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CONTENTS

ORIGINAL ARTICLES

CASE REPORT

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CONTENTS

INDEX

ORIGINAL ARTICLE

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The Relationship Between Chest Computed Tomography Severity Scores and Demographic Features, Laboratory Parameters and Mortality in Patients with COVID-19

COVID-19'lu Hastaların Toraks Bilgisayarlı Tomografi Şiddet Skorları ile Demografik Özellikleri, Laboratuvar Parametreleri ve Mortaliteleri Arasındaki İlişki

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ABSTRACT

Aim: We aimed to investigate the relationship between chest computed tomography-severity score (CT-SS) and demographic and laboratory findings and mortality in Coronavirus disease-2019 (COVID-19) patients.

Materials and Methods: Our study was a single-center retrospective analysis of 162 patients (aged ≥18 years) with COVID-19. We included laboratory-confirmed COVID-19 patients between October 2020 and April 2021. Chest CT imagings, laboratory findings, and demographic data were collected at admission. CT-SS was calculated using a visual semi-quantitative scoring system (total score 0-25). We divided the patients into three subgroups based on chest CT-SS, as mild (0-7), moderate (8-17) and severe (>18).

Results: The mild group consisted of 91 patients (56.2%) with a median CT-SS value of 2 [interquartile range (IQR) 0-5], the moderate group consisted of 65 patients (40.1%) with a median CT-SS value of 11 (IQR 9-12), and the severe group was composed of 6 patients (3.7%) with a median CT-SS value of 19.5 (IQR 18-24). We found statistically significant relationships between high CT-SS and lymphocytopenia (p=0.001), increased C-reactive protein (p<0.001), procalcitonin (p<0.001), lactate dehydrogenase (p<0.001), serum creatinine (p<0.001), D-dimer (p<0.001), prolonged prothrombin time levels (p=0.006), history of chronic obstructive pulmonary disease (p=0.014), chronic renal disease (p=0.001), and cerebrovascular disease (p=0.029) in chi-square test. In addition, high CT-SS was statistically correlated with high mortality risk (p<0.001).

Conclusion: There was a relationship between high CT-SS and high mortality, inflammatory and anticoagulant laboratory markers, and some comorbidities in COVID-19 patients. Evaluation of CT-SSs and risk factors of demographic characteristics and laboratory findings provide useful prognostic information about the survival of COVID-19 patients.

Keywords: COVID-19, computed tomography, pneumonia, mortality

ÖZ

Amaç: Çalışmamızda Koronavirüs hastalığı-2019 (COVID-19) hastalarında toraks bilgisayarlı tomografi-şiddet skoru (BT-ŞS) ile demografik ve laboratuvar verileri ve ölüm oranları arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmamız, COVID-19'lu 162 hastanın (≥18 yıl) tek merkezli retrospektif analiziydi. Ekim 2020 ile Nisan 2021 arasında laboratuvarca doğrulanmış COVID-19 hastaları çalışmaya dahil edildi. Başvuru sırasındaki toraks BT görüntülemeleri, laboratuvar bulguları ve demografik verileri toplandı. BT şiddet skoru, görsel bir yarı nicel puanlama sistemi kullanılarak hesaplandı (toplam skor 0-25). Hastalar toraks BT-ŞS'sine göre üç alt gruba ayrıldı; hafif (0-7), orta (8-17) ve şiddetli (>18).

Bulgular: Ortanca BT-ŞS değeri 2 [çeyrekler arası aralık (IQR) 0-5] olan 91 hasta hafif grubu (%56,2), ortanca BT-ŞS değeri 11 (IQR 9-12) olan 65 hasta (%40,1) orta grubu ve ortanca BT-ŞS değeri 19,5 (IQR 18-24) olan 6 hasta (%3,7) şiddetli grubu oluşturdu. Bu çalışmada, ki-kare testinde yüksek BT-ŞS ile lenfositopeni (p=0,001), artmış C-reaktif protein (p<0,001), prokalsitonin (p<0,001), laktat dehidrogenaz (p<0,001), serum kreatinin

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(p<0,001), D-dimer düzeyleri (p<0,001), uzamış protrombin zamanı düzeyleri (p=0,006), kronik obstrüktif akciğer hastalığı (p=0,014), kronik böbrek hastalığı (p=0,001) ve serebrovasküler hastalık (p=0,029) öyküsü arasında istatistiksel olarak anlamlı ilişkiler bulundu. Ayrıca yüksek BT-ŞS, yüksek mortalite riski ile istatistiksel olarak ilişkiliydi (p<0,001).

Sonuç: COVID-19 hastalarında yüksek toraks BT-ŞS ile yüksek mortalite, enflamatuvar ve antikoagülan laboratuvar belirteçleri ve bazı komorbiditeler arasında bir ilişki vardı. BT şiddet skorlarının, demografik özelliklerin ve laboratuvar bulgularının risk faktörlerinin değerlendirilmesi, COVID-19 hastalarının sağkalımı hakkında yararlı prognostik bilgiler sağlamaktadır.

Anahtar Kelimeler: COVID-19, bilgisayarlı tomografi, pnömoni, mortalite

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is an infectious disease caused by Severe acute respiratory syndrome-Coronavirus-2, which was firstly reported in Wuhan, China[1]. Most COVID-19 patients have a good prognosis and mild symptoms. However, in some patients, severe pneumonia, pulmonary edema, Acute respiratory distress syndrome (ARDS), multiple organ failure, and death were observed[2].

A specific viral nucleic acid test, real-time reverse transcriptase-polymerase chain reaction (RT-PCR) used for the diagnosis of COVID-19, was rapidly produced[3]. The RT-PCR test is standard for the diagnosis of COVID-19 but may give a false-negative result in some cases. False-negative RT-PCR results may depend on the early stages of the disease, possibly due to insufficient viral specimens in the sample or technical problems during nucleic acid extraction[4,5]. Based on past clinical information, chest computed tomography (CT) imaging can show abnormalities before RT-PCR testing. Currently, high-resolution CT has become one of the main screening methods for diagnosing and evaluating disease severity[6]. The typical chest CT findings in COVID-19 pneumonia are bilateral, peripheral, and basal predominant ground-glass opacities (GGOs) with or without consolidation and bronchovascular thickening[7].

In our study, the severity of lung involvement was visually scored according to the method proposed by Pan et al.[8]. We purposed to investigate the correlation between chest CT-severity score (SS) and age, gender, comorbidities, laboratory findings, and mortality in patients with COVID-19. As a result of our study, we aimed to detect high-risk COVID-19 patients who would require intensive treatment and might provide a risk stratification model for such patients.

MATERIALS AND METHODS

This study was approved by the Ethical Committee of Kanuni Training and Research Hospital and by the Ministry of Health of the Republic of Turkey and it was conducted according to the Declaration of Helsinki and Good Clinical Practice (date: 12.11.2020, no: 2020/68), and the requirement for informed consent was waived.

Study Population and Data Collection

Our study was a single-center retrospective analysis conducted on an original cohort of 162 patients with COVID-19, who underwent chest CT scans in the Radiology Department of Kanuni Training and Research Hospital between October 2020 and April 2021. We included only laboratory-confirmed patients determined by positive RT-PCR in samples acquired from oropharyngeal and nasopharyngeal sites in accordance with the World Health Organization interim guidelines. RT-PCR tests were repeated in patients with a high clinic and radiologic suspicion of COVID-19 when the initial PCR test was negative. We excluded the patients under 18 years of age or who had no chest CT scan.

We collected the data for retrospective analysis including demographic characteristics, comorbidities, laboratory findings, and chest CT imaging obtained at the time of admission. Chest CTs were performed on patients with fever, dry cough, respiratory distress, abnormal laboratory findings, and positive PCR test results. Chest CT scans of all patients were performed within 24 hours at the latest after admission to the hospital.

All patients underwent blood tests including complete blood count, kidney and liver function tests, troponin, D-dimer, prothrombin time (PT), and partial thromboplastin time (PTT), international normalized ratio (INR), C-reactive protein (CRP) and procalcitonin. We analyzed the laboratory results at the time of admission to the hospital.

CT Protocol

All patients underwent chest CT examinations on two multidetector CT scanners (16-slice Somatom Sensation; Siemens Healthineers or 128-slice GE Healthcare Computed Tomography Revolution EVO System). The non-contrast scans were performed with the following parameters: tube voltage=120 kV; tube current=70-280 automatic milliamperes; helical pitch=1.375; slice thickness=5 mm and interval=5 mm (128- slice GE Healthcare Computed Tomography Revolution EVO System) or tube voltage=130 kV; tube current=70-114 automatic milliamperes; helical pitch=1; slice thickness=5 mm and interval=5 mm (16- slice Somatom Sensation; Siemens

Healthineers). Images were reconstructed with a 1.25 mm slice thickness. All chest CT scans were assessed at a lung window of 1200 WW and -600 WL and a mediastinal window of 400 WW and 40 WL.

Image Analysis

A radiologist with more than 14 years of experience in chest CT imaging performed the CT image analysis in a standard clinical picture archiving and diagnostic system (PACS) workstation, blinded to the clinical data and laboratory indicators. The involvement of each pulmonary lobe was recorded and the 25 Point CT severity scores were calculated by using a semi-quantitative CT severity scoring system visually[8-10]. This scoring system depends on visual evaluation of pulmonary involvement based on the area in each of 5 lobes. Each lobe was scored from 0 to 5 as: 0, no involvement; 1, <5% involvement; 2, 25% involvement; 3, 26-49% involvement; 4, 50-75% involvement; 5, >75% involvement. Then, the total CT score was calculated by the sum of the CT scores of 5 lobes ranging from 0 (none) to 25 (maximum). Considering pulmonary involvement, we divided the COVID-19 patients into three subgroups based on the chest CT score, as mild (total severity score of less than 7), moderate (total severity score of 8-17) (Figure 1), or severe (18 and more), which was used by Saeed et al.[9].

Statistical Analysis

The study sample size was determined as 122 using the G-power program by taking impact size 0.30, α=0.05, power (1-β)=0.85 at a confidence level. A total of 162 were reached. Statistical analyses were performed by using IBM Statistical Package for the Social Sciences Statistics for Windows, version 25.0 (IBM Corp. Released 2017. Armonk, NY). Categorical variables were defined as frequency and percentage; continuous variables were defined as the mean±standard deviation or median [interquartile range (IQR)]. The conformity of the variables to the normal distribution was examined using the Kolmogorov-Smirnov. The Kruskal-Wallis and Mann-Whitney U tests were employed to compare the non-normally distributed variables according to the CT-SS groups. The chi-square test was used to determine the relationship between CT-SS groups and laboratory and demographic characteristics. The Fisher's test was used when the values displayed in the cells did not meet the assumptions of the chi-square test. The statistical significance level was accepted as 0.05 in the study.

RESULTS

Demographic Features

A total of 162 patients, including 69 male (42.6%) and 93 female (57.4%), were enrolled in the study. The mean age of total patients was 54.3±17.29 (ranging from 18 to 97) years. The most affected age group was the 61-70-year age group (37 patients; 22.8%) followed by the 51–60-year age group (35 patients; 21.6%), then the 41-50-year age group (28 patients; 17.3%) and the >70-year age group (26 patients; 16%).

The most common comorbidities were hypertension (HT) (77/162; 47.5%), diabetes mellitus (DM) (45/162; 27.8%), atherosclerotic heart disease (26/162; 16%), and congestive heart failure (16/162; 9.9%). Of the total 162 cases, 151 (93.2%) were discharged, and 11 (6.8%) died due to COVID-19 at hospital (Table 1).

Laboratory Parameters

In our study, most of the patients (109, 67.3%) had high CRP

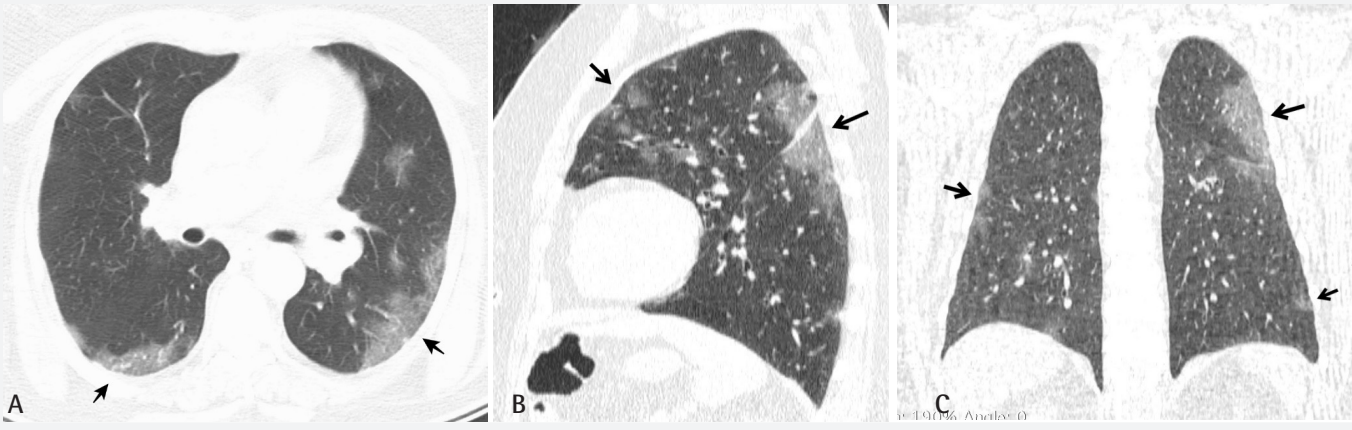

Figure 1. A 76-year-old woman with confirmed COVID-19 had a history of hypertension. Her CT-SS was calculated as 10 (moderate group) in CT that was performed at admission. She had got some abnormal laboratory findings (*). Axial (A), sagittal (B) and coronal (C) thin sections of unenhanced chest CT scans show bilateral multifocal rounded and peripheral ground-glass opacities (black arrows). She was discharged after 10 days of medical treatment in the service of the hospital (*elevated LDH, CRP values)

COVID-19: Coronavirus disease-2019, LDH: Lactate dehydrogenase, CRP: C-reactive protein, CT-SS: Computed tomography-severity score

values. Laboratory results showed elevated D-dimer in 42 (25.9%) patients, LDH levels in 62 (38.3%) patients, prolonged PT in 20 (12.3%) patients, PTT in 7 (4.3%) patients, increased INR in 14 (8.6%) patients, high troponin levels in 8 (4.9%) patients, lymphocytopenia in 15 (9.3%) patients, and anemia in 33 (20.4) patients (Table 1).

Chest CT Severity Scores

One hundred-twenty six (77.8%) COVID-19 confirmed cases had pneumonia and 36 (22.2%) COVID-19 confirmed cases had no pneumonia in their chest CT imaging at the time of admission. CT severity scores ranged from 0 to 24, with a mean value of 6.66±5.50 and a median value of 6 (IQR 1-11). The mild group (CT-SS of 0-7) consisted of 91 patients (56.2%), the moderate group (CT-SS of 8-17) consisted of 65 patients (40.1%) whereas the severe group (CT-SS of 18-25) was composed of 6 patients (3.7%). The median CT-SS value was 2 (IQR 0-5) for the mild group, 11 (IQR 9-12) for the moderate group, and 19.5 (IQR 18-24) for the severe group (Table 2).

Table 1. Demographic characteristics, comorbidities and laboratory findings of our study population at admission

Total patients=162	n (%)
Demographic information	
Age Mean±SD	54.3±17.29
Sex	
Female	93 (57.4%)
Male	69 (42.6%)
Comorbidities	
Hypertension	77 (47.5%)
Diabetes mellitus	45 (27.8%)
Atherosclerotic heart disease	26 (16%)
Congestive heart failure	16 (9.9%)
COPD	11 (6.8%)
Cerebrovascular disease	10 (6.2%)
Malignancy	8 (4.9%)
Chronic renal disease	7 (4.3%)
Chronic liver disease	3 (1.9%)
Laboratory findings	
Leukocytopenia <4000/mm^3	6 (3.7%)
Lymphocytopenia <800/mm^3	15 (9.3%)
Anemia Hgb <12 g/dL	33 (20.4%)
ALT >50 U/L	23 (14.2%)
AST >50 U/L	11 (6.8%)
Cr >1.1 mg/dL	6 (3.7%)
LDH >220 U/L	62 (8.3%)
CRP >5 mg/dL	109 (67.3%)
PT >12.6 sec	20 (12.3%)
PTT >48 sec	7 (4.3%)
INR >1.2	14 (8.6%)
Troponin >11 ng/L	8 (4.9%)
D-dimer >550 ng/mL	42 (25.9%)
Procalcitonin >0.5 ng/mL	4 (2.5%)

SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, Hgb: Hemoglobin, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Cr: Serum creatinine, LDH: Lactate dehydrogenase, CRP: C-reactive protein, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International normalized ratio

Pathological involvement was most common in the inferior lobes, in the right lower lobe in 113 patients (69.8%) and in the left lower lobe in 114 patients (70.4%). The right upper lobe was involved in 97 patients (59.9%), the right middle lobe was involved in 99 patients (61.1%), left upper lobe was involved in 110 patients (67.9%). The frequency of each lobe involvement of the CT-SS groups is shown in Table 3.

Correlation between CT Severity Score and Age, Gender, Laboratory Findings, Comorbidities, and Mortality

Age and Gender

There were 91/162 patients with 56 females in the mild group, 65/162 patients with 35 females in the moderate group, and 6/162 patients with 2 females in the severe group. The mean age was 53.15±16.37 years in the mild group, 55.28±18.52 years in the moderate group, and 61.17±17.88 years in the severe group. There was no statistical difference between the groups in terms of age (p=0.463) (Table 4).

Our results showed no significant statistical difference between CT-SS groups and gender (p=0.302). Also, there was no statistical correlation between age and CT-SS in the Spearman's test [correlation coefficient (r)=0.101; p=0.200].

Laboratory Results

In the current study, we found statistically significant relationships between CT-SS and lymphocytopenia (p=0.001), increased CRP (p<0.001), procalcitonin (p<0.001), LDH (p<0.001), Cr (p<0.001), alanine aminotransferase (ALT) (p=0.017) and aspartate aminotransferase (AST) (p<0.001), troponin (p=0.028), D-dimer levels (p<0.001) and prolonged PT levels (p=0.006) in the chi-square test (Table 5). A statistically significant difference was found by comparing groups 1-3 with regard to high procalcitonin, D-dimer, Cr, AST levels, prolonged PT levels, and lymphocytopenia. Also, a statistically significant difference was found by comparing groups 1-2 in terms of high LDH, CRP and D-dimer levels in the Pearson chi-square or Fisher's tests.

Comorbidities

In the mild group; 45/91 (49.5%) patients had a history of HT, 26/91 (28.6%) had DM, 13/91 (14.3%) had atherosclerotic heart disease, and 7/91 (7.7%) had congestive heart failure.

In the moderate group; 27/65 (41.5%) patients had a history of HT, 17/65 (26.2%) had DM, 12/65 (18.5%) had atherosclerotic heart disease, 8/65 (12.5%) had congestive heart failure, 9/65 (12.3%) had Chronic obstructive pulmonary disease (COPD), and 8/65 (12.3%) patients had cerebrovascular disease.

In the severe group; 5/6 (83.3%) patients had a history of HT, 2/6 (33.3%) had DM, 1/6 (16.7%) had atherosclerotic heart disease, 2/6 (33.3%) had chronic renal disease, 1/6 (16.7%) had congestive heart failure, and 1/6 (16.7%) patient had malignities.

Statistically significant relationships were found between high CT score and history of COPD (p=0.014), chronic renal disease (p=0.001) and cerebrovascular disease (p=0.029) in the chi-square test (Table 6). A statistically significant difference was found when the groups 1-2 were compared in terms of the history of COPD (p=0.008) and cerebrovascular disease (p=0.016) and groups 1-3 in terms of the history of chronic renal disease (p=0.009) in the Fisher's test.

Mortality

In our study, a total of 151 (93.2%) patients are alive, and 11 (6.8%) patients died due to COVID-19. Among the mild group, 91 (100%) patients are alive, and 0 patient died. In the moderate group, 77 (87.7%) patients are alive, and 8 (12.3%) died. In the severe group, 3 (50%) patients are alive, and 3 (50%) died (Figure 2). In the current study, a statistically significant correlation was found between the high CT-SS and the high risk for mortality (p<0.001) in the chi-square test.

Table 2. Frequency of patients (n) and mean±standard deviation, median-IQR values of chest CT severity scores of each group

Severity subgroups	n	Mean	Standard deviation	Minimum	Maximum	Percentiles		
						50th (Median)	25th	75th
Mild group (CT-SS 0-7)	91	2.62[c]	2.59	0	7	2	0	5
Moderate group (CT-SS 8-17)	65	11.05[b]	2.32	8	16	11	9	12
Severe group (CT-SS >18)	6	20.50[a]	2.81	18	24	19.5	18	24
Total	162	6.66	5.50	0	24	1	6	11

[a,b,c] Values in column with different superscripts indicate significant difference (p<0.01).

CT-SS: Computed tomography-severity score, IQR: Interquartile range

Table 3. Frequency of each lobe involvement on chest CT imaging of CT-SS groups

					Total	p value
		Group 1 n=91 (%)	Group 2 n=65 (%)	Group 3 n=6 (%)	n=162	
Right upper lobe involvement	Present	26 (28.6)	65 (100)	6 (100)	97 (59.9)	<0.001
	Absent	65 (71.4)	0 (0)	0 (0)	65 (40.1)	
Right middle lobe involvement	Present	30 (33)	63 (96.9)	6 (100)	99 (61.1)	<0.001
	Absent	61 (67)	2 (3.1)	0 (0)	63 (38.9)	
Right lower lobe involvement	Present	42 (46.2)	65 (100)	6 (100)	113 (69.8)	<0.001
	Absent	49 (53.8)	0 (0)	0 (0)	49 (30.2)	
Left upper lobe involvement	Present	40 (44)	64 (98.5)	6 (100)	110 (67.9)	<0.001
	Absent	51 (56)	1 (1.5)	0 (0)	52 (32.1)	
Left lower lobe involvement	Present	43 (47.3)	65 (100)	6 (100)	114 (70.4)	<0.001
	Absent	48 (52.7)	0 (0)	0 (0)	48 (29.6)	

CT-SS: Computed tomography-severity score, IQR: Interquartile range

Table 4. Comparison of the CT-SS groups in terms of age

CT-SS groups	n	Mean	Standard deviation	Minimum	Maximum	95% confidence interval for mean		p value
						Lower bound	Upper bound	
Mild group	91	53.15	16.37	18	85	49.75	56.56	0.463
Moderate group	65	55.28	18.52	19	97	50.69	59.87	
Severe group	6	61.17	17.88	28	81	42.4	79.93	
Total	162	54.3	17.29	18	97	51.62	56.99	

CT-SS: Computed tomography-severity score

A statistically significant difference was found by comparing groups 1-2 and groups 1-3 in terms of mortality in the Fisher's test (p<0.001).

DISCUSSION

The purpose of this study was to investigate the relationship between chest CT-SS and age, gender, comorbidities, laboratory findings, and mortality in COVID-19 patients. We found a statistically significant relationship between high CT-SS and high mortality rate. Due to the high comorbidity rate in the study population and the two pregnant patients who died due to COVID-19, the mortality in our study is above the Turkey average.

Although RT-PCR is thought to be the gold standard for the diagnosis of COVID-19 infection, it was reported that chest CT was diagnostic in cases with false-negative RT-PCR results. Chest CT is not used only for diagnosis, but also for providing important information in monitoring disease progression and evaluating medical treatment efficacy[11]. Ai et al.[12] reported that the sensitivity of chest CT imaging in indicating COVID-19 infection was 97%, the specificity was 25% with RT-PCR results as the reference standard in 1014 patients. Aslan et al.[13] reported that the sensitivity and specificity of the initial CT scan were 90.4% and 64.2% respectively in the study of 250 patients, finally diagnosed with COVID-19.

Different chest CT scoring systems have been used in previous studies on COVID-19 patients. Chest CT-SS can be assessed using software that describes the percentage of lung volumes affected or a visual scoring for each lobe[14-16]. In some studies, the calculated chest CT severity score visually ranged from 0 to

Table 5. Comparison of CT-SS in terms of laboratory findings

		Group 1 n=91 (%)	Group 2 n=65 (%)	Group 3 n=6 (%)	Total n=162	p value
Leukocytopenia <4000/mm^3	Present	5 (5.5)	1 (1.5)	0 (0)	6 (3.7)	0.386
	Absent	86 (94.5)	64 (98.5)	6 (100)	156 (96.3)	
Lymphocytopenia <800/mm^3	Present	4 (4.4)	8 (12.3)	3 (50)	15 (9.3)	**0.001**
	Absent	87 (95.6)	57 (87.7)	3 (50)	147 (90.7)	
Anemia Hgb <12 g/dL	Present	13 (143)	17 (26.2)	3 (50)	33 (20.4)	**0.036**
	Absent	78 (85.7)	48 (73.8)	3 (50)	129 (79.6)	
ALT >50 U/L	Present	9 (9.9)	11 (16.9)	3 (50)	23 (14.2)	**0.017**
	Absent	82 (90.1)	54 (83.1)	3 (50)	139 (85.8)	
AST >50 U/L	Present	3 (3.3)	5 (7.7)	3 (50)	11 (6.8)	**<0.001**
	Absent	88 (96.7)	60 (92.3)	3 (50)	151 (93.2)	
Cr >1.1 mg/dL	Present	1 (1.1)	3 (4.6)	2 (33.3)	6 (3.7)	**<0.001**
	Absent	90 (98.9)	62 (95.4)	4 (66.7)	156 (96.3)	
LDH >220 U/L	Present	25 (27.5)	34 (52.3)	3 (50)	62 (38.3)	**0.006**
	Absent	66 (72.5)	31 (47.7)	3 (50)	100 (61.7)	
CRP >5 mg/dL	Present	48 (52.7)	56 (86.2)	5 (83.3)	109 (67.3)	**<0.001**
	Absent	43(47.3)	9 (13.8)	1 (16.7)	53 (32.7)	
PT >12.6 sec	Present	7 (7.7)	10 (15.4)	3 (50)	20 (12.3)	**0.006**
	Absent	84 (92.3)	55 (84.6)	3 (50)	142 (87.7)	
PTT >48 sec	Present	4 (4.4)	2 (3.1)	1 (16.7)	7 (4.3)	0.293
	Absent	87 (95.6)	63 (96.9)	5 (83.3)	155 (95.7)	
INR >1.2	Present	5 (5.5)	7 (10.8)	2 (33.3)	14 (8.6)	**0.046**
	Absent	86 (94.5)	58 (89.2)	4 (66.7)	148 (91.4)	
Troponin >11 ng/L	Present	1 (1.1)	6 (9.2)	1 (16.7)	8 (4.9)	**0.028**
	Absent	90 (98.9)	59 (90.8)	5 (83.3)	154 (95.1)	
D-dimer >550 ng/mL	Present	15 (16.5)	22 (33.8)	5 (83.3)	42 (25.9)	**<0.001**
	Absent	76 (83.5)	43 (66.2)	1 (16.7)	120 (74.1)	
Procalcitonin >0.5 ng/mL	Present	0 (0)	2 (3.1)	2 (33.3)	4 (2.5)	**<0.001**
	Absent	91 (100)	63 (96.9)	4 (66.7)	158 (97.5)	

CT-SS: Computed tomography-severity score, Hgb: Hemoglobin, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Cr: Serum creatinine, LDH: Lactate dehydrogenase, CRP: C-reactive protein, PT: prothrombin time, PTT: Partial thromboplastin time, INR: International normalized ratio

Table 6. Comparison of CT-SS groups in terms of demographic data and comorbidities

		Group 1 (mild) n (%)	Group 2 (moderate) n (%)	Group 3 (severe) n (%)	Total	p value
Gender	Female	56 (61.5)	35 (53.8)	2 (33.3)	93 (57.4)	0.302
	Male	35 (38.5)	30 (46.2)	4 (66.7)	69 (42.6)	
Survival	Ex	0 (0)	8 (12.3)	3 (50)	11 (6.8)	**<0.001**
	Alive	91 (100)	57 (87.7)	3 (50)	151 (93.2)	
Hypertension	Present	45 (49.5)	27 (41.5)	5 (83.3)	77 (47.5)	0.125
	Absent	46 (50.5)	38 (58.5)	1 (16.7)	85 (52.5)	
Diabetes mellitus	Present	26 (28.6)	17 (26.2)	2 (33.3)	45 (27.8)	0.902
	Absent	65 (71.4)	48 (73.8)	4 (66.7)	117 (72.2)	
Atherosclerotic heart disease	Present	13 (14.3)	12 (18.5)	1 (16.7)	26 (16)	0.782
	Absent	78 (85.7)	53 (81.5)	5 (83.3)	136 (84)	
Congestive heart failure	Present	7 (7.7)	8 (12.3)	1 (16.7)	16 (9.9)	0.541
	Absent	84 (92.3)	57 (87.7)	5 (83.3)	146 (90.1)	
COPD	Present	2 (2.2)	9 (13.8)	0 (0)	11 (6.8)	**0.014**
	Absent	89 (97.8)	56 (86.2)	6 (100)	151 (93.2)	
Chronic renal disease	Present	1 (1.1)	4 (6.2)	2 (33.3)	7 (4.3)	**0.001**
	Absent	90 (98.9)	61 (93.8)	4 (66.7)	155 (95.7)	
Malignancy	Present	3 (3.3)	4 (6.2)	1 (16.7)	8 (4.9)	0.289
	Absent	88 (96.7)	61 (93.8)	5 (83.3)	154 (95.1)	
Chronic liver disease	Present	2 (2.2)	1 (1.5)	0 (0)	3 (1.9)	0.901
	Absent	89 (97.8)	64 (98.5)	6 (100)	159 (98.1)	
Cerebrovascular disease	Present	2 (2.2)	8 (12.3)	0 (0)	10 (6.2)	**0.029**
	Absent	89 (97.8)	57 (87.7)	6 (100)	152 (93.8)	

COPD: Chronic obstructive pulmonary disease, CT-SS: Computed tomography-severity score

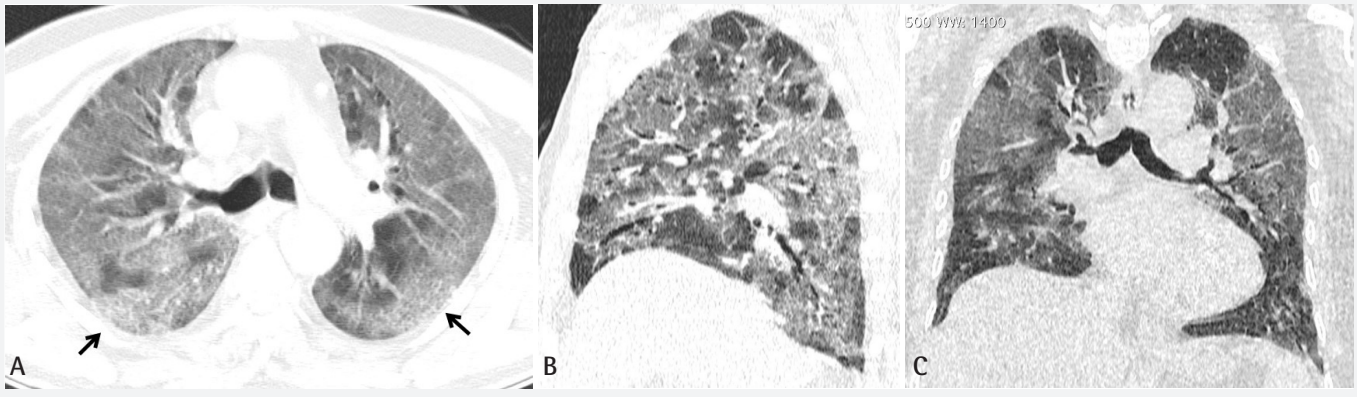

Figure 2. A 70-year-old man with confirmed COVID-19 had a history of prostate cancer and renal failure. His CT-SS was calculated as 24 (severe group) in CT that was performed at admission. He had got many abnormal laboratory findings (*). Axial (A), sagittal (B) and coronal (C) thin sections of unenhanced chest CT scans show bilateral extensive ground-glass opacities with interlobular and intralobular septal thickening (black arrows). The patient was transferred to the ICU on the same day of the CT scan and died 10 days after this scan (*lymphocytopenia, elevated AST, ALT, LDH, Cr, CRP, D-dimer, ferritin, procalcitonin, troponin, prolonged PT, INR values)

COVID-19: Coronavirus disease-2019, LDH: Lactate dehydrogenase, CRP: C-reactive protein, PT: Prothrombin time, CT-SS: Computed tomography-severity score, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Cr: Serum creatinine, LDH: Lactate dehydrogenase, INR: International normalized ratio, ICU: Intensive care unit

20[14-17]. We used the 25-point CT severity scoring system that was used in the literature[8-10].

Zhou et al.[18] reported that the total CT scores in COVID-19 patients who died were significantly higher than in those

who recovered. Francone et al.[10] reported that CT-SS was significantly higher in critical and severe patients than in mild ones. They reported that CT-SS ≥18 predicted a high patient mortality in COVID-19 patients. So, in the current study, the CT-SS ≥18 was accepted as the cut-off value between moderate and severe groups. We separated the patients into 3 groups as

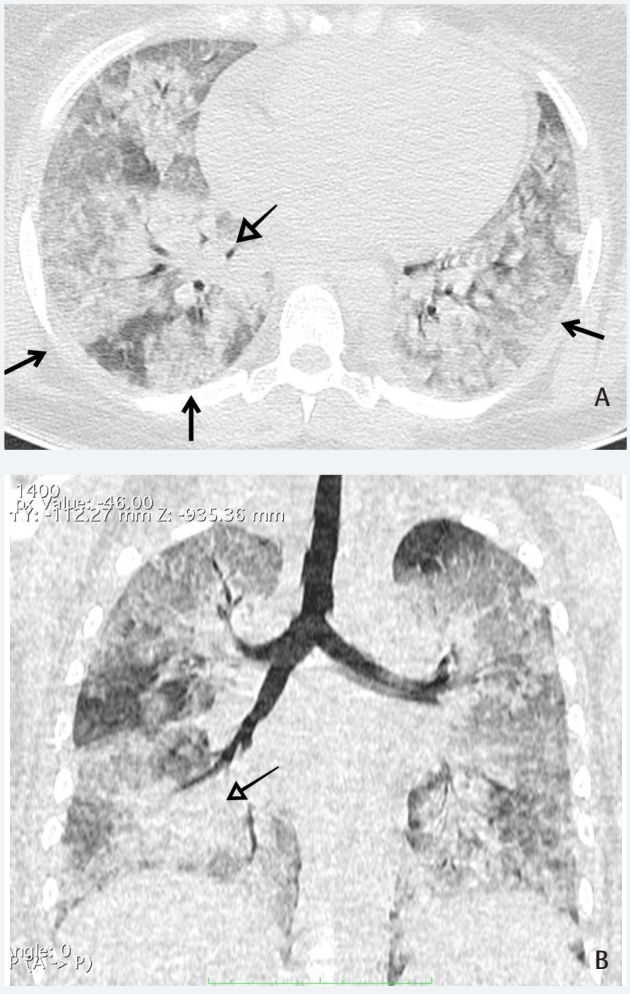

Figure 3. A 28-year-old patient with COVID-19 who was 29-week pregnant and taken to an emergency cesarean section. She died 17 days after this CT scan due to COVID-19 pneumonia, ARDS and septicemia. Her CT-SS was calculated as 24 (severe group) in CT. She had got many abnormal laboratory findings (*). Axial (a) and coronal (b) thin sections of unenhanced chest CT scans show extensive diffuse ground-glass opacities (black arrows) and few areas of consolidation with air bronchograms (empty arrows) and crazy-paving pattern giving a white lung appearance (*lymphocytopenia, elevated AST, ALT, LDH, Cr, CRP, D-dimer, ferritin, procalcitonin, troponin, prolonged PT, INR values)

COVID-19: Coronavirus disease-2019, LDH: Lactate dehydrogenase, CRP: C-reactive protein, PT: Prothrombin time, CT-SS: Computed tomography-severity score, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Cr: Serum creatinine, INR: International normalized ratio

in the recent study[9]. In our study, the mortality rates were 0% in the mild group, 12.3% in the moderate group, and 50% in the severe group. As a result, there was a statistically significant relationship between high CT-SS and high mortality in patients.

Increased levels of inflammatory biomarkers and infiltrating immune cells in lung lesions have been reported in patients with critical COVID-19. Cytokine storms can play a vital role in the increased disease severity of COVID-19 patients[19]. Francone et al.[10] reported statistically significant correlations between CT score and CRP and D-dimer levels. According to Saeed et al.[9], significant correlations were found between CT-SS and the male gender, with high inflammatory markers. They reported that CT-SS was found to be positively correlated with lymphopenia, increased serum CRP, D-dimer, and ferritin levels[9]. Zhang et al.[2] reported that chest CT score was found to be positively correlated with CRP, erythrocyte sedimentation rate, white blood cell count, procalcitonin, and abnormal coagulation function, and a negative association with lymphocyte count. In the current study, statistically significant correlations were found between CT score vs lymphocytopenia, high CRP, D-dimer, procalcitonin, LDH, Cr, ALT, AST, and troponin levels, and prolonged PT levels.

Different studies in the literature reported that older age, decreased lymphocytes, elevated CRP and D-dimer levels and comorbidities (cardiovascular and cerebrovascular diseases) were important high-risk factors that could lead to an increase in mortality in severe COVID-19 patients[20-22]. The male gender was most common in the severe group in the current study. However, the results showed no significant correlation between CT-SS and age and gender.

Several studies have reported that COVID-19 patients have a worse prognosis and severe clinical outcomes when multiple risk factors are present, particularly DM, HT, lung, and coronary artery disease[23,24]. Statistically significant correlations were found between CT score and chronic renal disease, COPD and cerebrovascular disease in the current study.

In addition, some special conditions such as pregnancy and malignancy are associated with the disease severity of COVID-19[25,26]. In our study, a 28-year-old woman in the severe group (CT-SS=24), who was 29-week pregnant and taken to emergency cesarean section, died due to COVID-19 pneumonia, ARDS, and septicemia (Figure 3).

Several recent studies have reported coagulation disorders, and liver and kidney dysfunctions in COVID-19 patients[20,27,28]. In our study, laboratory results showed also abnormal liver, kidney, and anticoagulation values. There were statistically significant correlations between CT-SS and high Cr, ALT and AST, D-dimer levels, and prolonged PT levels.

Study Limitations

Our study has some limitations. First, it is a retrospective study performed in a single center and a relatively limited cohort of patients was included in the study. Therefore, a multicenter study with a large sample size is needed for

further confirmation. Second, patients' CT-SSs were calculated by an experienced radiologist using a visual semi-quantitative CT severity scoring system. The accuracy of the study could be increased by two or more observers.

CONCLUSION

There was a relationship between high chest CT-SS and high mortality, inflammatory and anticoagulant laboratory markers, and some comorbidities (chronic renal disease, cerebrovascular disease, COPD) in COVID-19 patients. Chest CT-SS is a useful method for evaluating the severity and extent of COVID-19 pneumonia and it can provide clinicians with more detailed information about patients' prognosis and can be helpful for early intervention planning.

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Ethics

Ethics Committee Approval: This study was approved by the Ethical Committee of Trabzon Kanuni Training and Research Hospital and by the Minister of Health of the Republic of Turkey and it was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (date: 12.11.2020, no: 2020/68).

Informed Consent: The requirement for informed consent was waived.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.A., H.A.A.K., Design: B.A., Data Collection or Processing: B.A., H.A.A.K., Analysis or Interpretation: B.A., Literature Search: B.A., H.A.A.K., Writing: B.A.

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ORIGINAL ARTICLE

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Perceived Stress and Need for Social Relationships in University Students in Pandemic

Pandemide Üniversite Öğrencilerinin Algıladıkları Stres ve Sosyal İlişki İhtiyacı

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ABSTRACT

Aim: The spread of infectious diseases has become inevitable with the increase in international cooperation, commerce and cultural values via the technological developments through the World. Coronavirus disease-2019 (COVID-19) pandemic has created stress and anxiety all over the World. Young adults are one of the most affected social groups in the isolation days. This study aimed to evaluate the university students' perceived stress and need for relatedness with the profound change in educational and social life conditions.

Materials and Methods: In order to determine the socialization needs and stress levels of university students, university students throughout Turkey were reached. Demographic characteristics, and the scores of Perceived Stress Scale and The Need for Relatedness Scale were collected by applying a web-based questionnaire in 402 students.

Results: It was observed that the COVID-19 timeframe increased the stress levels and social needs of university students. The perceived stress of female students was found to be higher than that of male students ($p<0.001$) while no statistically significant difference was found among regions and departments.

Conclusion: It has become necessary to consider the fact that the educational lives of university students are affected by the parameters of anxiety, stress and needs during this new normalization process and has become necessary to improve their psychological status.

Keywords: COVID-19, need for relatedness, perceived stress, university students

ÖZ

Amaç: Dünya genelinde, teknolojik gelişmeler ile birlikte ülkeler arası iş birliklerinin, alışverişin, bilgi ve kültürel paylaşımların artması ile beraber bulaşıcı hastalıkların da yayılması kaçınılmaz olmuştur. Koronavirüs hastalığı-2019 (COVID-19) pandemisi hızla yayılırken hastalığın tanımı, bulaş yolları ve alınan önlemler değiştikçe tüm dünyada stres ve kaygı yaratmıştır. Sosyal izolasyonun çözüm olarak görüldüğü bu günlerde gençlerin en çok etkilenen sosyal gruplardan biri olduğu görülmüştür. Bu çalışma kapsamında, üniversiteye giden gençlerin eğitim ve sosyal yaşam koşullarının derinden değişmesi ile algıladıkları stres ve sosyal iletişim gereksinimlerinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Sosyalleşme gereksinim ve stres düzeylerinin üniversite okuyan öğrencilerde belirlenmesi için Algılanan Stres ve Sosyal İletişim Gereksinim ölçekleri kullanılarak Türkiye genelinde farklı bölgelerdeki üniversite ve farklı bölümlerde okuyan öğrencilere ulaşıldı. Web tabanlı anket uygulanarak 402 öğrencinin demografik özellikleri, Algılanan Stres Ölçeği ve Sosyal İlişki Gereksinimi Ölçeği puanları toplandı.

Bulgular: COVID-19 sürecinde üniversite öğrencilerinin stres ve sosyal gereksinim skorlarının arttığı görüldü. Kız öğrencilerin algıladıkları stres erkek öğrencilerden daha yüksek bulundu ($p<0,001$), bölgeler ve bölümler arasında anlamlı bir farka rastlanmadı.

Sonuç: Yeni normalleşme sürecinde tüm dünyadaki üniversite öğrencilerinin eğitim ve öğretim hayatları için kaygı, stres ve gereksinim parametrelerinin etkilendiğinin göz önüne alınmasına ve psikolojik durumlarının iyileştirilmesine ihtiyaç duyulmuştur.

Anahtar Kelimeler: COVID-19, sosyal ilişki gereksinimi, algılanan stres, üniversite öğrencileri

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INTRODUCTION

This age, in which cooperation and exchange among countries have accelerated with technological changes, has paved the way for diseases to find a way of easy and quick transmission. The best example of this is the Coronavirus disease-2019 (COVID-19) pandemic, which is still in effect today and started in Wuhan, China. The disease rapidly affected the whole world, and with the increase in the number of cases and deaths, the disease was declared as a pandemic by the World Health Organization on March 11, 2020[1].

The effects of the disease on the society, especially on health, social and psychological aspects, were felt. The uncertain and sudden change of the life order has affected the daily functioning, and the change in the ordinary situation in education and working life has affected the sociological structure and this has brought some global problems[2]. Countries have sought to provide quality, fair and uninterrupted education, and online education has been started to be used instead of face-to-face education[2,3]. It has been stated that compulsory social isolation has negative effects on learning, development and communication at every stage from primary education to higher education, mental health problems of the young population in particular have increased at least twice, and depression and anxiety have increased by 30-80% compared to adults[4,5].

It is reported that young adults exhibit higher levels of anxiety, depression, substance use and irregular eating habit during the university years compared to the general population, when they gain new experiences in terms of finding solutions to the changes and difficulties they encounter in their lives and it is suggested that there are significant changes in parameters such as anxiety, fear and worry in public health emergencies such as epidemics and pandemics[6-8]. In the COVID-19 pandemic, it was observed that university students tried to adapt to online lessons and exams, and they were one of the groups that were most affected psychologically due to both the disruption of their routine and the unequal new conditions[9]. In addition, the fact that there are studies reporting a significant increase in the depression and anxiety levels and in the general suicidal tendency, observing an increase in the time of sleep but a worsening of its quality and a decrease in the quality of life reveals the seriousness of the issue[10,11]. When it comes to university students, the negative effects of stress on health, emotions, learning and memory also gain importance[12]. Studies examining the perceived stress and social isolation needs of university students living in various regions of Turkey and studying in different departments during the COVID-19 period were observed to be limited[13]. In this study, it is aimed to examine the psychological status and social relationship needs of university students in detail according to some demographic characteristics during this ongoing pandemic process.

MATERIALS AND METHODS

The research was designed as a prospective study and was carried out using a web-based questionnaire created by examining the literature. Volunteer participants reached through social media groups of university students were included in the survey. The survey was conducted in such a way that if they said yes to the "I have read, I approve" option, which was the purpose of the study and the informative text in the first part, they could continue. It was also stated in the informative text that personal and contact information was not collected from the participants, that the questions in the survey were not compulsory and that they could leave whenever they wanted.

Study Population and Sample

While determining the sampling criteria, groups that were socially severely affected by the pandemic conditions were evaluated and young people were decided according to the literature review. Since the socioeconomic criteria of the young people who went to and did not go to university were not the same, the young people who were not in the education life were not included in the sample, and the age range of 18-25 years, which covered the general age range of those who went to university, was chosen in order to obtain the data set for our purpose in a homogeneous and healthy way.

Based on 921,886 university students who settled in the university chosen as the population, or more than seven and a half million university students who were currently students, it was determined that at least 385 people were needed as the sample number, with 95% reliability and 5% confidence interval, while the mean and variance of the population were unknown[14].

Data

University students at the age range of 18-25 years were reached through a web-based survey between January 1 and February 29, 2020 across Turkey. The Perceived Stress Scale (PSS) scores and the Need for Relatedness Scale (NRS) scores of the university students were measured, and demographic parameters (age, gender, faculty, region of residence, monthly income, and family history of COVID-19), which were thought to have an impact, were also added to the survey. In the 407 questionnaires collected, 5 people were excluded from the data set because they left their demographic characteristics and most of the scale questions blank, and analyses were carried out with 402 people. Since some of the scale questions were left blank, the PSS scale was studied with 399 people and the NRS scale with 390 people (acceptance subscale with 390, intimacy subscale with 393), and the gap filling method for missing data was not used.

Perceived Stress Scale

The PSS was originally developed by Cohen et al.[15] in 1983, and its Turkish adaptation was published in 2013 by Eskin et al.[16].

PSS, consisting of fourteen items, was created to measure how stressful the situations experienced by the individual were perceived. A 5-point Likert-type scale is applied to individuals to evaluate each item ranging from "Never (0)" to "Very often (4)". In the scale, 7 items (4., 5., 6., 7., 9., 10. and 13.) with positive expressions are evaluated in reverse. The total score of the PSS-14 scale ranges from 0 to 56, and an increasing score indicates that the individual's perceived stress is high.

Need for Relatedness Scale

It is a scale developed by Richer and Vallerand[17] (1996) on the basis of the Self-Determination Theory, and its original form was developed in English in Canada as "The NRS-10". It was adapted into Turkish by Karagüven et al.[18] in 2020.

NRS-10 was created to evaluate the social relationship levels of individuals in different environments. It is a scale consisting of 10 items, 5 of which (items 1., 3., 5., 7., 9.) are included in the sub-dimension of "acceptance" and 5 of which (items 2., 4., 6., 8., 10.) in the sub-dimension of "intimacy". The expression at the beginning of the scale (such as with my colleagues, with my schoolmates) can be changed so that the scale could be used easily in different environments. Each item is evaluated between 1 (strongly disagree) and 7 (strongly agree).

The scores of the NRS-10 scale range from 10 to 70, and the increasing scale score indicates a high level of social relationship.

For this study, official approval was obtained from the Non-Invasive Clinical Research Ethics Committee of Haliç University with the number 242 on 24.12.2020.

Statistical Analysis

Descriptive statistics results were given as frequency and percentage for categorical variables, and as mean, standard deviation, median, minimum and maximum for continuous variables. The Shaphiro-Wilk test results were used to examine the normality distribution of continuous variables, and the comparison of continuous variables between the two groups was performed with the Independent Samples t-test for normally distributed data and with the Mann-Whitney U Test for not normally distributed data. The Pearson or Spearman's correlation analysis was applied according to the distribution of the variables in the analysis of the correlation between the variables. The Cronbach's alpha values of the scales were given and principal components, factor loads and explained coefficients of variance were calculated with the help of Factor Analysis. Statistical analyses were performed with the Statistics Package for Social Sciences (SPSS) version 24.0 and the R programming language (4.0.3 version) "psych" program, and the $p<0.05$ value was considered statistically significant.

RESULTS

Demographic characteristics of 402 students participating in the study are presented in Table 1. The mean age of the students was 20.22±1.58 years. There was no significant difference between 139 male students [20.34±1.76 20 (18-25) years] and 263 female students [20.16±1.48 20 (18-25) years] in terms of age (p=0.587). While 28.6% of the participating students had a family history of COVID-19, 71.4% did not.

Table 1. Demographic characteristics of the students participating in the study

		n	%
Gender	Male	139	34.6
	Female	263	65.4
Faculty of education	Distance Education Faculty	1	0.2
	Faculty of Dentistry	34	8.5
	Faculty of Pharmacy	3	0.7
	Faculty of Education	8	2.0
	Faculty of Science and Literature	35	8.7
	Faculty of Fine Arts	3	0.7
	Faculty of Law	5	1.2
	Faculty of Administrative and Economic Sciences	16	4.0
	Faculty of Theology	3	0.7
	Faculty of Communication	1	0.2
	Faculty of Business Administration	5	1.2
	Faculty of Architecture	34	8.5
	Faculty of Engineering	64	15.9
	Faculty of Health Sciences*	24	6.0
	Faculty of Political Sciences	1	0.2
	Faculty of Medicine	132	32.8
	Others	33	8.2
Region of Residence	Mediterranean Region	36	9.0
	Eastern Anatolia Region	8	2.0
	Aegean Region	31	7.7
	Southeastern Anatolia Region	23	5.7
	Central Anatolia Region	40	10.0
	Black Sea Region	12	3.0
	Marmara Region	252	62.7
Monthly income (TL)	<2,200	138	34.3
	2,200-3,000	54	13.4
	3,000-4,000	48	11.9
	4,000-7,500	60	14.9
	7,500-10,000	37	9.2
	10,000-15,000	23	5.7
	>15.000	38	9.5
History of COVID-19	Yes	115	28.6
	No	287	71.4
Age, year**	20.22±1.58 20 (18-25)		

*Nursing, anesthesia, midwifery, nutrition and dietetics, child development.
**Mean±standard deviation, median (minimum-maximum).
COVID-19: Coronavirus disease-2019

The PSS and NRS scores are presented in Table 2 and it was seen that their averages were above the mean values of the scales (28 for PSS, 40 for NRS). Cronbach's alpha values were calculated as 87% for PSS and 97% for NRS, and the scales were found to have high reliability (Table 2)[19].

As a result of examining the scale scores according to demographic characteristics, a significant difference was found only between the genders in terms of PSS scores (p<0.001). It was observed that the PSS scores of the female students were higher than the PSS scores of the male students (Table 3).

In order to avoid problems in both meaning integrity and statistical analyses in group comparisons, the faculty type was grouped as "medical faculty and other", as well as "medical faculty and health sciences faculty students and other"; region of residence as "Marmara Region and other"; and income status as "low (<2.200) and high (≥2.200)". There was no significant difference in terms of PSS, NRS and NRS subscales (acceptance and intimacy) between those with and without a family history of COVID-19, between medical faculty students and others, between health sciences faculty students in addition to medical faculty students and others, between those residing in the Marmara region and other regions, and between those with low and high income (Tables 3, 4).

When medical faculty students were examined within themselves, it was found that the stress levels of female students were higher than those of male students, but there was no significant difference in terms of family history of COVID-19, income status and residence region (p<0.001, 0.780, 0.949, p 0.420, respectively).

When the relationship between the two scales was examined, a significant, reverse and very weak relationship was found between NRS and PSS (p<0.001, -0.208). It was observed that this relationship was insignificant only in male participants, but significant, reverse and very weak (-0.237) in female students. When examined in terms of COVID-19 history, a significant and reverse relationship, which was very weak in those without history of COVID-19 while weak in those with a history of COVID-19 although it was slightly higher, was found (-0.167, -0.344, respectively) (Table 5).

Table 2. PSS and NRS scale scores, Cronbach's alpha values

		n	Mean±SD Median (min-max)	Cronbach's alpha
PSS		399	35.08±9.36 35 (1-56)	0.874
NRS		390	45.81±16.49 49 (10-70)	0.965
NRS	Acceptance	393	22.93±8.26 24 (5-35)	0.935
	Intimacy	390	22.89±8.56 25 (5-35)	0.933

min-max: Minimum-maximum, SD: Standard deviation, PSS: Perceived Stress Scale, NRS: Need for Relatedness Scale

Factor Analysis, Principal Component Analysis

- For the NRS scale, the Cronbach's alpha was 97%, the explained variance was 76%, the Kaiser-Meyer-Olkin (KMO) value was 0.952, and the Barlett's test of Sphericity analysis result was p<0.001. Component coefficients varied between a minimum of 0.718 and a maximum of 0.926. For the subscales, the Cronbach's alpha values were observed as 94% for the acceptance subscale and 93% for the intimacy subscale.

- For the PSS scale, the Cronbach's alpha was 87%, the explained variance was 54%, the KMO value was 0.905, and the Barlett's test of Sphericity result was p<0.001.

Table 3. Comparison of PSS and NRS scales according to demographic characteristics

		PSS	p	NRS	p
Gender	Male	31.59±9.19 31.5	<0.001[a]	45.87±17.09 48.50	0.876[a]
	Female	36.92±8.92 37		45.78±16.20 49	
History of COVID-19	No	34.79±9.73 35	0.401[a]	46.01±16.67 48	0.719[a]
	Yes	35.79±8.35 35.5		45.32±16.10 50	
Faculty type (medicine)	Faculty of Medicine	34.88±9.82 35.5	0.766[b]	46.35±15.77 49	0.783[a]
	Other	35.18±9.13 35		45.54,±16.88 48.5	
Faculty type (health)	Faculties of Medicine and Health Sciences	34.66±9.88 35	0.489[a]	46.14±16.04 49	0.871[a]
	Others	35.35±9.02 35		45.60±16.82 48	
Region of residence	Marmara Region	35.33±9.81 35.5	0.426[a]	46.17±16.55 49	0.533[a]
	Others	34.65±8.55 35		45.21±16.43 49	
Income status	Low	36.30±9.19 36	0.058[b]	45.11±17.62 49	0.786[a]
	High	34.43±9.40 35		46.18±15.89 49	

[a]Mann-Whitney U test, [b]Independent sample t-test.
PSS: Perceived Stress Scale, NRS: Need for Relatedness Scale

DISCUSSION

In our study, which revealed that routine lives of 402 university students, whose average age was 20.22±1.5 years and 65.4% were female students, and who participated in the survey from different geographical regions and different faculties, were affected during the COVID-19 pandemic, and which evaluated the levels of social relations and stress that they experienced while adapting to digital transformations, it was found that PSS scores of female students were higher than those of male students.

Table 4. Comparison of NRS subscales according to demographic characteristics

		Acceptance	p	Intimacy	p
Gender	Male	22.64±8.58 24	0.705[a]	23.23±8.90 25	0.441[a]
	Female	23.08±8.10 24		22.71±8.39 25	
History of COVID-19	No	23.06±8.32 24	0.677[a]	22.93±8.70 24	0.832[a]
	Yes	22.60±8.12 24		22.78±8.25 25	
Faculty type (medicine)	Faculty of Medicine	23.04±7.86 24	0.993[a]	23.31±8.24 25	0.577[a]
	Other	22.87±8.47 24		22.67±8.73 24.5	
Faculty type (health)	Faculties of Medicine and Health Sciences	23.09±7.99 24.5	0.808[a]	23.09±8.36 25	0.819[a]
	Others	22.82±8.45 24		22.76±8.71 25	
Region of residence	Marmara Region	22.98±8.29 24	0.914[a]	23.18±8.59 25	0.332[a]
	Other	22.84±8.24 25		22.39±8.52 24	
Income status	Low	22.22±8.77 24	0.344[a]	22.84±9.20 25	0.835[a]
	High	23.30±7.97 24		22.91±8.23 24.5	

[a]Mann-Whitney U test.

PSS: Perceived Stress Scale, NRS: Need for Relatedness Scale

Table 5. The relationship between NRS and PSS scales

		p	r
General		<0.001	-0.208
Gender	Male	0.113	-0.137
	Female	<0.001	-0.237
History of COVID-19	No	0.005	-0.167
	Yes	<0.001	-0.344

Spearman's correlation test.

COVID-19: Coronavirus disease-2019, PSS: Perceived Stress Scale, NRS: Need for Relatedness Scale

As a result of the prospective cohort study conducted by Savage et al.[20] on the mental health and physical behaviors of university students during the pandemic, a decrease in the mental health of young people, students and women, who are more sensitive than the general society, and an increase in their stress and sedentary states were observed. Moreover, in the same study, it was stated that female students were more stressed than male students[20]. In the current study, PSS scores of female students were detected to be higher, which was found to be consistent with the literature.

When only medical faculty students were examined within themselves, it was found that the stress levels of female students were higher than those of male students, but no significant difference was found in terms of income status. In the study conducted by Torun and Torun[21] with medical faculty students, it was emphasized that the perceived stress level of female students was higher than that of male students, and that low income also affected students' perceived stress and anxiety. The income level, which was found to be significant In a single-center study conducted with only medical faculty students, was observed to have lost its significance on COVID-19 considering the students studying in medical faculties throughout Turkey, and it was observed to be at a trend level among students studying in all regions and faculties in Turkey. It is thought that more comprehensive studies on perceived stress depending on income are needed.

In the study of perceived stress conducted by Tuğut et al.[22] with a web-based survey on 295 university students studying only in the field of health, excluding the medical faculty, in a university in the period of COVID-19, and in the study of perceived stress conducted by Bayar et al.[23] on only 565 university students, mostly studying in the field of health at Mardin Artuklu University, it was stated that the PSS scores were above the average level.

Compared to the study conducted by Hancıoğlu[24] in 2017 with students at Ankara University Faculty of Political Sciences, Department of Business Administration before COVID-19, it was found that the stress perceived by university students during the COVID-19 period increased even more. In the PSS validation study conducted by Eskin et al.[16] with students studying at Adnan Menderes University Aydın Health High School and Faculty of Science and Literature in 2013, it was observed that the perceived stress scores of university students during the pandemic were even higher. In our study, which also included students studying in health-related and other departments and from other regions, it was observed that university students' PSS scores were even higher during the

COVID-19 period. It was concluded that university students were negatively affected by the pandemic, independent of region, faculty, department and income level, except for gender.

Study Limitations

The lack of knowledge on the pre-pandemic stress and social relationship status of the university students participating in the study was determined as a limitation of the study.

CONCLUSION

As a result, in our study, an increase was observed in the stress and social needs scores of university students during the COVID-19 process, it was clearly observed that this increase was not a determinant in terms of demographic characteristics except for gender, and all university student groups were similarly affected by the restrictions brought by the pandemic. It is thought that there is a need to make common arrangements for university students in general, to consider the anxiety and stress parameters in their education lives, and to improve their psychological status.

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Ethics

Ethics Committee Approval: For this study, official approval was obtained from the Non-Invasive Clinical Research Ethics Committee of Haliç University with the number 242 on 24.12.2020.

Informed Consent: Survey study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: A.B., A.D.U., E.U., I.B., M.M., M.S.T., M.B.Ç., U.E.C., Z.B.Y.

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Systemic Treatment Outcomes of Progressive Medullary Thyroid Carcinoma from the Registries of a Tertiary Cancer Center

Üçüncü Basamak Kanser Merkezi Kayıtlarından Progresif Medüller Tiroid Karsinomunun Sistemik Tedavi Sonuçları

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ABSTRACT

Aim: Medullary thyroid carcinoma (MTC) originating from parafollicular C cells is a sporadic endocrine tumor. A unique aspect of the disease is that it is 25% familial and component of multiple endocrine neoplasia 2 syndromes. Surgical resection has curative potential in the early stages. Systemic treatment options are available for unresectable or advanced disease. Due to the rare and limited treatment options for the disease, we found it appropriate to share the results of our patients in our center.

Materials and Methods: We enrolled 47 progressive MTC patients in the study between June 2000 and June 2019. Demographic and clinical characteristics of the patients, as well as treatment outcomes, were evaluated. Statistical analyses were performed to identify risk factors associated with survival.

Results: The median age was 46 years, and the male to female ratio was 32/15. All patients' Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) was 0 (66.7%) or 1 (33.3%). While 73% of the patients had lymph node metastasis, 22% had distant organ metastasis at initial diagnosis. Local recurrence was found to be the most common progression type (80.9%). The most frequent distant metastatic sites at progression were the bone (68.1%) and lung (23.4%). From the start of systemic therapy, the median progression-free survival and median overall survival (OS) were 51.7 months and 55.6 months, respectively. Vandetanib was associated with a better OS than systemic treatments (84.7 months vs. 37.1 months, respectively; p=0.047). Patients whose ECOG-PS was 0 had better OS than those with ECOG-PS 1 (77.2 months vs. 34.4 months, respectively; p=0.002). Also, ECOG-PS was determined as an independent prognostic factor [hazard ratio (HR): 14.7; 95% confidence interval (CI): 1.7-124.7; p=0.013].

Conclusion: Although the patients with progressive MTC have relatively long survival, systemic treatment options are limited. The ECOG-PS needs to be evaluated in absolute terms in patient management. In addition to tyrosine kinase inhibitors, chemotherapy and ^{177}Lu-octreotate may be effective in selected patients.

Keywords: Survival, vandetanib, cancer, progression, thyroid

ÖZ

Amaç: Parafoliküler C hücrelerinden kaynaklanan medüller tiroid karsinomu (MTC) oldukça nadir bir endokrin tümördür. Hastalığın en özgün yanı %25 ailesel olması ve multiple endokrin neoplazi 2 sendromlarının komponenti olmasıdır. Cerrahi rezeksiyon erken evrelerde küratif potansiyele sahiptir. Rezeke edilemeyen veya ileri evre hastalıkta sistemik tedavi seçenekleri mevcuttur. Hastalığın nadir ve sınırlı tedavi seçeneklerinin olması nedeniyle merkezimizde takip edilen hastalarımızın sonuçlarını paylaşmayı uygun bulduk.

Gereç ve Yöntem: Haziran 2000 ile Haziran 2019 arasında 47 progresif MTC hastası çalışmaya dahil edildi. Hastaların demografik ve klinik özellikleri ile tedavi sonuçları değerlendirildi. Sağkalım ile ilişkili risk faktörlerini belirlemek için istatistiksel analizler yapıldı.

Bulgular: Ortanca yaş 46 yıl ve erkek/kadın oranı 32/15 idi. Tüm hastaların Doğu Kooperatifi Onkoloji Grubu - Performans Statüsü (ECOG-PS) 0 (%66,7) veya 1 (%33,3) idi. Hastaların %73'ünde ilk tanı anında lenf nodu metastazı görülürken, %22'sinde uzak organ metastazı vardı. Lokal nüks

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en fazla görülen progresyon tipiydi (%80,9). Progresyonda uzak metastazın en sık olduğu bölgeler sırasıyla kemik (%68,1) ve akciğerdi (%23,4). Sistemik tedavinin başlangıcından itibaren medyan progresyonsuz sağkalım ve medyan genel sağkalım sırasıyla 51,7 ay ve 55,6 aydı. Vandetanib diğer sistemik tedavilere kıyasla (sırasıyla 84,7 ay ve 37,1 ay; p=0,047) daha iyi bir genel sağkalım (OS) ile ilişkiliydi. ECOG-PS 0 olan hastalar, ECOG-PS 1 olanlardan daha iyi OS'ye sahipti (sırasıyla 77,2 ay ve 34,4 ay; p=0,002). Ayrıca ECOG-PS bağımsız prognostik faktör olarak belirlendi (tehlike oranı: 14,7; %95 güven aralığı: 1,7-124,7; p=0,013).

Sonuç: Progresif MTC görece uzun bir sağ kalımla ilişkili olsa da sistemik tedavi seçenekleri kısıtlıdır. ECOG-PS'nin hasta yönetiminde mutlak bir şekilde değerlendirilmesi gerekmektedir. Tirozin kinaz inhibitörlerinin yanında seçilmiş hastalarda kemoterapi ve ^{177}Lu-octreotate etkin olabilir.

Anahtar Kelimeler: Sağkalım, vandetanib, kanser, progresyon, tiroid

INTRODUCTION

1.5% of all tumors derived from the thyroid gland constitute medullary thyroid carcinoma (MTC). MTC originates from parafollicular C cells of the thyroid gland, and it is the most common thyroid gland tumor after differentiated thyroid cancers[1,2]. At diagnosis, the median age is 50 years, and the disease is observed with similar frequency in both genders[3,4]. Unlike other thyroid cancers, medullary thyroid cancer has a familial transition at a rate of 25%[5]. The familial forms inherited by autosomal dominant inheritance consist of 3 subtypes: Multiple endocrine neoplasia (MEN) 2A, MEN 2B, and familial-MTC. MEN 2A is characterized by pheochromocytoma, primary parathyroid hyperplasia, and, rarely, cutaneous lichen amyloidosis. Although parathyroid hyperplasia and a marfanoid habitus are observed in MEN 2B, pheochromocytoma is not observed. On the other hand, familial-MTC occurs as isolated. In familial cases, MTC is observed at earlier ages and tends to be multifocal. The most common presentation for familial and sporadic cases is a solitary thyroid nodule (90%). Up to 70% of patients with palpable thyroid nodules have cervical lymph node metastases. *De novo* metastasis to the liver, lung, bone, and brain may be observed in 10% of the patients[6].

The gain of function mutations in the rearranged during transfection (RET) proto-oncogene observed in the parafollicular C cell has a crucial role in MTC carcinogenesis. Germline mutations are associated with familial forms, while somatic mutations are responsible for sporadic MTC[7]. As a result, mutations triggering autophosphorylation in tyrosine residues of the RET transmembrane protein lead to the initiation of a series of downstream signaling pathways and carcinogenic processes such as cell survival and proliferation[8].

The most important prognostic factors of the disease are age, tumor diameter, stage, calcitonin, and carcinoembryonic antigen (CEA) levels[3,9-11]. In a large-scale analysis performed according to Surveillance, Epidemiology, and End Results data, 10-year survival was reported as 95%, 75%, and 40% in local, regional, and distant metastases, respectively[3]. Calcitonin and CEA are highly specific MTC markers and have prognostic significance. There is a highly correlated relationship between high calcitonin levels, regional lymph nodes, and distant organ metastasis at diagnosis[12]. The assessment of computed tomography should be performed to detect systemic metastases, especially at levels above 400 pg/mL.

The only curative method for the disease is surgery. In addition to total thyroidectomy and central lymph node dissection, surgical intervention can be extended depending on serum calcitonin level and suspected distant cervical lymph node metastasis. The median overall survival (OS) is 8.6 years after diagnosis[13]. There is no effective adjuvant treatment option after surgery. In case of stage 4 disease, systemic treatment is not preferred for asymptomatic patients until symptomatic or radiological progression is observed, according to Response Evaluation Criteria in Solid Tumors (RECIST)[14,15]. Studies assessing the efficacy of systemic chemotherapy have limitations, such as a low number of patients and retrospective design, and a minimal effect was observed with systemic chemotherapy in these studies[16,17]. Two tyrosine kinase inhibitors have been demonstrated to contribute to progression-free survival (PFS) in metastatic disease in a phase 3 study. In the study of vandetanib compared to placebo, the PFS times were found to be 30.5 months and 19.3 months, respectively. Another agent with proven efficacy, cabozantinib, had a PFS contribution of 60 weeks versus 20 weeks compared to a placebo. Peptide receptor radionuclide therapy (PRRT), an alternative treatment, is another treatment option in MTC due to the development of resistance to both drugs and grade 3-4 side effects. The expression of somatostatin receptors *in vivo* and *in vitro* by MTC cells has been the basis for PRRT therapy in MTC patients[18,19]. ^{90}yttrium and ^{177}Lu-octreotate have been used commonly in clinical practice, and their contribution to the median OS varies between 8 and 14 months[20,21]. Current studies demonstrate that no effective treatment will contribute to OS in postoperative progression. Therefore, we considered it appropriate to share the experiences of our center to contribute to the literature.

MATERIALS AND METHODS

We retrospectively obtained clinical data of 47 patients diagnosed with progressive MTC between June 2000 and June 2019 in our oncology department. Patients aged 18 years and older, who were diagnosed with MTC pathologically and who progressed after the thyroidectomy +/- regional lymph node

dissection, were included in the study. Data regarding age, gender, family history of MTC, symptoms at first admission, and Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) were extracted from the patients' medical records. Primary tumor diameter and metastatic sites of the tumor were recorded based on the preoperative images. Clinical staging was performed according to the 8th edition American Joint Committee on Cancer stage classification for MTC. Treatment responses of all patients were evaluated radiologically by computerized tomography. The RECIST 1.1 was used to evaluate radiological progression[22]. In progressive MTC patients, systemic therapy was initiated in case of symptomatic progression in vital organs. Another indication for systemic therapy was rapid progression (within one year).

OS and PFS were primarily targeted in the survival analysis. OS was considered as the time from the start of systemic therapy to death or the last visit. PFS was considered as the time from the onset of systemic treatment to tumor progression.

Statistical Analysis

All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 21.0 (SPSS Inc, Chicago, Ill). For descriptive statistics, categorical variables were presented as count and percent. Numerical variables were presented as mean, standard deviation, and minimum and maximum values. OS and PFS were assessed using the Kaplan-Meier methods. The multivariate Cox regression models were used for each subgroup's potential prognostic risk factors on OS. The log-rank test was performed for all prognostic variables. Survival and regression analyses were performed only in progressive MTC patients receiving systemic therapy. The statistical significance level of alpha was accepted as $p<0.05$

RESULTS

Demographic and Clinicopathologic Features

Detailed demographic and clinical features of patients were summarized in Table 1. The median age was 46 (17-72) years in metastatic MTC patients. The number of males (32; 68.1%) was considerably higher than female patients (15; 31.9%). The most common clinical presentation at first admission was solitary thyroid nodule (89.4%), followed by constitutional symptoms (46.8%) and dysphagia (12.8%). At the time of diagnosis, 28 patients had T3-T4 disease, while 11 patients had T1-T2 disease. There were 31 (73.8%) patients with lymph node metastases and 8 (20.5%) patients with distant organ metastases. When we evaluated the first progression after thyroidectomy, local recurrence was found to be the most common progression type (80.9%), which was followed by bone (68.1%) and lymph node metastasis (66.0%). In our cohort, we observed visceral metastasis in 3 organs, including the lung (23.4%), liver (12.8%), and pancreas (2.1%). Thirty-four of the 47 progressive MTC patients received systemic therapy due to symptomatic or rapid progression. Vandetanib (18; 52.9%), ^{177}Lu-octreotate (9; 26.5%), and capecitabine + temozolomide (7; 20.6%)

Table 1. Demographic and clinical features of medullary thyroid carcinoma patients

Features	n (47)	(%)
Age at diagnosis (years, median±SD, min-max)	46.3±15.4	17-72
Gender		
Male	32	(68.1)
Female	15	(31.9)
Familial MTC	4	(8.5)
Clinical presentations		
Solitary nodule	42	(89.4)
Dyspnea	2	(4.3)
Dysphagia	6	(12.8)
Constitutive	22	(46.8)
Diarrhea	4	(8.5)
Bone pain	1	(2.1)
Other	1	(2.1)
Stage at diagnosis		
T stage		
T1-T2	11	(23.4)
T3-T4	28	(59.6)
Unknown	8	(17.0)
Lymph node involvement	31	(73.8)
Distant metastasis	8	(20.5)

SD: Standard deviation, min: Minimum, max: Maximum, MTC: Medullary thyroid carcinoma

Table 2. First progression type and systemic treatment options

Features	n	(%)
ECOG-PS		
0	31	(66.7)
1	16	(33.3)
Progression type		
Locally recurrent	38	(80.9)
Bone metastasis	32	(68.1)
Lymph node metastasis	31	(66.0)
Lung metastasis	11	(23.4)
Liver metastasis	6	(12.8)
Pancreas metastasis	1	(2.1)
Systemic treatments		
Capecitabine + temozolomide	7	(20.6)
Vandetanib	18	(52.9)
^{177}Lu-octreotate	9	(26.5)

ECOG-PS: Eastern Cooperative Oncology Group - Performance Status

treatments were administered as the systemic therapy (Table 2). Of our cohort, eight patients did not develop symptomatic or rapid progression after thyroidectomy. Four patients died within three months of progression, and one patient did not come to follow-up after progression. Therefore, 13 patients in the study did not receive any systemic therapy.

Survival and Risk Factors

The median time from diagnosis to death was 194.2±21.8 months (151.4-236.9 mos). After thyroidectomy, the median time to the first recurrence was 31.3±5.2 months (21.0-41.6 mos). The median time from the first recurrence to initiation of the systemic therapy was 17.6±26.8 (0.0-118.54 mos) months.

OS and PFS analyses were performed on 34 patients who received systemic therapy. Four patients died within three months of progression during the follow-up period without any systemic treatment. The mortality and progression rates were 58.8% (14 patients) and 44.1% (15 patients) in patients receiving systemic therapy, respectively. From the start of systemic therapy, the median PFS and the median OS were 51.7±11.9 months (28.2-75.1 mos) and 55.6±20.9 months (14.6-96.7 mos), respectively (Figure 1).

When systemic therapies were divided into two groups as vandetanib and other treatments, the Kaplan-Meier survival analysis showed that the patients receiving vandetanib had a better OS compared to those receiving other treatments (84.7 months vs. 37.1 months, respectively; p=0.047; Figure 2). ECOG-PS was another significant parameter for OS; patients with ECOG-PS 0 had higher median OS compared to those with ECOG-PS 1 (77.2 months vs. 34.4 months, respectively; P=0.002; Figure 3). The presence of liver or bone metastases did not affect survival (p>0.05, for both). Also, there was no difference between familial and sporadic MTC subgroups for OS (p=0.131). The univariate survival analysis (Kaplan-Meier analysis) and log-rank test results are shown in Table 3.

Multivariate analysis of the factors related to OS demonstrated that ECOG-PS 1 was an independent prognostic factor and associated with poor outcomes (HR: 14.7; 95% CI: 1.7-124.7; p=0.013; Table 4).

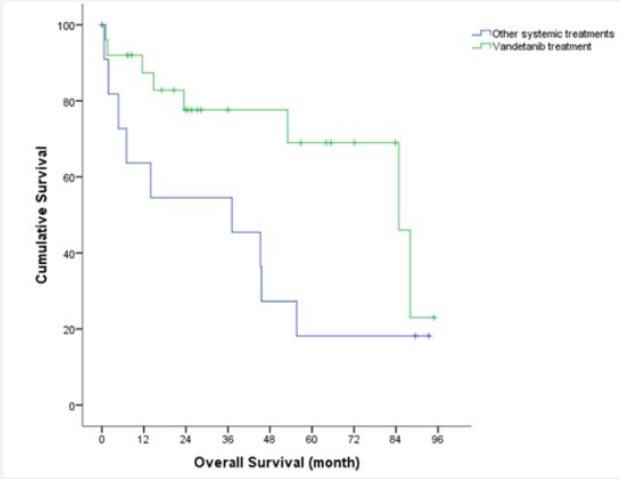

Figure 2. Patients treated with vandetanib had a favorable overall survival compared to other treatment arms (84.7 months vs. 37.1 months, respectively; p=0.047)

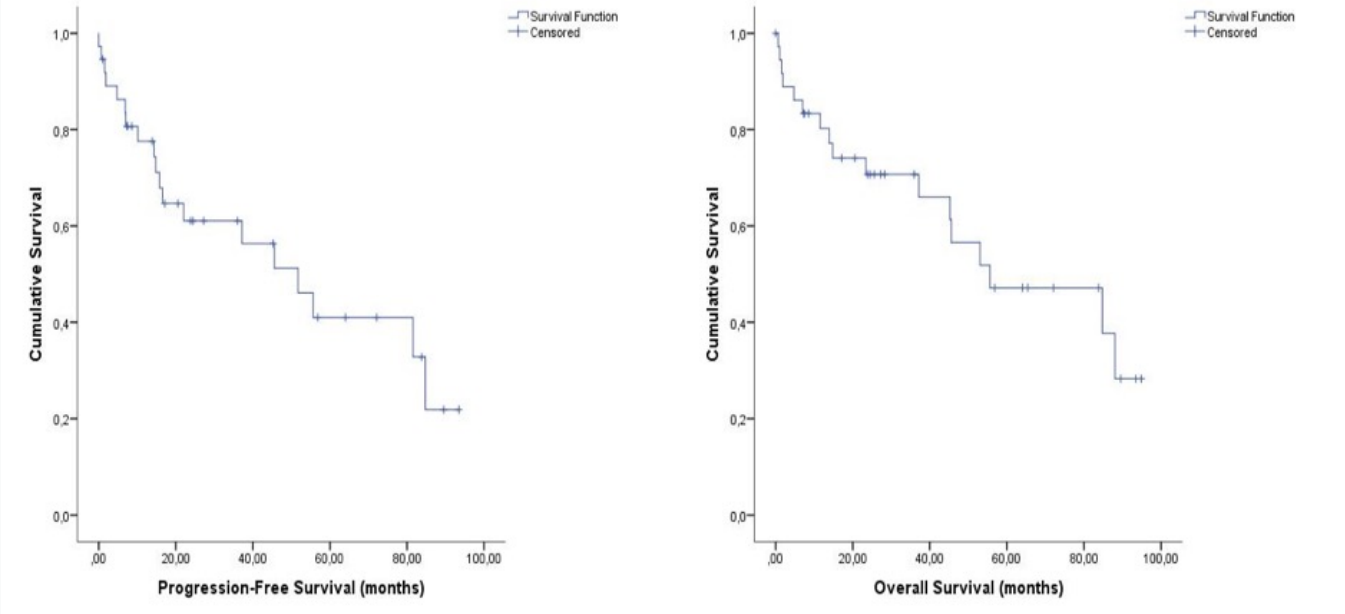

Figure 1. The mean progression-free survival is 51.7±11.9 months after the beginning of systemic treatment in progressive medullary thyroid cancer patients (left). The median overall survival is 55.6±20.9 months in the same patient cohort (right)

DISCUSSION

Our study aimed to determine the prognostic risk factors affecting survival in MTC patients who received systemic therapy after surgery. When we reviewed the demographic data, we observed that the median age was 46 years, and the male gender was dominant (68.1%). In a phase 3 study, in which Wells et al.[23] assessed the efficacy of vandetanib in metastatic MTC, the median age was 50.7 years, and the male ratio was 53.4%. In the study of Elisei et al.[24], who assessed the efficacy of cabozantinib in progressive MTC patients, the median age was 55 years, and the male ratio was 68.9%. Both studies show male gender dominance, consistent with our study. However, in our study, the median age of patients with progressive MTC was younger. The median time to the first recurrence after thyroidectomy in our cohort was 31.3±5.2 months (21.0-41.6 mos). It seems that our patients had a faster progression after thyroidectomy compared to the literature[25,26]. Most of our patients had advanced T and N stages at first diagnosis (Table 1). In addition, reasons such as residual disease after thyroidectomy and persistence of calcitonin may be responsible for rapid progression. Due to the retrospective nature of our study, we lacked sufficient data to assess these factors.

Table 3. Univariate survival analysis (Kaplan-Meier analysis) and log-rank test results

Risk factors	n (%)	Events (%)	Five-year survival rate	p
ECOG-PS 0	19 (55.9)	5 (26.3)	82.6	0.002
ECOG-PS 1	15 (41.1)	12 (80.0)	9.8	
Non-visseral metastasis	20 (58.8)	8 (40.0)	65.3	0.547
Visseral metastasis	14 (41.2)	9 (64.2)	29.4	
^{177}Lu-octreotate or capecitabine + temozolomide treatment	16 (47.1)	9 (56.2)	18.2	0.047
Vandetanib treatment	18 (52.9)	8 (44.4)	69.0	

ECOG-PS: Eastern Cooperative Oncology Group - Performance Status

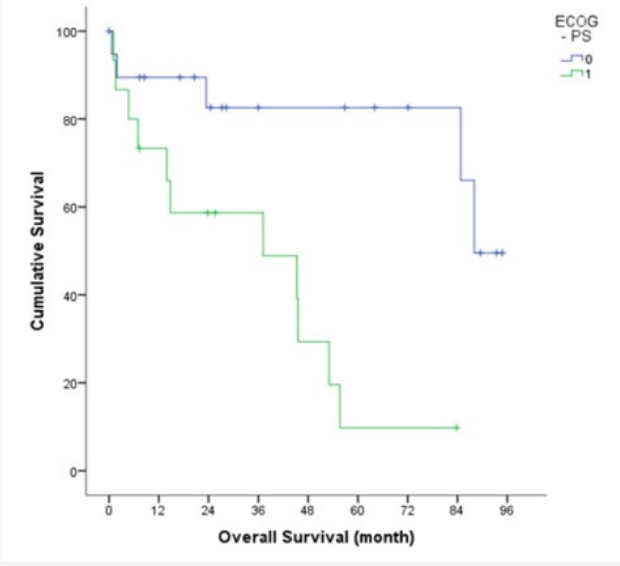

Figure 3. Patients with ECOG-PS 1 are associated with a poor survival outcome than patients with ECOG-PS 0 (77.2 months vs. 34.4 months, respectively; p=0.002)

ECOG-PS: Eastern Cooperative Oncology Group - Performance Status

Local recurrence was the most common one among the progression patterns, followed by bone and lymph node metastases, respectively. The most frequent visceral metastatic organ was the lung. In prospective studies assessing the efficacy of vandetanib and cabozantinib, the liver was observed to be the most common visceral metastasis site[23,24]. In a phase 2 study assessing the efficacy of pazopanib in 35 MTC patients, the liver was reported to be the most common visceral metastasis site[27]. Our results seem to contradict other studies in the literature. The fact that our study was conducted with a sample from a single center may be the reason for this discordance. Our results need to be confirmed by multicenter studies.

Although vandetanib and cabozantinib are Food and Drug Administration-approved treatments for progressive disease (PD), not every patient can access the drug due to its cost and reimbursement conditions. Approximately half of the patients in our study received vandetanib treatment. There were also patients treated with ^{177}Lu-octreotate or a combination of capecitabine-temozolomide chemotherapy. In retrospective studies on ^{177}Lu-octreotate, PD was observed in 37.6% of MTC patients[21,28]. PD with ^{177}Lu-octreotate was observed in 11.1% of our patients. In the study of Nocera et al.[16], in which they assessed the effectiveness of chemotherapy in progressive MTC patients, the PD rate was 45%. In our patients receiving vandetanib, compared to the patients in the study of Wells et al.[23], the PD rate was 38.8% to 13%, respectively. Although vandetanib and cabozantinib have PFS advantages in MTC,

Table 4. Multivariate analysis for disease-related death

Risk factors	n (%)	p	HR	95% CI
ECOG-PS 0	19 (55.9)	-	1	
ECOG-PS 1	15 (41.1)	0.013	14.7	1.74-124.78
Non-visceral metastasis	20 (58.8)	-	1	
Visceral metastasis	14 (41.2)	0.117	0.29	0.06-1.35
^{177}Lu-octreotate or capecitabine + temozolomide treatment	16 (47.1)	-	1	
Vandetanib treatment	18 (52.9)	0.287	0.59	0.22-1.55

CI: Confidence interval, ECOG-PS: Eastern Cooperative Oncology Group - Performance Status, HR: Hazard ratio

^{177}Lu-octreotate and chemotherapy may provide significant benefits in selected patients.

The median OS was 55.6 months after the first systemic therapy (Figure 1). Factors affecting survival within the subgroups were vandetanib use and ECOG-PS. Also, ECOG-PS was the only prognostic factor on OS in multivariate analysis. Classical risk factors known to affect survival in MTC patients are age, disease stage, and biomarker elevation at diagnosis. In our study, ECOG-PS was an independent prognostic risk factor, unlike these factors. In a retrospective study, Valerio et al.[29] evaluated 79 MTC patients treated with vandetanib and found that ECOG-PS was an important factor in predicting the longer and durable response. Current findings show that ECOG-PS is an important prognostic marker in progressive MTC patients receiving systemic therapy.

Study Limitations

The important limitations of our study are that it was a single-center study and it included a limited patient group. In addition, as a retrospective-based analysis, it is not possible to generalize the study results.

CONCLUSION

MTC is a rare endocrine malignancy and has limited systemic treatment options in PDs. Apart from tyrosine kinase inhibitors with evidence-based efficacy, chemotherapy and ^{177}Lu-octreotate treatments may provide additional contributions to selected patients. Multicenter studies involving more patients are required to understand the efficacy of alternative treatments.

Ethics

Ethics Committee Approval: The Academic Committee approved retrospective analyses of clinical data of İstanbul University (protocol no: 2021/2103, date: 04.03.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Pratices: F.F., N.P., M.B., Concept: N.P., M.B., Design: F.F., Data Collection or Processing: N.P., M.B., Analysis or Interpretation: F.F., M.B., Literature Search: F.F., N.P., Writing: F.F., N.P., M.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Evaluation of Factors Affecting the Selection of Histology and Embryology in the Medical Specialization Examination

Tıpta Uzmanlık Sınavı'nda Histoloji ve Embriyoloji Branşının Seçimini Etkileyen Faktörlerin Değerlendirilmesi

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ABSTRACT

Aim: The medical specialty preference process is a complex and dynamic process that includes many direct and indirect variables. Investigating the factors that affect physicians' specialization preferences is important for physicians who will choose their specialty in the future. We aimed to define the importance of the factors affecting the selection of Histology and Embryology in the medical specialization.

Materials and Methods: In this descriptive, cross-sectional study, a questionnaire was applied to residents and specialist physicians in Histology and Embryology. A total of 108 participants were included in the study, and the statistical analysis of the obtained data was done with Statistical Package for the Social Sciences program version 22.0.

Results: The mean age was 35±9 years and 64.8% were married. The most effective factors in choosing Histology and Embryology were determined as ability to take time for themselves (52.8%), night shift number/intensity (48.10%), patient intensity (46.30%), number of on-call duty (41.7%), and less probability of exposure to violence (38.9%), respectively. 38.89% of the physicians were considering working abroad, and 50% of them thought of resigning from this branch. Exposure to mobbing was found to increase the thought of resignation. The current professional title and gender affected the idea of working abroad.

Conclusion: The thought of choosing the branch of Histology and Embryology is influenced by various factors. It is essential to improve the working conditions, to make economic arrangements, and take measures to prevent mobbing and burnout of physicians working in the field of Histology and Embryology.

Keywords: Specialization in medicine, career choice, histology, embryology

ÖZ

Amaç: Tıpta uzmanlık tercih süreci, doğrudan ve dolaylı birçok değişkeni barındıran karmaşık ve dinamik bir süreçtir. Hekimlerin uzmanlık alan tercihlerini etkileyen faktörlerin araştırılması, bu eğitim ve öğretimi planlayanlar ve gelecekte uzmanlık alan tercihi yapacak olan hekimler için önem taşımaktadır. Bu çalışmada, tıpta uzmanlıkta Histoloji ve Embriyoloji'nin seçimini etkileyen faktörlerin öneminin tanımlanması amaçlanmıştır.

Gereç ve Yöntem: Tanımlayıcı, kesitsel tipteki bu araştırmada, Histoloji ve Embriyoloji alanında uzmanlık eğitimi alan araştırma görevlilerine ve uzman hekimlere anket uygulandı. Toplam 108 katılımcı çalışmaya dahil edilerek, elde edilen verilerin istatistiksel analizi Statistical Package for the Social Sciences programı versiyon 22.0 ile yapıldı.

Bulgular: Çalışmaya dahil edilen 108 katılımcının ortalama yaşı 35±9 yıl idi ve %64,8'i evliydi. Histoloji ve Embriyoloji alanında çalışan hekimlerin bu branşı seçmesini etkileyen faktörler incelendiğinde; %52,8 ile "kendine vakit ayırabilme", %48,10 ile nöbet sayısı/yoğunluğu, %46,30 hasta yoğunluğu, %41,7 ile icap sayısı, %38,9 ile şiddete maruz kalma ihtimali olduğu bulundu. Histoloji ve Embriyoloji alanında çalışan hekimlerin %38,89'u yurt dışında çalışmayı düşünürken, %50'si bu branştan istifa etmeyi düşünmekteydi. Mobbinge maruziyetin, istifa düşüncesini artırdığı görüldü.

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Sonuç: Histoloji ve Embriyoloji branşını seçme düşüncesi çeşitli faktörlerden etkilenmektedir. Histoloji ve Embriyoloji alanında çalışan hekimlerin iş ve çalışma koşullarının iyileştirilmesi, ekonomik anlamda düzenlemeler yapılması ve mobbing ve tükenmişliğin önüne geçmek için önlemler alınması oldukça önemlidir.

Anahtar Kelimeler: Tıpta uzmanlık, kariyer seçimi, histoloji, embriyoloji

INTRODUCTION

Profession of a doctor is one of the critically important professions that require discipline, theoretical knowledge, skills, abilities and attention[1,2]. The legal basis for the profession of medicine is stated in the Law on the Practice of Medicine and Medical Arts of 1928/1219: "Those who have the qualifications indicated in this law for the practice of medicine in Turkey generally have the right to treat the diseases. However, in order for any branch to be specialized in medicine and to be able to declare that title, it must have a specialization certificate issued from the Turkish Medical Faculty or an institution to be accepted and announced by the Ministry of Health, or given from a well-known hospital or laboratory in foreign countries and approved by the Turkish Medical Faculty." explained in Article 8. In the 1st article of the same law, it is stated that "it is necessary to have a diploma from the medical faculty to practice medicine and to treat patients in any way within the Republic of Turkey" and it is stated that they have the title of "physician" only after graduating from medical school, and in this case, they can obtain the right to give treatment[3]. Basic features of professionalism include having theoretical knowledge, using theoretical knowledge in practice, having connection with the values of the society, education, ethical rules, accountability, self-sacrifice, excellence, honesty, honor and respect for others[4,5].

Specialization education in medicine has a structure created and maintained with the participation of multiple stakeholders. In this educational structure, there are many stakeholders such as students receiving specialization training, faculty members, universities and training and research hospitals providing specialization education, the Board of Specialization in Medicine, which regulates the infrastructure of education, and the Ministry of Health. This education is an important process that has both a service delivery dimension and a health service delivery dimension[6]. The main purpose of specialization education in medicine is to train specialist physicians that society needs and to provide health services by increasing the competence of these physicians in their field of specialization. To receive specialization education in Turkey, it is necessary to take the Medical Specialization Examination (TUS) and get a certain level a score, then make a choice and be eligible for training in the relevant department. Both state and foundation university hospitals and training and research hospitals carry out this education as formal education[7]. TUS was made by "Ölçme, Seçme Ve Yerleştirme Merkezi" (ÖSYM) for the first time in September 1987, in accordance with the Regulation on Medical Specialization Education Entrance Exams and the decision of the Higher Education Executive Board dated 25.12.1986 and numbered 86.50.1164, protocols signed between the Ministry of Health and the Higher Education Council, and between the General Staff and the Higher Education Council[8]. TUS, which has been applied uninterruptedly for 35 years since the first year, is applied twice a year by OSYM with multiple choice test method, and the institution and branch where the training will be held according to the scores obtained after the exam are determined by OSYM with the central system according to the preference of the candidates.

The science that we call tissue science in Turkish is called Histology, derived from the Greek words "*histo*" meaning membrane or tissue and "*logos*" meaning science, which examines the cell units, which are the most important building blocks of tissue, and the properties of these cells in different tissues, body tissues and the arrangements of these tissues to form organs[9]. The science of histology is a branch that deals with the functions performed at the cell and tissue level by examining and teaching normal cells, tissues and organs microscopically and it has an important place in medical education since it forms the basis of physiology and pathology[10].

Although embryology means the branch of science that studies the embryo, this term refers to prenatal development, that is, both embryo and fetus development[11]. All developmental events in the process from fertilization to birth constitute the subject of embryology. Human embryology investigates the development and functioning of cells different from the zygote formed by sperm fertilization of the oocyte, tissues and organs, and the underlying causes of abnormal development. Because it clarifies the origins of various pathological cases and diseases, it can be a guide for clinical applications of gynecology and obstetrics, pediatrics, pediatric surgery, teratology, plastic and reconstructive surgery, as well as being in close relation with anatomy, histology, physiology, genetics and pathology. In addition, "Assisted Reproductive Techniques" applied in the treatment of infertility is the laboratory application area of embryology[12,13].

In the career possibilities specified in the Histology and Embryology Specialization Education Core Curriculum of the Medical Specialization Board Curriculum Creation and Standard Setting System, it is stated that "Histology and

Table 1. Questionnaire items					
Your gender?					
Your age?					
Your age at the time when you have chosen the department?					
Place of birth?					
Do you have a specialization other than Histology and Embryology?					
If you have a specialization other than Histology and Embryology, what is it?					
Have you worked as a resident in another field?					
If you worked as a resident in another field, which branch/branches were they? How long did it take?					
What is your marital status?					
What was your marital status when you entered the department?					
Did you have children when you entered the department?					
Did you have a child after entering the department?					
If you had a child after completing the department, was it during the residency or after getting the specialization?					
Which medical faculty did you graduate from (Bachelor's degree)? Graduation year?					
Where did you get your specialization? What was the year?					
Have you worked as a general practitioner?					
If you worked as a general practitioner, how long did you work?					
If you were a general practitioner, in which unit did you do it? (More than one can be selected)					
Your current professional title?					
Are you considering being an academic?					
Are you considering doing your job abroad?					
Was Histology and Embryology your first choice as a branch in the Medical Specialization Exam?					
If the branch of Histology and Embryology was not your first choice in the Medical Specialization Exam, which branch was your first choice?					
Indicate to what extent the following factors influenced your choice of this specialization (1: never, 5: very much)					
[Loving the branch]	Never affected	Not affected	Undecided	Affected	Very much affected
[TUS score]	Never affected	Not affected	Undecided	Affected	Very much affected
[The prestige of the department in society]	Never affected	Not affected	Undecided	Affected	Very much affected
[Personal talent and interest]	Never affected	Not affected	Undecided	Affected	Very much affected
[Advice from people with knowledge on the subject]	Never affected	Not affected	Undecided	Affected	Very much affected
[Professional satisfaction opportunity]	Never affected	Not affected	Undecided	Affected	Very much affected
[Academic advancement/possibility to do research]	Never affected	Not affected	Undecided	Affected	Very much affected
[Financial return]	Never affected	Not affected	Undecided	Affected	Very much affected
[Patient intensity]	Never affected	Not affected	Undecided	Affected	Very much affected
[Workload or stress brought by the department]	Never affected	Not affected	Undecided	Affected	Very much affected
[Department's level of risk/responsibility/malpractice]	Never affected	Not affected	Undecided	Affected	Very much affected
[Communication between seniors]	Never affected	Not affected	Undecided	Affected	Very much affected
[Possibility of exposure to violence]	Never affected	Not affected	Undecided	Affected	Very much affected
[Possibility to be assigned to city centers/major cities]	Never affected	Not affected	Undecided	Affected	Very much affected
[Length of residency]	Never affected	Not affected	Undecided	Affected	Very much affected
[Order of working hours]	Never affected	Not affected	Undecided	Affected	Very much affected
[Number and intensity of shifts]	Never affected	Not affected	Undecided	Affected	Very much affected
[Opportunity to set aside time for oneself]	Never affected	Not affected	Undecided	Affected	Very much affected
[Number of standby duties]	Never affected	Not affected	Undecided	Affected	Very much affected

[Need to provide emergency service]	Never affected	Not affected	Undecided	Affected	Very much affected
[Performance system]	Never affected	Not affected	Undecided	Affected	Very much affected
[Choosing a specialty so as not to be a general practitioner]	Never affected	Not affected	Undecided	Affected	Very much affected
[Preference of branches with teamwork]	Never affected	Not affected	Undecided	Affected	Very much affected
[Whether it requires physical strength]	Never affected	Not affected	Undecided	Affected	Very much affected
[The possibility of using high-end technology]	Never affected	Not affected	Undecided	Affected	Very much affected
[Comfort of residency training]	Never affected	Not affected	Undecided	Affected	Very much affected
[The possibility of preparing for TUS again after entering the department]	Never affected	Not affected	Undecided	Affected	Very much affected
[My gender suitable for the branch]	Never affected	Not affected	Undecided	Affected	Very much affected
[Possibility of benefiting infertile patients with the applied treatments]	Never affected	Not affected	Undecided	Affected	Very much affected
Have you considered resigning during your residency or specialization?					
If you have considered resigning during your residency or specialization, what has compelled you to do so? (More than one can be selected)					
Were you exposed to mobbing while you were a research assistant or specialist in your branch?					
If you were exposed to mobbing while you were a research assistant or specialist in your branch, can you explain?					
Considering the techniques applied by Histology and Embryology specialists today, which does the branch of Histology and Embryology belong to? (More than one answer may be given.)					
Is there any additional factor you would like to specify in choosing the branch of Histology and Embryology?					
TUS: Medical Specialization Examination					

Embryology specialists are employed as an embryologist in assisted reproductive technical laboratories and in andrology laboratories within the framework of legal regulations, as well as working as lecturers in universities. They work in stem cell centers, cellular therapies, cord blood banking, bioengineering, in producing artificial organs for research and therapy, and they provide consultancy at the clinical diagnosis and research level regarding developmental anomalies". The branch of Histology and Embryology is one of the ideal branches to be preferred by physicians who are passionate about doing research and have the ability to follow the literature. During the specialization training process of this branch, in addition to classical Histology and Embryology training, studies are carried out in areas such as stem cells, cord blood, bioengineering, artificial organs, developmental anomalies, various types of microscopes, molecular techniques, cell culture, organ culture, immunohistochemistry, and immunofluorescence[14].

Among the most important choices made in human life, the choice of profession is the first. Choosing a profession that enables individuals to realize their expectations and wishes, directs and concerns their lives is a very complex process[15-17]. In this study, it was aimed to define the factors affecting the selection of Histology and Embryology as the branch in TUS and to emphasize their importance.

MATERIALS AND METHODS

The study was approved by Muğla Sıtkı Koçman University Medical and Health Sciences Ethics Committee (protocol no: 220041, decision no: 39, date: 28.04.2022). Research assistants who were in the process of specialization training in medicine in the field of Histology and Embryology and specialist physicians who had completed their specialization training formed the population of the study. All of the people who met these qualifications and constituted the study population in Turkey were reached, and 108 people who agreed to participate in the study were included.

The research was carried out by filling out the online questionnaire prepared via Google forms. Volunteering consent form was obtained through the Google form and the participants were informed at the beginning of the form that the approximate time required to answer the questionnaire was 6-10 minutes. These questionnaires did not contain any identifying information, and no questions that could reveal the identities of the volunteers were asked. Demographic data such as gender, age, and marital status were recorded. Questions about subjects such as considering working abroad, and resigning during the residency and specialization process in Histology and Embryology were prepared and presented as multiple choice items. In Table 1, the questions are given in detail. In order to determine the factors affecting the preferences of specialization in medicine, Nazife Öztürk developed the "Physicians' Preference Tendencies of Specialty Branch Scale", consisting of 42 items and 7 dimensions, based on qualitative data, within the scope of the research conducted in 2019 with a total of 502 people who were medical faculty students and preparing for the specialization exam[18]. In our study, these scales were made suitable for physicians working in the field of Histology and Embryology and some revisions were made, and the factors affecting the choice

of specialty were prepared as 29 questions. Responses to the statements in the questionnaire were structured as a 5-point Likert type, and they were listed as 1: Never affected, 2: Not Affected, 3: Undecided, 4: Affected 5: Very much affected. All questionnaires were administered in Turkish.

Statistical Analysis

Descriptive statistics were expressed as mean, standard deviation, median, and minimum-maximum values for continuous data, and percentage (%) and frequency (n) for discrete variables. The conformity of continuous data to normal distribution was evaluated with the Kolmogorov-Smirnov test and the Shapiro-Wilk test. The Mann-Whitney U test was used to compare two independent groups, and the Kruskal-Wallis test was used to compare more than two groups for non-parametric data. For parametric data, the Student's t-test was used to compare two independent groups, and the ANOVA test was used to compare more than two groups. The Pearson chi-square test was employed to compare categorical data. For statistical significance, p-values below 0.05 at the 95% Confidence interval were considered significant. IBM Statistical Package for the Social Sciences, Chicago, IL, USA version 22.0 was used for statistical analysis.

RESULTS

Demographic Features of the Participants

The mean age of the participants was 35±9 years, and the mean age was found as 29±5 years at the time when they chose the department. Of the Histology and Embryology physicians participating in the study, 82 (75.92%) were women. While 46.3% of the participants were married when they entered the department, 53.7% were single. When the survey was conducted, the rate of those who were married reached 64.8%. While 6.5% of the participants had children after residency, 29.6% had children during residency, and 63.9% did not have children (Table 2).

Professional Characteristics of the Participants

While 23% of the participants had a residency in another field, only 2.8% had specializations other than Histology and Embryology. The fields from which they resigned and transferred to Histology and Embryology were child health and diseases with 21.7%, anesthesiology and reanimation with 17.40%, and family medicine with 8.7%, respectively. It was observed that the average duration of being a resident in another department before the resignation was 12±10 months. 81.20% of the participants had worked as general practitioners and the average duration of working as a general practitioner was found to be 4±4 years. When the current professional titles of the participants were examined, it was detected that 46.30% of them were research assistant physicians, 3.70% were instructor physicians, 32.40% were specialist physicians, 9.30% were assistant professors, 3.70% were associate professors, and 4.60% were professors. While 33.3% of the participants were considering working as an academician in the future, 13% did not. 18.5% of them are still working as academicians. While 39.8% of the participants preferred the Histology and Embryology branch in the first place in TUS, 60.2% of the participants preferred the other branches shown in detail in Table 3.

Views of Participants About the Profession

While 50% of the study participants were considering resigning during their residency and specialization, the other 50% did not consider it. When the reasons for resigning were examined, it was found that 24.19% of the participants stated that they had concerns for the future. 23.38% of the participants were considering resigning due to 'unsatisfaction with the branch', 21.77% due to 'financial return', 15.32% due to 'mobbing' and 8% due to 'wanting another branch'. In addition, among the reasons for considering resignation were 'Loss of Prestige', ' Non-Medical Branches' Being More Advantageous', 'Wanting to Change University', 'Stressful Work Environment', 'Child Care', 'Lack of Education' and 'Problematic Team Workers'. 34.3% of the participants stated that they thought they were exposed to mobbing. When the participants were asked about the scope of their specialization, Histology and Embryology were thought to be involved in Basic Sciences by 81 participants, in Surgical Sciences by 57 participants, and in Internal Medicine Sciences by 33 participants (Table 4).

While 38.89% of the physicians working in the field of Histology and Embryology were considering working abroad, 25.93% were not considering working abroad. 35.19% of the participants were undecided on this issue (Figure 1).

Table 2. Demographic features of the participants

		Mean±SD/N (%)
Age		35±9
Age at the time of choosing the department		29±5
Gender	Male	26 (24.08%)
	Female	82 (75.92%)
Marital status (current)	Single	38 (35.2%)
	Married	70 (64.8%)
Marital status (at the time when the department was won)	Single	58 (53.7%)
	Married	50 (46.3%)
Time of having child	Not have a child	69 (63.9%)
	During residency	32 (29.6%)
	After specialization	7 (6.5%)

SD: Standard deviation

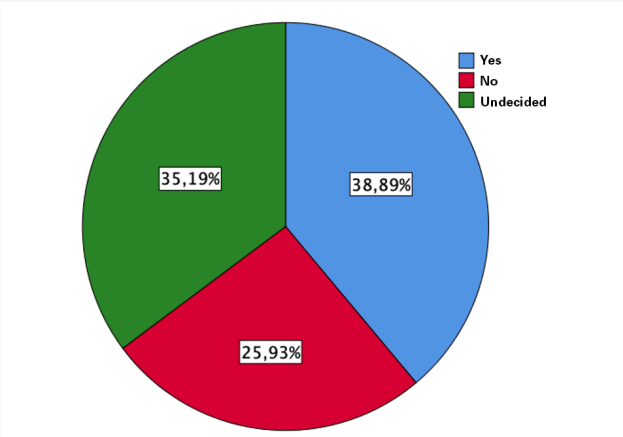

Figure 1. Evaluation of the thought of working abroad

Factors Affecting Choosing the Field of Specialization

When the factors affecting the choice of the specialization field of physicians working in the field of Histology and Embryology were examined, it was determined that the factor that affected the most was 'setting aside time for oneself' with the rate of 52.8%. The following most affecting factors were 'Number/Intensity of Shifts' with the rate of 48.10%, 'Patient Intensity' with the rate of 46.30%, 'Number of Standby Duty' with the rate of 41.7%, 'Probability of Exposure to Violence' with the rate of 38.9%, 'Order of Working Hours' with the rate of 38%, 'Risk/Responsibility/Malpractice Level of the Department' with the rate of 37%, and 'Workload Stress Brought by the Department' with the rate of 36.10%. It was determined that the factor that affected the choice of specialization the least was 'Possibility to Prepare for TUS again after Winning

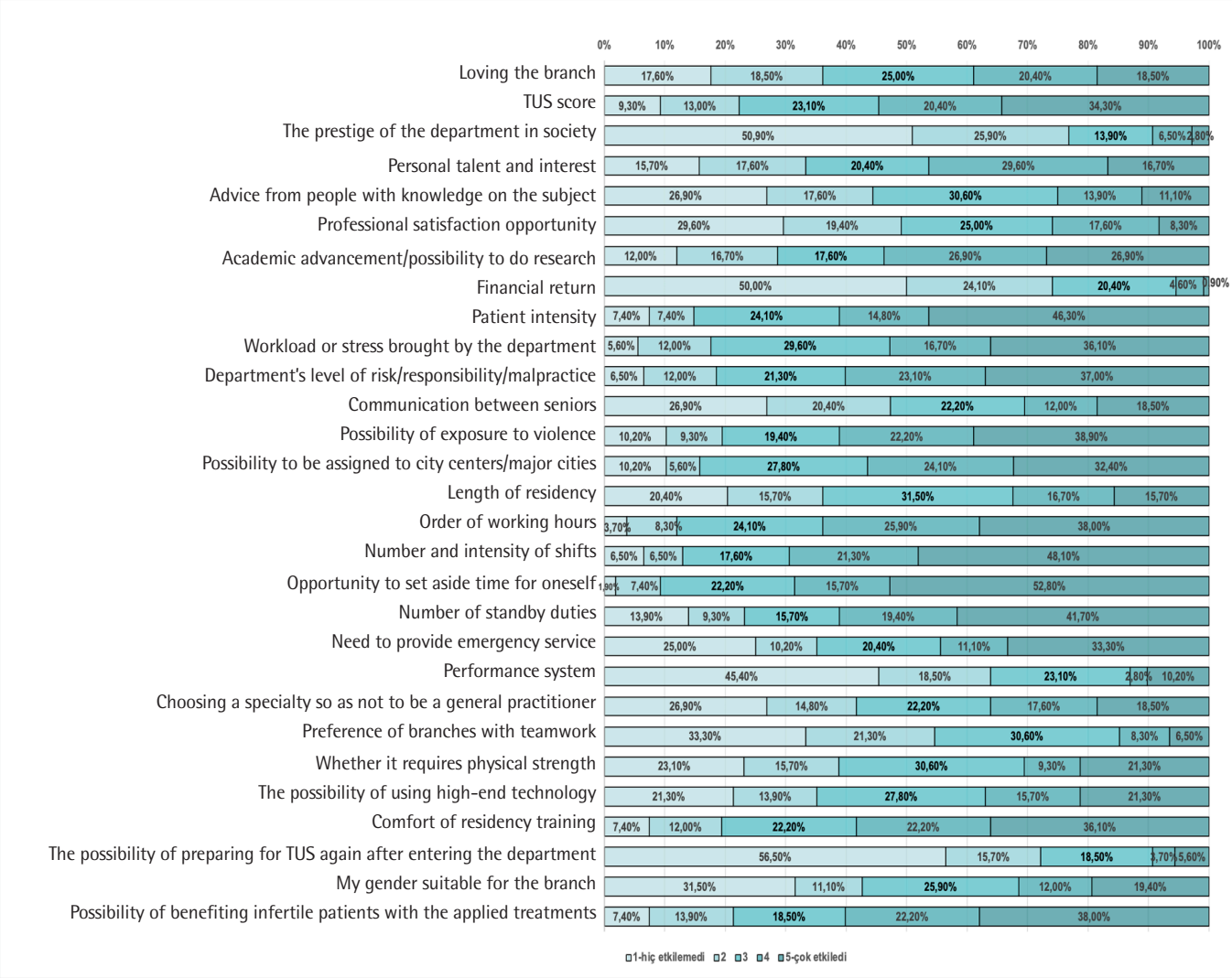

Figure 2. Factors affecting the choice of specialization

TUS: Medical Specialization Examination

Table 3. Evaluation of participants' professional characteristics

		Number/ Mean±SD	Percentage %
Specialization branch other than Histology and Embryology	None	105	97.20%
	Family medicine	1	0.90%
	Child health and diseases	2	1.90%
Being resident in another branch	Yes	25	23.10%
	No	83	76.90%
Department of residency	Ophthalmic diseases	1	4.30%
	Cardiology	1	4.30%
	Family medicine	2	8.70%
	Anesthesiology and reanimation	4	17.40%
	Child health and diseases	5	21.70%
	Neurology	1	4.30%
	Chest diseases	1	4.30%
	Gynecology and obstetrics	1	4.30%
	Internal diseases	1	4.30%
	Pediatric surgery	1	4.30%
	Public health	1	4.30%
	Medical pathology	1	4.30%
	Emergency medicine	3	13.00%
Duration of residency (month)		12±10	
Working as a general practitioner	Yes	88	81.50%
	No	20	18.50%
Duration of working as a general practitioner (year)		4±4	
Current professional title	Research assistant (for the Ministry of Health)	20	18.50%
	Research assistant (Foreign Nationality)	2	1.90%
	Research assistant (for the Higher Education Board)	28	25.90%
	Lecturer physician	4	3.70%
	Specialist physician	35	32.40%
	Assistant professor	10	9.30%
	Associate professor	4	3.70%
	Professor	5	4.60%
Thought of being academician	Already academician	20	18.50%
	Yes	36	33.30%
	No	14	13.00%
	Undecided	38	35.20%
The firstly preferred branch in TUS	Histology and embryology	43	39.80%
	Other	65	60.20%

TUS: Medical Specialization Examination, SD: Standard deviation

the Department' with the rate of 56.5%. Apart from this, it was determined that the least influencing factors were the 'Reputation of the Department in the Society' with the rate of 50.90%, 'Its Financial Return' with the rate of 50%, and 'Performance System' with the rate of 45.5% (Figure 2).

There was no statistically significant difference between age and thinking that the branch of Histology and Embryology belonged to internal sciences, surgical sciences or basic sciences ($p>0.05$). There was no statistically significant difference between thinking of being an academician and thinking that the branch of Histology and Embryology belonged to internal sciences, surgical sciences or basic sciences ($p>0.05$). A statistically significant difference was found between the academic title and the thought that the Histology and Embryology branch belonged to internal sciences, surgical sciences or basic sciences ($p=0.030$). While 80% of professors and 50% of associate professors thought that histology was a branch of basic sciences, most of the assistant professors, research assistants, lecturers and specialists thought that histology included more than one branch (Table 5).

Table 4. Evaluation of participants' views on the profession

		Number	Percentage
Thought of resigning	Yes	54	50.00%
	No	54	50.00%
Reason for the thought of resigning	Mobbing	19	15.32%
	Financial return	27	21.77%
	Concern for future	30	24.19%
	Unsatisfaction with the branch	29	23.38%
	Wanting another branch	10	8.00%
	Wanting to change the university	1	0.80%
	Stressful work environment	1	0.80%
	Child care	1	0.80%
	Lack of education	1	0.80%
	Loss of reputation	2	1.60%
	Non-medical branches' being more advantageous	2	1.60%
	Problematic team workers	1	0.80%
	Total	124	100.00%
Thought of being exposed to mobbing	Yes	37	34.30%
	No	71	65.70%
Participants' views for the branch of Histology and Embryology	Basic sciences	81	47.36%
	Internal sciences	33	19.29%
	Surgical sciences	57	33.33%
	Total	171	100%

Table 5. Investigation of factors affecting the choice of Histology and Embryology branch

		Scope of Histology and Embryology branch								
		Surgical		Internal		Basic		More than one		
		N%/M±SD		N%/M±SD		N%/M±SD		N%/M±SD		p
Age		40±9		35±10		35±9		34±8		0.065[1]
Thought of being academician	Already academician	3	15.00%	2	10.00%	7	35.00%	8	40.00%	0.636[2]
	Yes	4	11.10%	1	2.80%	10	27.80%	21	58.30%	
	No	4	28.60%	0	0.00%	4	28.60%	6	42.90%	
	Undecided	7	18.40%	4	10.50%	8	21.10%	19	50.00%	
Title	Research assistant	5	10.00%	4	8.00%	17	34.00%	24	48.00%	**0.030[2]**
	Specialist physician	10	28.60%	1	2.90%	4	11.40%	20	57.10%	
	Lecturer physician	0	0.00%	1	25.00%	0	0.00%	3	75.00%	
	Assistant professor	2	20.00%	0	0.00%	2	20.00%	6	60.00%	
	Associate professor	1	25.00%	0	0.00%	2	50.00%	1	25.00%	
	Professor	0	0.00%	1	20.00%	4	80.00%	0	0.00%	

[1]Kruskal-Wallis, [2]Pearson chi-square.
M: Mean, SD: Standard deviation, n: Number

While 83% of those who thought they were exposed to mobbing were considering resigning from Histology and Embryology residency or specialization, 32% of those who were not exposed to mobbing were considering resigning for different reasons. A statistically significant difference was found between the two groups (p=0.001). The thought of being exposed to mobbing can increase the thought of resigning. Respectively, 38% of the research assistants, 100% of the lecturer physicians, 68% of the specialist physicians, 40% of the assistant professors, 50% of the associate professors and 20% of the professors thought to resign in sometime of their professional life in Histology and Embryology. There was a statistically significant difference between the professional title and the thought of resigning (p=0.016). There was no significant difference in terms of other factors (p>0.05) (Table 6).

It was observed that the current professional title and gender affected the thought of working abroad. Of the participants, 69% of men and 29% of women thought to work abroad. A statistically significant difference was found between both groups (p=0.001). There was no significant difference in terms of other factors (p>0.05) (Table 7).

DISCUSSION

How the physicians having graduated from the faculty of medicine continue their careers is very important both for their own future and for the appropriate evaluation of the human resources in the health system they are involved in. Physicians in Turkey graduate with the title of general practitioner after completing 6 years of medical education. All graduated physicians are appointed as general practitioners by the Ministry of Health within the first two months following graduation. Physicians can specialize in a branch according to the scores they get by entering the TUS, which is held twice a year throughout the country. There are many factors that affect the branch to be preferred in specialization education. In this study, we aimed to evaluate the reasons for choosing this branch, the factors affecting the selection of the branch, and the current views of the residents and specialist doctors who prefer the Histology and Embryology branch.

While the mean age of the participants in our study was 35 years, the mean age was 29 years when they preferred the branch of Histology and Embryology. Considering that the average age for graduation from medical faculties in Turkey is 24 years[19], it is seen that this department is preferred 5 years after graduation. Considering the reasons for this, it was seen that 23% of the participants worked as an assistant in another department after graduation, then changed their departments and preferred Histology and Embryology. The fields from which they resigned and transferred to Histology and Embryology were Child Health and Diseases with 21.7%, anesthesiology and reanimation with 17.40%, and Family Medicine with 8.7%, respectively. These departments are clinical branches that deal intensively with patients, and it can be said that Histology and Embryology come to the forefront as a branch that physicians head after leaving these departments.

Of the Histology and Embryology physicians participating in our study, 75.92% were women. Yılmaz et al.[20] (2021) reported in their study that gender was effective in determining the fields of specialization in medicine and that Histology and Embryology was the third most preferred branches by female physicians. In this respect, our findings are compatible with the literature.

Table 6. Examining the factors affecting the thought of resignation

		Thought of resignation				
		Yes		No		
		Number%/M±SD		Number%/M±SD		p
Gender	Male	9	34.60%	17	65.40%	0.072[1]
	Female	45	54.90%	37	45.10%	
Age		35±8		36±10		0.605[2]
Age at the time of choosing the department		30±5		29±4		0.675[2]
Specialization apart from Histology and Embryology	Yes	0	0.00%	3	100.00%	0.079[1]
	No	54	51.40%	51	48.60%	
Being resident in another branch	Yes	11	44.00%	14	56.00%	0.494[1]
	No	43	51.80%	40	48.20%	
Marital status	Single	19	50.00%	19	50.00%	1[1]
	Married	35	50.00%	35	50.00%	
Working as a general practitioner	Yes	44	50.00%	44	50.00%	1[1]
	No	10	50.00%	10	50.00%	
Duration of working as a general practitioner (year)		4±4		4±5		0.188[2]
Histology as the first choice in TUS	Yes	17	39.50%	26	60.50%	0.077[1]
	No	37	56.90%	28	43.10%	
Thought of being academician	Already academician	9	45.00%	11	55.00%	0.080[1]
	Yes	13	36.10%	23	63.90%	
	No	7	50.00%	7	50.00%	
	Undecided	25	65.80%	13	34.20%	
Current professional title	Research assistant	19	38.00%	31	62.00%	**0.016**[1]
	Specialist physician	24	68.60%	11	31.40%	
	Lecturer physician	4	100.00%	0	0.00%	
	Assistant professor	4	40.00%	6	60.00%	
	Associate professor	2	50.00%	2	50.00%	
	Professor	1	20.00%	4	80.00%	
Thought of being exposed to mobbing	Yes	31	83.80%	6	16.20%	**0.001**[1]
	No	23	32.40%	48	67.60%	

[1]Pearson chi-square, [2]Mann-Whitney U.
M: Mean, SD: Standard deviation, TUS: Medical Specialization Examination

When the factors affecting the choice of the specialty department of the physicians working in the field of Histology and Embryology were examined, it was determined that the factor that affected the most was 'setting aside time for oneself' with the rate of 52.8%. The following most affecting factors were 'Number/Intensity of Shifts' with the rate of 48.10%, 'Patient Intensity' with the rate of 46.30%, 'Number of Standby Duty' with the rate of 41.7%, 'Probability of Exposure to Violence' with the rate of 38.9%, 'Order of Working Hours' with the rate of 38%, 'Risk/Responsibility/Malpractice Level of the Department' with the rate of 37%, and 'Workload Stress Brought by the Department' with the rate of 36.10%.

In the literature, Cansever et al.[21] (2020), in their study investigating the factors that affected medical students' preferences for specialization in medicine, reported that the factors that most affected their preferences in the pre-specialization period were 'interest/ability for the specialization field', 'perception/view of society' and 'family desire/pressure'. The authors stated that the factors that mostly affected the preferences of people who started to receive specialization training in any field, after starting their education, were 'financial satisfaction', 'working conditions (number of shifts, working hours, easiness of the work)', 'academic career opportunity', 'professional satisfaction', 'personal development and career chances' and 'malpractice'. In the study of Balcı Yapalak et al.[22] (2019), in which they examined the factors affecting the specialization preferences of medical faculty students in all state and foundation universities in Istanbul, they reported that the most important factors in choosing the department were 'liking the department', 'personal talent and interest' and 'professional satisfaction', respectively. Açıkgöz et

al.[23] (2019) reported that 85.7% of medical faculty students had a career plan based on specialization. In this study, the authors stated that the main reasons for seeking specialization in medical faculty students were "the desire to work in a specific field that will provide professional satisfaction", "status and career expectation" and "financial concerns". The reasons for these choices of students who did not think of specialization and wanted to work as general practitioner were reported as 'existence of the Medical Specialization Exam', 'difficulty of the residency process' and 'health policies in our country'. In the study in question, the authors did not specifically ask a question about Histology and Embryology in choosing the branch. Ergin et al.[24] (2011) evaluated the post-graduation career choices of students studying in the first, third and sixth grades of the medical faculty. Accordingly, the most important reason for students to want to become a 'specialist physician' after graduation was reported as 'professional satisfaction'. In another study, the factors that most affected the specialty preferences of senior medical school students were reported as their own interests (80.3%), TUS scores (72.1%), presence and number of shifts (59.0%), intensity of working hours (57.9%), financial return (51.9%) and malpractice risk (42.6%)[25].

Table 7. Examining the factors affecting the thought of working abroad

		Thought of working abroad						
		Yes		No		Undecided		
		Number%/Mean±SD		Number%/ Mean±SD		Number%/ Mean±SD		p
Gender	Male	18	69.20%	5	19.20%	3	11.50%	**0.001**[1]
	Female	24	29.30%	23	28.00%	35	42.70%	
Age		35±7		40±12		33±7		0.172[2]
Age at the time of choosing the branch		30±4		30±5		29±5		0.684[2]
Marital status	Single	16	42.10%	8	21.10%	14	36.80%	0.691[1]
	Married	26	37.10%	20	28.60%	24	34.30%	
Specialization apart from Histology and Embryology	Yes	1	33.30%	1	33.30%	1	33.30%	0.955[1]
	No	41	39.00%	27	25.70%	37	35.20%	
Working as a general practitioner	Yes	32	36.40%	23	26.10%	33	37.50%	0.470[1]
	No	10	50.00%	5	25.00%	5	25.00%	
Duration of working as a general practitioner (year)		4±4		5±6		4±4		0.557[2]
Current professional title	Research assistant	24	48.00%	11	22.00%	15	30.00%	**0.009**[1]
	Specialist physician	13	37.10%	9	25.70%	13	37.10%	
	Lecturer physician	1	25.00%	0	0.00%	3	75.00%	
	Assistant professor	4	40.00%	1	10.00%	5	50.00%	
	Associate professor	0	0.00%	2	50.00%	2	50.00%	
	Professor	0	0.00%	5	100.0%0	0	0.00%	
Working as a resident in another branch	Yes	11	44.00%	5	20.00%	9	36.00%	0.717[1]
	No	31	37.30%	23	27.70%	29	34.9%0	
Thought of being academician	Already academician	4	20.00%	7	35.00%	9	45.00%	0.261[1]
	Yes	18	50.00%	5	13.90%	13	36.10%	
	No	6	42.90%	5	35.70%	3	21.40%	
	Undecided	14	36.80%	11	28.90%	13	34.20%	
Histology as the first choice in TUS	Yes	14	32.60%	9	20.90%	20	46.50%	0.133[1]
	No	28	43.10%	19	29.20%	18	27.70%	
Thought of being exposed to mobbing	Yes	15	40.50%	10	27.00%	12	32.40%	0.911[1]
	No	27	38.00%	18	25.40%	26	36.60%	
Thought of resigning	Yes	20	37.00%	14	25.90%	20	37.00%	0.905[1]
	No	22	40.70%	14	25.90%	18	33.30%	

[1]Pearson chi-square, [2]Kruskal-Wallis.

M: Mean, SD: Standard deviation, TUS: Medical Specialization Examination

In our study, 39.8% of the participants preferred Histology and Embryology in the first place in TUS. On the other hand, it is striking that 50% of the residents and specialists, who participated in the study, had the thought of resigning, despite the fact that some left other departments and transferred to the Histology and Embryology branch. Among the reasons for considering resignation, 'concern for the future' was stated as the most common reason. 'Not being satisfied with the branch' and 'financial return' were expressed as some other reasons. 38% of research assistant doctors, 68% of specialist doctors, 100% of lecturer doctors, 40% of assistant professors, 50% of associate professors and 20% of professors stated to have considered resigning in their professional life. 34.3% of the participants thought that they were subjected to mobbing. As expected, thinking of being exposed to mobbing significantly increases the thought of resigning. Dikmetaş et al.[26] (2011) investigated burnout and occupational mobbing levels on 270 residents. While the highest level of mobbing was 5, the average level of mobbing was 1.87 among residents. Researchers evaluated this as 'low mobbing average'. In studies conducted abroad, it has been reported that there is a serious relationship between mobbing and burnout. Grunau[27] (2007), in his study, published a report about that mobbing could be held responsible for 25% of this situation in people with burnout. Erol et al.[28] (2007), in their study on resident physicians, reported that higher number of working hours and shifts increased emotional burnout. In the same study, the authors also determined that as job satisfaction increased, burnout decreased. As a result, mobbing and burnout are the situations that are frequently encountered in healthcare workers, especially physicians, and that pose a serious threat and should be considered as occupational health and safety risks. All these situations may cause physicians to resign. In our study, it is a remarkable finding that all of the instructor physicians (100%) have considered resigning at sometime. Working conditions should be improved in order to reduce the rate of resignation thoughts and people to be more productive in the jobs and positions they work. Limiting the daily working hours and the number of monthly shifts may be effective in reducing burnout in research assistant physicians[28].

38.89% of physicians working in the field of Histology and Embryology are considering working abroad. It has been observed that the current professional title and gender affect the thought of working abroad. While professors do not think about working abroad, men think more than women. Human resources in the field of health constitute an extremely important qualified manpower for all countries. Considering the difficulty of the training process of health workers and especially physicians, it is extremely important for the health policies of the relevant country that they stay in the country where they are educated. In a study on the migration of healthcare workers in 2021, it was reported that physicians could migrate for various reasons, even from developed countries. Healthcare professionals and physicians' staying in the country where they are educated and of which they are citizens or immigrating with the intention of working abroad is a very complex issue that can be affected by global, regional and personal factors[29]. In the health system, it is known that the age, work relations, working conditions and economic conditions of the employees can be effective in their migration decision. It has been reported that approximately 25% to 50% of physicians working in the United Kingdom work for increasing hours, their work-life balance is deteriorating and therefore their job satisfaction is reduced[30]. In a study conducted in Poland, it was determined that one third (34%) of physicians wanted to immigrate to a different country. When asked about their reasons, the physicians stated that they wanted to work abroad because they thought that there was "better working conditions abroad, higher financial gains, better educational opportunities" and "a chance to get rid of the problems arising from their current job"[31]. It has been stated that the reasons for physicians in Ireland wanting to immigrate stem from dissatisfaction with their working conditions[30]. Many research findings in Europe show that physicians can give up their thoughts of migration if working conditions in the workplace are improved[31].

Study Limitations

Not all physicians who chose the Histology and Embryology specialization at TUS and worked actively were not included in the study, so our study may not reflect the views of all research assistant doctors and specialist doctors. Since our study is a cross-sectional study, the cause-effect relationship is not clear. Since the study was carried out in a certain time period, it reflects the conditions specific to the period in which it was made.

CONCLUSION

As a result, it has been determined that the most common factors affecting the reasons for choosing the Histology and Embryology branch of the physicians participating in our study are those such as 'setting aside time for oneself', 'number/intensity of shifts', 'patient intensity', 'number of standby duty' and 'probability of exposure to violence'. It is very important to improve the working conditions of physicians working in the field of Histology and Embryology, to make arrangements in working conditions in which they can set aside time for themselves and economic conditions, and to take measures in all stages for preventing mobbing and burnout. In future studies, studying the factors affecting the choice of specialization of physicians working in different specialties with a larger sample will contribute to the clarification of this issue.

Ethics

Ethics Committee Approval: The study was approved by the Muğla Sıtkı Koçman University Medical and Health Sciences Ethics Committee (protocol no: 220041, decision no: 39, date: 28.04.2022).

Informed Consent: Voluntary consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.Ç., H.E., Design: D.Ç., H.E., Data Collection or Processing: D.Ç., H.E., E.N.K., Analysis or Interpretation: E.N.K., S.Y., Literature Search: D.Ç., E.N.K., S.Y., Writing: D.Ç., H.E., E.N.K., S.Y.

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The Impact of COVID-19 Pandemic on Pediatric Emergency Admissions: Comparison with the Previous Year

COVID-19 Pandemisinin Çocuk Acil Başvurularına Etkisi: Önceki Yıl ile Karşılaştırma

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ABSTRACT

Aim: After lockdown decisions taken to prevent the spread of the Coronavirus disease-2019 (COVID-19) epidemic all over the world, admissions to emergency department (ED) were interrupted in many hospitals. This study aims to evaluate the change by comparing the number of patients admitted to pediatric ED in the same period of previous year, distribution characteristics of diseases, and rates of hospitalization with the period at the onset of pandemic.

Materials and Methods: This was a retrospective, observational study. During the COVID-19 pandemic, 4943 patients aged 0-18 years, who were admitted to Pediatric ED between March 10, 2020 and April 10, 2020 and in the same period of previous year, were included in our study. It was conducted by taking medical data such as demographic characteristics, emergency status, history of comorbid disease, diagnosis, and hospitalization status.

Results: By years, 80.7% (n=3989) of the admissions were made in 2019 and 19.3% (n=954) in 2020. There was a significant decrease of 76% in emergency admissions during COVID-19 pandemic compared to same period last year. The rate of comorbid disease in those who were admitted to the pediatric ED was 23.7% in 2019 and was 27.9% in 2020 (p=0.007). The rate of patients evaluated as priority emergencies was 10.6% in 2019 and 17.9% in 2020 (p<0.001). Neurology, endocrinology, hematology-oncology and neonatal group pathologies and home accidents were found to be statistically significantly higher in 2020 (p=0.037, p=0.002, p<0.001, p=0.040, p<0.001). When the rates of asthma attack, foreign body intake and severe anemia were evaluated by years, they were found to be significantly higher in 2020 (p<0.001, p<0.001, p=0.022).

Conclusion: As in the COVID-19 outbreak, the decrease in admissions to ED may lead to delayed diagnosis and treatment, and increased morbidity and mortality in common pediatric emergencies. Despite the decrease in the number of patients admitted to pediatric ED, it should be kept in mind that admissions may be due to critical illnesses.

Keywords: COVID-19, emergency, pediatrics

ÖZ

Amaç: Koronavirüs hastalığı-2019 (COVID-19) salgınının tüm dünyaya yayılmasını önlemek için alınan karantina kararlarının ardından acil servislere (AS) başvurular birçok hastanede kesintiye uğramıştır. AS'lerde pandemiye yönelik yeni triyaj birimleri oluşturulmuştur. Çalışmamızda pandemi öncesindeki yılın aynı döneminde çocuk AS'ye başvuran hasta sayısını, hastalıkların dağılım özelliklerini pandeminin başladığı dönemle karşılaştırarak değişimi değerlendirmeyi amaçladık.

Gereç ve Yöntem: COVID-19 pandemisi süresince 10.03.2020-10.04.2020 tarihleri arasında ve bir önceki yılın aynı döneminde çocuk AS'ye başvuran 0-18 yaş arası 4943 hasta çalışmamıza dahil edildi. Hastanenin elektronik kayıtlarından demografik ve epidemiyolojik özellikler, başvuru tarihi, acil durum, komorbid hastalık öyküsü, tanı ve yatış durumu gibi tıbbi veriler alınarak retrospektif bir çalışma yapıldı.

Bulgular: Yıllara göre başvuruların %80,7'si (n=3989) 2019 yılında ve %19,3'ü (n=954) 2020 yılında oldu. Hasta sayısında %76'lık bir azalma görüldü. Beş yaş altı çocuk AS'ye başvuru oranı 2020 yılında %39 (n=372) iken 2019 yılında %43,6 (n=1739) (p=0,010) olarak bulundu. Çocuk AS'ye başvuranlarda komorbid hastalık oranı 2019 yılında %23,7 iken 2020 yılında %27,9 idi (p=0,007). Öncelikli acil olarak değerlendirilen hasta oranı 2019 yılında %10,6 olup 2020 yılında ise %17,9 olarak saptandı (p<0,001). 2019 yılında servis yatışı olan hasta oranı %5,2 iken bu oran 2020 yılında %13,8 idi (p<0,001). Nöroloji, endokrinoloji, hematoloji-onkoloji ve yenidoğan grubu patolojileri ve ev kazaları 2020 yılında istatistiksel olarak

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anlamlı derecede yüksek bulundu (p=0,037, p=0,002, p<0,001, p=0,040, p<0,001). Astım atağı, yabancı cisim alımı ve ağır anemi oranları yıllara göre değerlendirildiğinde 2020 yılında anlamlı olarak yüksekti (p<0,001, p<0,001, p=0,022).

Sonuç: COVID-19 salgınında olduğu gibi, AS'ye başvuruların azalması yaygın pediyatrik acil durumlarda tanı ve tedavinin gecikmesine, morbidite ve mortalitenin artmasına neden olabilir. Bu çalışma, doktorların pediatrik AS'lerde acil teşhis ve tedavi süreçlerini yeni bir pandeminin başlaması veya mevcut pandeminin devam etmesi nedeniyle hızlı bir şekilde yönetmelerini sağlayabilir. Olası pandemi durumlarında çocuk acile başvuran hastaların sayısında azalma görülmesine rağmen başvuruların kritik hastalık grubundan olabileceği unutulmamalıdır.

Anahtar Kelimeler: COVID-19, acil, pediatri

INTRODUCTION

Coronavirus disease-19 (COVID-19) first appeared in Wuhan, China at the end of 2019[1]. The World Health Organization declared an international public health emergency on January 30, 2020. On March 11, 2020, the novel Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) outbreak was officially identified as a pandemic[2]. Schools were closed on March 16, 2020 and shelter-in-place was ordered for those whose birth dates were on or after January 1, 2000 on April 3, 2020 in Turkey.

Following lockdown decisions taken to prevent spread of COVID-19 epidemic all over the world, most of routine and elective procedures, especially emergency department (ED) service, have been interrupted in many hospitals. Triage units were created in EDs and reorganized to separate suspected COVID-19 cases from other emergency cases[3,4]. At the onset of COVID-19 outbreak, just before lockdown was implemented, a sudden decline in the number of patients with non-COVID-19 complaints was reported in EDs of different countries[5-9]. It was determined that this decrease in ED admissions was primarily in very urgent patients with high morbidity and mortality. These patients, who needed urgent intervention, were not admitted to EDs and were waited at home for a long time. Also, decreases were observed in admissions of children who were expected to continue their admission to EDs due to acute exacerbations of underlying problems such as neurological, endocrinological and oncological diseases or surgical reasons[7,8,10]. Initially, decrease in the number of patients in EDs was welcomed worldwide to allocate more space and time to COVID-19 patients, but the continuance of decrease in admissions began to raise concerns. Decrease in admissions to hospitals and EDs may have various probable negative effects on child health. Children with various metabolic, neurological, hematological, immunological, and syndromic diseases and accordingly using devices such as tracheostomy cannula, ventriculoperitoneal shunt, home-ventilator, nebulizer, and non-invasive mechanical ventilator, and those who have special needs such as percutaneous endoscopic gastrostomy and urinary and venous catheter are potentially at higher risk of more serious illness than healthy children due to lack of access to healthcare.

There are various reasons and different alternative solution methods for the decrease in emergency admissions. Concerns about being infected with SARS-CoV-2 at hospitals, high number of patients, overcrowded waiting areas and insufficient personal protective equipment for medical staff were reported as the reasons for decrease in the number of emergency admissions[8,11,12]. The fact that patients and their families delay or stop seeking treatment for emergencies will pose a significant risk in terms of preventable causes of morbidity and mortality in the future. One of unclear situations of COVID-19 epidemic is uncertainty regarding the management of patients not admitted to ED or hospitals. During pandemics, it is necessary to plan how to help patients who are not admitted to ED due to the concern of transmission of causative disease. Examining changes in the admission features of emergent and non-emergent patients will help arrangements to be made in this regard.

Therefore, we aimed to evaluate the change by comparing number of patients admitted to pediatric ED in the same period of the previous year, distribution characteristics of diseases, rates of hospitalization, and follow-up status with the period at the onset of the pandemic.

MATERIALS AND METHODS

Separated areas for evaluation and inpatient follow-up were created at our hospital for suspected or positive COVID-19 patients and for other patients in the light of current guidelines. In this sense, it was thought that anxiety and fear of patients and their families would be alleviated and number of admissions to ED would not be affected.

During COVID-19 pandemic, 4943 patients aged 0-18 years who were admitted to Pediatric ED between March 10th and April 10th of 2019 and in the same days of 2020 were included in our study. A retrospective, observational study was conducted by taking medical data such as demographic and epidemiological characteristics, admission date and time, emergency status, history of comorbid disease, diagnosis, and hospitalization status from the hospital's electronic records. The percentage of change in information such as ED visits, patient characteristics and diagnoses for 2020 was calculated and compared to that for 2019. Interactions between each factor and overall variation in ED visits were assessed. Patients were divided into specific groups according to systems and diagnoses. According to the follow-up status, ward, intensive care unit and pediatric

emergency follow-ups were accepted as hospital admissions. Diseases were evaluated individually or by categorization.

As the exclusion criteria for the study, cases in which there was a problem in reaching the data to be used in the study were determined.

The primary purpose of this study is to determine the effects of this pandemics on EDs, Its secondary purpose is to develop an ED procedure for the pandemic and other future pandemics.

Statistical Analysis

Analyses were made with Statistical Package for the Social Sciences 26.0 (for macOS) program. The normal distribution of data was evaluated using the Kolmogorov-Smirnov test. In descriptive statistics, categorical data were presented as numbers and percentages and non-categorical data were presented as median (25-75 percentile) because they were not normally distributed. In analytical statistics, the chi-square test and Fisher's exact test were used. Type-1 error (a) was accepted as 5%.

This study was approved by İstanbul University, İstanbul Medical Faculty Medical Ethics Committee (approval date: 15/02/2020, decision number: 10).

RESULTS

The median age of 4943 patients admitted to the pediatric ED in both time periods were 5.0 years (2-10). Of the children, 45.9% (n=2270) were girls. A total of 24.5% of the children (n=1211) had comorbid diseases. Respectively, 80.7% (n=3989) of the admissions were in 2019 and 19.3% (n=954) were in 2020. There was a 76% reduction in the number of admissions within years. While the rate of admissions to the pediatric ED under the age of 5 years was 39% (n=372) in 2020, it was 43.6% (n=1739) in 2019, which was significantly important (p=0.010). When evaluated according to the days when they were admitted to the hospital, it was found that 28% of the patients were admitted at the weekend in 2019 and 23.7% in 2020. Weekend admissions in 2019 were significantly higher compared to those in 2020 (p=0.007). In comparison of admission time to hospital by years, it was found that there was a significant difference in terms of admission rates in three different time periods (p=0.021). In subgroup analysis, it was determined that the difference between these groups originated from 00:00-07:59 hours and that there were more admissions in these hours in 2020 compared to 2019.

The rate of comorbid diseases among those admitted to the pediatric ED was 23.7% in 2019, while it was 27.9% in 2020 and this difference was statistically significant (p=0.007). The rate of patients who were considered as priority emergencies was 10.6% in 2019 and 17.9% in 2020, and this difference was significant (p<0.001). While the rate of patients requiring service admission was 5.2% in 2019, this rate was 13.8% in 2020, which was significantly different (p<0.001).

While the rate of intensive care unit admissions was 0.5% (n=5) in 2020, it was found to be 0.3% (n=13) in 2019, and there was no statistical difference (p=0.369). In 2020, COVID-19 polymerase chain reaction test was positive in 21 (2.2%) cases (Table 1). When the admission rates of cases such as seizures, pneumonia, acute appendicitis, invagination, metabolic decompensation, drug intoxication and toxic substance intake were examined by years, no significant difference was found. When the rates of asthma attack, foreign body aspiration and severe anemia were evaluated by years, admissions in 2020 were found to be significantly higher (p<0.001, p<0.001, p=0.022) (Table 2).

Patients admitted to pediatric ED were divided into specific groups according to their diagnoses and evaluated according to years. The patient's pathologies who were followed up in neurology, endocrinology, hematology-oncology and neonatal units and home accidents were found to be significantly higher in 2020 (p=0.037, p=0.002, p<0.001, p=0.040, p<0.001, respectively). Dermatological diseases such as urticaria, respiratory tract diseases such as upper respiratory tract infection and gastrointestinal system pathologies such as acute gastroenteritis were significantly lower in 2020 (p=0.003, p<0.001, p=0.002, respectively). Although a statistical evaluation could not be made in the diagnosis of headache-dizziness considered within neurological pathologies, a significant decrease was observed in 2020 compared to 2019. While the rate of palpitations among the diagnoses evaluated within the cardiological pathologies increased significantly in 2020, the rate of chest pain cases decreased significantly. It was noted that the percentages of acute bronchiolitis and asthma attack diagnosis evaluated within respiratory tract pathology increased significantly in 2020 compared to 2019. Although there was no case of intoxication with cologne/disinfectants in 2019, the increased percentage of intoxication cases in 2020 drew attention. When the diagnoses in the Hematology/Oncology group were evaluated, a significant decrease was observed in the percentage of bleeding cases due to factor deficiency in addition to febrile neutropenia cases in 2020 compared to 2019 (Table 3).

DISCUSSION

Our data showed that there was a significant decrease of 76% in emergency admissions during COVID-19 pandemic compared to the same period last year. Although it was reported that admissions to ED in emergencies with high mortality were reduced by half in adults, it was observed in our study that there was no decrease in admissions for priority red.

Some studies have reported a decrease in ED admissions at the onset of the COVID-19 pandemic before lockdown has just started[6,7,13,14]. The number of admissions to the pediatric ED at weekends decreased significantly in 2020 compared to 2019. The curfew, which was only admitted at the weekends during the lockdown, might have caused this situation. When admission hours to the ED for children were observed, it was determined that the number of admissions increased significantly from 12.00 am to 08.00 am in 2020 compared to 2019. The fact that there were more admissions at these hours in 2020 might indicate that patients were admitted to the hospital without waiting in case of complaints or they might think that they would be exposed to less crowding in ED at specified hours. In a study examining the admissions to the pediatric ED, it was shown that there were more admissions on the weekend throughout the whole time and a striking decrease was observed in the number of daily admissions during the pandemic period[15].

Studies in adults have reported unexpected and disproportionate decreases in emergency admissions with high morbidity and mortality, such as cerebrovascular events, stroke, and myocardial infarction[7,13]. There are also studies that have reported an increase in morbidity and mortality in pediatric patients due to delay in admission of critically ill patients to EDs[8,15]. In our study, there were 5 (0.5%) patients hospitalized in intensive care unit and no fatalities occurred.

Despite the decrease in hospital admissions during the pandemic, the rate of cases considered as priority emergencies was found to be statistically higher compared to the previous year. Considering the increase in the rates of priority emergencies and the rate of hospitalized patients, it was thought that critical patients continued to be admitted to EDs despite the pandemic and it might be concluded that a sufficient number of experienced healthcare workers should be organized in EDs for these patients.

Angoulvant et al[16]. reported that there was more than 70% decline in acute gastroenteritis, common cold, acute bronchiolitis and acute otitis media complaints in pediatric ED admissions. In our study, the rate of admissions in 2020 due to diseases with high morbidity and mortality such as asthma

Table 1. Comparison of pediatric emergency admissions between March 10 and April 10 by years

Variables	2019		2020		x^2	p
	Number (n)	Percent (%)*	Number (n)	Percent (%)*		
Age						
<5 years	1739	43.6	372	39.0	**6.661**	**0.010**
≥5 years	2250	56.4	582	61.0		
Sex						
Female	1851	46.4	419	43.9	1.910	0.167
Male	2138	53.6	535	56.1		
Comorbid disease						
Yes	945	23.7	266	27.9	**7.316**	**0.007**
No	3044	76.3	688	72.1		
Time of admission to the hospital (day)						
Weekdays	2873	72.0	728	76.3	**7.154**	**0.007**
Weekend	1116	28.0	226	23.7		
Time of admission to the hospital (hour)						
00.00-07.59	525	13.2	158	16.6	**7.708**	**0.021**
08.00-16.00	1652	41.4	372	39.0		
16.01-23.59	1812	45.4	424	44.4		
Priority emergency						
Yes	424	10.6	171	17.9	**38.697**	**<0.001**
No	3565	89.4	783	82.1		
Follow-up status						
Outpatient	3783	94.8	822	86.2	**90.891**	**<0.001**
Hospitalization	206	5.2	132	13.8		
Intensive care hospitalization	13	0.3	5	0.5	-	**0.369****
COVID-19 PCR positive	-	-	21	2.2	-	-
Total	**3989**	**100.0**	**954**	**100.0**		

*Column percentage. **Fisher's exact test.

COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction

attack, foreign body intake and severe anemia were found to be significantly higher than in 2019. Foreign body intake might have increased due to having to spend more time at home. It was thought that the increase in asthma attack admissions was due to the increase in awareness of families to cough and respiratory distress symptoms related to COVID-19. The reason for the increase in severe anemia might be the result of deterioration and delayed follow-up of chronic diseases.

It has been reported that the percentage of hospital admissions increased in pediatric patients due to diseases with high morbidity and mortality, and patients in need of urgent medical care were admitted to pediatric ED without causing a significant delay during lockdown[9]. In our data, no significant change was found in cases of seizures, pneumonia, acute appendicitis, drug intoxication, invagination, decompensation of metabolic diseases and toxic substance intake by years. Unlike adults, families brought their children to pediatric ED because they thought that these diseases, which have high morbidity and mortality, could not be cured at home.

While analyzing the results of our study, the patients were divided into specific groups according to their systems and diagnoses, and neurological, endocrinological, hematological-oncological and neonatal diseases and home accidents were found to be significantly higher in 2020 compared to 2019. In a study, it was reported that there was an increase in the rate of neoplastic diseases from 5.6% to 14.9% and a decrease in the rate of perinatal pathologies and cardio-circulatory system diseases from 22.5% to 8.1% and from 5.6% to 0%,

Table 2. Comparison of the diseases considered as very urgent by years

	2019		2020		x^2	p
	Number (n)	Percent (%)*	Number (n)	Percent (%)*		
Seizure						
Yes	68	1.7	24	2.5	2.772	0.096
No	3921	98.3	930	97.5		
Pneumonia						
Yes	55	1.4	15	1.6	0.207	0.649
No	3934	98.6	939	98.4		
Acute appendicitis						
Yes	14	0.4	6	0.6	-	0.224**
No	3975	99.6	948	99.4		
Severe anemia						
Yes	9	0.2	7	0.7	-	**0.022****
No	3980	99.8	947	99.3		
Asthma attack						
Yes	46	1.2	26	2.7	**13.258**	**<0.001**
No	3943	98.8	928	97.3		
Drug intoxication						
Yes	10	0.3	3	0,3	-	0.725**
No	3979	99	951	99.7		
Invagination						
Yes	4	0.1	2	0.2	-	0.327**
No	3985	99.9	952	99.8		
Metabolic decompensation						
Yes	16	0.4	8	0.8	-	0.114**
No	3973	99.6	946	99.2		
Toxic substance intake						
Yes	21	0.5	6	0.6	0.149	0.700
No	3968	99.5	948	99.4		
Foreign body intake						
Yes	18	0.5	15	1.6	**14.591**	**<0.001**
No	3971	99.5	939	98.4		
Total	**3989**	**100.0**	**954**	**100.0**		

*Column percentage. **Fisher's exact test.

Table 3. Comparison of the diseases evaluated according to the departments by years

	2019		2020		
	Number (n)	Percent (%)	Number (n)	Percent (%)	p
Neurology	157	3.9*	52	5.5*	**0.037**
Headache-dizziness	63	40.1	13	25.0	
Seizure	68	43.3	24	46.2	
Status epilepticus	0	0.0	2	3.8	
Syncope	12	7.6	5	9.6	
Other	14	9.0	8	15.4	
Dermatology	210	5.3*	28	2.9*	**0.003**
Urticaria	100	47.6	14	50.0	
Angioedema	10	4.8	1	3.6	
Other	100	47.6	13	46.7	
Surgery	36	0.9*	13	1.4*	**0.197**
Acute appendicitis	14	38.9	6	46.2	
Invagination	4	11.1	2	15.4	
Other	18	50.0	5	38.4	
Endocrinology	8	0.2*	9	0.9*	**0.002****
Diabetic ketosis	0	0.0	2	22.2	
Hypoglycemia	2	25.0	3	29.4	
Other	6	75.0	4	48.4	
Respiratory diseases	2115	53*	430	45.1*	**<0.001**
Acute upper respiratory tract	1696	80.2	320	74.4	
Croup	22	1.0	8	1.9	
Acute otitis	161	7.6	22	5.1	
Acute bronchiolitis	61	2.9	25	5.8	
Asthma attack	46	2.2	26	6.0	
Pneumonia	55	2.6	15	3.5	
Other	74	3.5	14	3.3	
Home accidents	18	0.5*	15	1.6*	**<0.001**
Foreign body intake	18	100	15	100	
Intoxication	33	0.8*	10	1.0*	**0.509**
Drug intoxication	10	30.3	3	30.0	
Cologne-disinfectant	0	0.0	4	40.0	
Other	23	69.7	3	30.0	
Metabolism	18	0.5*	8	0.8*	**0.137**
Metabolic decompensation	18	100	8	100	
Hematology-oncology	25	0.6*	19	2.0*	**<0.001**
Anemia (insufficiency)	9	37.5	7	36.8	
Factor deficiency (bleeding)	7	28.0	2	10.5	
Febrile neutropenia	3	12.5	1	5.3	
Other	6	22.0	9	47.4	
Newborn	12	0.3*	8	0.8*	**0.040****
Jaundice	11	91.7	7	87.5	
Other	1	8.3	1	12.5	
Renal-urogenital	147	3.7*	37	3.9*	**0.777**
Urinary tract infection	102	69.4	27	73.0	
Nephrotic syndrome	3	2.0	1	2.7	
Other	42	28.6	9	24.3	
Cardiology	57	1.4*	12	1.3*	0.686
Palpitation	12	21.1	7	58.3	
Chest pain	40	70.2	3	25.0	
Arrhythmia	2	3.5	0	0.0	
Other	3	5.2	2	16.7	

Gastrointestinal	1010	25.3*	147	15.4*	**<0.001**
Acute gastroenteritis	752	74.5	101	68.7	
Constipation	81	8.0	16	10.9	
Colic	92	9.1	10	6.8	
Other	85	8.4	20	13.6	
Rheumatology	18	0.5*	7	0.7*	0.306**
Arthritis	4	22.2	1	14.5	
FMF	4	22.2	2	28.5	
HSP	10	55.6	2	28.5	
Other	-	-	2	28.5	

*Percentage of the disease for the current year. **Fisher's exact test.
FMF: Familial Mediterranean Fever, HSP: Henoch-Schönlein purpura

respectively[15]. It was thought that families did not prefer to stay at home even during the pandemic, since the diseases belonging to these diagnostic groups are the diseases with more serious complaints. It was found that there was an increase in home accidents depending on the length of time that children stayed at home. It was concluded that the rate of serious illnesses in the number of emergency admissions increased due to the decrease in the number of ED admissions for non-urgent diseases.

The number of dermatological, respiratory diseases and gastrointestinal system pathologies decreased significantly compared to previous year. For the diseases of these diagnostic groups with milder complaints, families might have preferred home follow-up and treatment or the frequency of getting ill might have decreased as a result of home isolation. While the rates of headache, dizziness and chest pain decreased in 2020, rate of palpitation increased. The complaint of palpitation might have increased due to anxiety arising from the pandemic. The fact that patients and their families wanted to be followed up at home for a while, instead of coming to ED, might have been effective in the decrease of admissions with subjective complaints such as headache and chest pain. In 2020, we did not have any critical patient who was lately admitted to our pediatric ED due to complaints such as headache and chest pain. It was reported in a study conducted in pediatric patients that there were significant decreases in respiratory tract infection symptoms such as fever, respiratory distress, cough, sore throat, earache, headache and symptoms related to functional syndromes such as dizziness and chest pain and a decrease in injuries following lockdown[9].

While the number of patients with important diseases, who can be treated, decreased in other studies[5], the decrease in the number of admissions for non-serious complaints was more remarkable[17]. In our study, the number of patients with upper respiratory tract infections in the common but non-emergency category of the pediatric ED in the respiratory tract disease group decreased. The admission rate of patients diagnosed with acute bronchiolitis and asthma attacks increased in 2020 compared to 2019. It was thought that this situation was caused by the awareness of families for COVID-19-like symptoms such as fever, cough and respiratory distress. When the diagnoses in the hematology-oncology group were examined, it was observed that the percentage of admission decreased in 2020 compared to 2019 in cases of bleeding disorders due to factor deficiency and febrile neutropenia. It was thought that the decrease in the rate of patients presenting with bleeding due to factor deficiency may be due to the decrease in trauma exposure as a result of home isolation period. It was predicted that the decrease in the rate of patients with febrile neutropenia may be the effect of protection from infectious agents due to home isolation during the pandemic period.

The rate of hospitalization of patients admitted to the pediatric emergency in 2020 was significantly higher than in 2019. This situation made us think that unlike adults during the pandemic, pediatric patients were admitted to the pediatric ED in cases with more serious complaints and hospitalization indications and that mild complaints might also be followed at home with different methods by their own means. However, there was no statistical difference between the intensive care unit hospitalization rates of the patients who were admitted by years. It was thought that the patients were brought to ED before they became sufficiently severe to require intensive care. It has been reported that hospitalization rates have been increased in studies[15,18]. The increase in hospitalization in our findings is consistent with the literature.

The rate of patients with comorbid diseases in 2020 was statistically higher compared to 2019. Since these patients were followed up due to chronic diseases, they knew that the disruptions in outpatient services and acute exacerbations due to chronic diseases could rapidly worsen during the pandemic period, so they came to ED for routine examinations, follow-up and nasogastric tube replacement. Severe illness or death was not observed among our patients with comorbid diseases.

While there was no case of intoxication with cologne or disinfectants in 2019, a high rate of 40% of intoxication cases

with cologne or disinfectants was observed in 2020. It may be considered that colognes and disinfectants were in more accessible areas during the pandemic. In a study, a lack of information has been found on keeping hand disinfectants out of the reach of children[19]. During the COVID-19 pandemic, it has been reported that search for information about hand sanitizers has increased in the National Poison Center[20]. It has been thought that the increase in intoxication cases were due to rise of disinfectant usage and their presence in areas that children could reach.

Study Limitations

The limitation of the study is that it was single centered and cross-sectional study. The first strength of our study is that it covered the first period of the lockdown, where significant changes took place. The second is that demographic factors in ED admissions, the characteristics of admission to the ED, their diagnoses, the severity of the diseases, and their comorbidities were examined on the basis of both diseases and systems. In addition, potential risk factors for future pandemics were also evaluated.

CONCLUSION

Prolongation of the COVID-19 outbreak or future pandemics may lead to a generalized inadequacy of health care for children. We think that the results of our study can enable physicians to quickly manage emergency diagnosis and treatment processes in pediatric EDs during the lockdown admission as a result of the onset of another new pandemic or the continuation of the existing one.

Ethics

Ethics Committee Approval: This study was approved by İstanbul University, İstanbul Medical Faculty Medical Ethics Committee (approval date: 15/02/2020, decision number: 10).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.U., R.Y., S.G., Concept: M.U., R.Y., S.G., Design: M.U., R.Y., S.G., Data Collection or Processing: R.Y., S.G., Analysis or Interpretation: M.U., R.Y., Literature Search: R.Y., S.G., Writing: M.U., R.Y., S.G.

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ORIGINAL ARTICLE

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Alterations in Expression of Neurodegeneration-Related Genes After Long-Term Potentiation in the Hippocampus of Hyperthyroid Rats

Hipertiroidili Sıçanların Hipokampüsünde Uzun Dönemli Güçlenme Sonrası Nörodejenerasyonla İlgili Genlerin Anlatımındaki Değişiklikler

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ABSTRACT

Aim: Imbalances in plasma thyroid hormone levels cause changes in synaptic response, resulting in impairments in learning and memory. It is not well understood how the excess of these hormones (T3 and T4 hormones), which modulate gene transcription, affects gene expression after high-frequency stimulation (HFS). Therefore, in this study, it was aimed to investigate the transcriptional changes accompanying long-term potentiation (LTP) in genes related to neurodegeneration in rats with hyperthyroidism.

Materials and Methods: 12 male Wistar-albino rats were used in the study. The rats were divided into two groups as control and hyperthyroidism groups. To induce hyperthyroidism, L-tyroxine was administered intraperitoneally at a dose of 400 µg/kg/day for 21 days, starting on the 39th day. To investigate LTP, when rats were 60-day-old, LTP was induced by giving HFS at 100 Hz for 1 second at 5-minute intervals after 15 minutes of basal recording to the perforating pathway and the excitatory postsynaptic potential (EPSP) slope and population spike (PS) amplitude were recorded in the granule cell layer of the dentate gyrus. The mRNA levels of genes related to neurodegeneration in stimulated hippocampus were measured by reverse transcription-polymerase chain reaction method.

Results: After HFS, LTP was induced in the control group at the EPSP slope, while LTP was not induced in the hyperthyroid group. However, LTP was induced at the PS amplitude in both groups. In hyperthyroid rats, Gsk3β, P35(Anxa) Calpn1 and Bace1, Psen2-mRNA levels were not significantly different compared to the control group, while Akt1, Cdk5 and Mapt-mRNA levels were found to be increased significantly compared to the control group ($p<0.05$).

Conclusion: These findings suggest that the excess of thyroid hormone during neuronal plasticity partially alters the expression of genes related to neurodegeneration.

Keywords: Hippocampus, hyperthyroidism, neuroplasticity, gene expression

ÖZ

Amaç: Plazma tiroid hormon (T3 ve T4) düzeyindeki dengesizlikler sinaptik yanıtta değişikliklere neden olarak öğrenme ve bellekte bozulmalara neden olur. Gen transkripsiyonunu modüle eden T3-T4 hormon fazlalığında, yüksek frekanslı uyarı (YFU) sonrası gen anlatımının nasıl etkilendiği çok iyi anlaşılmamıştır. Çalışmamızda, hipertiroidi oluşturulan sıçanların hipokampüsünde uzun dönemli güçlenmenin (UDG) indüklenmesi ile plastisite indüksiyonuna eşlik eden, nörodejenearatif proteinlerle bağlantılı olan, amiloid prekürsör protein (APP) ilişkili (Bace1 ve Psen2) ve tau fosforilasyonuyla ilişkili proteinlerin (Gsk3β, Cdk5, Akt1, Mapt P35(Anxa) ve Calp1) mRNA düzeyindeki değişiminin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Sıçanlar kontrol ve hipertiroidi grupları olarak ikiye ayrıldı. Hipertiroidi grubu sıçanlara yaşamlarının 39. gününden başlanarak 21 gün süresince 400 µg L-tiroksin/kg/gün intraperiteonal (ip) yolla verildi, kontrol grubuna ise aynı şartlarda serum fizyolojik verildi. Sıçanlar 60 günlük olduklarında, test uyaran şiddet belirlenmesi, bazal kayıt alınmasının ardından 5 dakika arayla 1 saniye boyunca 100 Hz YFU verilerek UDG

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indüklendi ve dentat girus granül hücre tabakasında eksitatör postsinaptik potansiyel (EPSP) eğimi ve popülasyon spike (PS) genliği kaydedildi. Bazal kaydın EPSP, PS ortalama değerleri 100 kabul edildi, UDG'nin indüksiyon ve idame dönemlerine ait EPSP ve PS değerleriyle karşılaştırıldı. İstatistiksel analizler için Mann-Whitney U testi kullanıldı. Uyarılmış hipokampüslerdeki APP ilişkili ve tau fosforilasyonuyla ilişkili proteinlerin mRNA seviyeleri real-time-polimeraz zincir reaksiyonu yöntemiyle ölçüldü.

Bulgular: Kontrol grubunda YFU verilmesini takiben EPSP eğiminde UDG indüklenirken hipertiroidi grubunda UDG indüklenmedi. Her iki grupta PS genliğinde UDG indüklendi. Hipertiroidili sıçanlarda, Gsk3β, P35(Anxa) Calpn1 ve Bace1, Psen2-mRNA seviyesi kontrol grubuna göre anlamlı düzeyde farklılık göstermezken, Akt1, Cdk5 ve Mapt-mRNA seviyeleri kontrol grubuna göre anlamlı düzeyde arttı ($p<0,05$).

Sonuç: Bu bulgular, tiroid hormon fazlalığının, nöronal plastisite sırasında nörodejenerasyonla ilgili genlerin ekspresyonunu kısmen değiştirdiğini göstermektedir.

Anahtar Kelimeler: Hipokampüs, hipertiroidizm, nöroplastisite, gen ifadesi

INTRODUCTION

Thyroid hormones have genomic and non-genomic effects. Thyroid hormones cause the activation of intracellular PI3K-Akt/Gsk3β and Mapk signaling pathways by interacting with the specialized membrane proteins monocarboxylate transporter 8 and integrin αVβ3, which are involved in the communication between the extracellular and intracellular environment, with their non-genomic effect. The non-genomic effects of thyroid hormones are short term[1-4]. The main effect of thyroid hormone is genomic, it binds to its receptors in the nucleus and initiates various transcription events and directly affects the biological functions of the cell[1]. Changes in hormone level can affect the expression levels of genes associated with synaptic plasticity and neurodegenerative diseases. The underlying cause of the majority of neurodegenerative diseases is based on defects in gene expression. In recent years, studies performed to explain the causes of neurodegenerative diseases have focused on changes in gene expression[5,6]. The hippocampus is considered one of the most important brain regions affected by these diseases. In the previous studies conducted in our laboratory, it was determined that high or low thyroid hormone levels caused significant changes on hippocampal synaptic plasticity forms[7,8].

Long-term potentiation (LTP) means permanently increasing the strength and number of synaptic connections, depending on the increase in the frequency of neural activity from a presynaptic neuron or nerve pathway, and is a form of synaptic plasticity that is the most studied and well-known. A growing number of studies on synaptic plasticity have shown that LTP not only strengthens synaptic connections during learning, but also promotes the formation of new neurons in the hippocampus[9,10]. LTP requires the phosphorylation of some critical kinases[11]. At the molecular level, the effect of an increase in kinase or phosphatase activity is relatively short term, and longer maintenance of these changes requires gene transcription and synthesis of neuronal proteins[12].

Changes in the expression of certain genes following the induction of the forms of synaptic plasticity that underlie learning and memory allow these forms of plasticity to persist through protein synthesis[13]. On the other hand, the over- or under-synthesized protein products formed by genes with changed expression in thyroid hormone deficiency or excess may cause tau and amyloid beta proteins, which are associated with some neurodegenerative diseases, to be synthesized and phosphorylated at different levels. As a result, the incidence of neurodegenerative diseases such as Alzheimer's disease, characterized by dementia, may increase.

In our study, it is aimed to investigate the change in mRNA level of amyloid precursor protein (APP)-associated (Bace1 and Psen2) and tau phosphorylation-related proteins (Gsk3β, Cdk5, Akt1ve Mapt, P35(Anxa), Capn1), associated with neurodegenerative proteins and accompanying the induction of LTP in the hippocampus of hyperthyroid induced rats.

METARIALS AND METHODS

Experimental Animals

This study was carried out within the scope of the project numbered TDK-2019-9405 supported by Erciyes University Scientific Research Projects Unit and with the approval of Erciyes University Animal Experiments Ethics Committee dated 17.07.2019 and numbered 19/133. For the study, 12 Wistar albino male rats, weighing 180-200 gr, produced in Erciyes University Hakan Çetinsaya Experimental and Clinical Research Center, were used. Ethical principles were taken into account in the study in order not to use unnecessary experimental animals and not to cause pain on experimental animals. Rats were divided into two groups, as the control group (n=6) and the hyperthyroidism group (n=6).

Creating Hyperthyroidism

To induce hyperthyroidism (n=6), 39-day-old animals were given 400 µg/kg/day L-thyroxine (Sigma, catalog number: T2501-5G, 0.5 mL) intraperitoneally (ip) for 21 days[14]. The control group (n=6) rats were given saline ip in the volumes given to the experimental group rats for 21 days starting from the 39th day.

Electrophysiological Recording

After rats were anesthetized with urethane (1.2 g/kg), they were placed in stereotaxis using ear and mouth sticks. The stimulating electrode was lowered into the hippocampus according to the coordinates of anteroposterior (AP): 6.5 and mediolateral (ML): 3.8 mm, and the recording electrode according to the coordinates of AP: 3 mm ML: 2.13 mm, and the two-channel glass micropipette filled with 3 M NaCl was lowered into the hippocampus until a typical response was observed.

The perforating pathway was stimulated with stimuli varying in the range of 0.1-1.5 mA with the stimulus electrode, and the stimulus intensity (test stimulus intensity), which constituted half of the maximum intensity of the responses received from the dentate gyrus granule cells, was determined by input/output experiments. The basal record of the experiment was recorded for 15 minutes. During the basal recording, the perforating pathway was stimulated with this determined stimulus intensity every 30 seconds, and the excitatory postsynaptic potential (EPSP) slope, field potentials in the dentate gyrus granule cell layer, and population spike (PS) amplitude, were recorded for 15 minutes. For the LTP response, a stimulus was given every 30 seconds, followed by a 15-minute basal recording, and by induction with high-frequency stimulation (HFS) at 100 Hz for 1 second at 5 minutes intervals (15 minutes in total). EPSP slope and PS amplitude were recorded by continuing the stimulation with a test stimulus every 30 seconds for a total of 60 minutes following HFS stimulation.

After the electrophysiological recordings were taken, the blood of the rats were taken intracardiacly, then they were decapitated, and their brains removed, and their hippocampi were isolated. The collected blood was centrifuged and the plasma was stored at -20 °C until the study day. Isolated hippocampi were stored at -80 °C until real-time PCR (rt-PCR) analysis. The level of fT4 in plasma and mRNA levels of APP-related (Bace1 and Psen2) and tau phosphorylation-related proteins (Gsk3β, Cdk5, Akt1 P35(Anxa), Calpn1 and Mapt) in hippocampus tissue were measured.

Measuring Plasma Free T_4 Levels

After collecting plasma samples from all groups, plasma fT4 levels were measured in a plate reader (Multiskan™ FC Microplate Photometer) with a commercial ELISA kit (Cloud Cone Corporation, USA).

Real-Time-PCR Measurements

RNA Isolation from Hippocampus Tissue

Hippocampus tissues taken into tubes each containing 1000 µL of RNA isolation solution (PureZOL™: BioRad, USA) were homogenized with the help of a homogenizer. They were then incubated at room temperature for 5 min. 400 µL of chloroform was added to them and vortexed for 15 seconds. They were incubated for 15 min at room temperature and centrifuged at 14000 g for 20 min at +4 °C. The aqueous phase formed at the end of centrifugation was taken into a new eppendorf tube. 300 µL of isopropanol was added to it (depending on the amount of aqueous phase) and inverted several times. It was incubated at room temperature for 10 minutes and centrifuged at 14000 g for 30 minutes at +4 °C. The supernatant obtained at the end of centrifugation was discarded. 1 mL of 75% ethanol was added to the pellet portion at the bottom and vortexed. Afterwards, it was centrifuged at 7500 g for 5 min at +4 °C. The supernatant formed at the end of centrifugation was discarded and the ethanol around the pellet was pipetted and cleaned. The pellet was dried at room temperature for 10-15 minutes until the ethanol evaporated. After drying, 20 µL of NFW (Nuclease Free Water) was added and the pellet was resuspended. It was then placed in ice and kept in a refrigerator at +4 °C for 10-15 minutes. At the end of this period, RNA concentration (ng/µL) was measured in the nanodrop.

cDNA Synthesis

Before starting the study, all RNA samples from rats were numbered and these numbers were written on the PCR tubes. The iScrip™cDNA synthesis Kit (1708890, BioRad, USA) was used for cDNA synthesis. cDNA synthesis was performed according to the iScrip™cDNA Kit protocol. In order to create a reaction with equal amount of RNA in each sample, the amounts of RNA and water to be added were calculated according to the RNA quantification results. Desired amount of NFW and RNA samples were added to the PCR tubes with a total volume of 15 µL. Afterwards, 5 µL of 5X reaction buffer (4 µL) and Reverse Transcriptase (1 µL) mixture was dispensed into each PCR tube and the tubes were placed in the PCR device (CFX Connect rt-PCR Detection System BioRad). At the end of PCR, 20 µL of cDNA product was formed. In the PCR device (CFX Connect rt-PCR detection System, BioRad), it was kept for the steps of the incubation, denaturation and extension and annealing for 5 minutes at 25 °C, 30 minutes at 42 °C and 5 minutes at 85 °C, respectively.

mRNA Expression Study

The mRNA expressions of Gsk3β, Akt1, Cdk5, Mapt, P35(Anxa), Calpn1, Bace1, and Psen2 genes were studied on the BIORAD CFX Connect rt-PCR instrument (BIORAD, USA), using the SsO Advanced Universal IT SYBR Green Supermix kit (10000076382, BIORAD, USA). A reaction mixture consisting of SYBR Green Supermix (10 µL), Nuclease Free Water (8 µL), Primer F (0.5 µL) and Primer R (0.5 µL) included in the kit was prepared and dispensed into the wells in on a 96-well plate, and cDNA (1 µL)

was added to each well. Then, it was placed in the CFX Connect rt-PCR Detection System PCR device.

PCR was held at 95 °C for 3 min, at 95 °C for 5 sec, and at 60 °C for 15 sec (45 cycles) and at 40 °C for 30 sec for pre-incubation, amplification, and cooling conditions, respectively. All samples were duplicated in order to avoid errors that might arise due to manipulation. *β-Actin* gene was used as house-keeping gene. Ct (thresholdcycle) values obtained at the end of the process were calculated using the $2^{-\Delta Ct}$ method and normalized.

Statistical Analysis

The slope of the EPSP wave was calculated as 20-80% of the voltage difference between the beginning of the wave and the beginning of the PS wave. PS amplitude was calculated as the mean of the first negative spike and the next positive spike. The mean slope and amplitude values of EPSP and PS of 30 field potentials triggered during the initial 15-minute baseline recording time were accepted as 100. The averages of EPSP slope and PS amplitude values were calculated from 10 field potentials recorded in the first 5-minute period after HFS and in the last 5-minute period at the end of the experiment.

A single sample t-test was used to compare the values obtained within a group with the baseline values. The non-parametric Mann-Whitney U test was used to determine whether there was significance between the groups. Significance level was accepted as $p<0.05$.

Non-parametric Mann-Whitney U test was employed to determine whether there was significance between groups in fT4 level analysis. Significance level was accepted as $p<0.05$.

The conformity of the data obtained with rt-PCR to normal distribution was evaluated with histogram, q-q graphs and Shapiro-Wilk test, and homogeneity of variance was evaluated with the Levene's test. Analysis of the data was performed using GraphPad Prism software. Statistical significance level was accepted as $p<0.05$. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software (SPSS, Chicago, IL).

RESULTS

Plasma Free T_4 Level

Plasma fT4 levels of rats belonging to control and hyperthyroidism groups were measured after electrophysiological recording (Figure 1). In the L-thyroxine group, higher plasma fT4 level was measured than in the control group ($p<0.004$). This result is an indication of the development of hyperthyroidism in rats.

Analysis of Input/Output Curves

The effect of L-thyroxine administration on the basal activity of synapses and neurons before plasticity induction was evaluated with input-output curves. The mean and standard error values of EPSP slope and PS amplitude measured against stimulus intensity were given graphically (Figure 2D; Figure 3D).

Baseline efficacy, ANOVA test results, with repeated measurements of input/output curves obtained by applying pulses of varying intensity between 0.1 mA-0.5 mA before HFS, revealed a significant increase in EPSP slopes ($F_{7.70}=6.017$; $p<0.001$ Figure 2D) and PS amplitudes ($F_{7.70}=13.460$; $p<0.001$ Figure 3D) as the stimulus intensity increased, as expected. Insignificant interaction between EPSP slope ($F_{7.70}=1.32$; $p=0.27$) and PS amplitude ($F_{7.70}=0.46$; $p=0.515$ after lower-bound correction) and stimulus intensity showed that this increase was similar in all groups. The group effect was not found to be significant for EPSP slope ($F_{1.10}=0.33$; $p=0.577$) and PS amplitude ($F_{1.10}=2.65$; $p=0.134$). These findings indicate that the efficacy of the perforating pathway-dentate gyrus synapses before the triggering of LTP with HFS was similar in the control and hyperthyroid groups.

The Effect of HFS on EPSP and PS

LTP responses were measured using EPSP slope and PS amplitude. The 5-minute period (15th min-20th min) after induction was called the post-HFS period, and the 5-minute period between 70th and 75th minutes at the end of the experiment was called the maintenance period.

With single-sample t-test, EPSP slopes of the control (154.2±16.0%, $t_5=8.261$, $p=0.000$; Figure 2B) and hyperthyroidism (148.5±18.2%, $t_5=5.993$, $p=0.002$; Figure

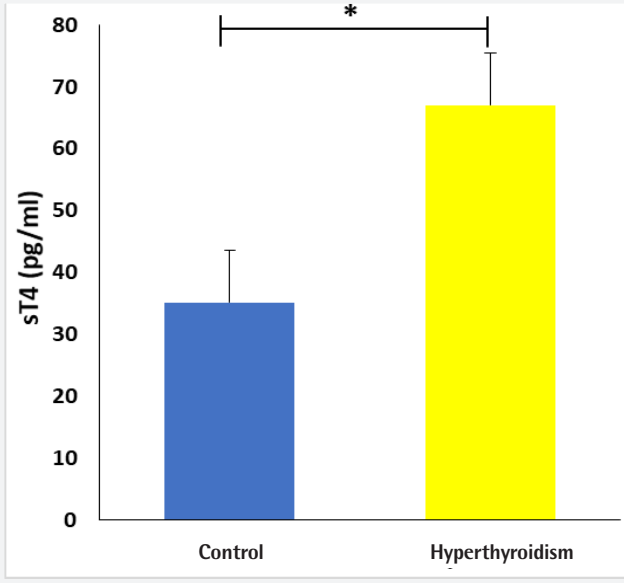

Figure 1. Plasma free T_4 values of control and experimental group rats. Values were given as mean±standard error (n=6)

**Indicates a significant difference compared to the control group (p<0.004)*

2B) groups were detected to be statistically higher after HFS compared to the recording of baseline period. During the maintenance period, EPSP slopes were found to be statistically significantly higher in the control group (119.3±9.0%, t_5=5.202 p=0.003, Figure 2C) compared to baseline recording. No statistically significant difference was found in the hyperthyroidism (109.0±12.5, t_5=1.765 p=0.138, Figure 2C) groups according to baseline recording. This finding shows us that LTP response did not occur in the synaptic component in the hyperthyroidism group.

When the differences between the groups were examined with the Mann-Whitney U test for EPSP slope, there was no statistically significant difference in EPSP slope between the groups in the post-HFS period (Z=-0.801 p=0.4) and the maintenance period (Z=-0.601 p=0.1).

When PS amplitude was evaluated considering baseline values, with single sample t-test, PS amplitudes of the control (271.0±62.4%, t_5=6.716, p=0.01; Figure 3B) and hyperthyroidism (213.47±23.2%, t_5=11.967, p=0.00; Figure 3B) groups in the post-HFS period were found to be statistically higher compared to the baseline recording. In the maintenance period, PS amplitudes of the control (212.3±21.9%, t_5=12.536, p=0.00; Figure 3C) and hyperthyroidism (182.5±35.3, t_5=5.723, p=0.02 Figure 3D) groups increased significantly compared to the baseline recording.

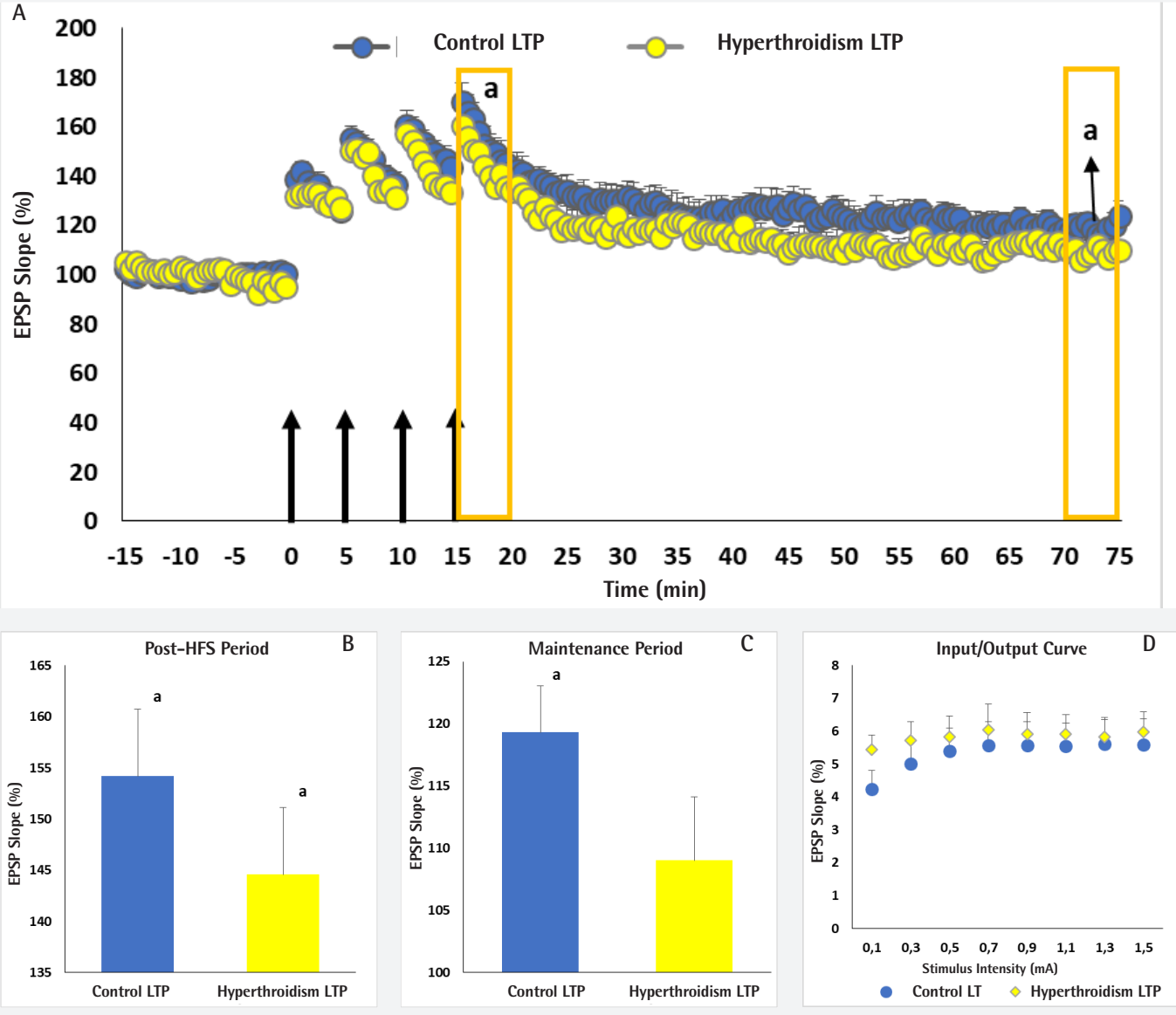

Figure 2. EPSP slopes A) EPSP slopes recorded during the experiment. B) EPSP slopes of the post-HFS period. C) EPSP slopes of the maintenance period. D) Input/output curves of EPSP slopes. [a](p<0.004) represents a significant increase compared to the baseline value

EPSP: Excitatory postsynaptic, LTP: Long-term potentiation, HFS: High-frequency stimulation

When the differences between the groups were examined for PS amplitude with the Mann-Whitney U test, no statistically significant difference was found between the groups in PS amplitude in the post-HFS period (Z=-0.922 p=0.055) and in the maintenance period (Z=-0.281 p=0.2).

Analysis of Real-Time PCR Outcomes

The mRNA expression levels of tau protein and amyloid beta precursor protein-related genes in the hippocampus, which were removed at least 60 minutes after HFS, obtained by rt-PCR method are graphically shown in Figure 4.

According to the Mann-Whitney U test, there was a statistically significant difference between the groups in the expression levels of tau-associated Akt1-mRNA (p=0.02), Cdk5-mRNA (p=0.03), and Mapt1-mRNA (p=0.006), while no statistically significant difference was found in the expression levels of tau-associated Gsk3β - P35(Anxa)-mRNA and Capn1-mRNA expression and amyloid beta precursor protein-associated Bace1-mRNA and Psen2-mRNA (p>0.05).

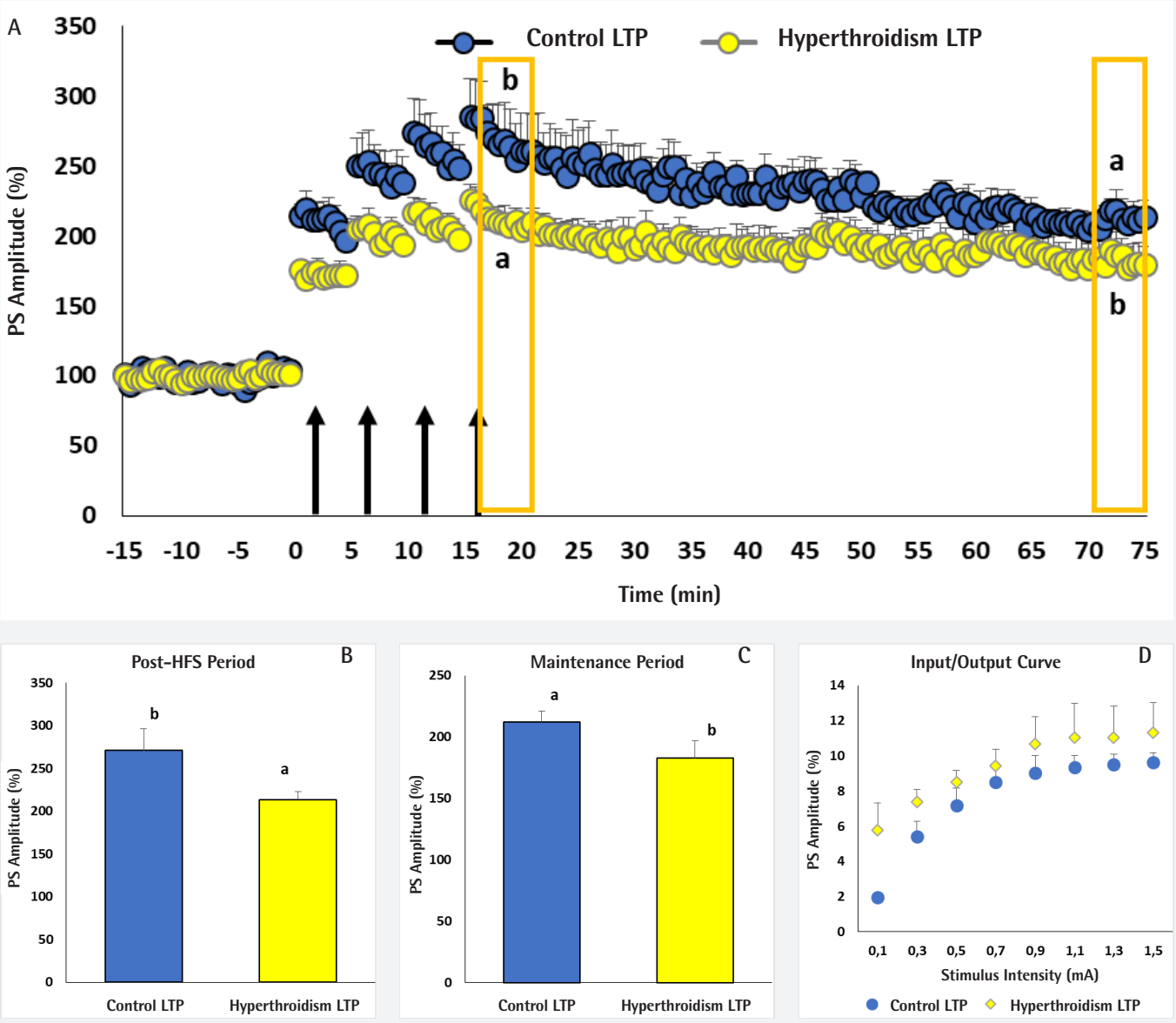

Figure 3. PS amplitudes. A) PS amplitude recorded during the experiment. B) PS amplitudes of the post-HFS period. C) PS amplitudes of the maintenance period. D) Input/output curves of the PS amplitudes. [a](p<0.004), [b](p<0.02) indicate a significant increase compared to the baseline value

PS: Population spike, LTP: Long-term potentiation, HFS: High-frequency stimulation

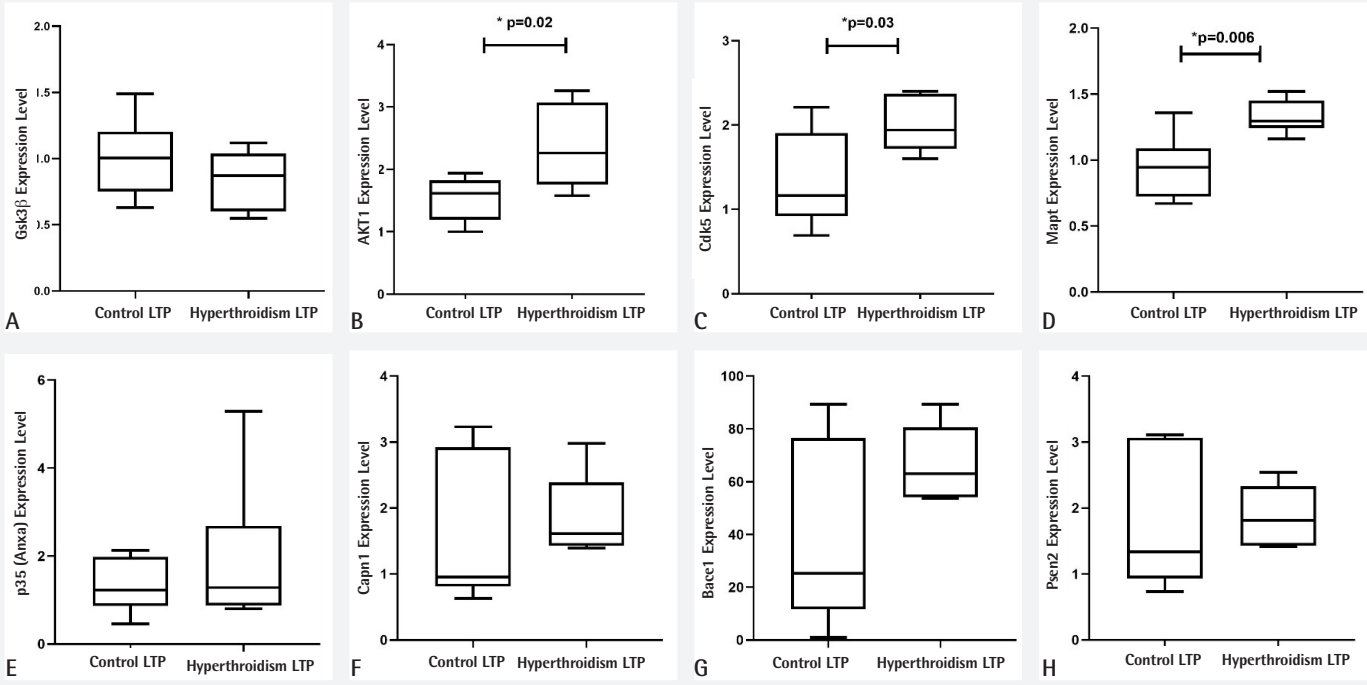

Figure 4. A-F) mRNA expression levels of tau protein- and amyloid precursor protein-related genes (n=6). Data are expressed as median (1st quartile - 3rd quartile)

**Indicates a significant difference compared to the control group*

LTP: Long-term potentiation

DISCUSSION

Changes in LTP and Gene Expression in Thyroid Hormone Excess

Tetanic stimulation with a frequency of one hundred Hz and a duration of 1 second can be applied as a series or as four repetitive sequences as in our study. Powerful four-repeat induction protocols are often preferred because they cause increased transcription factors and gene expression, and thus have greater potential for longer persistence of LTP. In our study, the fact that both the EPSP slope and PS amplitude were significantly higher in the control (euthyroid) group 1 hour after the application of the induction protocol indicates that this protocol is sufficient to induce a permanent LTP (Figures 2, 3). However, this protocol, which was able to induce LTP lasting at least 1 hour in rats in the control group, was able to induce a non-permanent synaptic LTP in the hyperthyroid group. There was an increase in PS amplitude 1 hour after induction in both control and hyperthyroid groups. These findings, which are consistent with the previous findings of our group[7,15,16], can be interpreted as the effect of hyperthyroidism is limited to the synapse level.

While mRNA expression levels of *Gsk3β*, *P35 (Anxa), Capn1, Bace1* and *Psen2* genes evaluated in the hippocampus tissue after LTP recording did not differ significantly between the groups, Akt1, Cdk5 and Mapt-mRNA expression levels were increased in the hyperthyroidism group compared to the control group.

The absence of a difference between the groups in the mRNA levels of *Gsk3β*, *P35 (Anxa), Calpn1, Bace1* and *Psen2* genes in hyperthyroid rats that did not show a permanent synaptic LTP 1 hour after HFS indicates that the products of these genes cannot be responsible for the deterioration in LTP.

Gsk3β is an important kinase that exhibits persistent activity under basal conditions and is inhibited by phosphorylation from the ser9 position by many kinases, including Akt[17]. Gsk3β ser9 phosphorylation, which occurs with the increased activity of the PI3K-Akt pathway during HFS, inhibits this kinase and promotes the formation of LTP, while preventing the formation of UDB[18]. In other words, the formation of LTP (with the effect of Akt1) requires Gsk3β to remain inactive, while the formation of UDB (with the activity of protein phosphatases) requires it to remain active[19].

Akt and Cdk5 proteins, which are the target products of Akt1 and Cdk5 gene expression, are proteins with strong tau kinase properties[20-23]. Serum tau levels of hyperthyroid cases are significantly increased compared to the controls[24]. Therefore, the increase in Akt1 and Cdk5 mRNA in hyperthyroid rats is consistent with the hyperthyroid condition having a higher risk of dementia than the euthyroid condition[25]. The increase

in LTP-related tau expression in the hyperthyroid condition may have a function that prevents the persistence of synaptic LTP and triggers neurodegenerative changes. The fact that Cdk5 down-regulation potentiated UDB by causing BDNF/CREB activation in hippocampal sections[26] supports the role of increased Cdk5 expression in the synaptic LTP disorder we observed in hyperthyroid rats.

Cdk5 is a neuron-specific kinase that plays important roles in many cellular functions and is mainly involved in many neurodevelopmental processes such as synaptic plasticity, learning, and memory[27]. For Cdk5 activation, it requires the binding of p35, p39, or p25 (a proteolytic part of p35) to Cdk5[28]. In Alzheimer's disease, p35, which is Cdk5 activator protein, undergoes N-terminal cleavage by calpain (calcium-dependent protease) to form p25. p25 forms a stable complex with Cdk5, which retains its active state longer, leading to hyperphosphorylation of tau. p25-bound Cdk5 also acts as a priming kinase and promotes Gsk3β-mediated Tau phosphorylation[23]. Although the monomeric form of Cdk5 is enzymatically inactive, it has been reported that it may cause an increase in Cdk5 tau phosphorylation and neurodegeneration in Alzheimer's disease[29]. Cdk5 inhibitors have been shown to protect hippocampal neurons against both abnormal tau phosphorylation and neuronal death[27]. In addition, some study findings show that Cdk5 activity facilitates LTP by increasing the number of NMDA receptors NR2A and NR2B[30]. Therefore, apart from the expression level of Cdk5, how the effect of thyroid hormones will change the activity of this kinase should also be investigated.

β-secretase, known as Bace1, is one of the first enzymes involved in the APP cleaving, and this is a neurotoxic abnormal cleaving. At the end of this cleaving, amyloid beta peptide production occurs and contributes to the development of AH[31]. However, it has been reported that Bace1 deficiency impairs the formation of LTP by causing a decrease in synaptic proteins (mGluR1 and postsynaptic PSD-95 proteins). In other words, it has been reported that inhibition or deficiency of Bace1 causes a decrease in glutamate (Glu) release with a decrease in the distribution of synaptic vesicles to the active site, and thus a weaker activation of NMDA and AMPA receptors on the postsynaptic membranes of a small number of glutamate, thereby impairing the formation of LTP[32]. On the other hand, it has been reported that Gsk3β activation increases Bace1 gene expression and increases amyloid peptide formation[17]. In our study, while there was no significant difference in Gsk3β-mRNA expression level between the control group and the hyperthyroidism group, there was no difference between both *Bace1* and *Psen2* genes.

Study Limitations

The following limitations should be taken into account when interpreting the results of our study, which examined the changes in the expression of genes related to neurodegeneration after LTP in the hippocampus of hyperthyroid rats: compared to the control group, measurement of plasma free T4 level in the L-thyroxine group as higher confirms that hyperthyroidism has occurred. Although changes in free T3 and TSH levels, consistent with the change in T4 level, are expected, plasma fT3 and TSH levels could not be measured (due to limited financial support). The real-time quantitative PCR method used in the study only gives information about the mRNA levels of the measured proteins. It does not provide information about the loss, destruction or activity of protein that may occur while being synthesized. For this reason, there is a need for further studies in which protein analyses will be performed.

CONCLUSION

Physiological levels of thyroid hormones are important for the expression of some genes accompanying the induction of plasticity to remain within physiological limits. Changes in hormone level can alter mRNA expression of genes related to neuronal plasticity, depending on the induction protocol.

Ethics

Ethics Committee Approval: The study was approved of Erciyes University Animal Experiments Ethics Committee dated 17.07.2019 and numbered 19/133.

Informed Consent: This is an animal experiment study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A., Concept: M.A., N.D., C.S., Design: M.A., N.D., C.S., Data Collection or Processing: M.A., Analysis or Interpretation: M.A., N.D., C.S., Literature Search: .A., N.D., C.S., Writing: M.A., N.D., C.S.

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The Effect of Sleep Disorders and Fatigue on In-vehicle Traffic Accidents

Araç İçi Trafik Kazalarına Uyku Bozuklukları ve Yorgunluğun Etkisi

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ABSTRACT

Aim: Traffic accidents have been reported by the World Health Organization as a global problem affecting the whole world. Many studies have shown that the majority of traffic accidents are associated with inadequate and/or disturbed sleep. We aimed to define possible sleep disorders and chronic fatigue in people who had had an in-vehicle traffic accident with applicable scales and to take the necessary precautions.

Materials and Methods: Our study included 104 people with a suitable general condition and physical examination, who had an in-vehicle traffic accident and applied to Pamukkale University Faculty of Medicine Emergency Service. For all patients, demographic data inquiries were made, and the 'Epworth Sleepiness Scale (ESS)', 'Pittsburg Sleep Quality Index (PUKİ)', 'Berlin Questionnaire' and 'Fatigue Severity Scale' were applied.

Results: Increased daytime sleepiness was determined in 10 (9.62%) people according to the ESS, poor sleep quality in 15 (14.42%) people according to the PUKİ, high risk of Obstructive sleep apnea syndrome (OSAS) in 15 (14.42%) people according to the Berlin Questionnaire, and chronic fatigue in 30 (29.1%) people according to the Fatigue Severity Scale.

Conclusion: In our study, we showed with scales that people who had an in-vehicle traffic accident could have various sleep disorders and chronic fatigue syndrome that had not been diagnosed before. However, contrary to what is mentioned in the literature, we found the prevalence of OSAS risk to be low. Necessary measures should be taken to minimize the risk of preventable accidents while driving. In case of suspicion of respiratory disorder, which is one of the sleep disorders we frequently see, gold standard tests such as polysomnography should be used before saying that there is no respiratory disorder in sleep with scales, especially in people who will be driving as a profession.

Keywords: Traffic accident, sleep disorders, obstructive sleep apnea syndrome, daytime sleepiness, fatigue

ÖZ

Amaç: Trafik kazaları, Dünya Sağlık Örgütü tarafından tüm dünyayı etkileyen global bir problem olarak bildirilmiştir. Trafik kazalarının büyük çoğunluğunun yetersiz ve/veya bozuk uyku ile ilişkili olduğu birçok çalışmada gösterilmiştir. Biz de araç içi trafik kazası geçiren kişilerdeki olası uyku bozuklukları ve kronik yorgunluk durumunu uygulanabilir ölçeklerle tanımlamayı ve gerekli önlemeleri almayı amaçladık.

Gereç ve Yöntem: Çalışmamıza araç içi trafik kazası geçiren ve Pamukkale Üniversitesi Tıp Fakültesi Acil Servisi'ne başvuran, genel durumu ve fizik muayenesi uygun 104 kişi dahil edildi. Tüm hastalara demografik veri sorgulaması yapıldı, 'Epworth Uykululuk Ölçeği (EUÖ)', 'Pittsburg Uyku Kalitesi İndeksi (PUKİ)', 'Berlin Anketi' ve 'Yorgunluk Şiddet Ölçeği' uygulandı.

Bulgular: EUÖ'ye göre 10 (%9,62) kişide artmış gündüz uykululuğu, PUKİ'ye göre 15 (%14,42) kişide kötü uyku kalitesi, Berlin Anketi'ne göre 15 (%14,42) kişide yüksek Obstrüktif uyku apne sendromu (OUAS) riski, Yorgunluk Şiddet Ölçeği'ne göre 30 (%29,1) kişide kronik yorgunluk saptandı.

Sonuç: Çalışmamızda, araç içi trafik kazası geçirmiş kişilerde, daha önce tanı almamış olmalarına rağmen, çeşitli uyku bozukluklarının ve kronik yorgunluk sendromunun olabileceğini ölçeklerle gösterdik. Fakat literatürde bahsedilenin aksine özellikle OUAS riskinin prevalansını düşük bulduk. Araç kullanımında önlenebilir kaza riskini en aza indirmek amacıyla gerekli tedbirler alınmalıdır. Özellikle meslek olarak şoförlük yapacak kişilerde, sıklıkla gördüğümüz uyku bozukluklarından solunum bozukluğu şüphesi halinde uykuda solunum bozukluğu olmadığını ölçeklerle söylemeden önce polisomnografi gibi altın standart tetkikler kullanılmalıdır.

Anahtar Kelimeler: Trafik kazası, uyku bozuklukları, obstrüktif uyku apne sendromu, gün içi uykululuk, yorgunluk

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INTRODUCTION

Motor vehicle accidents are expected to be the fourth leading cause of death in the world by 2030[1]. Driving a motor vehicle is a skill that requires the integration of complex functions such as higher cortical function, alertness, concentration and eye-hand coordination. Considering the causes of traffic accidents, it has been seen that they may be caused by human errors, bad weather conditions, bad road conditions and mechanical problems related to the vehicle. It has been reported that up to 20% of traffic accidents are due to driver fatigue and sleepiness[2]. Sleep disorders are one of the leading causes of traffic accidents and can lead to serious injuries and high mortality[3]. Falling asleep while driving has become an important international public health problem due to the heavy cost of traffic-related morbidity and mortality[4]. Between 10 and 30 percent of fatal accidents are associated with falling asleep while driving[5]. In the studies of Masa et al.[6] and Lloberes et al.[7], it was shown that perceived sleepiness at the wheel before a collision was significantly associated with accident risk. In a study by Connor et al.[8], it was reported that approximately 20% of fatal accidents were associated with driver fatigue. It was also shown in another study that sleepiness at the wheel increased the risk of an accident by 2 times[5]. It has been stated by the National Sleep Foundation that 100,000 traffic accidents occur every year due to tired drivers, and long-distance drivers are at a higher risk of having an accident due to fatigue and sleepiness[9]. In many previous studies, it has been shown that sleepiness-related traffic accidents are caused by many sleep-related diseases such as Obstructive sleep apnea syndrome (OSAS). The predictors of driver sleepiness with largest evidence to date are younger age, male gender, duration of driving, increased daytime sleepiness (EDS) and increased risk of obstructive sleep apnea. In addition, underlying diseases also significantly affect EDS[10]. In our study, we aimed to examine the relationship between traffic accidents and sleep quality, sleep disorders and fatigue in people who applied to the emergency department due to a traffic accident, and to determine that the treatment of people's known sleep disorders is an important step in preventing traffic accidents.

MATERIALS AND METHODS

Our study included 104 conscious patients over the age of 18 years, who applied to the Emergency Department of Pamukkale University Medical Faculty and had an in-vehicle traffic accident as a driver. Motorcycle and other non-vehicle traffic accidents were not included in the study. After the necessary initial examinations and evaluations of the patients were made, questions including demographic data, year of driving, number of accidents, time of accident, alcohol use in the accident, traffic accidents had in the last 6 months and the presence of someone with them during the accident were asked. The 'Epworth Sleepiness Scale' (ESS)[6] measuring daytime sleepiness, 'Pittsburgh Sleep Quality Index' (PSQI)[7] measuring sleep quality, 'Berlin Questionnaire' used for screening in the diagnosis of OSAS and 'Fatigue Severity Scale'[8] assessing fatigue severity, Turkish reliability and validity of which were proven, were applied. The time interval of the accident was analyzed as 00:01-06:00, 06:01-12:00, 12:01-18:00, 18:01-24:00 by dividing 24 hours into 4.

Those who scored 10 or higher on the ESS were evaluated as 'increased daytime sleepiness'. PSQI was examined in 7 categories, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disorders, use of sleeping pills, and daytime functions, and poor sleep quality was determined for those with a total score of 5 and above. The Berlin Questionnaire was examined in 3 categories within itself, and a high risk of OSAS was determined for those who scored 2 points or more. Finally, the Fatigue Severity Scale consisted of 9 questions, and those with a score above 6.1, obtained by dividing the total score by 9, were diagnosed with chronic fatigue syndrome.

Written consent forms were obtained from all participants stating that they volunteered for the study, and the study was carried out in line with the decision of the Medical Ethics Committee of Pamukkale University no. 60116787-020/34134 (date: 09.06.2020).

Statistical Analysis

Data were analyzed with Statistical Package for the Social Sciences (SPSS) 25.0 [IBM SPSS Statistics 25 software (Armonk, NY:IBM Corp.)] package program. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as numbers and percentages. The conformity of the data to the normal distribution was examined using the Shapiro-Wilk test. The Mann-Whitney U test was used to analyze the independent group differences. The Spearman's correlation analysis was used to examine the relationships between continuous variables. A p value of <0.05 was considered statistically significant in all analyses.

RESULTS

One hundred four patients who were conscious and in good general condition after having had an in-vehicle traffic accident were included in our study. The mean age of the patients was 38.97±13.69 years, and 15 (14.4%) were female and 89 (84.6%) were male. It was determined that 4 of the patients (3.8%) did not have a driver's license. The average driving time of the individuals was calculated as 15.52±11.68 years. Considering the type of vehicle in the accidents, 90 (86.5%) were cars, 8 (7.7%) were pickup trucks, 4 (3.8%) were trucks, and 2 (1.9%) lorries. When the education levels of the individuals were

examined, it was determined that 43 (42.6%) were primary school graduates, 32 (31.7%) were high school graduates and 26 (25.7%) were university graduates. It was determined that 18 of the patients (17.3%) had a previously known chronic disease, and 5 (4.8%) of the patients were drunk at the time of the accident. Considering the time interval of the accidents, it was seen that 44 (45.4%) of them were between 06:01 and 12:00. When the histories of previous traffic accidents were examined, it was determined that 5 people (4.8%) had at least one in-vehicle traffic accident in the last 6 months. It was learned that 51 (49.1%) people were with at least one person at the time of the accident (Table 1).

The mean score of the ESS was 3.66±4.01 and EDS was detected in 10 (9.62%) people. The mean of the PSQI was 3.46±2.64, and 15 (14.42%) people showed poor sleep quality. The mean of the Berlin Questionnaire was 1.55±1.83, and the risk of OSAS was considered high in 15 (14.42%) individuals. The mean of the Fatigue Severity Scale was 18.2±14.48, and chronic fatigue was found in 30 (29.1%) individuals (Table 2).

The mean body mass index (BMI) of the subjects was 26.25±4.54, and a statistically significant negative correlation was found between education level and BMI (r=-0.200, p<0.05).

When the ESS was compared with the Berlin Questionnaire (r=0.519, p<0.001), the Fatigue Severity Scale (r=0.420, p<0.001) and the PSQI (r=0.374, p<0.005), a statistically significant positive correlation was observed between them (Table 3).

There was a statistically significant positive correlation between the Berlin Questionnaire and the Fatigue Severity

Table 1. Demographic characteristics of people who had an in-vehicle traffic accident

	Patient (n=104)
Age, mean±SD, y	38.97±13.69
Gender Female (%) Male (%)	15 (14.4%) 89 (84.6%)
Duration of driving Mean±SD, y	15.52±11.68
BMI, Mean±SD	26.25±4.54
Vehicle type Otomobile Truck Pickup truck Lorry	90 (86.5%) 4 (3.8%) 8 (7.7%) 2 (1.9%)
Educational level Primary school High school University	43 (42.6%) 32 (31.7%) 26 (25.7%)
Period of education Mean±SD, y	10.75±2.82
Time of accident 06:01-12:00 12:01-18:00 18:01-24:00 00:01-06:00	44 (45.4%) 28 (28.9%) 16 (16.5%) 9 (9.3%)
ESS Mean±SD	3.66±4.01
Berlin Questionnaire Mean±SD	1.55±1.83
FSS Mean±SD	18.2±14.48
PSQI total Mean±SD	3.46±2.64

BMI: Body mass index, ESS: Epworth Sleepiness Scale, FSS: Fatigue Severity Scale, PSQI: Pittsburgh Sleep Quality Index, SD: Standard deviation

Table 2. The clinical status of the patients according to the results of the scales

Fatigue Severity Scale	Fatigue	
	+	30 (29.1%)
	-	73 (70.9%)
Epworth Sleepiness Scale	Day sleepiness	
	+	10 (9.6%)
	-	94 (90.4%)
Berlin Questionnaire	OSAS high risk	15 (14.4%)
PSQI	Poor sleep quality	15 (14.4%)

OSAS: Obstructive sleep apnea syndrome, PSQI: Pittsburgh Sleep Quality Index

Table 3. Correlation of Epworth Sleepiness Scale with other scales

Epworth Sleepiness Scale		
	p	**r**
Berlin Questionnaire	<0.001*	0.519
Fatigue Severity Scale	<0.001*	0.420
PSQI	<0.05*	0.374

*Statistically significant.
PSQI: Pittsburgh Sleep Quality Index

Table 4. Correlation of the Berlin Questionnaire with scales, age and duration of education

Berlin Questionnaire		
	p	**r**
Fatigue Severity Scale	<0.001*	0.343
PSQI	<0.05*	0.341
Age	<0.05*	0.210
Duration of education	<0.05*	-0.201

*Statistically significant.
PSQI: Pittsburgh Sleep Quality Index

Scale (r=0.343, p<0.001) and the PSQI (r=0.341, p<0.05). While a statistically significant positive correlation (r=0.210, p<0.05) was found between the Berlin Questionnaire and age, a negative correlation was observed with education level (r=-0.201, p<0.05) (Table 4).

According to the results of the Berlin Questionnaire, the ESS, Fatigue Severity Scale, and PSQI scores were found to be statistically significantly higher in those with a high risk of OSAS (p=0.021, p=0.0001, p=0.009) (Table 5).

There was a statistically significant positive correlation between the Fatigue Severity Scale and the PSQI (r=0.308, p<0.05). A statistically significant positive correlation was demonstrated between the PSQI and the number of accidents related to absent-mindedness (r=0.340, p<0.05). A statistically significant negative correlation was observed between the training periods and the number of accidents due to absent-mindedness (r=-0.232, p<0.05) (Table 6).

Table 5. Relationship between the results of Berlin Questionnaire and other scales

Berlin Questionnaire	OSAS low risk (n=89)	OSAS high risk (n=15)	
	Mean±SD	Mean±SD	p
Epworth Sleepiness Scale	3.35±3.95	5.53±3.98	0.021* (z=2.302)
Fatigue Severity Scale	15.9±13.19	31.73±14.71	0.0001*(z=3.626)
PSQI	3.05±2.31	6.11±3.26	0.009* (z=-2.608)

*Statistically significant; z: Mann-Whitney U test.

OSAS: Obstructive sleep apnea syndrome, PSQI: Pittsburgh Sleep Quality Index, SD: Standard deviation

Table 6. Other statistically significant correlations

		(A)	(B)	(C)	(D)	(E)
PSQI (A)	r					
	p					
FSS (B)	r	0.308				
	p	0.011*				
Number of accidents due to absent-mindedness (C)	r	0.340	-0.031			
	p	0.005*	0.756			
Duration of education (D)	r	-0.039	0.107	-0.232		
	p	0.759	0.289	0.020*		
BMI (E)	r	0.729	-0.035	0.169	-0.200	-
	p	0.146	0.729	0.090	0.046*	

*Statistically significant.

PSQI: Pittsburgh Sleep Quality Index, FSS: Fatigue Severity Scale, BMI: Body mass index

DISCUSSION

Injuries caused by traffic accidents are an important global and public health problem affecting societies. It is known that an important part of this situation is due to driver fatigue and sleepiness[2]. According to the National Transportation Safety Board in the United States (USA), sleep deprivation is the most common cause of sleepiness[11]. Sleep deprivation affects attention, performance, concentration and motor coordination along with neurobiological functions, especially psychomotor and neurocognitive functions. All these lead to an increased risk of accidents while driving[12].

Young age, male gender, EDS, and increased risk of OSAS are known risk factors for driver's sleepiness[10], and in our study, there was a middle aged male predominance. In a study by Filomeno et al.[13], as in our study, it was reported that EDS was more common in the middle-aged group compared to the young-aged group, and this might be associated with higher alcohol consumption in the middle-aged group than in the younger age group.

Traffic accidents are also a hot topic in our country due to the loss of life, and it is thought that the accidents are often related to drowsy driving due to daytime sleepiness[14]. While daytime sleepiness was found to be increased by 9.62% in our study, the increased prevalence of EDS in traffic accidents was found to be 3% in the USA, 10% in France, and 33% in New Zealand in previous studies[15]. It has been stated that these differences in studies may be related to differences according to ethnic populations. An example of this is the correlation between increased BMI and daytime sleepiness, and a similar risk ratio in Asian people with normal BMI, regardless of BMI[16]. We also did not find any correlation between BMI and increased EDS in our study, but we found a negative correlation between education level and BMI. We thought that this might be related to the increase in awareness about healthy nutrition as the level of education increased.

In our study, according to the Berlin Questionnaire applied to people who applied with a traffic accident, 14,42% had the risk of OSAS, and this rate was found to be lower than expected. There are many studies proving the relationship between OSAS and traffic accident risk. This relationship has been clearly demonstrated in polysomnography (PSG) studies[17]. However, in studies conducted in our country with the questioning of OSAS symptoms, results showing that the risk of accident with OSAS symptoms are low or unrelated have been obtained. This situation has been thought to be related to the OSAS symptoms' being personal and/or the person's lack of awareness or their being hidden due to professional concerns in drivers[14]. Since the relationship between OSAS and accident is a proven fact, routine PSG application is one of the

topics discussed in order to reveal this risk in people who will be driving as a profession[17].

In our study, a positive correlation was found in the results of the ESS and the Berlin Questionnaire evaluating the risk of OSAS. This result, which supports that OSAS affects daytime sleepiness, was not supported in some studies. It was thought that this was mostly due to the lack of motivation of people and their inability to evaluate themselves and the disease[18]. However, daytime sleepiness is an inevitable consequence as a result of sleep interruptions during night, autonomic dysfunction and hypoxia due to OSAS. In addition, another important cause of EDS is impaired sleep quality[19]. In our study, we also found a statistically significant positive correlation between ESS and PSQI. In addition, considering the patients with a history of in-vehicle traffic accident in the last 6 months, it was shown that the sleep quality was worse in these individuals, although there was no statistically significant difference compared to those without a history of traffic accidents. It was thought that this was actually an important finding, but that statistical differences could not be shown due to the inadequacy of the numbers.

Although fatigue and daytime sleepiness are different definitions, in clinical practice these two conditions cannot be distinguished from each other[19]. In our study results, a significant positive correlation was found between ESS and fatigue severity scale. In the studies, fatigue was defined in drivers while driving, and Mayor et al.[20] determined the fatigue rate of drivers as 32% while driving. Similarly, we found chronic fatigue syndrome in 29.1% of drivers in our study.

When PSG results are examined in people with OSAS, it is seen that the time spent in stage 1 and in wakefulness increase, which is thought to be associated with impaired sleep quality[18]. In our study, we found poor sleep quality in people at high risk of OSAS. It is inevitable to have a chronic fatigue process related to reasons such as poor sleep quality and deterioration of oxygenation during the night caused by OSAS. In relation to this, in our study, we found that the Fatigue Scale scores were high in people with high OSAS risk.

In a study examining age and sleep disorders in traffic accident victims, it was seen that sporadic causes such as alcohol and drug use are more common in young and middle ages, and more chronic causes such as respiratory disorders at sleep in older ages[5]. In our study, we found a significant positive correlation between the increased risk of OSAS and age in those who had a traffic accident.

Studies examining the relationship between education level and traffic accidents have shown that low education level leads to more fatal accidents[21,22]. In our study, a negative correlation was found between the duration of education and the number of accidents due to absent-mindedness, and a positive correlation with the risk of OSAS. We thought that this was associated with greater attention and awareness as the duration of education increased, as well as a lower risk of OSAS and a lower risk of traffic accidents caused by it.

Finally, the effect of sleep disorders on traffic accidents is a fact that has been researched and revealed by the whole world. In some studies on the solution, it has been shown that some measures to be taken against sleepiness (stopping and taking a short walk, listening to music, opening the window, consuming coffee) reduce the risk of accidents in drivers[23].

CONCLUSION

The relationship between in-vehicle traffic accidents and daytime sleepiness, OSAS risk, chronic fatigue, and poor sleep quality has been demonstrated, and both loss of life and property can be largely prevented by recognizing these, even with easy-to-apply scales, and taking the necessary precautions.

However, the relationship between the risk of OSAS obtained by questioning the risk of OSAS, which is a common cause of sleep disorder, and having an accident was observed at a low rate. PSG examinations should be recommended in cases of clinical suspicion and in occupational groups such as professional driving, and traffic accidents should be prevented by using continuous positive airway pressure if OSAS is detected.

Ethics

Ethics Committee Approval: The study was carried out in line with the decision of the Medical Ethics Committee of Pamukkale University no. 60116787-020/34134 (date: 09.06.2020).

Informed Consent: Written consent forms were obtained from all participants stating that they volunteered for the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.S., Design: S.T., Data Collection or Processing: M.S., Analysis or Interpretation: S.T., Literature Search: M.S., Writing: S.T.

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Psychological Resilience and Adaptation Difficulties in Older Adults

Yaşlı Bireylerde Psikolojik Dayanıklılık ve Uyum Zorlukları

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ABSTRACT

Aim: Mental health structural characteristics, such as psychological resilience, in addition to the physical and social losses which occur with ageing are effective in providing adaptation to the changes that occur in the normal ageing process.

Materials and Methods: The study was conducted with 200 individuals aged 60 years and above, and living in İstanbul. Data were collected using a Socio-demographic Form, Assessment Scale of Adaptation Difficulty for the Elderly, and the Resilience Scale for Adults.

Results: According to the results of this study, as psychological resilience increased, difficulty in adaptation to ageing decreased. The study results demonstrated that female gender, advanced age, and not being married constituted disadvantages in respect of both psychological resilience and adaptation difficulty, while a high income and literacy reduced difficulty in adaptation to ageing.

Conclusion: Measures to increase psychological resilience may be beneficial to reduce adaptation difficulties due to aging.

Keywords: Mental health, aging, adaptation difficulty, psychological resilience, geropsychiatry

ÖZ

Amaç: Yaşlanma ile ortaya çıkan fiziksel ve sosyal kayıplara ek olarak psikolojik dayanıklılık gibi ruh sağlığı yapısal özellikleri, normal yaşlanma sürecinde meydana gelen değişikliklere uyum sağlamada etkilidir.

Gereç ve Yöntem: Araştırma, İstanbul'da yaşayan 60 yaş ve üzeri 200 kişi ile yapıldı. Veriler Sosyo-demografik Form, Yaşlılar için Uyum Zorluğu Değerlendirme Ölçeği ve Yetişkinler için Dayanıklılık Ölçeği kullanılarak toplandı.

Bulgular: Bu çalışmanın sonuçlarına göre psikolojik dayanıklılık arttıkça yaşlanmaya uyum güçlüğü azalmaktadır. Araştırma sonuçları, kadın cinsiyet, ileri yaş ve evli olmamanın hem psikolojik dayanıklılık hem de uyum güçlüğü açısından dezavantaj oluşturduğunu, yüksek gelir ve okuryazarlığın ise yaşlılarda uyum güçlüğünü azalttığını gösterdi.

Sonuç: Dünya nüfusu hızla yaşlanmaktadır. Bu nedenle özellikle bu grupların iyi oluşları açısından uyum güçlüğünü azaltacak ve psikolojik dayanıklılığı artıracak önleyici tedbirler alınmalıdır.

Anahtar Kelimeler: Ruh sağlığı, yaşlanma, uyum zorluğu, psikolojik dayanıklılık, geropsikiyatri

INTRODUCTION

Just as stressful life events can create immediate effects on the psychological well-being and physical health of individuals, they can also have a cumulative effect[1]. Psychological resilience is defined as a process of successful adaptation against significant sources of stress such as trauma, problems arising from threats, family, workplace, and close relationships, serious health problems, and financial problems[2-4]. The American Psychological Association defines resilience as "the process of adapting well in the face of adversity, trauma, tragedy, threats, or significant sources of stress," or "bouncing back" from difficult experiences[5]. It is also expressed as the ability to gather one's strength and make changes to overcome difficult processes faced throughout life[6,7].

According to Zautra[8], there are two aspects of resilience, namely improvement and sustainability. Improvement is defined as the

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ability to regain function after stressful situations or trauma, and sustainability as the ability to resist and continue against difficulties encountered throughout life. Some individuals can transform stressful experiences into growth and learning opportunities which increase their capabilities of overcoming difficulties in the future.

As individuals grow older, there is an increasing probability of encountering new difficulties in life. For some people, the ageing process is a time to acquire new skills, and a time of growth and personal discovery, whereas for others, it is a process greatly affected by physical losses, emotional losses such as the loss of a spouse, and environmental barriers. In this respect, the importance of psychological resilience is clear in the period of old age, which is a period when there is an increased frequency of many different stressful life events[9,10]. When psychological resilience studies are evaluated in this field in literature, it can be seen that most studies have focused on pediatric and adolescent groups, although there has been an increase in studies related to resilience in the elderly in the last decade[11-13]. The concept of psychological resilience in old age is affected by components such as the internal plasticity of an individual and cognitive reserve capacity. The personal resources, environmental factors, and social support of an individual can change the effects of stress on the health and welfare of the person[14,15]. Personal resources which increase resilience are personality traits, coping skills, and spiritual and physical health, whereas the environmental and social support resources include age-friendly household practices, easy access to medical facilities, and close relationships with friends and family[14,15]. In this context, this study aims to determine the adaptation difficulties of older adults according to their psychological resilience. From this point of view, the main research question of this study is as follows: Is there a relationship between the psychological resilience of older adults and adjustment difficulties?

MATERIALS AND METHODS

Research Model

In this study, a descriptive type of relational screening model was formed with the aim of comparing the adaptation difficulties of older adults according to psychological resilience levels and socio-demographic characteristics. In the relational screening model, it was aimed to determine the presence and/or degree of change in two or more variables. Relational analysis can be obtained by correlation type relationship or comparison[16].

Study Sampling

The study universe consisted of 200 individuals aged ≥60 years and living in İstanbul. The participants were contacted in places with a high density of older adults, such as cafes, public libraries, parks and gardens, and areas around mosques. The participants were first informed about that a study was being conducted in the field of geriatrics and they were invited to participate. After establishing a suitable environment for individual interviews with the older adults who volunteered to participate in the study, detailed information was given about the aim of the study in the scope of gerontological interview techniques. The study sample comprised these 200 subjects who voluntarily agreed to participate in the study and were fully cognisant and in good mental health. In this context, the mental health status of the participants was evaluated by a psychiatrist by performing a basic mental health examination. The number of subjects to be selected from this area was determined using a simple sampling method based on probability sampling techniques.

Data Collection Tools

Data for the study were collected using a face-to-face data collection technique. Informed consent was obtained from all the subjects before the study. The data collection process lasted for an average of 40 mins for each subject. A 17-item Socio-demographic Data Form, the Resilience Scale for Adults (RSA), and the Assessment Scale of Adaptation Difficulty for the Elderly (ASADE) were used as the data collection tools. All assessment tools were self-rating scales, but when necessary, the interviewer explained what the questions and options meant.

The Resilience Scale for Adults

This scale was developed by Friborg et al.[17] and was adapted to Turkish by Basım and Çetin[18]. The scale has 33 items in the sub-dimensions of "perception of self", "perception of future", "structural style", "social competence", "family cohesion", and "social resources". The Cronbach's alpha coefficient calculated for reliability of the whole scale was found to be 0.86, and between 0.66 and 0.81 for the sub-dimensions. In the context of this study, increasing scores indicated higher psychological resilience and in the evaluation selecting the items, the response boxes were evaluated from left to right as 1, 2, 3, 4, 5. Taking this into consideration, the items numbered 1-3-4-8-11-12-13-14-15-16-23-24-25-27-31-33 were coded in reverse[18].

Perception of Self is related to self-awareness of the individual and is expressed by the total responses to the question "who am I?" of how the person evaluates themself. *Perception of Future* is related to whether or not the person has a positive view of the future, expressing all of their thoughts about the future. *Structural Style* expresses characteristics such as self-confidence, personal strengths, and self-discipline[19]. *Social Competence* is the evaluation of the interpersonal relationships of the subject within society and positive evaluation by others[20].

Family Cohesion is related to support for the subject from the family and whether or not there is a compatible relationship with the family. *Social Resources* express the strength of the relationships of the subject with their social environment[21].

Assessment Scale of Adaptation Difficulty for the Elderly

This scale was developed by Şişman and Kutlu[22], and its reliability and validity studies were performed. The Cronbach's alpha value of 0.93 was evaluated as high internal consistency of the scale. The ASADE consists of 24 items with 4-point Likert-type responses to determine the ability to adapt to ageing. The responses for each item are scored as 0 for "never", 1 point for "a little", 2 points for "very much", and 3 points for "extremely". The total of the item points is divided by the number of items to give an average score for the scale from 0 to 3, with points approaching 3 indicating a low level of adaptation to ageing and points approaching 0 indicating better adaptation. The scale has 4 sub-dimensions of "Role and Self-actualization" (items 1, 5, 9, 12, 13, 14, 15, 16, 24), "Interdependence" (items 17, 18, 19, 20, 21, 22, 23), "Physiological State" (items 2, 4, 10, 11) and "Self-Concept" (items 3, 6, 7, 8).

The sub-dimensions of the scale are consistent with the four adaptation forms of the Roy Adaptation Model. The scale can be evaluated as a whole or the factors can be assessed separately. The first factor of role and self-actualization is important in respect of determining what the functions are in the new role of the subject that has developed in association with ageing. The underlying basic requirement for role and self-actualization is social integrity. Insufficient adaptation of the elderly subject to the basic role is evaluated as a warning of associated problems. The second factor of interdependence encompasses the relationships of the elderly person with support systems. Problems experienced in this area can cause problems in maintaining emotional integrity. The third factor of physiological state is related to the physical reactions of the person to stimuli in the environment. This factor provides important data showing the physical behavior to stimuli that affect adaptation of the elderly subject. The fourth and final factor of self-concept is defined as the underlying basic requirement for psychological integrity. To determine adaptation problems in this area, it is important to determine the ability of the subject to improve or maintain health.

Ethical approval was received from the Social and Human Sciences Ethics Committee of İstanbul University (date: 01/04/2019 and no: 35980450-663.05). Verbal and written informed consent was provided by all the participants. The study was carried out in accordance with the Declaration of Helsinki. Informed consent for the procedure was obtained from the volunteers before starting the study.

Statistical Analysis

Data obtained in the study were analyzed statistically using Statistical Package for the Social Sciences 21.0 software. Data control and any necessary corrections were made before starting the analyses. Descriptive statistics and hypothesis tests were applied to the characteristics of the study participants. Conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test, and as the data did not show normal distribution, non-parametric tests were used. To determine the relationships between the data obtained from two scales, the Spearman's correlation analysis was applied. In the comparisons of the mean points obtained from the continuous data of paired groups (gender, marital status), the Mann-Whitney U test was used, and for the comparisons of more than two groups (age, education level, living environment, income level), the Kruskal-Wallis test was applied. A value of $p<0.05$ was accepted as statistically significant in all the analyses.

RESULTS

The socio-demographic characteristics of the study participants are presented in Table 1.

Table 1. Distribution of the socio-demographic characteristics of the older adult participants

Variables	Categories	n	%
Gender	Female	100	50
	Male	100	50
Age group	Age group of 61-65 years	21	10.5
	Age group of 66-70 years	80	40
	Age group of 71-75 years	46	23
	Age group of 75+ years	53	26.5
Marital status	Married	121	60.5
	Single	4	2
	Widowed	75	37.5
	Divorced	-	-
Education level	Illiterate	11	5.5
	Primary school	151	75.5
	Middle school	7	3.5
	High school	10	5
	University graduate	21	10.5
Living environment	Alone	64	32
	With their spouse only	106	53
	With their spouse and children	30	15
Income level	Level below the minimum wage	94	47
	Minimum wage	50	25
	2-fold higher than the minimum wage	30	15
	3-fold higher than the minimum wage	26	13

The RSA points according to the socio-demographic characteristics of the study participants are presented in Table 2.

No statistically significant difference was determined in the RSA points according to gender, education level and income (p>0.05). Considering RSA points according to age groups and marital status. there were determined to be a significant difference in the sub-dimensions of Perception of Future (X^2_{AG}=11.101; p_{AG}=0.011; U_{MS}=3598.00; p_{MS}=0.003) and Social Competence (X^2_{AG}=14.520; p_{AG}=0.002; U_{MS}=3987.50; p_{MS}=0.047). The study participants at the age group of ≥76 years were determined to have lower points and those who were married were determined to have higher points in the Perception of Future and Social Competence sub-dimensions compared to other groups. Considering RSA points according to the living environment, there was determined to be a significant difference in the sub-dimensions of Perception of Future (X^2=12.032 p=0.002), Perception of Self (X^2=9.170 p=0.010), and Social Competence (X^2=9.947 p=0.007). The study participants who lived together only with their spouse were determined to have higher points in the Perception of Future, Perception of Self, and Social Competence sub-dimensions compared to those who lived with their spouse and children or who lived alone.

The ASADE points according to the socio-demographic characteristics of the study participants are presented in Table 3.

Considering ASADE points according to gender, marital status and education level, there was determined to be a significant difference in the sub-dimensions of Role and Self-actualization (U_G=3841.00; p_G=0.004; U_{MS}=3641.00; p_{MS}=0.004; X^2_E=8.906; p_E=0.012), Physiological State (U_G=3559.50; p_G=0.000; U_{MS}=3625.00; p_{MS}=0.002; X^2_E=7.207; p_E=0.027), and Self-concept (U_G=3172.00; p_G=0.000; U_{MS}=3674.00; p_{MS}=0.005; X^2_E=19.099; p_E=0.000). The study participants who were female and illiterate were determined to have higher points and those who were married were determined to have lower points in the Role and Self-actualization, Physiological State and Self-concept sub-dimensions compared to other groups. In terms of ASADE points according to age groups, a significant difference was determined in the sub-dimensions of Role and Self-actualization (X^2=24.431; p=0.000) and Physiological State (X^2=8.029; p=0.045). The study participants at the age group of ≥76 years were seen to have higher points in the Role and Self-actualization and Physiological State sub-dimensions compared to the other age groups. In terms of ASADE points according to the living environment, there was determined to be a significant difference in the sub-dimensions of Role and Self-actualization (X^2=7.624; p=0.022), Interdependence

Table 2. Comparison of resilience scale scores according to the socio-demographic characteristics of the participants

Variables	Categories	n	Structural Style (mean rank)	Perception of Future (mean rank)	Family Cohesion (mean rank)	Perception of Self (mean rank)	Social Competence (mean rank)	Social Resources (mean rank)
Gender	Female	100	107.09	93.46	103.37	99.75	104.94	102.95
	Male	100	93.92	107.55	97.63	101.25	96.06	98.06
			U=4341.50 p=0.106	U=4295.50 p=0.084	U=4713.00 p=0.482	U=4925.00 p=0.854	U=4556.00 p=0.276	U=4755.50 p=0.549
Age group	61-65 years	21	103.55	110.21	118.86	122.95	138.12	114.88
	66-70 years	80	106.38	114.30	102.00	106.16	105.48	103.44
	71-75 years	46	101.68	92.54	91.30	98	93.75	99.66
	76+ years	53	89.40	82.73	98.94	85.24	83.94	91.09
			X^2=2.876 p=0.411	**X^2=11.101 *p=0.011**	X^2=3.391 p=0.335	X^2=7.737 p=0.052	**X^2=14.520 *p=0.002**	X^2=2.936 p=0.402
Marital status	Married	121	101.48	110.26	104.81	105.99	107.05	106.70
	Widowed/divorced	79	99.01	85.54	93.91	92.09	90.47	91.01
			U=4661.50 p=0.767	**U=3598.00 *p=0.003**	U=4258.50 p=0.191	U=4115.00 p=0.096	**U=3987.50 *p=0.047**	U=4029.50 p=0.060
Living environment	Alone	64	100.24	87.50	89.85	95.43	90.30	93.80
	With their spouse only	106	105.97	113.69	105.99	110.54	112.26	107.09
	With their spouse and children	30	81.72	81.62	103.82	75.85	80.68	91.52
			X^2=4.142 p=0.126	**X^2=12.032 *p=0.002**	X^2=3.243 p=0.198	**X^2=9.170 *p=0.010**	**X^2=9.947 *p=0.007**	X^2=2.979 p=0.225

*p<0.05

(X^2=12.145; p=0.002), and Physiological State (X^2=17.587; p=0.000). The study participants who lived together only with their spouse were determined to have lower points in the Role and Self-actualization, Interdependence, and Physiological State sub-dimensions compared to those who lived with their spouse and children or who lived alone. In terms of ASADE points according to income level, A significant difference was determined in the Self-Concept sub-dimension (X^2=30.839; p=0.000). The study participants with an income level 3-fold higher than the minimum wage were seen to have lower points in the Self-Concept sub-dimension compared to those with lower income levels.

The comparisons of the RSA points and the ASADE points of the study participants are shown in Table 4.

A significant negative correlation was determined between the RSA Structural Style sub-dimension points and the points of the ASADE sub-dimensions of Role and Self-actualization (r=-0.277; p=0.000), Interdependence (r=-0.157; p=0.026), Physiological State (r=-0.185; p=0.009) and Self-Concept (r=-0.161; p=0.023). A significant negative correlation was determined between the RSA Perception of Future sub-dimension points and the points of the ASADE sub-dimensions of Role and Self-actualization (r=-0.516;

Table 3. Comparison of the scores of the development of an assessment scale on adaptation according to the socio-demographic characteristics of the participants

Variables	Categories	n	Role and Self-actualization (mean rank)	Interdependence (mean rank)	Physiological State (mean rank)	Self-Concept (mean rank)
Gender	Female	100	112.09	97.79	114.91	118.78
	Male	100	88.91	103.22	86.10	82.22
			U=3841.00 *p=0.004	U=4725.50 p=0.484	**U=3559.50 *p=0.000**	**U=3172.00 *p=0.000**
Age group	61-65	21	91.48	90.00	92.24	114.05
	66-70	80	80.80	101.13	90.21	96.43
	71-75	46	104.24	107.78	103.73	95.59
	76+	53	130.57	97.39	116.51	105.55
			X^2=24.431 *p=0.000	X^2=1.765 p=0.623	**X^2=8.029 *p=0.045**	X^2=2.354 p=0.502
Marital status	Married	121	91.09	97.16	90.96	91.36
	Widowed/divorced	79	114.91	105.62	115.11	114.49
			U=3641.00 *p=0.004	U=4375.00 p=0.286	**U=3625.00 *p=0.002**	**U=3674.00 *p=0.005**
Education level	Illiterate	11	149.18	126.36	142.32	151.77
	Primary school	151	99.32	98.16	99.31	103.98
	Middle school and more than middle school	38	91.09	102.32	93.12	71.82
			X^2=8.906 *p=0.012	X^2=2.767 p=0.251	**X^2=7.207 *p=0.027**	**X^2=19.099 *p=0.000**
Living environment	Alone	64	113.16	103.11	112.68	114.17
	With their spouse only	106	89.92	90.64	85.81	92.16
	With their spouse and children	30	110.88	129.78	126.42	100.80
			X^2=7.624 *p=0.022	**X^2=12.145 *p=0.002**	**X^2=17.587 *p=0.000**	X^2=5.955 p=0.051
Income level	Level below the minimum wage	94	92.71	105.05	105.12	120.77
	Minimum wage	50	105.84	96.69	90.53	99.09
	2-fold higher than the minimum wage	30	118.80	99.60	107.00	72.28
	3-fold higher than the minimum wage	26	97.29	92.42	95.46	62.50
			X^2=5.243 p=0.155	X^2=1.462 p=0.691	X^2=2.983 p=0.394	**X^2=30.839 *p=0.000**

*p<0.05

p=0.000), Interdependence (r=-0.308; p=0.001), Physiological State (r=-0.465; p=0.001) and Self-Concept (r=-0.382; p=0.001). A significant negative correlation was determined between the RSA Family Cohesion sub-dimension points and the points of the ASADE sub-dimensions of Role and Self-actualization (r=-0.241; p=0.001), Interdependence (r=-0.314; p=0.000), Physiological State (r=-0.236; p=0.001) and Self-Concept (r=-0.274; p=0.000). A significant negative correlation was determined between the RSA Perception of Self sub-dimension points and the points of the ASADE sub-dimensions of Role and Self-actualization (r=-0.421; p=0.000), Interdependence (r=-0.341; p=0.000), Physiological State (r=-0.439; p=0.000) and Self-Concept (r=-0.364; p=0.000). A significant negative correlation was determined between the RSA Social Competence sub-dimension points and the points of the ASADE sub-dimensions of Role and Self-actualization (r=-0.338; p=0.0001), Interdependence (r=-0.408; p=0.0001), Physiological State (r=-0.269; p=0.0001) and Self-Concept (r=-0.171; p=0.015). A significant negative correlation was determined between the RSA Social Resources sub-dimension points and the points of the ASADE sub-dimensions of Role and Self-actualization (r=-0.299; p=0.000), Interdependence (r=-0.400; p=0.0001), Physiological State (r=-0.269; p=0.000) and Self-Concept (r=-0.331; p=0.000).

DISCUSSION

In the examination of the psychological resilience data obtained in this study, the subjects aged ≥76 years were found to have lower scores than those in other age groups in the sub-dimensions of Perception of Future and Social Competence. As there is a range of factors that can affect both of these results, a broader evaluation is given below. This result shows that there is a decrease in the positive view of the future in line with increasing age. Similarly, previous studies have found that different age groups show a significant difference in respect of the psychological resilience of the elderly, and the resilience of the 60-69-year age group has been found to be higher[9,23]. This can be interpreted as a decrease in goals and dreams for the future due to decreasing life expectancy with increasing age, and because of increasing functional dependence on others, a negative perception of the future is formed.

In our study, it was found that individuals aged 76 years and older received lower scores from the Social Competence sub-dimension in terms of psychological resilience compared to other age groups. Social Competence refers to the development of good interpersonal relationships within society and positive evaluation of the subject by others[20]. As older people have less adequate relationships with others in society, they may be evaluated less positively by others. Gooding et al.[24] investigated resilience in early adulthood and in old age and determined that the effect of the age variable on resilience was supported at younger ages by social support independent of age, and at older ages, it progressed in direct proportion to emotional regulation and the development of coping skills. This could be related to the greater exposure of older people to social isolation and loneliness with factors such as chronic diseases, physical disabilities, loss of income and less socialization.

There are also studies in literature showing that individuals aged ≥85 years have the same or higher resilience capacity as younger older adults[10,25,26]. This can be explained by the longer lifespan of more resilient individuals. There are few studies in literature about psychological resilience in the very elderly (≥85 years). According to Hayman et al.[27], the susceptibility of this age group to damage is characterized by a balance

Table 4. Comparison of the scores of the development of an assessment scale on adaptation difficulty according to the psychological resilience scale scores of the participants

			Development of an Assessment Scale of Adaptation Difficulty			
			Role and Self-Actualization	Interdependence	Physiological State	Self-Concept
Resilience Scale for Adults	Structural Style	r	-0.277	-0.157	-0.185	-0.161
		P	*0.000	*0.026	*0.009	*0.023
	Perception of Future	r	-0.516	-0.308	-0.465	-0.382
		P	*0.000	*0.000	*0.000	*0.000
	Family Cohesion	r	-0.241	-0.314	-0.236	-0.274
		P	*0.001	*0.000	*0.001	*0.000
	Perception of Self	r	-0.421	-0.341	-0.439	-0.364
		P	*0.000	*0.000	*0.000	*0.000
	Social Competence	r	-0.338	-0.408	-0.269	-0.171
		P	*0.000	*0.000	*0.000	*0.015
	Social Resources	r	-0.299	-0.400	-0.269	-0.331
		P	*0.000	*0.000	*0.000	*0.000

*p<0.05

between potential benefits such as autonomy, knowledge, and experience and losses such as limited resources. Although maturation after difficulties is possible, the maintenance of daily capabilities is related more closely to resilience at an advanced age[27].

These different results can also be attributed to variations in sampling, cultural differences, differences in retirement or access to healthcare services, or that different resilience scales have been used in the studies, together with the fact that the nature of psychological resilience is due to the temperament characteristics of the individual from birth or the mental capacity that has been gained later. Therefore, it can be recommended that studies to be conducted on this subject include temperament scales that can evaluate the effect of innate temperament characteristics on psychological resilience. From the results of the current study, it was seen that individuals aged ≥76 years were not hopeful about the future and felt socially inadequate, so it can be concluded that from at least this age threshold, older adults require more social and psychological support.

In this study, married subjects had higher points in the Perception of Future and Social Competence sub-dimensions compared to those who were single or widowed. Based on these results, it can be said that being married has a positive effect both on having a positive view of the future and on the establishment of good relationships with others in society. Those who were living together with their spouse were also determined to have higher points in the sub-dimensions of Perception of Future, Perception of Self, and Social Competence. Thus, it can be said that the subjects who were able to maintain a life together with their spouse had high self-awareness and perceptions of their relationships and were hopeful about the future.

Although the findings of the study indicate that living with a spouse has a more positive effect, at least in terms of the relevant sub-dimensions of resilience, it is not possible to directly infer that marriage increases resilience because the study was cross-sectional and the sample's premarital resilience status was unknown. Although the data of the current study are generally compatible with the literature in this respect, there are also studies that have shown no significant relationship between marital status and psychological resilience[28,29].

When the data of difficulties of adaptation were examined according to the socio-demographic characteristics of the study participants, the points obtained for males were determined to be statistically significantly lower than those for females. This finding indicates that males showed better adaptation to ageing. Females obtained higher points than males in the ASADE sub-dimensions of Role and Self-actualization, Physiological State, and Self Concept, showing that they experienced more difficulty in adaptation to ageing in these areas. This means that females experienced more difficulty than males in accepting and releasing the new roles associated with age (Role and Self-actualization) and had greater physical reactions to stimuli originating from their surroundings (Physiological State). Their psychological integrity, which is necessary for improvement capabilities or maintenance of health, is more fragile (Self Concept). Moreover, epidemiological studies related to mental health have indicated that females are more vulnerable than males in respect of mood disorders, primarily depression, post-traumatic stress disorder, and several other diseases. For example, it is universally accepted that females experience more depression than males[30]. In several studies that have used the Geriatric Depression Scale, females at advanced age have been found to have higher mean points than males[31,32]. Aşiret and Dutkun[33] showed that adaptation difficulty was reduced and cognitive functions improved with recall therapy applied to females aged ≥50 years. This and similar studies are important as they show that adaptation difficulty related to age can be treated. In the light of these data, as also our study indicates, it can be concluded that it is necessary to plan more supportive interventions for elderly females experiencing age-related adaptation difficulties.

Adaptation to ageing has been studied more with adaptation and coping scales, and there are extremely few studies directly indicating adaptation difficulty in the literature so far. Adults aged 76 years and older scored higher on the Role and Self-Actualization and Physical Status sub-dimensions compared to other age groups. They showed more physical response to stimuli from their environment in accepting and performing new age-related roles. In a study by Jopp et al.[34], it was shown that the adaptation of the elderly was affected by age, and adaptation decreased especially as age increased. Thus, the critical age threshold is as important in showing adaptation to ageing as it is in psychological resilience. Individuals of advanced age experience difficulty in a social respect in knowing their function in the new role that emerges with ageing. The new conditions brought about by ageing, which disrupt adaptation, create more difficulty at an older age and lead to more physical reactions. This can be explained by an increase in health problems, physical losses, and dependence on others together with ageing, and a decrease in functionality. The results of our study show that older adults are a more disadvantaged group in terms of both psychological resilience and age-related adjustment difficulties.

In the current study, the married participants obtained lower points than those who were single or widowed in the sub-dimensions of Role and Self-actualization, Physiological State, and Self Concept. This was interpreted as marriage facilitated the acceptance of new roles coming with age, enabled the person to be more psychologically whole, and reduced the physical reactions to environmental stimuli. As in psychological

resilience, those who were living together with their spouse obtained lower points than those living in other circumstances in the sub-dimensions of Role and Self-actualization, Interdependence, and Physiological State, which showed that those living with their spouse accepted age-related roles more easily, formed better relationships with social support systems and had fewer physical reactions to environmental stimuli.

In this study, the illiterate participants obtained higher points than those with a higher level of education in the sub-dimensions of Role and Self-actualization, Physiological State, and Self Concept, which was interpreted as illiteracy created more difficulty in accepting and realising new age-related roles, more physical responses to environmental stimuli, and was related to experiencing more difficulty in psychological integrity. Jopp et al.[34] reported a positive relationship between a high level of education and adaptation to the ageing process. In the light of these data, it can be concluded that education and continuous learning have a role in reducing adaptation difficulties.

The current study participants with an income level 3-fold higher than the minimum wage obtained lower points than those with lower income levels in the sub-dimension of Self Concept, which was interpreted as a good income level contributed to the psychological integrity of elderly individuals. Those with income 3-fold higher than the minimum wage had better psychological integrity and were more able to determine what was necessary to deal with age-related problems, and to improve or maintain health. A decrease in income that comes with retirement and increasing healthcare costs can make old age a more difficult time and increase the difficulty in adaptation. In the current study, although the level of income was only found to be related to the Self Concept sub-dimension of ASADE, there could be a relationship with other sub-dimensions. There is no previous study in literature that has directly used ASADE, but several studies, consistent with this research, have emphasized the importance of economic factors in respect of adaptation to ageing and coping with the difficulties encountered in old age[35,36].

Finally, according to the results of this research, there was a statistically significant negative correlation between all the RSA sub-dimensions and all the ASADE sub-dimensions. Therefore, as psychological resilience increases, the difficulty to adapt decreases, and an individual who is psychologically resilient adapts more easily to life.

Structural style refers to self-confidence and self-discipline, and when this is increased in an elderly individual, it can be said that they more easily accept age-related roles, are more successful in self-actualization, form better relationships with societal support systems and others around them, are more physically resistant to environmental stimuli, and have a higher level of psychological integrity. A positive perception of the future and compatibility with the family enable easier acceptance of age-related roles, more successful self-actualization, the forming of better relationships with societal support systems and others around them, more physical resistance to environmental stimuli, and these individuals have a higher level of psychological integrity. Just as all of these factors render the individual psychologically resilient, they also facilitate adaptation to age-related changes.

Studies conducted on resilience to date are almost all in agreement with that psychological resilience is related to successful adaptation to difficult circumstances[37].

Study Limitations

There are some limitations of our study. The study's main limitation was that it used face-to-face self-report questionnaires, which might be subject to individual bias. Second, the results cannot be generalized to older adults living in institutions because the study participants were community-dwelling older adults. The strengths of our study are that it included an acceptable number of participants for data extraction and that there are very few similar studies examining this issue in the Turkish population.

CONCLUSION

In conclusion, the results of this study have demonstrated that all the sub-dimensions of psychological resilience affect adaptation to ageing. Individuals with high psychological resilience experience less difficulty in adapting to old age. Therefore, it can be concluded that the developmental stages are important, and early mental health structure together with the mental health gains in childhood, youth, and middle-age can be protective in old age. Although our research is one of the first studies on psychological resilience and adjustment difficulties in the elderly, we hope that stronger evidence will be obtained on this subject as research increases.

Ethics

Ethics Committee Approval: Ethical approval was received from the Social and Human Sciences Ethics Committee of İstanbul University (date: 01/04/2019 and no: 35980450-663.05). The study was conducted in compliance with the principles of Declaration Helsinki.

Informed Consent: Informed consent was obtained from all the subjects before the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: S.Ç., H.S.I.

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Electrocardiographic Effects of Cholinesterase Inhibitors in Patients with Alzheimer's Disease

Alzheimer Hastalığı Tedavisinde Kullanılan Kolinesteraz İnhibitörlerinin Elektrokardiyografik Etkileri

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ABSTRACT

Aim: Cholinesterase inhibitors (ChEIs), such as donepezil and rivastigmine, are used safely in the treatment of Alzheimer's disease (AD). However, the effects of these drugs on the cardiac conduction system are not clear. In this study, we aimed to investigate the effect of donepezil and rivastigmine treatment on the cardiac conduction system in comparison with the controls, especially on the QTc interval.

Materials and Methods: We retrospectively enrolled 38 consecutive patients with AD, who were prescribed ChEIs for at least 3 months, and age, sex, and comorbidity-matched treatment-naive 37 control subjects. The electrocardiographic (ECG) parameters including heart rate, PR interval, QRS duration, QT interval, and QTc interval were recorded for each patient and control subject.

Results: A total of 24 patients were enrolled in the donepezil treatment group, 14 patients in the rivastigmine treatment group, and 37 patients in the control group. Donepezil treatment resulted in significant prolongation in PR interval, QT interval and QTc interval (p=0.027, p=0.001, p=0.023, respectively). Rivastigmine treatment resulted in significant prolongation only in QTc interval (p=0.018). There was no significant difference between the donepezil and rivastigmine treatment groups for all ECG parameters.

Conclusion: Donepezil and rivastigmine treatments significantly prolong QTc interval compared to controls in patients with AD. The donepezil treatment also prolongs PR and QT intervals. The donepezil and rivastigmine therapy had comparable effects on the cardiac conduction system.

Keywords: Alzheimer's disease, QTc prolongation, donepezil, rivastigmine

ÖZ

Amaç: Donepezil ve rivastigmin gibi kolinesteraz inhibitörleri Alzheimer hastalığının (AH) tedavisinde güvenle kullanılmaktadır. Ancak bu ilaçların kardiyak ileti sistemi üzerindeki etkileri net değildir. Bu çalışmada donepezil ve rivastigmin tedavisinin kontrol grubuna göre elektrokardiyografik (EKG) değişikliklerle ilişkili olup olmadığını araştırmayı ve özellikle QTc aralığı üzerindeki etkilerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmamıza AH tanısı almış ve en az 3 aydır kolinesteraz inhibitör tedavisi kullanan 38 hasta ve yaş, cinsiyet ve komorbiditeler açısından eşleştirilmiş, tedavi almayan 37 kontrol grubu retrospektif olarak dahil edildi. Tüm hastaların ve kontrol grubunun kalp hızı, PR intervali, QRS süresi, QT intervali ve QTc intervali gibi EKG parametreleri kaydedildi.

Bulgular: Toplamda 24 hasta donepezil tedavi grubuna, 14 hasta rivastigmin tedavi grubuna ve 37 hasta kontrol grubuna dahil edildi. Donepezil tedavisinin PR intervali, QT intervali ve QTc intervalini anlamlı olarak uzattığı saptandı (p=0,027, p=0,001, p=0,023, sırasıyla). Rivastigmin tedavisinin sadece QTc intervalini anlamlı olarak uzattığı saptandı (p=0,018). Tüm EKG parametreleri değerlendirildiğinde donepezil ile rivastigmin tedavisi arasında anlamlı bir fark saptanmadı.

Sonuç: AH tanısı almış hastalarda donepezil ve rivastigmin tedavisinin kontrollere kıyasla QTc intervalini anlamlı derecede uzattığı saptanmıştır. Donepezil tedavisi ayrıca PR ve QT intervalini de uzatmaktadır. Donepezil ve rivastigmin tedavisinin kardiyak ileti sistemi üzerindeki etkileri birbirine benzerdir.

Anahtar Kelimeler: Alzheimer hastalığı, QTc uzaması, donepezil, rivastigmin

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INTRODUCTION

Cardiovascular diseases and cognitive impairment often coexist in elderly patient populations. Alzheimer's disease (AD) is the most frequent cause of dementia in these elderly patients[1]. AD causes progressive deterioration in cognitive functions. The primary therapeutic target for the treatment is the cholinesterase enzyme[2]. Cholinesterase enzyme inhibitors (ChEIs), including donepezil and rivastigmine, are the first-line treatment options that have a positive effect on promoting the cognitive functions of AD patients[3].

The effects of ChEIs are not limited to the central nervous system. ChEIs also affect intrinsic cardiac neurons in mammalian hearts which modulate the chronotropic and dromotrophic functions of the heart[4]. The donepezil treatment significantly reduces heart rate[5] and it has also been demonstrated that there is a strong link between donepezil treatment and QTc prolongation and risk of Torsades de pointes (TdP) but data on rivastigmine are scarce so it is challenging to clarify the effect of rivastigmine on QTc prolongation[6]. On the other hand, recent studies have shown the cardioprotective effects of ChEIs. A retrospective database study has demonstrated that therapy with ChEIs has significantly decreased the risk of cardiac pacemaker implantation[7].

The potential electrocardiographic (ECG) effects of each ChEIs were evaluated in the literature[6,8]. However, the comparison between donepezil and rivastigmine therapy on ECG parameters with respect to controls was not extensively studied. Thus, we aimed to investigate the effects of donepezil and rivastigmine treatment on ECG parameters including heart rate, PR interval, QRS duration, QT, and QTc interval in comparison with control subjects and between each treatment group.

MATERIALS AND METHODS

We retrospectively enrolled 38 consecutive patients who had been diagnosed with AD according to the National Institute on Aging-Alzheimer Association criteria between November 2021 and September 2022[9]. Thirty-seven age, sex, and comorbidity-matched control subjects were also recruited for the study. We included patients aged 55-85 years, who had a 12-lead ECG as a part of any outpatient clinic visit while taking cholinesterase inhibitors for at least 3 months. All patients were compliant in taking their medication and reached steady state of donepezil 10 mg and rivastigmine 13.3 mg. The route of administration for donepezil included oral tablets and transdermal patches for rivastigmine. Patients with atrial fibrillation, heart failure, and pacemaker implantation, having a history of catheter ablation for any arrhythmia, thyroid abnormality, and chronic renal disease requiring dialysis were excluded from this study. Patients who were treated with antiarrhythmic medications (except beta blockers) and drugs that affected QT interval were also excluded. All data were collected from institutional electronic medical records.

Baseline patient characteristics and comorbidities were recorded. The current use of blood pressure-lowering medication was defined as hypertension and the current use of medication for diabetes was defined as diabetes mellitus. Hyperlipidemia was defined as the current use of cholesterol-lowering therapy. The presence of coronary artery disease was defined as prior history of myocardial infarction or coronary artery revascularization. Ischemic cerebrovascular disease was defined as having a history of minor stroke caused by a small or big blood vessel pathology. Among laboratory data, baseline hemoglobin, thyroid function tests, serum creatinine, estimated glomerular filtration rate, and serum electrolytes including sodium, potassium, and calcium levels were noted. A resting 12-lead ECG was recorded from all patients by using 25 mm/sec paper speed and standardized at 0.1 mV/mm. ECG parameters including heart rate, PR interval, QRS duration, QT interval, and QTc interval were calculated automatically by the ECG apparatus and reviewed by a cardiologist. QTc was corrected for heart rate using the Bazett's formula (QTc=QT/ÖRR)[10].

This study was approved by the Dokuz Eylül University Local Ethics Committee (approval no: 2021/27-01, date: 06.10.2021).

Statistical Analysis

A standard statistical software program [Statistical Package for the Social Sciences (SPSS) version 26; SPSS, Inc., Chicago, IL] was used. The Kolmogorov-Smirnov test was used to check continuous variables for normality. The categorical variables were represented as numbers and percentages and continuous variables were represented as the mean±standard deviation and median (interquartile range). If results were asymmetrically distributed, nonparametric tests were used. Comparisons between the three groups were performed using the Kruskal-Wallis test for non-normally distributed data, the one-way ANOVA test for normally distributed data, and the chi-square test for categorical variables. Multivariate analysis of variance test was used to examine ECG parameters including PR interval, QT duration, and QTc. A p-value <0.05 was considered to be statistically significant.

RESULTS

The study population was divided into three groups: The donepezil treatment group, the rivastigmine treatment group, and control group. A total of 24 patients were in the donepezil treatment group, 14 patients were in the rivastigmine treatment group, and 37 patients were in the control group. Table 1 represents the clinical and laboratory characteristic of the treatment and control groups. There were no significant

differences in age, sex, comorbidities, baseline laboratory parameters, and beta-blocker usage among the three groups (Table 1).

Among ECG parameters, PR interval, QT interval and QTc interval were significantly different among three groups (p=0.03, p=0.001, p=0.005, respectively) whereas heart rate and QRS duration were not different between three groups (p=0.12, p=0.19, respectively) (Figure 1, Table 2).

Pairwise comparisons revealed that the PR interval was significantly different between the donepezil treatment group and control group (p=0.027). There were no significant differences between the rivastigmine treatment group and control group and between the donepezil and rivastigmine treatment groups (p=0.43, p=0.64, respectively) (Table 3). For QT interval, the analysis revealed a significant difference between the donepezil treatment group and control group (p=0.001) whereas there was no significant difference between the rivastigmine treatment group and control group and between the donepezil and rivastigmine treatment groups (p=0.57, p=0.12, respectively) (Table 3). For QTc interval, significant differences emerged for the donepezil treatment group and control group and between the rivastigmine treatment group and control group (p=0.023, p=0.018, respectively). There was no significant difference between the donepezil and rivastigmine treatment groups for QTc (p=0.87) (Table 3).

DISCUSSION

Our study demonstrates that among ECG parameters, no significant difference was observed in heart rate and QRS duration among the three groups. The PR interval and QT interval were significantly prolonged only in the donepezil treatment group, whereas QTc interval was significantly longer in both donepezil and rivastigmine treatment groups. Regarding all ECG parameters, no significant difference was detected between the donepezil and rivastigmine treatment groups.

The previous reports suggest that ChEIs are associated with cardiovascular side effects, including bradycardia, complete atrioventricular block, and TdP[11-14]. As increased levels of acetylcholine in the heart enhance vagal tone, it is evident that ChEIs may decrease heart rate[15]. However, in concordance with our results, Isik et al.[16] demonstrated that none of the ChEIs including donepezil, rivastigmine, and galantamine was associated with an increased risk of bradycardia. The discrepancies between these results may have been related to several factors. First, comorbidities of patients including ischemic heart disease differ among these studies. Second, serum electrolytes, especially potassium and calcium, may affect heart rate[17] and not all studies report serum electrolyte levels that may affect their results. Finally, concomitant use of other medications may have been responsible for these discordant ChEIs-associated ECG changes.

The QT interval corresponds from the beginning of ventricular depolarization to the end of ventricular repolarization and QTc prolongation is associated with an increased risk of ventricular arrhythmias[18], TdP, and sudden death[19]. When acetylcholinesterase receptors are inhibited in the heart, intracellular calcium concentrations increase. As a result, phase 2 of the cardiac action potential prolongs and increases the subsequent risk of ventricular arrhythmias[20]. Reports

Table 1. Baseline clinical and laboratory characteristics of the treatment and control groups

	Donepezil (n=24)	Rivastigmine (n=14)	Controls (n=37)	p value
Age (years)†	76 (73-79)	73 (65-81)	72 (68-75)	0.11‡
Women, n (%)	9 (37.5)	7 (50)	15 (40.5)	0.74§
Hypertension, n (%)	16 (66.7)	9 (64.3)	25 (67.6)	0.97§
Diabetes, n (%)	8 (33.3)	8 (57.1)	14 (37.8)	0.33§
Hyperlipidemia, n (%)	11 (45.8)	6 (42.9)	16 (43.2)	0.97§
CAD, n (%)	10 (41.7)	3 (21.4)	10 (27)	0.34§
ICVD, n (%)	6 (25)	2 (14.3)	5 (13.5)	0.48§
Hemoglobin (gr/dL)*	13.3±1.7	12.6±1.4	13.2±1.4	0.43¶
Creatinine (mg/dL)†	0.94 (0.87-1.1)	0.83 (0.73-1.1)	0.9 (0.8-1)	0.66‡
eGFR*	71.1±17.6	71±18.9	73±17.5	0.88¶
Serum sodium (mmol/L)†	141 (138-142)	141 (139-142)	141 (139-142)	0.91‡
Serum potassium (mmol/L)*	4.4±0.4	4.3±0.5	4.4±0.4	0.97¶
Serum calcium (mmol/L)†	9.6 (9.4-9.9)	9.6 (9.1-10)	9.7 (9.2-9.9)	0.94‡
TSH [m(IU)/L]†	1.1 (0.85-1.9)	1.35 (0.98-1.7)	1.4 (0.9-2)	0.82‡
Beta blocker, n (%)	6 (25)	5 (35.7)	9 (24.3)	0.69§

*Mean±standard deviation, †Median (interquartile range), ‡Kruskal-Wallis test, §Chi-square test, ¶One-way ANOVA test.
CAD: Coronary artery disease, ICVD: Ischemic cerebrovascular disease, eGFR: Estimated glomerular filtration rate, TSH: Thyroid stimulating hormone

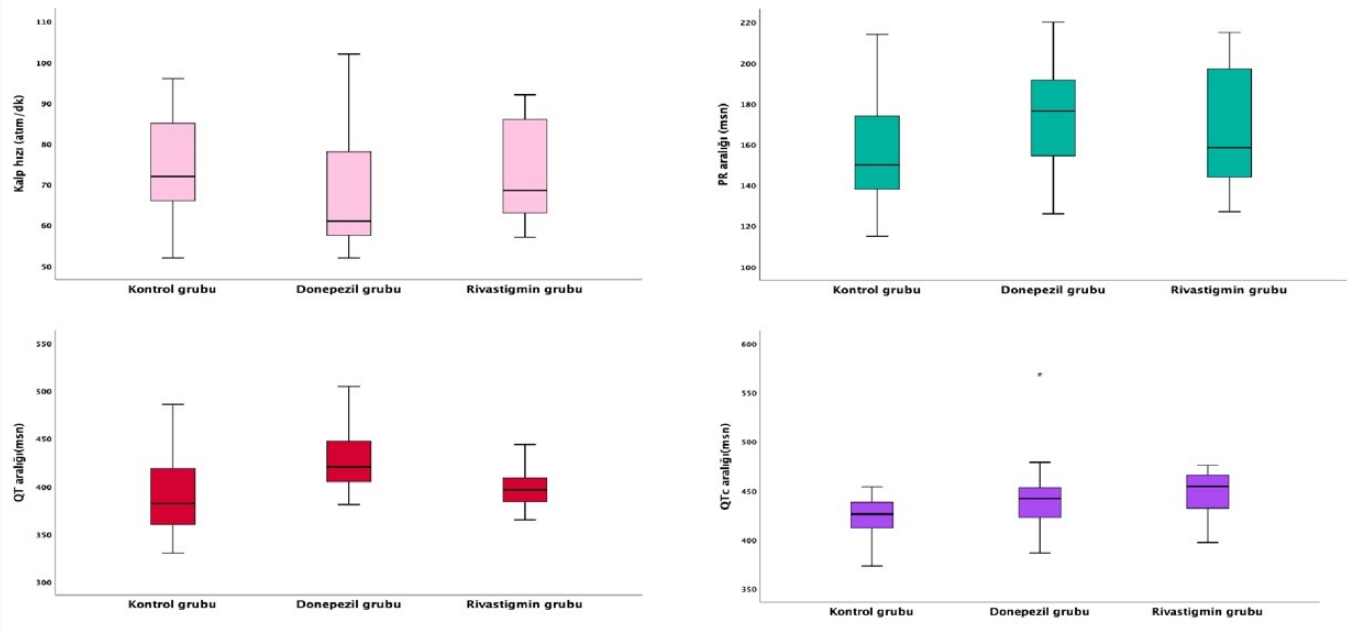

Figure 1. Comparisons of ECG parameters between groups

ECG: Electrocardiography

Table 2. Effects of donepezil and rivastigmine treatment on ECG parameters

	Donepezil (n=24)	Rivastigmine (n=14)	Controls (n=37)	p value
Heart rate (bpm)*	67±14	72±12	74±12	0.12¶
PR interval (msec)*	175±26	167±28	157±26	**0.03¶**
QRS duration (msec)†	98 (92-105)	88 (86-95)	98 (86-106)	0.19†
QT interval (msec)*	422±39	399±21	389±34	**0.001¶**
QTc interval (msec)*	443±38	447±22	423±19	**0.005¶**

*Mean±standard deviation, †Median (interquartile range), †Kruskal-Wallis test, ¶One-Way ANOVA test, ECG: Electrocardiographic

Statistically significant values are shown in bold type

Table 3. Comparisons of ECG parameters between the donepezil group and controls, the rivastigmine group and controls, and the donepezil and rivastigmine groups

	Donepezil vs. control p value	Rivastigmine vs. control p value	Donepezil vs. rivastigmine p value
PR interval (msec)	**0.027****	0.43**	0.64**
QT interval (msec)	**0.001****	0.57**	0.12**
QTc interval (msec)	**0.023****	**0.018****	0.87**

**MANOVA test. Statistically significant values are shown in bold type.

MANOVA: Multivariate analysis of variance

on the effects of ChEIs on QT interval prolongation and QTc are scarce. To date, most studies examining the effects of donepezil treatment on QT interval and QTc found that therapy with donepezil was associated with an increased risk of QT interval and QTc prolongation[6,14,21], whereas some studies found no associations[8,16]. We demonstrated that therapy with both donepezil and rivastigmine significantly increased the QTc interval in comparison with control subjects. It has been shown that drug-associated QT prolongation and the risk of TdP are aggravated by the presence of at least one risk factor including female gender, presence of cardiac disease, electrolyte imbalances, overdosing, drug-drug interactions, and familial history of long QT syndrome[22]. For our present report and other clinical studies, it may be difficult to determine the alternative cause for this adverse effect as most cases and clinical studies included patients with at least one other risk factor for QT prolongation.

Besides, our study showed that donepezil and rivastigmine had similar effects on the cardiac conduction system. This result of the present study is in accordance with a previous study that demonstrated similar effects on ECG parameters of all three ChEIs including donepezil, rivastigmine, and galantamine[16].

Study Limitations

Our study has several limitations. First, this is a retrospective study in a single center with a relatively small number of patients. Second, as this is a retrospective study, we could

not examine the confounding factors that might prolong QTc interval including active infections, hypomagnesemia, metabolic problems, and other QTc-prolonging drugs. Finally, a 24-hour Holter monitoring would allow a more reliable evaluation of cardiac conduction abnormalities in patients taking QTc-prolonging agents.

CONCLUSION

In conclusion, donepezil and rivastigmine treatment significantly prolongs QTc interval compared to controls in patients with AD. The donepezil treatment also prolongs PR and QT intervals. The donepezil and rivastigmine therapy had comparable effects on the cardiac conduction system. Elderly patients are more susceptible to drug-induced arrhythmias because of age-related prolongation of the QT interval and repolarization dispersion. The risk of arrhythmias could be minimized with a multidisciplinary approach both for the initiation of ChEI therapies and the follow-up of AD patients.

Ethics

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Dokuz Eylül University Faculty of Medicine (decision no: 2021/27-01, date no: 06.10.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ç., D.Ö., Design: A.Ç., D.Ö., Data Collection or Processing: A.Ç., D.Ö., Analysis or Interpretation: A.Ç., D.Ö., Literature Search: A.Ç., D.Ö., Writing: A.Ç.

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Nailfold Dermatoscopic Findings and Its Relationship with Proteinuria

Tırnak Yatağı Dermatoskopi Bulgularının Proteinüri ile İlişkisi

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ABSTRACT

Aim: Proteinuria is estimated to be a marker of microvascular damage. The aim of this study was to identify dermatoscopic findings of the nailfold capillary in patients with proteinuria and the relationship of these findings with the level of proteinuria.

Materials and Methods: Our study is observational cross-sectional study. Eighty five proteinuric patients whose albumin/creatinine ratio was found to be above 30 mg/gr in the spot urine in routine tests and eighty five non-proteinuric patients participated in this study. Proteinuric patients were separated into three groups (microalbuminuria, macroalbuminuria and overt proteinuria). Nailfold capillaroscopy was examined by a specialist dermatologist with a hand dermatoscope.

Results: The presence of at least one capillary dermatoscopic finding was significantly higher in the patient group with proteinuria when compared to the control group (62 vs. 14%, $p<0.05$). Capillary ectasia and presence of giant capillaries, appearance of subpapillary venous plexus, capillary disorganization and decrease in capillary density were found to be significantly higher in patients with proteinuria compared to the control group ($p<0.05$). However, there was no significant difference between the levels of proteinuria with nailfold dermatoscopic findings.

Conclusion: In our study, the presence of at least one capillary dermatoscopic finding was significantly higher in patients with proteinuria. We reported that dermatoscopic examination of nailfold capillaries in diseases with proteinuria might be an indicator of the microvascular damage. Further investigations with more patients are needed in this area.

Keywords: Proteinuria, albuminuria, nailfold capillaroscopy, dermatoscopy

ÖZ

Amaç: Proteinürinin mikrovasküler hasarın bir belirteci olduğu düşünülmektedir. Bu çalışmanın amacı proteinürik hastalarda tırnak kıvrımı kapillerlerinin dermatoskopik bulgularını ve bu bulguların proteinüri düzeyi ile ilişkisini belirlemektir.

Gereç ve Yöntem: Çalışmamız gözlemsel kesitsel bir çalışmadır. Rutin tetkiklerde spot idrarda albümin/kreatinin oranı 30 mg/gr'ın üzerinde saptanan 85 proteinürik hasta ve 85 proteinürisi olmayan hasta bu çalışmaya dahil edildi. Proteinürik hastalar üç gruba ayrıldı (mikroalbüminüri, makroalbüminüri ve aşikar proteinüri). Tırnak yatağı kapiller morfolojisi uzman bir dermatolog tarafından el dermatoskopuyla incelendi.

Bulgular: En az bir kapiller dermoskopik bulgu varlığı proteinürili hasta grubunda kontrol grubuna göre anlamlı olarak daha yüksekti (%62'ye karşı %14, $p<0,05$). Kapiller ektazi ve dev kapiller varlığı, subpapiller venöz pleksus görünümü, kapiller dezorganizasyon ve kapiller dansitede azalma proteinürili hastalarda kontrol grubuna göre anlamlı derecede yüksek bulundu ($p<0,05$). Tırnak yatağı dermatoskopik bulguları ile proteinüri düzeyleri arasında ilişki saptanmadı.

Sonuç: Çalışmamızda proteinürisi olan hastalarda en az bir kapiller dermatoskopik bulgu varlığı anlamlı olarak daha yüksekti. Proteinüri düzeyleri ile dermatoskopi bulguları arasında ilişki saptanmadı. Sınırlılığımız hastalarda proteinüri süresinin bilinmemesi ve proteinürinin etiyolojisine göre gruplandırma yapılmamış olmasıdır. Proteinüri ile seyreden hastalıklarda tırnak yatağı kapillerlerinin dermatoskopik incelemesinin hastalığın mikrovasküler alanda yaptığı hasarın yaygınlığına dair bir gösterge olabileceğini düşünüyoruz. Bu alanda yapılacak, daha çok sayıda hastanın yer aldığı kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Proteinüri, albüminüri, tırnak yatağı kapilleroskopisi, dermatoskopi

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INTRODUCTION

Nail capillaroscopy is a non-invasive method for imaging of capillary vessel microcirculation by magnifying the proximal nailfold with lens[1]. It has an increasing importance among rheumatologists because it can be used in the early diagnosis of patients with systemic sclerosis and gives an idea about the prognosis[2]. Recently, studies are increasing rapidly in terms of diagnostic and prognostic importance of capillaroscopy in diseases that cause microvascular damage such as diabetes and hypertension[3].

Dermatoscopy is a non-invasive technique that allows us to visualize morphological features that are invisible to the naked eye and to establish a connection between skin lesions and their pathological counterparts[4]. Since dermatoscopy is easy and practical method, it has been started to be used instead of nail capillaroscopy, and similar success has been achieved in studies in this field[5].

The increased excretion of albumin is one of the earliest signs of vascular damage in renal diseases. Many processes, such as diabetes, hypertension, and metabolic syndrome, can trigger the inflammatory response in the body and cause microalbuminuria in the glomerular capillaries due to endothelial dysfunction. Therefore, microalbuminuria is considered to be a marker of diffuse microvasculopathy at various levels, including cerebral, cardiac, and renal microcirculations[6]. Studies have shown that albuminuria is associated with many diseases related to vascular pathology such as retinopathy and heart failure[7,8]. Numerous studies have provided convincing evidence that greater levels of albuminuria are independently related to mortality, cardiovascular events, and the rate of end stage renal disease[9,10].

Measurement of albumin or protein level in 24-hour urine is used to detect albuminuria or proteinuria. In addition, it has been shown that the albumin/creatinine ratio and the protein/creatinine ratio, which is measured more practically in the spot urine, is a successful marker in the detection of albuminuria and proteinuria. Besides, the albumin/creatinine ratio is used to evaluate the degree of microvascular damage in chronic kidney disease[9].

Based on that albuminuria and proteinuria is an important marker of diffuse microvascular damage, we evaluated the nailfold dermatoscopic findings in patients with proteinuria and the relationship of these findings with the level of proteinuria.

MATERIALS AND METHODS

Our study was planned as a descriptive, observational study in patients with albuminuria. Study participants were the patients of either gender, between the age of 18 and 80 years. Patients who applied to Muğla Sıtkı Koçman University Training and Research Hospital Nephrology Outpatient Clinic and whose albumin/creatinine ratio was found to be above 30 in the spot urine in routine tests were included in the study. Proteinuric patients were separated into three groups according to the albumin/creatinine and protein/creatinine levels detected in the spot urine. Microalbuminuria was described as the albumin/creatinine ratio between 30 and 300 mg/gr. Macroalbuminuria was described as the albumin/creatinine ratio at 300 mg/gr and above. Overt proteinuria was described as the protein/creatinine ratio at 1000 mg/day and above[9-11]. The patient who had macroalbuminuria and overt proteinuria was separated into the overt proteinuria group. Normoalbuminuric and nonproteinuric patients who applied to the dermatology outpatient clinic only for local dermatological diseases (such as tinea unguim, verruca vulgaris) were included in the study as the control group. The study protocol was approved by the Muğla Sıtkı Koçman University Institutional Ethical Committee and was conducted in accordance with the Declaration of Helsinki (decision no: 16, date: 16.12.2021). All participants gave written informed consent.

Exclusion Criteria

Exclusion criteria were having periungal trauma on the nails of the 4th and 5th fingers of both hands or diseases that locally disrupted the nail structure (for example, tinea unguium), having nail polish or aesthetic interventions on the 4th and 5th fingers of both hands, the presence of disease that disrupted the regional peripheral vascular system, such as peripheral arterial disease, systemic sclerosis. Patients with end stage renal disease and malignancies were excluded.

Dermatoscopic Examination

The nailfolds of the 4th and 5th fingers were examined by a specialist dermatologist with a hand dermatoscope (Dermlite 4), in both hands of the patients held at the level of the heart in a sitting position, and recorded on an android phone with a telephone apparatus. The recordings were stored on a personal computer in jpeg format and re-evaluated by the same person without looking at the previous findings. Patients who were interpreted differently in the evaluations made during and after the examination were excluded from the study.

In the nailfold in dermatoscopic examination, previous studies were taken as reference and the specified parameters were evaluated[1,3,12,13].

- Capillary ectasia and presence of giant capillaries,
- Presence of tortuous capillaries and torsion,
- Decrease in capillary density,
- Microhemorrhage,

- Subpapillary venous plexus view,
- Cuticulitis capillary,
- Avascular area,
- Capillary disorganization.

Statistical Analysis

Comparison of the findings between the patient group and the control group was evaluated with the Pearson's chi-square test. Comparison among 3 subgroups separated according to the severity of albuminuria was made with the Fisher's Exact test. Statistical significance was assessed at $p<0.05$ and all statistical analyses were performed using R software (R software, version 4.0.5, package: arsenal, R Foundation for Statistical Computing, Vienna, Austria; http://r-project.org).

RESULTS

Differences in Nailfold Dermatoscopic Findings Between Patients with Proteinuria and the Control Group

As a result of the study, nail dermatoscopy findings among 85 patients with proteinuria and 85 control patients were evaluated. There was no difference between the groups in terms of sex distribution. The mean age of the patients in the proteinuria patient group was 58.3 (±16.5) years, and the mean age was 52.6 (±18.7) years in the control group. In the logistic regression analysis, it was observed that the results obtained in terms of age and sex did not change between the groups.

The presence of at least one capillary dermatoscopic finding was significantly higher in the patient group with proteinuria when compared to the control group (62% vs. 14%, $p<0.05$). Capillary ectasia and presence of giant capillaries, appearance of subpapillary venous plexus, capillary disorganization and decrease in capillary density were found to be significantly higher in patients with proteinuria compared to the control group ($p<0.05$) (Figure 1). On the other hand, there was no significant difference between the two groups in terms of the presence of tortuous capillaries, avascular area, microhemorrhage and cuticulitis capillaries (Table 1).

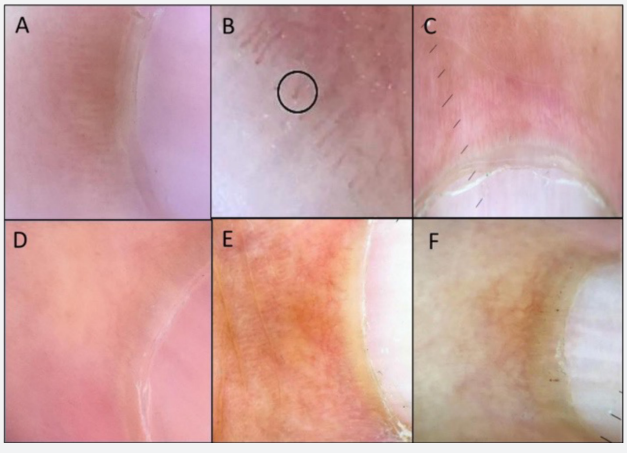

Figure 1. Differences in nailfold dermoscopic findings between patients with proteinuria and the control group; (a) Normal findings in control group. (b) Capillary disorganization and presence of giant capillaries. (c) Capillary ectasia. (d) Decrease in capillary density. (e, f) Subpapillary venous plexus view (x80 magnification, o: presence of giant capillaries)

Differences Between Nailfold Dermatoscopic Findings According to the Level of Proteinuria

Patients with proteinuria were put in 3 groups, 36 patients with microalbuminuria, 25 patients with macroalbuminuria, and 24 patients with overt proteinuria. The dermatoscopic findings of the patients in these groups were evaluated statistically. There was no significant difference between the patient groups with proteinuria in terms of mean age and sex and there was no significant difference among the microalbuminuria, macroalbuminuria and overt proteinuria groups in terms of nailfold dermatoscopic findings (Table 2).

DISCUSSION

Albuminuria is an important marker of endothelial dysfunction and it is proven that it predicts adverse renal and cardiovascular events in diabetic and hypertensive patients, even in healthy individuals[14,15]. Microalbuminuria is apparently associated with increased universal vascular sieving of albumin in terms of the transcapillary escape rate of albumin (TER-alb). The pathophysiology of increased TER-alb is unknown, but could be caused by haemodynamics or damage to the functional properties of the vascular wall[16]. Putative mechanisms involved in the development of microalbuminuria are increased vascular permeability, impaired systemic endothelium-dependent vasodilation and elevated plasma levels of pro-thrombotic and pro-inflammatory endothelial markers[16].

Nail capillary abnormalities in patients with albuminuria may be another indicator of endothelial tissue damage. Nailfold capillaroscopy enables the study of various aspects of capillaries, including morphology, distribution, density and blood flow. In the literature, capillaroscopic findings have been investigated in many diseases ranging from diabetes, hypertension and glaucoma, which are clearly related to microvascular damage, to rarer diseases such as tetralogy of Fallot, pseudoxanthoma elasticum, acromegaly and chronic viral hepatitis[3]. In a meta-analysis study about capillaroscopic examinations in non-rheumatic systemic diseases, 10 of 11 studies with diabetic patients found significantly abnormal capillary findings compared to the control group[3]. In addition to nail capillaroscopy and videocapillaroscopy methods,

Table 1. Comparison of nailfold dermatoscopic findings between patient with proteinuria and control groups

Nailfold dermatoscopic findings	Control (n=85)	With proteinuria (n=85)	Total (n=170)	p value
Ectasia and giant capillaries	4 (4.7%)	15 (17.6%)	19 (11.2%)	**0.007**
Torsional capillary	7 (8.2%)	15 (17.6%)	22 (12.9%)	0.068
Avascular area	0 (0.0%)	1 (1.2%)	1 (0.6%)	1.000
Microhemorrhage	3 (3.5%)	9 (10.6%)	12 (7.1%)	0.072
Subpapillary venous plexus view	8 (9.4%)	21 (24.7%)	29 (17.1%)	**0.008**
Cuticulitis capillary	10 (11.8%)	15 (17.6%)	25 (14.7%)	0.279
Capillary disorganization	0 (0.0%)	23 (27.1%)	23 (13.5%)	**<0.001**
Decrease in capillary density	3 (3.5%)	19 (22.4%)	22 (12.9%)	**<0.001**

Table 2. Comparison of nailfold dermatoscopic findings between microlbuminuria, macroalbuminuria and overt proteinuria groups

Nailfold dermatoscopic findings	Micro-albuminuria (n=36)	Macro-albuminuria (n=25)	Overt proteinuria (n=24)	p value
Ectasia and giant capillaries	6 (16.7%)	5 (20.0%)	19 (11.2%)	0.935
Torsional capillary	6 (16.7%)	5 (20.0%)	22 (12.9%)	0.935
Avascular area	1 (2.8%)	0 (0.0%)	1 (0.6%)	0.502
Microhemorrhage	5 (13.9%)	3 (12.0%)	12 (7.1%)	0.469
Subpapillary venous plexus view	9 (25.0%)	6 (24.0%)	29 (17.1%)	0.995
Cuticulitis capillary	7 (19.4%)	3 (12.0%)	25 (14.7%)	0.672
Capillary disorganization	8 (22.2%)	10 (40.0%)	23 (13.5%)	0.221
Decrease in capillary density	6 (16.7%)	3 (12.0%)	22 (12.9%)	0.025

more practical and accessible hand dermatoscopes can be used instead of capillaroscopy in recent years. In a study, it is suggested that this method adequately shows the severity of the disease in patients with systemic sclerosis[17]. In our study, hand dermatoscope was used to evaluate nail capillary abnormalities in patients with proteinuria.

According to the results of our study, the presence of at least one capillary finding in patients with proteinuria was found to be significantly higher than in the control group. These findings support the knowledge that proteinuria is an indicator of microvascular damage.

Decreased capillary density is a quantitative finding of microvascular injury, unlike other capillaroscopic findings[18]. Similar to our study, a decrease in capillary density and the presence of irregular capillary distribution were reported in studies on diabetic patients. In addition, it has been reported that more specific abnormalities such as increase in tortuous vessels and dilated capillaries, microhemorrhages, branched capillaries and avascular areas can be seen in different studies[3]. In a study in the literature, which argued that albuminuria was associated with capillary sparseness, capillaroscopic examination of the return after arterial occlusion was performed and it was claimed that albuminuria was independently associated with low capillary density[19]. In our study, the findings of capillary disorganization and decrease in capillary density were observed to be significantly higher than the control group; however, no correlation was found between the severity of proteinuria and the decrease in capillary density. This may be related to the wide range of proteinuria causes in our study.

The presence of giant capillaries, microhemorrhages and avascular areas in capillaroscopy has been called the "sclerodermoid pattern" and has become a reference pattern in rheumatology[2]. In our study, a significant difference was observed in the presence of ectasia and giant capillaries in the capillaries between the proteinuria and control groups. No significant difference was observed in terms of microhemorrhages, presence of tortuous veins and presence of avascular area. Considering that diseases causing albuminuria/proteinuria can occur with many different pathogeneses besides scleroderma, the absence of capillary findings in sclerodermoid pattern is an expected result of the study.

The appearance of the subpapillary venous plexus is a capillary appearance that becomes evident with slowed blood flow and age[13]. There was a significant difference between the patients with proteinuria and the control group; however, considering the high mean age of the patients in our study, the specificity of this finding in relation to patients with proteinuria should be investigated by evaluating the younger age group as well.

Cuticulitis vein is a capillaroscopic finding characterized by only high-intensity small red dots in which the appearance of the vessel body is lost, representing hyperemia and interstitial edema[20]. In a study by Maldonado et al.[21], it was observed to be significantly higher in diabetic patients compared to the control group, and this situation was found to be associated

with the presence of retinopathy. In our study, no significant difference was found between the two groups in terms of the presence of cuticulitis vessels. Large-scale studies are needed to determine the predictive value of this finding in patients with proteinuria.

In the literature, the effect of poor glycemic control and disease duration on microvascular changes in patients with diabetes was evaluated, and it was emphasized that clinical and metabolic measurements should be taken into account in order not to cause biased results[22]. In the study of Kuryliszyn-Moskal et al.[23] with patients with type-1 diabetes, it was shown that capillaroscopic findings were associated with poor metabolic control and that branched capillary findings progress in people with a disease duration of 10 years or more. In another study, the mean diabetes duration of patients with capillaryoscopic findings was 12.8; it was determined that this period was 8.5 years in patients with no abnormal capillary findings[21]. In our study, no significant correlation was found between the severity of proteinuria and abnormal capillary findings. However, the duration of albuminuria or proteinuria was not known in the patients, so we may not have been able to detect the development of microvascular changes over time.

Although nail capillaroscopic findings have been proven in many different diseases, the results differ widely from each other. In a study examining the capillaroscopic differences between never-smokers and non-smokers, significant differences were found between two groups[24]. In addition, in a study on elderly dyslipidemic women treated or not with lipid-lowering therapies, Lopes et al.[25] reported that they did not observe any difference in capillary density compared to the control group.

We could not find any study in the literature on nailfold capillary morphology and abnormalities in which dermatoscope was used in patients with proteinuria. One of the most important limitations of our study is the lack of previous videocapillaroscopic examination in patients with proteinuria. We believe that studies with nail capillaroscopy and videocapillaroscopy, which provide more detailed observation of microvascular changes in patients with proteinuria, will expand our knowledge of microvascular changes. In addition, we think that studies evaluating the effects of the diseases causing proteinuria and the duration of proteinuria on these findings may more accurately reveal the role of capillaroscopy in the follow-up of patients with proteinuria.

Study Limitations

Previous videocapillaroscopic examination in patients with proteinuria was not performed. The duration of proteinuria was not known in the patients, and no grouping was made according to the etiology of proteinuria.

CONCLUSION

As a result, we propounded that dermatoscopic examination of nailfold capillaries in diseases with proteinuria maight be an indicator of the extent of damage caused by the disease in the microvascular space. Large prospective studies of nailfold capillary examination in patients with proteinuria are needed to evaluate this hypothesis.

Ethics

Ethics Committee Approval: The study protocol was approved by the Muğla Sıtkı Koçman University Institutional Ethical Committee and was conducted in accordance with the Declaration of Helsinki (decision no: 16, date: 16.12.2021).

Informed Consent: All participants gave written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.T.A., Concept: C.T.A., D.G.G., Design: C.T.A., D.G.G., Data Collection or Processing: C.T.A., D.G.G., Analysis or Interpretation: C.T.A., D.G.G., Literature Search: C.T.A., D.G.G., Writing: C.T.A., D.G.G.

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Pertussis Awareness and Vaccination Status of Healthcare Workers in the Neonatal Intensive Care Unit

Yenidoğan Yoğun Bakım Ünitesindeki Sağlık Çalışanlarının Boğmaca Farkındalıkları ve Aşılanma Durumları

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ABSTRACT

Aim: Pertussis is a disease that is transmitted by droplets and has a long contagious period. It can cause severe illness presentation and hospital-acquired outbreaks, especially in preterm babies and infants whose vaccinations have not been completed. For this reason, it is recommended that the mother should be vaccinated with Tdap (tetanus, adult-type diphtheria and acellular pertussis vaccine) during pregnancy and people who will come into contact with the baby should be vaccinated. This practice is called the cocoon strategy and healthcare workers are also included in the cocoon strategy. The aim of this study is to determine whooping cough awareness and Tdap vaccination status of healthcare workers working in the neonatal intensive care unit (NICU) within the scope of the cocoon strategy.

Materials and Methods: Our research was designed as a cross-sectional and descriptive face-to-face survey study. Health workers working in Samsun Training and Research Hospital NICU were invited to the research. The questionnaire consisted of four parts, including 21 questions, in order to learn the demographic data of the participants, the level of knowledge about pertussis disease, the level of knowledge about the pertussis vaccine and their vaccination status.

Results: Of the 89 participants whose mean age was 38.7±7.3 years, 76% (n=68) were nurses/midwives and doctors. The level of knowledge about pertussis and its vaccines was significantly higher in doctors than in other groups ($p<0.001$, $p<0.003$). There was no one vaccinated with Tdap among the participants. A high Pertussis vaccine knowledge score was found to be associated with a positive intention to be vaccinated ($p=0.02$). When evaluated according to occupations, the intention to be vaccinated was higher among doctors than other groups ($p=0.007$).

Conclusion: As a result, although the Ministry of Health recommends that health workers working in the NICU be vaccinated with Tdap, it is thought that there are problems in practice. There is a need for all physicians who recommend vaccines to healthcare professionals to raise their awareness of whooping cough disease and put the cocoon strategy into practice. Interventions are needed to increase the level of knowledge of allied health personnel about whooping cough disease and pertussis vaccines.

Keywords: Pertussis vaccine, healthcare workers, neonatal, intensive care

ÖZ

Amaç: Boğmaca hastalığı, damlacık yoluyla bulaşan, bulaştırıcılık süresi uzun bir hastalıktır. Özellikle preterm doğanlarda ve aşıları tamamlanmamış süt çocuklarında ağır hastalık tablolarına, hastane kaynaklı salgınlara sebep olabilir. Bu nedenle, gebelikte annenin ve bebeğe temas edecek kişilerin Tdap (tetanos, erişkin tip difteri ve asellüler boğmaca aşısı) ile aşılanması önerilmektedir. Bu uygulama koza stratejisi olarak adlandırılır ve sağlık çalışanları da koza stratejisi kapsamında yer almaktadır. Bu çalışmanın amacı, koza stratejisi kapsamında yenidoğan yoğun bakım ünitesinde (YYBÜ) görev yapan sağlık çalışanlarının boğmaca farkındalıklarını ve Tdap aşı olma durumlarını belirlemektir.

Gereç ve Yöntem: Araştırmamız, kesitsel ve tanımlayıcı tipte yüz yüze anket çalışması şeklinde tasarlandı. Samsun Eğitim ve Araştırma Hastanesi YYBÜ'de görev yapan sağlık çalışanları araştırmaya davet edildi. Anket, katılımcıların demografik verileri, boğmaca hastalığı hakkındaki bilgi düzeyleri, boğmaca aşısı hakkındaki bilgi düzeyleri (BABD) ve aşılanma durumlarını öğrenmek amacıyla 21 sorudan oluşmaktadır.

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Bulgular: Yaş ortalamaları 38,7±7,3 yıl olan 89 katılımcının %76'sı (n=68) hemşire/ebe ve doktorlardan oluşmaktaydı. Boğmaca hastalığı ve aşıları hakkındaki bilgi düzeyi doktorlarda diğer gruplara göre anlamlı derecede yüksekti (sırasıyla p<0,001, p<0,003). Katılımcılar arasında Tdap ile aşılı kimse yoktu. BABD puanın yüksek olması, Tdap aşısı olma niyetinin olumlu olması ile ilişkili bulundu (p=0,02). Mesleklere göre değerlendirildiğinde ise doktorlar arasında, diğer gruplara göre Tdap aşısı olma niyeti daha yüksekti (p=0,007).

Sonuç: Sağlık Bakanlığı YYBÜ'de görev yapan sağlık çalışanlarının Tdap ile aşılanmasını önermesine rağmen, uygulamada sorunların olduğu düşünülmektedir. Sağlık çalışanlarına aşı önerisi veren tüm hekimlerin boğmaca hastalığı hakkındaki farkındalıklarının arttırılıp, koza stratejisini uygulamaya geçirmelerine ihtiyaç vardır. Yardımcı sağlık personellerinin de boğmaca hastalığı ve aşıları hakkındaki bilgi düzeylerini arttıracak müdahaleler gerekmektedir.

Anahtar Kelimeler: Boğmaca aşısı, sağlık çalışanı, yenidoğan, yoğun bakım ünitesi

INTRODUCTION

Pertussis is a highly contagious respiratory disease caused by *Bordetella pertussis*. It is more severe in infants younger than six months, preterm infants and unvaccinated infants[1]. In infancy, the need for mechanical ventilation due to pneumonia, pulmonary hypertension, leukocytosis requiring complete exchange transfusion, seizures, and death have been reported[2]. For this reason, in order to prevent pertussis cases under the age of one year, it is primarily necessary for mothers to be vaccinated with Tdap (tetanus, adult-type diphtheria and acellular pertussis vaccine) between the 27th and 36th weeks of the pregnancy and in addition, people who will have close contact with the baby are recommended to be vaccinated with Tdap.

The Centers for Disease Control and Prevention (CDC) has called this practice a cocoon strategy since 2005 and recommends vaccination of those with close contacts with the baby[3]. Similarly, it is recommended that people and healthcare workers who come into contact with unvaccinated infants younger than six months should be vaccinated against influenza[4].

Pertussis may start as an upper respiratory tract infection and its diagnosis may be missed in the early period. In untreated cases, it can be contagious for three weeks. It has been observed that pertussis causes hospital-acquired epidemics. Healthcare workers are also included in the cocoon strategy in order to prevent nosocomial pertussis. Nosocomial pertussis outbreaks have been reported in different units such as the surgical ward and neonatal intensive care unit (NICU)[5-7]. In the study of Calugar et al.[8], a baby with pertussis was shown to infect 17 healthcare workers and cost the hospital 74,000 dollars. CDC recommends a single dose of Tdap to healthcare workers who have direct contact with patients, regardless of previous Tetanus, adult-type diphtheria (Td) vaccine status. Giving priority to health personnel who have contact with infants younger than one year old emphasizes the application of a vaccine that includes nurses, nurse assistants, radiology technicians, medical and nursing students, secretariat workers as well as physicians[9].

Within the scope of vaccination of healthcare workers by the Ministry of Health, Tdap vaccine is recommended especially for healthcare personnel and cleaning personnel working in NICU, delivery room, bone marrow transplantation units, 112 emergency health services and National Medical Rescue Team personnel. In this way, it is aimed to protect the newborn and immunocompromised patient group, whom pertussis can progress with severe morbidity and mortality, with the cocoon strategy. In addition, within the scope of the secondary gains of vaccines, it will also be possible to prevent the loss of workforce of qualified health personnel[10].

The primary purpose of this study is to determine pertussis awareness and Tdap vaccination status of healthcare workers working in the NICU within the scope of the cocoon strategy. Secondly, it is aimed to determine other recommended vaccination conditions for healthcare professionals, to inform personnel about the vaccines recommended by the Ministry of Health, and to determine their intentions for Tdap vaccination.

MATERIALS AND METHODS

Selection of Patients

Our research was designed as a cross-sectional and descriptive questionnaire study using face-to-face interview technique and conducted at Samsun Training end Research Hospital NICU between May and June, 2021. Ninety-one health workers, consisting of nurses/midwives, medical secretaries, cleaning staff, and pediatricians working in rotations working in the unit, were invited to the research and 89 people agreed to be interviewed.

The questionnaire consisted of four parts, including 21 questions, in order to learn about the demographic data of the participants, their level of knowledge about pertussis disease (LKPD), their level of knowledge about pertussis vaccine and their vaccination status. Thirteen questions aiming to measure the level of knowledge were prepared considering the informative writings of the Ministry of Health and Child Health Association about pertussis disease and vaccines to cover all healthcare professionals. The questions prepared to measure the level of knowledge were asked to be answered

as Yes-No-I don't know. While scoring, correct answers were evaluated as 3 points, answers of 'I have no idea' as 2 points, and wrong answers as 1 point. The sum of the scores of the eight questions about pertussis disease was named the LKPD, and the sum of the scores of the answers to the five questions about the pertussis vaccine was named the LKPV.

On pertussis, questions were asked about the contagion rate and transmission route of the disease, the clinical picture it caused, whether permanent immunity was acquired by having the disease, and the regional outbreaks that occurred every three years. For pertussis vaccines, it was asked whether the vaccine was included in the vaccine calendar of the Ministry of Health, whether there were different forms for adults, whether the person having suffered from the disease needed to be vaccinated, and whether it was on the list of vaccines recommended to healthcare professionals. After the written consent of the participants was obtained, the survey, which lasted approximately 7 minutes, was administered face-to-face by the researcher. The last question in the questionnaire was about the participants' intention to get vaccinated. Before asking about the vaccination intention, the participants were informed verbally and in writing about the Tdap vaccine recommendation of the Ministry of Health. Immediately after the briefing, the participants were asked if they were considering getting the Tdap vaccine to determine their vaccination intentions.

Ethics committee approval was obtained from Samsun Training end Research Hospital for the study (protocol no: GOKA/2021/10/3, date: 26.05.2021).

Statistical Analysis

Comparison of the results between the groups was analyzed with the Statistical Package for the Social Sciences (version 23) program. The chi-square test was used for categorical variables. The distribution of independent variables in the groups was examined with the Shapiro-Wilk test, and those with normal distribution were compared with the t-test and those without normal distribution were compared with the Mann-Whitney U test. A p value of <0.05 was considered significant.

RESULTS

91% (n=81) of the participants were female and 9% (n=8) were male, and their mean age was calculated as 38.7±7.3 years. 76% of those interviewed consisted of nurses/midwives and doctors. The professional characteristics of the participants are given in Table 1.

The LKPD and vaccines were significantly higher in physician participants than in other groups (LKPD: p<0.001 - LKPV: p<0.003). While 14 (16%) of the participants answered the information questions about pertussis disease correctly, only 3 people answered the questions about vaccines correctly. The questions aiming to measure the level of knowledge and the rates of correct answers are shown in Table 2.

The health workers working in the unit were asked about their vaccination status based on their own notification. None of the participants were vaccinated with Tdap. Figure 1 shows the rate of the team vaccinated with the highest rate of Td (n=66.74%) and the other vaccinations.

When the participants were asked about the vaccines which were mostly recommended because they were healthcare professionals, 67% (n=60) stated that they did not receive any advice. There were 21 people who received recommendations for more than one vaccine. Vaccines recommended for healthcare workers are shown in Figure 2. When it was evaluated from whom they received the recommendation to be vaccinated, 20 of the 29 people getting recommendation stated that they received this recommendation from the workplace doctor, 2 from the family doctor and 2 from the infectious diseases specialist.

When asked about their Tdap vaccination intentions after debriefing, more than half of the participants stated that they were not considering getting the Tdap vaccine. There were

Table 1. Occupations of the participants and duration of their working experience

Occupation	n=89 (%)
- Physician	17 (19)
- Nurse/midwife	51 (57)
- Medical secretary	5 (6)
- Cleaning staff	16 (18)
Occupational experience	
- <5 years	7 (8)
- 5-15 years	35 (39)
- 15 years <	47 (53)

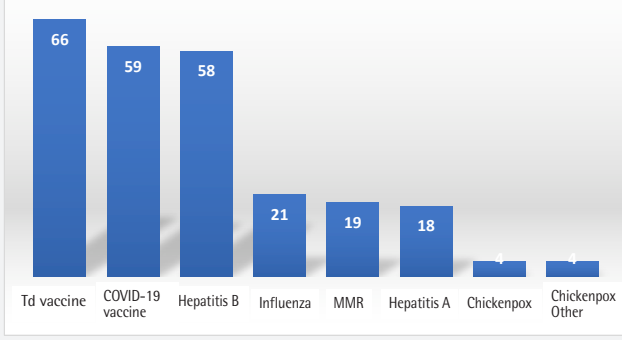

Figure 1. Vaccination status of the participants

COVID-19: Coronavirus disease-2019

32 (36%) people stating that they would be vaccinated if the vaccine was provided by the hospital, and 6 (7%) people stated that they would be vaccinated by covering the cost of the vaccine, even if it was by their own means. A high score of LKPV was found to be associated with a positive intention to be vaccinated (p=0.02) (Table 3). When evaluated according to occupations, the intention to get Tdap vaccine was determined as 71% among doctors, and this rate was statistically significantly higher than in other groups (p=0.007) (Table 4).

Table 2. Questions asked to determine the level of knowledge and participants' answers

Questions about pertussis disease	Correct n (%)	No idea n (%)	Incorrect n (%)
Pertussis is a common disease all over the world.	59 (66)	13 (15)	17 (19)
*Pertussis can cause regional epidemics every 3-4 years.	38 (43)	26 (29)	25 (28)
Pertussis is only seen in the childhood age group.	52 (58)	10 (11)	27 (30)
Pertussis can cause lung infections, brain hemorrhages, and convulsions in infants.	68 (76)	18 (20)	3 (4)
Pertussis can cause death in young infants.	78 (87)	8 (9)	3 (4)
Pertussis is transmitted from person to person through droplets produced during coughing and sneezing.	75 (83)	10 (11)	4 (4)
Pertussis is not a very contagious disease.	65 (73)	15 (17)	9 (10)
*Individuals who have had pertussis once develop a lifelong permanent immunity.	33 (37)	32 (36)	24 (27)
Questions about pertussis vaccines			
Pertussis vaccines are very effective.	61 (68)	21 (24)	7 (8)
*There are separate vaccines for pertussis for children and adults.	22 (25)	37 (42)	30 (33)
In the Vaccination Calendar of the Ministry of Health, there is a total of 5 doses of pertussis vaccine, at the 2nd, 4th, 6th and 18th months, and then at the 48th month.	57 (64)	27 (30)	5 (6)
*Pertussis vaccine is also included in the list of vaccines recommended by the Ministry of Health for healthcare professionals.	28 (32)	26 (29)	35 (39)
* Even if pertussis disease is passed, pertussis vaccine should be taken.	36 (40)	31 (35)	22 (25)
*It was correctly known by less than half of the participants.			

DISCUSSION

In our research, it was aimed to determine the pertussis awareness and Tdap vaccination status of healthcare professionals working in the NICU. There were no healthcare workers in the unit vaccinated with Tdap. It was known by a small number of participants (n=28, 32%) that pertussis vaccine was among the vaccines recommended by the Ministry of Health to health workers. High level of knowledge about vaccination was found to be significantly associated with positive vaccination intention (p=0.02).

Tdap vaccination rates in healthcare workers vary according to the vaccination strategies of countries. While countries such as the United States of America (USA), England, and Germany recommend all healthcare personnel to be vaccinated with Tdap, it is recommended for healthcare professionals who may have contact with a risky group in France, Austria and Turkey[9-11]. Vaccination rates of healthcare workers in the USA and France are included in national data record systems. In a systematic review evaluating 28 studies, mostly of which are from these two countries, it has been reported that vaccination rates are still low, but vaccination among healthcare workers has become widespread with interventions over the years. In the USA, Tdap vaccination rates among healthcare workers

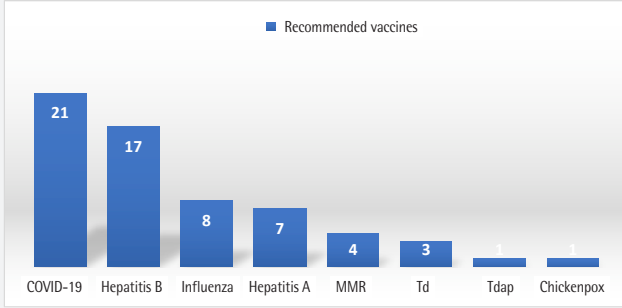

Figure 2. Vaccines recommended to participants

COVID-19: Coronavirus disease-2019

Table 3. Vaccination intentions of the participants according to their level of knowledge

Vaccination intention (n=88)	Yes (n=38)		No (n=50)		p[&]
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
LKPD	20.5±2.6	21 (15-24)	19.6±3.08	19 (12-24)	0.135
LKPV	11.7±2.1	12 (7-15)	10.7±1.7	11 (6-15)	**0.02**

[&]Mann-Whitney U test.

min-max: Minimum-maximum, LKPD: Level of knowledge about pertussis disease, LKPV: Level of knowledge about pertussis vaccine, SD: Standard deviation

increased from 6.1% to 45.1% between 2007 and 2015. In France, the rate of being vaccinated with Tdap was reported to be 63.9%[12].

Table 4. Intention to be vaccinated according to occupations

	Intention to be vaccinated (n=88)		p*
Occupations	Yes (n=38) (%)	No (n=50)(%)	**0.007**
Physician (n=17)	12 (71%)	5 (29%)	
Nurse-midwife (n=51)	15 (29%)	36 (70%)	
Medical secretary (n=5)	1 (20%)	3 (60%)	
Cleaning staff (n=16)	10 (62.5%)	6 (37.5%)	
*Chi-square test.			

Since there is no such registration system in our country, studies on Tdap vaccination rates among healthcare professionals gain importance. In a seroprevalence study involving nurses and doctors working in a pediatric clinic, 39.6% of 169 participants were found to be seronegative against pertussis, while only 1.8% (n=3) were vaccinated with Tdap[13]. In the seroprevalence study conducted by Tanriover et al.[14] on 1303 people, 35 participants were healthcare workers, and the rate of seropositivity against pertussis was found to be 5.7% among healthcare professionals. Data on the vaccination status of the participants in this study were not shared. In our study, there was no healthcare worker vaccinated with Tdap among the participants.

Accurate perception of the benefits/risks of the vaccine based on evidence is among the factors affecting vaccine acceptance. The knowledge of healthcare professionals about vaccines affects their own vaccination practices and vaccine recommendations[15]. The vast majority of participants knew correctly that pertussis could cause death in young children and that the disease was transmitted by droplets. However, more than half did not know that pertussis could cause regional epidemics every 3-4 years, and that pertussis did not leave permanent immunity for life. Only 28 (32%) people knew that the Ministry of Health recommended Tdap to health workers working in specific departments. In our study, the increase in the level of knowledge about vaccines was found to be statistically significantly associated with the intention to be vaccinated (p=0.002).

Health workers are seen as the most reliable source for vaccines. In a study with the participation of occupational physicians in Italy, the rate of Tdap vaccination recommendation was found to be 52.7%[16]. The awareness of family physicians in our country in terms of the cocoon strategy was examined, and 47.4% stated that they did not have sufficient knowledge on this subject, and nearly 60% stated that they needed expert opinion for the application of the cocoon strategy[17]. In our study, the participants stated that they received their vaccination recommendations from the occupational physician, family physician and infectious diseases specialist, but only one person stated that Tdap vaccine was included in these recommendations. Healthcare workers in our study were mostly recommended for Coronavirus disease-2019, hepatitis B and influenza vaccines, and similarly, they were found to be vaccinated at a higher rate with these vaccines. Although the recommendation rates for Td vaccine were low, it was observed that the rate of getting vaccinated was high. It was thought that this situation might be caused by the accidents that required tetanus prophylaxis.

When the studies conducted in our country are evaluated, no study has been encountered regarding Tdap vaccine applications in departments where the cocoon strategy is very important in terms of pertussis, such as the NICU. In this respect, our study is the first study that will contribute to this field and raise awareness. Evaluation of all healthcare professionals other than physicians and nurses is another strength of the research.

Study Limitations

Participants were asked about their vaccination intentions, but it was not investigated why they were not vaccinated. Once the underlying reasons for vaccine preferences are learned, a more effective policy can be created to increase vaccine acceptance.

Our research suggests that there is a need for further studies evaluating the knowledge and attitudes of physicians, especially occupational physicians, family physicians and infectious diseases, about the cocoon strategy.

CONCLUSION

Although it is recommended by the Ministry of Health to vaccinate healthcare workers working in the NICU with Tdap, it is thought that there are problems in practice. There is a need for all physicians, especially occupational physicians, family physicians and infectious disease specialists, who recommend vaccination to healthcare professionals, to increase their awareness of pertussis and to put the cocoon strategy into practice. Interventions are needed to increase the level of knowledge of allied health personnel about pertussis disease, its risks and pertussis vaccines.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Samsun Training end Research Hospital for the study (protocol no: GOKA/2021/10/3, date: 26.05.2021).

Informed Consent: The written consent of the participants was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.K., S.Ç.Ç., R.K., Concept: Ş.K., S.Ç.Ç., R.K., Design: Ş.K., S.Ç.Ç., Data Collection or Processing: Ş.K., R.K., Analysis or Interpretation: Ş.K., S.Ç.Ç., Literature Search: Ş.K., S.Ç.Ç., R.K., Writing: Ş.K., S.Ç.Ç., R.K.

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Vitamin D Status and Its Relationship with Clinical Presentation Characteristics in Children with the Diagnosis of Type 1 Diabetes

Tip 1 Diyabet Tanısı Alan Çocuklarda D Vitamini Durumu ve Klinik Başvuru Özellikleri ile İlişkisi

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ABSTRACT

Aim: This study is conducted to examine the correlation between vitamin D deficiency and type 1 diabetes since diabetes incidence is rising and recent studies have revealed extra osseous effects of vitamin D.

Materials and Methods: Eighty patients with newly diagnosed type 1 diabetes and 30 patients with no systemic disease were included in the study. Serum 25-hydroxyvitamin D (25-OHD), parathormone (PTH), calcium (Ca), phosphorus (P), and alkaline phosphatase (ALP) samples were obtained from both groups. Blood gas parameters were also obtained from the diabetic group. Information concerning vitamin D usage during pregnancy and infancy was acquired through personal interviews with patient's mothers.

Results: 25-OHD levels were lower in the diabetic group than in the controls (24.43±16.25 ng/mL vs. 34.55±15.03 ng/mL, respectively, p=0.001), but the difference was not significant when seasonal variation was taken into consideration (33.44±17.23 ng/mL, vs. 34.55±15.03 ng/mL, p>0.05). Vitamin D levels were similar between the groups with diabetic ketoacidosis and non-acidotic group (p>0.05, for all). Ca, P, ALP and PTH levels were also similar at the time of diagnosis in the acidotic and non-acidotic groups (p>0.05, for all). The relationship between vitamin D use during pregnancy and infancy and the development of type 1 diabetes was similar between the diabetic and control groups (p>0.05).

Conclusion: No significant effects of vitamin D deficiency/insufficiency on the development of diabetes and clinical status at admission was detected. Vitamin D intake in infancy and pregnancy exhibited no protective effect against the progression of diabetes. Therefore, it does not seem possible to reach a definitive conclusion about the relationship of vitamin D and type 1 diabetes.

Keywords: Type 1 diabetes, diabetic ketoacidosis, vitamin D

ÖZ

Amaç: Bu çalışma, diyabet insidansının artması ve D vitamininin ekstra osseöz etkilerini ortaya koyması nedeniyle D vitamini eksikliği ile tip 1 diyabet arasındaki ilişkiyi incelemek amacıyla yapılmıştır.

Gereç ve Yöntem: Çalışmaya yeni tanı almış tip 1 diyabetli 80 hasta ve sistemik hastalığı olmayan 30 hasta dahil edildi. Her iki gruptan da serum 25-hidroksivitamin D (25-OHD), parathormon (PTH), kalsiyum (Ca), fosfor (P) ve alkalen fosfataz (ALP) örnekleri alındı. Diyabetik gruptan kan gazı parametreleri de alındı. Gebelik ve bebeklikte D vitamini kullanımı, hastaların annelerinden karşılıklı görüşme ile öğrenildi.

Bulgular: 25-OHD düzeyi diyabetik grupta kontrollere göre daha düşüktü (sırasıyla 24,43±16,25 ng/mL, 34,55±15,03 ng/mL, p=0,001), ancak mevsimsel değişkenlik dikkate alındığında fark anlamlı değildi (33,44±17,23 ng/mL, 34,55±15,03 ng/mL, p>0,05). (D vitamini düzeyleri ketoasidoz olan gruplar ve asidoz olmayan grup arasında benzerdi (p>0,05, hepsi için). Asidoz olan ve olmayan grupta tanı anında Ca, P, ALP ve PTH düzeyleri de benzerdi (p>0,05, hepsi için). Gebelik ve bebeklik döneminde D vitamini kullanımı ile tip 1 diyabet gelişimi arasındaki ilişki diyabetli ve kontrol grupları arasında benzerdi (p>0,05).

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Sonuç: D vitamini eksikliği/yetersizliğinin diyabet gelişimi ve başvuru anındaki klinik durum üzerinde anlamlı bir etkisi saptanmamıştır. Bebeklik döneminde ve gebelikte D vitamini alımı diyabetin ilerlemesine karşı koruyucu bir etki göstermemiştir. Bu nedenle D vitamini ve tip 1 diyabet ilişkisi hakkında kesin bir sonuca varmak mümkün görünmemektedir.

Anahtar Kelimeler: Tip 1 diyabet, diyabetik ketoasidoz, D vitamini

INTRODUCTION

In children, type 1 diabetes is one of the most common chronic diseases, the incidence of which is growing. Despite the improvements in science and technology, the factors involved in the etiopathogenesis of type 1 diabetes are still not fully understood in all respects. This has encouraged the performance of further studies on type 1 diabetes. Accordingly, research has investigated the genetic factors involved in the pathogenesis of type 1 diabetes and environmental factors triggering the disease in the presence of genetic factors[1].

Vitamin D deficiency has been implicated in the pathogenesis of diabetes as an environmental factor[1,2]. In addition to many current studies of the relationship between vitamin D and type 1 diabetes, knowledge obtained from studies on vitamin D receptor (VDR) knock-out mice has strengthened the possibility of such a relationship. The immune system has been shown to increase the risk of the development of autoimmune diseases such as type 1 diabetes and inflammatory bowel disease in the presence of triggering factors in "roughly" normal cases with knockout VDRs or vitamin D deficiency[3].

Recent studies have observed low levels of vitamin D at the time of diagnosis in patients with type 1 diabetes. Vitamin D deficiency causes cellular cytotoxicity and cellular destruction as a result of its effects on the immune system, leading to diabetes by impairing the synthesis and secretion of insulin[4]. It also predisposes to infections and facilitates the presentation of patients with diabetic ketoacidosis (DKA). Vitamin D deficiency also increases the tendency to DKA, while on the other hand, acidosis in DKA causes low levels of vitamin D by reducing the conversion of 25-hydroxyvitamin D (25-OHD) to its active form and the synthesis of vitamin D-binding proteins[5].

In the light of this role of vitamin D in the pathogenesis of diabetes, studies have investigated the protective role of sufficient vitamin D levels against the development of diabetes. Research has focused on vitamin D supporting programs and the importance of babies using vitamin D in the first year of their lives. The use of supplements including vitamin D by mothers during pregnancy also affects serum levels of vitamin D in early infancy[6].

The objective of this study was to evaluate vitamin D levels in newly diagnosed patients with type 1 diabetes, and to examine the effects of vitamin D levels according to clinical manifestations at presentation. This study was conducted to evaluate vitamin D levels at presentation in patients newly diagnosed with type 1 diabetes, and the relationship between clinical presentation characteristics and vitamin D levels, and to assess the status of vitamin D intake by mothers during pregnancy and by infants in the first year of life, between a diabetic patient group and a control group.

MATERIALS AND METHODS

This study was performed in Kocaeli University Medical Faculty Department of Pediatrics. The patient group consisted of 80 patients who were admitted to the pediatric endocrinology and diabetes outpatient clinics, pediatric clinics, or pediatric emergency departments with newly diagnosed type 1 diabetes during 20 months between March 1, 2009 and November 1, 2010. The control group consisted of 30 patients admitted to pediatric clinics for various reasons during 3 months in the summer between June 1, 2010 and September 1, 2010. The members of the control group were selected from patients with no chronic disease capable of affecting vitamin D metabolism (renal failure, liver disease, gastrointestinal resection, hyperparathyroidism etc.), and not receiving drugs affecting that metabolism (such as phenytoin, phenobarbital, insulin, and thyroid hormone).

A questionnaire investigating the use of vitamin D during infancy and maternal use of vitamin D and similar supplements during pregnancy was performed. Vitamin D intake during infancy was evaluated based on the duration of intake and regularity of use.

Body mass indices (BMI) [weight (kg)/height (m^2)] were calculated in all patients and controls.

Laboratory Measurements

Venous blood glucose, blood ketone, and blood gas parameters were studied in patients with newly diagnosed type 1 diabetes. Patients were divided into two groups - those with and without DKA. The degree of DKA was evaluated based on pH values and 2006-2007 consensus guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD). pH values <7.3 were classified as mild DKA, pH<7.2 as moderate DKA, and pH<7.1 as severe DKA[7].

Levels of calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), parathormone (PTH), and 25-OHD were studied in both the patient and control groups.

The reference values for 25-OHD recognized by the American Academy of Pediatrics and the Pediatric Endocrinology Society are used to evaluate vitamin D status in the human body. Accordingly, 25-OHD>100 ng/mL was regarded as excess, 20-100 ng/mL as normal (sufficiency), 15-20 ng/mL as insufficiency, 5-15 ng/mL as deficiency, and <5 ng/mL as severe deficiency[8]. The study were approved by the Kocaeli University Faculty of Medicine of Local Ethics Committee [protocol number: 24.02.09-(5/17), date: 21.03.2011-(1/6)]. Informed consent was obtained from children and their parents.

Statistical Analysis

The study data were analyzed using Statistical Package for the Social Sciences 13.0 for Windows software. Normal distribution of the variables, variance homogeneity, and numbers of subjects were examined, and appropriate tests were applied. The Student's t-test, and the Mann-Whitney U, chi-square, and Kruskal-Wallis tests were used in the analysis. P<0.05 values were considered statistically significant.

RESULTS

Eighty patients with newly diagnosed type 1 diabetes were included in the patient group and 30 patients in the control group. No significant difference was found between the patients with type 1 diabetes and the control group in terms of demographic characteristics except for BMI (p=0.002). However, the mean 25-OHD and PTH values differed significantly between the two groups (p=0.001) (Table 1).

Since the control group was investigated in summer, that group was compared with diabetic patients diagnosed in summer in order to determine whether the difference between the groups was seasonal in nature. The mean 25-OHD levels were 33.44±17.23 ng/mL in the patient group and 34.55±15.03 ng/mL in the control group, the difference was not statistically significant (p>0.05). However, the mean PTH values differed significantly between the patient and control groups (p=0.020) (Table 2).

The rates of regular vitamin D intake in the first year of life and during pregnancy were similar between the patients with type 1 diabetes and the control group (p>0.05) (Table 3).

No significant correlation was found between vitamin D levels and pH, HCO_3, osmolarity, Na values, or duration of symptoms (p>0.05) (Table 4).

In terms of the relationship between clinical manifestations at presentation and vitamin D levels, 25 (31%) patients presented with mild DKA, 10 (12.5%) patients with moderate DKA, 13 (16%) patients with severe DKA, and 32 (40%) patients without developing metabolic acidosis. The mean 25-OHD was <15 ng/mL in 26% of patients and 15-20 ng/mL in 21% of patients.

Table 1. Comparison of demographic features and Ca, P, ALP, 25-OHD, and PTH parameters between the patient and control groups

	Patients with type 1 diabetes Number / (%)	Controls* Number / (%)	p
Gender			
Male	44 / (55.0)	15 / (50.0)	>0.050
Female	36 / (45.0)	15 / (50.0)	
Age			
<5 years	21 / (26.2)	10 / (33.3)	
5-10 years	25 / (31.2)	8 / (26.6)	
10-15 years	32 / (40.0)	9 / (30.0)	
>15 years	2 / (2.5)	3 / (10.0)	
Mean age (years)	8.38±4.25	8.45±5.39	>0.050
BMI	16.08±2.90	18.72±5.68	**=0.002**
Ca (mg/dL)	9.41±0.58	9.65±0.50	0.970
P (mg/dL)	4.26±1.01	4.62±0.60	0.690
ALP (U/L)	231.76±99.31	203.57±110.77	0.142
25-OHD (ng/mL)	24.43±16.25	34.55±15.03**	**0.001**
PTH (pg/mL)	25.29±15.01	40.02±14.6**	**0.001**

*Investigations were performed in summer in the control group.

**The Mann-Whitney U test was used since this was not normally distributed.

Ca: Calcium, P: Phosphorus, ALP: Alkaline phosphatase, 25-OHD: 25-hydroxyvitamin D, PTH: Parathormone, BMI: Body mass index

Table 2. Mean vitamin D and PTH values in patients with type 1 diabetes who were diagnosed in the same season as the controls

	Patients with type 1 diabetes (n=20)	Controls (n=30)	p
25-OHD (ng/mL)	33.44±17.23	34.55±15.03	>0.050
PTH (pg/mL)	28.87±20.28	40.02±14.65	**0.020***

*Mann-Whitney U test, Student's t-test.

25-OHD: 25-hydroxyvitamin D, PTH: Parathormone

Table 3. Evaluation of regular vitamin D intake in the first year of life and during pregnancy

	Patients with type 1 diabetes Number / (%)	Controls Number / (%)	p
Regular vitamin D intake in the 1st year (Yes)	29 / (44.6)	15 / (68.1)	>0.050
Regular vitamin D intake in the 1st year (No)	36 / (55.4)	7 / (31.9)	>0.050
Vitamin supplements intake during pregnancy (Yes)	35 / (51.5)	9 / (37.5)	>0.050
Vitamin supplements intake during pregnancy (No)	33 / (48.5)	15 / (62.5)	>0.050

There was no statistically significant difference between the patient and control groups when vitamin D levels were classified according to their serum concentration. Fourteen patients in our study had acidosis presented with vitamin D levels <15 ng/mL, and 34 patients with acidosis had vitamin D >15 ng/mL. Metabolic acidosis existence ratio values were also similar between the patients with mean 25-OHD< 15 ng/mL and those with mean 25-OHD>15 ng/mL among the patients with type 1 diabetes (p>0.05) (Table 5).

There was no significant difference between the patients and control groups in terms of the relationship between DKA status and 25-OHD, Ca, P, ALP, or PTH (p>0.05) (Table 6).

DISCUSSION

The increasing incidence of type 1 diabetes with increasing incidence of vitamin D deficiency also supports the idea that vitamin D deficiency may be a potential factor in the pathogenesis of type 1 diabetes. Accordingly, several studies have been conducted on the subject. Data obtained from animal studies about the relationship between type 1 diabetes and vitamin D have most commonly been obtained from non-obese diabetic (NOD) mice[3]. Mathieu and Badenhoop[9] showed that the incidence of autoimmune diabetes decreased from 56% to 8% after 200 days in NOD mice after using active vitamin D analogues. Similar results were obtained by Zella and DeLuca[10], who reported that Ro-262198, a vitamin D analogue, was effective in the control of type 1 diabetes and led to improvement in the clinical manifestation of the disease. In Finland, a northern country with a cold climate during the long months of winter, the incidence of type 1 diabetes was 18/100,000 and the recommended dose of vitamin D was 4500 IU/day before 1964 and the prophylaxis dose was reduced to 2000 IU/day in 1965. Since, the incidance of type 1 diabetes was 64/100,000 in 2005, vitamin D was addes to the formulae, and the incidance continued to decrease[11]. Infante et al.[12] also suggested an inverse relationship between vitamin D levels and the prevalence of type 1 diabetes. However, Reinert-Hartwall et al.[13] stated that these findings did not support a crucial role of circulating 25-OHD as a regulator of beta-cell autoimmunity.

Table 4. Relationships between vitamin D levels and blood gas and biochemical parameters and duration of symptoms

	Vitamin D			
	Normal or excess (n=42)	Insufficiency (n=17)	Deficiency and severe deficiency (n=21)	p
pH	7.24±0.13	7.25±0.18	7.23±0.14	p>0.050
HCO_3 (mg/dL)	12.63±6.62	14.35±7.21	13.41±6.23	p>0.050
Osmolarity (osm)	293.98±10.62	296.74±10.58	296.92±9.82	p>0.050
Na (mEq/L)	137±4.7	137.4±4.2	137±4.0	p>0.050
Duration of symptoms (day)	23.90±23.27	33.00±24.38	36.43±26.86	p>0.050

HCO_3: Bicarbonate, Na: Sodium

Table 5. Clinical manifestations at presentation according to vitamin D levels in patients with type 1 diabetes compared with controls

Patients with type 1 diabetes						Controls	p
25-OHD (ng/mL)	No Acidosis n / (%)	Mild DKA n / (%)	Moderate DKA n / (%)	Severe DKA n / (%)	Total n / (%)	Total n / (%)	
25-OHD>20	16 / (38.1)	12 / (28.6)	8 / (19.0)	6 / (14.3)	42 / (53)	26 / (86.6)	>0.050
25-OHD 15-20	9 / (52.9)	5 / (29.4)	-	3 / (17.6)	17 / (21)	2 / (6.7)	>0.050
25-OHD<15	7 / (33.3)	8 / (38.1)	2 / (9.5)	4 / (19.0)	21 / (26)	2 / (6.7)	>0.050
Total	32 / (40)	25 / (31)	10 / (12.5)	13 / (16)	80 / (100)	30 / (100)	>0.050

25-OHD: 25-hydroxyvitamin D, DKA: Diabetic ketoacidosis, n: Number

Table 6. Relationships between clinical pictures at presentation and vitamin D, Ca, P, ALP, PTH in patients with type 1 diabetes

DKA status	25-OHD (ng/mL)	Ca (mg/dL)	P (mg/dL)	ALP (U/L)	PTH (pg/mL)
Mild (n=25)	22.86±13.42	9.21±0.52	4.16±0.22	185.32±67	23.38±11.67
Moderate (n=10)	24.90±10.19	9.55±0.64	4.29±0.92	297.30±128.93	25.60±24.03
Severe (n=13)	23.14±15.54	9.49±0.81	3.39±1.43	253.92±141.51	18.53±10.57
No DKA (n=32)	26.03±20.12	9.48±0.54	4.70±0.85	229.92±76.34	28.32±14.18
p	>0.05	>0.05	>0.05	>0.05	>0.05

ALP: Alkaline phosphatase, Ca: Calcium, DKA: Diabetic ketoacidosis, P: Phosphorus, 25-OHD: 25-hydroxyvitamin D, PTH: Parathormone

Pozzilli et al.[14] reported lower 25-OHD levels in 88 newly diagnosed pediatric diabetic patients compared to healthy children. Vitamin D levels were low in both winter and summer in that study, thus the seasonal factors affecting vitamin D levels were ruled out. Littorin et al.[15] observed low 25-OHD levels at the time of diagnosis in newly diagnosed diabetic adolescents in Sweden. In a study from Qatar conducted in 2000, the authors stated that although vitamin D deficiency was frequently seen in children due to lifestyle and nutritional factors, severe deficiency was more common in children with type 1 diabetes[16]. Svoren et al.[17] reported vitamin D insufficiency in 61% and vitamin D deficiency in 15% of 128 patients with newly diagnosed type 1 diabetes. Franchi et al.[18] also stated in their study that vitamin D levels were low at the onset of type 1 diabetes without seasonal variation.

In our study 25-OHD levels were also significantly lower among diabetic patients compared to the control group. However, blood samples were collected throughout the year from the diabetic patient group, but only in summer from the control group, when the synthesis of vitamin D is highest. In order to clarify whether higher vitamin D levels in the control group were seasonal in nature, we compared vitamin D levels between the control group and diabetic patients diagnosed in the same period and the mean vitamin D levels were found to be similar between the two groups in the same season.

Bierschenk et al.[19] analyzed 415 individuals living in Florida, a sunny region of the USA. The participants consisted of 153 controls, 46 newly diagnosed type 1 diabetes patients, 110 patients under follow-up with type 1 diabetes (for ≥5 months from the diagnosis), and 106 first-degree relatives of the diabetic patients. No significant difference was found in 25-OHD levels among the control group, the newly diagnosed diabetic patients, the patients under follow-up for diabetes, and first-degree relatives. The mean 25-OHD level was under 30 ng/mL in all four study groups. Low serum 25-OHD levels were not therefore thought to be associated with type 1 diabetes[19]. A study performed in Kocaeli, a city in Turkey, in 2010, involving 120 patients with type 1 diabetes under follow-up, reported the mean 25-OHD level as 25.6±16.2 (ng/mL) (4.6-101), and the mean time since diagnosis as 3.2±2.3 (0.7-12.8) years. Vitamin D deficiency or insufficiency was present in 36% of the patients[20]. These findings showed that vitamin D levels were low, not only in newly diagnosed patients, but also in patients who had been diagnosed previously. In another study from the same city, which was conducted on 301 obese children in 2006, vitamin D insufficiency/deficiency rate was revealed as 65.1%[21]. One other study, also performed in the same city in 2002, evaluated adolescent girls, and reported vitamin D insufficiency and deficiency in 50% of patients living in rural areas and 57% of those living in urban areas[22]. The participants in our study were living also in Kocaeli city and the rate of vitamin D insufficiency/deficiency was defined as 47%. This rate was a bit higher than the rate detected in 2011 among diabetic patients but lower than the rates in 2002 and 2006 among non-diabetic patients, supporting the idea that vitamin D deficiency/insufficiency is not an additional risk factor for diabetes, its prevalence is high among the children and adolescents in general. Brody et al.[23] stated that vitamin D insufficiency was largely prevalent among Israeli youth with type 1 diabetes mellitus, as is in Israeli youth in general stating that vitamin D level is associated with seasonality, clothing habits[23]. Mäkinen et al.[24] supported the idea in their study that serum vitamin D concentrations were not associated with the development of type 1 diabetes in Finland. Simpson et al.[25] declared that neither vitamin D intake nor 25-OHD levels throughout childhood were associated with the risk of progression to type 1 diabetes in their population.

In terms of the relationship between acidosis and decreased vitamin D levels, acidosis has been shown to affect the physiology of vitamin D. Decreased vitamin D levels reduce insulin secretion or activity and change natural immunity, leading to presentation of patients with DKA[26-28]. Low 25-OHD levels have been associated with acidemia, and usually return to normal once the acidosis has resolved. Devidayal et al.[29] supported this knowledge and stated that metabolic acidosis could alter vitamin D metabolism through different mechanisms, while low vitamin D levels could play a role in presentation of children with acidosis in type 1 diabetes. Franchi et al.[18] reported lower vitamin D levels at DKA than those without acidosis. Al-Zubeidi et al.[30] stated that vitamin D deficiency and insufficiency are common, even in Caucasians, at the onset of type 1 diabetes in pediatrics, worse in those with DKA. In a study from Australia performed by Huynh et al.[5] between July 2006 and December 2007, the relationship between metabolic acidosis and 25-OHD levels at the time of diagnosis in 64 children was investigated. 25-OHD levels were under 50 nmol/L (20 ng/mL) in 14 of these patients. Of these 14 children, 12 had metabolic acidosis, while no metabolic acidosis was present at the time of diagnosis in two, but metabolic acidosis was present in the remaining 50 patients with normal vitamin D levels. 25-OHD levels returned to normal when acidosis resolved in all cases except one. The authors attributed the low vitamin D levels to low exposure to sunlight for religious reasons in this patient[5].

Forty-eight patients were presented with metabolic acidosis in our study, 25 (31%) with mild DKA, 10 (12.5%) with moderate DKA, and 13 (16.5%) with severe DKA. No significant difference was observed between these groups in terms of 25-OHD levels measured at the time of diagnosis. The similar initial mean vitamin D levels thus show that mean vitamin D levels were independent from the form of presentation like the previous study performed by Huynh et al.[5]. It may therefore be

concluded that the presence or absence of acidosis and the degree of acidosis were not associated with vitamin D levels.

The intrauterine period and first years of life have been shown to be important for the development of diabetes. Vitamin D status in infants reflects vitamin D status in mothers during pregnancy[6]. The first year of life is a period in which breastfeeding is predominant, and includes subsequent transition to additional foods, and vitamin D supplementation is important in this period. Comprehensive studies have therefore investigated both periods. In the All Babies in Southeast Sweden (ABIS) study in Sweden, Brekke and Ludvigsson[31] investigated the relationship between the use of vitamin D supplements in infancy and pregnancy and type 1 diabetes in infants aged one year and 2.5 years and the correlation with diabetes-related autoimmunity. That study involved 16,070 infants and was completed with 11,081 patients aged one year, and 8805 aged 2.5 years. At the end of the follow-up period, four of the one-year-old children and 22 of the infants aged 2.5 years developed diabetes. No significant correlation was found in terms of the development of autoantibodies in children aged 1 and 2.5 years among the patients who received 10 mcg (400 IU) vitamin D containing supplements in infancy. However, a decrease was detected in diabetes-related autoimmunity in one-year-old infants whose mothers used vitamin D supplements during pregnancy, with no correlation being observed at 2.5 years of age. The authors were unable to suggest any clear reason why a protective effect was seen at 1 year of age but not at 2.5 years. Granfors et al.[32] declared in their study, as the continued study of ABIS study, that maternal use of vitamin D containing multivitamin supplements during pregnancy was not associated with the risk of developing type 1 diabetes in children before 14-16 years of age in Southeast of Sweden. Hyppönen et al.'s[33] study from Northern Finland in 2001 also investigated the relationship between vitamin D and diabetes. A relationship between the frequency and dosage of vitamin D intake and progression of diabetes was recorded after follow-up of 30 years. The results of that study showed that the incidence of type 1 diabetes was lower in patients receiving vitamin D supplements, independently of dosage and with regular usage. There was no significant difference between the patients with type 1 diabetes whose mothers used vitamin D in pregnancy and the control group[33]. The EURODIAB Substudy 2 Study Group[34] investigated the relationship between vitamin D and diabetes, with the inclusion of 820 diabetic children and 2335 controls. The use of vitamin D during pregnancy and in the first year of life was evaluated. Patients were evaluated after 15-year follow-up. The risk of diabetes was found to decrease by 1/3 in children who received vitamin D during infancy, and the risk of type 1 diabetes was even lower among individuals whose mothers received vitamin D during pregnancy. In our study, the rates of use of vitamin D supplements during pregnancy and during the first year of life were similar between the patient and the control groups, showing that there was no effect on the development of diabetes. These findings were different from the findings mentioned previously but in accordance with the study performed by Thorsen et al.[35]. They completed their study with the suggestion that the role of 25-OHD levels in utero or in early childhood and the later risk for developing type 1 diabetes needed further investigation.

Study Limitations

The principal limitation of the study is that more patients are needed in order to evaluate the relationship between vitamin D and type 1 diabetes more exactly.

CONCLUSION

Vitamin D deficiency/insufficiency had no significant effects on the development of diabetes, or clinical status at presentation such as metabolic acidosis. Metabolic acidosis has no effect on vitamin D, Ca, P, ALP, or PTH levels. Vitamin D intake in infancy and pregnancy exhibited no protective effect against the progression of diabetes. Therefore, it does not seem possible to reach a definitive conclusion concerning the relationship between vitamin D and type 1 diabetes because of the high prevalence of vitamin D deficiency in general and also in diabetic children.

Presented in and Note: The oral presentation titled "The Evaluation of Vitamin D Status and Clinical Presentation Characteristics in Children Diagnosed with Type 1 Diabetes" related to this article was made on September 29-October 2, 2022 at the 2nd Eastern Pediatrics Congress in Diyarbakır. The study conducted in this article was carried out by 1st author as the Child Health and Diseases Speciality Thesis at Kocaeli University Faculty of Medicine with the title of "Vitamin D Status and Its Relationship with Clinical Presentation Characteristics in children with type 1 diabetes".

Ethics

Ethics Committee Approval: The study were approved by the Kocaeli University Faculty of Medicine of Local Ethics Committee [protocol number: 24.02.09-(5/17), date: 21.03.2011-(1/6)].

Informed Consent: Informed consent was obtained from children and their parents.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.M.M., Ş.H., Concept: A.M.M., Ş.H., Design: A.M.M., Ş.H., Data Collection or Processing: A.M.M.,

Analysis or Interpretation: A.M.M., Ş.H., Literature Search: A.M.M., Writing: A.M.M., Ş.H.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

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A Rare Case in Intensive Care Unit: Eagle Syndrome

Yoğun Bakımda Nadir Bir Olgu: Eagle Sendromu

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ABSTRACT

Eagle syndrome is the lengthening of the styloid process or calcifying of the stylohyoid and stylomandibular ligament. Although symptoms are non-specific, such as a sore throat and difficulty swallowing, severe conditions such as syncope may also be seen. This study presented a case of a 57-year-old patient diagnosed with Eagle syndrome while syncope etiology was being investigated, and the diagnosis and treatment processes of this uncommon syndrome were explained.

Keywords: Eagle syndrome, stiloid process, syncope

ÖZ

Eagle sendromu, stiloid proçesin uzaması veya stylohyoid ve stylomandibular ligamentin kalsifikasyonu olarak tanımlanır. Genellikle boğaz ağrısı, yutma güçlüğü gibi non-spesifik bulgulara sebep olsa da senkop gibi ciddi klinik durumlar görülebilir. Bu olgu sunumunda 57 yaşında senkop etiyolojisi araştırılırken yoğun bakımda Eagle sendromu tanısı konulan bir hasta ve nadir görülen bu sendromun tanı ve tedavi süreci anlatılmıştır.

Anahtar Kelimeler: Eagle sendromu, stiloid proçes, senkop

INTRODUCTION

Eagle's syndrome is a sporadic syndrome defined as the elongation of the styloid process (SP) or calcification of the stylohyoid and stylomandibular ligament. Its anatomical location facilitates the movement of the tongue, pharynx, larynx, hyoid bone, and mandible. In advanced cases, syncope with sudden head movements may occur. Some authors also call this syndrome styloid syndrome or styloid-carotid artery syndrome. The fact that it is a rare syndrome and the findings are non-specific makes it challenging to diagnose[1,2].

In this case report, we presented the patient who developed respiratory arrest while investigating the etiology of syncope and was followed and treated in the intensive care unit because he was diagnosed with eagle syndrome in the intensive care unit, and the follow-up treatment process is a rare condition.

CASE REPORT

A 57-year-old male patient was admitted to the intensive care unit as intubated due to respiratory arrest from the neurology service. In his anamnesis, it was learned that he had been diagnosed with diabetes mellitus and hypertension for about 5 years and regularly used the medical treatment for these conditions. He was admitted to the neurology clinic to investigate the etiology due to the complaints of a constricting headache extending from the neck to the skull base, lasting two to three times a day for about 1 year, tremors in the hands, and short-term fainting two or three times a week. It was learned that the patient, who had been admitted to the psychiatry ward for about 6 months before hospitalization and had been using quetiapine and sertraline for about 6 months in an external center, had short-term fainting complaints two or three times a week, and used levetiracetam 1000 mg/day with

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a preliminary diagnosis of epilepsy. Electroencephalography, brain computed tomography (CT), brain magnetic resonance, positron emission tomography-CT examinations of the patient, who was followed in the service for the etiology of syncope, were found to be normal. Myocardial perfusion scintigraphy revealed perfusion loss in the apicoseptal and inferolateral wall midventricular segment, and follow-up was recommended. After midazolam was administered to the patient, who had seizure-like activity during the follow-ups, after respiratory arrest and cardiac arrest developed, cardiopulmonary resuscitation was performed for 5 minutes, and the patient was intubated and transferred to the anesthesia intensive care unit. On physical examination, it was observed that the left carotid pulse was significantly weaker than the right one, and despite the sedation, the patient's neck was deviated to the left. Consciousness and motor examination could not be performed in the patient under sedation. In the carotid Doppler performed for carotid pulses, no abnormal flow was found bilaterally and bilateral currents were evaluated as normal. In the neck CT performed due to limitation of neck movements and deviation to the left, the right SP length was 36 mm (Figure 1), the left was 28 mm, and the patient was diagnosed with Eagle syndrome because of clinical symptoms. The operation was planned for the patient evaluated by the ear nose and throat clinic. Intraoperatively, under general anesthesia, the long styloid segment was excised using the intraoral approach after tonsillectomy. The patient, who was taken to the postoperative intensive care unit, was extubated on the same day and transferred to the service on the 4th postoperative day without any problems. Informed consent was obtained from the patient.

DISCUSSION

Eagle[3] describes Eagle syndrome in 1937. The SP is 25-30 mm long, located antero-inferiorly at the lowest part of the temporal bone. Anatomically, the SP is located between the internal and external carotid arteries and lateral to the tonsillar fossa. Generally, patients are older than 30 years[4]. Its etiology is not fully known. However, there are many hypotheses[3]. Lengths over 30 mm are defined as a long process, and it is reported that an elongated SP is seen in 4% of the general population. It has been reported that only 4-5% of these cases are symptomatic.

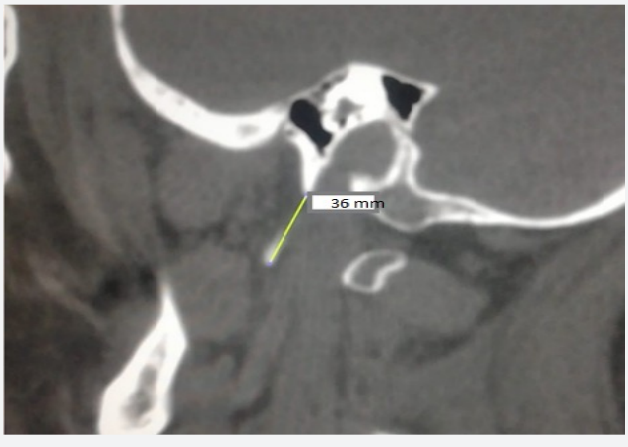

Figure 1. Right styloid process

Although the symptoms are usually mild, diagnosing severe conditions such as syncope and Eagle syndrome should be considered in the differential diagnosis. The important thing is whether these patients are symptomatic[5]. Clinically, it has been reported that it is most common in the third or fourth decade and is more common in women. Contrary to these, our case was a 57-year-old male patient. Clinically, non-specific findings such as pain localized in the tonsillar fossa, foreign body sensation in the pharynx, dysphagia, painful swallowing, otalgia, headache, facial pain, and tinnitus may be seen.

In some cases, more severe clinical findings may occur due to the compression of the carotid artery by the SP. These findings may include pain along the carotid artery distribution while turning the head or more clinical severe conditions such as a transient ischemic attack, vertigo, or syncope, as in our patient[6]. Since these findings can be confused with the clinic of many diseases, it may lead to misdiagnosis and wrong medication. Our patient had been using antipsychotic and antiepileptic therapy for months. Since the symptoms are severe during sudden neck movements, patients may try to avoid sudden movements and reduce styloid compression. In our patient, the neck deviated to the left, and the patient was probably trying to reduce the pressure in this position to reduce the proper process compression.

In some cases, it is stated that Eagle syndrome occurs after a tonsillectomy operation or trauma. However, these reasons were not present in our patient. An essential thing in this syndrome, which has no specific signs, symptoms, or imaging method in its diagnosis, is suspicion among conventional radiographs, panoramic radiography, and CT imaging methods. CT is a valuable diagnostic tool for evaluating the region's anatomy and making a surgical plan[7]. In our case, SPs were identified on neck CT, and their exact lengths could be measured.

Treatment can be managed conservatively or surgically[8]. Analgesics, antidepressant drugs, anticonvulsants, non-steroidal anti-inflammatory drugs, steroids, and lidocaine transpharyngeal injections are used as conservative treatments today. However, the most effective treatment is the surgical shortening of the SP. An intraoral or extraoral approach can be performed surgically. The intraoral approach was used in our patient. The advantages of this approach are that it is relatively simple, has a short operation time, and can be

performed without scarring. On the other hand, the extraoral approach ensures that the surgery is performed with a better command of the surgical field and that all structures are more visible. However, it takes too much time, and the risk of injury to the facial nerves or branches, visible scarring, and a lengthy recovery period have led us to prefer the intraoral technique[9].

CONCLUSION

As a result, serious complications that can cause mortality and morbidity can be seen in this rare disease, which has non-specific findings. The diagnosis of the disease can be made after suspicion. Early diagnosis is essential in preventing severe life-threatening complications by starting treatment early and preventing unnecessary medications by making other diagnoses to the patient.

Ethics

Informed Consent: Consent form was filled out by a participant.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.E.S., Concept: A.K., Design: H.Ö.O., A.K., Data Collection or Processing: E.S.Ö., Analysis or Interpretation: P.K., A.K., Literature Search: P.K., A.K., Writing: A.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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ERRATUM

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Tacar SY, Yılmaz M, Gültürk İ, Tural D. Prosnostic Significance of Prognostic Nutrition Index in Metastatic Renal Cell Carcinoma Patients Treated with Tyrosine Kinase Inhibitors. Nam Kem Med J. 2022;10:228-34.

The mistake has been made inadvertently by the author.

The title English on page 228 of the related article has been corrected by the author as below.

The incorrect English title

Prosnostic Significance of Prognostic Nutrition Index in Metastatic Renal Cell Carcinoma Patients Treated with Tyrosine Kinase Inhibitors

The corrected English title

Prognostic Significance of Prognostic Nutrition Index in Metastatic Renal Cell Carcinoma Patients Treated with Tyrosine Kinase Inhibitors

2022 Referee Index

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2022 Author Index

2022 Author Index

2022 Author Index

2022 Subject Index

2022 Subject Index

2022 Subject Index