı Karatekin University (No. 463/010321). Approval from the Ministry of Health in regards to studies involving COVID-19 cases was obtained (2020-12-24T18_44_57). All patients read and signed the consent form before being included in the study.

Patient Considerations

The surgical unit at Çankırı Karatekin Hospital; a secondary step state hospital, is the only center in the region performing complex spinal surgeries serving a population over 250,000. It is also based near a major route connecting the black sea region to the capital city Ankara and the most populous city of Turkey, Istanbul, hence becoming a referral trauma center. The present investigation consists in a retrospective one center analysis of a 9-month period from March 17 till December 17. All patients referred from the emergency room (ER), COVID wards and the outpatient clinic for possible spine surgery indications were evaluated. Inclusion criteria for surgery are listed in table 1. The surgical procedures were categorized into two major groups; 1. No-low risk group, 2. High risk-definite group (Table 2).

Table 1. Patient Selection Criteria

Inclusion
Vertebra fracture with a score of 4 or higher in the SLIC or TLICS classification regardless of American Spinal injury Association (ASIA) impairment scale (AIS)
Vertebra fracture causing root or cord injury evidenced by neurological examination
Spinal stenosis or herniation of nucleus pulposus causing; **- unbearable radicular pain resistant to all sorts of analgesic treatment** **- motor strength at the affected level of muscles is less than 4/5** **- myelopathy / myelomalacia**
Progressive weakness, foot drop and cauda equine syndrome
Malignancy or infectious diseases of the spine needing urgent intervention
Failed previous spinal instrumentation; **- Screw loosening, pull out, rod fracture, cage migration**
Exclusion
Herniation of nucleus pulposus; **- at any level responsive to analgesic treatment** **- with affected level of muscles having a motor strength of 4/5 or more** **- with possible COVID-19 infection**
Chronic lumbar degenerative disorders with aggravated pain
Patient with a grade of 3 or higher in the American Society of Anaesthesiologists' (ASA) classification of Physical Health that may require post operative ICU stay

At the outpatient department, if surgery was indicated, the patient was questioned for fever, cough, fatigue, anorexia, shortness of breath, sputum production, loss of taste and smell, sore throat, diarrhea and nasal congestion. If no symptoms were present, nasopharyngeal swab polymerase chain reaction (PCR) test was performed at least 48 hours before the surgery day. If the patient presented with mild symptoms or had a history of contact with a COVID-19 patient, at least 2 negative PCR tests were obtained with at least 48 hours separated between the tests. If the patient presented with major symptoms such as fever, cough, shortness of breath, loss of taste and smell, or close contact with a COVID-19 patient, a non contrast enhanced thorax computerized tomography (CT) along with 2 negative PCR tests separated by 48 hours were obtained prior to surgery. The patient was advised to quarantine themselves at the interval between the test and surgery. Any patient with a positive PCR test or a positive CT scan at the outpatient department were first referred to the infectious diseases department for treatment, after the COVID treatment was finalized at least two negative PCR results timed 48 hours apart was obtained before surgery.

Table 2. Patient Risk Categories

Group	Category	COVID-19 Symptoms	Investigation
1	None	No symptoms	Negative PCR test
	Low	Mild* symptoms	2 negative PCR tests 48h apart
2	High	Major** symptoms or undetermined ER patient	2 negative PCR tests 48h apart and a negative Thorax CT scan
	Definite	Major symptoms	Positive PCR test and/or positive Thorax CT findings

Mild: fatigue, sore throat, nasal congestion, myalgia
**Major: fever, cough, shortness of breath, loss of taste and smell or close contact with a diagnosed patient*

For urgent cases evaluated at the ER, a nasopharyngeal swab PCR test was ordered and a thorax CT was obtained. For vertebral fractures, patients with a score of 4 or higher in the thoracolumbar injury classification and severity score (TLICS) and subaxial cervical spine injury classification (SLIC) were operated. All these cases were operated as a high risk group. The patients were followed up on at the ward as a COVID positive patient until the first swab test at the ER and postoperative 24th hour swab test revealed to be negative with a normal thorax CT. If the patient presented with a typical thorax CT scan of COVID pneumonia, COVID treatment was started right after the operation. After the surgical follow up period was finalized, the patient was transferred to the COVID ward. The process of preparing the patient surgery is summarized in figure 1. All patients indicated for surgery were informed of the ongoing pandemic, the possible risk of nosocomial infection and the necessary precautions that have to be made by the patient and their relatives.

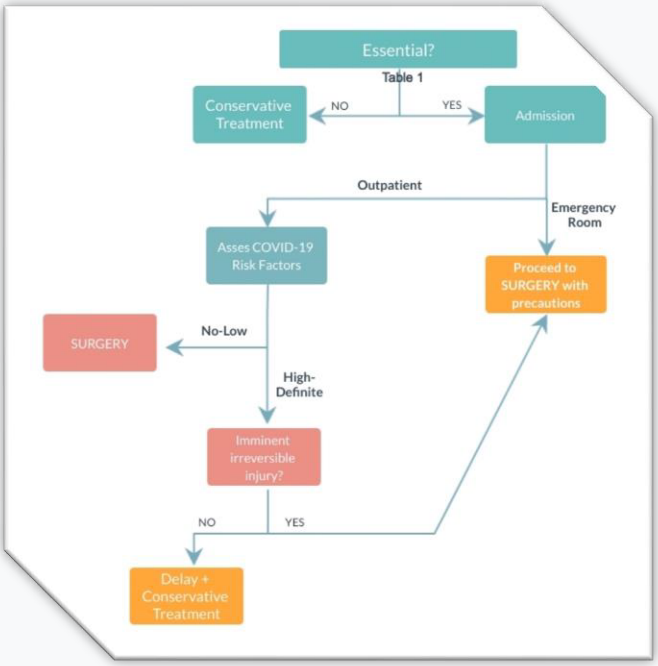

Figure 1. Pre Operative Patient Planning

Institutional Considerations

Although the Ministry of Health continuously published guidelines to all hospitals, each hospital improvised these guidelines according to the hospital size, number of other pandemic hospitals in the city, number of patients, staff number and intensive care unit (ICU) capacity. At our hospital, elective cases have been halted since March 17 and surgeons have been advised to evaluate patients and postpone elective surgeries where possible.

All admittance to the hospital required temperature measurement along with risk factor screening and a strict mask requirement and social distancing were implemented. A stern no visitor rule was applied at the wards. All patients were monitored, attended to and ambulated by nurses. The patients were educated about the precautions required in regards to the ongoing pandemic such as hand hygiene, mask, social distancing and visitor restriction.

All staff was routinely screened for fever, symptoms, and contact with a COVID-19 patient without personal protective equipment (PPE). They were also trained for PPE usage and careful attention to other staff in order to warn them of any improper use of PPE.

After discharge, the patients were scheduled for a one-time follow up examinations 10 days after the surgery. Thereafter, they were given contact details of the hospital and all questions were handled via phone conversation and only when the surgeon deemed it fit, the patient was called back to the hospital in order to minimize face to face clinic visits. All patients were questioned for COVID symptoms up until 10 days after discharge.

Surgical Considerations

The patients were operated on 2 categories. The first group of patients were either no to low risk group, who had no symptoms of COVID-19 and had a negative PCR result or mild flu like symptoms with 2 normal PCR tests and a negative thorax CT. This group of patients were operated via standard operating room (OR) techniques. The second group of patients was the high risk to definite positive group. These patients were unavoidable patients from the ER with undetermined status or a pre operative CT scan typical of COVID-19 pneumonia. During the high risk group operations, all OR personnel used FFP3 type masks with an addition of face shields along with standard surgical PPE. All the surgical equipment went through standard sterilization techniques.

If the patients were transferred to the ward postoperatively and had no previous history of ICU stay, 1-4 days of observance were allowed before discharge. The patients were educated on red flag signs that may appear at home, mobilization techniques and wound care.

OR Considerations

The individual rooms of the OR had separate air-handling units with high efficiency particulate air (HEPA) filters. All non-essential personnel were restricted in entering the OR. All patients had a surgical mask until the intubation period. The approach for the high risk to definite patients differed from this point on.

The surgical team attended the surgery with N95 masks, hooded AAMI level III gown and gloves but did not receive any prophylactic treatment (Figure 2). During intubation and extubation, the operating team exited the room and only the anesthesia team consisting of two was allowed to remain in the OR to decrease contamination risk. The patient was allowed to recover in the OR when possible to avoid being transferred to the recovery room before the ward. Postoperatively, the surfaces of all equipment in the operating room were thoroughly wiped and when possible allowed for a 6 hour off period. The surgeon and the surgical team changed the scrubs and masks after each operation.

Figure 2. Scrub nurse with PPE during a lumbar fracture operation

The OR was stocked with all possible medications, fluids and other equipment that may be necessary intraoperatively to minimize room traffic. Prone position was the most commonly employed approach but when anterior approach was necessary, the patient's nostrils and mouth was covered by a cotton sponge after intubation.

If the patient needed time in the recovery room, only 2 patients were allowed at one time at a three bed recovery room. All the staff in the recovery room used N-95 masks. The patients had a surgical mask over the oxygen mask. The stay in the recovery room was minimized as much as possible.

3. Results

The patients referred from the COVID wards were evaluated for the surgical inclusion criteria as well. But no patient met the inclusion criteria so only conservative treatment and a follow up examination after COVID treatment were advised. During this 9 month period, a total of 70 patients were operated on and are summarized in table 2. 11 of the patients were operated from the ER and included in group 2 whereas the rest were from the outpatient clinic and other wards and included in group 1. None of the patients were diagnosed with COVID-19 during their hospital stay and 10 days following discharge. Patients operated for Cervical and Lumbar HNP (herniated nucleus pulposus) were discharged on the first day after surgery. The patient with C5-6 dislocation was transferred to a physical therapy and rehabilitation hospital 6 days after the surgery and the patient with T11 CSF fistulae received IV anti biotic for 14 days after surgery, the rest of patients were discharged on average 3.1 days after surgery. No patient experienced any complications or problems during their stay at the hospital. All patients but the C5-6 dislocation was ambulatory at the time of discharge.

Table 3. List of Operated Patients

Diagnosis	Number	Referral	Group
Thoracolumbar Fracture	*9*	*ER*	*2*
T9 Burst	2		
T12 Burst	2		
L1 Burst	4		
L4 Burst	1		
Cervical Fracture	*2*	*ER*	*2*
C5-6 Dislocation Fracture	1		
C5 Flexion tear drop fracture + unilateral facet dislocation	1		
Vertebral Malignancy + Infections	*6*		*1*
T11 CSF fistulae / paravertebral muscles abscess	1	Outpatient Clinic	
Wound infection after C1 anterior arch fracture	1	Infectious Diseases Ward	
T1-2 intradural meningioma	1	Outpatient Clinic	
Giant cell tumor of sacrum	1	Outpatient Clinic	
L4 metastasis of prostate cancer (Tomita 4)	1	Internal Medicine Ward	
T8 metastasis of prostate cancer (Tomita 6)	1	Outpatient Clinic	
Spinal Stenosis	10	Outpatient Clinic	1
Cervical	1		
Thoracic	1		
Lumbar	8		
Herniation of Nucleus Pulposus (HNP)	37	Outpatient Clinic	1
Cervical	9		
Lumbar	28		
Instrumentation Failure/Revision	6	Outpatient Clinic	1
Lumbar Stenosis	3		
Lumbar Fracture	2		
Thoracic Fracture	1		
TOTAL	70		

4. Discussion

Although besides a few case reports, the COVID-19 virus does not seem to have a major impact on the spinal cord and peripheral nerves. But the high contagiousness of the virus along with worldwide depleting resources such as doctors, operating rooms, ICU beds, etc., has brought the necessity of adequate adjustments to everyday clinical entities including spine surgery. All medical specialties at this time of pandemic, has halted all possible elective treatment modalities in order to preserve resources. Thus a clear algorithm encapsulating all aspects of the disease must be developed. This paper aimed to evaluate the selection criteria and all considerations pertaining to spinal surgery during the COVID-19 pandemic at a single institution performing the only spinal surgeries of a city in Anatolia.

Before the COVID-19 pandemic broke out all spine surgeons had their own surgical considerations based on literature and experience. However as elective operations are halted, non essential surgical considerations have been postponed. There are no clear guidelines on which operations should be postponed or operated on during the pandemic. The dilemma arises from operating patients that may increase contamination when they could be postponed. Although the normal incubation period of COVID-19 is 5-14 days there have been cases of up to 24

days. The alarming level of mortality of 3.6% just adds to the complexity of the issue. Last but not least, the increasing rate of infection among health care workers should limit surgeons on operating non essential patients (11).

The inclusion criteria used at this institution was constructed in order to delay possible surgeries to minimize risk of contamination and conserve valuable resources. Previous similar studies where experiences have been shared, a wide variety of inclusion criteria have been implemented (9,11). But there are also proposes where nothing but traumatic fractures and malignancies should be operated. In this experience, four major considerations have guided the inclusion criteria; pain, instability, neurological deficit and irreversible injury.

As the Hippocratic dictum states "'Divinum est opus sedare dolorem" - Divine is the work to subdue pain. The patients operated on disc hernias at the institution who did not present with major neurological deficits, foot drops or cauda equine syndrome where surgery was considered essential, all possible analgesic treatments were given including NSAIDs, opioid analgesics, short course of rest and epidural steroid injections. However, when these modalities failed and the patient was unable to continue standard daily activities the operation was considered essential.

The criteria for instability were considered for ER patients presenting with a vertebral fracture. While other studies evaluated American Spinal Injury Association (ASIA) impairment scale for surgical indication (11), this institution only used the TLICS and SLIC scale. These scales both include neurological status; however the presence or absence of neurological deficit does not allow the determination of instability. The TLICS and SLIC scale allows for instability evaluation and we did not discharge or transfer a patient with an unstable vertebra just because there were no neurological deficits. This is part due to allowing for more contamination risk whilst and after the patient is transferred to another institution.

Major neurological deficits defined as the affected muscle group having a motor strength less than 4/5 and the possibility of irreversible injury was considered to be an inclusion criteria. As the North American Spine Society suggests (3) "progressive or severe neurologic deficits due to neurologic compression from any cause (infection, tumor, fracture, disc herniation)" requires urgent surgical intervention without any delay. Thus all acute spinal cord injuries, vertebral fractures that had a 4 or higher score in the TLICS and SLIC scale, spinal stenosis and HNP patients and any malignancies with neurological deficits, infectious causes and failed previous instrumentation that were unstable have been included for urgent and essential surgery criteria.

After the selection process, the obstacle of categorizing the patient in to group 1 – no or low risk and group 2 – high risk to definite arises. Although the sensitivity the PCR test varies from 71-98% (12), all surgical candidates were ordered for PCR screening. In addition, if the patient applied with mild symptoms of COVID-19, a second PCR test was ordered for confirmation as studies out of China show that 96% of patients presented fever, 76% with cough and 44% with myalgia (5). Although specificity of the test has been reported to be 95%, another study where 4653 close contact patients underwent throat swabs every 48 h, the initial sensitivity of the test was 71% (6), thus a second PCR test was ordered at this institution to minimize false negative results. In order to further minimize false negative PCR results, patients presenting with major symptoms such as fever, cough, shortness of breath, loss of taste and smell or close contact with a diagnosed patient were ordered for a thorax CT scan. The sensitivity of thorax CT scan for COVID-19 was found to be 97% in the largest available study from Wuhan (2). Although there are no conclusive studies evaluating the sensitivity of a CT scan in asymptomatic patients, since an unprotected distance of 1m is considered to be a mode of transmission by the WHO, we decided it would be best to be over cautious than sorry. Fever was considered to be major symptoms since in adults it almost always is caused by an infection or inflammation. Cough is very specific for upper and lower respiratory tract infections and shortness of breath is a major symptom defined by the

WHO. A systematic review of 24 studies revealed an olfactory dysfunction in 41% and gustatory dysfunction in 38.2% of patients (1). At a time of pandemic, such a specific symptom must be handled cautiously before a surgical planning.

A framework from an Orthopedic Hospital in New York City outlined a policy in order to minimize the spread of the virus to patients and the staff within the hospital whilst continuing urgent operations. In short the authors advised for patient and visitor screening, use of patient-PPE, self surveillance of symptoms by the staff and staff testing when returning to work after quarantine (8). Our institution held weekly meetings with the administrative staff along with representatives from doctors including surgeons and other healthcare workers to continuously update the algorithms and precautions taken at every department of the hospital. The administration applied a strict no visitor policy with all applying patients going through temperature check and risk factor screening before entering the hospital. All staff according to their positions were educated on the usage of PPE along with frequent announcements from the hospital loudspeakers urging all those that are in the hospital to keep their masks on and check for social distancing. All secretaries were advised for a swift record taking and caretakers to transport patients with pre organized time frames to decrease the amount of delay. All staff at the hospital was also educated for signs and symptoms of COVID-19 and when they developed were advised to stay at a student dormitory reserved for healthcare workers that are suspected or diagnosed. The families of the healthcare workers were also at an increased risk so this was done to minimize contamination. In addition, all staff responsible for handling phone calls were educated on handling all possible matters via phone, as an increasing number of patients also favored phone calls when feasible.

In a comprehensive paper from a large tertiary hospital in Singapore, operating room measures for the outbreak has been reviewed. An OR with a negative pressure environment was advised since intubation, extubation, manual ventilation and open suctioning of the respiratory tract are all aerosol generating procedures (AGPs), thus becoming a potential transmission threat. Although it is a comprehensive paper, it did not mention the number of patients operated on and if any were diagnosed before or after surgery with COVID-19 (13). At our institution, there 6 operating rooms with only 1 having a negative pressure environment where all group 2 patients were operated. As advised by Wong et al. (13), all staff before the procedure held a meeting before wearing PPE which would make it difficult to communicate. Again all necessary equipment, drugs and fluids were made available in the room to decrease traffic. The anesthesiologists also took precautions to minimize postoperative coughing or emesis, whilst reducing AGPs by careful intubation, face mask ventilation and airway suctioning.

In a similar study from where similar precautions besides PCR testing has been taken in India (11), a 4-month period at a tertiary teaching hospital was evaluated with 13 patients that were operated for spine disorders and only 4 had available data for COVID-19 testing. Since the beginning of the pandemic our institution had enough PCR kits so that any suspicion of infection would be readily evaluated by a swab. A parallel study from Italy analyzed spine surgeries in a 4-month period as well and all patients underwent PCR testing preoperatively however patients with mild and major symptoms underwent thorax CT as well. Out of the 54 patients operated for spinal disorders only 2 patients were diagnosed with COVID-19 (9). The paper also failed to mention the precautions and recommendations for spine surgeons and focused more on the reduction of surgeries compared to the same time frame from a year ago. In a study where a review of literature was performed to categorize the patients into elective, urgent and emergent categories, similar indications for surgery was formed. A comprehensive guide on the preparation of the patient has been shared but only 2 cases have been discussed and results of this cautionary approach has not been evaluated (7).

Herein, the experiences of a single trauma center in classifying essential spine surgeries, handling the process of preparation,

institutional and operational considerations are shared. During this 9-month period 70 spine surgeries were performed with none of them being diagnosed with COVID-19 pre or postoperatively. A 10-day follow up was made to diagnose latent infections and revealed negative results as well. Experiences and recommendations of large centers dealing with similar problems should be evaluated by spine surgeons globally to allow for proper treatment without overdoing it. Non essential patients, especially those who would not present with irreversible injury and conservatively manageable conditions should for now wait until the alarming level of pandemic patients begin to decline. The virus continues to spread and all updates should me made readily available for healthcare workers to clarify a proper framework.

5. Conclusion

The battle against COVID-19 is still ongoing. It has become an evolutionary process where guidelines are constantly being formed and changed. Scientists around the world are trying their best to share their experiences in this process to allow for better management of patients and keep the health care system functional. Herein, the experiences of a single referral trauma center in a city managing spinal disorders during the COVID-19 pandemic are shared. Although it is not meant to be an all inclusive algorithm in the management of spine disorders during the pandemic, it has aimed to raise awareness of the importance of acting precautions, eliminating unnecessary contamination and preserving the trauma resources of the hospital. It also sheds hope for safe surgery during the pandemic. Finally, this study has its limitations as it is a single center experience thus the results may not be generalized to a larger population or an advanced institution.

Abbreviation List

WHO	*World Health Organization*
COVID-19	*Coronavirus Disease 2019*
ER	*Emergency Room*
PCR	*Polymerase chain reaction*
CT	*Computerized tomography*
ICU	*Intensive care unit*
PPE	*Personal protective equipment*
HNP	*Herniated nucleus pulposus*
NSAID	*Nonsteroidal anti-inflammatory drugs*
ASIA	*American Spinal Injury Association*
TLICS	*Thoraco-Lumbar Injury Classification and Severity score*
SLIC	*Subaxial Cervical Spine Injury Classification*
OR	*Operating room*
CSF	*Cerebrospinal fluid*
AGPs	*Aerosol generating procedures*
SARS-CoV-2	*Severe acute respiratory syndrome coronavirus 2*

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Research Article / Araştırma Makalesi

The Relationship Between Neutrophil/Lymphocyte Ratio (NLR) and Mean Platelet Volume (MPV) with Microalbuminuria in Participants with Different Glucose Tolerances

Farklı Glukoz Toleranslarına Sahip Katılımcılarda No trofil/Lenfosit Oranı (NLO) ve Ortalama Trombosit Hacmi (MPV) ile Mikroalbu minu ri Arasındaki İ lişki

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Abstract

Neutrophil/lymphocyte ratio (NLR) is a simple and inexpensive marker of subclinical inflammation for chronic diseases. Mean platelet volume (MPV) is a platelet function index. This study aimed to evaluate the relationship of NLR and MPV with microalbuminuria in participants with different glucose tolerances. 951 patients (male/female=302/649) were divided into five groups according to their oral glucose tolerance test (OGTT) results: group 1=normal glucose tolerance (NGT), group 2=impaired fasting glucose (IFG), group 3=isolated impaired glucose tolerance (IGT), group 4=both IFG and IGT, and group 5=type 2 diabetes mellitus (DM). Additionally, patients were divided into three groups according to their glycated hemoglobin (HbA1c) results: group 1=NGT, group 2=prediabetes, and group 3=type 2 DM. Outcomes were compared between groups. According to the OGTT, HbA1c, and OGTT+HbA1c criteria, there was a significantly positive correlation of microalbuminuria with MPV and NLR in all DM patients ($p<0.001$). Additionally, according to the OGTT, HbA1c, and OGTT+HbA1c criteria, there was a significantly positive correlation between MPV and microalbuminuria in all NGT patients ($p<0.001$). According to the OGTT and OGTT+HbA1c criteria, there was no significant correlation between NLR and microalbuminuria in prediabetic patients ($p>0.05$); however, there was a significantly positive correlation between NLR and microalbuminuria in the group with HbA1c 5.7–6.49 ($p<0.001$). Except isolated IFG and IGT, there was a significantly positive correlation between MPV and microalbuminuria in all prediabetic patients according to the OGTT, HbA1c, and OGTT+HbA1c criteria ($p<0.001$). NLR and MPV levels may be reliable predictive markers for the detection of microalbuminuria in prediabetes and DM.

Keywords: Neutrophil/Lymphocyte Ratio, Mean Platelet Volume, Microalbuminuria, Prediabetes, Diabetes Mellitus.

Özet

Nötrofil/lenfosit oranı (NLO), kronik hastalıklar için subklinik inflamasyonun basit ve ucuz bir belirtecidir. Ortalama trombosit hacmi (MPV) bir trombosit fonksiyon indeksidir. Bu çalışma, farklı glukoz toleranslarına sahip katılımcılarda NLO ve MPV'nin mikroalbüminüri ile ilişkisini değerlendirmeyi amaçladı. 951 hasta (erkek / kadın = 302/649) oral glukoz tolerans testi (OGTT) sonuçlarına göre beş gruba ayrıldı: grup 1 = normal glikoz toleransı (NGT), grup 2 = bozulmuş açlık glikozu (BAG), grup 3 = izole bozulmuş glukoz toleransı (BGT), grup 4 = hem BAG hem de BGT ve grup 5 = tip 2 diabetes mellitus (DM). Ek olarak, hastalar glikolize hemoglobin (HbA1c) sonuçlarına göre üç gruba ayrıldı: grup 1 = NGT, grup 2 = prediyabet ve grup 3 = tip 2 DM. Sonuçlar gruplar arasında karşılaştırıldı. OGTT, HbA1c ve OGTT + HbA1c kriterlerine göre tüm DM hastalarında mikroalbüminüri ile MPV ve NLO arasında anlamlı pozitif korelasyon vardı ($p <0.001$). Ayrıca OGTT, HbA1c ve OGTT + HbA1c kriterlerine göre tüm NGT hastalarında MPV ile mikroalbüminüri arasında anlamlı pozitif korelasyon vardı ($p <0.001$). OGTT ve OGTT + HbA1c kriterlerine göre prediyabetik hastalarda NLO ile mikroalbüminüri arasında anlamlı bir ilişki yoktu ($p> 0.05$); ancak HbA1c 5,7–6,49 olan grupta NLO ile mikroalbüminüri arasında anlamlı pozitif korelasyon vardı ($p <0,001$). İzole BAG ve BGT dışında OGTT, HbA1c ve OGTT + HbA1c kriterlerine göre tüm prediyabetik hastalarda MPV ile mikroalbüminüri arasında anlamlı pozitif korelasyon vardı ($p <0,001$). NLO ve MPV seviyeleri prediyabet ve DM'de mikroalbüminüri tespiti için güvenilir prediktif belirteçler olabilir.

Anahtar Kelimeler: Nötrofil/Lenfosit Oranı, Ortalama Trombosit Hacmi, Mikroalbüminüri, Prediyabet, Diabetes Mellitus.

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1. Introduction

Diabetes mellitus (DM) is a chronic, systemic disease characterized by severe microvascular and macrovascular complications. Its worldwide incidence is rapidly increasing; according to the International Diabetes Federation, there will be approximately 580 million people with T2DM by the year 2030(1). Prediabetes is a metabolic disease defined by impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both based on oral glucose tolerance test (OGTT) results (2). Prediabetes refers to the process of hyperglycemia from normal glucose tolerance (NGT) to DM. It is of clinical importance due to its number of cases, which is over 300 million worldwide, its association with micro- and macrovascular complications, and its progression to diabetes (3).

Microvascular complications include neuropathy, retinopathy, and nephropathy, while macrovascular complications include stroke, cardiovascular diseases, and peripheral vascular diseases (1). Diabetic nephropathy (DN) is observed in 25%–40% patients with DM (4,5). Diagnosis and monitoring of DN progression is performed by detecting microalbuminuria in the urine (6). The relationship between chronic inflammation and the progression of DM and the development of its complications has been described (7,8). Many inflammatory cytokines (interleukin-1, 6, 8, etc.) are also related to the pathogenesis of DN. However, the use of these inflammatory markers in daily practice is. During the inflammatory response, changes in the circulating leukocyte ratio are accompanied by neutrophilia and relative lymphopenia. According to recent studies; the neutrophil/lymphocyte ratio (NLR) is a marker of subclinical systemic inflammation for chronic diseases. NLR is also used as a prognosis predictor in cardiovascular diseases, chronic kidney disease (CKD), malignancies, and metabolic syndrome (9-12). NLR is also thought to be a marker of systemic inflammation at CKD and DN (13,14). Low NLR can be used as a new marker of early-stage DN and lower hospitalization risk in diabetic patients receiving hemodialysis (15,16).

Mean platelet volume (MPV) can be a guide for diseases associated with platelet production or destruction. MPV increases when thrombocyte production increases in the bone marrow. High MPV may be an indication of increased platelet destruction due to inflammation (17,18). Patients with IGT and IFG have been reported to have increased MPV (19). MPV is higher in those having retinopathy or microalbuminuria in patients with DM (20).

It has been reported that microalbuminuria is a risk factor for vascular complications in patients with DM and even IGT (21,22). However, few studies about the relationship of NLR and MPV with urinary albumin excretion (UAE) in individuals with different glucose tolerances. We planned this study to evaluate the association of NLR and MPV with microalbuminuria in participants with different glucose tolerances.

2. Materials and Methods

This was a retrospective, single-center, observational study. Between January 2015 and June 2020, OGTT was applied to 5853 patients in total in Akdeniz University Faculty of Medicine Internal Medicine outpatient clinic, and the microalbumin levels of 1120(19.1%) of them were also measured.Patients with type 1 DM, chronic liver disease, CKD (Estimated Glomerular Filtration Rate (eGFR)<60 mL/min/1.73 m^2, serum creatinine>1.3 mg/dL and/or urine microalbuminuria≥300 mg/g Cr), gestational diabetes, morbid obesity, acute and chronic ischemic heart disease, active infection, acute massive bleeding, intoxication, malignancy, nephrotic syndrome causing urinary protein excretion, hematuria, renal vascular disease, dehydration, platelets, neutrophils, patients with hematological diseases or drug use that may affect lymphocyte production, and patients whose data was not available were not included in the study. A total of 951 patients (male/female = 302/649) were included in the study, with 169 patients excluded due to exclusion criteria.

Based on the diagnostic criteria for DM specified by the World Health Organization,

the patients were divided into five groups (NGT, IFG, IGT, both IFG and IGT, and DM) according to their OGTT results (2). Additionally, the patients were divided into NGT (HbA1c<5.7%), prediabetes (HbA1c 5.7%–6.49%) and DM (Hba1c≥6.5%) groups according to their HbA1c results. Microalbuminuria and creatinine levels were evaluated from the first morning urine of the patients, and UAE of 30–300 mg/g Cr was evaluated as microalbuminuria.

OGTT procedure: OGTT and microalbumin measurement were performed at the same outpatient admission that remained open for 10 days. For OGTT, patients were tested in the biochemistry laboratory with 75 g glucose and 0.5 L water, without having any food or drink on the day of the test. Before the patients were given the glucose solution, blood sample were taken, which was recorded at hour 0. Patients with glucose level ≥126 mg/dL were considered T2DM and the test was discontinued for them. Furthermore, 75 g glucose was administered to the patient within 5–10 minutes and glucose values were measured at the 1st and 2nd hour. The patient remained in a sitting position without any food intake during the test.

Laboratory data: All biochemical examinations were performed in the central laboratory of our hospital. In the venous blood serum samples, glucose was measured using the hexokinase enzymatic method and creatinine was measured using the Jaffe method. Additionally, albumin was measured using bromocresol green via a spectrophotometric method using Siemens Advia Chemistry XP (Siemens Healthcare Diagnostics, Forchheim, Germany). Glycated hemoglobin (Hba1c) was measured using high performance liquid chromatography (Bio-Rad Laboratories, Marnes-la-Coquette, France). Results were expressed as % values. The eGFR was calculated using the formula CKD-EPI 2009 (Chronic Kidney Disease Epidemiologic Collaboration) (23). Complete blood count was performed using Sysmex XN 1000 (Sysmex Corporation, Kobe, Japan). Low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and triglyceride levels were measured by enzymatic colorimetric method, C-reactive protein (CRP) by immunoturbidimetric method, and microalbuminuria by immunoturbidimetric method using Siemens Advia 2400 biochemistry autoanalyzer (Siemens Healthcare Diagnostics, Forchheim, Germany).

Ethics: Local ethics committee approval was obtained for the study (XXX Ethics Committee-08/07/2020/492). During the realization of this study, where informed consent was not obtained due to its retrospective nature; the principles of the Declaration of Helsinki and all applicable local regulations have been complied with.

Statistical analysis: IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY) was used for statistical analysis. Shapiro-Wilk test was used to test normality. Median (min-max), mean±SD, or n (%) were used for the presentation of descriptive analyses. Mann-Whitney U test, Student's t test, and Pearson's chi-square test were used for the analysis of non-normally distributed numerical data, normally distributed numerical data, and categorical data, respectively. Kruskal–Wallis test was used for comparing nonparametric variables between groups. Bonferroni–Dunn test was used as a post hoc test for cases that had significant results, whereas one-way ANOVA with post hoc Tukey's honestly significant difference test was used for parametric variables. Spearman's correlation coefficient was applied for investigating the correlation between continuous variables. Multivariate analyses of independent predictors of microalbuminuria were performed using a binary logistic regression model. Odds ratio (OR) was reported with corresponding 95% confidence intervals. A value of $p \leq 0.05$ was accepted as statistically significant. In tables; if there is a significant difference between any two groups, it was shown with different lower letters, if not, with the same lower letters.

3. Results

The mean age of the 951 patients was 50.77±13.23 years; 31.8% (302 patients) were males and 68.2% (649 patients) were females. According to OGTT results, 29.3% (n=279) patients had NGT, 49% (n=466) were

prediabetic, and 21.6% (n=206) were diabetic. The mean age and percentage of male patients were higher in the DM group (p<0.001) (Tables 1-2).

Table 1. Comparison of patients' characteristics according to OGTT groups

Variables	Overall	NGT	Pre-diabetes	DM	p values
Number (%)	951(100)	279(29.3)	466(49)	206(21.7)	-
Age (years)	51.12±13.04	45.1±14.45[a]	52.8±11.84[b]	55.47±10.56[c]	**<0.001**
Gender					
Male,n(%)	302(31.8)	76(27.2)[a]	132(28.3)[a]	94(45.6)[b]	**<0.001**
Female,n(%)	649(68.2)	203(72.8)	334(71.7)	112(54.4)	
Hemoglobin (g/dL)	13.51±1.54	13.14±1.69[a]	13.52±1.41[b]	13.99±1.47[c]	**<0.001**
Creatinine (mg/dL)	0.75±0.17	0.72±0.17[a]	0.76±0.16[b]	0.79±0.17[c]	**<0.001**
eGFR (mL/min/1.73m^2)	111.23±15.65	118.31±17.14[a]	109.53±14.05[b]	105.49±13.45[c]	**<0.001**
CRP (g/dL)	0.32(0-30.39)	0.22(0-3.04)[a]	0.32(0.01-30.39)[a,b]	0.37(0.04-4.79)[b]	**0.022**
Triglyserides (mg/dL)	135(33-1265.54)	116.89(33-469)[a]	135(38-1265.54)[b]	160.73(45-1201)[c]	**<0.001**
LDL (mg/dL)	134(31-270)	127(31-248.91)[a]	133.7(53.8-270)[a,b]	141(48-229.1)[b]	**0.033**
HDL (mg/dL)	46.45(15.3-121.1)	47.33(23-121.1)[a]	47.05(15.3-102.3)[a]	44(30-68)[b]	**0.002**
Albumin(g/dL)	4.46(2.63-5.65)	4.42(3.64-4.9)	4.49(3.71-5.65)	4.45(2.63-5.14)	0.113
Urine microalbumin (mg/day)	9.1(0-165.01)	4.73(0-116.7)[a]	10.15(0.1-165.01)[b]	13.59(0.1-130.5)[c]	**<0.001**
Microalbuminuria, n (%)	167(17.5)	29(10.4)[a]	89(19.1)[b]	49(23.8)[c]	**<0.001**
ANC (cells×10^9/L)	3.99(1.38-15.16)	3.86(1.48-10.85)	4(1.59-15.16)	4.1(1.38-7.28)	0.114
ALC (cells ×10^9/L)	2.22(0.7-5.31)	2.26(1.08-5)[a]	2.24(0.86-5.31)[a]	2.01(0.7-4.98)[b]	**0.001**
AMC (cells ×10^9/L)	0.42(0.17-1.32)	0.41(0.17-1.32)	0.41(0.2-1.29)	0.44(0.17-1.15)	0.515
APC (cells ×10^9/L)	260(50-799)	258(132-434)[a,b]	266(110-799)[a]	248(50-560)[b]	**0.028**
NLR	1.79(0.54-9.24)	1.69(0.59-6.03)[a]	1.76(0.55-9.24)[a]	2.03(0.54-4.98)[b]	**<0.001**
MPV (fL)	8.1(5.4-12.8)	7.6(5.7-12)[a]	8.1(5.4-12)[b]	9(6-12.8)[c]	**<0.001**

OGTT, oral glucose tolerance test; NGT, normal glucose tolerance; DM; diabetes mellitus; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ANC, absolute neutrophil count; ALC, absolute lymphocytecount; AMC, absolute monocyte count; APC, absolute platelet caunt; NLR, Neutrophil/Lymphocyte Ratio; MPV, mean platelet volume

Data are presented as mean±SD, median (min-max) or n (%). ANOVA, Kruskal-Wallis test, Pearson chi-square test. Different lowercase letters in a row indicate a statistically significant differences between groups.

Table 2. Comparison of patients' characteristics according to OGTT sub groups

		Pre-diabetes				
Variables	**NGT**	**IFG**	**IGT**	**IFG+IGT**	**DM**	**p values**
Number (%)	279(29.3)	211(22.2)	77(8.1)	178(18.7)	206(21.7)	
Age (years)	45.1±14.45[a]	50.82±11.88[b]	51.16±13.7[b]	55.86±10.25[c]	55.47±10.56[c]	**<0.001**
Gender						
Male,n(%)	76(27.2)[a]	57(27)[a]	17(22.1)[a]	58(32.6)[a,b]	94(45.6)[b]	**<0.001**
Female,n(%)	203(72.8)	154(73)	60(77.9)	120(67.4)	112(54.4)	
Hemoglobin (g/dL)	13.14±1.69[a]	13.53±1.27[a,b]	13.19±1.63[a]	13.66±1.42[b]	13.99±1.47[c]	**<0.001**

Creatinine (mg/dL)	0.72±0.17[a]	0.75±0.14[a,b]	0.76±0.18[b]	0.76±0.18[b]	0.79±0.17[b]	**<0.001**
eGFR (mL/min/1.73m^2)	118.31±17.14[a]	111.48±13.25[b]	110.74±16.2[b,c]	106.7±13.58[c]	105.49±13.45[c]	**<0.001**
CRP (g/dL)	0.22(0-3.04)	0.44(0.01-30.39)	0.37(0.01-2.1)	0.24(0.02-1.67)	0.37(0.04-4.79)	0.052
Triglyserides (mg/dL)	116.89(33-469)[a]	123.53(38-1265.54)[a,b]	141.25(47-413)[b,c]	143.61(51-743)[c]	160.73(45-1201)[c]	**<0.001**
LDL (mg/dL)	127(31-248.91)[a]	138.7(53.8-270)[a,b]	127.75(70.29-259.9)[a,b]	136.32(55.7-238)[a,b]	141(48-229.1)[b]	**0.048**
HDL (mg/dL)	47.33(23-121.1)[a]	48.2(18-83.3)[a]	44.9(21.9-102.3)[a,b]	45.8(15.3-72.4)[a,b]	44(30-68)[b]	**0.003**
Albumin (g/dL)	4.42(3.64-4.9)	4.51(3.86-5.65)	4.47(3.71-5.05)	4.43(3.77-5.16)	4.45(2.63-5.14)	0.195
Urine microalbumin (mg/day)	4.73(0-116.7)[a]	8.2(0.1-165.01)[b]	10.43(0.1-104.7)[b,c]	13(0.1-123.2)[c,d]	13.59(0.1-130.5)[d]	**<0.001**
Microalbuminuria, n (%)	29(10.4)[a]	37(17.5)[a]	15(19.5)[a,b]	37(20.8)[b]	49(23.8)[b]	**<0.001**
ANC (cells × 10^9 /L)	3.86(1.48-10.85)[a]	3.87(1.59-10.67)[a]	4.06(1.9-11.15)[b]	4.17(1.87-15.16)[a,b]	4.1(1.38-7.28)[a,b]	**0.023**
ALC (cells × 10^9 /L)	2.26(1.08-5)[a]	2.34(1.07-4.52)[a]	2.19(1.09-3.78)[a,b]	2.21(0.86-5.31)[a,b]	2.01(0.7-4.98)[b]	**0.001**
AMC (cells × 10^9 /L)	0.41(0.17-1.32)	0.4(0.2-0.9)	0.42(0.23-1.29)	0.43(0.2-1.08)	0.44(0.17-1.15)	0.419
APC (cells × 10^9 /L)	258(132-434)	262(144-799)	272.5(134-499)	267(110-493)	248(50-560)	0.108
NLR	1.69(0.59-6.03)[a]	1.61(0.55-7.26)[a]	1.94(0.86-3.81)[b,c]	1.8(0.67-9.24)[b]	2.03(0.54-4.98)[c]	**<0.001**
MPV (fL)	7.6(5.7-12)[a,b]	7.9(5.4-11.6)[b,c]	8.2(5.8-12)[c,d]	8.4(5.9-11.3)[d]	9(6-12.8)[e]	**<0.001**

OGTT, oral glucose tolerance test; NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ANC, absolute neutrophil count; ALC, absolute lymphocytecount; AMC, absolute monocyte count; APC, absolute platelet caunt; NLR, Neutrophil/Lymphocyte Ratio; MPV, mean platelet volume

Data are presented as mean±SD, median (min-max) or n (%). ANOVA, Kruskal-Wallis test, Pearson chi-square test. Different lowercase letters in a row indicate statistically significant difference between groups.

As we progressed from the NGT group to the prediabetic and diabetic groups, the levels of hemoglobin, creatinine, triglycerides, microalbuminuria, and MPV increased, whereas eGFR decreased (p<0.001). Additionally, the prevalence of microalbuminuria increased (p<0.001) (Table 1-2). CRP (p=.022) and direct LDL (p=0.033) levels of the DM group were higher than those of the NGT group. HDL (p=0.002) and absolute lymphocyte count (ALC) (p=0.001) values of the DM group were lower than that of the other groups, whereas NLR (p<0.001) of the DM group was higher than that of the other groups.

Using ROC analysis for microalbuminuria, the optimal cut-off point for MPV was ≥8.35 (area under the curve [AUC]=0.723 [95% CI:0.681–0.766, p<0.001], sensitivity=70.1%, specificity=63.7%) (Figure 1).

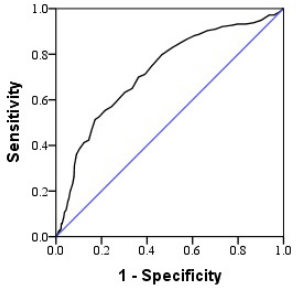

Figure 1. A ROC curve for MPV to predict microalbuminuria

According to OGTT, 466 prediabetic patients were divided into three groups: IFG (n=211), IGT (n=77), and IFG+IGT (n=178). The mean ages of the IFG+IGT and DM groups were higher than those of the other three groups, and the mean ages of the IFG and IGT groups were higher than those of the NGT group (p<0.001). The creatinine levels were higher in the IGT, IFG+IGT, and diabetic groups than in the NGT group (p<0.001). There was no difference between the eGFR values of the IGT, IFG+IGT, and DM groups, but the eGFR value of the IFG group was higher than that of the IFG+IGT and DM groups (Table 2).

Triglyceride levels of IFG+IGT and DM groups were higher than those of the NGT and IFG groups (p<0.001). LDL levels of the DM group were higher than those of the NGT group (p=0.048). However, HDL levels of the NGT and IFG groups were higher than those of the DM group (p=0.003).

While the lowest median level of microalbuminuria was observed in the NGT group, the highest was in the DM group (p<0.001). The prevalence of microalbuminuria was higher in the IFG+IGT and DM groups compared to NGT and IFG groups (p<0.001). NLR was highest in the DM group and lowest in the NGT and IFG groups (p<.001). MPV increased as we progressed from NGT group to DM group (p<0.001) (Table 2).

According to the HbA1c levels, the patients were divided into three groups: <5.7 (n=336), 5.7–6.49 (n=531), and ≥6.5 (n=84). The mean age of the NGT group was the lowest (p<0.001). The difference between the NLR levels of the HbA1c groups was not significant. The creatinine and triglyceride levels were higher and the HDL levels were lower in the HbA1c≥6.5 group compared to the other two groups (Table 3). The eGFR values of the HbA1c<5.7 group were higher than those of the other two groups (p<0.001). As the HbA1c level increased, the level of microalbuminuria and the prevalence of MPV and microalbuminuria also increased (p<0.001) (Table 3).

Table 3. Comparison of patients' characteristics according to HbA1c groups

Variables	<5.7	5.7-6.49	≥6.5	p values
Number (%)	336(35.3)	531(55.8)	84(8.8)	
Age (years)	46.39±14.03[a]	53.75±11.85[b]	53.4±10.67[b]	**<0.001**
Gender				
Male,n(%)	101(30.1)[a]	163(30.7)[a]	38(45.2)[b]	**0.020**
Female,n(%)	235(69.9)	368(69.3)	46(54.8)	
Hemoglobin (g/dL)	13.55±1.65	13.45±1.44	13.75±1.72	0.265
Creatinine (mg/dL)	0.74±0.16[a]	0.76±0.17[a]	0.81±0.18[b]	**0.002**
eGFR (mL/min/1.73m^2)	116.01±16.17[a]	108.93±14.56[b]	106.63±15.66[b]	**<0.001**
CRP (g/dL)	0.29(0-30.39)	0.32(0.01-4.79)	0.58(0.07-4.2)	0.171
Triglyserides (mg/dL)	123.83(33-654.98)[a]	134.81(38-1265.54)[a]	164(51-450)[b]	**0.003**
LDL (mg/dL)	132.7(32.6-270)	133(31-247)	143.8(58.66-206)	0.427
HDL (mg/dL)	45.2(21.9-121.1)[a]	47.5(15.3-83.9)[a]	41.1(30.3-64)[b]	**0.002**
Albumin(g/dL)	4.46(3.71-4.9)	4.46(3.44-5.65)	4.44(2.63-5.05)	0.981
Urine microalbumin (mg/day)	6.72(0.1-152.39)[a]	10.5(0-165.01)[b]	19.15(0.1-128.12)[c]	**<0.001**
Microalbuminuria, n (%)	36(10.7)[a]	103(19.4)[b]	28(33.3)[c]	**<0.001**
ANC (cells × 10^9 /L)	4.03(1.48-11.42)	3.96(1.38-15.16)	4.14(1.88-9.2)	0.094
ALC (cells × 10^9 /L)	2.22(0.91-4.2)	2.21(0.7-5.31)	2.29(1.11-4.98)	0.990

AMC (cells × 10^9 /L)	0.42(0.18-1.32)	0.41(0.17-1.29)	0.45(0.19-1.07)	0.338
APC (cells × 10^9 /L)	254(50-799)	264(89-493)	256.5(108-560)	0.533
NLR	1.81(0.59-7.26)	1.75(0.54-9.24)	1.95(0.85-4)	0.351
MPV (fL)	7.6(5.7-12.8)[a]	8.3(5.4-12.2)[b]	9.3(6.1-11.7)[c]	**<0.001**

HbA1c: glycated hemoglobin; eGFR, estimated glomerular filtration rate; CRP, C-reactiveprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ANC, absolute neutrophil count; ALC, absolute lymphocytecount; AMC, absolute monocyte count; APC, absolute platelet caunt; NLR, Neutrophil/Lymphocyte Ratio; MPV, mean platelet volume

Data are presented as mean±SD, median (min-max) or n (%). ANOVA, Kruskal-Wallis test, Pearson chi-square test. Different lowercase letters in a row indicate statistically significant difference between groups.

The patients were divided into groups as normal (n=146), prediabetes (n=569) and DM (n=236) according to OGTT results and/or HbA1c levels (Table 4). The mean age and ratio of male patients were the highest in the DM group (p<0.001). Hemoglobin, CRP, triglyceride, and NLR levels of the DM group were higher, but ALC was lower, compared with the other groups (Table 4). The creatinine levels, microalbumin levels, MPV, and prevalence of microalbuminuria was higher, whereas the eGFR levels were lower (p<0.001) in the DM group. The LDL levels of the DM group were higher than those of the NGT group. Additionally, HDL levels were higher in the prediabetes group than in the DM group (Table 4).

Table 4. Comparison of patients' characteristics according to OGTT-HbA1c combined groups

Variables	NGT	Pre-diabetes	DM	p
Number (%)	146(15.4)	569(59.8)	236(24.8)	
Age (years)	39.62±13.45[a]	52.43±12.13[b]	55.08±10.84[c]	**<0.001**
Gender				
Male,n(%)	38(26)[a]	161(28.3)[a]	103(43.6)[b]	**<0.001**
Female,n(%)	108(74)	408(71.7)	133(56.4)	
Hemoglobin (g/dL)	13.36±1.79[a]	13.38±1.44[a]	13.91±1.56[b]	**<0.001**
Creatinine (mg/dL)	0.71±0.15[a]	0.75±0.17[b]	0.79±0.17[c]	**<0.001**
eGFR (mL/min/1.73m^2)	123.59±15.47[a]	110.19±14.61[b]	106.1±14.23[c]	**<0.001**
CRP (g/dL)	0.27(0-3.04)[a]	0.28(0.01-30.39)[a]	0.43(0.04-4.79)[b]	**0.012**
Triglyserides (mg/dL)	115(33-469)[a]	130.98(38-1265.54)[a]	160.68(45-1201)[b]	**<0.001**
LDL (mg/dL)	125.36(32.6-248.91)[a]	132.7(31-270)[a,b]	141.1(48-229.1)[b]	**0.024**
HDL (mg/dL)	44.5(26.1-121.1)[a,b]	47.65(15.3-102.3)[a]	43.7(30-68)[b]	**0.001**
Albumin(g/dL)	4.41(3.93-4.9)	4.47(3.64-5.65)	4.46(2.63-5.14)	0.449
Urine microalbumin (mg/day)	3.3(0.1-63)[a]	9(0-165.01)[b]	16.8(0.1-130.5)[c]	**<0.001**
Microalbuminuria, n (%)	12(8.2)[a]	93(16.3)[b]	62(26.2)[c]	**<0.001**
ANC (cells × 10^9 /L)	4.13(1.48-10.85)	3.96(1.56-15.16)	3.99(1.38-9.2)	0.176
ALC (cells × 10^9 /L)	2.32(1.08-3.97)[a]	2.23(0.86-5.31)[a]	2.08(0.7-4.98)[b]	**0.002**
AMC (cells × 10^9 /L)	0.42(0.18-1.32)	0.41(0.17-1.29)	0.44(0.17-1.15)	0.352
APC (cells × 10^9 /L)	257(132-433)	263.5(110-799)	251(50-560)	0.136
NLR	1.75(0.59-6.03)[a]	1.72(0.55-9.24)[a]	1.96(0.54-4.98)[b]	**0.001**

MPV (fL)	7.1(5.7-10.6)[a]	8(5.4-12)[b]	9.1(6-12.8)[c]	**<0.001**

HbA1c: glycated hemoglobin; OGTT, oral glucose tolerance test; NGT, normal glucose tolerance; DM; diabetes mellitus; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ANC, absolute neutrophil count; ALC, absolute lymphocytecount; AMC, absolute monocyte count; APC, absolute platelet caunt; NLR, Neutrophil/Lymphocyte Ratio; MPV, mean platelet volume

Data are presented as mean±SD, median (min-max) or n (%). ANOVA, Kruskal-Wallis test, Pearson chi-square test. Different lowercase letters in a row indicate statistically significant difference between groups.

Microalbuminuria was detected in 17.5% (n=167) patients. Age, CRP, microalbumin, NLR, and MPV were higher, whereas ALC was lower in patients with microalbuminuria (Table 5). Other results have been presented in Table 5.

Table 5. Comparison of patients' characteristics according to microalbuminuria

Variables	Without	With	p values
Number (%)	784(82.5)	167(17.5)	
Age (years)	50.67±13.1	52.81±12.7	**0.040**
Gender			
Male,n(%)	255(32.5)	47(28.1)	0.403
Female,n(%)	529(67.5)	120(71.9)	
Hemoglobin (g/dL)	13.52±1.53	13.48±1.55	0.768
Creatinine (mg/dL)	0.75±0.16	0.76±0.18	0.696
eGFR (mL/min/1.73m^2)	111.62±15.62	109.73±15.72	0.130
CRP (g/dL)	0.28(0-30.39)	0.37(0.01-4.79)	**0.026**
Triglyserides (mg/dL)	131.75(33-779)	147(45-1265.54)	**0.032**
LDL (mg/dL)	132.7(31-270)	139.8(53.8-238)	0.746
HDL (mg/dL)	46.85(15.3-121.1)	44.45(21.9-83.3)	0.081
Albumin(g/dL)	4.45(3.64-5.14)	4.48(2.63-5.65)	0.721
Urine microalbumin (mg/day)	6.5(0-19.87)	35.85(20-165.01)	**<0.001**
ANC (cells × 10^9 /L)	3.96(1.38-15.16)	4.14(1.94-11.15)	0.064
ALC (cells × 10^9 /L)	2.25(0.88-5.31)	2.1(0.7-4.24)	**0.001**
AMC (cells × 10^9 /L)	0.41(0.17-1.32)	0.43(0.18-1.29)	0.502
APC (cells × 10^9 /L)	259(50-799)	262(89-560)	0.466
NLR	1.74(0.54-9.24)	2.05(0.7-5.25)	**<0.001**
MPV (fL)	7.9(5.4-12.2)	9.1(5.9-12.8)	**<0.001**

eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ANC, absolute neutrophil count; ALC, absolute lymphocytecount; AMC, absolute monocyte count; APC, absolute platelet caunt; NLR, Neutrophil/Lymphocyte Ratio; MPV, mean platelet volume

Data are presented as mean±SD, median (min-max) or n (%). Student's t test, Mann-Whitney U test, Pearson chi-square test.

In all models, MPV was identified as a predictive factor associated with microalbuminuria. In Model 1 (with 3 OGTT groups), MPV was positively associated with microalbuminuria (OR: 2.157; 95% CI: 1.430–3.254; p<0.001) (Table 6). Additionally, patients with DM (OR: 5.822; 95% CI: 1.226–27.641; p=0.027) had higher risk of microalbuminuria compared to patients with NGT. In Model 2 (with 5 OGTT groups), increasing MPV (OR: 2.169; 95% CI: 1.434–3.279; p<0.001) was associated with microalbuminuria. Moreover, patients with DM were 5.76 times more likely to have microalbuminuria than patients with NGT (OR: 5.762; 95% CI: 1.205–27.55; p=0.028). In Model 3 (with HbA1c groups), increased MPV (OR: 2.303; 95% CI: 1.535–3.456; p<0.001) was associated with microalbuminuria. Patients with HbA1c value

between 5.7 and 6.5 (OR: 4.988; 95% CI: 1.327–18.755; p=0.017) or ≥6.5 (OR: 23.444; 95% CI: 3.634–151.244; p=0.001) had a higher risk of microalbuminuria compared to patients with NGT. In Model 4 (with OGTT or HbA1c groups), MPV was positively associated with microalbuminuria (OR: 2.098; 95% CI: 1.446–3.042; p<0.001). Patients with DM had a higher risk of microalbuminuria compared to patients with NGT (OR: 15.15; 95% CI: 1.691–135.702; p=0.015) (Table 6).

Table 6. Multivariate logistic regression analysis for microalbuminuria

	Model 1 with OGTT 3 groups		Model 2 with OGTT 5 groups		Model 3 HbA1c groups		Model 4 with OGTT or HbA1c groups	
Variables	**OR(95%CI)**	**p values**	**OR(95%CI)**	**p values**	**OR(95%CI)**	**p values**	**OR(95%CI)**	**p values**
Age (years)	1.015(0.976-1.057)	0.456	1.015(0.973-1.058)	0.489	1.014(0.974-1.056)	0.493	1.016(0.98-1.052)	0.392
CRP	1.051(0.862-1.28)	0.624	1.046(0.858-1.276)	0.655	1.083(0.846-1.387)	0.527	1.053(0.884-1.255)	0.560
Triglyserides	1.004(0.999-1.009)	0.129	1.004(0.999-1.009)	0.135	1.006(1-1.012)	0.060	1.001(0.998-1.004)	0.359
HDL	1.018(0.98-1.058)	0.367	1.018(0.978-1.059)	0.387	1.022(0.98-1.067)	0.309	1.009(0.965-1.025)	0.406
NLR	1.576(0.923-2.691)	0.096	1.619(0.926-2.829)	0.091	1.629(0.916-2.895)	0.097	1.154(0.733-1.818)	0.536
MPV	2.157(1.43-3.254)	**<0.001**	2.169(1.434-3.279)	**<0.001**	2.303(1.535-3.456)	**<0.001**	2.098(1.446-3.042)	**<0.001**
OGTT 3 groups								
NGT	Reference	-	-	-	-	-	-	-
Pre-diabetes	1.988(0.469-8.423)	0.351	-	-	-	-	-	-
DM	5.822(1.226-27.641)	**0.027**	-	-	-	-	-	-
OGTT 5 groups								
NGT	-	-	Reference	-	-	-	-	-
IFG	-	-	2.228(0.442-11.225)	0.332	-	-	-	-
IGT	-	-	1.638(0.246-10.913)	0.610	-	-	-	-
IFG+IGT	-	-	1.952(0.36-10.581)	0.438	-	-	-	-
DM	-	-	5.762(1.205-27.55)	**0.028**	-	-	-	-
HbA1c								
<5.7	-	-	-	-	Reference	-	-	-
5.7-6.49	-	-	-	-	4.988(1.327-18.755)	**0.017**	-	-
≥6.5	-	-	-	-	23.444(3.634-151.244)	**0.001**	-	-
OGTT or HbA1c								
NGT	-	-	-	-	-	-	Reference	-
Pre-diabetes	-	-	-	-	-	-	3.841(0.448-32.949)	0.220
DM	-	-	-	-	-	-	15.15(1.691-135.702)	**0.015**

OGTT, oral glucose tolerance test; *HbA1c: glycated hemoglobin****; NGT, normal glucose tolerance; DM; diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; CRP, C-reactive protein; HDL, high-density lipoprotein; NLR, Neutrophil/Lymphocyte Ratio; MPV, mean platelet volume***

According to the OGTT, HbA1c, and OGTT+HbA1c criteria, there was a significantly positive correlation of microalbuminuria with MPV and NLR in all DM patients ($p<0.001$) (Table 7). Additionally, according to the OGTT, HbA1c, and OGTT+HbA1c criteria, there was a significantly positive correlation between MPV and microalbuminuria in all NGT patients ($p<0.001$). However, no significant correlation was found between NLR and microalbuminuria in any group (Table 7). According to the OGTT and OGTT+HbA1c criteria, there was no significant correlation between NLR and microalbuminuria in prediabetic patients ($p>0.05$); however, there was a significantly positive correlation between NLR and microalbuminuria in the group with HbA1c 5.7–6.49 ($p<0.001$) (Table 7). Except isolated IFG and IGT, there was a significantly positive correlation between MPV and microalbuminuria in all prediabetic patients according to the OGTT, HbA1c, and OGTT+HbA1c criteria ($p<0.001$) (Table 7).

Table 7. Correlation of microalbumin with NLR and MPV in different glucose tolerance levels

	NLR		MPV	
Groups	**r**	**p**	**r**	**p**
OGTT 3 groups				
NGT	0.065	0.312	0.433	**<0.001**
Pre-diabetes	0.060	0.230	0.187	**<0.001**
DM	0.303	**<0.001**	0.396	**<0.001**
OGTT 5 groups				
NGT	0.065	0.312	0.433	**<0.001**
IFG	0.003	0.971	0.141	0.062
IGT	0.129	0.288	0.213	0.079
IFG+IGT	0.042	0.591	0.165	**0.036**
DM	0.303	**<0.001**	0.396	**<0.001**
HbA1c				
<5.7	0.024	0.700	0.406	**<0.001**
5.7-6.49	0.203	**<0.001**	0.238	**<0.001**
≥6.5	0.326	**0.005**	0.441	**<0.001**
OGTT and HbA1c				
NGT	0.052	0.574	0.366	**<0.001**
Pre-diabetes	0.081	0.070	0.153	**<0.001**
DM	0.288	**<0.001**	0.423	**<0.001**

OGTT, oral glucose tolerance test; NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; DM; diabetes mellitus; HbA1c: glycated hemoglobin; CRP, C-reactive protein; HDL, high-density lipoprotein; NLR, Neutrophil/Lymphocyte Ratio; MPV, mean platelet volume

Spearman correlation test.

4. Discussion

In our cohort study including 951 patients, we investigated the predictive value of hematological indices, such as NLR and MPV, for predicting microalbuminuria in prediabetic patients. In our study, we found that NLR and MPV levels were significantly associated with decreased eGFR and increased UAE in prediabetes and DM patients.

Microalbuminuria is the earliest detectable sign of kidney damage in diabetic patients. In our study, as the glucose tolerance disorder progressed, the prevalence and level of microalbuminuria increased. In a study by Wang et al.(24) evaluating 2,394 individuals with different glucose tolerances, UAE was higher in the newly diagnosed T2DM, IFG + IGT, and isolated IGT groups compared to that of the isolated IFG and NGT group, with

it being higher in the isolated IFG group than the NGT group.

In this study, MPV was significantly higher in patients with microalbuminuria than in patients without microalbuminuria, and there was a significantly positive correlation between MPV and microalbuminuria in all groups, except the IFG and IGT groups. Many studies have reported that prediabetic processes, such as IFG, IGT, and overt DM, are associated with increased MPV (18,19,25). MPV has also been associated with vascular complications in patients with DM (26). Also, various studies report that MPV reflects many acute and cronic disease conditions, in addition to inflammatory burden or systemic inflammation (27). In a previous study in DM patients, MPV was found to be significantly higher in patients with poor diabetic control, and according to the results of the same study, MPV levels were also significantly positively correlated with UAE (28). In our study, when the MPV value was 8.35, the sensitivity and specificity for microalbuminuria was 70.1% and 63.7%, respectively.

MPV reflects a simple, fast, and easily attainable platelet size and prothrombotic potential. Platelets with increased MPV are hemostatically more active and show a stronger prothrombotic state with increased thromboxane A2 levels. However, MPV can be influenced by various factors (age, gender, blood pressure, and smoking). Increased MPV levels are a risk factor for atherosclerotic, cardiac, and cerebrovascular diseases. Large platelets are more active than normal sized platelets and secrete more prothrombotic factors. In this study, the difference between MPV levels in NGT, prediabetic, and diabetic groups was statistically significant. A significantly positive correlation was found between MPV and microalbuminuria, except for IFG and IGT. In multivariate logistic regression analysis, MPV was an independent risk factor for microalbuminuria in all groups. This may partially explain the increased risk of atherosclerosis and macrovascular complications during the prediabetic period.

NLR is an inexpensive indicator of systemic inflammation, which has been reported to be an inflammation marker in various studies. The systemic inflammatory response is often characterized by an increase in neutrophil count and a decrease in lymphocyte count. Leukocytes affect the initiation and progression of renal disease through noninfectious inflammatory mechanisms (such as free oxygen radicals and proteolysis in mesangial cells). As an indicator of inflammation, NLR shows a significant correlation with inflammation parameters. In our study, NLR increased significantly when we progressed from the NGT to the diabetic group. Additionally, CRP levels increased from the NGT to the DM group, which are an indicator of inflammation. NLR and microalbuminuria were positively correlated in the diabetic group and in those with HbA1c 5.7–6.4. In the multivariate logistic regression analysis, NLR was not considered as a significant risk factor for microalbuminuria ($p>0.05$). With this result, our study differs from other studies in the literature. In the study of Shiny et al.(29), NLR was higher in patients with DM than in patients with IGT and NGT. Furthermore, NLR was positively correlated with fasting glucose and HbA1c levels, and it was stated that NLR could be used for detecting micro-and macrovascular complications (29). In another small-scale study, NLR was shown to has a positive predictive value for UAE in patients with DM (30). In another study involving geriatric patients with diabetes, NLR was indicated as a predictor for microvascular complications (28). In the study of Solak et al.(31), increased NLR was inversely related to reduced flow-mediated dilatation and was reported to predict cardiovascular endpoints in patients with CKD, regardless of traditional risk factors. Moreover, NLR has been identified as a predictor of CKD progression (13).

In conclusion, in all subgroups of prediabetic patients, MPV and NLR are higher than in the NGT group and lower than in the diabetic group. In the prediabetic groups, MPV and albuminuria had a significantly positive correlation. NLR and MPV levels may be reliable predictive markers for the detection of microalbuminuria in prediabetes and DM. Extensive prospective controlled studies with more subjects are required in the future to

increase the use of NLR and MPV for predicting albuminuria.

Our study has some significant limitations. First, individuals with a history of obesity were excluded from the study, and anthropometric measurements, such as body mass index and abdominal circumference, could not be evaluated due to the lack of data on body composition. Second, although individuals taking medication or those with a history of hypertension were excluded from the study, the lack of data on blood pressure levels and antiplatelet drug use was another limitation. Third, we lacked data on liver function tests, family history of DM, smoking, and alcohol consumption; hence, evaluations related to these parameters could not be performed. Fourth, the cross-sectional nature of this study makes it difficult to interpret the relationship between NLR and MPV with microalbuminuria. Additionally, the change in microalbuminuria over time and the relationship between MPV and NLR were not determined. However, despite the study's retrospective nature, the study's major strength is the relatively large number of participants.

Main Points

In all subgroups of prediabetic patients, MPV and NLR are higher than in the NGT group and lower than in the diabetic group.

In the prediabetic groups, MPV and albuminuria had a significantly positive correlation.

NLR and MPV levels may be reliable predictive markers for the detection of microalbuminuria in prediabetes and DM.

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Research Article / Araştırma Makalesi

Preoperative Investigation of Malnutrition in Elective Surgery Cases and Relationship with Serum Magnesium Level

Elektif Cerrahi Olgularda Malnutrisyonun Preoperatif Araştırılması ve Serum Magnezyum Seviyesi ile İlişkisi

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Abstract

Presence of hypomagnesemia in the perioperative period can significantly increase morbidity (1). Preoperative nutritional deficiency may accompany magnesium deficiency. The aim of this study is; To investigate malnutrition by mini nutritional assessment-short form (MNA-sf) in patients scheduled for elective surgery and to examine the relationship between magnesium level, age, gender, surgical departments, BMI and ASA classification. Patients over the age of 18 who were scheduled for elective surgery were included in the study. The study was conducted with 387 patients according to statistical power analysis. In our study, magnesium level was found to be significantly lower in inverse proportion to age only in preoperative patients hospitalized in the general surgery department. It was found that the magnesium level of preoperative male patients hospitalized in the general surgery department was significantly higher than that of female patients. It was determined that the mini nutritional screening and evaluation tests showed statistically significant correlation in all surgical departments. Malnutrition is thought to have adverse effects on morbidity in the perioperative period. It may be very useful to detect malnutrition that can be detected by hypomagnesemia with a simple test beforehand.

Keywords: Magnesium; MNA; malnutrition; MNA-SF

Özet

Perioperatif dönemde hipomagnezemi varlığı morbiditeyi önemli ölçüde artırabilir (1). Preoperatif beslenme eksikliği magnezyum eksikliğine eşlik edebilir.:Bu çalışmanın amacı; Elektif cerrahi planlanan hastalarda mini nütrisyonel değerlendirme-kısa form (MNA-sf) ile malnütrisyonun araştırılması ve magnezyum düzeyi, yaş, cinsiyet, cerrahi bölümler, BMI ve ASA sınıflaması arasındaki ilişkinin incelenmesi. Çalışmaya elektif cerrahi planlanan 18 yaş üstü hastalar dahil edildi. Çalışma istatistiksel güç analizine göre 387 hasta ile yapılmıştır. Çalışmamızda sadece genel cerrahi bölümünde yatan preoperatif hastalarda magnezyum düzeyi yaşla ters orantılı olarak anlamlı derecede düşük bulundu. Genel cerrahi servisine yatırılan ameliyat öncesi erkek hastaların magnezyum düzeylerinin kadın hastalara göre anlamlı derecede yüksek olduğu saptandı. Mini beslenme tarama ve değerlendirme testlerinin tüm cerrahi bölümlerde istatistiksel olarak anlamlı korelasyon gösterdiği belirlendi. Malnütrisyonun perioperatif dönemde morbidite üzerine olumsuz etkileri olduğu düşünülmektedir. Hipomagnezemi ile tespit edilebilecek malnütrisyonun önceden basit bir test ile tespit edilmesi çok faydalı olabilir.

Anahtar Kelimeler: Magnezyum; MNA, malnütrisyon; MNA-SF

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1. Introduction

Magnesium has vital functions in the human body. Presence of hypomagnesemia in the perioperative period can significantly increase morbidity (1). In addition, serum magnesium level decreases even more, especially after abdominal or orthopedic surgeries (2). Since magnesium is an absolute requirement, it should be taken in sufficient amounts with diet. Therefore, preoperative nutritional deficiency may accompany magnesium deficiency.

Malnutrition occurs in patients requiring surgery due to many factors. Preoperative malnutrition is associated with increased mortality and morbidity (3). By determining this situation, biochemical and immunological abnormalities can be corrected before surgery. The first step in detecting malnutrition is the application of screening methods (4). Nutrition screening tools have been developed for this. Mini nutritional assessment (MNA) and mini nutritional assessment short form (MNA-SF) are used for elderly patients. In addition, it has been stated that MNA-SF can be used in determining malnutrition in young and middle age group patients and adults (5).

The aim of our study is to determine the preoperative nutritional status of surgical patients using MNA-SF and to determine the hypomagnesemia that may accompany malnutrition.

2. Material and Methods

The study was initiated after obtaining the ethical approval of Eskişehir Osmangazi Medical Faculty Hospital, dated 18.12.2012 and numbered 21. The study was planned prospectively. After the statistical power analysis, the number of patients was planned to be 387. The study was conducted in Eskişehir Osmangazi University Faculty of Medicine Hospital with patients over 18 years of age who were scheduled for elective surgery in a month duration after obtaining ethical approval. Written consent was obtained the day before the operation. MNA and MNA-SF questionnaires were applied to the patients. Patients who did not give their consent, and those using magnesium, lithium, thyroid hormone, diuretic, amphoterecin B, aminoglycoside, alcohol and theophylline were excluded from the study. In addition, patients with diabetes mellitus and chronic renal failure were excluded from the study.

Age, gender and ASA scores of the patients were recorded. In addition, the reference range of serum magnesium levels measured on the day of malnutrition assessment was taken as 0.8-1.1 mmol / L.

Statistical Analysis

Statistical package program SPSS 17 was used for statistical analysis in the study. Descriptive statistical methods (Frequency, Percent, Average, Standard deviation) were used while evaluating the study data.

Pearson's chi-square test was used to compare qualitative data. Independent samples t-test was used for comparisons between groups in case of two groups for comparison of quantitative data. One-way Anova test was used for intergroup comparisons of parameters in cases of more than two groups. Bonferroni test was used to identify the group that caused the difference. Pearson Correlation Analysis was used for the correlational analysis of quantitative data.

The results were at 95% confidence interval, $p < 0.05$ significance level and $p < 0.01$; $P < 0.001$ was evaluated at the advanced significance level.

3. Results

387 patients over the age of 18 who were scheduled for elective surgery were included in the study. The dermographic distributions and ASA scores of the patients included in the study are shown in Table 1. The average age of our study was 48.97 ± 14.01 and the number of male patients was 187, and the number of female patients was 200. The ASA score distribution of the patients was 145 patients with ASA I, 91 patients with ASA II, 106 patients with ASA III and 45 patients with ASA IV, respectively. The distribution of

patients' MNA scores among surgical departments is shown in Table 2. MNA, MNA-SF and magnesium levels of the patients are shown in Tables 2, 3, 4,5,6,7, respectively.

Table 1. Demographic data, Osmangazi 2012 (N=387)

Age (mean+Sd)	**48,97±14,01**			
Gender	Male (n)		Female (n)	
	187		200	
*ASA score	ASA I (n)	ASA II (n)	ASA III (n)	ASA IV (n)
	145	91	106	45

** ASA score, American Society of Anesthesiologists score; M, mean; Sd, standard deviation*

Table 2. Distribution of patients' MNA scores, Osmangazi 2012 (N = 387)

Surgical department	N	Mean:	Sd	F	p
Orthopedics and traumatology	42	23,190	4,843	3,703	**0,000*** **
Cardiac surgery	10	24,200	1,874		
Gynecology and Obstetrics	58	26,397	2,997		
Thoracic surgery	11	23,136	1,951		
Ear, nose and throat surgery	47	26,862	3,371		
Plastic and reconstructive surgery	33	25,712	3,808		
Brain and neurosurgery	30	25,033	4,204		
Urological surgery	75	25,653	4,218		
General surgery	69	25,804	3,122		
Eye surgery	12	23,417	7,824		

*MNA, mini nutritional assessment; M, mean; Sd, standard deviation; advanced statistical significance, p <0.001 ****

No significant difference was found in Mg levels in the surgical groups according to the group variable in preoperative surgical patients (F = 1.652; p = 0.099> 0.05). A significant difference was found in the level of MNA-SF scores depending on the group variable (F = 2.354; p = 0.014 <0.05). The MNA-SF scores of the cases in the ENT service (12,660 ± 2,057) were found to be significantly higher than the MNA-SF scores of the cases in the orthopedic service (10,880 ± 2,787). The MNA-SF scores of the cases in the general surgery service (12.350 ± 2.099) were found to be significantly higher than the MNA-SF scores (10.880 ± 2.787) of the cases in the orthopedic service are shown in Table 3.

Table 3.Distribution of Patients' MNA-SF scores, Osmangazi 2012 (N = 387)

Surgical department	N	Mean	Sd	F	p
Orthopedics and traumatology	42	10,881	2,787	2,354	0,014*
Cardiac surgery	10	11,700	1,767		
Gynecology and Obstetrics	58	12,207	2,015		
Thoracic surgery	11	10,909	1,375		
Ear, nose and throat surgery	47	12,660	2,057		
Plastic and reconstructive surgery	33	12,121	2,190		
Brain and neurosurgery	30	11,867	2,460		
Urological surgery	75	12,307	2,552		
General surgery	69	12,348	2,099		
Eye surgery	12	12,750	1,913		

*MNA-SF, mini nutritional assessment short form; M, mean; Sd, standard deviation; advanced statistical significance, p <0.001 ****

Table 4. Magnesium level, Osmangazi 2012 (N = 387)

Surgical department	N	Mean: (mmol/L)	Sd	F	p
Orthopedics and traumatology	42	0,833	0,148	1,652	0,099
Cardiac surgery	10	0,765	0,152		
Gynecology and Obstetrics	58	0,845	0,087		
Thoracic surgery	11	0,805	0,091		
Ear, nose and throat surgery	47	0,798	0,152		
Plastic and reconstructive surgery	33	0,801	0,110		
Brain and neurosurgery	30	0,838	0,091		
Urological surgery	75	0,856	0,091		
General surgery	69	0,839	0,125		
Eye surgery	12	0,813	0,104		

M, mean; S, standard deviation; advanced statistical significance, p <0.001 ***

A significant difference was found in the MNA score level depending on the group variable (F = 1.652; p = 0.099> 0.05). The MNA scores of the cases in the obstetrics service (26,397 ± 2,997) were found to be significantly higher than the MNA scores of the cases in the orthopedic service (23,190 ± 4,843). The MNA scores of the cases in the ENT service (26,862 ± 3,371) were found to be significantly higher than the MNA scores of the cases in the orthopedic service (23,190 ± 4,843). The MNA scores of the cases in the urology service (25,653 ± 4,218) were found to be significantly higher than the MNA scores of the cases in the orthopedic service (23,190 ± 4,843). The MNA scores of the cases in the general surgery service (25,804 ± 3,122) were found to be significantly higher than the MNA scores of the cases in the orthopedic service (23,190 ± 4,843) are shown in Table 2.

In cases in the general surgery service; A negative correlation of 28.6% was found between age and Mg levels (r = -0.286; p = 0.017 <0.05). In the patients in the general surgery ward, it was found that the Mg level decreased as the age got older. There was no statistically significant relationship between Mg and Age in other groups (p> 0.05). There was no statistically significant relationship between Mg and Age in all cases (p> 0.05).

There was no statistically significant relationship between Mg and MNA-SF on a group basis (p> 0.05). There was no statistically significant relationship between Mg and MNA-SF in all cases (p> 0.05). Table 5. No statistically significant relationship was found between Mg and MNA on the basis of the group (p> 0.05). No statistically significant relationship was found between Mg and MNA in all cases (p> 0.05). Table 6.

Table 5 Patients' Mg levels and its relationship with MNA-SF, Osmangazi 2012 (N=387)

Surgical department	n	r	p
Orthopedics and traumatology	42	-0,235	0,134
Cardiac surgery	10	-0,247	0,492
Gynecology and Obstetrics	58	0,074	0,580
Thoracic surgery	11	0,204	0,548
Ear, nose and throat surgery	47	0,061	0,682
Plastic and reconstructive surgery	33	-0,089	0,624
Brain and neurosurgery	30	0,337	0,069
Urological surgery	75	0,167	0,151
General surgery	69	0,116	0,345
Eye surgery	12	-0,014	0,966
All cases	387	0,036	0,481

MNA-SF;mini nutritional assessment short form,Mg levels (mmol / L) unit, r; correlation coefficient

Table 6 Patients' Mg levels and its relationship with MNA, Osmangazi 2012 (N=387)

Surgical department	n	r	p
Orthopedics and traumatology	42	-0,212	0,177
Cardiac surgery	10	-0,399	0,254
Gynecology and Obstetrics	58	0,048	0,720
Thoracic surgery	11	0,036	0,917
Ear, nose and throat surgery	47	0,007	0,965
Plastic and reconstructive surgery	33	-0,115	0,523
Brain and neurosurgery	30	0,317	0,088
Urological surgery	75	0,198	0,089
General surgery	69	0,101	0,407
Eye surgery	12	0,051	0,875
All cases	387	0,027	0,594

MNA; mini nutritional assessment, Mg levels (mmol / L), r, correlation coefficient, statistical significance; p <0.05

In cases in the orthopedic service; A significant positive correlation was found between MNA and MNA-SF at the level of 81.9% (r = 0.819; p = 0.000 <0.001) Table 7. In cases in the cardiovascular surgery service; A positive significant correlation was found between MNA and MNA-SF at the 69.1% level (r = 0.691; p = 0.027 <0.05) Table 7. In the cases in the obstetrics service; A significant positive correlation was found between MNA and MNA-SF at the 84.6% level (r = 0.846; p = 0.000 <0.001) Table 7. In cases in the thoracic surgery service; A significant positive correlation was found between MNA and MNA-SF at the 78.8% level (r = 0.788; p = 0.004 <0.01) Table 7. In cases in the otorhinolaryngology service; A significant positive correlation was found between 92% MNA and MNA-SF (r = 0.920; p = 0.000 <0.001) Table 7. In the cases in the plastic surgery service; A significant positive correlation at the level of 90% was found between MNA and MNA-SF (r = 0.900; p = 0.000 <0.001) Table 7. In cases in the neurosurgery service; There was a significant positive correlation between MNA and MNA-SF at the 94.8% level (r = 0.948; p = 0.000 <0.001) Table 7.

Table 7 Relationship between patients' MNA-SF and MNA scores, Osmangazi 2012 (N=387)

Surgical department	n	r	p
Orthopedics and traumatology	42	0,819	**0,000*** **
Cardiac surgery	10	0,691	**0,027***
Gynecology and Obstetrics	58	0,846	**0,000*** **
Thoracic surgery	11	0,788	**0,004****
Ear, nose and throat surgery	47	0,920	**0,000*** **
Plastic and reconstructive surgery	33	0,900	**0,000*** **
Brain and neurosurgery	30	0,948	**0,000*** **
Urological surgery	75	0,938	**0,000*** **
General surgery	69	0,826	**0,000*** **
Eye surgery	12	0,925	**0,000*** **
All cases	387	0,859	**0,000*** **

*MNA; mini nutritional assessment, MNA-SF;mini nutritional assessment short form, r; correlation coefficient, statistical significance; *p<0,05, **p<0,01, ***p<0,001*

A positive significant relationship was found between MNA and MNA-SF at the level of 93.8% in cases in the urology service (r = 0.93.8; p = 0.000 <0.001) Table 7. In the cases in the general surgery service; A significant positive correlation was found between MNA and MNA-SF at the level of 82.6% (r = 0.826; p = 0.000 <0.001) Table 7.A positive significant relationship was found between MNA and MNA-SF at the level of 92.5% in patients in the eye service (r = 0.92.5; p = 0.000 <0.001) Table 7. In all cases; A significant positive correlation was found between MNA and MNA-SF at the level of 85.9% (r = 0.859; p = 0.000 <0.001) Table 7.

4. Discussion and Conclusion

It is known that the duration of hospital stay is shortened and postoperative outcomes are improved in patients whose nutritional status is optimized in the preoperative period (3). In the preoperative period, hypomagnesemia is common and is associated with malnutrition (6). In countries with middle-low income, the detection of malnutrition and associated electrolyte disturbances can be useful in surgical patients and contribute to the appropriate use of resources (3).

Preoperative malnutrition may arise from the primary disease that causes surgery or may result from completely different reasons (7). Malnutrition caused by primary disease is generally seen in cancer patients. The main secondary reasons are the decrease in oral intake and high ASA score due to old age (7).

In our study, we used MNA and MNA-SF to determine the risk of preoperative malnutrition. Thus, we thought that a rapid malnutrition risk assessment could be made in the preoperative period. MNA-SF is a six-question test that can be applied on an outpatient basis in outpatient settings and is recommended for use especially in the elderly (8). The average age of the patients included in our study is 49, and they consist of a relatively young age group. It has been shown that MNA-SF values are associated with the determination of nutritional status and mortality due to malnutrition in the young-middle age group (1), (9). In addition, the measurement of middle-upper arm diameter and the MNA-SF combination were found to be successful in detecting malnutrition in young and middle-aged hospitalized patients. It has been stated that it can be applied in this age group due to its ease of use (1), (5). In our study, it was observed that 24% of 387 patients operated in different surgical branches were under the risk of malnutrition when evaluated with MNA-SF and 17% when evaluated with MNA. A statistically significant positive correlation was found between MNA values and MNA-SF values in all preoperative surgical cases. In our study, it was determined that the MNA-SF form could be used in all preoperative elective surgery group cases to predict malnutrition in outpatient clinic conditions instead of the longer form MNA. When we look at the surgical branches, when the mean MNA score of the groups were compared, the patients who will undergo orthopedics, thoracic surgery and eye surgeries were found to be at risk of malnutrition. According to the mean MNA-SF score, orthopedics, cardiovascular surgery, thoracic surgery, and neurosurgery patients were found to be at risk of malnutrition. When both scoring systems are evaluated, it can be said that the sensitivity of MNA-SF values is higher.

Magnesium deficiency was detected in 7-11% of hospitalized patients, and it was observed that 40% had accompanying hypokalemia, hypophosphothemia, hyponatremia and hypocalcemia (10). Therefore, it may be important to detect hypomagnesemia in the perioperative period in patients with malnutrition, which may lead to significant consequences in anesthesia management (10-12).

Known causes of hypomagnesemia in surgical patients; decreased dietary intake, poor gastrointestinal absorption, increased loss of the gastrointestinal tract, alcoholism, diabetes mellitus and increased renal loss (12). In addition, it is important to detect it in the perioperative period due to its interaction with agents such as anesthetic agents, diuretics, thiazides, and valproic acid (10). Although the height of the intracellular amount of magnesium in general is known, rapid mobilization of intracellular magnesium stores and intracellular magnesium stores to the extracellular area is not possible. Therefore, a

negative magnesium balance rapidly causes hypomagnesemia (10). In our study, when we looked at hypomagnesemic conditions that we may encounter in patients with possible malnutrition risk during the perioperative period and that may cause complications in the perioperative process, hypomagnesemia was not encountered in the laboratory. However, the magnesium level of cardiovascular surgery patients was found to be lower than the other groups, although it was not statistically significant. Postoperative arrhythmia and low cardiac output may occur, since hypomagnesemia, which is present after surgery, especially in cardiac surgeries, can reach up to 70% in the postoperative period (10), (13). For this reason, its importance increases in patients who have undergone this type of surgery. Finally, there was no relationship between MNA-SF and MNA and magnesium levels in patients with malnutrition risk. This may be due to the fact that our patients are at risk of malnutrition, not malnutrition. It can also be interpreted as a result of the possibility that blood magnesium levels were checked and normalized before surgery.

The main limitation of our study is that the risk of malnutrition is not supported by other malnutrition scores. In addition, patients determined to be at risk with MNA-SF were not followed up intraoperatively and postoperatively. Therefore, possible complications associated with malnutrition and hypomagnesemia have not been identified.

As a result; hypomagnesemia is an electrolyte disorder that may accompany malnutrition. Considering that this situation alone has a significant effect on morbidity and mortality in the peroperative period, early detection of its association with malnutrition may have positive returns. No significant correlation was found between MNA score and MNA-SF score and magnesium levels. Although a correlation was shown between hypomagnesemia and malnutrition, the relationship between MNA and MNA-SF scores could not be demonstrated. A significant positive correlation was found between MNA score and MNA-SF score in all preoperative elective surgery cases in detecting preoperative malnutrition. MNA-SF may be more suitable for the detection of malnutrition in preoperative elective surgery patients in polyclinic conditions in terms of easy applicability and time saving. This application may have positive results in the preoperative early detection and treatment of malnutrition in patients scheduled for surgery.

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Research Article / Araştırma Makalesi

Chiari Malformasyonlu Hastaların BOS Akım Parametrelerinin Normal Sağ lıklı Grup ile Kıyaslaması

Comparison of CSF Flow Parameters of Patients with Chiari Malformation with Healthy Individuals

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Özet

Chiari malformasyonu (CM) serebellar tonsillerin foramen magnumun altına 5 mm'den fazla indiği bir hastalıktır. Semptomatik olmayan Chiari hastalarının nasıl yönetileceği konusunda fikir birliği yoktur. Çalışmamızda Chiari malformasyonu olan hastalarda BOS akım parametrelerinin normal sağlıklı grup ile kıyaslayarak farklılıkları ortaya koymayı hedefledik. Ocak 2016 ile Aralık 2019 arasında faz kontrast BOS akım MRG incelemesi yapılan 85 Chiari malformasyonlu hastayı ardışık olarak değerlendirdik. 18 ile 60 yaş arasındaki bireyleri dahil ettik. Ayrıca 29 adet sağlıklı gönüllü dahil edilerek faz-kontrast BOS akım MR görüntülemesi yapıldı. İleri hacim (FV), ters hacim (RV), akuaduktal strok hacmi (ASV), ortalama alan ve tepe hızı içeren BOS akış parametrelerini değerlendirildi. Ayrıca CM hastaların volümetrik T2 CISS görüntülemelerinden herniye tonsil ve foramen magnum çapları da kaydedildi. Akuaduktal strok volümünün CM hastalarında anlamlı olarak arttığı gözlendi (p = 0,049). Ortalama AS alanı CM hastalarında normal gruba oranla istatistiksel olarak anlamlı geniş bulunmuştur (p <0,001). Herniye tonsil ile foramen magnum çaplarının BOS akım parametreleri ile karşılaştırıldığında; herniye tonsil çapı arttıkça ASV azalmakta (p = 0.002, r = -0.333), foramen magnum çapı arttıkça da ASV azalmakta idi (p = 0.020, r = -0.251). CM hastalarında faz kontrast MR tekniği ile BOS akım parametrelerinin değerlendirmede akuaduktus Silvi düzeyi kolay ve pratik olması ve daha doğru sonuçlar vermesi nedeni ile kullanılabilecek anatomik bölgedir. CM hastalarında artmış ASV ve ortalama AS alan değerleri izlenmekte birlikte olağan dışı BOS akım değerlerini bize bildirmektedir.

Anahtar Kelimeler: BOS akım, mr, chiari malformasyonu, akuaduktal vurum hacmi, faz kontrast MR

Abstract

Chiari malformation (CM) is a disease in which cerebellar tonsils descend more than 5 mm below the foramen magnum. There is no consensus on how to manage non-symptomatic patients with CM. In our study, we tried to reveal the differences in CSF flow parameters in patients with Chiari malformation by comparing them with the normal healthy group.We evaluated 85 patients with Chiari malformation, who underwent phase contrast CSF flow MRI between January 2016 and December 2019, consecutively. We included individuals aged between 18 and 60 years. In addition, 29 healthy volunteers were included and phase-contrast CSF flow MR imaging was performed. CSF flow parameters including forward volume (FV), reverse volume (RV), aqueductal stroke volume (ASV), mean area, and peak velocity were evaluated. In addition, the diameters of the herniated tonsil and foramen magnum were recorded from volumetric T2 CISS images of CM patients. It was observed that the aqueductal stroke volume increased significantly in CM patients (p = 0.049). The mean area of AS was found to be statistically significantly larger in CM patients compared to the normal group (p <0.001). When the diameters of the herniated tonsil and foramen magnum were compared with the CSF flow parameters; ASV decreased as the diameter of the herniated tonsil increased (p = 0.002, r = -0.333), and as the diameter of the foramen magnum increased, ASV decreased (p = 0.020, r = -0.251). Aqueductus Sylvii level is an anatomical location that can be used in CM patients for the evaluation of CSF flow parameters with phase contrast MR technique, since it is easy and practical and gives more accurate results. Increased ASV and average AS field values are observed in CM patients, and these are unusual CSF flow values.

Keywords: MR, aquaductal stroke volume, phase contrast MR, CSF flow

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1. Giriş

Chiari malformasyonu (CM) serebellar tonsillerin foramen magnumun altına 5 mm'den fazla indiği bir hastalıktır (1-3). CMI, hastaların% 50'sinden fazlasında siringomiyeli ile ilişkilidir (4-5). Hipoplastik posterior fossa ve kranioservikal bileşkede stenozun neden olduğu düşünülen CMI ile ilişkili siringomiyelinin karakteristik nörolojik ve radyolojik özellikleri olmasına rağmen, kesin mekanizması bilinmemektedir (6). Semptomatik olmayan Chiari hastalarının nasıl yönetileceği konusunda fikir birliği yoktur. Tedavi kararı vermede hasta kliniğinin yanı sıra posterior fossa ve kranioservikal bileşke düzeyine yönelik magnetik rezonans (MR) görüntülemesi faydalı olabilmektedir. Faz kontrast MR görüntüleme (PC-MRI) ile CM olan hastalarda BOS akım dinamikleri ile alakalı değerli bilgiler elde edilebilmektedir (7). Çalışmamızda Chiari malformasyonu olan hastalarda BOS akım parametrelerinin normal sağlıklı grup ile kıyaslayarak farklılıkları ortaya koymayı hedefledik.

2. Yöntem ve Gereçler

Hasta seçimi

Ocak 2016 ile Aralık 2019 arasında faz kontrast BOS akım MRG incelemesi yapılan 85 Chiari malformasyonlu hastayı ardışık olarak değerlendirdik. 18 ile 60 yaş arasındaki bireyleri dahil ettik. 5 mm'den fazla tonsil ektopisi olan hastalar dahil edildi. Operasyon sonrası yapılan çekimler dışlandı. Çalışmamıza ayrıca 29 adet sağlıklı gönüllü dahil edilerek faz-kontrast BOS akım MR görüntülemesi yapıldı. Hastaları chiari (n = 85) ve normal (n = 29) olmak üzere iki gruba ayırdık. İleri hacim (FV), ters hacim (RV), akuaduktal strok hacmi (ASV), ortalama alan ve tepe hızı içeren BOS akış parametrelerini değerlendirdik. ASV, FV ve RV toplamının yarısı olarak hesaplandı. Çalışmamıza Bezmialem Vakıf Üniversitesi etik komitesi tarafından onay verilmiştir.

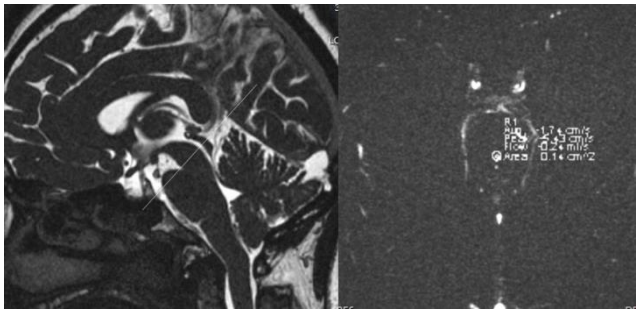
Görüntüleme Tekniği

1.5 Tesla MR cihazı ile (Avanto; Siemens Medical Solution, Erlangen, Almanya) kafa sarmalı kullanılarak MR yapıldı. BOS akışının kantitatif değerlendirmesi, iki boyutlu (2D) Q FLOW faz-kontrast MR anjiyografi tekniği ile eksenel düzlemde elde edilen görüntülerle gerçekleştirildi. Akuaduktus Silvinin (AS) en geniş yeri olan orta üçte birlik kısımdan axial planda görüntüler elde edildi. Her hasta için PC-MRI süresi yaklaşık 5 dakikaydı. İlk olarak orta hat sagital, koronal ve aksiyal T1 W ön görüntüler elde edildi. “Mean modulus,” “magnitude of complex difference” ve“directional phase difference” görüntülemeler semiaksiyel planda AS ye dik olacak şekilde elde edildi. Aksiyel düzlemde görüntüler için, kalp hızına göre 14–30 kardiyak faz kesiti için kullanılan parametreler: TR: 31,25 ms, TE: 8,06 ms, kesit kalınlığı: 3 mm, NSA: 1, FOV: 16 × 10 cm, matris 128 × 256 ve flip angle 10 °. Kardiyak tetikleme, MR uyumlu elektrotlarla (Kendall, Arbo, Tyco International, Neustadt, Almanya) geriye dönük olarak gerçekleştirildi. Akış hassasiyeti (venc) 20 cm / s olarak belirlendi. Kaudokraniyal yöndeki akım (diyastolik veya ters akış) negatif olarak tanımlanırken kraniokaudal yöndeki akış (sistolik veya ileri akış) pozitif olarak belirlendi. PC-MRI dan sonra sagital T2 CISS ve T2 SPACE sekansları da elde edildi. 3D-T2 CISS için kullanılan parametreler şunlardı: kesit kalınlığı: 1 mm, FOV: 200 mm, matris 290 × 320, TR: 6,06 ms, TR: 2,61 ms ve flip angle 70 °. 3D-T2 SPACE için kullanılan parametreler şunlardı: kesit kalınlığı: 1 mm, FOV: 240 mm, matris 231 × 256, TR: 2500 ve TR: 501.

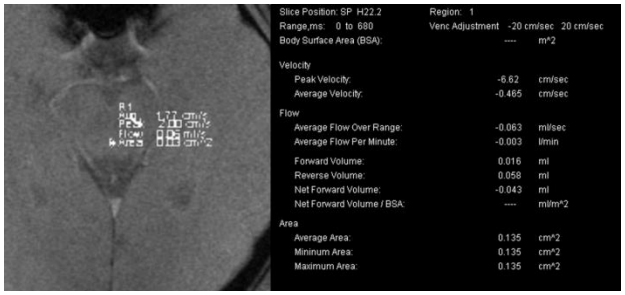
MR analizi

Tüm hastalardan ve kontrol grubundan elde edilen görüntüler Siemens kullanıcı konsolu (Argus yazılımı, Siemens, Erlangen, Almanya) kullanılarak değerlendirildi. BOS akış ölçümü için ‘PC-MRI aksiyel through plane’ görüntüler kullanıldı. Aksiyel görüntüde AS en geniş yerinden ölçümler yapılmıştır. Akış konturları ‘Region of Interest (ROI)’ tarafından çizildi (Şekil 1) ve ROI, bir kardiyak döngü sırasında elde edilen aksiyel faz görüntülerine tamamen kopyalandı. Tepe ve ortalama hız (cm/s), ileri ve geri akış hacmi (µl), net ileri akış hacmi (µl), ASV (aqueductal strok hacmi) (µl), AS

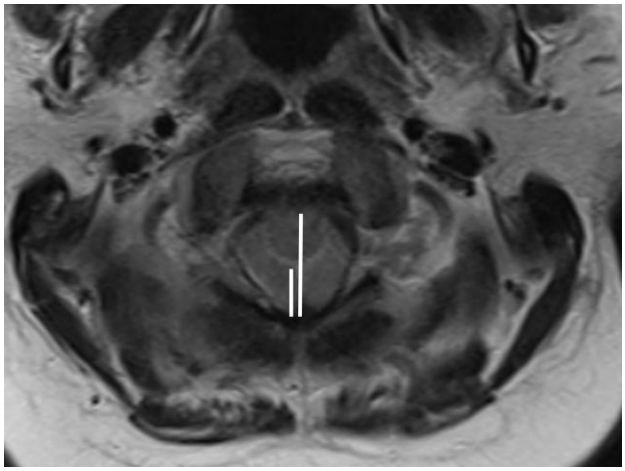
alanı (mm2) hesaplandı (Şekil 2). Ayrıca CM hastaların volümetrik T2 CISS görüntülemelerinden herniye tonsil ve foramen magnum çapları da kaydedildi (Şekil 3).



Şekil 1. Ampulla'ya dik olarak alınan aksiyel görüntüler ve tüm akuaduktus'u içerecek şekilde ROİ'nin yerleştirilmesi



Şekil 2. Sylvian akuaduktus tan elde edilen BOS akış parametrelerinin özet tablosu.



Şekil 3. Aksiyel T2 ağırlıklı görüntülemede herniye tonsil ve foramen magnum çaplarının ölçümü

Tablo 1. İstatistiksel veriler

	n	PPS/AS (mean±SD)	ASV (mean±SD)	Ortalama alan (mean±SD)	İleri Volüm (mean±SD)	Geri Volüm (mean±SD)	Pik akım hızı (mean±SD)
CM hastaları	85	2.30±0.62	31.24±27.17	0,08±0.05	23,32±25,07	39,15±33,70	5,00±2,44
Normal grup	29	4.12±0.86	23.88±12.14	0,04±0.02	17,79±10,58	30,28±14,63	5,02±1,62
P değeri		***0,001***	***0,049***	***0,004***	*0.102*	*0.054*	*0.949*

CM: Chiari malformasyonu

İstatistiksel analiz

Tüm istatistiksel analizler SPSS Windows sürüm 26.0 yazılım paketi (IBM Corp., New York, NY; eski adıyla SPSS Inc., Chicago, IL) kullanılarak yapıldı. CM olguları ile normal grup karşılaştırıldı. İlk olarak değişkenlerin iki gruptan dağılımı Shapiro – Wilk normallik testi kullanılarak değerlendirildi. Değişkenlerin iki farklı grup arasında dağılımı normal olduğundan grup karşılaştırması için bağımsız t testi kullanıldı. P <0,05 değeri istatistiksel olarak anlamlı kabul edildi. Herniye tonsil ve foramen magnum çapları ile BOS akım parametreleri arasındaki ilişki Spearman korelasyon testi kullanılarak yapıldı.

Sonuçlar

CM hastaların yaş ortalaması 34.15 ± 16.84, normal grubun ise 36.14 ± 11.37 idi. İleri ve ters BOS akımının ortalamasını temsil eden akuaduktal strok volümünün CM hastalarında anlamlı olarak arttığı gözlendi (p = 0,049). Ortalama AS alanı CM hastalarında normal gruba oranla istatistiksel olarak anlamlı geniş bulunmuştur (p <0,001). Pik hız, ileri volüm, geri volüm açısından istatistiksel olarak anlamlı bir fark yoktur. CM hastalarının kendi içlerinde herniye tonsil çapı ile foramen magnum çaplarının BOS akım parametreleri ile karşılaştırıldığında herniye tonsil çapı arttıkça ASV azalmakta (p = 0.002, r = -0.333), foramen magnum çapı arttıkça da ASV azalmakta idi (p = 0.020, r = -0.251).

3. Tartışma

CM olan hastalarda günümüze kadar yapılmış birçok çalışma bulunmaktadır. Krueger ve arkadaşları CM hastalarında, semptomatik olan ve olmayan hastalarda pik hız araştırması yapmış olup bunu foramen magnum seviyesinde ölçmüşlerdir çalışmalarında semptomatik durumun foramen magnum düzeyinde hızlarda değişikliğe neden olmadığını göstermişlerdir (8). Biz çalışmamızda normal hasta grubu ile CM hastaları arasında farklılık gösteremedik. Bu konuda ayrıca McGirt ve arkadaşları, baş ağrısı ile BOS akım parametreleri arasındaki ilişkiyi araştıran yazılarında, oksipital baş ağrısının BOS akım dinamiklerindeki bozulma ile daha yakından ilişkili olduğunu ortaya koymuşlar (9) .Biz çalışmamızda, CM hastalarının normal gruba göre BOS akım dinamiklerinde oluşturduğu farklılıkları araştırdık ve semptomatik duruma göre ayrım yapmadık.

Koç ve arkadaşları ise siringomyeli ile prezente tip 1 CM hastalarında foramen magnum ve sirinks kavitesinden faz kontrast MR incelemesi yaparak operasyon öncesi ve sonrası BOS akım dinamiklerinin karşılaştırmışlar. Operasyon sonrası BOS akımındaki heterojen paternin %61 oranda sinüzoidal paterne döndüğünü bildirmişlerdir (3). Bizim çalışmamızda amaç operasyon öncesi yapılan inceleme ile BOS akım parametrelerindeki normal dışı değişimleri göstererek operasyona ışık tutmaktır. BOS akım analizini rutin görüntüleme olan akuaduktus silvi seviyesinden yapmamızın nedeni günlük pratikte CM olan hastaların olağandışı bulgularını ortaya koymaktır.

Subaraknoid boşluklarda, özellikle foramen magnum seviyesinde BOS parametrelerinin ölçümleri zor olup hata ve artefaktlara neden olabilir (10-12). ASV ölçümü akuaduktus silvi düzeyinde daha kolay ve daha pratiktir. Özellikle kemik komşuluğu olmaması, sıvı yumuşak doku geçişinin MR da artmış uzaysal rezolüsyon bağlı daha iyi yapılması, akuaduktus silvinin foramen magnum ve

servikal düzeye göre daha kolay değerlendirebilir olması ve yuvarlak şekli ile daha kolay ROI yerleştirilebilmesi nedeni ile BOS akımı hakkında daha doğru bilgi sağlar. Bu nedenle, foramen magnum seviyesinde ve üst servikal seviyede hız ölçümü yapılmadı.

AS alanının CM olan hastalarda yüksek olmasını lateral medüller sisternde tonsiller ektopiye sekonder daralma ve buna bağlı BOS akışındaki zorlanmaya bağladık. ASV değerinin CM hastalarındaki yüksekliği ortalama AS alanındaki artışa ve foramen magnum seviyesindeki BOS klirensindeki azalmaya bağladık. Foramen magnum ve herniye tonsil çapı ile ASV arasındaki negatif korelasyon da hipotezimizi desteklemekte akuaduktus Silvi düzeyindeki BOS akım değerlendirmesinin önemini vurgulamaktadır.

Çalışmamıza ait birtakım kısıtlamalar mevcuttur. Bunlardan ilki çalışmamızın retrospektif ve tek merkezli olmasıdır. İkincisi dekompresyon cerrahisi öncesinde ve sonrasında aquaduktus silvi düzeyinden BOS akım parametrelerinin ölçülmemesi ve ayrıca postoperatif takiplerinin yapılmamış olmasıdır. Üçüncüsü CM hastalarına tiplendirme yapılıp birbirleri ile kıyaslama yapılmamış olmasıdır.

4. Sonuç

CM hastalarında faz kontrast MR tekniği ile BOS akım parametrelerinin değerlendirmede akuaduktus Silvi, kolay ve pratik olması ile daha az artefakta bağlı daha doğru sonuçlar verebilecek olması nedeni ile kullanılabilecek anatomik bölgedir. CM hastalarında artmış ASV ve ortalama AS alan değerleri izlenmekte birlikte olağan dışı BOS akım değerlerini bize bildirmektedir. Bu değerlerin gelecek çalışmalar ışığında operasyon öncesi kullanılabilecek parametreler olabileceğini düşünmekteyiz.

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Research Article / Araştırma Makalesi

Düşük Serum Albumin Düzeyi Geriatrik Sendromlar İçin Risk Faktorü Olabilir mi?

Could Low Serum Albümin Level Be a Risk Factor for Geriatric Syndromes?

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Özet

Düşük serum albümin düzeyinin yaşlı hastalarda morbidite ve mortalite risk artışı ile ilişkisi çalışmalarla gösterilmiştir. Bu çalışmada, yaşlılarda serum albümin düzeyleri ile geriatrik sendromlar arasında bir ilişki olup olmadığının incelenmesini amaçladık. Ocak 2014-Nisan 2018 tarihleri arasında geriatri kliniğine ayaktan başvuran ve ayrıntılı geriatrik değerlendirme ile eş zamanlı serum albümin düzeyi bakılan 65 yaş üstü hastaların dosyaları retrospektif olarak incelendi. Dahil edilme kriterlerini karşılayan ve dışlama kriteri bulunmayan 802 hasta çalışmaya dahil edildi. Bütün hastaların demografik verileri, komorbiditeleri, kan serum albümin düzeyleri, geriatrik sendromlar kaydedildi. Katılımcıların yaş ortalaması 72,96±8,14 yıl ve %66,7'si kadın idi. Hastaların %30,5'inde düşme, %49,4'ünde ağrı, %48,1'inde üriner inkontinans, %47,7'sinde polifarmasi, %19,3'ünde demans, %29,7'sinde depresyon, %20,6'sinde malnütrisyon riski ve %5,9'unda malnütrisyon saptandı. %49,3'ü kırılgan adayı ve %21,2'si kırılgandı. Ek olarak, %30,9 hastada muhtemel sarkopeni, %5,2 hastada sarkopeni ve %4,2 hastada şiddetli sarkopeni saptandı. Tüm hastaların ortalama serum albümin düzeyi 4,12±0,36 g/dl idi. Serum albümin düzeyi ile geriatrik sendromlar arasındaki ilişki incelendiğinde serum albümin düzeyindeki düşüşün düşme, ağrı, üriner inkontinans, polifarmasi, demans, malnütrisyon, kırılganlık ve sarkopeni riskini artırdığı görüldü ($p<0,05$). Bu ilişki yaş, cinsiyet ve nütrisyon durumunun etkisi ortadan kaldırıldığında devam etti ($p<0,05$). Serum albümin düzeyi ve depresyon arasında ilişki saptanmadı ($p>0,05$). Düşük serum albümin düzeyleri düşme, ağrı, üriner inkontinans, polifarmasi, demans, malnütrisyon, kırılganlık ve sarkopeni gibi geriatrik sendromlar için bir öngördürücü olabilir. Serum albümin düzeyinde düşüş olan hastalarda eşlik edebilecek geriatrik sendromlar akılda tutulmalıdır.

Anahtar Kelimeler: Albümin; geriatrik sendrom; inflamasyon; nütrisyon; yaşlı

Abstract

There are many studies showing that low serum albumin levels increase the risk of morbidity and mortality in older adults. In this study, we aimed to examine whether there is a relationship between serum albumin levels and geriatric syndromes in older adults. The records of patients over the age of 65 who were admitted to the geriatric clinic between January 2014 and April 2018 and whose serum albumin levels were measured simultaneously with a comprehensive geriatric assessment were reviewed retrospectively. 802 patients who met the inclusion criteria and had no exclusion criteria were included in the study. Demographic data, comorbidities, serum albumin levels, geriatric syndromes were recorded for all patients. The mean age of the participants was 72.96±8.14 years and 66.7% were women. We determined falling in 30.5% of the patients, pain in 49.4%, urinary incontinence in 48.1%, polypharmacy in 47.7%, dementia in 19.3%, depression in 29.7%, malnutrition risk in 20.6% and malnutrition in 5.9%. Of the patients, 49.3% were prefrail and 21.2% were frail. In addition, probable sarcopenia was found in 30.9%, sarcopenia in 5.2%, and severe sarcopenia in 4.2% of the participants. The mean serum albumin level of all participants was 4.12±0.36 g/dl. When the relationship between serum albumin level and geriatric syndromes was examined, it was observed that the decrease in serum albumin level increased the risk of falls, pain, urinary incontinence, polypharmacy, dementia, malnutrition, frailty, and sarcopenia ($p<0.05$). This relationship continued when the effects of age, gender and nutritional status were removed ($p<0.05$). No relationship was found between serum albumin level and depression ($p>0.05$). Low serum albumin levels may be a predictor of geriatric syndromes such as falls, pain, urinary incontinence, polypharmacy, dementia, malnutrition, frailty, and sarcopenia. Geriatric syndromes that may accompany patients with decreased serum albumin levels should be kept in mind.

Keywords: Albumin; geriatric syndrome; inflammation; nutrition; older adults

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1. Giriş

Bilim, teknoloji ve sağlık alanındaki gelişmeler sayesinde tüm dünyada beklenen yaşam süresi uzamıştır. Yaşlanma beraberinde getirdiği fizyolojik değişikliklerle birlikte doğal bir süreçtir ve yaşlanmanın tüm kronik hastalıklar ve geriatrik sendromlar için önemli bir risk faktörü olduğu iyi bilinmektedir. Uzayan yaşam süresi ile artan yaşlı popülasyonu beraberinde geriatrik sendromları gündeme getirmektedir. Geriatrik sendromlar klasik sendromlardan farklı olarak multifaktöriyel etiyolojisi olan belirti ve bulguların varlığı ile karakterizedir (1). Yaşlılarda ciddi morbiditelere ve mortaliteye yol açabilen düşme, malnütrisyon, inkontinans, sarkopeni, kırılganlık, demans, depresyon, ağrı multifaktöriyel etiyolojileri kanıtlanmış ya da muhtemel sık karşılaşılan geriatrik sendromlar arasında yer almaktadır (1).

Yaşla birlikte gelişen ve yaşa bağlı patolojilere yatkınlığı öngören kronik, düşük dereceli inflamasyonu tanımlamak için 'inflammaging' terimi 2000 yılından itibaren kullanılmaktadır (2). Birçok çalışma, inflamatuar biyo-belirteçlerin yaşlı insanlarda morbidite (diyabetes mellitus, koroner arter hastalığı, geriatrik sendromlar vb.) ve mortalitenin güçlü prediktörleri olduğunu göstermektedir (3,4). Geriatrik sendrom ve inflamasyon arasındaki ilişkiyi araştıran çalışmalarda kırılganlık ile yüksek Tümör Nekrozis Faktör-α (TNF- α), Interlökin-6 (IL-6) düzeyleri ve de düşük serum albümin düzeyi ilişkili saptanırken (5), yine sarkopenisi olan hastalarda serum albümin düzeyi düşük, eritrosit sedimentasyon hızı ise yüksek saptanmıştır (6).

Albümin, plazmada en yüksek oranda bulunan protein olup sadece karaciğerde sentezlenir. Plazma albümin düzeyi, klinik olarak stabil olan bireylerde beslenmenin ana göstergelerinden biridir. Ancak albüminin plazma düzeyini etkileyen beslenmeden dışında da birçok faktör mevcuttur. Düşük serum albümin düzeyinin yaşlı bireylerde hem malnütrisyon, kas kaybı, günlük yaşam aktivitelerinde gerileme ile ilişkili olduğu hem de mortalite için prognostik bir faktör olduğu çalışmalarla gösterilmiştir (7). Geriatrik sendromlardan biri olan malnütrisyon ile düşük serum albümin düzeyi arasındaki ilişki iyi bilinmektedir. Malnütrisyon, kırılganlık, sarkopeni pek çok açıdan ortak etyopatogenezi paylaşan geriatrik sendromlar olmakla birlikte, serum albümin düzeyi ile ilişkilerinin yalnızca malnütrisyona bağlanması yeterli değildir. Nitekim serum albümin düzeyi beslenme durumunu değerlendirmek için iyi bir biyo-belirteç olsa da özellikle son çalışmalar düşük serum albümin düzeyinin daha çok altta yatan kronik bir inflamasyon durumunu yansıttığını göstermektedir (8–12).

Biz de bu çalışmada, kliniğimize başvuran yaşlı hastalarda serum albümin düzeyi ile sık görülen geriatrik sendromlar arasında bir ilişki olup olmadığını değerlendirmeyi hedefledik.

2. Gereç ve Yöntem

Hasta Seçimi

Çalışma için Ocak 2014-Nisan 2018 tarihleri arasında Dokuz Eylül Üniversitesi Tıp Fakültesi Hastanesi Geriatri Polikliniği'ne başvuran, 65 yaş ve üstü, ayrıntılı geriatrik değerlendirme yapılmış 2370 hastanın dosyaları retrospektif olarak incelendi. Dosyasında eş zamanlı ayrıntılı geriatrik değerlendirme, biyoimpedans analizi ve serum albümin düzeyi olan 878 hasta belirlendi. Dışlama kriteri olan 76 hasta dışlandıktan sonra toplam 802 hasta çalışmaya dahil edildi.

Dışlama Kriterleri

- 65 yaşın altında olanlar,
- Çalışmaya katılmayı reddedenler,
- Akut serebrovasküler olay, gastrointestinal kanama, sepsis, akut böbrek yetmezliği, akut koroner sendrom, akut karaciğer yetmezliği, akut solunum yetmezliği, akut enfeksiyonlar, ciddi anemi (hemoglobin <10 g/dL) ya da kanser gibi genel sağlık durumlarını bozabilecek ciddi hastalık geçmişi olanlar,
- Serum albümin düzeyini etkileyebilecek nefrotik sendrom,

kronik enfeksiyonlar, gastroenteropati, glomerülenefrit, karaciğer fonksiyon bozuklukları, paraproteinemiler, kalp yetersizliği gibi hastalık öyküsü olanlar

- Biyoimpedans ölçümü için kontrendikasyon teşkil eden kalp pili olan hastalar,

- Alkol ya da madde bağımlılığı olanlar çalışmadan dışlanmıştır.

Hasta özellikleri

Hastaların demografik verileri (yaş, cinsiyet, eğitim durumu), kronik hastalık öyküsü (hipertansiyon, diyabet, konjestif kalp yetmezliği, tiroid hastalığı, serebrovasküler olay, demans), Charlson komorbidite indeksi ve kullanılan ilaç sayısı hasta dosyalarından kaydedildi.

Laboratuvar Bulguları

Hastaların biyokimyasal, metabolik ve nütrisyonel durumlarını belirlemek için yapılan laboratuvar tetkikleri kaydedildi. Serum albümin düzeyi, glukoz, C-reaktif protein (CRP), alanin aminotransferaz (ALT), kreatinin, glomerüler filtrasyon hızı (GFR), tiroid uyarıcı hormon (TSH), vitamin B12 ve folik asit Diagnostic Modular Systems Autoanalyzer (Roche E170 ve P-800, İsviçre) kullanılarak analiz edildi. Serum 25-OH D vitamini, Cobas e601 otoanalizöründe (Mannheim, Almanya) radyoimmunoassay yöntemi ile ölçüldü.

Ayrıntılı Geriatrik Değerlendirme

Hastalara kognitif fonksiyon değerlendirmesi için yapılan MMSE (13), duygu durum değerlendirmesi için yapılan Geriatrik Depresyon Ölçeği (GDS) (14,15), nütrisyon değerlendirmesi için yapılan Mini-Nütrisyonel Değerlendirme Ölçeği-Kısa Formu (MNA-KF) (16), denge ve yürüme fonksiyonlarını değerlendirmek için yapılan Tinetti Denge ve Yürüme Testi (17) ve Kalk ve Yürü Testi skorları (18), Temel ve Enstrümental Günlük Yaşam Aktiviteleri (TGYA, EGYA) (19,20) ölçü ve boy, kilo, vücut kitle indeksi (VKİ), 4m yürüme hızı, el kavrama gücü (21) ve biyoimpedans analizi ölçümleri kaydedildi.

Geriatrik Sendromlar

Düşme, kişinin bilinç kaybı ya da dışarıdan uygulanan bir güce bağlı olmaksızın, istemeden yere veya bulunduğu düzeyin daha altına inmesi ile sonuçlanan beklenmedik olay olarak tanımlandı. Son bir yıl içinde tanımlanan şekilde en az bir kez düşme öyküsü olan hastalar düşme pozitif olarak kabul edildi.(22) Ağrı, hastanın "Vücudunuzun herhangi bir yerinde ağrı var mı?" sorusuna verdiği yanıtla değerlendirildi.(23) Üriner inkontinans, idrar yolu enfeksiyonu olmaksızın son 3 ayda istemsiz idrar kaçırma olarak tanımlandı.(23) Hastaların kullandıkları ilaçlar ve ilaç sayıları kaydedildi. Beş ve daha fazla ilaç kullanmak polifarmasi olarak kabul edildi.(24) Demans ve depresyon tanıları DSM-V (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) tanı kriterlerine göre koyuldu.(25) Nütrisyonel durum ise Mini-Nütrisyonel Değerlendirme -Kısa Formu (MNA-KF) ile yapıldı. Bu forma göre total skor 0-7 arası malnütrisyon, 8-11 arası malnütrisyon riski olarak değerlendirilirken, 12-14 arasındaki değerler normal nütrisyonel durum olarak değerlendirildi.(16) Kırılganlık değerlendirmesi Fried Fiziksel Kırılganlık ölçeği kullanılarak yapıldı. Buna göre istemsiz kilo kaybı, düşük fiziksel aktivite, düşük yürüme hızı, azalmış kas kuvveti ve tükenmişlik parametrelerinden 3 veya daha fazlası bulunanlar kırılgan, 1 veya 2 parametre bulunanlar ise kırılgan adayı olarak değerlendirildi. Sarkopeni tanısı, Avrupa Sarkopeni Çalışma Grubu (EWGSOP)'nun 2019 yılında revize ettiği tanı kriterlerine göre konuldu.(26) Ülkemizde yapılan cut-off kriterlerine göre iskelet kas indeksinin (SMI) erkeklerde <8,33 kg/m2, kadınlarda <5,70 kg/m2 olması düşük kas kütlesi olarak tanımlanırken, Jamar el dinamometresi ile ölçülen el kavrama gücünün (ortalama 3 ölçüm) erkeklerde <28 kg, kadınlarda <14 kg olması düşük kas gücü olarak tanımlandı.(21) Kas gücü normal olan hastalar sarkopeni yok olarak değerlendirildi. Yalnızca düşük kas gücü olan hastalar muhtemel sarkopeni, muhtemel sarkopeniye ek olarak düşük kas

kitlesi olan hastalar sarkopeni ve sarkopeniye ek olarak düşük fiziksel performansı olan hastalar da şiddetli sarkopeni olarak değerlendirildi.(26)

Çalışmanın Etik Boyutu

Çalışma, Dokuz Eylül Üniversitesi Girişimsel Olmayan Araştırmalar Etik Kurulu'nun 17.02.2020 tarih 2020/04-51 protokol nolu kararı ile uygun bulunmuş ve Helsinki Deklarasyonu ile uyumlu olarak yürütülmüştür. Çalışmaya dahil edilen katılımcılardan bilgilendirilmiş gönüllü olur formu alınmıştır.

İstatistiksel Analiz

İstatistiksel analizler SPSS Windows 23 (SPSS Inc, Chicago, IL) paket programı ile yapıldı. Tablo I'de yapılan tanımlayıcı istatistikler ortalama ± standart sapma veya yüzde olarak verildi. Tablo II'de geriatrik sendromları olan hasta gruplarını tek tek kontrol gruplar ile karşılaştırmak ve olasılık oranlarını (OR) hesaplamak için multinominal lojistik regresyon analizi kullanıldı. Tablo II'de verilen tüm sonuçlarda yaş, cinsiyet ve nütrisyon durumuna göre düzeltme yapıldı. p <0.05 sonuçları istatistiksel olarak anlamlı kabul edildi.

3. Bulgular ve Analizler

Çalışmaya dahil edilen toplam 802 hastanın yaş ortalaması 72,96±8,14 yıl idi. Hastaların %66,7'si kadın ve %33,3'ü erkekti. Hastaların demografik verileri, komorbiditeleri, laboratuvar verileri ve ayrıntılı geriatrik değerlendirme sonuçlarına ilişkin bilgiler Tablo 1'de gösterilmiştir. Katılımcıların %30,5'inde düşme, %49,4'ünde ağrı, %48,1'inde üriner inkontinans, %47,7'sinde polifarmasi, %19,3'ünde demans, %29,7'sinde depresyon, %20,6'sinde malnütrisyon riski ve %5,9'unda malnütrisyon saptandı. Katılımcıların %49,3'ü kırılgan adayı ve %21,2'si kırılgandı. Yine %30,9 hastada muhtemel sarkopeni, %5,2 hastada sarkopeni ve %4,2 hastada şiddetli sarkopeni saptandı. Tüm hastaların ortalama serum albümin düzeyi 4,12±0,36 g/dl idi. Serum albümin düzeyi <3,5 mg/dl olan 21 ve <4,0 g/dl olan 215 kişi vardı. Serum albümin düzeyinin geriatrik sendromlar üzerine etkileri tek tek incelendiğinde serum albümin düzeyindeki düşüşün düşme, ağrı, üriner inkontinans, polifarmasi, demans, malnütrisyon, kırılganlık ve sarkopeni riskini artırdığı görülmüştür (p<0,05). Serum albümin düzeyi ile depresyon arasında ise herhangi bir ilişki saptanmamıştır. Ayrıca analizlerde yaş, cinsiyet ve nütrisyon durumuna göre düzeltme yaptıktan sonra düşük serum albümin düzeyi ile düşme, ağrı, üriner inkontinans, polifarmasi, demans arasındaki anlamlı ilişki devam etmiştir (p<0,05). Yine yaş, cinsiyet ve nütrisyon durumunun etkisi ortadan kaldırıldığında düşük serum albümin düzeyinin kırılgan adayı, kırılganlık, sarkopeni ve şiddetli sarkopeni riskini artırdığı görülmüştür (p<0,05). Serum albümin düzeyinin geriatrik sendromlar üzerindeki etkileri Tablo 2'de gösterilmiştir.

Tablo 1. Demografik Özellikler

Yaş	72,96±8,140
Cinsiyet (kadın/erkek)%	%66,7/33,3
Eğitim yılı	7,57±4,693
CCI	1,37±1,337
İlaç sayısı	4,82±3,208
Komorbiditeler	
Diyabet	%24,8
Hipertansiyon	%60,7
Koroner arter hastalığı	%14,1
Serebrovasküler olay	%6,7
Demans	%19,3
Laboratuvar Bulguları	

Albümin (mg/dL)	4,12±0,36
Glukoz (mg/dL)	108,32±39,50
Hematokrit (%)	39,58±4,63
GFR (CKD-EPI)	83,21±14,19
ALT (U/L)	16,87±6,61
C-reaktif protein (mg/L)	3,48±2,21
TSH (µIU/mL)	1,61±1,20
Vitamin B12 (pg/mL)	429,17±342,08
Vitamin D (ng/mL)	21,14±4,63
Folik asit (ng/mL)	10,13±34,97
Ayrıntılı Geriatrik Değerlendirme	
MMSE	23,25±6,90
Temel GYA	90,61±16,14
Enstrümental GYA	17,94±8,11
MNA-KF	12,01±2,35
Tinetti-Total	24,86±6,04
Kalk ve Yürü Testi (sn)	13,27±8,035
Vücut kütle indeksi (kg/m^2)	28,39±5,11

ALT:Alanin aminotransferaz; CCI:Charlson Komorbidite İndeksi; GFR: Glomerüler Filtrasyon Hızı; GYA: Günlük Yaşam Aktiviteleri; MMSE: Mini Mental Durum Değerlendirme; MNA-KF (Mini Nutrisyonel Değerlendirme-Kısa Form); TSH: Tiroid Stimülan Hormon

Tablo 2. Serum albumin düzeyinin geriatrik sendromlar üzerine etkileri

	OR	p	%95 CI
Düşme	0,585	**0,004**	0,405-0,843
Kronik ağrı	1,482	**0,024**	1,053-2,084
Üriner inkontinans	0,586	**0,002**	0,416-0,827
Polifarmasi	0,696	**0,034**	0,497-0,973
Depresyon	0,901	0,655	0,571-1,423
Demans	0,439	**<0,001**	0,286-0,674
Nutrisyon*			
• **Malnütrisyon riski**	0,474	**<0,001**	0,317-0,709
• **Malnütrisyon**	0,207	**<0,001**	0,110-0,390
Kırılganlık			
• **Kırılgan adayı**	0,517	**0,021**	0,296-0,904
• **Kırılgan**	0,187	**<0,001**	0,090-0,388
Sarkopeni			
• **Muhtemel sarkopeni**	0,658	0,121	0,388-1,117
• **Sarkopeni**	0,258	**0,009**	0,094-0,709
• **Şiddetli sarkopeni**	0,232	**0,014**	0,072-0,742

*Serum albumin düzeyinin geriatrik sendromlar üzerine etkileri yaş, cinsiyet ve nutrisyon durumuna göre düzeltme yapılarak verilmiştir. * Serum albumin düzeyinin nutrisyon üzerine etkileri ise yaş ve cinsiyete göre düzeltme yapılarak verilmiştir.*

4. Tartışma

Bu kesitsel retrospektif çalışmada, serum albümin düzeyi ile geriatrik sendromlar arasındaki ilişki incelenmiş ve serum albümin düzeyindeki düşüşün düşme, ağrı, üriner inkontinans, polifarmasi, demans, malnütrisyon, kırılganlık ve sarkopeni riskini artırdığı görülmüştür. Serum albümin düzeyi ile depresyon arasında ise anlamlı ilişki saptanmamıştır.

Albümin, plazmada en yüksek oranda yer alan, intravasküler ozmotik basıncın sağlanması, yağ ve safra asitleri, kolesterol, metal iyonları, steroid hormonlar ile bazı

ilaçların plazma konsantrasyonları ve transportundan sorumlu bir proteindir.(27) Son yıllarda, düşük serum albümin düzeyinin post-operatif dönem, akut bir nedenle hastaneye yatış gibi birçok durumda mortalite ve diğer olumsuz sonuçlar için bir risk faktörü olduğu gösterilmiştir.(27) Yapılan çalışmalarda hipoalbümineminin bu olumsuz etkilerinin başlıca malnütrisyon ve inflamasyon ile ilgili olduğu düşünülmektedir.(28) Malnütrisyon birçok morbidite ve mortaliteye yol açabilen bir geriatrik sendromdur. (29) Günümüzde düşük serum albümin düzeylerinin malnütrisyonun bir sonucu olmasının yanı sıra, negatif akut faz reaktanı olan albüminin enfeksiyon ve yaşa bağlı düşük düzeyde inflamasyonu yansıtabileceği ve inflamasyona bağlı iştah kaybı ile malnütrisyon için bir neden ve belirteç de olabileceği görüşü vardır.(29) Literatür ile uyumlu olarak çalışmamızda da yaş ve cinsiyete göre düzeltme yapıldıktan sonra dahi serum albümin düzeyindeki azalma hem malnütrisyon riski hem de malnütrisyon ile anlamlı düzeyde ilişkili saptanmıştır. Malnütrisyon ve kronik inflamasyon aynı zamanda pek çok ortak risk faktörüne sahip kırılganlık ve sarkopeninin de ortak patogenezinde yer almaktadır. Bu çalışmada serum albümin düzeyindeki düşüş yaş, cinsiyet ve nütrisyon durumundan bağımsız hem kırılgan adayı olmak ve kırılganlık için hem de sarkopeni ve şiddetli sarkopeni için bir risk faktörü olarak saptanmıştır. Beslenme durumuna göre düzeltme yaptıktan sonra dahi bu ilişkinin sürmesi sarkopeni ve kırılganlık ortak etyopatogenezinde rol alan inflamasyon ve serum albümin düzeyi arasındaki ilişkiyi düşündürmektedir. İnflamasyon süreci, iştah azalmasına bağlı yetersiz beslenme ve protein yıkımına neden olmasının yanı sıra doğrudan da negatif akut faz reaktanı olan albümin sentezinin azalmasına neden olmaktadır. Ek olarak inflamatuvar süreçte kapiller permeabilite artışına bağlı da bir miktar albümin de ekstravasküler alana geçebilmektedir.(27) Ayrıca, yapılan çalışmalar sarkopeni tanısının temel taşlarından olan kas gücünün hem kadın hem de erkek hastalarda inflamasyondan bağımsız olarak da serum albümin düzeyi ile ilişkili olduğunu göstermektedir.(29) Ek olarak, 65 yaş üstü 676 kadın ve 644 erkek hastanın değerlendirildiği prospektif bir çalışmada yaş, yaşam tarzı faktörleri, kronik durumlar, total serum kolesterolü, parathormon ve D vitamini için düzeltme yaptıktan sonra dahi kas gücünün, normal aralıkta ancak daha düşük serum albümin düzeyleri ile ilişkili olduğunu gösterilmiştir.(29) Sarkopeni kriterlerinden olan kas kitlesi de yaş, protein-enerji alımı, fiziksel aktivite, hormonel faktörler dışlandıktan sonra serum albümin düzeyi ile ilişkili bulunmuştur.(30)

Azalmış kas kitlesi, kas gücü ve ilerleyen yaşla ortaya çıkan düşük düzeyde inflamasyon aynı zamanda bir diğer geriatrik sendrom olan düşme için de önemli risk faktörleri arasındadır.(22,29) Her ikisi için de bir gösterge olan düşük serum albümin düzeyi çalışmamızda da düşme ile ilişkili bulunmuştur. Benzer şekilde literatürde de düşük serum albümin düzeyi yaşlılarda düşme için bağımsız bir risk faktörü olarak saptanmıştır.(31) Düşük serum albümin düzeyi pek çok çalışmada kas kitlesi, kas gücü, düşme, dizabilite ve fiziksel performans ile ilişkili bulunmasının yanı sıra kognitif fonksiyonlarla da ilişkisini gösteren çalışmalar vardır.(32–34) Bu çalışmada da serum albümin düzeyinin yaş, cinsiyet ve nütrisyon durumundan bağımsız demans riskini artırdığı gösterilmiştir. Serum albümin düzeyi ile demans arasındaki ilişkiyi incelerken özellikle demans patolojisinde yer alan inflamatuvar sitokinlerin, endojen ve eksojen nörotoksinler ile oksidatif stresin yarattığı nöronal hasar üzerinde durulmuştur. Serum albümini hem negatif akut faz reaktanı olarak inflamasyonu göstermekte hem de endojen ve eksojen oksitleyici ajanlara karşı birincil antioksidan savunmayı oluşturmaktadır. Bunun yanı sıra amiloid-beta peptidin (Aβ) beyin ve kan plazması arasındaki dinamik dengesi, Aβ'yi bağlayan periferik serum albümini tarafından kan dolaşımına doğru kaydırılabilir. Bu nedenle, kandaki serum albüminine Aβ bağlanmasındaki bir azalma, beyinden kana Aβ atılım kapasitesinde bir azalmaya yol açarak beyinde Aβ birikmesine neden olabilir.(32–34) Yapılan çalışmalarda düşük serum albümin düzeyinin diğer değişkenlerden bağımsız hem demans hem de hafif bilişsel bozukluk riskini artırdığı gösterilmiştir.(32,33)

Yaşlılarda düşük serum albümin düzeyleri ve tüm geriatrik sendromları tek tek inceleyen çok sayıda çalışma olmasa da yapılan meta-analizlerde hipoalbümineminin yaşlanmanın doğal bir sonucu olmadığı ve düşük serum albümin düzeylerinin yaşlılarda olumsuz bir prognostik faktör olduğu görülmüştür.(28) Literatürde serum albümin düzeyi ile üriner inkontinans, ağrı ya da polifarmasi ilişkisini inceleyen detaylı çalışmalar bulunmamakla birlikte çalışmamızda düşük serum albümin düzeyi her üç geriatrik sendrom ile de ilişkili saptanmıştır. Bu konuda nedenselliği açıklayabilmek için ileri çalışmalara ihtiyaç olsa da düşük serum albümin düzeyi ile ilişkili olan düşük düzey kronik inflamasyon, sarkopeni, kırılganlık, multimorbidite her üç durum için de risk faktörü olabilir. (35–38)

Çalışmanın belli noktalarda kısıtlılıkları mevcuttur. Bunlardan en önemlisi çalışmanın kesitsel ve retrospektif bir çalışma olması ve çalışma tasarımı gereği nedenselliğin incelenememesidir. Ancak yüksek örneklem sayısı ve tüm geriatrik sendromlar ile serum albümin düzeyleri arasındaki ilişkiyi inceliyor olması da çalışmanın güçlü yönleridir.

5. Sonuç

Bu çalışma, düşük serum albümin düzeylerinin düşme, ağrı, üriner inkontinans, polifarmasi, demans, malnütrisyon, kırılganlık ve sarkopeni gibi geriatrik sendromlar için bir risk faktörü olabileceğini göstermektedir. Serum albümin düzeyleri ve geriatrik sendromlar arasındaki ilişkinin nedenselliği ileri çalışmalarla araştırılmalı ve yaşlı hastalarda serum albümin düzeyindeki düşüşlere geriatrik sendromların eşlik edebileceği akılda tutulmalıdır.

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Research Article / Araştırma Makalesi

64 Dedektörlü Bilgisayarlı Tomografide Kontrast Madde Enjeksiyonu Sonrası Nonfatal Venöz Hava Embolisi Sıklığı ve Lokalizasyonu

Frequency and Localization of Nonfatal Venous Air Embolism After Contrast Substance Injection in 64-Detector Computed Tomography

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Özet

Tanısal ve girişimsel radyolojik işlemlerde kontrast madde verilmesi sırasında venöz hava embolisi nonfatal bir olay olarak görülmektedir. Bu çalışmada, kontrastlı bilgisayarlı tomografide (BT) nonfatal venöz hava embolisinin sıklığını ve lokalizasyonunun tespit edilmesi amaçlanmıştır. Hastanemiz Radyoloji Ünitesinde 1 Ocak 2019-31 Aralık 2019 tarihleri arasında çekilen 1654 kontrastlı toraks bilgisayarlı tomografi tetkiki intravenöz hava varlığı retrospektif olarak değerlendirildi. Tespit edilen venöz hava embolilerin lokalizasyonu, boyutları, kontrast maddenin hangi taraftan verildiği kaydedildi. Bu çalışmada iatrojenik venöz hava embolisi %3.14 oranında görülmüştür. En sık görüldüğü lokalizasyon ana pulmoner arter olup (%1.81) diğer görüldüğü lokalizasyonlar sıklık sırasına göre sol brakiosefalik ven (%0.66), sol subklavyen ven (%0.36), sağ brakiosefalik ven (%0.30), sağ subklavyen ven (%0.24), sağ ventrikül (%0.18) ve sağ atriumdur (%0.18). Venöz hava embolisinin boyutlarına bakıldığında %2.5 oranında küçük, %0.50 oranında orta ve %0.12 oranında büyük hava embolisi görüldü. Radyologlar BT taramada kontrast madde enjeksiyonu sonrası vasküler hava embolisi olabileceğini bilmeli ve dikkatli olmalıdır.

Anahtar Kelimeler: Venöz hava embolisi; bilgisayarlı tomografi; kontrast; iatrojenik

Abstract

During diagnostic and interventional radiological procedures, venous air embolism is seen as a nonfatal event. In this study, it was aimed to determine the frequency and localization of nonfatal venous air embolism in contrast enhanced computed tomography (CT). 1654 contrast-enhanced thorax computed tomography examinations performed in the Radiology Unit of our hospital between January 1, 2019 and December 31, 2019. The localization and size of the detected venous air emboli and from which side the contrast agent was administered were recorded. In this study, iatrogenic venous air embolism was seen in 3.1%. The most common localization is the main pulmonary artery (1.81%) and other localizations in order of frequency are left brachiocephalic vein (0.66%), left subclavian vein (0.36%), right brachiocephalic vein (0.30%), right subclavian vein (0.24%), right ventricle (0.18%) and right atrium (0.18%). Looking at the size of the venous air embolism, 2.5% small, 0.50% moderate and 0.12% large air embolism were seen. Radiologists should be aware of the possibility of vascular air embolism after contrast agent injection in CT scanning and should be careful.

Keywords: Venous air embolis; computed tomograph; contrast; iatrogenic

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1. Giriş

Venöz hava embolisi (VHE) intravenöz kateterlerin takılması, çıkarılması ve kullanımı gibi medikal durumlarda, travma, cerrahi ve jinekolojik işlemler sırasında olabildiği gibi biyopsi, anjiografi ve kontrastlı görüntüleme gibi radyolojik durumlarda da olabilir (1). Kontrastlı bilgisayarlı tomografi (BT) sonrası görülen VHE, tanısal amaçlı BT'nin giderek artan kullanımı nedeniyle nonfatal olarak görülmeye başlanmıştır (2). BT'de kontrast madde enjeksiyonu sonrası VHE insidansı %11 ile %23 arasında bildirilmiştir (2,3).Genellikle küçük hava kabarcıkları minimal VHE olarak kabul edilir ve klinik olarak önemsizdir (4). VHE'nin çoğu asemptomatik olmakla beraber paradoksal hava embolisi için potansiyel risk oluşturan durumlar vardır. Sağdan sola şant veya pulmoner arterivenöz malformasyon gibi risk faktörü olan hastalarda küçük bir hava embolisinin bile nörolojik defisit için yüksek bir risk olduğu belirtilmiştir (5). Kazara 100 cc hava enjeksiyonu fatal kabul edilmekle beraber vücut pozisyonu, enjeksiyon hızı, enjekte edilen toplam hava miktarı, genel sağlık durumu gibi faktörler fatal VHE'sinde önemli rol oynar (2,5). Genellikle venöz sistemde küçük az miktardaki hava girişi sıklıkla dağılır ve hava embolisi kendiliğinde çözülebilir. Bu nedenle çoğu zaman hastalar özel bir tedavi gerektirmeksizin sadece gözleme alınır (6).

Bu çalışmada, kontrastlı BT'de nonfatal venöz hava embolisinin sıklığını ve lokalizasyonunun tespit edilmesi amaçlanmıştır.

2. Gereç ve Yöntem

Hatay Mustafa Kemal Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan (14/01/2021 tarihli 22 nolu karar) gerekli izin alınarak yapılan bu çalışmaya, Hatay Mustafa Kemal Üniversitesi Tayfur Ata Sökmen Tıp Fakültesi Radyoloji Ünitesinde 1 Ocak 2019-31 Aralık 2019 tarihleri arasında, gündüz 08:00-16:00 saatleri arasında poliklinik ve servislerden çeşitli nedenlerle çekilen 1654 hastanın kontrastlı toraks BT tetkikleri çalışmaya dahil edildi. Görüntüler ünitemizde bulunan 64 dedektörlü BT (Toshiba Aquilion 64 MDCT, Toshiba Medical Systems, Otawara, Japan) ile alınmıştı. Rutin çekim prokolünde rotasyon süresi 0.75 sn, dozu 120 kV ve 250 mAs, kolimasyon 64x0.625, pitch değeri 1.375 ve kesit kalınlığı 5 mm şeklinde otomatik olarak ayarlanmıştı. Non-iyonik kontrast madde açılan damar yolundan otomatik enjektör (Mallinckrodt Optivantage injection system model) ile 80 mL 2.5 mL/sn hız ile verilmişti. Çekimler gündüz olduğu için kontrast madde enjeksiyonu tecrübeli aynı iki radyoloji teknisyeni tarafından verilmişti. Elde edilen görüntüler ünitemizdeki görüntüleme monitörlerindeki Osirix MD (Pixmeo Labs, Geneva, Switzerland) programı ile retrospektif olarak değerlendirildi. Acil servis hastaları, yakın zamanda travma ve cerrahi geçiren, santral venöz kateteri olan hastalar çalışma dışı bırakıldı. Hastaların yaşları, cinsiyetleri, tespit edilen venöz hava embolisinin lokalizasyonu, boyutu, hangi taraftan kontrast madde verildiği kaydedildi. Boyutu 1 cm'nin altında olan küçük, 1-2 cm arasında olanlar orta ve 3 cm'den büyük olanlar büyük hava embolisi olarak kabul edildi (3,7). Elde edilen veriler SPSS Windows 21.0 (Statistical Package for Social Sciences) programına girilerek istatistiksel çalışması yapıldı. İstatistiksel olarak iki grup arasındaki ilişkiyi belirlemek için Ki-kare testi kullanıldı. $p<0.05$ istatistiksel olarak anlamlı kabul edildi.

Çalışma Hatay Mustafa Kemal Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurul Başkanlığı'nın 14.01.2021 Tarih ve 22 sayılı kararı ile onaylandı ve yapıldı.

3. Bulgular

Venöz hava embolisi yönünden retrospektif olarak incelenen 1654 kontrastlı toraks BT tetkikinin 52'sinde (%3.14) insidental venöz hava embolisi tespit edildi. Hastaların 19'u (%36.54) kadın, 33'ü (%63.46) erkek hasta idi. Hastaların yaş aralığı 20 ile 93 arasında olup yaş ortalaması 60.54±16.78 idi. Hastaların 27'sinde sağ koldan, 25'inde sol koldan kontrast madde verilmiş idi. 6 hastada multiple lokalizasyonda hava embolisi tespit edildi (4 hastada 2 lokalizasyonda, 1 hastada 3

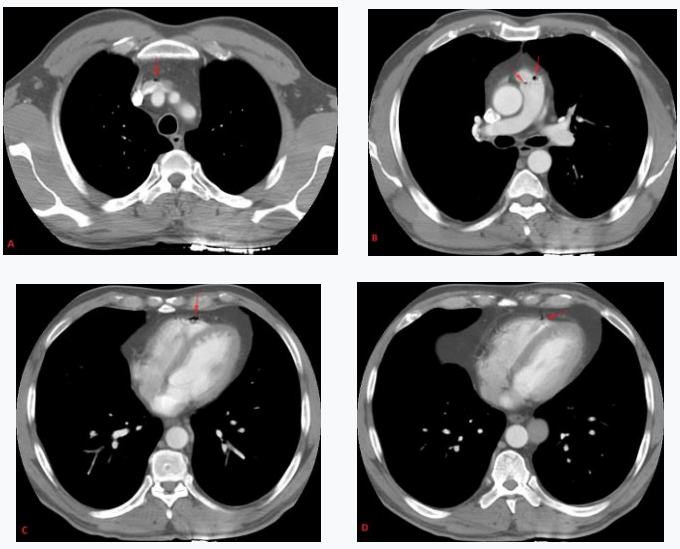
lokalizasyonda ve 1 hastada 4 lokalizasyonda) (Resim 1). 52 hastada toplam 61 seviyede (%3.68) intravenöz hava tespit edildi. 61 hava embolisinin 30'u (%1.81) ana pulmoner arterde, 11'i (%0.66) sol brakiosefalik vende, 4'ü (%0.24) sağ brakiosefalik vende, 6'sı (%0.36) sol subklavyen vende, 4'ü (%0.24) sağ subklavyen vende, 3'ü (%0.18) sağ ventrikülde ve 3'ü (%0.18) sağ atriumda tespit edildi (Tablo 1). 52 hastanın 41'inde (%2.5) küçük, 9'unda orta (%0.5) ve 2'sinde (%0.12) büyük hava embolisi görüldü (Tablo 2, Resim 2). Kontrast maddenin verildiği kol yönünden yapılan istatistiksal analizde p değeri 0.148 bulumuş olup anlamlı fark izlenmedi (p>0.05).

Tablo 1. Hava embolisinin görüldüğü lokalizasyonlar ve kontrast maddenin verildiği yön.

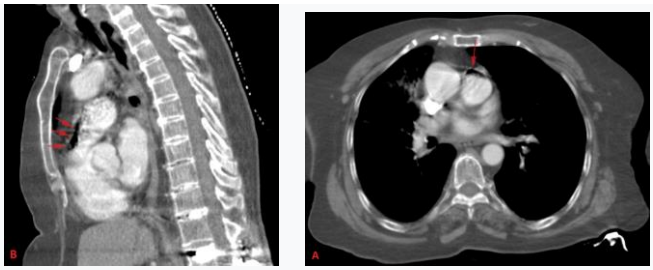
Emboli Lokalizasyon	Kontrast maddenin verildiği yön		p değeri
	Sağ	*Sol*	0.148
Ana pulmoner arter	14	16	
Sol brakiosefalik ven	5	6	
Sol subklavyen ven		6	
Sağ brakiosefalik ven	4		
Sağ subklavyen ven	4		
Sağ ventikül	*2*	*1*	
Sağ atrium	**3**		

Tablo 2. Hava embolisi büyüklük sınıflaması.

Emboli tipi	Hava embolisi çapı (cm)	Hava embolisi sayısı
Küçük	<1	1-3
Orta	1-2	>3
Büyük	>2	Sayıya bakılmaksızın



Resim 1. Aynı hastada sol brakiosefalik ven (A), ana pulmoner arter (B), sağ atrium (C) ve sağ ventrikül (D) olmak üzere 4 farklı lokalizasyonda orta büyüklükte venöz hava embolisi.



Resim 2. Ana pulmoner arterde büyük venöz hava embolisi aksiyel (A) ve sagittal (B) BT görüntüsü.

4. Tartışma

Hava embolisi dolaşım sistemine gaz girişiyle oluşmaktadır. Bu durum birçok medikal-cerrahi durumlarda ortaya çıkabilir. Bu durum intravenöz girişime yada intravenöz infüzyona sekonder oluşuyorsa intravenöz hava embolisi olarak tanımlanır (1). Kontrast madde enjeksiyonu sonrası olabilecek subklinik VHE'ni BT tarama ile tespit etmek, hava volümünü analiz etmek mümkündür.

Kontrastlı BT sırasında oluşan VHE giderek artan bir oranda non fatal bir olay olarak raporlanmaya başlanmıştır. Literatürde postkontrast BT'de nonfatal VHE ile ilgili birkaç tane çalışma mevcuttur. Woodring ve ark'larının (2) yaptığı çalışmada kontrastlı toraks BT sonrası VHE insidansını %23 olarak bulmuşlardır. Groell ve ark 'ları (3) ise kontrastlı BT sonrası %11.7 oranında ve kontrastsız taramada ise %5.5 oranında VHE tespit etmişlerdir. Sodhi ve ark'larının (7) 200 hasta ile yaptıkları prospektif çalışmada ise toraks BT'lerin %7'sinde insidental VHE tespit etmişlerdir. X. Jia ve ark.'larının (6) yaptığı çalışmada kontrastlı koroner anjiografide VHE insidansını %4.65 oranında bulmuşlardır. Biz retrospektif olarak yaptığımız çalışmamızda kontrastlı toraks BT incelemesinde kontrast madde enjeksiyonu sonrası insidental VHE insidansını %3.1 oranında literatürdeki oranlardan daha az bulduk.

Groell ve ark.'larının (3) elektron-beam BT ile 677 hastada yaptıkları geniş seride VHE en sık ana pulmoner arterde (%8) bulmuşlardır. Diğer lokalizasyonlar ise sıklık sırasına göre superior vena kava, sağ ventrikül, subklavyen veya brakiosefalik ven ve sağ atriumdur. Sodhi ve ark'larının (7) yaptıkları çalışmada ise en sık ana pulmoner arterde görülmüş olup sol brakiosefalik ven, sağ atrial apendiks ve superior vena kava da VHE tespit etmişlerdir. Bizim çalışmamızda da literatür ile benzerlik göstererek VHE'sini gördüğümüz en sık lokalizasyon ana pulmoner arterdir (%1.8). Diğer lokalizasyonlar ise sağ-sol brakiosefalik ven, sağ-sol subklavyen ven, sağ atrium ve sağ ventriküldür.

Küçük venöz emboliler çoğu zaman kan veya akciğerde alveollerden absorbe olur. Hastalar genellikle asemptomatiktir veya dispne gibi nonspesifik bulgulara neden olabilir. Fakat daha büyük emboliler sağ ventrikül çıkışını tıkayarak dolaşım yetmezliğine neden olabilir. Masiv VHE (200-300 ml hava) fatal kabul edilir (8). Bununla birlikte Pham ve ark.'ları (9) kontrastlı BT çekimi sırasında 135 ml venöz sisteme hava girişi olan 2 hastada nonfatal seyrettiği vaka bildirmişlerdir. Sepmtomatik VHE'sinde yaygın olmayan klinik bulgular akut nefes dalığı, göğüs ağrısı, siyanoz, hipotansiyon, pulmoner ödem, paralizi ve nöbettir. Venöz sistemdeki VHE' sinin bulgu şiddeti total hava miktarı, dolaşım sistemindeki pozisyonu ve etkilenen hastanın genel sağlık durumuna bağlıdır (10). Amerikan Radyoloji Kolej'i (ACR) 2017'de hava embolisi ve kontrast madde ekstravazayonu sonucu oluşabilecek potansiyel komplikasyonları önlemek için radyoloji personelinin doğru teknikle kontrast maddeyi vermesi gerektiğini belirtmiştir. (11). Bununla birlikte bu konuda hala belli bir standart bir prosedür yoktur. VHE non fatal iken küçük bir arterial veya pulmoner hava embolisi miyokard enfarktüsü nedeniyle ciddi doku hasarına ve iskemiye ve hatta ölüme

neden olabilir (12). Bu nedenle radyologlar ve radyoloji teknisyenleri tespit edilen hava miktarı çok az olsa bile çok dikkatli olmalılardır.

Sodhi ve ark.'larının (7) yaptığı 200 hastalık çalışmada iatrojenik venöz hava embolisi ile kontrast miktarı, akım hızı, intravenöz damar yolu boyutu ve hangi taraftan enjeksiyon yapıldığı ile yaptıkları analizde p değeri anlamlı çıkmamıştır. Price ve ark'ları (13) yaptıkları çalışmada ise başınçlı verilen kontrast madde enjeksiyonu ile büyük venöz hava embolisinin miktarının artırdığını bildirmişlerdir.

Yüksek kontrast madde konsantrasyonu nedeniyle oluşan beam-hardening artefaktı (ışın demetinin sertleşmesi) büyük venlerde yanılgılara neden olabilir. Beam-hardening nedeniyle oluşan düşük atenüasyon alanları özellikle santral venlerde hava kabarcığı varmış gibi görüntüye neden olabilir. Bu teknik artefakt görüntü iş istasyonlarında dansite ayarı yapılarak yanılgılar ortadan kaldırılabilir (7).

Atrial veya ventriküler septal defekt, arteriovenöz malformasyon, patent foramen ovale VHE'nin arteryal dolaşıma geçişine neden olarak komplikasyon riskini artırmaktadır. Komplikasyonlar serebral (akut-fokal nörolojik defisit veya generalize/global ensefalopati) veya koroner embolizm (daha az sıklıkta) ile sonuçlanabilir. Serebral dolaşımdaki havayı tespit etmek veya daha sonra ortaya çıkabilecek fokal enfarktları değerlendirmek için beyin BT taraması gerekir (14,15).

Küçük ve orta VHE'sinde tedaviye gerek yoktur. Şiddetli VHE' sinde hastalar sol lateral dekubit ve trendelenburg pozisyonuna getirilerek (Durant manevrası) hava kabarcığını sağ ventrikül apeksinde tutarak sağ ventrikül çıkış yoluna hava girişi azaltılmalıdır. Bu manevra ayrıca pulmoner arterdeki hava embolisini en aza indirir. %100 oksijen tedavisi vasküler sistemde sıkışmış havanın emilimini kolaylaştırır (16).

Çalışmamızın limitasyonları retrospektif olması, çalışmaya sadece kontrastlı toraks BT incelemelerin dahil edilmesidir.

5. Sonuç

Radyologlar BT taramada yaygın, benign iatrojenik bir bulgu olan venöz hava embolisinin farkında olmalıdır. Küçük hava embolisi asemptomatik olmakla beraber orta ve büyük hava embolisi klinik yönden takip edilmelidir. BT taramada infüzyon şişesinde, damar yolu kanülünde serbest hava varlığını tespit edip müdahale etmek oluşabilecek iatrojenik venöz hava embolisini azaltacaktır.

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Research Article / Araştırma Makalesi

Physicians Working At Different Clinical Settings: Can They Recognize and Manage Anaphylaxis?

Farklı Düzey Sağlık Basamaklarında Çalışan Hekimlerin Anafilaksi Tanı ve Yönetimi ile İlgili Bilgi Düzeyleri

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Abstract

Anaphylaxis is defined as a severe hypersensitivity reaction that can cause sudden onset and death. Therefore, it is vital that the diagnosis is made and the timely administration of epinephrine. In this study, it was aimed to determine the knowledge and attitudes of the physicians in Edirne city center regarding the diagnosis and treatment of anaphylaxis. The study was designed as cross sectional survey. Physicians were visited in their institutions. A written questionnaire was applied face-to-face and it included questions about diagnosis and management of anaphylaxis. A total of 347 physician agreed to participate in the study. 43.5% of the physicians did not read any literature, book chapters or guidelines about the diagnosis criteria. Only 16.7% of responders knew all sign and symptoms of anaphylaxis. Twenty eight percent of physicians knew that correct route and dose of epinephrine administration. Associated factors with the knowledge about correct dose and route of epinephrine administration were the number of encounters with anaphylaxis cases and presence of treatment scheme in the institution; OR (95% CI) were 3.520 (1.879-6.593) and 1.961 (1.168-3.290) respectively. 45.5% of the responders knew that there are no absolute contraindications to administer epinephrine in the case of anaphylactic shock. The study revealed that, knowledge of physicians relating diagnosis, treatment and management of anaphylaxis is unsatisfactory in our city. We think that it would be beneficial to provide physicians with in-service training regarding the diagnosis and management of anaphylaxis.

Keywords: Anaphylaxis; anaphylaxis management; physician; knowledge

Özet

Anafilaksi, ani başlangıçlı ve ölüme neden olabilen ciddi bir aşırı duyarlılık reaksiyonu olarak tanımlanır. Bu nedenle tanının konulması ve epinefrinin zamanında uygulanması hayati önem taşımaktadır. Bu çalışmada Edirne il merkezindeki hekimlerin anafilaksi tanı ve tedavisine ilişkin bilgi ve tutumlarının belirlenmesi amaçlanmıştır. Çalışma, kesitsel araştırma olarak tasarlandı. Hekimler kurumlarında ziyaret edildi. Yüz yüze yazılı bir anket uygulandı. Anket anafilaksi tanı ve yönetimi ile ilgili soruları içeriyordu. Toplam 347 hekim çalışmaya katılmayı kabul etti. Hekimlerin toplam %43,5'i tanı kriterleri ile ilgili herhangi bir literatür, kitap bölümü veya kılavuz okumamıştı. Yanıt verenlerin yalnızca %16,7'si anafilaksinin tüm belirti ve semptomlarını biliyordu. Hekimlerin yüzde yirmi sekizi, epinefrin uygulamasının doğru yolunu ve dozunu biliyordu. Epinefrinin doğru dozu ve uygulama yolu bilgisi ile ilişkili faktörler; anafilaksi vakaları ile karşılaşma sayısı ve kurumda tedavi şemasının varlığı; OR (%95 GA) sırasıyla 3,520 (1,879-6,593) ve 1,96 (1,168-3,290) idi. Yanıt verenlerin %45,5'i, anafilaktik şok durumunda epinefrin uygulamak için mutlak kontrendikasyon olmadığını biliyordu. Çalışma, ilimizde anafilaksi tanı, tedavi ve yönetimine ilişkin hekimlerin bilgilerinin yetersiz olduğunu ortaya koymuştur. Anafilaksi tanı ve yönetimi konusunda hekimlere hizmet içi eğitim verilmesinin faydalı olacağını düşünmekteyiz.

Anahtar Kelimeler: Anafilaksi, anafilaksi yönetimi, hekim, bilgi

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1. Introduction

Anaphylaxis is a serious, rapid onset allergic reaction that can be fatal (1). Although it is not known exactly, its lifetime prevalence is estimated to be 0.05-2% (2). Anaphylaxis is diagnosed by recognizing the characteristic symptoms and signs that occur in a short time after exposure to a potential or known trigger. Despite the increasing incidence of anaphylaxis, many cases have not been recognized or reported (3).

Intramuscular epinephrine is the main treatment for anaphylaxis. Steroids and antihistamines are considered to be second line therapies (3). One of the most important factors affecting mortality in anaphylaxis is the delay of epinephrine administration (4). Therefore, it is vital that the diagnosis is made and the timely administration of epinephrine. Physicians, should be knowledgeable and confident in the management of anaphylaxis. Previous studies revealed that physicians cannot adequately recognize anaphylaxis and provide appropriate treatment (5-9).

The main purpose of this study was to assess the knowledge and attitudes of the physicians in Edirne city center regarding the diagnosis and treatment of anaphylaxis.

2. Material and Methods

Ethics committee approval from Trakya University Faculty of Medicine Ethics Committee (TUTF-BAEK 2017/36) and necessary permissions from the centers where the data will be collected were obtained from Trakya University Faculty of Medicine, Trakya University Faculty of Dentistry, private hospital directorate, Edirne Provincial Health Directorate and Edirne Public Health Directorate.

Study population

The total number of physicians working in Edirne city center (university hospital, state hospital, private hospital, oral and dental health center, family health centers, Trakya University Faculty of Dentistry, 112 Emergency Health Service Stations) with 0-30 years of professional experience was 774, 420 physicians were reached, and 347 (46%) agreed to participate in the study. A questionnaire was applied to evaluate the knowledge and attitude of the physicians regarding anaphylaxis. Physicians were asked to answer questions without revealing their identity.

Study design

The study was designed as a cross-sectional survey. Physicians were visited in their institutions in June-July 2018 and a face-to-face questionnaire was applied. During the face-to-face interview with the physician, the necessary information was given verbally and in writing about the content, purpose and method of the study. Physicians who signed the informed consent form were included in the study. The guidelines of the World Allergy Organization, the European Academy of Allergy and Clinical Immunology were used to prepare the survey questions (3-10). The time required to complete the questionnaire was 5-10 minutes. Our study data were obtained from completed questionnaires. The questionnaire form consists of 4 closed-ended questions that evaluate demographic data; 4 true/false questions and 5 multiple choice questions that evaluate the knowledge; 5 multiple choice questions evaluating the attitude and 2 open-ended questions and a total of 20 questions. Correct situations or answers were scored as 1, and incorrect situations or answers were scored as 0 in the questions that evaluated the knowledge. Questionnaire form were evaluated over a total of 43 points.

Statistical analyses

The results obtained from the questionnaire were analyzed using the IBM SPSS Statistics for Windows, V.22.0 (IBM, Armonk, New York, USA) software. The data were presented as number and percentage (n,%), mean ± standard deviation was used for numerical data. Demographic data and responses to survey items are presented as proportions with 95% CIs. Multivariate logistic regression was used to identify factors associated that using of epinephrine correct administration dose and route. P value less than 0.05 considered statistically significant.

3. Results

Of the 347 physicians participating in the survey, 257 (74.1%) were resident, 61 (17.6%) were specialists and 29 (8.4%) were general practitioners. One hundred seventy nine (51.6%) of the physicians were male. The demographic characteristics and specialities of the physicians participating in the study are shown in Table 1.

Table 1. Demographic characteristics of physicians

Characteristic	Primary and Secondary Care		Tertiary Care		All Responders	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Overall	89	25.6 (21.0-30.3)	258	74.4 (69.7-79.0)	347	-
Age						
25-30	23	25.8 (16.9-34.8)	204	79.1 (73.6-84.1)	227	65.4 (60.2-70.6)
31-35	21	23.6 (15.7-32.6)	47	18.2 (13.6-23.3)	68	19.6 (15.6-23.9)
36-40	21	23.6 (14.6-32.6)	1	0.4 (0.0-1.2)	22	6.3 (4.0-9.2)
41-45	13	14.6 (7.9-22.5)	4	1.6 (0.4-3.1)	17	4.9 (2.6-7.2)
46-50	7	7.9 (3.4-13.5)	1	0.4 (0.0-1.2)	8	2.3 (0.9-4.0)
51-55	3	3.4 (0.0-7.9)	1	0.4 (0.0-1.2)	4	1.2 (0.3-2.6)
>56	1	1.1 (0.0-4.5)	0	0.0	1	0.3 (0.0-1.2)
Sex						
Male	54	60.7 (49.5-70.8)	125	48.4 (42.2-54.7)	179	51.6 (46.1-56.5)
Female	35	39.3 (29.2-50.5)	133	51.6 (45.3-57.8)	168	48.4 (43.5-53.9)
Education						
General practitioner	29	32.6 (23.6-42.7)	0	0.0	29	8.4 (5.5-11.5)
Resident	0	0.0	257	99.6 (98.8-100.0)	257	74.1 (68.9-78.7)
Specialist	60	67.4 (57.3-76.4)	1	0.4 (0.0-1.2)	61	17.6 (14.1-22.2)
Clinical experience						
< 5 years	17	19.1 (11.2-28.1)	195	75.6 (70.2-81.0)	212	61.1 (55.9-66.0)
5-10 years	28	31.5 (22.5-41.6)	55	21.3 (16.3-26.4)	83	23.9 (19.9-28.2)
11-15 years	22	24.7 (15.7-33.7)	4	1.6 (0.4-3.1)	26	7.5 (4.9-10.4)
16-20 years	12	13.5 (6.7-21.3)	2	0.8 (0.0-1.9)	14	4.0 (2.3-6.1)
>20 years	10	11.2 (5.6-18.0)	2	0.8 (0.0-1.9)	12	3.5 (1.7-5.8)

While 38% of the physicians had not encountered any anaphylaxis cases, 58% had encountered anaphylaxis cases between 1-10 and 3.7% of them had more than 10 anaphylaxis cases. Total of 63.3% physicians who encountered anaphylaxis case stated that they did not hesitate in the treatment of anaphylaxis in terms of to administer epinephrine or not.

Considering the responses to the symptoms that may be seen in anaphylaxis, the rate of physicians who stated that all the symptoms given in the question could be seen was 9% in primary and secondary care and 19.4% in tertiary care.

To the question of the first drug to be administered in the treatment of anaphylaxis, 87.6% of the physicians answered epinephrine, 7.5% dexamethasone, 3.2% phenyramine, 1.4% isotonic and 0.6% dopamine. In the question of the route of administration, 51.9% of the physicians preferred intramuscular, 28.5% intravenous, and 19.6% subcutaneous injection administration. While 45% of the physicians knew the treatment dose of epinephrine, which was 0.01 mg/kg, correctly, 42.4% stated wrong dose and 12.7% stated that they did not know the dose. Total of 28% physicians correctly knew 0.01 mg/kg intramuscular epinephrine dose, the first drug to be administered in the treatment of anaphylaxis, so they had “correct knowledge about adrenaline treatment”. The situations in which epinephrine is absolutely contraindicated in the treatment of anaphylactic shock was questioned, 45.5% of the physicians stated that there were no absolute contraindications. To the question for at least how long the patient with anaphylaxis should be followed up in the hospital after being stable with the first intervention, 14.4% of the physicians replied as 6-8 hours. Assessment of physicians' responses regarding symptoms, signs and managements of anaphylaxis are shown in Table 2.

Table 2. Assessment of physicians' responses regarding symptoms, signs and managements of anaphylaxis

Responses	Primary and Secondary Care		Tertiary Care		All Responders	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Initial medication						
Epinephrine	77	86.5 (79.8-93.3)	227	88.0 (83.3-91.9)	304	87.6 (83.9-90.8)
Dexametasone	12	13.5 (6.7-20.2)	14	5.4 (2.7-8.1)	26	7.5 (4.9-10.7)
Pheniramine	0	0.0	11	4.3 (1.9-7.0)	11	3.2 (1.4-5.2)
Isotonic fluid	0	0.0	5	1.9 (0.4-3.9)	5	1.4 (0.3-2.9)
Dopamine	0	0.0	1	0.4 (0.0-1.2)	1	0.3 (0.0-1.2)
Glucogon	0	0.0	0	0.0	0	0.0
Administration route						
Intravenous	32	36.0 (27.0-46.1)	67	26.0 (20.6-31.4)	99	28.5 (23.9-33.1)
Intramuscular	39	43.8 (34.8-53.9)	141	54.7 (48.4-60.9)	180	51.9 (46.4-57.3)
Subcutaneous	18	20.2 (12.4-29.2)	50	19.4 (14.3-24.4)	68	19.6 (15.6-23.6)
Administration dose						
0,01mg/kg	31	34.8 (24.7-44.9)	125	48,4 (42.3-54.3)	156	45 (40.1-50.1)
Unknown	17	19.1 (11.2-28.1)	27	10.5 (7.0-14.7)	44	12.7 (9.5-16.1)
Wrong doses	41	46.1 (36.0-56.2)	106	41.1 (34.9-46.9)	147	42.4 (37.2-47.8)
Symptom						
Respiratory distress	83	93.3 (87.6-97.8)	250	96.9 (95.0-98.8)	333	96.0 (93.7-98.0)
Urticaria	74	83.1 (75.3-89.9)	239	92.6 (89.1-95.7)	313	90.2 (86.8-93.1)
Hypotension	57	64.0 (53.9-74.2)	220	85.3 (81.0-89.5)	277	79.8 (75.5-84.1)
Loss of consciousness	59	66.3 (57.3-76.4)	187	72.5 67.1-77.5)	246	70.9 (66.0-75.5)
Collapse	47	52.8 (42.7-62.9)	177	68.6 (63.6-74.0)	224	64.6 (59.7-70.3)
Anxiety	41	46.1 (36.0-56.2)	169	65.5 (59.7-70.9)	210	60.5 (55.6-65.7)
Itchy throat	53	59.6 (49.4-69.7)	150	58.1 (52.3-64.0)	203	58.5 (53.3-64.0)
Cough	42	47.2 (36.0-57.3)	110	42.6 (36.8-48.8)	152	43.8 (38.6-49.3)
Vomiting	38	42.7 (32.6-52.8)	111	43.0 (36.8-49.2)	149	42.9 (37.5-48.7)
Itching in the palm	31	34.8 (24.7-44.9)	118	45.7 (39.5-51.9)	149	42.9 (37.8-48.7)
Abdominal pain	19	21.3 (13.5-30.3)	90	34.9 (29.1-40.7)	109	31.4 (26.8-36.3)
Diarrhea	16	18.0 (10.1-26.9)	72	27.9 (22.9-33.7)	88	25.4 (21.0-30.3)
Marking all symptoms	8	9.0 (3.4-15.7)	50	19.4 (14.3-24.0)	58	16.7 (12.7-20.7)

Factors associated with epinephrine preference, correct dosage and administration were determined. In a logistic regression model, encounters with anaphylaxis cases and presence of treatment scheme in the instutition was independent factor affecting the "correct knowledge about adrenaline treatment" (OR:3.52, 95% CI:1.89-6.59, p<0.001; OR:1.96, 95% Cl:1.16-3.29, p=0.011) (Table 3).

Table 3. Factors associated that using of epinephrine correct administration dose and route

Variable	OR (95% CI)	*p*
Age	0.876 (0.339-2.263)	0.784
Sex	1.372 (0.830-2.269)	0.217
Clinical experience	0.911 (0.360-2.305)	0.844
Clinical settings	1.295 (0.660-2.541)	0.452
Number of encounters with anaphylaxis cases	3.520 (1.879-6.593)	**<0.001**
Presence of treatment scheme in the instutition	1.961 (1.168-3.290)	**0.011**

The relationship between knowledge score and educational status, clinical experience, clinical setting and encounter with anaphylaxis case were evaluated. The knowledge score of the residents was found to be significantly higher than general practitioners and specialist (p<0.001). The knowledge score of physicians working at the tertiary care was significantly higher than those at primary and secondary care (p<0.001) (Table 4).

Table 4. Evaluation of physicians' knowledge scores

	Knowledge Score (mean ± SD)	*p*
Education		**<0.001**
General practitioner	28.00 ± 5.38	
Research asistant	30.50 ± 5.44	
Specialist	27.56 ± 5.55	
Clinical Experience		0.149
<5 years	30.12 ± 5.32	
≥5 years	29.23 ± 5.94	
Clinical settings		**<0.001**
Primary and secondary care	27.71 ± 5.50	
Tertiary care	30.48 ± 5.44	
Encounters with anaphylaxis cases		0.650
Encounters	29.88 ± 5.86	
Non-encounters	29.60 ± 5.12	

In our study, 83.9% of physicians reported that the centers they worked did not have a treatment scheme for anaphylaxis. After graduation from medical school or specialty training, 43.5% of the physicians did not read any literature, book chapters or guidelines about the diagnosis criteria and treatment of anaphylaxis and preferred an easy-to-understand treatment scheme that they could apply in case of emergency. Thirty two percent of them stated that they felt the need to read when they encountered such a patient, 12.7% did not read, thought their knowledge was sufficient, 11.5% did not read and did not think it was related to their specialities.

4. Discussion and Conclusion

Our study revealed that important gaps in knowledge of physicians regarding diagnosis and management of anaphylaxis.

As anaphylaxis can be fatal, it is important to know all system findings in terms of the importance of diagnosis for its correct and effective treatment. Only 16.7% of responders knew all sign and symptoms of anaphylaxis. Cough (43.8%), vomiting (42.9%), itching in the palm (42.9%), abdominal pain (31.4%), and diarrhea (25.4%) were reported by less than half of the physicians. Bekdas et al. (11) reported that, 47.3% of the physicians associated gastrointestinal symptoms with anaphylaxis. In another study from US, knowledge of physicians regarding symptoms of anaphylaxis was questioned, cough was associated with 30-55%, itching 6-15%, and abdominal pain 6-46% with anaphylaxis (12). Gastrointestinal symptoms (vomiting, abdominal pain, diarrhea), cough and itching on the palms/soles that were failure to associate with anaphylaxis may cause some cases to go undiagnosed and delays in epinephrine administration.

For a patient diagnosed with anaphylaxis, initiating fast, accurate and effective treatment is life-saving. In our study, 87.6% of the physicians stated epinephrine as the first treatment to be applied in anaphylaxis as in previous studies (5,9). In studies, the rate of physicians who chose the intramuscular route as the route of administration of epinephrine was found to be 44.7-85% (6,13-15). These rates were similar to our study. However only 28% of them correctly specified epinephrine as first treatment to be applied in anaphylaxis, its dose and route of administration. Celik et al. (16) reported in their study that only 15.3% of responders answered all three questions correctly. Depending on the fact that those in this study were dentists, the results may be considered poor, but although most of our participants were graduates of medical faculties working in tertiary care the results were worrisome even though those who knew 3 questions at the same time.

Associated factors that using of epinephrine's correct administration dose and route were the number of encounters with anaphylaxis cases and presence of treatment scheme. In our study, as the number of encounters with cases increased, the use of epinephrine at the correct dose and administration route increased. Similarly Grossman et al. (9) reported that the

use of intramuscular epinephrine was associated with an increasing volume of anaphylaxis cases.

Epinephrine usage in the treatment of anaphylactic shock has no absolute contraindication (17). More than one third of physicians who encountered anaphylaxis case stated that they hesitated in treatment of anaphylaxis in terms of to administer epinephrine or not. Intramuscular epinephrine is the main treatment for anaphylaxis. It should be administered as soon as possible and without hesitation (18). It has been shown that delayed epinephrine administration is a risk factor for mortality in cases of anaphylaxis (1,19). Our study revealed that 54.5% of the physicians thought there was an absolute contraindication in the use of epinephrine in the treatment of anaphylaxis. Altman et al. (12) reported that 16% of allergy/immunology specialists and 38% of family physicians stated that there is an absolute contraindication in the use of epinephrine in the treatment of anaphylaxis.

Another striking output of our study, the majority of the physicians (83.9%) reported that the centers they worked did not have a treatment scheme for anaphylaxis treatment. Approximately one third of the physicians (32%) stated that they read the diagnosis criteria and treatment of anaphylaxis after they encountered anaphylaxis, while nearly half of them (43.5%) stated that they had not read any informative resources on this subject before. Kahveci et al. (20) pointed out that 11.5% of family physicians and 8.3% of pediatricians read the information on the website after an anaphylaxis training, but 57.7% and 75%, respectively, read the written documents. We think it would be beneficial to have an easily accessible treatment scheme for physicians. In addition, one study suggested that it may be beneficial to have anaphylaxis guides on or near the resuscitation chart (21).

The European Academy of Allergy and Clinical Immunology recommends that patients presenting with respiratory complaints should be followed for 6-8 hours and those presenting with poor circulation for 12-24 hours (10). In the follow-up of patients admitted to the emergency department due to anaphylaxis, the clinical severity at presentation, the time between the administration of adrenaline and the onset of symptoms should be taken into account when determining the duration. The follow-up period can be limited to 6-8 hours in cases with positive all characteristics (17).

Considering the answers given to the question for at least how long the patient with anaphylaxis should be followed up in the hospital after being stable with the first intervention in our study, the rate of physicians who observe for at least 6-8 hours was 14.4%. Approximately half of the physicians prefer the 24-hour observation period. Baccioglu et al. (6) reported that almost half of the participants stated that patients with anaphylaxis should be monitored for at least 6-8 hours. In the studies, the observation period after treatment was insufficient in 38-70% of the participants (7,8). Although the 24-hour observation period, which is the most specified observation period in our study, is not an absolute mistake, the longer observation period causes an increase in the duration of stay and costs in the emergency services.

We found the knowledge score of the residents was found to be significantly higher than general practitioners and specialist and the knowledge score of physicians working at the tertiary care was significantly higher than those at primary and secondary care. There was no statistical difference between the clinical experience and the encounter with anaphylaxis case and the knowledge score. This situation can be explained by the fact that the information of residents is up to date. It is seen that the level of knowledge has decreased over time. It would be beneficial to keep information on anaphylaxis up-to-date and to provide training in this direction at certain time intervals.

Our study is limited by the nature of our survey instrument. Physicians performed self-assessments of their own knowledge, which is not an objective evaluation. However, in this type of questionnaire surveys, it must be assumed that the responses are correct. In addition, our study is local, which compromises the generalizability of the results.

The majority of physicians did not seem to be aware knowledge and attitudes in the diagnosis, treatment and management of anaphylaxis, which is a common and life-threatening condition. Inexperience and lack of training to manage anaphylaxis may lead to undesirable outcomes. We believe that it would be beneficial to provide physicians with in-service training within the framework of a national training program in order to improve patient care, to prevent misdiagnosed cases and deaths due to anaphylaxis regarding the diagnosis and management of anaphylaxis

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Research Article / Araştırma Makalesi

Is There A Relationship Between Critical Shoulder Angle and Fatty Degeneration and Number of Damaged Tendons in Rotator Cuff Arthropathy Patients?

Rotator Manşet Artropatili Hastalarda Kritik Omuz Açısı ile Yağlı Dejenerasyon ve Hasarlı Tendon Sayısı Arasında İlişki Var Mıdır?

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Abstract

The aim of this study was to investigate the correlation of critical shoulder angle (CSA) in rotator cuff arthropathy patients with number of damaged rotator cuff tendons and muscle fatty degeneration. Rotator cuff arthropathy patients were included in this study. True antero-posterior radiographs (Grashey view) were used to measure the angle by the first author. The critical shoulder angles were measured on radiographs. The Magnetic resonance images (MRI) of same patients were assessed in terms of number of tendon involvements and fatty degeneration of rotator cuff muscles. There were 28 rotator cuff arthropathy patients comprising 16 females and 12 males. The mean age was 69.92±8.84 years. The right shoulder was affected in 20 patients. The left side was affected in 8 patients. The damaged rotator cuff tendons were as follows; supraspinatus tendon was affected in all patients, infraspinatus tendon was affected in 25 patients, teres minor was affected in 14 patients, and subscapularis tendon was affected in 24 patients. The critical shoulder angle was found 37.60°±1.66° CSA values were found to be higher in patients having fatty degeneration than others having no fatty degeneration, and it was statistically significant (p<0.001). The CSA values were found to be higher in patients with having increased number of damaged tendons and with having fatty degeneration of rotator cuff muscles. The higher CSA means the worse rotator cuff arthropathy patients, therefore care should be taken for planning surgical treatment options.

Keywords: Critical shoulder angle; shoulder; rotator cuff tears; radiography; fatty degeneration

Özet

Bu çalışmanın amacı rotator manşet artropatili hastalarda kritik omuz açısının (KOA) hasarlı rotator manşet tendon sayısı ve kasların yağlı dejenerasyonu ile ilişkisini araştırmaktı. Rotator manşet artropatisi hastaları bu çalışmaya dahil edildi. İlk yazar tarafından açıyı ölçmek için gerçek ön-arka radyografiler (Grashey görünümü) kullanıldı. Kritik omuz açıları radyografilerde ölçüldü. Aynı hastaların Manyetik rezonans görüntüleri (MRG), tendon tutulumlarının sayısı ve rotator manşet kaslarının yağlı dejenerasyonu açısından değerlendirildi. 16 kadın ve 12 erkekten oluşan 28 rotator manşet artropati hastası vardı. Ortalama yaş 69.92±8.84 idi. 20 hastada sağ omuz etkilenmişti. 8 hastada sol taraf etkilenmişti. Hasarlı rotator manşet tendonları şu şekildeydi; Hastaların tamamında supraspinatus tendonu, 25 hastada infraspinatus tendonu, 14 hastada teres minör ve 24 hastada subskapularis tendonu etkilenmişti. Kritik omuz açısı 37.60°±1.66°olarak bulundu. Yağlı dejenerasyonu olan hastalarda KOA değerleri, yağlı dejenerasyonu olmayanlara göre daha yüksek bulundu ve istatistiksel olarak anlamlıydı (p<0,001). Hasarlı tendon sayısı fazla olan ve rotator manşet kaslarında yağ dejenerasyonu olan hastalarda KOA değerleri daha yüksek bulundu. Daha yüksek KOA, daha kötü rotator manşet artropati hastaları anlamına gelir, bu nedenle cerrahi tedavi seçeneklerinin planlanması için özen gösterilmelidir.

Anahtar Kelimeler: Kritik omuz açısı; omuz; rotator manşet yırtığı; radyografi; yağlı dejenerasyon

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1. Introduction

Rotator cuff tears (RCTs) are a common pathologic finding among patients who have shoulder complaints (1,2). Many factors are related with RCTs, such as smoking, advanced age, and activity level (3,4). Rotator cuff tears also can lead to a characteristic series of degenerative changes including proximal humeral migration, superior wear, and inferior osteophyte formation, which are collectively termed rotator cuff tear arthropathy (5). Assessing the critical shoulder angle (CSA) can be helpful during diagnostic evaluation of patients with shoulder pain and can help predict the exact pathology. The CSA is the angle between the plane of the glenoid and the connecting line to the most lateral border of the acromion on the true antero-posterior (AP) radiograph of the shoulder. The measurement is simple and can be obtained from plain radiographs. First, Moor et al. (6) described the CSA, and reported that smaller CSA was associated with glenohumeral osteoarthritis (OA) and a larger CSA was associated with rotator cuff tear (RCT). Biomechanical studies also support the theory that higher CSA is associated with a greater risk for development of an RCT. Massive RCTs often contain a high degree of muscle atrophy, tendon adhesion, and abnormal fatty infiltration; In this study, we aimed to investigate the correlation of CSA with fatty degeneration of cuff muscles and number of torn cuff tendons.

2. Materials and Methods

This study was approved by the University Hospital Institutional Review Board Ethics Committee (Number: E-25403353-050.99-171587-02.03.202/17). This study is a retrospective analysis of longitudinally collected data between 2019 and 2021. The inclusion criteria for the patients were as follows; 1) Patients diagnosed as rotator cuff arthropathy disease 2) Patients who have not been treated surgically for rotator cuff disease before admitted to our clinic 3) Patients who have had true shoulder AP radiograph and MRI of the affected shoulder joint. Patients exclusion criteria were as follows; 1) If they had previous humerus, scapula, or clavicle fractures 2) If Grashey shoulder radiographs were not available 3) If radiographs were not suitable for measurement because of unclear visualization of bony landmarks 4) If they had previous rotator cuff surgery 5) Other criteria for exclusion were diagnoses of avascular necrosis and inflammatory arthritis. Grashey (true antero-posterior) views were taken with patients in standing-up position while rotating the affected shoulder 30-40 degrees towards to opposite side. Only radiographs with visible joint space and minimal overlap of the posterior and anterior rim of the glenoid were included into this study. All measurements were performed electronically on a picture archiving and communication system (PACS) workstation in our hospital. The CSA was calculated using the technique described by Moor et. al. (6). It was formed between two lines. First line is formed by connecting the superior and inferior bony margins of the glenoid, and second line is drawn from the inferior bony margin of the glenoid to the most lateral border of the acromion bony edge. All patients underwent standardised antero-posterior radiographs and a standard 3-Tesla (T) MRI of the shoulder, using a 3.0 T Siemens Magnetom Verio MRI (Siemens Medical Solutions, Erlangen, Germany) and 4-channel dedicated shoulder coil, with the arm positioned in neutral rotation by the patient's side. The standard shoulder MRI protocol included oblique coronal, oblique sagittal, and oblique axial images oriented to the axes of the glenohumeral joint. The number of damaged rotator cuff tendons were also assessed on MRI views and noted as how many tendons were affected per one patient. Fatty infiltration was evaluated with the criteria established by Goutallier et al., which classifies infiltration into 4 categories on the basis of the number of fatty streaks within the muscle belly on sagittal and coronal views (7). However, in this study fatty degeneration was assessed on MRI views and noted, only as whether presence or absence of pathology in rotator cuff muscles. The shoulder MRI of the patients were also evaluated according to number of involved torn tendons and fatty infiltration of the rotator cuff muscles as well.

Statistical Methods

The statistical analysis were performed using IBM SPSS Statistics version 25. The Mann-Whitney U test was used for the comparison of variables. The categorical variables were expressed as sample size (n) and percent, continuous variables were expressed as mean and standard deviation. $p<0.05$ was accepted as statistically significant for this study.

3. Results

There were 28 rotator cuff arthropathy patients comprising 16 females (57.1%), and 12 males (42.9%). The mean age was 69.92±8.84 years (range: 54-89). The right shoulder was affected in 20 (71.4%) patients. The left side was affected in 8 (28.6%) patients. The dominant extremity was involved in 21 (75%) patients. The damaged rotator cuff tendons were as follows; supraspinatus tendon was affected in all patients (28 patients, 100%), infraspinatus tendon was affected in 25 patients (25/28, 89.3%), teres minor was affected in 14 patients (14/28, 50%), and subscapularis tendon was affected in 24 patients (24/28, 85.7%). The critical shoulder angle was found 37.60±1.66 degrees (range: 35-40 degrees). Each damaged rotator cuff tendons and their relations with the critical shoulder angle are shown on Table 1. Patients with and without fatty infiltration of rotator cuff muscles and its relations with CSA values are presented on Table 2. CSA values were found to be higher in patients having fatty infiltration than others having no fatty infiltration, and it was statistically significant ($p<0.001$).

Table 1. The mean critical shoulder angle values of 28 patients, and their relevance with each damaged cuff tendon and with fatty degeneration of damaged tendon muscles.

	Damaged tendon (n)	Non-demaged tendon (n)	CSA (°) for damaged tendon	CSA (°) for non-damaged tendon	*p value*
Supraspinatus	28	0	37.60°±1.66°	-	p<0.001
Infraspinatus	25	3	37.80°±1.63°	36.00°±1.00°	p=0.090
Teres minor	14	14	38.35°±1.15°	36.85°±1.79°	p=0.021
Subscapularis	24	4	37.87°±1.56°	36.00°±1.41°	p=0.042

CSA (Critical shoulder angle mean±Std. Deviation)

Table 2. The relationship between CSA and fatty degeneration

	Patient (n)	CSA (°)
Fatty infiltration (+)	22	38.13°±1.35°
Fatty infiltration (-)	6	35.66°+1.21°

CSA (Critical shoulder angle mean±Std. Deviation)

4. Discussion

Moor et al. (6) first described the critical shoulder angle (CSA) for patients, who have high propensity for rotator cuff problems. The benefit of using the CSA is that it combines the lateral extension of the acromion and the inclination of the glenoid fossa into a single quantifiable measurement. Once it was introduced, studies demonstrated its strong relationship with rotator cuff tears (8). In addition, the literature has quantified measurement ranges, suggesting that patients with CSAs from 35° to 39° are at the highest risk for rotator cuff disease (6). Gerber et al. showed that CSAs >38° substantially increase the ratio of joint shear to joint compression forces (instability ratio) and lead to compensatory supraspinatus tendon overload (9). Moor et al. stated that, the mean CSA was 38.0° (29.5° to 43.5°) in the RCT group and 28.1° (18.6° to 35.8°) in the OA group. Of patients with a CSA>35°, 84% were in the RCT group and of those with a CSA < 30°, 93% were in the OA group (6). Despite using CSA in rotator cuff disease patients evaluation

preoperatively, also Garcia et al. (10) reported that increased CSA was significantly correlated with worse postoperative outcomes. The average CSA values correlated with rotator cuff disease vary in the literature from 35° to 39° (6). Our results obtained for this study was similar with the literature. CSA measurements on radiography could provide a better guidance for assessing and predicting the severity of damaged rotator cuff muscles compared to MRI, which is expensive and time consuming imaging modality according to radiography. It has been shown that a malrotation in the conventional radiographs exceeding 20° leads to substantial overlap between the anterior and posterior glenoid rims, decreasing the reproducibility (6). Hence, all CSA measurements in this study was done on true antero-posterior (Grashey views) radiographs.

As mentioned by Chalmers et al. (11), the CSA is not correlated with tear size or tear progression, and does not seem to change with time. Their results suggest that the CSA is unlikely to be related to rotator cuff disease and they have found no change in the CSA at a mean of 6 years, suggesting this is a stable measurement. In contrast to this, it was stated that the CSA also may correlate with tear size (12) and might be larger in patients with degenerative cuff tears than in patients with traumatic tears (13). It was reported in a study that (14), concurrent glenohumeral OA and full-thickness RCT are associated with greater CSA values compared with patients with glenohumeral OA alone. Our study results are consistent with these reports, as our average CSA was 37.60°±1.66° (range: 35°-40°). In our study, fatty degeneration of the damaged rotator cuff muscles had more CSA values than having no fatty degeneration and were found to be statistically significant ($p<0.001$). Scheiderer et al. reported a study, in which they have found higher CSA values associated with increased re-tear risk after isolated supraspinatus tendon repair at short-term follow up. The average CSA was 35.3° for the intact group and 37.4 for the re-tear group. They showed that, the mean CSA for the re-tear group was significantly higher than that for the intact group ($p=0.014$) (15). According to our results, we guess that worse damaged cuff muscles may show more CSA values than less damaged cuff muscles. Rotator cuff arthropaty patients need shoulder arthroplasty in their future life. Assessing the CSA values on true antero-posterior radiographs helps us to imagine the severity of the disease. As nearly all shoulder arthroplasty candidates receive preoperative radiographs, we believe the CSA should be measured and used as an adjunct to help determine the need for MRI preoperatively. On MR images, fatty degeneration of damaged cuff muscles can be seen and the best type of surgery planning also can be made for these patients easily. We believe that the CSA may prove to be a useful tool to help orthopaedic surgeons to determine when it is necessary to order a MRI study to evaluate the rotator cuff before surgery. As with all studies, this current study is not without limitations. First, the retrospective nature of the study may have introduced bias. Second, being lack of multiple observers grading radiographs, and increasing the number of graders may have changed our results. Third, having small number of patients.

5. Conclusions

This study results confirm an association between the CSA and RCTs. Assessing the CSA may be helpful during diagnostic evaluation of patients with severe rotator cuff disease and can help predict the magnitude of the pathology especially fatty degeneration of rotator cuff muscles. However, further prospective research with more patients is warranted to highlight the topic in more detail.

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Case Report / Olgu Sunumu

Microvillus Inclusion Disease: Can Mesenchymal Stem Cells Be a Potential Treatment Option?

Mikrovillus İnkluzyon Hastalığı'nda Mezenkimal Kök Hücreler Bir Tedavi Seçeneği Olabilir mi?

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Abstract

Microvillus inclusion disease (MVID; MIM #251850), is a rare life-threatening secretory and malabsorptive diarrhea of infancy due to mutations in the MYO5B gene. A 6-day-old male patient was referred to our neonatal intensive care unit for profuse diarrhea beginning on the 2nd day of life causing 17% weight loss, metabolic acidosis and hyponatremia. Our patient had a homozygous mutation in the MYO5B gene. On 110th day of life, mesenchymal stem cell treatment (1x106 cells trans duodenal and 2x106 cells intravenous) was administered. Although fluid and electrolyte requirements did not decrease after stem cell therapy, the rate of blood stream infections was reduced. Small bowel transplantation using cadaveric intestine was performed at the age of 20 months. Unfortunately, the infant died of sepsis one month after transplantation. In this case report, results of stem cell therapy in a newborn infant with MVID were presented and discussed with the relevant literature.

Keywords: Newborn; microvillus inclusion disease; mesenchymal stem cell; treatment

Özet

Mikrovillus inklüzyon hastalığı (MİH), Miyosin 5B genindeki mutasyonlara bağlı oluşan sekretuvar ve osmotik diyare ile seyreden hayatı tehdit edici bir hastalıktır. Mezenkimal kök hücre (MKH) tedavisi intestinal yetmezlikte sınırlı sayıda olguda uygulanmıştır ancak MİH'de sadece hayvan çalışmaları bulunmaktadır. Altı günlük erkek bebek postnatal 2. günde başlayan, ishal, metabolik asidoz ve hiponatremi nedeniyle yenidoğan yoğun bakım ünitemize kabul edildi. 36 hafta 4 günlük, 2960 g olarak doğan bebeğin diyareye bağlı iki kardeş ölüm öyküsü vardı. Olgumuzda MYO5B geninde homozigot mutasyon tespit edildi. Enteral beslenme kesilerek total parenteral beslenme başlandı. Bebeğin yüksek sıvı (350 cc/kg/gün), sodyum (20-25 meq/kg/gün) ve bikarbonat (12-18 meq/kg/gün) ihtiyacı mevcuttu. Postnatal 110. gününde hastaya MKH tedavisi (1x106 Ü transduodenal ve 2x106 Ü IV) uygulandı. Kök hücre tedavisi sonrası her ne kadar sıvı ve elektrolit gereksinimleri azalmasa da sepsis sıklığında azalma gözlendi. Bebek 20 aylıkken kadavradan ince barsak nakli yapıldı, ancak nakilden bir ay sonra sepsis nedeniyle eksitus oldu.

Anahtar Kelimeler: Yenidoğan; mikrovillus inkluzyon hastalığı; mezenkimal kök hücre; tedavi

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1. Introduction

Microvillus inclusion disease (MVID; MIM #251850) is a rare, life-threatening secretory and malabsorptive diarrhea of infancy. Mutations in MYO5B gene which encodes actin-based motor protein Myosin 5B are responsible from the disease state. Myosin 5B is involved in the structure of microvilli cytoskeleton and is required for the regulation of polarized epithelial cells and eventually transport of brush border components. In electron microscopic evaluation accumulation of ‘‘inclusions’’ of microvilli in the cytoplasm of small-bowel biopsy specimens is characteristic finding (1,2). Typical presentation is abundant watery diarrhea starting early in the neonatal period even in the first hours of life. Some cases are defined as “later-onset” but never extend beyond the first 2-3 months of life. Mortality rate has been reported 80% by 18 months of age despite total parenteral nutrition (TPN) which is obligatory for survival (3). Whole organ allogeneic transplantation has improved the survival but most of the patients die before achieving the opportunity of bowel transplantation due to electrolytes and renal tubular function disturbances and complications of parenteral nutrition. Bowel transplantation is also associated with a high risk for morbidity and mortality. In a large case series of MVID, survival rates of children were 63% without small bowel transplantation (SBTx) and 77% with SBTx with a mean follow up period of 3 months to 14 years after bowel transplantation (3).

Recently, trials demonstrating potential regenerating capacity of stem cells in the field of many degenerating disease even in the patients with monogenic and polygenic forms of intestinal failure encourage us to introduce pluripotent stem cells to our patient (4,5). Mesenchymal stem cell treatment was used to improve epithelium regeneration in this life-threatening disease. Results of mesenchymal stem cell (MSC) therapy in this MVID case were presented discussing with the relevant literature.

2. Case

A 6-day-old male patient was referred to our neonatal intensive care unit for profuse diarrhea beginning on the 2nd day of life causing 17% weight loss, metabolic acidosis and hyponatremia. He was born at 36+4 weeks of gestational age and body weight of 2960 g with a prenatal history of polyhydramnios and dilated bowel loops. He was the fourth child of nonconsanguineous parents. Second and third siblings died at 2 and 3,5 months due to complications of intractable diarrhea beginning in the first few days of life. Third child’s exome sequencing identified a homozygous, disease-causing nonsense variant C.4399C>T (p.Gin1467*) in the MYO5B gene. Both parents were found heterozygous for this mutation and did not accept prenatal test for our patient. With the knowledge of the family history, total parenteral nutrition was started immediately and maximum effort was directed to maintain fluid and electrolyte equilibrium. Patient had high fluid (350 ml/kg/day), sodium (20-25meq/kg/day) and bicarbonate requirements (12-18 mEq/kg/day). Sequencing by Illumina-Miseq revealed that he was homozygous for c.4399c>T (p.Q1467*)(p.Gin1467*). So, he was also affected by homozygous mutation in MYO5B gene. On 110th day of life, MSC treatment (1x106 cells trans duodenal and 2x106 cells intravenous) was administered. Although fluid and electrolyte requirements did not decrease after stem cell therapy, the rate of blood stream infections was reduced. Until transferring to a transplantation center at the age of 9 months and weighing 9120 g, he was dependent on TPN via central venous catheterization but free off cholestatic liver disease. Fluid requirement was 220 ml /kg/day and electrolyte equilibrium were maintained with 17 mEq/kg/day Na and 8 mEq//kg/day bicarbonate. Small bowel transplantation using cadaveric intestine was performed at the age of 20 months. Unfortunately, the infant died of sepsis one month after transplantation. Informed consent has been obtained from the parents to share the clinical details of their child.

3. Discussion

In MVID, mutations in the MYO5B gene which encodes a protein called myosin Vb contribute to the dysfunction of enterocytes (1). Survival rate is less than 25% at the age of 9 months. Parenteral nutrition and modification of electrolytes according to the needs of patients are the mainstay of therapy after the diagnosis. Life threatening catheter related infections, central venous thrombosis, and TPN associated liver disease are main complications of long-term parenteral nutrition. Recently genetic susceptibility to liver disease in conjunction with mutations in MYO5B gene was defined that result in aberrant expression of apical/canalicular membrane transporters preventing the normal secretion of bile salts and causing cholestatic liver disease (6).

Patients who survive beyond one year of age achieve the chance for allogeneic intestinal transplantation. More than half of the patients die while waiting for transplantation, and the 5-year survival of patients undergoing transplantation is approximately 60%. Halac et al. (3) described 24 patients with MVID from France, 9 of them were Turkish origin. Thirteen children (54%) underwent SBTx, at a median age of 3.5 years (range 1–12 years), after a mean waiting time of 1.5 years (1 month–2.5 years). Seven transplanted children (54%) are living with a functional graft and have been weaned off TPN. One-fourth (6/24) of children experienced several episodes of intrahepatic cholestasis.

To prevent from allograft rejection, lifelong potent immunomodulatory agents are required which predispose patients to severe recurrent infections and the risk for various post-transplant malignancies. Considering the waiting period for transplantation and the complications that may develop afterwards, it is obvious that treatment methods that will provide early enteral nutrition and eliminate fecal losses are needed in patients with MIVD.

Stem cell transplantation is a promising therapy for the devastating neonatal disorders such as intraventricular hemorrhage, bronchopulmonary dysplasia and hypoxic ischemic encephalopathy and many of the phase 1 clinical studies on the safety and feasibility were conducted. Systemically transplanted MSCs migrate and localize toward injured tissue under chemotactic guidance (7). Recently, stem cell therapy was presented as a promising alternative strategy for overcoming the current limitations of intestinal failure treatment. Hong et al.(5) stated that autologous intestinal stem cells (ISCs) transplantation will be a potential therapeutic strategy if modified ISCs can successfully engraft into the ablated small intestinal niche of intestinal failure patients. Although rodent models have established the feasibility of ISC-based therapies, various challenges must be overcome before these therapies may be used clinically, notably for MVID. And, many of the findings from rodent studies are not always applicable to human systems.

We concluded that the rapid turnover of gut epithelial cells and the absence of receptive surface resulting by the genetic defect were the reasons why our patient did not benefit from treatment. Also, the number of stem cells required to repopulate the immense surface area of the small bowel has not been determined, yet. With the permission of our country's ministry of health, we were allowed to provide this promising treatment once. If we had the opportunity to administer it in multiple doses, it might have an influence on tissue regeneration. Another explanation for the lack of response to MSC treatment was that there was no injured tissue to attract stem cells to the area via signaling. Furthermore, using modified ISCs instead of MSCs may be more beneficial.

In our patient, decreased incidence of infection with probable immunomodulatory effects of stem cells was the secondary gain. Although their mechanisms of action are not completely understood, MSCs have been shown to stimulate significant changes in immune responses and a reduction in inflammation through direct interactions with inflammatory cells, as well as through the release of cytokines (7). We wanted to give this opportunity to our patient. Despite the

fact that a single administration of pluripotent MSC did not appear to be effective in this case, we believe it is a worthwhile experience to share.

In this genetically originated disease, replacement of diseased epithelium by gene corrected epithelium with gene editing technique or the use of human leukocyte antigen-matched allogenic ISCs are seen as promising treatments for the future (8). The use of clustered regularly interspaced short palindromic repeats (CRISPR) to correct the monogenic disease, could increase the chances of success of autologous ISC transplantation. Also, enriching for subtypes of ISCs, such as those isolated from different areas of the gut or from different developmental ages, is necessary because they may respond differently to signaling cues, affecting their expandability (5).

Intestinal failure is a rare but potentially fatal condition caused by an inability to maintain growth and development with nutrition obtained through the enteral route. Recent advances in human intestinal stem cell expansion techniques have enabled the in vitro reconstitution of complex cellular structures that mimic the native bowel. Although the dose and route of administration are still being determined, replacing damaged epithelium with corrected epithelium derived from gene editing of autologous stem cells appears to be a viable therapeutic option in the future.

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Olgu Sunumu / Case Report

Pleksiform Miksoid Gastrointestinal Stromal Tümör, İnce Barsak Yerleşimli Nadir Bir Histolojik Patern: Olgu Sunumu

Plexiform Myxoid Gastrointestinal Stromal Tümör, A Rare Histological Pattern Located in the Small İntestine: A Case Report

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Özet

Gastrointestinal stromal tümör (GİST) gastrointestinal sistemin en sık görülen, kajal hücrelerinden köken alan mezenkimal tümörüdür. Sıklıkla 50 yaş sonrası ve %60 oranında midede, ikinci sıklıkla jejunum ve ileumda (%30) görülür. İnce barsak yerleşimliler midede bulunanlara göre %40-50 daha fazla malign seyirlidir. Ayrıca ince bağırsak GISTleri mide GISTleri gibi ayırt edici histolojik alt tipler oluşturmazlar. Çoğunlukla iğsi hücrelidirler. Epiteloidler ise çok küçük bir kısmını oluşturur. Bizim sunacağımız olguda epiteloid ve iğsi hücre özelliklerine ek olarak pleksiform büyüme paterni ve zeminde miksoid stroma bulunmaktadır.

Anahtar Kelimeler: GİST, İnce barsak, Pleksiform, Miksoid

Abstract

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal system originating from cajal cells. It is frequently seen after the age of 50 and 60% in the stomach, the second most frequently in the jejunum and ileum (30%). Small bowel residents have 40-50% more malignant prognosis than those in the stomach. In addition, small intestine GISTs do not constitute distinctive histological subtypes like gastric GISTs. They are mostly spindle cell. Epithelioids, on the other hand, constitute a very small part. In our case, in addition to epithelioid and spindle cell features, there is a plexiform growth pattern and myxoid stroma in the ground.

Keywords: GİST, Small bowel, Plexiform, Myxoid

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1. Giriş

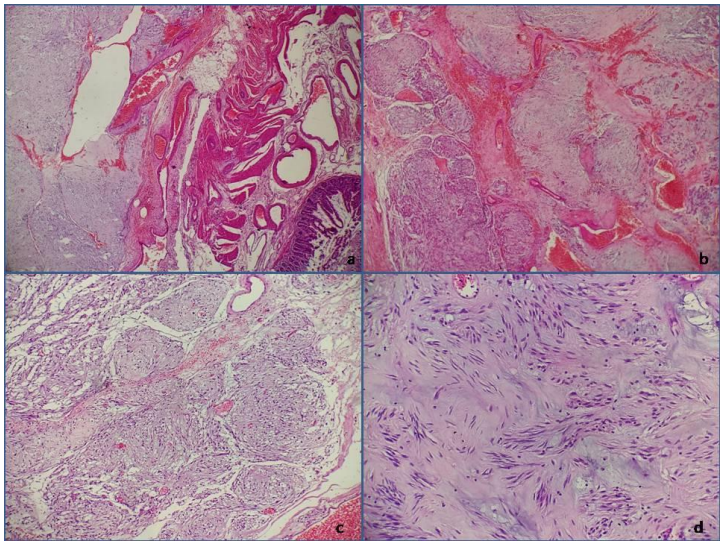
İnce barsaklar gastrointestinal mukozanın yaklaşık %90'ını ve gastrointestinal tractın total uzunluğunun %75'ini oluşturmasına rağmen tümörleri tüm gastrointestinal kanserlerin %5'inden azını oluşturur. İnce barsak kanserlerinin lokalizasyona göre görülme oranları duodenum %55-82, jejunum %11-25, ileum %7-17'dir. Histopatolojik olarak adenokarsinom %40'ını, nöroendokrin tümörler %40'ını, gastrointestinal stromal tümör, lenfoma ve sarkomlar ise %20'sini oluşturur (1).

Gastrointestinal stromal tümör (GİST) gastrointestinal sistemin en sık görülen, kajal hücrelerinden köken alan mezenkimal tümörüdür. Sıklıkla 50 yaş sonrası ve %60 oranında midede, ikinci sıklıkla jejunum ve ileumda (%30) görülür. En sık mutasyonlar c-KİT ve Platelet Derived Growth Factor Receptor Alpha (PDGFRA) geninde izlenir. İnce barsak yerleşimliler midede bulunanlara göre %40-50 daha fazla malign seyirlidirler. Histolojik yapıları çoğunlukla iğsi olsa da epiteloid ve mikst iğsi-epiteloid tipte de olabilir. İnce barsak GİST'lerinde immunohistokimyasal (İHK) CD117 ve CD34 pozitifliği görülür (2). Bizim sunacağımız olguda epiteloid ve iğsi hücre özelliklerine ek olarak pleksiform büyüme paterni ve zeminde miksoid stroma bulunmaktadır. Bu nadir histolojik özellikleri ve ayırıcı tanılarını sunmayı amaçladık.

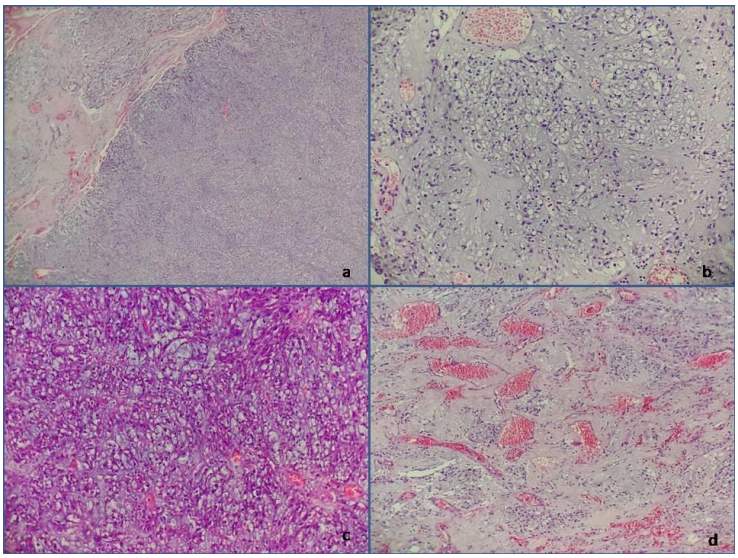
2. Olgu

Elli iki yaşında erkek hasta karın ağrısı şikayeti ile hastanemize başvurdu. Yapılan tüm batın bilgisayarlı tomografisi 'Pelvik bölgede her iki alt kadrana uzanım gösteren yaklaşık 162x126 mm boyutunda heterojen yoğun kontrastlanan lobule kontürlü hipodens lezyon izlenmiştir.'olarak yorumlandı. Kitle rezeksiyonu yapıldı. Patoloji isteminde ön bilgi olarak 'ileoçekal valvin 120 cm proksimalinde mesaneye yapışık kitle' yazmaktaydı. Patolojiye gönderilen materyalin makroskopik incelemesinde 4,5 cm uzunluğunda ince barsak segmentinin serozal bölgesinde 18x16 cm ölçülerinde, multinodüler, kesit yüzeyi kanamalı, nekrotik ve solid alanlar içeren lezyon görüldü (Resim 1). Örneklenen parçaların ışık mikroskobunda hematoksilen-eozin boyalı lamlarının incelenmesinde ince barsak serozal yağlı dokudan kaynaklanan, muskularis propriaya bitişik pleksiform nodüler lezyon izlendi. Tümör miksoid zeminde iğsi veya oval, intrastoplazmik vakuol içeren hücreler ve ince damar yapılarından oluşmaktaydı (Resim 2-3). Nekroz ve lenfovasküler tümör invazyonu izlendi. Mitotik aktivite 1/50 büyük büyütme sahası olarak sayıldı. İmmunohistokimyasal boyamalardan Vimentin, CD117, DOG-1 ve CD34 ile yaygın pozitiflik, S100 ile fokal tek tük hücrede pozitiflik görüldü (Resim 4). SMA, Desmin, PanCK ile negatif sonuç elde edildi. Ki-67 proliferasyon indeksi %3-5 civarındaydı. Vaka yerleşim yeri, histopatolojik ve immunohistokimyasal bulguların desteği ile 'Pleksiform miksoid gastrointestinal stromal tümör' olarak yorumlandı. Armed Forces Institute Studies Prior (AFİP)'e göre risk grubu 3b/ yüksek riskli prognostik grup şeklindeydi

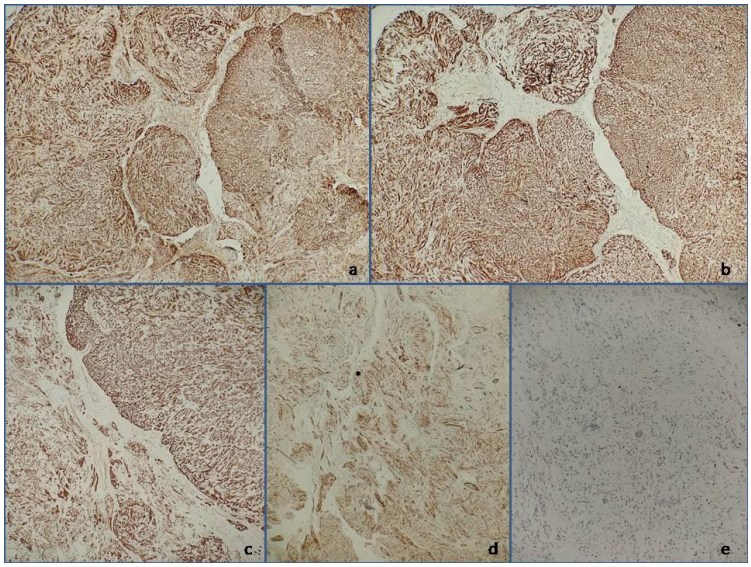
Resim 1. İnce barsak segmentinin serozasından köken alan dış yüzünde nodüler yapılar bulunan kitle. (Makroskopik görünüm)



Resim 2. a: İncebarsak muskularis propriaya yapışık seroza yerleşimli lezyon (HE, 40x)
b ve c: Pleksiform büyüme paterni (HE, b:40x, c:100x)
d: Pleksiform alanlardaki iğsi hücreler (HE, 400x)



Resim 3. a: Daha solid ve soluk boyanmış tümöral alanlar (HE, 40x)
b ve c: Miksoid zeminde oval, intrastoplazmik vakuol içeren hücreler (HE, 100x)
d: Çok sayıda ince vasküler yapılar ve arada epiteloid oval tümöral hücreler (HE,40x)



Resim 4. İmmunohistokimyasal boyamalar:
a: CD117 diffüz pozitif (IHK, 100x),
b: DOG-1 diffüz pozitif (IHK, 100x),
c: Vimentin diffüz pozitif (IHK, 100x),
d: CD34 fokal pozitif (IHK, 40x),
e: S100 fokal tek tük hücrede pozitif (IHK, 100x)

3. Tartışma

Gastrointestinal stromal tümörler tamamen asemptomatik olabileceği gibi yerleşim yeri, tümörün büyüklüğü, mukozal ülser ve nekroz varlığına bağlı olarak ağrı, gastrointestinal kanama, ele gelen kitle, kusma, anemi, ileus gibi semptomlar gösterebilirler (3). Bizim hastamız hastaneye karın ağrısı ile başvurmuştu ve yapılan radyolojik görütülemelerde kitle tespit edilerek opere edilmişti.

GİST'lerin potansiyel biyolojik davranışını belirlemek için AFİP kriterleri kullanılmaktadır. Bu kriterler tümör boyutu (≤ 2 cm, >2 ≤5 cm, >5 ≤10 cm ve >10 cm) ve 50 büyük büyütme sahasında (BBS) sayılan mitoz sayısına (≤5/50 BBS ve >5/50 BBS) göre verilmektedir. Gastrik ve ince barsak GİST'leri bu verilere göre çok düşük, düşük, orta, yüksek riskli gruplara ayrılmaktadır (4). Bizim olgumuzun tümör boyutu 18 cm ve mitoz sayısı 1/50 BBS idi. Bu veriler ile ince barsak GİST AFİP risk grubu 3b/ yüksek riskli prognostik grup olarak değerlendirildi.

Gastrik GİST'lerin 8 farklı ayırt edici histolojik alt tipi vardır. Bunlar sklerozan iğsi hücreli subtip, palizatlanan vakuollü iğsi hücreli subtip, hipersellüler iğsi hücreli subtip, sarkomatöz iğsi hücreli subtip, sklerozan epiteloid varyant, diskoheziv epiteloid subtip, hipersellüler epiteloid subtip ve sarkamotöz epiteloid subtiptir. Oysa ki ince barsak GIST'leri mide GIST'leri gibi ayırt edici histolojik alt tipler oluşturmazlar. Çoğunlukla iğsi hücrelidirler. Epiteloid patern ise sadece %5'ini oluşturur (5). Bizim olgumuzda iğsi ve epiteloid miks tipte histolojik yapıya ek olarak pleksiform büyüme paterni ve miksoid zemin izlenmiştir.

GİST'lerin normalde yetişkin barsağında myenterik pleksusun içinde ve etrafında gastrointestinal sistem peristaltizmini düzenleyen interstisiyel cajal hücrelerinin prekürsörlerinden kaynaklanan mezenkimal tümörler olduğu düşünülmektedir (6). Hirato ve ark 1998 yılında GİST'lerin %80'inden fazlasında tirozin kinaz reseptörü kodlayan c-kit gen mutasyonunu göstermiştir. C-kit proteini Kajal hücrelerinde bulunmaktadır ve immunohistokimyasal olarak CD117 ile %95 oranında ekspresyonu rapor edilmiştir (7). Ancak malign melanom, adenoid kistik karsinom, Merkel hücreli karsinom, Kaposi sarkomu, liposarkom ve hatta leiomyosarkom (nadiren) gibi diğer tümörlerde de eksprese edilebilir. Bu nedenle 2004 yılında DOG-1 immun markerı keşfedilmiştir. DOG-1 ve CD117 kombinasyonu GİST'lerin %98'inden fazlasında tanı koydurucudur. Ayrıca CD34 pozitifliği de tanıya yardımcıdır (8). Bizim vakamız da immunohistokimyasal olarak CD117, DOG-1 ve CD34 pozitifliği görüldü.

Bazı GİST'lerde c-kit mutasyonu yerine başka bir tirozin kinaz protoonkogeni olan PGFRA

geninde mutasyon tespit edilebilir (6). Ayrıca gastrik epiteloid GİST'lerde suksinat dehidrojenaz (SDH) enzim eksikliği de görülebilir. Bu enzim defekti pleksiform multinodüler özelliklerdeki GİST'lerde görülse de incebarsak GİST'lerinde görülmez. Bunlar imatinibe direnç gösterir ve mevcut risk değerlendirmeleri ile klinik davranışı belirlenemez (9). Bizim olgumuz 6 aydır takipte ve nüks izlenmedi. Bölümümüzde moleküler çalışma yapılamadığı için mutasyon varlığına bakamadık. Ancak pleksiform morfolojisine rağmen ince barsak yerleşimi ile SDH enzim eksikliği olamayacağını düşünmekteyiz.

Ayırıcı tanıda miksoid zeminiyle miksoid liposarkomdan, pleksiform büyüme paterni ile de nörofibrom, schwannom, pleksiform fibrohistiositik tümörlerden ayırt etmek gereklidir (10). Miksoid liposarkom intraperitoneal görüldüğünde öncelikle metastaz düşünülmelidir. Ayrıca immunohistokimyasal olarak MDM2 ve CDK4 pozitiftir (11). Pleksiform schwannom kutanöz bir tümör olmasına rağmen visseral bölgede de bulunabilir. Miksoid değişiklikler ve nekroz içerebilir. S100 pozitifliği ve CD117 negatifliği ile GİST'den ayrılır. Pleksiform nörofibrom da pleksiform shwannoma ile benzer immunohistokimyasal özellikler taşır (12). Pleksiform fibrohistiositik tümörler yine kutanöz yerleşimli ve CD68 pozitiftir (13).

4. Sonuç

Özellikle batın içi yerleşimli mezenkimal tümörlerde miksoid zeminde ve pleksiform yapıda da GİST olabileceği akılda tutulmalıdır. İHK olarak desteklemek için CD117, CD34, DOG-1 immun panele eklenmelidir. Özellikle miksoid zeminiyle miksoid liposarkomdan, pleksiform büyüme paterni ile de nörofibrom, schwannom, pleksiform fibröz histiositomdan ayırt etmek gereklidir. İHK çalışmalarla sonuç alınamaz ise genetik mutasyonlar ve tipik pleksiform mural gelişimi gösteren Suksinat dehidrojenaz (SDH) yetmezliği bakılabilir.

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Olgu Sunumu / Case Report

Trigeminal Sinir Dermatomu Yerleşimli Pediatrik Herpes Zoster

Pediatric Herpes Zoster Located İn The Trigeminal Nerve Dermatome

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Özet

Herpes zoster diğer ismi ile zona, dorsal kök ganglionlarında latent kalan varisella zoster virüsünün reaktivasyonu sonucu ciltte veziküler lezyon olarak karşımıza çıkar. Birincil suçiçeği enfeksiyonundan veya aşı uygulamasından sonra herhangi bir zamanda görülebilir. Sağlıklı çocuklarda nadiren görülür ve çoğunlukla kendi kendini sınırlar. Altta yatan herhangi bir immünsupresyon öyküsü veya kronik hastalığı olmayan sekiz yaşında kız hasta, trigeminal sinir tutulumu ile seyreden zona tanısı ile oral asiklovir tedavisi alırken yeni döküntülerin ortaya çıkması, şiddetli ağrı şikayeti oluşması üzerine intravenöz asiklovir ile tedavi edildi. Ağrı kontrolü için oral analjezikler ve topikal lidokain içerikli pomad uygulandı. Takiplerinde bakteriyel süperenfeksiyon gelişmesiyle trimetoprim-sulfametoksazol tedavisi verildi ve intravenöz asiklovir tedavisi 7 güne tamamlandı.

Anahtar Kelimeler: çocuk, herpes zoster, trigeminal sinir

Abstract

Herpes zoster, also known as shingles, appears as a vesicular lesion on the skin as a result of the reactivation of varicella zoster virus, which remains latent in the dorsal root ganglia. Herpes zoster can develop at any time after the primary varicella infection or vaccination. It occurs rarely in healthy children and is mostly self-limiting. An eight-year-old female patient without any underlying immunosuppression history or chronic disease was treated with intravenous acyclovir due to the emergence of new rashes and severe pain while receiving oral acyclovir treatment with the diagnosis of herpes zoster with trigeminal nerve involvement. Oral analgesics and topical lidocaine-containing ointment were applied for pain control. Trimethoprim-sulfamethoxazole treatment was given for bacterial superinfection and intravenous acyclovir treatment was applied for 7 days.

Keywords: child, herpes zoster, trigeminal nerve

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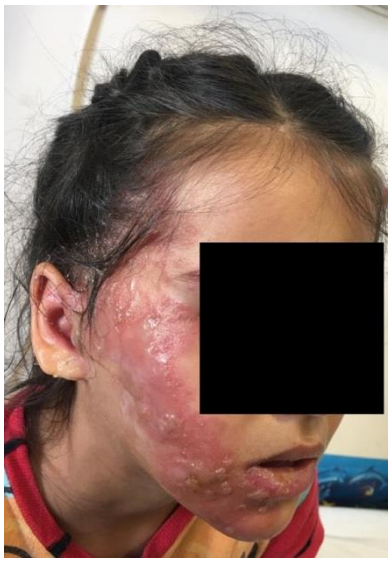
1. Giriş

Varisella zoster virüs (VZV), herpes virüs ailesinin alfa herpes grubundan olan çift sarmallı bir DNA virüsüdür. VZV'nin neden olduğu primer enfeksiyon suçiçeği olup virüs duyu sinirlerinin arka kök gangliyonlarında latent olarak kalır. Vahşi tip veya aşı tipi VZV ile ortaya çıkan primer bir enfeksiyon, herpes zoster için ön koşuldur (1). Latent virüsün konakta aktivasyonu herpes zoster ile sonuçlanır.

Herpes zoster gelişimi için risk faktörleri kadın cinsiyet, siyah ırk, aile öyküsü ve komorbidite varlığıdır (2). Küçük çocuklarda herpes zoster daha çok servikal ve sakral dermatoma yerleşir (3). Yetişkinlerde lezyonlar alt torasik ve üst lomber dermatomlarda daha sık görülür ve trigeminal siniri içerebilir (3). Herpes zoster tanısı, belirgin klinik görünüm ve semptomatolojiye dayanarak klinik olarak konulur (4). Antiviral tedavinin amacı viral yükü azaltmak, kutanöz lezyonların iyileşmesini hızlandırmak, yeni lezyon oluşumunu önlemek, akut nörit ile ilişkili ağrıyı ve muhtemel komplikasyonları azaltmaktır (5). Bu çalışmada altta yatan herhangi bir hastalığı olmayan ve trigeminal sinir tutulumu ile seyreden sekiz yaşındaki zona olgusu sunulmuştur.

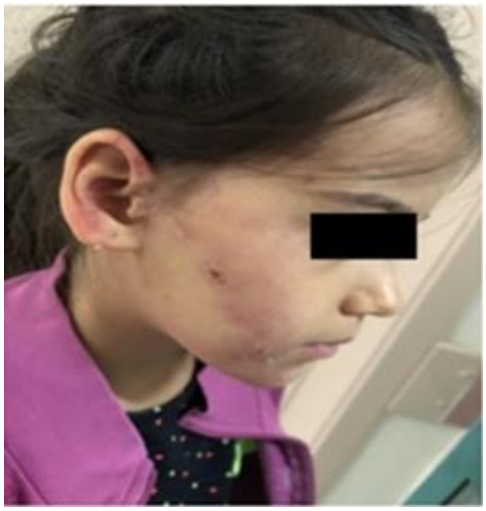
2. Olgu Sunumu

8 yaşında kız hasta 1 hafta önce sağ tragustan başlayıp ağzın sağ köşesine kadar yayılım gösteren döküntü şikayetiyle Çocuk Acil Birimine başvurdu. Döküntü dışında ek bir şikayeti yoktu. Hikayesinden bir hafta önce sağ tragus cildinde birkaç adet veziküler döküntü gelişmesi nedeniyle dış sağlık kuruluşuna başvurduğu ve azitromisin antibiyoterapisi başlandığı öğrenildi. Hastanın bilinen kronik hastalık öyküsü veya düzenli ilaç kullanımı yoktu. Suçiçeği aşısı uygulanmamış olup suçiçeği geçirme öyküsü mevcuttu. Döküntüleri herpes zoster olarak değerlendirilerek oral asiklovir (80 mg/kg/gün, 4 dozda) tedavisi başlandı. Oral asiklovir tedavisinin ikinci gününde döküntülerin gerilememesi, 4-5 adet benzer döküntünün sırtta da görülmesi ve şiddetli ağrı şikayetleriyle hasta tekrar başvurdu. Fizik muayenede; trigeminal sinirin mandibuler dalı tutulumu ile uyumlu olacak şekilde sağ dış kulak yolunda, sağ tragustan ağız köşesine kadar uzanan eritemli zeminde veziküler lezyonlar görüldü, şiddetli ağrısı mevcuttu (Resim 1). Sırtta herhangi bir dermatoma uymayan dağınık yerleşimli 5 adet veziküler döküntü görüldü. Fizik muayenesinde ek bulgu saptanmayan hastanın laboratuvar tetkiklerinde tam kan sayımı, kan biyokimyası, akut faz reaktanları normal bulundu.



Resim 1. Trigeminal sinir dermatomu yerleşimli herpes zoster ile uyumlu veziküler döküntü

Herpes zoster tanısı konulan hastaya intravenöz asiklovir (30 mg/kg/gün, 3 dozda) tedavisi başlandı. Lezyonların olduğu bölgede şiddetli ağrı olması üzerine Algoloji Bilim Dalının önerisiyle ibuprofen (8 mg/kg/doz günde 1 kez) ve parasetamol (10 mg/kg/doz günde 3 kez) tedavisi verildi, lezyonlara topikal lidokain içerikli pomad uygulandı; hastanın ağrı şikayeti geriledi. Dış kulak yolundaki veziküler lezyonlar nedeniyle Kulak Burun Boğaz Anabilim Dalının önerisiyle %3 burrow solüsyonu 3x5 damla 10 gün süreyle uygulandı. İşitme testinde her iki kulak duyma fonksiyonu normal olarak değerlendirildi. İntravenöz asiklovir tedavisinin ikinci gününde 38 °C ateşi görülen hastanın fizik muayenesinde mevcut cilt lezyonları haricinde ateş odağı saptanmadı, laboratuvar tetkiklerinde akut faz reaktanlarında artış görülmedi, gönderilen kan kültüründe patojen bakteri üremesi görülmedi. Ciltte sekonder bakteriyel enfeksiyon düşünülerek trimetoprim-sulfametoksazol tedavisi başlandı. Döküntüleri ve ağrı şikayeti gerileyen hastanın intravenöz asiklovir tedavisi ve trimetoprim-sulfametoksazol tedavisi 7 güne tamamlandı. Hastanın taburculuk sonrası ikinci ay poliklinik kontrolünde fizik muayenede; sağ auriculadan malar bölge ve çeneye doğru uzanan dermatomal hat üzerinde yer yer eritemli, yer yer hiper veya hipopigmente maküler ve krutlu lezyonlar saptandı (Resim 2). Hastanın bir yıllık klinik izleminde iyilik halinin sürdüğü, ağrısının olmadığı belirlendi.



Resim 2. Trigeminal sinir dermatomu yerleşimli hiper ve hipopigmente maküler ve krutlu lezyonlar

3. Tartışma

Herpes zoster, virüse özgü hücresel bağışıklığın azalmasıyla latent VZV'nin yeniden aktive olmasından kaynaklanır. Genellikle ileri yaşlı veya immunsüpresif bireylerde görülsede tüm yaş gruplarında ve immünkompetan bireylerde de görülebilir (6). Yirmi altı ülkeden 130 çalışmanın dahil edildiği meta-analizde herpes zoster görülme sıklığı yılda 3-5/1000 kişi arasında saptanmıştır (7). Yaş ve cinsiyete göre bakılan herpes zoster insidansı ise genel populasyonda 3.2/1000 kişi iken bu oran 0-14 yaş arası çocuklarda 1.1/1000 kişidir (8). Genel olarak, yaşamın ilk yılında enfekte olanlar hariç 10 yaş altında herpes zoster görülmesi nadirken, primer enfeksiyonu erken dönemde geçiren çocuklarda herpes zoster gelişme olasılığı daha fazladır (9). İmmün sistemi baskılanmış bireyler, aynı yaştaki immünkompetan bireylerden belirgin daha yüksek risk taşır (10). Ayrıca altta yatan astım, diyabet, böbrek yetmezliği, malignite gibi hastalık öyküsü olan çocuklarda zona gelişme riski daha fazladır (11,12). Bizim olgumuz 8 yaşında kız

hasta olup altta yatan herhangi bir hastalığı bulunmamaktaydı.

Herpes zoster, aşılama sonrası VZV aşı suşuna bağlı gelişebilmekte fakat vahşi tip su çiçeği sonrası gelişenden daha hafif seyretmektedir (1, 13). Varisella aşısı olan hem sağlıklı hem de bağışıklığı baskılanmış çocuklarda herpes zoster insidansı, doğal varisella enfeksiyonu yaşayan çocuklardan daha azdır (1,13). Aşılı hastalarda herpes zostere bağlı döküntüler daha çok lumbosacral dermatomda ve az sayıda görülürken, 10 yaş altı vahşi tip varisellaya bağlı zona enfeksiyonu daha çok torasik dermatomda gözlenir (13). Ülkemizde suçiçeği aşısı Ocak 2012 tarihinden itibaren doğan 12. aydaki çocuklara tek doz olarak yapılmakta olup bizim olgumuzun suçiçeği aşısı bulunmamaktaydı (14).

Herpes zoster genellikle bir veya daha az yaygın olarak iki veya üç komşu dermatom alanında lokalize veziküler lezyon olarak başlar. Etkilenen bölgede parestezi, yanma veya kaşıntı olabilir (10). Lezyonlar genellikle orta hattı geçmez (4). Klinik çocuk yaş grubunda erişkine göre genellikle daha hafif seyirlidir. Veziküller büllöz lezyonlar oluşturmak için birleşebilirler (10). Veziküler ve büllöz lezyonlar 7-10 gün içerisinde püstüler veya bazen de hemorajik hale gelebilir ve sonuçta krutlanır (10,15). Herpes zoster ilişkili iki tür ağrı tanımlanmış olup ilki duyusal nöronlarda VZV'ün reaktivasyonunun neden olduğu akut ağrıdır. İkincisi ise hastalığın akut fazı geçtikten sonra, genellikle iyileşmiş döküntü alanında gelişen postherpetik nevralji adı verilen ağrıdır. Çocuklarda postherpetik nevralji nadiren görünür (16). Bizim olgumuzda belirtiler sağ tragus cildinde birkaç adet veziküler döküntü ile başlamış olup 2 gün içerisinde sağ ağız köşesine kadar yayılmış, sırtta da orta hattı geçmeyecek şekilde veziküler döküntüler izlenmiştir. Ağrı ilk döküntü çıkmasının yedinci gününde şiddetlenmiştir.

Tanı için laboratuvar testleri genellikle gerekli değildir (4). Doğrudan floresan inceleme (FDA) tahlili kullanılarak cilt sıyrıklarında veya veziküllerde spesifik viral antijenlerin gösterilmesi ile teşhis gerekirse doğrulanabilir. Lezyonun polimeraz zincir reaksiyonu (PCR) ile viral DNA analizi, vahşi tip ile aşı tipini ayırt etmek için kullanılabilir (4). Belirgin klinik görünümü ve tipik ağrısı olması nedeniyle olgumuzda herhangi bir laboratuvar tanı testine gerek duyulmamıştır.

Sık görülen komplikasyonlar ikincil bakteriyel enfeksiyon, inflamasyon sonrası depigmentasyon ve skar gelişimidir (17,18). Herpes zoster oftalmik tutulumu şiddetli göz ağrısı, konjonktivit, retina nekrozu, oftalmoparezi / pleji, sklerokeratit, ön üveit ve optik nörite yol açabilir (4). Herpes zoster akut döneminden sonra düzelmeyen bir ağrı sürekliliğini temsil eden postherpetik nevralji, çocuklarda nadir görülür (15). Diğer nadir komplikasyonlar arasında Ramsay Hunt sendromu, Guillain-Barré sendromu, alt solunum yolu enfeksiyonu, aseptik menenjit, ensefalit, meningoensefalit, ventrikülit, miyelit, kraniyal ve periferik sinir parezi/pleji görülebilir (4,10,17,19). Bizim olgumuza da asiklovir tedavisinin 2. gününde gelişen ateşinin sekonder bakteriyel enfeksiyon kaynaklı olabileceği düşünüldüğünden antibiyotik tedavisi 7 gün süreyle verildi. Oftalmik tutulum düşündüren herhangi bir bulgu saptanmadı, izleminde postherpetik nevralji görülmedi.

İmmünkompetan çocuklarda herpes zoster çoğunlukla kendi kendini sınırlayan bir enfeksiyon olması nedeniyle antiviral tedavi tartışmalıdır, bununla birlikte asiklovir kullanımı cilt lezyonlarının daha hızlı iyileşmesinde ve akut ağrının giderilmesinde etkilidir (16). Immün sistemi baskılanmış yaygın hastalık riski taşıyan çocuklarda veya ciddi herpes zoster vakalarında intravenöz asiklovir tercih edilen tedavi yöntemidir (4,16). İdeal ilaç uygulaması döküntü başlangıcının ilk 72 saatidir (15). Nevralji önlenmesinde antiviraller, topikal analjezikler ve nonsteroid anti inflamatuar ilaçlar kullanılabilir (4). Bizim olgumuzda, hastanın şikayetinin bir haftadır olması ve döküntünün bu süreçte giderek yaygınlaşması ayrıca akut şiddetli ağrının gelişmesi nedeniyle asiklovir tedavisi intravenöz olarak 7 gün boyunca verildi. Nevralji için oral ve lokal analjezik tedavi uygulandı. Tedavi sonrası birinci hafta kontrolünde tüm lezyonlarda belirgin gerileme gözlendi.

Sonuç olarak sağlıklı çocuklar da herpes zoster enfeksiyonu geçirebilmekte olup, klasik

tutulum yerleri dışında atipik yerleşim görülebilmektedir. İmmunkompetan bireylerde hastalık genelde iyi seyirlidir ve komplikasyonsuz iyileşir. Hastamızda antiviral ve analjezik tedavi ile akut nörite bağlı ağrı azalmış olup; kutanöz lezyonlarda iyileşme görülmüştür.

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Derleme / Review

Organofosfatlı bir insektisit: Klorpirifos

An organophosphate insecticide: Chlorpyrifos

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Özet

Organofosfatlı bir insektisit olan klorpirifos tarımsal alanlarda üretimi ve verimliliği arttırmada, evlerde ve çeşitli kapalı alanlarda haşere ve patojenlerin kontrolünde en fazla tercih edilen geniş spektrumlu bir böcek öldürücüdür. Elde edilebilmesinin kolaylığı ve ucuz olması nedeniyle kontrolsüzce ve sıkça kullanılabilen klorpirifos, toprak, hava, gıda ve su gibi maruziyet yollarıyla vücuda girmekte ve hızla dağılarak özellikle yağ dokusu olmak üzere çeşitli doku ve organlarda birikmektedir. Klorpirifos insanların da dahil olduğu birçok hedef dışı organizmada toksisite sebebidir. Organofosfatların neden olduğu toksisitede semptomların görülme hızı ve etkinliği, organofosfata ne kadar süre ile ve hangi yolla maruz kalındığına, organofosfatın kimyasal yapısına bağlı olduğu gibi yıkım hızı ve metabolik aktivasyonda bu mekanizmada etkilidir. Klorpirifosun kolinerjik sinapslarda asetilkolinesterazın (AChE) geri dönüşümsüz inhibisyonuna bağlı nörotoksisiteyi içeren etki mekanizması, sinir sistemi üzerinde istenmeyen etkilere sebep olmaktadır. Klorpirifosun aktif metabolitleri olan 3,5,6-trikloro-2-piridinol (TCP) ve klorpirifos-oksonun yarılanma ömürlerinin klorpirifosa kıyasla daha uzun olması vücuttan atılım sürecini uzattığı için ciddi sağlık komplikasyonlarına yol açmaktadır. Klorpirifos toksisitesi nörolojik disfonksiyonlar, endokrin sistem hastalıkları ve kardiyovasküler hastalıklar ile ilişkilendirilmekle birlikte hematolojik maligniteleri, genotoksisiteyi, histopatolojik, gelişimsel ve davranışsal anomalileri ve oksidatif stresi de indükleyebilir. Ayrıca maruz kalmaya bağlı olarak göz tahrişi ve dermatolojik kusurlar da görülebilmektedir. Bu derleme, klorpirifos ile ilgili çalışmalar dikkate alınarak hazırlanmış olup klorpirifosun yapısı, klorpirifosa maruz kalma yolları, klorpirifosun toksik etkilerinin oluşum ve tespit edilebilme mekanizmaları konusunda bilgiler içermektedir.

Anahtar kelimeler: Klorpirifos; İnsektisit; AChE; Toksisite

Abstract

Chlorpyrifos, an organophosphate insecticide, increases production and productivity in agricultural areas, it is a broad spectrum insecticide most preferred in the control of pests and pathogens in homes and various indoor areas. Chlorpyrifos which can be used uncontrollably and frequently due to its ease of obtainment and cheapness, enters the body through exposure ways such as soil, air, food and water, and rapidly disperses and accumulates in various tissues and organs, especially in adipose tissue. Chlorpyrifos is a cause of toxicity in many non-target organisms, including humans. The rate and effectiveness of symptoms in toxicity caused by organophosphates depend on how long and in which way the organophosphate is exposed, the chemical structure of the organophosphate, as well as the rate of destruction and metabolic activation. The mechanism of action of chlorpyrifos, which includes neurotoxicity due to irreversible inhibition of acetylcholinesterase (AChE) at cholinergic synapses, causes undesirable effects on the nervous system. The longer half-lives compared to chlorpyrifos cause serious health complications as it prolongs the excretion process from the body. Although chlorpyrifos toxicity is associated with neurological dysfunctions, endocrine system diseases and cardiovascular diseases. It can also induce hematological malignancies, genotoxicity, histopathological, developmental and behavioral abnormalities, and oxidative stress. In addition, eye irritation and dermatological defects may occur due to exposure. This review has been prepared by taking into account the studies related to chlorpyrifos and includes information on the structure of chlorpyrifos the ways of exposure to chlorpyrifos the formation and detection mechanisms of the toxic effects of chlorpyrifos

Keywords: Chlorpyrifos; Insecticide; AChE; Toxicity

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1. Giriş

Pestisitler, uzun yıllardır tarım ürünlerinin işlenmesi, üretilmesi, depolanması ve pazarlanması süreçlerinde besin değeri ve verimliliğini azaltan ve pest olarak bilinen zararlı organizmaları ortadan kaldırmak, kontrol altında tutmak veya zararlarını azaltabilmek amacıyla kullanılan kimyasal madde ve bileşiklerdir. Pestisitler içindeki insektisitler grubunda organofosfatlar kimyasal özellikleri nedeniyle özel bir öneme sahiptirler. Organofosfatlı insektisitler, dünya çapında toplam insektisit kullanımının % 50'sinden fazlasını oluşturmaktadır (1). 2018-2023 yılları arasında dünya çapındaki organofosfat pazarının bileşik yıllık büyüme oranının % 5,5 olacağı tahmin etmektedir.

Geniş spektrumlu klorlu organofosfatlı insektisit olan klorpirifos, tarım alanlarında üretimi ve verimliliği arttırmada, ormancılık sektöründe çeşitli böcek ve patojenlerin kontrol edilmesinde, ev kullanımında ise haşerelerden korunmada dünya çapında en yaygın kullanılan organofosfatlı insektisitlerdendir. Klorpirifosun termitler, pireler, yaprak bitleri, böcekler, çene böcekleri, hamam böcekleri, kesici kurtlar, pire böcekleri, mısır deliciler, toprak kurtları, keneler, çekirgeler ve sivrisineklere karşı oldukça etkili olduğu bilinmektedir. Pamuk, tahıl (mısır, soya fasulyesi, buğday) ve sebze tarlalarında, fındık ve meyve bahçelerinde (elma, üzüm, şeftali ve narenciye ağaçları), çimen, çayırlık alan ve süs bitkilerinde böcek ilacı olarak hem gelişmiş hem de gelişmekte olan ülkelerde sıklıkla kullanılmaktadır (2-4). Düşük maliyet ve yüksek etki sebebiyle ülkemizde de geniş ölçüde kullanılan klorpirifosun aşırı ve gereksiz kullanımı hedef dışı organizmaların ölümü ve çevre kirliliği başta olmak üzere birçok olumsuzluğu da beraberinde getirmektedir. Klorpirifos, zararlıları kontrol etmede ve sonuç olarak mahsul verimini iyileştirmede etkili olmasına rağmen insan ve hayvan sağlığını riske edecek problemlere sebep olabilmektedir (Şekil 1). Yapılan araştırmalarda mesleki yolla, besin döngüsü yoluyla, kaza ya da intihar amaçlı maruz kalınan organofosfatların yılda ortalama 200.000 kişinin ölümüne ve yaklaşık 3 milyon kişinin zehirlenmesine neden olduğu bildirilmiştir (5).

2. Klorpirifosun Fiziksel ve Kimyasal Özellikleri

Klorpirifosun moleküler formülü C9H11Cl3NO3PS, molekül ağırlığı 350,59 g/mol, yoğunluğu 1,398 g/cm3, erime noktası 41,5–42,5ºC , kaynama noktası ise 160 0C'dir. Klorpirifos etil [O,O-dietil-O-(3,5,6-trikloro-2-piridil) fosforotiyonat] Dünya Sağlık Örgütü tarafından orta derecede toksik - (Sınıf II) insektisid olarak sınıflandırılmıştır ve LD50 değeri 82 - 270 mg / kg olarak belirlenmiştir (6). LD50, toksik maddenin test edilen populasyonun yarısını öldürmek için gereken dozdur ve maddenin akut toksisitesini göstermek için kullanılmaktadır. Literatür çalışmalarında erkek Wistar sıçan için belirlenen oral klorpirifos LD50 değeri 135 mg / kg'dır. Ancak bu değer farklı hayvan türlerine göre değişkenlik göstermektedir (7,8). Güncel literatüre göre, bu değer 66 ile 195 mg / kg vücut ağırlığı arasında değişkenlik göstermektedir (9). Klorpirifos piyasada Dursban, Lorsban, Equity, Suscon, Empire20 ve Whitmire PT270 gibi çeşitli ticari isimler altında, granül, toz ve emülsifiye konsantre formlarda satılmaktadır. Merkaptan benzeri (tiyol) kokuya sahip, renksiz, beyaz kristal toz olan klorpirifosun suda çözünürlüğü azdır (0.39 mg / L (19.5º C) ve 2 mg / L (25º C) ancak mısır yağı, benzen, dimetil sülfoksit, metanol, aseton, ksilen, metilen klorür ve Tween 20'de kolaylıkla çözünür. Klorprifos etil, nötral ve asidik ortamlarda kararlıdır fakat pH'ın yükseldiği ortamlarda kararlılığı azalır (10).

3. Klorpirifosun Etki Mekanizması

Klorpirifos etkisini organofosfatlı pestisitlerin tespit edilmesinde standart bir biyolojik belirteç olarak kabul edilen AChE enziminin inhibisyonu üzerinden gösterir. Nöronlardan gelen sinyallerinin iskelet kaslarına, düz kaslara, otonom sinir düğümlerine, salgı bezlerine, merkezi sinir sistemine iletiminin düzgün sağlanmasında önemli görevleri olan AChE, bir nörotransmitter olan asetilkolini kolin ve asetik asite çevirerek parçalayarak

aynı zamanda asetilkolinin miktarını da düzenler (11,12). (Şekil 2) (13). AChE'nin aktif bölgesinde yer alan serin aminoasitine fosfat bağıyla bağlanan klorpirifos, geri dönüşümsüz bir inhibisyona neden olur (14). Yağda çözünen (lipofilik) yapıda olan klorpirifos kan-beyin bariyerini rahatlıkla geçer ve okson metabolitleri aracılığı ile beyinde kolinerjik sinapslarda AChE inhibisyonuna neden olarak etkisini gösterir (15). Klorpirifos gibi birçok organofosfatlı insektisitin yapısında fosfora çift bağlı sülfür atomu vardır. Toksik hale gelmeleri için metabolik aktivasyon ile oksonlara dönüşmeleri, yani yapılarındaki P=S grubunun P=O grubuna dönüşmesi gerekir. Çünkü yalnızca yapısında P=O grubu bulunan organik fosforlu bileşikler AChE'ı baskılayabilir. Klorpirifos vücuda alındıktan sonra, oksidatif desülfürasyon yoluyla oksona metabolize edilir. Klorpirifosun oksijen ile bağlanması sonucu karaciğerde okson formuna dönüşmüş olan aktif metabolit klorpirifos-oksondur. Klorpirifosun biyotransformasyonu sitokrom P450 (CYP450) ve karaciğerin mikrozomal membranlarında yer alan ilgili enzimler aracılığıyla katalizlenir. Klorpirifosun toksik metabolitleri klorpirifos-okson, TCP ve dietiltiofosfat (DETP), CYP450 aracılığıyla gerçekleşen oksidatif desülfürasyon ve dearilasyon reaksiyonları sonucunda sırasıyla oluşur. Klorpirifosun biyoaktivasyonunun büyük kısmı karaciğerde, detoksifikasyonu ise hem karaciğer hem de plazmada gerçekleşir (16-18). Klorpirifosun vücuttaki kalıcılığı az olduğundan TCP, DETP ve dietilfosfat (DEP) gibi klorpirifos metabolitleri, kanda veya idrarda biyolojik belirteç olarak işlev görür. Bu metabolitlerin ölçümleri klorpirifos emiliminin in vivo değerlendirilmesine yardımcı olur. İnsektisitler nörotoksisitelerini, hedeflenen organizmanın sinir sisteminde yer alan sodyum, potasyum ve klor iyonları ile ilişkili membran transportuna, özgün enzimlere veya sinir uçlarında yer alan nörotransmitterlere müdahale ederek gösterirler.

Enzim inhibisyonu sonucu otonom ve merkezi sinir sistemlerinde, sinir-kas kavşağında, asetilkolinin birikmesi presinaptik, nikotinik ve muskarinik reseptörlerin aşırı uyarılması ile düz kaslarda kasılmaya ve salgı bezlerinden yüksek miktarlarda salgı üretilmesine neden olur. Açığa çıkan bu aşırı uyarıyı kolinerjik sinaptik iletim felci takip eder ve bu durum kolinerjik sendrom ya da kolinerjik kriz olarak nitelendirilir (12-14). Organofosfatlı insektisitlerin toksisite mekanizmaları ile hedeflediği organlar tüm organizmalarda hemen hemen aynıdır, ancak ortaya çıkan toksik etkinin şiddeti büyük oranda doza bağlıdır. AChE enziminin tekrar etkinlik gösterebilmesi için vücut içerisinde tekrardan üretilebilmesi yada oksim türü maddelerin kullanımı ile tekrar etkili hale getirilmesi gerekmektedir. Bir maddenin kan-beyin bariyerini geçme derecesi yağdaki çözünürlüğüne, serum proteinlerine bağlanma affinitesine, yüküne ve molekül ağırlığına bağlıdır. Maddenin lipofilik özelliği ne kadar fazlaysa kan-beyin bariyerinden geçişi de o kadar hızlı olur. Bunun nedeni, klorpirifos gibi nörotoksik etkisi olduğu bilinen lipofilik maddelerin, endotel hücrelerinin lipit membranlarında çabuk çözülmesi ve beyne basit difüzyon ile girmesidir (19). Timchalk ve ark. (2002) mısır yağı içinde çözdürülerek hayvan modellerine uygulanan klorpirifosun absorpsiyon seviyelerini % 80'lere çıkardığını bildirmiştir (20). Organofosfatlı bileşikler vücuda girdikten sonra hızlıca dağılarak yağ dokusu başta olmak üzere karaciğer ve böbrek dokularında birikirler. Oral yoldan klorpirifos uygulanan sıçanların yağ dokularında diğer dokulara kıyasla fazla miktarda klorpirifos birikimi tespit edilmiştir (21,22). Eaton ve ark. (2008), vücut ağırlığı başına 50 mg klorpirifosun oral yolla uygulanmasının ardından 3 saat içinde gerçekleştirdikleri ölçümlerinde klorpirifos metabolitleri olan DEP, DETP ve TCP'nin kandaki seviyelerinin en yüksek değerde olduğunu ortaya koymuşlardır (4). Kısırlık problemi olan 322 erkeğin idrar örnekleri ile gerçekleştirilen başka bir çalışmada idrarda TCP artarken östradiol düzeylerinde doza bağlı bir azalma korelasyonu elde edilmiştir (23). Klorpirifosun ana metaboliti, idrarla atılan ve üriner klorpirifos metabolitlerinin varlığını artırabilen TCP dir. Sıçanlarda tek geçişli bağırsak perfüzyon yöntemi kullanılarak klorpirifosun asimilasyonunu araştıran çalışmada klorpirifos emiliminin ince bağırsağın tamamında gerçekleştiği ve

uygulanan klorpirifosun neredeyse % 99'unun emildiği görülmüştür. Klorpirifos en çok karaciğer ve böbrekte birikmektedir ve oral maruziyeti takiben, çoğu memelide klorpirifos boşaltımının ana yolu idrardır (4).

4. Klorpirifosa Maruz Kalma Yolları

Klorpirifos kalıntıları omurgalılardan omurgasızlara kadar neredeyse tüm canlı organizmalarda tespit edilebilen geniş bir bant etkisine sahiptir. İnsanlar ve hayvanlar klorpirifosa çevresel, oral, dermal ve inhalasyon yolları başta olmak üzere çeşitli yollarla maruz kalabilirler (4, 24). Klorpirifosun bulaş yolu ve/veya ne kadar dozda alındığı vücuttaki etkinliğinde ve emiliminde belirleyicidir. Pestisitlerin çoğunlukla püskürtme yoluyla uygulanması sırasında bir miktarı yapraklara, bitki yüzeyine ve toprağa kadar ulaşıp bağlanarak toprak yapısının bozulmasına ve burada yaşayan canlıların olumsuz şekilde etkilenmesine sebep olur. Kalan kısmı ise dağılma ve buharlaşma nedeniyle kaybolur (25). Sudaki çözünürlüğü 20-25 ° C'de 0,7 ila 2,0 mg/L olan pestisitler, akarsulara ve yer altı sularına, yağışlar ve sızıntı kanalları aracılığıyla karışabilirler. Bu karışma sonunda sucul ortama girerek, denizde yaşayan canlılarının zehirlenmesine ve ölümüne neden olmakla kalmayıp içme suyu kaynaklarını da kirletebilirler. Kuşlar, arılar, balıklar çeşitli mikroorganizmalar ile omurgasızlar gibi hedef dışı organizmaların üreme dengelerinde bozulmaya ve hatta ölümüne neden olabilirler. Pestisitler doğrudan toprağa uygulanma sonrasında, topraktan buharlaşma yoluyla veya rüzgâr aracılığıyla atmosfere girer ve sonrasında su aracılığıyla yeraltına ulaşır. Hava aracılığıyla uzun mesafeler boyunca taşınabilir ve atmosfere giren pestisitler yağmur, sis ya da kar şeklinde yeniden yeryüzüne dönebilirler (26). Bu hidrolojik döngü sürekli olarak devam eder (Şekil 3) (27).

Çiçek yetiştiricileri, tarımsal çiftlik işçileri, fümigatörler veya pestisit uygulayıcıları, mesleki veya işyeri maruziyeti sebebiyle klorpirifosa yüksek oranda ve yaygın olarak maruz kalırlar. Öte yandan klorpirifosa eser düzeyde maruz kalanlar, mesleki maruziyet dışındaki vakaların birincil kaynağını oluşturmaktadır. Bolognesi (2003), maruziyet süresi ve pestisit konsantrasyonunun yanı sıra kişisel koruyucu ekipman kullanımının / kullanılmamasının da maruziyet sonuçlarını etkilediği sonucuna varmıştır (28). Diyet yoluyla maruz kalma, klorpirifosun mahsul uygulamalarından sonra, gıda maddeleri üzerindeki ayrışmamış formunun ya da TCP gibi artık formlardaki kalıntılarının vücuda alınması ile gerçekleşir (29). Bu durum, kaçınılmaz olarak, insanları ve hayvanları, tam tahıllı gıdalarda bulunan veya çeşitli işlenmiş gıda ürünlerinde görülen klorpirifos izlerine maruz bırakabilir. Mesleki maruziyet dışında klorpirifosa maruz kalmanın en önemli nedeni diyettir ve bu gerek bitkilerle gerekse çiftlik hayvanlarıyla beslenme ile gerçekleşmektedir. Klorpirifosa maruz kalmış bireylerin idrarlarındaki % 50'lik TCP artışı, temel gıda maddelerindeki klorpirifos varlığı ile açıklanabilir. Al-Badrany ve ark. (2007), civciv modellemesi (7-15 gün) ile gerçekleştirdikleri çalışmalarında klorpirifosun oral uygulamasının etkilerini yedi gün boyunca incelemişlerdir (30). 5 mg / kg, 10 mg / kg ve 20 mg / kg oral klorpirifos uygulamasından 2 saat sonra plazma (% 40-70), karaciğer (% 31-46) ve beyinde (% 43-69) klorpirifosa bağlı kolinerjik toksisitenin geliştiğini ve klorpirifosun bu dokuların işlevselliklerini önemli ölçüde düşürdüğünü ortaya koymuşlardır. Düşük klorpirifos dozlarının (2 mg / kg, 4 mg / kg) ise lokomotor aktivitede azalmaya sebep olduğu ancak anlamlı toksisite belirtilerine yol açmadığı kaydedilmiştir. Dermal yolla maruz kalma olasılığı ve etkinliği, oral veya inhalasyon yollarıyla karşılaştırıldığında daha azdır. Nolan ve ark. (1984), oral klorpirifos dozundan sonra, idrarda %70 oranında TCP ölçerken dermal maruziyetten sonra idrarda tespit ettikleri TCP değerinin yalnızca % 1 olduğunu açıklamışlardır (31). Bu sonuç, klorpirifosun dermiste yer alan keratinize tabakalar sebebiyle dermal yolla çok iyi absorbe edilemediğini, ancak ağız yoluyla alındığında hızla asimile edildiğini açıklayan önemli bir bulgudur. Griffin ve ark. (1999) oral yolla klorpirifosun % 100'ünün dermal yolla ise metabolitlerinin % 1'nin absorbe edildiğini bildirmişlerdir (32). Kimyasal toksisite için önemli bir yol olan dermal

maruziyetin etkisi temas edilen cilt alanına ve maruz kalma süresine bağlıdır. Klorpirifosun dermal eliminasyon fazının oral eliminasyon fazına kıyasla yaklaşık 2 kat yarılanma ömrüne sahip olmasının sebebi olarak olası lipofilisite ve zaman fazları gösterilmektedir. Meuling ve ark. (2005), gönüllülerin kollarına 5 veya 15 mg klorpirifos uygulayarak gerçekleştirdikleri çalışmalarında uygulama dozunun % 42-67'sinin emilemediğini ve 4,3-5 mg TCP'nin de idrarla atıldığını ortaya koymuşlardır. Böylece emilen tüm dozun idrarla atılmayacağını bildirmişlerdir (33). Soluma yoluyla gerçekleşen maruziyetin semptomları, oral ve dermal absorpsiyona kıyasla daha hızlı ortaya çıkar. Birçok ülkede klorprifosun ev ortamında kullanımı yasaklandığından, inhalasyon maruziyeti çoğunlukla sürüklenmenin bir sonucu olarak, tarımsal alanlarda (mesleki) ve/veya kırsal konutlarda kullanımından kaynaklanmaktadır. Bu nedenle mevcut çalışmaların çoğu, mesleki maruziyete odaklanarak yalnızca çiftlik işçilerinde ve pestisit uygulayıcılarında gerçekleştirilmektedir. Sprague Dawley sıçanlarında klorpirifos maruziyetine ilişkin kısa süreli gerçekleştirilen araştırma çalışmaları, 3 ila 5300 mg / m3 arasında değişen konsantrasyonları içermektedir. 4 saat boyunca uygulanan 5300 mg / m3'lük klorpirifos dozunun, çalışma grubunun % 80'i için ölümcül olduğunu kanıtlanmıştır (4). Diyetle alınan ürünler miktarı çok düşük de olsa bir veya birden fazla pestisit kalıntısı içerebilmekte ve bu pestisitlerin kalıntıları nedeniyle oluşan toksisite ciddi sağlık sorunlarına sebep olmaktadır. Birçok gelişmiş ülke pestisitlerin bıraktığı kalıntı değerlerinin tespit ve tayini için gıda analizlerinin yapılmasının gerekliliğini ifade etmektedir.

Kalıntı değerleri kabul edilebilir günlük miktar (ADI) olarak ifade edilen toksisite kriterleri ya da maksimum kalıntı limitleri (MRL) olarak isimlendirilen ticari standartlar ile karşılaştırılarak değerlendirilir. ADI toksisite ölçüsü iken, MRL tüm dünyada kaliteli ve sağlıklı gıda ticareti kontrolünün yapılabilmesi için hem ulusal hem de uluslararası birimlerce oluşturulmuş bir standarttır. Birçok gelişmiş ülkede olduğu gibi bizim ülkemizde de tarımsal ürünlerde bulunmasına izin verilen maksimum pestisit miktarları, Gıda, Tarım ve Hayvancılık Bakanlığı tarafından ilaç ve ürün bazında belirlenmektir. Klorpirifos kalıntıları, kan veya idrar TCP, DETP veya DEP seviyelerinin ölçümleriyle belirlenebilir. Klorpirifosun başlıca reaktif metaboliti olan klorpirifos-okson organizmalar için nispeten daha toksiktir (34). Klorpirifosun toprak stabilitesi birkaç günden 4 yıla kadar değişmektedir ve bu kararlılık durumu çevresel faktörlerin yanı sıra toprağın yapısına da bağlıdır. Su ekosisteminde klorpirifosun parçalanmasına karşı oluşan kararlılık durumu topraktakine kıyasla daha fazla olduğu için su ortamında klorpirifosun kalıcılığı da fazladır.

5. Klorpirifos Toksisitesi ve Tanı

Klorpirifos gibi organofosfatların toksisitesinde semptomların görülme hızı ve göstereceği etki, hangi organofosfata maruz kalındığına dolayısıyla kimyasal yapısına bağlıdır. Ayrıca toksisite, organofosfata maruz kalma süresi ve hangi yollarla maruz kalındığına bağlı olarak hangi metabolik yolu izleyebileceği ve yıkım mekanizmaları gibi diğer birçok faktörle de ilişkilidir (11). İlk klinik bulgular genellikle organofosfatlı bileşiğe maruz kalındıktan sonra 30 dakika ile 3 saat arasında görülür. Organofosfat bileşiğinin ağız yoluyla yüksek miktarda alımında ise semptomlar 5 dakika gibi kısa bir sürede ortaya çıkarken, 15 dakika sonrasında ölüm gerçekleşebilir. Dermal yolla organofosfat bileşiğine az miktarda maruz kalınması ölümcül bir tehlike yaratmazken basit belirtilerin görülmesine neden olabilir (35). Organofosfatlı insektisitler lipofilik özelliktedirler ve bundan dolayı kolaylıkla kan-beyin bariyerini geçerler (36). Klorpirifos gibi organofosfat bileşiklerinin yağ dokusunda birikmesi ve sonrasında tekrar dolaşıma geçmesi, toksisite semptomlarının gecikmesine, sistemik etki süresinin uzamasına ve hatta iyileşme sonrası klinik bulguların nüksetmesine neden olabilir. Bu nedenle, klorpirifostan farklı olarak yağda çözünmeyen organofosfatlı bileşiklere maruz kalınılan durumlarda semptomlar yaklaşık 12 saatlik bir süre içerisinde ortaya çıkmaya başlarken klorpirifos gibi yağda çözünen bileşikler için bu süre herhangi bir etkiye neden olmayabilir (37). Organofosfat nedenli

zehirlenmelerde oldukça önemli olan klinik bulgular nukotinik, muskarinik ve merkezi sinir sistemi bulguları olarak 3 farklı kategoride sınıflandırılır (38, 39) (Tablo 1).

Tablo 1. Organofosfat zehirlenmesine bağlı klinik bulgular

Nukotinik Bulgular	Muskarinik Bulgular	Merkezi Sinir Sistemi Bulguları
Solgunluk	Aşırı terleme	Uykusuzluk
Konuşma bozukluğu	Tükürük artışı	Halusinasyon
Hipertansiyon	Burun akıntısı	Anksiyete
Göz bebeklerinde büyüme	Göz yaşarması	Titreme
Kas zayıflığı	Bronş salgısında artma	Mental konfüzyon
Kas krampları	Brokospazm	Emosyonel labilite
Kas seyirmeleri	Karın ağrısı	Baş ağrısı
Solunumun baskılanması	Kusma	Baş dönmesi
Taşikardi	Bradikardi	Deliryum
Paralizi	İdrar kaçırma - İshal	Koma - Nöbet

İlk olarak anamnez alınması, toksisiste kaynaklı kolinerjik belirtilerin görülmesi, nefes ve varsa kusmukta hidrokarbon ya da sarımsak benzeri bir kokunun tespiti tanı koymada klinik bulgulara ek olarak değerlendirilen başlıca kriterlerdir. Zehirlenmenin tespit edilmesinden sonra, maruz kalınan pestisitin belirlenmesi ve pesitisite ait kutu veya şişenin temini, antidotlara ulaşmada ve tedavi sürecini hızlandırmada büyük kolaylık sağlar (22,40). Ancak insektisit ve kolinesteraz inhibitörlerinin tamamı organofosfat olmadığından bu kriterler her zaman için çok güvenilir değildir. Bu nedenle laboratuvar ölçümleri ile klinik bulgulara her zaman ihtiyaç vardır. Dokularda organofosfat ve metabolitlerini ölçülebilmek için gerekli olan ölçümleri yapan laboratuvar sayısının az olması, ölçüm yapılabilse bile sonuçların geç çıkması ayrıca birçok organofosfat bileşiğinin toksik referans aralığının bilinmemesi gibi dezavantajlar söz konusudur. Alternatif bir diğer test yöntemi doku AChE enzim düzeyinin ölçümüdür.

Bu biyopsi gerektiren cerrahi bir yöntem olması sebebiyle oldukça zahmetlidir. Ölçüm sonucunun değerlendirilebilmesi için kişinin bazal AChE düzeyinin bilinmesi gerekir ve bu durum pek mümkün değildir. Midtling ve ark. (1985), orta ya da ciddi düzeyde zehirlenme bulguları olan hastaların AChE düzeylerinin değerlendirilmesinde laboratuvar referans aralığı kriter olarak alındığında AChE aktivite sonuçlarının normal sınırlar içinde olduğunu ancak hastaların kendi bazal durumuna göre değerlendirildiğinde ise bu aktivitelerin yarı yarıya azalmış olduğunu göstermişlerdir (41).

Serum ve eritrosit AChE ölçümleri pratikte en yaygın kullanılan yöntemlerdir. Eritrosit AChE iskelet kası ve sinir dokusunda bulunduğu için ölçüm sonucu periferik dokudaki, beyindeki ve kastaki AChE enzim aktivitesini de yansıtır. Ancak eritrosit AChE ölçümleri organofosfat zehirlenmelerinin tespitinde daha spesifik olsa da ölçüm kolaylığı ve ulaşılabilir olması sebebiyle serum AChE ölçümleri daha çok tercih edilmektedir (42). Popülasyonda Serum AChE aktivitesi bireysel farklılıklar gösterdiğinden yapılan tedavi sonucu verilen cevabın değerlendirilmesinde bir referans aralığı yerine azalan veya artan serum AChE aktivitesinin tespit edilmesinin daha doğru olduğu kabul edilmektedir (40). Klinik olarak AChE aktivitesinin azalması yönündeki değişiklikler önemlidir. Maruz kalınan maddenin antikolinesteraz özelliğinin olduğunu kanıtlar ve onun inhibisyon derecesi hakkında fikir verir. AChE aktivite değerinin hafif şiddetli zehirlenmelerde %20 ile %50 arasında, orta şiddetli zehirlenmelerde %10-20, şiddetli zehirlenmelerde ise %10'un altına düşüyor olması tanı koyma açısından önem arz eder. AChE referans değerlerinin laboratuvarlar arasında farklılık göstermesi durumunda yalancı negatif sonuçlar ortaya çıkabilmektedir (42). Organofosfat toksisitesi şüphesi ile başvuran hastalara ilk olarak yapılan rutin kan tetkiklerine ek olarak

elektromiyografi ve elektrokardiyografi ölçümleri ile beraberinde posteroanterior akciğer grafisi çekilmelidir. Elektromiyografi'de erken dönemde saptanan tekrarlı potansiyel ile fasikülasyonlar tanıyı desteklemektedir. Pulmoner ödem elimine edilerek ve elektrokardiyografi sonucu dikkatle değerlendirilmelidir (22).

6. Sonuç

Bir organofosfat olan klorpirifos, gıda mahsullerinde, evlerde ve işyerlerinde böcek zararlılarının imhası için dünya çapında en yaygın kullanılan pestisitlerden biridir. Klorpirifos kullanımı 1960'larda zirveye ulaşmıştır ve 1974 ile 2005 yılları arasında klorpirifos nedeniyle zehirlendiği kaydedilen yaklaşık 278 vaka olmuştur. Genotoksisite, immünotoksisite, sitotoksisite, oksidatif stres, nörotoksisite ve mutajenite gibi toksik etkileri göz önüne alındığında, bazı ülkelerde klorpirifosun yasaklanması durumları doğmuştur. EPA, 2011 yılında kapsamlı bir insan sağlığı risk değerlendirmesi gerçekleştirmiş, 2014 ve 2016'da revize etmiş ve nihayetinde 2018'de klorpirifos kullanımının yasaklanmasına ilişkin ABD mahkemesinden karar çıkartmıştır. Kalıntı formdaki kalıcılığı ve etkinliği nedeniyle gelişmekte olan ülkelerde kullanımı halen büyük ölçekte devam etmekte olan bu insektisitin gıda ve sağlık güvenliği açısından yeniden değerlendirilmesi ve düzenlenmesi gerekmektedir. Dünya nüfusunun giderek artıyor olması ve kullanılabilir tarım alanlarının azalması nedeniyle, pestisit kullanımı olmadan tarım ekonomisini sürdürmek ve nüfusunun yeterli beslenmesini sağlamak gittikçe imkansız hale gelmektedir. Bir yandan nüfus artışı ve ihtiyaçları temin etmek adına yapılan girişimler, diğer yandan teknolojik ve endüstriyel alandaki gelişmeler havada, toprakta ve suda kirliliğin artışına yol açmaktadır. Gıdalardaki klorpirifos konsantrasyonlarının azaltılmasında etkili işlemlerin geliştirilmesi oldukça önemlidir. Bu amaçla gıdalardaki kalıntı miktarının kısa sürede tespit edilebilmesini sağlayabilecek sensör mekanizmalarının geliştirilmesi ve kullanılması büyük bir gereklilik olarak görülmektedir. Pestisit kaynaklı sağlık sorunlarının üstesinden gelebilmek ve toksisiteyi önleyebilmek adına gerçekleştirilen çalışmalar insan sağlığı başta olmak üzere birçok canlı için önem arz etmektedir klorpirifosun diğer organofosfat pestisitlerine göre avantajlı kullanımının desteklenebilmesi için potansiyel toksisitesi ve güvenliği hakkındaki tüm soru işaretlerinin giderilmesi gerekmektedir. Bunun için uygun kantitatif testler ile gerçekleştirilmiş yeterli sayıda hayvan deneyleri ve ileriye dönük insan çalışmalarına ihtiyaç duyulmaktadır.

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