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Research

The Seroprevalence Trend of *Helicobacter pylori* Infection in a Turkish Tertiary Hospital: A 4-year Retrospective Study

Türkiye'de Bir Üniversite Hastanesinde *Helicobacter pylori* Enfeksiyonu Prevalans Eğilimi: 4 Yıllık Retrospektif Bir Çalışma

Fatih Çubuk, Ayşe Hümeyra Taşkın Kafa, Mürşit Hasbek, Rukiye Aslan, Cem Çelik

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ABSTRACT

Objective: *Helicobacter pylori* (*H. pylori*) is a Gram-negative microaerophilic bacterium that is associated with diseases such as peptic ulcer, chronic gastritis, gastric MALT lymphoma, and gastric cancer. *H. pylori* infection is more common in developing countries. The high socioeconomic conditions and elimination of bacterial carriage by antimicrobial treatment reduce the prevalence of *H. pylori* in developed countries. The fecal *H. pylori* antigen test has been widely used recently. This test with high sensitivity and specificity constitutes a significant diagnostic method alternative due to its cost-effectiveness and rapid results. In this study, we retrospectively analyzed the presence of *H. pylori* antigen in the stool samples of patients with gastroduodenal complaints from laboratory records.

Methods: Test results of patients who underwent *H. pylori* antigen rapid cassette test from fresh fecal samples between January 2018 and May 2022 in the Medical Microbiology Laboratory were included in the study. Fresh fecal samples from patients were analyzed using *H. pylori* Antigen Rapid Test Cassette (Acro Biotech Inc, USA) kits. The statistical analysis of the research was made with IBM-SPSS 25.0 (IBM Co., USA). The chi-square test was used to evaluate the research data. P<0.05 value was considered statistically significant.

Results: A total of 5,718 patients, 3,285 (57.5%) women with gastroduodenal complaints, were included in the study. Fecal *H. pylori* antigen test positivity was determined in 1,429 (25%) of these patients. The antigen positivity rate was found to be higher in women (26.6%) compared to men (22.9%) (p<0.05). In addition, this rate was higher in adult patients (27.4%) than in pediatric patients (10.1%). In addition, this rate was higher in adult patients (27.4%) compared with pediatric patients (10.1%) (p<0.01).

Conclusion: The regional prevalence data are informative about the development levels of countries in socioeconomic issues such as urbanization, infrastructure services, and access to clean water. In addition, these data may provide insight into the future prevalence of *H. pylori*-related diseases. We think that this study, in which the data of our region is shared, contributes to the literature.

Keywords: Antigen, *Helicobacter pylori*, seroprevalence, stool

ÖZ

Amaç: *Helicobacter pylori* (*H. pylori*), peptik ülser, kronik gastrit, mide MALT lenfoması ve mide kanseri ile ilişkilendirilen Gram-negatif mikroaerofilik bir bakteridir. *H. pylori* enfeksiyonu gelişmekte olan ülkelerde daha yaygın olup, gelişmiş ülkelerde iyi sosyoekonomik koşullar ve antimikrobiyal tedavi yoluyla taşıyıcılığın ortadan kaldırılması *H. pylori* prevalansını azaltmaktadır. Dışkıda *H. pylori* antijeni testi son dönemde yaygın olarak kullanılmaktadır. Yüksek duyarlılığa ve özgüllüğe sahip bu test, uygun maliyetli olması ve hızlı sonuç vermesi nedeniyle önemli bir tanı alternatifi oluşturmaktadır. Bu çalışmada, gastroduodenal şikayetleri bulunan hastaların dışkı örneklerinde *H. pylori* antijen varlığının laboratuvar kayıtlarından retrospektif olarak analiz edilmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya Ocak 2018-Mayıs 2022 tarihlerinde Tıbbi Mikrobiyoloji Laboratuvarı'nda taze dışkı örneğinden *H. pylori* antijen hızlı kaset testi çalışılan hastalara ait test sonuçları dahil edilmiştir. Hastalardan alınan taze dışkı örnekleri *H. pylori* Antigen Rapid Test Cassette (Acro Biotech Inc, ABD) kitleri kullanılarak incelenmiştir. Araştırmanın istatistiksel analizi IBM-SPSS 25.0 (IBM Co., ABD) programı ile yapılmıştır. Verilerin değerlendirmesinde ki-kare testi kullanılmış ve p<0,05 istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular: Çalışmaya gastroduodenal şikayetleri bulunan 3.285 (%57,5) kadın olmak üzere toplam 5.718 hasta dahil edilmiştir. Bu hastaların 1.429'unda (%25) dışkıda *H. pylori* antijen testi pozitifliği belirlenmiştir. Antijen pozitiflik oranı kadınlarda (%26,6) erkeklere (%22,9) göre daha

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yüksek tespit edilmiştir (p<0,05). Ayrıca, bu oran yetişkin hasta grubunda (%27,4) çocuklara (%10,1) kıyasla daha yüksek bulunmuştur (p<0,01).

Sonuç: Bölgesel prevalans verileri ülkelerin kentleşme, alt yapı hizmetleri ve temiz su erişimi gibi sosyoekonomik konulardaki gelişmişlikleri hakkında bilgi verici özelliktedir. Ayrıca, bu veriler *H. pylori* ile ilişkili hastalıkların gelecekteki prevalansı üzerine öngörü sağlayıcı olabilir. Bölgemize ait verilerin paylaşıldığı çalışmamızın literatüre katkı verici özellikte olduğunu düşünmekteyiz.

Anahtar Kelimeler: Antijen, *Helicobacter pylori*, seroprevalans, gayta

INTRODUCTION

Helicobacter pylori (H. pylori) is a Gram-negative, spiral-shaped, microaerophilic bacterium that is widely distributed all over the world (1). This bacterium is an important pathogen associated with diseases such as peptic ulcers, chronic gastritis, gastric MALT lymphoma, and gastric cancer. For treating diseases caused by *H. pylori*, long-term and intensive use of antibiotics is necessary. Colonization formed by the bacteria is mostly asymptomatic, but these people are in the risk group rega rding gastric diseases (2). Approximately 1% of people infected with *H. pylori* develop gastric cancer (3). Although it remains unclear how the infection is transmitted, it is thought that it can be transmitted in different ways such as fecal-oral, oral-oral, or gastro-oral (4).

Age, race, rural life, population density, socioeconomic status, poor health conditions, low education level, malnutrition, and insufficient water resources are important risk factors for the transmission of *H. pylori* (4,5). In consideration of all these factors, it can be stated that the disease is more common in developing countries. In developed countries, adequate socioeconomic conditions, effective hygiene and sanitation, and elimination of disease carriers with antimicrobial therapy reduce the prevalence of *H. pylori* (4,5).

Invasive and non-invasive techniques can be used for the diagnosis of *H. pylori* infection. Invasive methods such as immunohistochemistry tests, rapid urease tests, culture methods, and polymerase chain reaction require endoscopy, and these tests are known as biopsy method-based tests. Non-invasive methods include the gaita-antigen test, urea breath test, and ELISA *H. pylori*-IgG antibody tests. The sensitivity, specificity, and the cost of the test and clinical conditions are among the main factors affecting test selection (4,6,7).

H. pylori antigen search tests in feces have been widely used recently. It is stated that these tests using monoclonal anti-*H. pylori* antibodies have high sensitivity and specificity. It has been reported that these tests are useful for planning appropriate treatment methods because they are an alternative to invasive methods, cost-effective, and give rapid results (8).

This study retrospectively analyzed the presence of *H. pylori* antigen in the fecal samples of patients who applied to Sivas Cumhuriyet University Medical Faculty Practice and Research Hospital between January 2018-May 2022 with gastroduodenal complaints.

METHODS

This study, carried out at Sivas Cumhuriyet University Medical Faculty Hospital, was planned retrospectively to cover January 2018-May 2022 dates. The laboratory test results of patients who had gastroduodenal complaints and whose *H. pylori*-antigen rapid test cassette kit were studied from fresh feces samples in the medical microbiology laboratory within the specified time were included in the study.

Fresh feces samples from patients were analyzed using *H. pylori*-Antigen Rapid Test Cassette (Acro Biotech Inc, USA) kits, a qualitative chromatographic immunoassay test. According to the producer company bulletin, the sensitivity of the test kits using monoclonal anti-*H. pylori* antibodies is 99.9% and the specificity is 98.4%.

All tests were studied based on the guides of the producer company. The fecal samples were transferred to sample collection tubes containing the extraction buffer and homogenized. Two drops of this mixture were taken and dropped into the sample well in the test cassette. After waiting for 10 minutes, the formed bands were evaluated according to company guide. The formation of a colored line in the control (C) region of the test strips indicates that the test was performed following the guideline and the test result is valid. Only the formation of a colored line in the C region is interpreted as a negative result. A colored line in both the C region and the test (T) region is interpreted as a positive result.

Statistical Analysis

The statistical analysis of the research was made with IBM-SPSS 25.0 (IBM Co., USA). The numerical variables are given as frequencies (percentages). Chi-square test was used to evaluate the data. A value of $p<0.05$ was considered significant statistically.

This study was conducted with the approval of the Sivas Cumhuriyet University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (decision no: 2022-06/14, date: 22.06.2022).

RESULTS

The 5,718 patients [3,285 patients were females (57.5%) and 2,433 were males (42.5%)] with gastroduodenal complaints were included in the study. The ages of the patients ranged from 0 to 96. The 791 patients (13.8%) were in the child age group and 4,927 patients (86.2%) were in the adult age group. When the ranges of laboratory tests by years were examined, it was determined that the maximum number of laboratory tests was made in 2021 (33.4%). The ranges of the patients according to age, gender and laboratory test dates are given in Table 1.

H. pylori antigen positivity was determined in fecal samples of 1,429 patients (25%) included in the study. The antigen positivity rate was determined as 26.6% in women and 22.9% in men. This difference between men and women was considered statistically significant ($p<0.05$) (Table 1).

Antigen positivity in feces was detected in 80 persons (10.1%) of the pediatric patients (0-18 age) included in the study. Antigen positivity in feces was detected in 1,349 persons (27.4%) of the adult patients (≥19) included in the study (Figure 1).

Table 1. Demographic data of the patients

	Positive samples (%)	Number of tests (%)
Gender		
Woman	873 (26.6)	3285 (57.5)
Man	556 (22.9)	2433 (42.5)
Age (range)		
0-9	28 (6.1)	459 (8)
10-18	52 (15.7)	332 (5.8)
19-29	275 (25)	1099 (19.2)
30-39	290 (31.1)	931 (16.3)
40-49	269 (28.3)	952 (16.7)
50-59	263 (29.2)	901 (15.8)
60-69	172 (26.1)	659 (11.5)
>70	80 (20.8)	385 (6.7)
Test order date		
2018	216 (18.6)	1163 (20.3)
2019	393 (29.8)	1320 (23.1)
2020	257 (25.2)	1020 (17.8)
2021	488 (25.6)	1907 (33.4)
2022	75 (24.4)	308 (5.4)
Total	1429 (25)	5718 (100)

The *H. pylori* antigen positivity rate was found to be statistically significantly higher compared to the adult age group and the pediatric age group ($p<0.01$).

In this study, the range of *H. pylori* antigen positivity rates in age groups was also examined. It was determined that the fecal *H. pylori* antigen test was mostly performed in patients aged 19-29 years and 40-49 years old (Table 1). It has been determined that patients in the 30-39 age group have a higher *H. pylori* antigen positivity rate compared to patients in other age groups (Figure 2).

DISCUSSION

H. pylori continues to be a significant public health problem because it causes diseases such as peptic ulcers, chronic gastritis, and gastric cancer (9,10). It is thought that more than 50% of people worldwide are infected with *H. pylori*. However, the prevalence of *H. pylori* varies due to regional differences worldwide. While the prevalence of *H. pylori* is 25-40% in industrialized and developed countries, it is reported to be 60-85% in developing countries (9,10).

There are data in the literature indicating that the prevalence of *H. pylori* tends to decrease in different regions of the

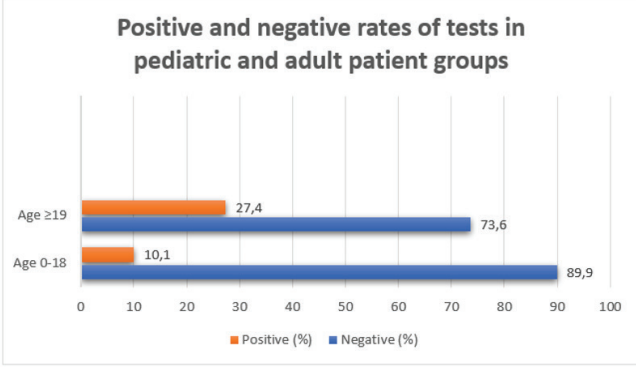

Figure 1. Positive and negative rates of tests in pediatric and adult patient groups

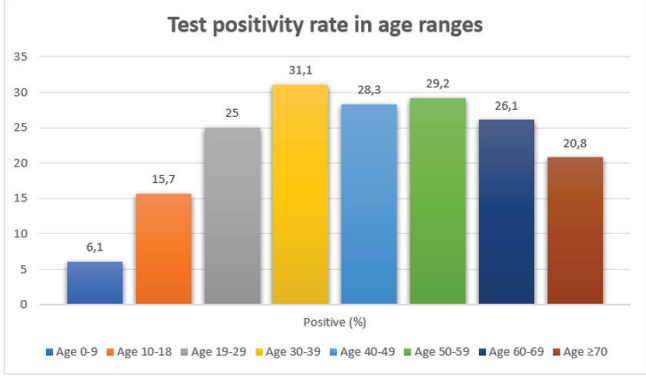

Figure 2. Test positivity rates by age range

world compared to the past (9-11). It has been stated that the prevalence of *H. pylori* is low, especially in children and young people in developed countries (10,12). However, it is argued that for developing countries, a similar assessment is not yet possible. In addition, the uncontrolled population growth and immigrant problem caused by socioeconomic reasons may negatively affect regional prevalence data (9,12).

Regional prevalence data can be informative about the development levels of countries in socioeconomic issues such as urbanization, infrastructure services, and access to clean water compared to the past. In addition, these data may offer implications for the future prevalence of *H. pylori*-related diseases, such as peptic ulcers, especially gastric cancer, and chronic gastritis (9).

A meta-analysis was recently published, presenting data from 412 studies in China (13). In this study, the prevalence of Chinese *H. pylori* was determined to be 44.2%. However, the authors noted that the prevalence of *H. pylori* in China, which has wide geography, shows regional variations. In this study, it was reported that a higher prevalence of *H. pylori* was observed in adults (46.1%) compared with children (28%). In addition, the prevalence level in women (42%) was lower than in men (44.9%). In this study, in which the data of the last 40 years of the country were examined, it was determined that there was a significant decrease in the prevalence of *H. pylori*, especially in the last 10 years. The researchers stated that this is related to their country's socioeconomic developments such as infrastructure services, health services, and an increase in quality of life.

Alsulaimany et al. (14) published a review aiming to determine the prevalence of *H. pylori* in the Middle East and North African countries in 2020. In this study, high prevalence rates of 7-50% in children and 40-90% in adults were reported in countries such as Egypt, Iran, Israel, Lebanon, Libya, Saudi Arabia and Tunisia. The researchers reported that they did not detect a significant difference in terms of the gender variant in the prevalence of *H. pylori*, except a few studies (14). Lower prevalence rates have been reported in regions with advanced infrastructure and high socioeconomic status, such as Oceania (24%), Western Europe (34%), and North America (37%) (9).

In recent studies in Türkiye, the prevalence of *H. pylori* was found to be between 11 and 65% (15-21). It was determined that the prevalence range in these studies varied in terms of the age group variable. Lower prevalence rates have been reported in children and individuals over the age of 65. It has also been reported that there has been a recent decrease in *H. pylori* prevalence rates compared with previous years in Türkiye. In our study, similar to other studies conducted in Türkiye, *H. pylori* antigen test positivity in feces was found to be 25%. This rate was determined as 10.1% for children and 27.4% for adults ($p<0.01$).

In many studies conducted in our country, it has been determined that the prevalence of *H. pylori* does not make a significant difference in terms of gender (16-21). However, Maçin et al. (15) found a higher rate of antigen positivity in women compared to men in their study. Similarly, Alim et al. (22) reported a higher prevalence rate in women in their study in our province. In our study, similar to the results of this study, a higher *H. pylori* antigen positivity was found in female patients (26.6%) than in male patients (22.9%) ($p<0.05$).

A prevalence study was conducted in our province in 2004 involving 620 adult patients aged 28-69 years. In this study, the presence of *H. pylori* IgG-antibody in serum samples of patients was investigated by the ELISA method. The antibody test was positive in 70.1% of the patients (22). When these results are compared with the results of our study in which we present the data of our region, we can be stated that the prevalence of *H. pylori* has decreased compared with previous years. This situation can be evaluated as an indicator of socioeconomic developments such as the improvement of infrastructure services in our province, access to clean water, access to qualified health services, increase in education level, and increase in quality of life. Another reason for determination of positivity rates at different amounts can be said to be the difference in the methods used. A rapid cassette test based on the chromatographic immunoassay method was used in this study. Antigen search tests in feces, which have become more common recently, are among the non-invasive techniques that can be used in the diagnosis of *H. pylori* infection. These tests, which are an alternative to invasive methods, are advantageous because of their cost-effectiveness and rapid results. On the other hand, the feces antigen test and ^{13}C-urea breath tests have higher sensitivity and specificity compared to the *H. pylori* IgG antibody test (23,24). It is also reported in the literature that the feces-antigen tests are useful for epidemiological studies and screening, are affordable in terms of cost and equipment, and give reliable results, which were used methodologically in this study too (24). In addition, there is currently no technique accepted as the gold standard for the diagnosis of *H. pylori*.

CONCLUSION

Regional prevalence data provide information on socioeconomic issues such as the city's infrastructure

services, access to clean water, health services, education level of people, and quality of life. Regular testing and presentation of the prevalence of *H. pylori* in Türkiye will contribute to the development of screening and diagnostic approaches for *H. pylori*. We think that this study, in which the data of our region is shared, is significant at this point.

ETHICS

Ethics Committee Approval: This study was conducted with the approval of the Sivas Cumhuriyet University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (decision no: 2022-06/14, date: 22.06.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: F.Ç., M.H., Design: F.Ç., A.H.T.K., M.H., C.Ç., Data Collection or Processing: F.Ç., A.H.T.K., M.H., C.Ç., Analysis or Interpretation: F.Ç., A.H.T.K., Literature Search: F.Ç., A.H.T.K., R.A., Writing: F.Ç., A.H.T.K., R.A.

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

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REFERENCES

1. Robinson K, Atherton JC. The Spectrum of Helicobacter-Mediated Diseases. Annu Rev Pathol 2021;16:123-44.
2. Yamamoto Y, Fujisaki J, Omae M, Hirasawa T, Igarashi M. Helicobacter pylori-negative gastric cancer: characteristics and endoscopic findings. Dig Endosc 2015;27:551-61.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424. Erratum in: CA Cancer J Clin 2020;70:313.
4. Sabbagh P, Mohammadnia-Afrouzi M, Javanian M, Babazadeh A, Koppolu V, Vasigala VR, et al. Diagnostic methods for Helicobacter pylori infection: ideals, options, and limitations. Eur J Clin Microbiol Infect Dis 2019;38:55-66.
5. Omosor KI, Omosor OH, Ibeh IN, Adejumo BIG, Abdulkadir UI, Dimkpa U, et al. Seroprevalence of Helicobacter pylori Infection and Risk Factors among Asymptomatic Subjects in Delta State, Nigeria. Advances in Microbiology 2017;7:641-52.
6. Khalifehgholi M, Shamsipour F, Ajhdarkosh H, Ebrahimi Daryani N, Pourmand MR, Hosseini M, et al. Comparison of five diagnostic methods for Helicobacter pylori. Iran J Microbiol 2013;5:396-401.
7. Peng NJ, Lai KH, Lo GH, Hsu PI. Comparison of noninvasive diagnostic tests for Helicobacter pylori infection. Med Princ Pract 2009;18:57-61.
8. Gisbert JP, de la Morena F, Abraira V. Accuracy of monoclonal stool antigen test for the diagnosis of H. pylori infection: a systematic review and meta-analysis. Am J Gastroenterol 2006;101:1921-30. Erratum in: Am J Gastroenterol 2006;101:2445.
9. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, et al. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. Gastroenterology 2017;153:420-9.
10. Eusebi LH, Zagari RM, Bazzoli F. Epidemiology of Helicobacter pylori infection. Helicobacter 2014;19 Suppl 1:1-5.
11. Leja M, Grinberga-Derica I, Bilgilier C, Steininger C. Review: Epidemiology of Helicobacter pylori infection. Helicobacter 2019;24 Suppl 1:e12635.
12. Burucoa C, Axon A. Epidemiology of Helicobacter pylori infection. Helicobacter 2017;22 Suppl 1.
13. Ren S, Cai P, Liu Y, Wang T, Zhang Y, Li Q, et al. Prevalence of Helicobacter pylori infection in China: A systematic review and meta-analysis. J Gastroenterol Hepatol 2022;37:464-70.
14. Alsulaimany FAS, Awan ZA, Almohamady AM, Koumu MI, Yaghmoor BE, Elhady SS, et al. Prevalence of Helicobacter pylori Infection and Diagnostic Methods in the Middle East and North Africa Region. Medicina (Kaunas) 2020;56:169.
15. Maçin S, Çiftçi N, Başer S. Prevelance of helicobacter pylori infection, in a Turkish tertiary hospital. Genel Tıp Derg 2021;31:45-9.
16. Sarp TZ, Dinç H, Özbey D, Akkuş S, Aslan B, Cihan M, et al. Retrospective Evaluation of Helicobacter pylori Antigen Positivity in the Stool Samples of Patients with Gastroduodenal Complaints. Turk Mikrobiyol Cemiy Derg 2021;51:61-9.
17. Sakman A, Bayram Y, Parlak M, Güdücüoğlu H. The Frequency of Helicobacter pylori in Patients Admitted to Family Health Center. TJFMPC 2021;15:418-23.
18. Okullu SÖ, Işık OC, Kocagöz AS, Akyar I. Detection of H. pylori in Pediatric Patients' Stool Sample by Multiplex Urease PCR. Acıbadem Univ Sağlık Bilim Derg 2022;13:16-20.
19. Kosekli, M. Helicobacter pylori prevalence associated with the family population? Exp Biomed Res 2022;5:217-24.
20. Turan G, Altun E. Helicobacter pylori frequency in endoscopic biopsies containing gastrit response in the Balıkesir region. Balıkesır Medıcal Journal 2017;1:17-21.
21. Çiftel S, Okçu N, Dursun H, Albayrak F, Usta S. Bölgemizde Helicobacter pylori sıklığı. Akademik Gastroenteroloji Dergisi 2016;15:1-4.
22. Alim A, Ataş AD, Güneş T, Ataş M, Yıldırım M, Öztekin A, Yıldızbaş H. Sivas ili merkezinde semptomatik ve asemptomatik yetişkin bireylerde Helicobacter pylori seroprevalansı. CÜ Tıp Fak Derg 2004;26:75-80.
23. Atkinson NS, Braden B. Helicobacter Pylori Infection: Diagnostic Strategies in Primary Diagnosis and After Therapy. Dig Dis Sci 2016;61:19-24.
24. Wang YK, Kuo FC, Liu CJ, Wu MC, Shih HY, Wang SS, et al. Diagnosis of Helicobacter pylori infection: Current options and developments. World J Gastroenterol 2015;21:11221-35.

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Research

The Coexistence of Early Repolarization and Atrioventricular Nodal Reentrant Tachycardia: A Case Control Study

Erken Repolarizasyon ve Atriyoventriküler Nodal Reentrant Taşikardinin Birlikte Bulunması: Bir Olgu Kontrol Çalışması

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ABSTRACT

Objective: It has been reported that early repolarization (ER) abnormalities, which have been considered benign for many years, may be associated with many cardiac arrhythmias both malign and benign in the recent period. In our study, we investigated that may be coexisting the atrioventricular nodal reentrant tachycardia (AVNRT), which the most common in paroxysmal tachycardias, with ER abnormalities.

Methods: Our study was designed as a single-centered retrospective descriptive study. The study enrolled 53 patients who underwent ablation due to AVNRT and 50 control group patients. Demographic, clinical, and laboratory data of patients were retrieved from our database. ER, the diagnosis and types of the pattern were determined based on the consensus report published by in 2015. Electrocardiographic measurements were performed semi-automatically by EP caliper application.

Results: Of the patients enrolled in the study, 34 (64.2%) in the AVNRT group and 31 (62%) in the control group were female. The mean age was 47.11±12.79 years in the AVNRT group and the mean age was 44.88±13.02 years in the control group. Although the presence of an ER pattern was numerically higher in the AVNRT group compared with the control group, this difference was not statistically significant. A comparison was made between subgroups, and the slurring with ST elevation type of ER pattern was significantly higher in men [7 people (58.3%) in males 0 in female, p<0.001], the slurring without the ST elevation type of ER pattern was significantly higher [15 people (93.8%) in females and 5 people (41.7%) in males, p<0.002].

Conclusion: In our study, we determined that the pattern of early repolarization, especially the slurring type, was more frequent in patients with AVNRT; however, but this difference was not statistically significant. Additionally, we found that the slurring with ST elevation type of ER is significantly more common in males, whereas the slurring without the ST elevation type of ER is significantly more common in females.

Keywords: Atrioventricular nodal reentrant tachycardia (AVNRT), early repolarization, radiofrequency ablation

ÖZ

Amaç: Uzun yıllar boyunca iyi huylu olarak kabul edilen erken repolarizasyon (ER) bozukluklarının, son dönemde gerek ölümcül gerekse iyi seyirli birçok kardiyak aritmi ile ilişkili olabileceği bildirilmektedir. Biz bu çalışmamızda ER paternleri ile en sık görülen paroksizmal taşikardi olan atriyoventriküler nodal reentran taşikardi (AVNRT) arasındaki ilişkiyi inceledik.

Gereç ve Yöntem: Çalışmamız tek merkezli retrospektif tanımlayıcı çalışma olarak dizayn edildi. Çalışmaya AVNRT tanısı ile ablasyon işlemi yapılan 53 hasta ile 50 kontrol grubu hastası dahil edildi. Hastaların demografik klinik laboratuvar verileri geriye dönük olarak sistemden elde edildi. ER paterni tanısı ve tipleri 2015 yılında tarafından yayınlanan konsensus raporu baz alınarak belirlendi. Elektrokardiyografik ölçümler EP kalipers uygulaması ile yarı otomatik olarak gerçekleştirildi.

Bulgular: Çalışmaya alınan hastaların AVNRT grubunda 34'ü (%64,2), kontrol grubunda 31'i (%62) kadındı. AVNRT grubunda yaş ortalaması 47,11±12,79 yıl, kontrol grubunda yaş ortalaması 44,88±13,02 yıl idi. ER patern varlığı AVNRT grubunda kontrol grubuna kıyasla sayısal olarak fazla olsa da bu fark istatistiksel olarak anlamlı değildi. Alt gruplar arasında karşılaştırma yapıldığına ise ST yükselmeli slurring tip ER paterni

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erkeklerde [7 kişi (%58,3) erkeklerde, kadınlarda 0, p<0,001), ST yükselmesiz slurring tip ER paterni kadınlarda anlamlı olarak daha yüksek saptandı [kadınlarda 15 kişi (%93,8), erkeklerde 5 kişi (%41,7) p<0.002].

Sonuç: Çalışmamızda AVNRT'li hastalarda ER paterninin, özellikle slurring tipinin daha sık olduğunu belirledik, fakat bu fark istatistiksel olarak anlamlı değildi. Ayrıca, ER'nin ST yükselmeli slurring tipi erkeklerde anlamlı olarak daha yaygın olduğunu, ST yükselmesiz slurring'in kadınlarda anlamlı olarak daha yaygın olduğunu saptadık.

Anahtar Kelimeler: Atriyoventriküler nodal reentrant taşikardi (AVNRT), erken repolarizasyon, radyofrekans ablasyonu

INTRODUCTION

The term early repolarization (ER) is often used to describe morphological changes called notch or slurring, where the end of the QRS junction the ST segment (with or without ST elevation) and its prevalence is reported from 2% to 31% (1). Previously, ER was mostly considered a benign electrocardiographic sign. In 2008, Haïssaguerre et al. (2) published their study, in which they reported that there may be a relationship between ER and idiopathic ventricular fibrillation. In subsequent studies, it has been reported that there is a relationship between ER and both atrial tachycardias and arrhythmic death (3,4). Furthermore, similarities in responses to physiological changes and pharmacological agents between Brugada syndrome (BrS) and ER have been demonstrated (5).

Atrioventricular nodal reentrant tachycardia (AVNRT) is a regular supraventricular tachycardia caused by dual pathways (usually slow/fast) within the atrioventricular node and in occasionally the peripheral atrial tissue. It has been reported by the study published by Hasdemir et al. (6) that BrS, which has close similarities with ER, may have co-existence with AVNRT. In our study, we investigated the relationship between the morphological changes (the ER patterns) observed in the junction region (J point) between complete depolarization and repolarization of the action potential curve with AVNRT.

METHODS

The present study was conducted as a single-centered retrospective and descriptive study. Seventy six patients who were underwent ablation therapy due to AVNRT in the electrophysiology laboratory of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Hospital between 2019-2022 were included in the current study. All AVNRT patients underwent successful ablation after the diagnosis was confirmed with differential maneuvers. Of these 76 patients, 12 patients had fascicular block, branch block, or fragmented QRS on basal electrocardiogram, 2 patients had ejection fraction below 50%, 2 patients had left ventricular hypertrophy, 2 patients had frequent ventricular extra beats after the procedure and were excluded from the study. The data of the remaining 53 patients without uncontrolled hypertension, chronic kidney disease, or stenosis of any coronary artery above 50%, which are our other criteria for exclusion, were analyzed and these patients were determined as the AVNRT group. Fifty healthy volunteers, who were similar to the AVNRT group in terms of their demographic and clinical characteristics and did not have any arrhythmic complaints, were identified as a control group.

ER morphologies were defined based on a consensus report published by Macfarlane et al. (7) in 2015. Accordingly, if there was a positive deflection of at least 0.1 mV above the isoelectric line after the onset of the J point, it was defined as a notch, if there was an angulation of more than 10% in the last half of the descent of the R wave, it was defined as slurring. If there is at least 0.1 mV ST segment above the isoelectric line after 100 ms from the beginning of the J point, was defined as the ST elevation (excluding leads V1 to V3).

This study was approved by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2022-16-06, date: 15.08.2022) and conducted in accordance with the principles of the Helsinki Declaration. Written informed consent was obtained from all the participants.

Statistical Analysis

Demographic characteristics of patients and collected data were entered into IBM® SPSS® (the Statistical Package for the Social Sciences) Statistics version 23. Variables were characterized using mean and percentage values were used for qualitative variables. Categorical variables were expressed using frequency and percentage, and numerical variables expressed using mean ± standard deviation. The normality of the distribution of quantitative variables was evaluated using the Kolmogorov-Smirnov test. To compare the two independent groups, the Student t-test for parametric numerical variables and the Mann-Whitney U test for nonparametric variables were used. Categorical variables were compared with the Pearson chi-square test. Statistical significance was considered $p<0.05$.

RESULTS

The mean age of the 103 patients included in the study was 47.11±12.79 years in the AVNRT group and the mean age of the control group was 44.88±13.02 years. There were 34 (64.2%) female individuals in the AVNRT group and 31 (62%) female individuals in the control group. No statistically significant difference was found between the two groups in terms of demographic, clinical, echocardiographic, and laboratory parameters (Table 1).

A comparison between both genders in terms of ER and its subtypes is shown in Table 2. Of the 65 female individuals included in the study, 16 (24.6%) and 12 (31.6%) of the 38 male individuals had any type of ER morphological changing; however, this difference between both genders was not statistically significant (p=0.495). When the subgroup analysis of the detected ER types was performed, it was found that slurring with ST elevation was statistically significantly higher in males than in females (p<0.001). The slurring without ST elevation type ER was determined to be significantly higher in female individuals compared with male individuals (p=0.002). Individuals were divided into two groups by accepting the cut-off value of 40 years, and no significant difference was found between the two groups in terms of the presence of ER and its subtypes (Table 3).

While 16 (30%) patients in the AVNRT group had any type of change in ER morphology, 12 (24%) individuals in the control group had any type of change in ER morphology. Although ER patterns were numerically more frequent in the AVNRT group compared with the control group, this difference was not statistically significant (p=0.480). Notch -type ER was observed in only 1 patient in the AVNRT group. All types of ER -detected individuals in the control group was the slurring type ER. ER with ST elevation was determined in 3 patients in the AVNRT group and in 4 volunteers in the control group. There was no significant difference the ER patterns with ST elevation between the groups. In Table 4, the AVNRT and control groups were compared in terms of electrocardiographic characteristics.

Additionally, no morphological changes were observed in the ER patterns after the procedure compared to before the procedure in patients who underwent successful ablation due to AVNRT.

DISCUSSION

After the studies published by Tikkanen et al. (3,8) showing an increased frequency of cardiac arrhythmias with ER patterns, the idea has arisen that ER patterns, contrary to popular belief, may not be innocent. In addition to their clinical importance, there is still no complete consensus on the terminology and definition of ER patterns. This study aimed to investigate the coexistence of AVNRT, the most

Table 1. Comparison of demographic, echocardiographic and laboratory parameters of the AVNRT group and the control group

	AVNRT group (n=53)	Control group (n=50)	p-value
Age	47.11±12.79	44.88±13.02	0.382
Sex (female, %)	34 (64.2%)	31 (62%)	0.821
HT	6 (11.3)	6 (12)	0.914
DM	2 (3.8)	2 (4.1)	0.936
CAD	1 (1.9)	1 (2.1)	0.944
EF	58.7 (60-60)	61.1 (60-60)	0.918
IVS	9.2 (10-10)	8.7	0.843
PW	8.6 (10-10)	8.4	0.952
LA	36 (35-37)	35 (34-37)	0.256
Na	138 (137-141)	139 (138-140)	0.441
K	4.36±0.29	4.24±0.32	0.156
Ca	9.30±0.28	9.33±0.50	0.571
CL	103 (101-104)	102 (100.25-104)	0.680
Hgb	13.57±1.47	13.67±1.41	0.776
Hct	40.74±4.07	40.85±3.89	0.915

AVNRT: Atrioventricular nodal reentrant tachycardia, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, EF: Ejection fraction, IVS: Interventricular septum, PW: Posterior wall, LA: Left atrium, Na: Sodium, K: Potassium, Ca: Calcium, Cl: Chlorine, Hgb: Hemoglobin, Hct: Hematocrit

common form of paroxysmal supraventricular tachycardia, with ER patterns (9).

ER syndromes and BrS, which have pathophysiologically similar features to it, are the main components of J wave syndromes (10). It is considered that J wave abnormalities are caused by mutations that develop in a way that disrupts the inward flow functions of the Ito ion channels, especially in the inferior region of the left ventricle (11). Furthermore, several publications are associated with J-point elevations in the inferior and lateral leads, increased frequency of idiopathic VF, and cardiovascular death (2,12,13). Defects of cardiac ion channels that lead to repolarization dysfunction are not limited to the ventricular myocardium but are also likely to affect the atrial tissue. It has been reported in previously studies that there may be a coexisting between BrS and atrial fibrillation and AVNRT (6,14).

Table 2. Comparison of ER and ER subtypes in male and female individuals

	Male (n=38)	Female (n=65)	p-value
Signs of ER of any type	12 (31.6%)	16 (24.6%)	0.495
Type of ER			
Slurring with ST elevation	7 (58.3%)	0	<0.001*
Slurring without ST elevation	5 (41.7%)	15 (93.8%)	
Notch with ST elevation	0	0	0.002**
Notch without ST elevation	0	1 (6.2%)	

ER: Early repolarization, *The result of post hoc analysis conducted between male and female in terms of slurring with ST elevation. **The result of post hoc analysis conducted between male and female in terms of slurring without ST elevation

Table 3. Comparison of ER and ER subtypes by age

	Age <40 years (n=27)	Age ≥40 years (n=76)	p-value
Signs of ER of any type	6 (21.4%)	22 (29.3%)	0.415
Type of ER			
Slurring with ST elevation	2 (33.3%)	5 (22.7%)	0.775
Slurring without ST elevation	4 (66.7)	16 (72.7%)	
Notch with ST elevation	0	0	
Notch without ST elevation	0	1 (4.5%)	

ER: Early repolarization

Table 4. Comparison of electrocardiographic parameters of the AVNRT group and the control group

	AVNRT group (n=53)	Control group n=50	p-value
Heart rate (bpm ± SD)	72.71±11.11	77.00±13.66	0.083
Signs of ER of any type	16 (30.2%)	12 (24%)	0.480
Type of ER			
Slurring with ST elevation	3 (18.8%)	4 (33.3%)	0.497
Slurring without ST elevation	12 (75%)	8 (66.7%)	
Notch with ST elevation	0	0	
Notch without ST elevation	1 (6.3%)	0 (0)	

AVNRT: Atrioventricular nodal reentrant tachycardia, bpm: Beat per minute, ER: Early repolarization, SD: Standard deviation

In our study, more patients in the AVNRT group had ER abnormalities than in the control group; however, this difference was not statistically significant. This may be related to the relatively small size of our sample group. AVNRT is a reentrant tachyarrhythmia that develops mainly in the presence of slow and fast pathways, in which the atrioventricular node is involved. However, some genetic variations (SCN1A, PRKAG2, RYR2, CFTR, NOS1, PIK3CB, GAD2, and HIP1R) and ion channel disorders may be responsible for the formation of pathways with different refractory periods and conduction velocities (15,16). The mutation of SCN5A, which affects INA channel functions, has been previously identified in both ER syndrome and AVNRT cases (6,17). Therefore, it is possible that these two diseases may coexist on a pathophysiological basis.

ER abnormalities are more common in men than in women because of sex hormones, especially testosterone and increased ventricular myocardial mass; on the other hand, AVNRT is more common in females (18,19). In our study, there was no statistically significant difference in the presence of ER abnormalities between male and female individuals. Nevertheless, when the comparison was performed in the subgroups, slurring with ST elevation was statistically more in men, in contrast, slurring without ST elevation was significantly higher in female individuals. Our findings are consistent with the previously reported results. However, new studies are still needed on the differences in the subtypes of ER patterns between the genders.

There are some limitations in our study. First, the study was conducted in a relatively small patient population. Additionally, the relationship between electrophysiological measurements and ER abnormalities in AVNRT patients included in the study was not examined. Finally, genetic test analyses were not available for all patients included in the study, which could be related to ER disorders and AVNRT.

CONCLUSION

To our best knowledge, the present study is the first study in the literature to investigate the co-existence of ER disorders and AVNRT. There have been many publications on the association of ER abnormalities, which have been considered benign for many years, with both ventricular and atrial arrhythmias recently. Although it is not statistically significant, we have found that the ER pattern, particularly the slurring type, is more frequent in patients with AVNRT. Additionally, determined that slurring with ST elevation type of ER is significantly more common in males, while slurring without ST elevation type is significantly more common in females. However, our findings need to be supported by larger-scale studies.

ETHICS

Ethics Committee Approval: Ethical committee approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2022-16-06, date: 15.08.2022).

Informed Consent: Written informed consent was obtained from all the participants.

Authorship Contributions

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

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REFERENCES

1. Maury P, Rollin A. Prevalence of early repolarisation/J wave patterns in the normal population. J Electrocardiol 2013;46:411-6.
2. Haïssaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008;358:2016-23.
3. Tikkanen JT, Junttila MJ, Anttonen O, Aro AL, Luttinen S, Kerola T, et al. Early repolarization: electrocardiographic phenotypes associated with favorable long-term outcome. Circulation 2011;123:2666-73.
4. Hwang KW, Nam GB, Han J, Kim YG, Choi HO, Kim J, et al. Incidence of Atrial Tachyarrhythmias in Patients With Early Repolarization Syndrome. Int Heart J 2017;58:43-9.
5. Barajas-Martínez H, Hu D, Ferrer T, Onetti CG, Wu Y, Burashnikov E, et al. Molecular genetic and functional association of Brugada and early repolarization syndromes with S422L missense mutation in KCNJ8. Heart Rhythm 2012;9:548-55.
6. Hasdemir C, Payzin S, Kocabas U, Sahin H, Yildirim N, Alp A, et al. High prevalence of concealed Brugada syndrome in patients with atrioventricular nodal reentrant tachycardia. Heart Rhythm 2015;12:1584-94.
7. Macfarlane PW, Antzelevitch C, Haissaguerre M, Huikuri HV, Potse M, Rosso R, et al. The Early Repolarization Pattern: A Consensus Paper. J Am Coll Cardiol 2015;66:470-7.
8. Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, et al. Long-term outcome associated with early repolarization on electrocardiography. N Engl J Med 2009;361:2529-37.
9. Delacrétaz E. Clinical practice. Supraventricular tachycardia. N Engl J Med 2006;354:1039-51.
10. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, et al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. Europace 2017;19:665-94.
11. Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic J wave. Circulation 1996;93:372-9.
12. Rosso R, Kogan E, Belhassen B, Rozovski U, Scheinman MM, Zeltser D, et al. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. J Am Coll Cardiol 2008;52:1231-8.
13. Rollin A, Maury P, Bongard V, Sacher F, Delay M, Duparc A, et al. Prevalence, prognosis, and identification of the malignant form of early repolarization pattern in a population-based study. Am J Cardiol 2012;110:1302-8.
14. Hunuk B, Cagac O, Turan OE, Durmus E, Kozan O. The prevalence of concealed Brugada Syndrome in patients with paroxysmal atrial fibrillation. EP Europace 2022;24.
15. Luo R, Zheng C, Yang H, Chen X, Jiang P, Wu X, et al. Identification of potential candidate genes and pathways in atrioventricular nodal reentry tachycardia by whole-exome sequencing. Clin Transl Med 2020;10:238-57.
16. George SA, Faye NR, Murillo-Berlioz A, Lee KB, Trachiotis GD, Efimov IR. At the Atrioventricular Crossroads: Dual Pathway Electrophysiology in the Atrioventricular Node and its Underlying Heterogeneities. Arrhythm Electrophysiol Rev 2017;6:179-85.
17. Antzelevitch C. Genetic, molecular and cellular mechanisms underlying the J wave syndromes. Circ J 2012;76:1054-65.
18. Ezaki K, Nakagawa M, Taniguchi Y, Nagano Y, Teshima Y, Yufu K, et al. Gender differences in the ST segment: effect of androgen-deprivation therapy and possible role of testosterone. Circ J 2010;74:2448-54.
19. Etaee F, Elayi CS, Catanzarro J, Delisle B, Ogunbayo G, Di Biase L, et al. Gender associated disparities in atrioventricular nodal reentrant tachycardia: A review article. J Cardiovasc Electrophysiol 2021;32:1772-7.

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Research

Parental Gender Role Attitudes and Depression/Anxiety Symptoms Under COVID-19 Outbreak Restrictions: An Investigation of School-aged Children and Their Parents

COVİD-19 Kısıtlamaları Altında Ebeveynlerin Cinsiyet Rol Tutumları ve Depresyon/Anksiyete Belirtileri: Okul Çağı Çocukları ve Ebeveynleri Üzerine Bir Araştırma

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ABSTRACT

Objective: This study aimed to investigate the relationships between gender role attitudes, depression/anxiety symptoms, and coronavirus disease-2019 (COVID-19) pandemic restrictions in families with school-aged children.

Methods: Couples with school-aged children were included in the study. Couples who were fully restricted due to the COVID-19 pandemic (group 1) are compared with couples who were partially restricted due to the COVID-19 pandemic (group 2). Both parents were assessed by Gender Role Attitudes scale (GRAS), Depression Anxiety and Stress scale-21 (DASS), and Life Events Checklist. Revised Child Anxiety and Depression scale-Parent Version (RCADS-P) was completed by mothers for children's assessment.

Results: In group 1, mother's GRAS scores were negatively correlated with mother's DASS Depression (r=-0.598, p=0.004) and RCADS-P scores (r=-0.69, p=0.005). In group 2, fathers' GRAS scores were positively correlated with fathers' DASS depression (r=0.56, p=0.006), stress (r=0.62, p=0.002) and anxiety (r=0.61, p=0.002). In addition, mother's GRAS scores are a negative determinant of mother's DASS depression, father's DASS total, and RCADS-P scores. Father's GRAS scores are a positive predictor of father's DASS total.

Conclusion: This study shows that while maternal gender-type attitudes were associated with psychiatric symptoms in mothers, fathers, and children, the relationship between paternal gender role attitudes and mental health is controversial. In addition, the restrictions of the COVID-19 pandemic impact mental symptoms related to gender role attitudes.

Keywords: Depression, anxiety, gender role attitude, child, mother, father

ÖZ

Amaç: Bu çalışmada, okul çağında çocuğu olan ailelerde, ebeveynlerin cinsiyet rol tutumları, ebeveyn ve çocuktaki depresyon/anksiyete semptomları ve koronavirüs hastalığı-2019 (COVİD-19) pandemisine bağlı kısıtlamaların ilişkisini incelemek amaçlanmıştır.

Gereç ve Yöntem: Okul çağında çocuğu olan çiftler çalışmaya dahil edilmiştir. COVİD-19 pandemisi nedeniyle tam kısıtlanan ebeveynler (grup 1), kısmi kısıtlanan ebeveynlerle (grup 2) karşılaştırılmıştır. Hem anne hem de babalar Toplumsal Cinsiyet Rolleri Tutum ölçeği (TCRT), Depresyon Anksiyete Stres ölçeği-21 (DASÖ-21) ve Yaşam Olayları ölçeğini doldurmuştur. Çocukların değerlendirmesi için ise Çocuk Ergen Anksiyete Depresyon ölçeği-Yenilenmiş-Ebeveyn Formu (ÇADÖ-Y-E) anneler tarafından doldurulmuştur.

Bulgular: Grup 1'de annelerin TCRT puanları anne DASÖ-21-depresyon alt ölçeği puanlarıyla (r=-0,598; p=0,004) ve ÇADÖ-Y-E puanlarıyla (r=-0,69; p=0,005) negatif yönde korelasyon göstermiştir. Grup 2'de babaların TCRT puanları babaların DASÖ-21 depresyon (r:0,56; p=0,006), stres (r:0,62; p=0,002) ve anksiyete (r=0,61; p=0,002) puanlarıyla pozitif yönde korele bulunmuştur. Ayrıca, annelerin TCRT puanları anne DASÖ-

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21 depresyon, baba DASÖ-21 toplam ve ÇADÖ-Y-E puanlarının negatif yönde belirleyicisi olarak bulunmuştur. Babaların TCRT puanları ise, babaların DASÖ-21 toplam puanlarının pozitif yönde belirleyicisi olarak bulunmuştur.

Sonuç: Bu çalışma, annelerin cinsiyete dayalı tutumlarının anne, baba ve çocuktaki psikiyatrik semptomlarla ilişkili olduğunu göstermiştir. Babaların cinsiyete dayalı tutumları ile psikiyatrik semptomlar arasındaki ilişki ise tartışmalıdır. Ayrıca, COVİD-19 pandemisine bağlı kısıtlamaların, cinsiyet rol tutumları ile ilişkili psikiyatrik semptomlar üzerinde etkisi olduğu düşünülmektedir.

Anahtar Kelimeler: Depresyon, anksiyete, cinsiyet rol tutumları, çocuk, anne, baba

INTRODUCTION

Gender roles refer to the roles expected from men and women in social and cultural terms (1). The development and socialization of gender roles begin in the family environment (2). Some of the most important aspects of human life are heavily regulated by the gender roles and gender development is vital in human life (3,4).

Gender roles are not only regarded as a difference but also indicate power inequality and imbalance mostly against women (5,6). Therefore, it has been reported that there is a relationship between mental health and gender roles (7). In another study which was conducted with a large sample of adults in Russia showed that traditional gender roles based on gender inequality are associated with depression and anxiety disorder (8). It has been reported that characteristics related to gender roles can also affect adolescent mental health. Gender inequalities were associated with a tendency to depression and conduct disorder (9,10).

The coronavirus disease-2019 (COVID-19) pandemic and quarantine have psychological effects on people (11-13). It is estimated that mental problems and the need for support increase in this period (14). In addition, face- to-face education was suspended in schools, out-of-home activities decreased, and the time spent at home increased (15-17). During the pandemic period, parents reported difficulties in balancing their responsibilities and providing motivation for learning due to practices such as distance education (18). In a study examining the effects of distance education on parenting activities during the pandemic period (17), it was reported that two out of five parents met the criteria for depression or anxiety disorder. In another study, depression and anxiety symptoms of parents with children in education were investigated in terms of variables such as marital relationship, perceived social support, and the school that child attended (19). During the pandemic, gendered power relations between spouses working from home were investigated and examined in a qualitative study. In that study, attention was drawn to the disadvantaged position of women (20). However, to the best of our knowledge, there is no study that examines the relationship between gender roles and depressive or anxiety symptoms in the COVID-19 pandemic period when parents' domestic responsibilities increase.

Gender role-related responsibilities in the family are important for the development of gender role attitudes in individuals (2). Also, gender - type attitudes are associated with mental problems (8). In the COVID-19 pandemic period, when the domestic responsibilities of parents increase (18), it is possible that the unequal role distribution may affect the mental health of the parents and indirectly the mental health of the children. Therefore, the purposes of this study were determined:

i. To study the effect of COVID-19 pandemic restrictions on depression/anxiety symptoms in the family,

ii. To investigate the relationship between parental gender role attitudes and children's depression/anxiety symptoms,

iii. To investigate the relationship between gender role attitudes and depression/anxiety symptoms in parents with school-aged children.

For these purposes, two study groups were formed on the basis of the severity of their experience with COVID-19 pandemic restrictions. Study groups were compared in terms of maternal gender role attitudes, paternal gender role attitudes, maternal depression/anxiety/stress symptoms, paternal depression/anxiety/stress symptoms, and depression/anxiety symptoms in children.

METHODS

This study is a cross-sectional comparative survey study. Only parents with school-aged children were included. To examine the impact of COVID-19 restrictions, two distinct groups of families were formed. Study groups were determined by participants' responses to three questions. Families that suspended all social, economic or educational face-to-face activities are grouped as group 1. On the other hand, families that maintain their face-to-face activities with minimal restrictions are grouped as group 2.

Hence, families in group 1 are affected more by restrictions. Both parents mostly stayed home for the entire period and suspended almost all face- to-face social, economic and educational activities. This criteria has particular importance

in our study, as having both parents affected by restrictions, the outcome could be more prominent. Therefore, if the parents had different restriction experiences, they were not included in the study.

Families in group 2 are significantly less affected by the restrictions compared with those in group 1. Both parents maintained face-to-face activities during COVID-19 pandemic restrictions. Couples in group 2 kept going out and continued their daily life because of their professions, and duties were considered less affected by restrictions.

Participants were recruited from Pediatric Outpatient Clinics in University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital between June 16 and July 16 2021. The target number is determined based on statistical significance and is explained in section 2.2.

All parents included in the study had at least one child between the ages of 6 and 18. Single parents were excluded. Due to the potential impacts on depression and anxiety symptoms, a history of chronic disease in oneself or a child, a history of loss of a loved one in the last six months, and being unemployed due to the pandemic were determined as exclusion criteria. Traumatic event history was also evaluated by the Life Events Checklist (LEC) as traumatic events are considered a risk factor for depression (21).

The minimum sample size (n) was found to be 21 patients and 21 controls (details can be found in the statistical analysis section). Group 1 consists of 21 couples, whereas group 2 consists of 22 couples.

The Declaration of Helsinki is used as the standard of medical ethics in the study design. University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital reviewed and approved all study materials (no: 2021.06.109, date: 02.07.2021). Informed consent was obtained from the parents who agreed to participate in the study.

Instruments

The sociodemographic data form was created by integrating the measurement tool developed by Kalaycıoğlu et al. (22). A socioeconomic status index (SES) is calculated as quantitative data. Higher scores mean higher socioeconomic level (22). Also, there were questions on the child's gender, parent's age, the number of children and education level.

The Gender Role Attitudes scale (GRAS) was developed by García-Cueto et al. (23). The scale was adapted to the Turkish population by Bakioğlu and Türküm (24). Higher scores mean egalitarian attitudes toward gender. Lower scores signified a gender-type attitude in this study. Depression Anxiety and Stress scale-21 (DASS-21) was developed by (Henry and Crawford, 2005) (25). It is widely used to assess depression, anxiety, and stress. DASS-21 was adapted to the Turkish population in community and clinical samples by Sarıçam (26) and found to be reliable. It is a self-report scale consisting of 21 questions on depression, anxiety, and stress subscales. In this study, clinical threshold levels are accepted as 9 for depression subscale, 7 for anxiety subscale, and 14 for stress subscale (27).

Revised Child Anxiety and Depression scale-Parent Version (RCADS-P) assesses parent reports of children's depression and anxiety symptoms and was renovated in 2000 by Chorpita et al. (28). The Turkish validity study was carried out by Gormez et al. (29). In this study, mothers were asked to complete the RCADS-P for their school-age children evaluated in the pediatric outpatient clinic.

The LEC was used to screen potentially traumatic events in the subject's lifetime (30). LEC is a 17-item self-report measure. For each question, subjects select one of the following answers: "happened to me", "witnessed it", "learned about it" and "part of my job". A past traumatic experiences score was calculated for each subject based on their answers, with a possible range of 0 to 68 points.

Statistical Analysis

Statistical analyses were conducted using SPSS 21.0 software (IBM Corp., Armonk, NY, USA; licensed to Istanbul University). The sample size was estimated using Epi Info 2000 Statcalc software (Centers for Disease Control, Atlanta, GA) with a predicted exposure of 10% and 50% for controls (group 2) and patients (group 1), respectively (31-33). Accordingly, the minimum sample size (n) based on the statistical power 0.80 was found to be 21 patients and 21 controls. The normal distribution of continuous variables was assessed using the skewness-kurtosis and the Kolmogorov-Smirnov test or Shapiro-Wilk test. The logarithmic transformation was used for nonnormal data. Pearson's chi-square test or Fisher's Exact test was used to compare categorical data. The Student t-test was performed on the continuous data with normally distributed. Spearman's rank correlation test was used to compare nonnormally distributed continuous variables. Finally, linear regression analysis was performed. A p-value of <0.05 was considered significant.

RESULTS

Descriptive Data of Study Groups

Demographic Variables

In this sample, 9 (42.9%) of the children in group 1 and 11 (50,0%) of the children in group 2 were female. Mean education level by years was 13.4 (±4.6) in group 1 and

significantly lower than that in group 2 (16.2±4.0, p=0.04). Mean parent ages were 40.2 (±4.3) in group 1 and 41.2 (±6.6) in group 2. The number of school-aged children that parents have were 1.6 (±0.6) in group 1 and 1.59 (±0.6) in group 2. The mean ages of children were 10.0 (±3.1) in group 1 and 10.9 (±4.1) in group 2. The child's gender, parent and child's mean ages and number of school-aged children that parents have were similar in the study groups (p=0.63; p=0.56; p=0.43; p=0.89). Mean SES is 70 (±20.8) in group 1 and 73.2 (±14.0) in group 2. There was no significant difference between SES of groups (Table 1).

Psychiatric Parameters

Fifteen (71.4%) mothers in group 1 and 12 (54.5%) mothers in group 2 had depressive symptoms higher than the clinical threshold. Seventeen (81.0%) mothers in group 1 and 20 (90,9%) mothers in group 2 had stress symptoms higher than the clinical threshold. Twenty one (100.0%) mothers in group 1 and 22 (100.0%) mothers in group 2 had anxiety symptoms higher than the clinical threshold. Nine (42.9%) fathers in group 1 and 8 (36.4%) fathers in Group 2 had depression symptoms higher than the clinical threshold. 12 (57.1%) fathers in group 1 and 11 (50.0%) fathers in group 2 had stress symptoms higher than the clinical threshold. Nine (42.9%) fathers in group 1 and 4 (18.2%) fathers in group 2 had depression symptoms higher than the clinical threshold. Differences between groups 1 and 2 were not statistically significant in terms of maternal depression (p=0.25), stress (p=0.34), anxiety and paternal depression (p=0.66), stress (p=0.63), and anxiety at the clinical level (p=0.07) (Table 1).

Comparison of DASS, RCADS-P, and LEC Scores Between Groups

The mean mother DASS anxiety score was 13.1±2.5 and mean father DASS anxiety score was 4.3±4.5 in group 1 and both of which were significantly higher than group 2 (Mother DASS: 11.7±3.9; p=0.09, Father DASS: 1.59±2.1, p=0.04). While mean mother GRAS scores were significantly lower in group 1 (47.5±18.4) compared to group 2 (56.0±11.3, p=0.03), mean father GRAS scores did not show significant difference between the groups (group 1: 64.9±19.4, group 2: 57.5±9.5, p=0.18). Mother LEC, mother DASS depression, mother DASS stress, father LEC, father depression, father stress, and RCADS-P scores were similar for both groups (p=0.50, p=0.24, p=0.94, p=0.95, p=0.18, p=0.38, p=0.14, p=0.27) (Table 2).

Correlational Relations Between GRAS, DASS, and RCADS-P Within Groups

In group 1, mother's GRAS scores were negatively and moderately correlated with mother's DASS depression scores (r=-0.598, p=0.004) and were also negatively and highly correlated with RCADS-P scores (r=-0.69, p=0.005). There was also a positive and moderate correlation between RCADS-P scores and father's GRAS scores (r=0.48, p<0.001).

Table 1. Comparison of sociodemographic variables between the groups

		Group 1 (21)		Group 2 (22)		p
	Mean ± SD/n-%		Mean ± SD/n-%			
Gender of child	Male	12	57.1%	11	50.0%	0.63*
	Female	9	42.9%	11	50.0%	
Parent's age		40.2	±4.3	41.2	±6.6	0.56+
Education level (year)		**13.4**	**±4.6**	**16.2**	**±4.0**	**0.04+**
Number of children (6-18)		1.6	±0.6	1.59	±0.6	0.89+
Child's age		10.0	±3.1	10.9	±4.1	0.43+
Mother depression		15	71.4%	12	54.5%	0.25*
Mother stress		17	81.0%	20	90.9%	0.41**
Mother anxiety		21	100%	22	100%	
Father depression		9	42.9%	8	36.4%	0.66*
Father stress		12	57.1%	11	50.0%	0.63*
Father anxiety		9	42.9%	4	18.2%	0.07*
SES		70.2	20.8	73.2	14.0	0.40+

*Chi-square, +Student t-test, **Fisher Exact test
Group 1: Fully restricted due to the COVID-19 pandemic, Group 2: Partially restricted due to the COVID-19 pandemic, t: Student t-test, SD: Standard deviation, SES: Socioeconomic status index, COVID-19: Coronavirus disease-2019

In group 2, while there was no association between mother's GRAS scores, DASS and RCADS-P scores; father's GRAS scores were positively and moderately correlated with father's DASS depression scores (r=0.56, p=0.006). Also, father's GRAS scores were positively and highly correlated with father's DASS stress and anxiety scores (r=0.62, p=0.002; r=0.61, p=0.002) (Table 3).

Predictors of DASS and RCADS-P Scores

Predictors of parameters that were defined as the scores significantly correlated with GRAS scores were investigated by stepwise regression analysis (Table 4).

First, father's DASS depression subscale scores were positive [β: 0.55, 95% confidence interval (CI): 0.20-0.54, p=0.001] and mother's GRAS scores were negative (β: -0.8, 95% CI: -0.92--0.03, p= 0.034) predictors of mother's DASS depression subscale scores. Mother's DASS total scores (β: 0.34, 95% CI: 0.31-1.34, p=0.002) and father's GRAS scores were positive (β: 0.62, 95% CI: 1.43-3.15, p=0.001) and mother's GRAS scores were negative (β: -0.35, 95% CI: -1.31-0.28, p=0.003) predictors of the father's DASS total scores. Mother's DASS total scores were positive (β: 0.49, 95% CI: 0.60-1.74, p=0.001) and mother's GRAS scores (β: -0.43, 95% CI: -1.53- -0.45, p=0.001) were negative predictors of the RCADS-P scores (Table 4).

Table 2. Comparison of DASS, LEC and RCADS-P scores between the groups

	Group 1 (21)		Group 2 (22)		p
	Mean ± SD/n-%		Mean ± SD/n-%		
Mother LEC	8.52	±3.6	12.6	±9.9	0.50⁺
Mother GRAS	**47.5**	**±18.4**	**56.0**	**±11.3**	**0.03⁺**
Mother DASS depression	7.8	±4.2	6.2	±4.4	0.24⁺
Mother DASS stress	11.4	±3.8	11.4	±3.9	0.94⁺
Mother DASS anxiety	**13.1**	**±2.5**	**11.7**	**±3.9**	**0.09⁺**
Father LEC	12.3	±8.0	15.1	±11.7	0.95⁺
Father GRAS	64.9	±19.4	57.5	±9.5	0.18⁺
Father DASS depression	5.6	±5.5	3.6	±3.3	0.38⁺
Father DASS stress	10.1	±5.4	7.6	±3.5	0.14⁺
Father DASS anxiety	**4.3**	**±4.5**	**1.59**	**±2.1**	**0.04⁺**
RCADS-P	38.2	±24.6	26.4	±15.3	0.27⁺

⁺Student t-test
Group 1: Fully restricted due to the COVID-19 pandemic, Group 2: Partially restricted due to the COVID-19 pandemic, t: Student t-test, SD: Standard deviation, GRAS: Gender Role Attitudes scale, DASS: Depression Anxiety and Stress scale-21, RCADS-P: Revised Child Anxiety and Depression scale-Parent Version, LEC: Life Events Checklist, COVID-19: Coronavirus disease-2019

Table 3. Intragroup correlations of GRAS, DASS and RCADS-P scores

Spearman correlation group 1		M. DASS depression	M. DASS stress	M. DASS anxiety	F. DASS depression	F. DASS stress	F. DASS anxiety	RCADS-P
M. GRAS	r	**-0.598**	-0.14	-0.17	-0.25	-0.30	-0.39	**-0.69**
	p	**0.004**	0.53	0.44	0.27	0.18	0.07	**0.005**
F. GRAS	r	-0.23	0.15	0.30	0.34	0.42	0.34	**0.48**
	p	0.31	0.50	0.17	0.12	0.05	0.12	**<0.001**
Spearman correlation group 2		**M. DASS depression**	**M. DASS stress**	**M. DASS anxiety**	**F. DASS depression**	**F. DASS stress**	**F. DASS anxiety**	**RCADS-P**
M. GRAS	r	-0.36	0.40	0.32	0.17	0.28	0.16	-0.20
	p	0.87	0.06	0.13	0.44	0.19	046	0.37
F. GRAS	r	0.18	0.33	0.38	**0.56**	**0.62**	**0.61**	0.20
	p	0.41	0.12	0.07	**0.006**	**0.002**	**0.002**	0.36

Group 1: Fully restricted due to the COVID-19 pandemic, Group 2: Partially restricted due to the COVID-19 pandemic, GRAS: Gender Role Attitudes scale, DASS: Depression Anxiety and Stress scale-21, RCADS-P: Revised Child Anxiety and Depression scale-Parent Version, M.: Mother, F.: Father, COVID-19: Coronavirus disease-2019

Table 4. Association of mother's DASS depression father's DASS total and RCADS-P with possible risk factors (adjusted for age)

Regression number	Dependent variable	Predictor variables	p	Exp β	95% CI
1-	M. DASS depression	F. DASS depression	0.001	0.55	0.20-0.54
		M. GRAS	0.034	-0.28	-0.92- -0.03
2-	F. DASS total	M. DASS total	0.002	0.34	0.31-1.34
		F. GRAS	0.001	0.62	1.43-3.15
		M. GRAS	0.003	-0.35	-1.31- -0.28
3-	RCADS-P	M. DASS total	0.001	0.49	0.60-1.74
		M. GRAS	0.001	-0.43	-1.53- -0.45

GRAS: Gender Role Attitudes scale, DASS: Depression Anxiety and Stress scale-21, RCADS-P: Revised Child Anxiety and Depression scale-Parent Version, M.: Mother, F.: Father, CI: Confidence interval

DISCUSSION

In this study, it was found that in group 1 both mothers and fathers had higher anxiety levels than in group 2. Gender-type attitudes of mothers are positively and moderately associated with maternal anxiety and are also positively and highly associated with child depression/anxiety symptoms. On the other hand, egalitarian attitudes of fathers in group 2 were positively associated with depression, stress, and anxiety symptoms in fathers. In regression analysis, maternal gender-type attitudes were found to be a predictor of maternal anxiety and depression/anxiety symptoms in children. Moreover, paternal egalitarian attitudes are found to be a predictor of paternal depression, stress, and anxiety symptoms.

Differences Related to COVID-19 Restrictions

Similar to our results, it was previously reported that parents with children younger than 18 years had very high rates of depression and anxiety disorders during the COVID-19 pandemic (34). In our sample, it is observed that parental anxiety levels in group 1 are higher than those in group 2. Social isolation and changes in daily routines may affect anxiety management (14) and cause parents to report higher anxiety. However, it can also be challenging to continue going out and working in pandemic conditions. As a matter of fact, parental depression and stress levels in group 2 do not show differences compared with those in group 1.

Gender-typed Attitudes and Depression/Anxiety/Stress Symptoms in Mothers

Although symptom levels are similar in the groups, associated factors might be different. In our study, gender role attitudes are examined among these factors. In group 1, maternal gender-type attitudes were associated with maternal anxiety and depression/anxiety symptoms in children. This relationship may have been found in group 1 as gender-type attitudes impose more domestic labor on women (35). Recently, gender inequality and mental health problems were investigated in a large sample in Russia, and traditional gender role attitudes were found to be associated with depressive symptoms in adults (8). Parallel to that study, in group 1, gender-type attitudes and depressive symptoms are associated in mothers. Additionally, gender-type attitudes were found to be predictors of mother depression. Consistent with interpersonal theory (36), spouse depression is also observed as a predictor of mother depression.

Gender-typed Attitudes and Depression/Anxiety/Stress Symptoms in Fathers

It has been claimed that most traditional gender roles create disadvantages for women (5,6). In our study, while gender-type attitudes were associated with mother's depression, egalitarian attitudes were significantly associated with fathers' depression, stress and anxiety. It has been reported in the literature that men who internalize traditional gender roles seek less psychological help and have limited emotional expression (37). Therefore, it can be suggested that in our sample, fathers who internalized egalitarian attitudes could recognize and express their symptoms more, while fathers with more gender-type attitudes may have masked the symptoms. However, the relationships between egalitarian attitudes and fathers' depression, stress, and anxiety symptoms were observed only in group 2. Therefore, it can be concluded that fathers have difficulties in domestic responsibilities while working with the COVID-19 pandemic conditions outside their homes.

Parental Gender Role Attitudes and Depression/Anxiety Symptoms in Children

Maternal gender-type attitudes were related to children's depression and anxiety symptoms. Although the relationship

between gender role attitudes and psychological symptoms in adolescents has been reported in the literature (10), no study investigating parental attitudes and child symptoms has been found. The positive association between maternal gender-type attitudes and child depression/anxiety symptoms can be explained by the fact that children with maternal depression are at risk for psychopathology. Our findings showing that gender-typed mothers have more depressive symptoms and that maternal depression and maternal gender-typed attitudes predict child depression/anxiety symptoms are consistent with this data. Gender role attitudes are reported to be transmitted from generation to generation; therefore, it is possible that children with gender-type mothers have more gender-type attitudes. However, as a limitation, children's gender role attitudes are not examined in this study, so we cannon make any comments about children's gender role attitudes. Based on the literature and these findings, it can be suggested that maternal gender-type attitudes are related with depression and anxiety symptoms in both children and mothers. On the other hand, fathers' egalitarian attitudes were positively associated with children's depression/anxiety symptoms in group 1. Before the pandemic, it was pointed out that paternal adaptive strategies are associated with children's emotional symptoms in a well-educated sample (38). After the pandemic, it was found that parental dynamics and children's well-being were negatively affected by COVID-19 pandemic restrictions (39). In parallel, in our study, differences between study groups were obtained in this term. Risks and protective factors such as individual characteristics, family relations, and family characteristics (39). Because of our study, it can be considered that gender-type attitudes may be one of these risk factors. A trancendecent perspective claimed that domestic labor must not be allocated by sex (40). More egalitarian fathers may have had more difficulty balancing their domestic responsibilities in the event of confinement due to restrictions. In addition, family dynamics may have been more affected.

The significance and contribution of this study can be summarized in four major points. First, this is the first study that investigates the relationship between gender role attitudes, mental health, and COVID-19 restrictions. Also, the relationship between parents' gender role attitudes and the child's mental symptoms has not been investigated before. Second, although psychiatric disorders have multifactorial etiologies, moderate/high correlation results are obtained through the study's exclusion criteria. Third, parents are included in the study as couples and a multidimensional evaluation is made. Fourth, by comparing families who were fully restricted with those who were partially restricted, it is shown that psychiatric symptoms associated with gender-type attitudes may differ according to living conditions. There are also some limitations to our study. The first limitation is that the gender role attitudes of children were not evaluated. Second, depression/anxiety symptoms in children were evaluated only from mothers. Lastly, participants were recruited from the pediatric outpatient clinic. Therefore, the generalization of the results is limited.

CONCLUSION

This study investigated the relationship between COVID-19 restrictions and gender role-associated psychiatric symptoms for the first time. Our findings showed that the restrictions of the COVID-19 pandemic impact mental symptoms related to gender role attitudes. The association between parental gender role attitudes and the child's psychological symptoms was also investigated for the first time in this study. Our results emphasize the importance of attitudes toward gender equality in terms of women's mental health. On the other hand, the relationship between gender role attitudes and men's mental health is controversial, and further investigation in this area is needed.

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ETHICS

Ethics Committee Approval: University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital reviewed and approved all study materials (no: 2021.06.109, date: 02.07.2021).

Informed Consent: Informed consent was obtained from the parents who agreed to participate in the study.

Authorship Contributions

Surgical and Medical Practices: Z.K., N.C.K., S.T., B.D., Concept: N.C.K., S.T., Design: Z.K., N.C.K., S.T., B.D., Data Collection or Processing: Z.K., N.C.K., S.T., B.D., Analysis or Interpretation: Z.K., N.C.K., S.T., Literature Search: Z.K., N.C.K., S.T., Writing: Z.K., N.C.K., S.T., B.D.

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REFERENCES

1. Fagot BI, Rodgers CS, Leinbach MD, Eckes T, Trautner HM. The Developmental Social Psychology of Gender. Nueva Yersey: Lawrence Erlbaum Associates Publishers; 2000.
2. Eccles JS, Freedman-Doan C, Frome P, Jacobs J, Yoon KS. Gender-role socialization in the family: A longitudinal approach. Dev Soc Psychol Gend 2000:333-60.
3. Leung NM, Henry KSNg. Sex Role Development and Education. In: Wright JD, editor. International Encyclopedia of the Social & Behavioral Sciences. 2nd ed. Oxford: Elsevier; 2015. p. 678-85.
4. Sharepour M. Gender role stereotypes among Iranian adolescents. J Soc Psychol 2005;145:491-6.
5. Un Women. Gendered power inequalities [Internet]. 2020. Available from: https://www.endvawnow.org/en/articles/1930-gendered-power-inequalities-.html
6. Jain S. Human Development, Gender and Capability Approach. Indian J Hum Dev 2020;14:320-32.
7. Upmanyu VV, Upmanyu S, Lester D. Depressive symptoms among U.S. and Indian college students: the effects of gender and gender role. J Soc Psychol 2000;140:669-71.
8. Jaehn P, Bobrova N, Saburova L, Kudryavtsev AV, Malyutina S, Cook S. The relation of gender role attitudes with depression and generalised anxiety disorder in two Russian cities. J Affect Disord 2020;264:348-57.
9. Bone JK, Lewis G, Lewis G. The role of gender inequalities in adolescent depression. Lancet psychiatry 2020;7:471-2.
10. King TL, Singh A, Milner A. Associations Between Gender-Role Attitudes and Mental Health Outcomes in a Nationally Representative Sample of Australian Adolescents. J Adolesc Health 2019;65:72-8.
11. Xiong J, Lipsitz O, Nasri F, Lui LMW, Gill H, Phan L, et al. Impact of COVID-19 pandemic on mental health in the general population: A systematic review. J Affect Disord 2020;277:55-64.
12. Luo Y, Chua CR, Xiong Z, Ho RC, Ho CSH. A Systematic Review of the Impact of Viral Respiratory Epidemics on Mental Health: An Implication on the Coronavirus Disease 2019 Pandemic. Front Psychiatry 2020;11:565098.
13. Wang C, Tee M, Roy AE, Fardin MA, Srichokchatchawan W, Habib HA, et al. The impact of COVID-19 pandemic on physical and mental health of Asians: A study of seven middle-income countries in Asia. PLoS One. 2021;16:e0246824.
14. Saha K, Torous J, Caine ED, De Choudhury M. Psychosocial Effects of the COVID-19 Pandemic: Large-scale Quasi-Experimental Study on Social Media. J Med Internet Res 2020;22:e22600.
15. F Francisco R, Pedro M, Delvecchio E, Espada JP, Morales A, Mazzeschi C, et al. Psychological Symptoms and Behavioral Changes in Children and Adolescents During the Early Phase of COVID-19 Quarantine in Three European Countries. Front Psychiatry 2020;11:570164.
16. Bates LC, Zieff G, Stanford K, Moore JB, Kerr ZY, Hanson ED, et al. COVID-19 Impact on behaviors across the 24-hour day in children and adolescents: physical activity, sedentary behavior, and sleep. Children (Basel) 2020;7:138.
17. Lee SJ, Ward KP, Chang OD, Downing KM. Parenting activities and the transition to home-based education during the COVID-19 pandemic. Child Youth Serv Rev 2021;122:105585.
18. Garbe A, Ogurlu U, Logan N, Cook P. COVID-19 and remote learning: Experiences of parents with children during the pandemic. Am J Qual Res 2020;4:45-65.
19. Wu M, Xu W, Yao Y, Zhang L, Guo L, Fan J, et al. Mental health status of students' parents during COVID-19 pandemic and its influence factors. Gen Psychiatry 2020;33:e100250.
20. Waismel-Manor R, Wasserman V, Shamir-Balderman O. No Room of her Own: Married Couples' Negotiation of Workspace at Home During COVID-19. Sex Roles 2021;85:636-9.
21. Saveanu RV, Nemeroff CB. Etiology of depression: genetic and environmental factors. Psychiatr Clin Nort Am 2012;35:51-71.
22. Kalaycıoğlu S, Çelik K, Çelen Ü, Türkyılmaz S. Developing A Tool For The Measurement Of Socio - Economic Status (Ses) From A Representative Sample: The Case Of Ankara City Center. Journal of Sociological Research 2010;13:182-220.
23. García-Cueto E, Rodríguez-Díaz FJ, Bringas-Molleda C, López-Cepero J, Paíno-Quesada S, Rodríguez-Franco L. Development of the Gender Role Attitudes Scale (GRAS) amongst young Spanish people. Int J Clin Health Psychol 2015;15:61-8.
24. Bakioğlu F, Türküm AS. Adaptation of Gender Role Attitudes Scale to Turkish: A Study of Validity and Reliability. Kastamonu Education Journal 2019;27:717-25.
25. Henry JD, Crawford JR. The short-form version of the Depression Anxiety Stress Scales (DASS-21): Construct validity and normative data in a large non-clinical sample. Br J Clin Psychol 2005;44:227-39.
26. Sarıçam H. The psychometric properties of Turkish version of Depression Anxiety Stress Scale-21 (DASS-21) in health control and clinical samples. J Cogn Psychother Res 2018;7:19-30.
27. Gomez F. A guide to the depression, anxiety and stress scale (DASS 21). Cent East Sydney Prim Heal Networks. 2016.
28. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. Behav Res Ther 2000;38:835-55.
29. Gormez V, Kilincaslan A, Ebesutani C, Orengul AC, Kaya I, Ceri V, et al. Psychometric Properties of the Parent Version of the Revised Child Anxiety and Depression Scale in a Clinical Sample of Turkish Children and Adolescents. Child Psychiatry Hum Dev. 2017;48:922-33.
30. Gray MJ, Litz BT, Hsu JL, Lombardo TW. Psychometric properties of the life events checklist. Assessment 2004;11:330-41.
31. Brehaut E, Neupane D, Levis B, Wu Y, Sun Y, Krishnan A, et al. Depression prevalence using the HADS-D compared to SCID major depression classification: An individual participant data meta-analysis. J Psychosom Res 2020;139:110256.
32. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci 2015;17:327-35.
33. Newby JM, O'Moore K, Tang S, Christensen H, Faasse K. Acute mental health responses during the COVID-19 pandemic in Australia. PLoS One 2020;15:e0236562.
34. Brown SM, Doom JR, Lechuga-Peña S, Watamura SE, Koppels T. Stress and parenting during the global COVID-19 pandemic. Child Abuse Negl 2020;110:104699.
35. Fetterolf JC, Rudman LA. Gender inequality in the home: The role of relative income, support for traditional gender roles, and perceived entitlement. Gender Issues 2014;31:219-37.
36. Klerman GL, Weissman MM. Interpersonal psychotherapy of depression: A brief, focused, specific strategy. Jason Aronson, Incorporated; 1994.
37. Seidler ZE, Dawes AJ, Rice SM, Oliffe JL, Dhillon HM. The role of masculinity in men's help-seeking for depression: A systematic review. Clin Psychol Rev 2016;49:106-18.
38. Psychogiou L, Moberly NJ, Parry E, Russell AE, Nath S, Kallitsoglou A. Does fathers' and mothers' rumination predict emotional symptoms in their children? Br J Clin Psychol? Br J Clin Psychol 2017;56:431-42.
39. Pérez JC, Aldoney D, Vivanco-Carlevari A, Coo S, Guzmán EJ, Silva JR. Adapting to Adversity: Effects of COVID-19 on Parenting in Chile. Front Psychol 2022;13:868817.
40. Baber KM, Tucker CJ. The social roles questionnaire: A new approach to measuring attitudes toward gender. Sex Roles 2006;54:459-67.

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Research

The Effect of Parental Smoking Exposure on Perioperative Respiratory Complications in Children

Çocuklarda Ebeveynlerin Sigara Dumanına Maruz Kalmanın Perioperatif Solunumsal Komplikasyonlara Etkisi

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ABSTRACT

Objective: To determine the effect of parental smoking (PS) exposure on the incidence of respiratory complications in children who received general anesthesia.

Methods: This study was conducted at a university hospital between April and October 2022. A total of 98 children aged 0-16 years who had an American Society of Anesthesiologists Physical Status score of 1-2 and underwent general anesthesia were included in the study. The children were divided into two groups: PS and non-PS groups. Parents were asked to provide basic demographic information about their children, such as age, sex, and medical conditions (presence of an allergy, history of surgery, and diagnosed diseases) as well as their household tobacco consumption. Respiratory complications (desaturation SpO_2 <92%, bronchospasm, laryngospasm, increased airway secretion, cough, breath-holding spells lasting longer than 15 seconds, wheezing, and croup) were recorded before induction, during the intraoperative period, after extubation, and in the post-anesthesia care unit.

Results: Our study indicated that the incidence of complications was significantly higher in children exposed to PS than in those who were not (35.7% and 16.7%, respectively; p=0.03). Most of the complications occurred following extubation, and the common complications were laryngospasm, increased airway secretion, and breath-holding spells. No statistically significant difference in the development of complications was observed based on the sex of the child, exposure time, duration and type of surgery, airway management technique, and number of cigarettes consumed by the parents. The incidence of complications increased as the distance of cigarette exposure decreased (p=0.03).

Conclusion: PS exposure increased the incidence of respiratory complications in children undergoing general anesthesia, and the frequency of complications increased as the distance of exposure decreased.

Keywords: Children, general anesthesia, smoke exposure, respiratory complication

ÖZ

Amaç: Pasif içiciliğe (PS) maruz kalan çocuklarda özellikle laringospazm, bronkospazm ve öksürük gibi perioperatif solunum komplikasyonları riski daha yüksektir. Çocuklar ebeveynleriyle önemli miktarda zaman geçirirler ve eğer ebeveynleri sigara içiyorsa bu onların birincil maruziyet kaynağı olabilir. Çalışmamızda genel anestezi uygulanan çocuklarda ebeveyn sigara maruziyetine bağlı solunum sistemi komplikasyonlarının görülme sıklığının belirlenmesi amaçlandı.

Metod: Bu çalışma, Nisan ve Ekim 2022 tarihleri arasında bir üniversite hastanesinde gerçekleştirildi. Çalışmaya genel anestezi uygulanan, Amerikan Anestezi Derneği Fizik Durumu skoru 1-2 olan, 0-16 yaş arası toplam 98 çocuk dahil edildi. Çocuklar PS grubu ve non-PS grubu olmak üzere iki gruba ayrıldı. Ebeveynlerden çocukları hakkında bazı temel demografik bilgiler vermeleri istendi: Yaş, cinsiyet ve tıbbi durumlar (alerji varlığı, ameliyat öyküsü ve teşhis edilmiş hastalıklar) ve evdeki tütün tüketimi. İndüksiyon öncesi, intraoperatif dönemde, ekstübasyon sonrası ve anestezi sonrası bakım ünitesinde, solunum sistemi komplikasyonları (desatürasyon SpO_2 <%92, bronkospazm, laringospazm, artmış hava yolu sekresyonu, öksürük, 15 saniyeden uzun süren nefes tutma, hırıltı ve krup) kaydedildi.

Bulgular: Çalışmamız, komplikasyon insidansının ebeveyn sigara dumanına maruz kalanlarda kalmayanlara göre istatistiksel olarak anlamlı derecede yüksek olduğunu gösterdi (sırasıyla %35,7 ve %16,7; p=0,03). Komplikasyonların çoğu ekstübasyonu takiben meydana geldi ve yaygın

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komplikasyonlar laringospazm, artan hava yolu sekresyonu ve nefes tutma olarak bulundu. Çocuğun cinsiyeti, maruz kalma süresi, ameliyat süresi ve tipi, hava yolu yönetimi tekniği ve ebeveynlerinin içtiği sigara sayısına göre komplikasyon gelişmesinde istatistiksel olarak anlamlı bir fark yoktu. Dumana olan mesafe azaldıkça komplikasyon insidansı arttı (p=0,03).

Sonuç: Çalışmamızda ebeveynlerin sigara dumanına maruziyet, genel anestezi uygulanan çocuklarda solunum sistemi komplikasyonlarının insidansını artırdı ve maruz kalma mesafesi kısaldıkça komplikasyon sıklığını daha da artırmaktadır.

Anahtar Kelimeler: Çocuklar, genel anestezi, pasif duman maruziyeti, solunumsal komplikasyonlar

INTRODUCTION

Despite significant global struggles, tobacco consumption seems to be a ubiquitous addiction (1). Second-hand smoking, also known as passive smoking, occurs when people who do not smoke inhale tobacco smoke. Smokers breathe in air containing more than 4,000 chemical compounds, many of which are hazardous and/or carcinogenic (1,2). Exposure to tobacco smoke residues on the surfaces of goods is known as third-hand smoking (3). Toxic substances can linger for a long time on skin, hair, clothes, or furniture (4). Therefore, contact with harmful chemicals is possible even without direct inhalation of cigarette smoke. Children are more vulnerable and sensitive to second- and third-hand smoking exposure than adults because their immune systems are still immature, their airways are narrower, their breathing rates are higher, and they display more hand-to-mouth contact behavior. They also spend a significant amount of time with their parents, which could be a source of exposure if their parents smoke. Children whose parents smoke are exposed to passive smoking nine times more than children from non-smoking families (3,5).

Environmental tobacco smoke exposure is a major preventable risk factor for a child's overall health. Passive smoking increases the incidence of sudden infant death syndrome, lower respiratory tract infections, severe and frequent asthma attacks, ear infections, and meningitis in children (6). Furthermore, children exposed to passive smoking have a higher risk of perioperative respiratory complications, particularly laryngospasm, bronchospasm, and cough (7). Our study aimed to determine the effect of cigarette smoke exposure on the incidence of respiratory complications in children who received general anesthesia. Furthermore, the frequency of complications was evaluated in relation to the number of parents who smoked, exposure distance, airway management technique, and daily cigarette consumption.

METHODS

This was a single-center prospective cross-sectional study and was approved by the Ondokuz Mayıs University Clinical Researches Ethics Committee (decision no: OMÜ KAEK 2022/103, date: 15.03.2022). Written informed consent was obtained from all parents before their children enrollment in the study. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Study Population

The data for this study was obtained through patient-reported paper surveys distributed between April and October 2022 to the parents of children aged 0-16 years. All patients with an American Society of Anesthesiologists Physical Status score of 1-2 who underwent general anesthesia were included in the study. The exclusion criteria were as follows: (i) Patients with a known history of lung disease (asthma, bronchitis, etc.) and cardiothoracic and neurosurgical procedures, (ii) a recent history of upper (<4 weeks) or lower respiratory tract infections (<6 weeks), (iii) a recent history of coronavirus disease-2019 (<4 weeks for asymptomatic patients and <6 weeks for symptomatic patients), (iv) scheduled upper or lower respiratory tract surgery, (v) expected difficult airway (e.g., Mallampati 3-4, thyromental distance <6 cm, and short muscular length), (vi) chronic organ failure, and (vii) procedures lasting more than 2 hours, as well as (viii) patients for whom consent could not be obtained.

Anesthetic Protocol

The children were not allowed to consume solid or fluid foods for 6 hours preoperatively. No premedication was administered to the patients before the procedures, and standard American Society of Anesthesiologists Physical Status monitoring (electrocardiogram, non-invasive blood pressure, and pulse oximetry) was performed.

Given the length of surgery and the clinical characteristics of the patients, we decided to use a laryngeal mask (LMA) or perform endotracheal intubation. The LMA was placed during anesthesia induction by administering 4 mg/kg intravenous (IV) propofol; 0.6 mg/kg IV rocuronium was also administered to those who underwent tracheal intubation, with endotracheal intubation performed after adequate muscle relaxation. O_2/air (FiO_2 40%), 1 MAC (age-adjusted) sevoflurane, and remifentanil IV infusion (0.2-0.5 mcg/kg/min) were used for maintenance of anesthesia. The remifentanil infusion rate was determined by considering hemodynamic parameters. In patients who were intubated with muscle relaxants, 0.05 mg/kg neostigmine and 0.02

mg/kg atropine sulfate reversed neuromuscular blockade. Tracheal extubation was performed after the return of satisfactory spontaneous breathing and protective reflexes. All patients were administered 15 mg/kg IV paracetamol at the end of the operation. Patients <8 years old were administered 0.5 mcg/kg fentanyl, while patients ≥8 years old were administered 1 mg/kg tramadol as a rescue analgesic.

Outcomes

Parents were asked to provide basic demographic information about their children, such as age, sex, and medical conditions (presence of an allergy, history of surgery, and diagnosed diseases) as well as their household tobacco consumption. Respiratory complications (desaturation SpO_2 <92%, bronchospasm, laryngospasm, increased airway secretion, cough, breath-holding spells lasting longer than 15 seconds, wheezing, and croup) were recorded before induction, during the intraoperative period, after extubation, and in the post-anesthesia care unit (PACU).

The children were divided into two groups: parental smoking (PS) and non-PS groups. At least a parent/caregivers in the PS group smoked cigarettes at home. In the non-PS group, none of the parents smoked cigarettes at home. Close exposure was defined as either parent/caregiver smoking inside a room/car with the child present. It was considered distant exposure if they smoked on the balcony, in another room, or when the child was absent.

The sample size was calculated using Minitab 16 (2013 Minitab Inc.) program. To determine the exposure status of children, the consumption number of the parents was considered. In the pilot study, including the parents of 10 patients, the average cigarette consumption was 15.2±2.18 packs/year. The sample size calculation revealed that at least 88 patients were needed to reach a significant level of 0.05 and 90% power. Taking into account-possible data losses, with an increase of 10%, we decided to include 98 patients in the study.

Statistical Analysis

The Statistical Package for the Social Sciences application (version 26) was used for statistical analysis (IBM Corp. Armonk, NY, USA). The Kolmogorov-Smirnov test was used to analyze the normal distribution of the groups. Based on the normality test results, data are presented as mean ± standard deviation or median for quantitative data and frequency (percentage) for categorical data. The Mann-Whitney U test or Student's t-test was used to compare quantitative variables, whereas the chi-square test was used to compare categorical variables. A p-value of <0.05 was considered statistically significant for all tests.

RESULTS

In total 125 patients were assessed for eligibility, and finally 98 of them were analyzed. Excluded patients are indicated in the flow diagram (Figure 1). The mean age of the 98 pediatric patients in this study was 63.07±48.7 (range: 1-225)

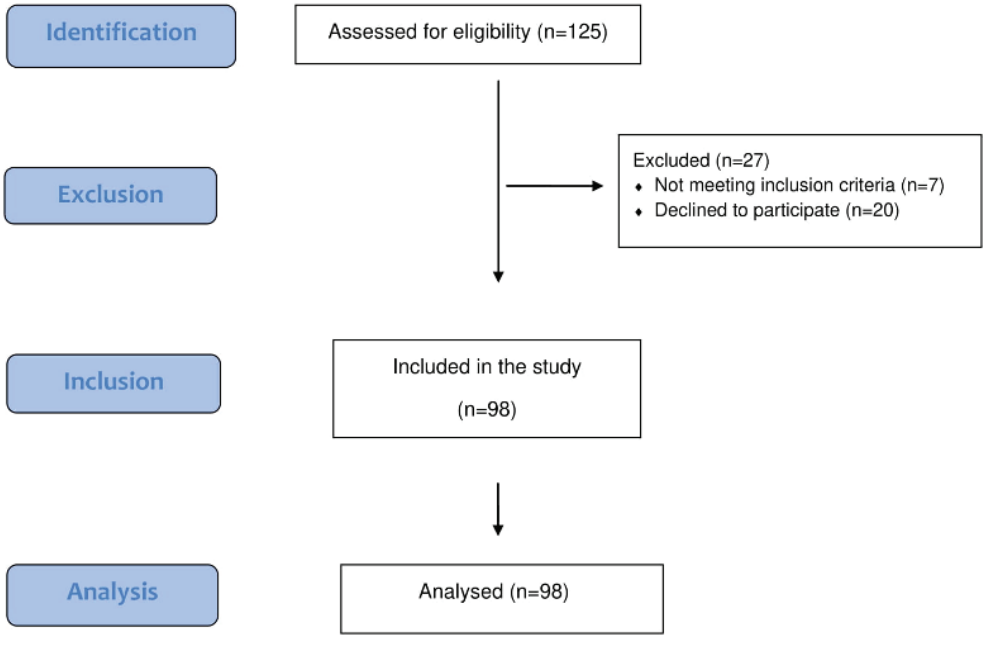

Figure 1. Flow diagram of patient data distribution

months, and 64 (65.3%) were males. The demographic data of the patients, a type of surgery, and duration of surgery are shown in Table 1. While only the fathers of 42.9% of the children and the mothers of 2.0% of the children smoked, both parents of 12.2% of the children smoked. While 14 smoking mothers consumed an average of 8.2±5.1 packs per year, 54 smoking fathers consumed an average of 10.5±5.6 packs per year. In terms of the consumption amount, no difference was observed between the mothers and fathers (p=0.13). In terms of cigarette exposure distance, 42.9% of the children had no exposure, 20.4% had close exposure, and 36.7% had distant exposure.

When the incidence of additional respiratory complications was examined based on the evaluation times, most complications were observed following extubation. The most common complications were laryngospasm, increased airway secretion, and breath-holding spells.

During the evaluation period, 27 (27.6%) children developed at least one respiratory complication. No statistically significant difference was observed in the development of complications based on the sex of the child, exposure time, duration and type of surgery, airway management, and number of cigarettes consumed by the parents (p>0.05). However, the incidence of complications was significantly higher in those exposed to cigarette smoke than in those who did not (35.7% and 16.7%, respectively; p=0.03). While there was no statistically significant difference in complications based on which parent smoked (p=0.14), the incidence was lowest in those who had never been exposed to cigarettes (16.7%) and highest in those who had close exposure (40.0%). However, no statistically significant difference was observed between them (p=0.09). According to the linear-by-linear chi-square results, the incidence of complications increased as the distance of cigarette exposure decreased (p=0.03) (Table 2).

When each type of complication that occurred during extubation was individually compared with the child's

Table 1. Demographics: Anesthetic and surgical characteristics of the patients

Variables	
Gender	Male 64 (65.3)
	Female 34 (34.7)
Age (months)	63.07±48.7 (1-225)
Airway management	Endotracheal tube 59.2
	LMA 40.8
Surgery type	Urogenital (39.8)
	Abdomen (26.4)
	Ophthalmic (20.4)
	Limb (13.3)
ASA physical status	ASA-1 68 (69.4)
	ASA-2 29 (29.6)
	ASA-3 1 (1.0)
Surgery time (min)	69.5±27.9 (20-120)

Data are expressed as mean ± standard deviation, (minimum-maximum) or number (%).
ASA: American Society of Anesthesiologists, LMA: Laryngeal mask

Table 3. Respiratory complications observed during extubation in the awakening process in children exposed to smoking

Variables	Smoking exposure yes (n=56)	Smoking exposure no (n=42)	p-value
Desaturation	6 (10.7)	2 (4.8)	0.46
Laryngospasm	13 (23.2)	4 (9.5)	0.07
Increased airway secretion	9 (16.1)	3 (7.1)	0.22
Coughing	4 (7.1)	0 (0.0)	0.13
Breath holding	8 (14.3)	3 (7.1)	0.34
Wheezing	5 (8.9)	1 (2.4)	0.23

Data are expressed as number (%).

Table 2. Comparison of complications according to smoking exposure among the patients

Variables		Complication not observed (n=71)	Complication observed (n=27)	p-value
Smoking exposure	No	35 (83.3)	7 (16.7)	0.03
	Yes	36 (64.3)	20 (35.7)	
Exposure distance	Not exposed	35 (83.3)	7 (16.7)	0.09
	Distant	24 (66.7)	12 (33.3)	0.03*
	Near	12 (60.0)	8 (40.0)	

Data are expressed as number (%). *Linear-by-linear chi-square

exposure to smoking (Table 3) and the parent that smoked (Table 4) ($p>0.05$), no statistically significant difference was observed.

DISCUSSION

More than 50% of the patients in our study were exposed to cigarette smoke, which increased the incidence of respiratory complications during extubation, particularly during the awakening process. Laryngospasm increased airway secretion, and breath-holding spells were the most common complications. Although the airway management technique (endotracheal intubation vs. LMA) had no effect on the frequency of complications, it increased as the distance of exposure decreased.

According to our findings, 57.1% of the children included in this study were exposed to cigarette smoke. While similar ratios were revealed in cigarette smoke exposure studies conducted in Türkiye in different years (8-10), these ratios were lower in studies conducted in the United States (11-13). Türkiye is a country with high rates of cigarette consumption (14). However, for many years, the world and Türkiye have been engaged in a comprehensive struggle against smoking addiction. Türkiye was one of the two countries that most successfully implemented measures in accordance with the World Health Organization Framework Convention on Tobacco Control (15). With the policies in place, tobacco use is expected to fall to 20.4% globally and 29.9% in Türkiye by 2025 (16). However, the exposure rates revealed in our study and previous studies highlight the importance of combating smoking addiction and continuing these measures.

In our study, we observed that smoking increased the likelihood of respiratory complications by approximately three-fold, which is consistent with the findings of Chiswell et al. (7) (~2.5 times) systematic review. Jones et al. (12) discovered that the risk of intraoperative laryngospasm and airway obstruction in children exposed to passive smoking was 4.9 and 2.8 times higher, respectively, than in those who did not. According to Lakshmipathy et al. (17), the risk of laryngospasm during anesthesia awakening can increase by up to 10-fold in the presence of cigarette smoke exposure. However, some studies have shown that cigarette smoke exposure has little effect on airway complications (13,18,19). For instance, Thikkurissy et al. (13) found that cigarette smoking had no effect on respiratory events in patients undergoing dental treatment under general anesthesia. They hypothesized that this was because the study included relatively healthy children and excluded patients whose smoking exposure caused a more serious morbidity during the preoperative evaluation. In another study, no relationship was observed between cigarette exposure and respiratory complications (19). Nonetheless, the vast majority of research suggests that cigarette smoke exposure harms children's health and increases perioperative respiratory complications.

Exposure to cigarette smoke is a known preoperative risk factor for respiratory complications among pediatric patients in PACU (20). According to Seyidov et al. (9), complications occurred in 12 of 234 patients who had a history of exposure during surgery and 38 patients in the PACU. In contrast, Drongowski et al. (11) indicated that the frequency of respiratory events occurring during emergence from anesthesia and the time spent in the recovery room were comparable. Unlike others, complications were most frequently observed during extubation during the awakening process in our study. In the PACU, respiratory complications developed in three patients. This may be attributed to the early detection of complications during the extubation period and the transfer of patients to the PACU after the required interventions were performed.

Our study, which demonstrated that the most common respiratory complications were laryngospasm, increased

Table 4. Distribution of symptoms observed in children according to their parents' smoking status during extubation in the awakening process

Variables	Mother only (n=2)	Father only (n=42)	Both (n=12)	None (n=42)	p-value
Desaturation	0 (0.0)	6 (14.3)	0 (0.0)	2 (4.8)	0.26
Laryngospasm	0 (0.0)	11 (26.2)	2 (16.7)	4 (9.5)	0.21
Increased airway secretion	0 (0.0)	8 (19.0)	1 (8.3)	3 (7.1)	0.35
Choughing	0 (0.0)	4 (9.5)	0 (0.0)	0 (0.0)	0.13
Breath holding spells	1 (50.0)	7 (16.7)	0 (0.0)	3 (7.1)	0.09
Wheezing	0	4 (9.5)	1 (8.3)	1 (2.4)	0.55

Data are expressed as number (%)

airway secretion, and breath-holding spells, showed both differences and similarities with the literature. In the literature, laryngospasm, bronchospasm, and cough have been reported most frequently in children exposed to cigarette smoke (7). Drongowski et al. (11) reported cough and shortness of breath as the most common complications, whereas Lyons et al. (18) reported desaturation in the PACU as the most common complication. According to a previous report, being exposed to cigarette smoke and having a reactive airway can increase a child's risk of laryngospasm by up to 10-fold (17). Laryngospasm was the most frequent complication observed in our study. Other factors that increase the risk of laryngospasm besides cigarette smoking could be related to the patient, anesthesia, or surgical procedure. The risk factors include young age, superficial anesthesia, blood, secretions, inexperienced anesthesiologist, ear, nose, and throat surgery, and urological procedures (21,22). In our study, anesthesia was administered to all patients by the same team, and the frequency of complications did not vary based on the type of surgery.

Various outcomes have been reported in studies examining the effects of LMA or endotracheal intubation on anesthesia-related airway complications. In their meta-analysis, Li et al. (23) revealed that LMA reduced perioperative respiratory episodes, particularly in pediatric patients. However, cigarette exposure was not considered in this study. When patients with complications were compared based on airway treatment, no significant differences were detected in our study. Similar studies in the literature suggest that supraglottic airway and endotracheal intubation in airway management have no effect on the occurrence of complications in children exposed to cigarette smoke. In a study conducted among children undergoing general anesthesia in day surgery, no difference in complication development was reported between children who underwent airway management with a face mask, LMA, or endotracheal tube (18). Another study reported that the frequency of complications in children with or without cigarette smoke exposure did not differ significantly when LMA ProSeal or intubation was used (9). Although it is difficult to draw conclusions from the available data, we observed that the use of LMA in children exposed to cigarette smoke did not reduce the development of respiratory complications in our study.

Our study revealed that as the distance of cigarette exposure decreased, the frequency of complications increased. The amount of smoke that reaches a person exposed to cigarette smoke is affected by the size of the area, the amount of air change in the environment, and the distance from the source of the smoke (24). In an experimental study, Licht et al. (25) reported that the amount of respirable suspended particles increased as the distance between the smoking location and the monitor used for measurement decreased. Hence, it is not surprising that the associated side effects worsen as exposure increases. The benefits of 'smoke-free airspace' rules in public places to protect public health have been demonstrated recently. However, a consequence of this could be increased household smoking. Legal restrictions on cigarette consumption on private property seem impossible. Therefore, raising awareness and encouraging parents to create smoke-free houses may be beneficial in protecting their children's health.

This study has some limitations. With a larger sample size, we could have developed a correlational study design to investigate the relationship between cigarette smoke exposure and respiratory complications. Furthermore, we determined the amount and distance of exposure of the children based on parental statements.

CONCLUSION

In our study, we found that a history of PS exposure increased the likelihood of respiratory complications in children undergoing general anesthesia, and the frequency of complications increased as the distance of exposure decreased.

ETHICS

Ethics Committee Approval: This was a single-center prospective cross-sectional study and was approved by the Ondokuz Mayıs University Clinical Researches Ethics Committee (decision no: OMÜ KAEK 2022/103, date: 15.03.2022).

Informed Consent: Written informed consent was obtained from all parents before their children enrollment in the study.

Authorship Contributions

Surgical and Medical Practices: S.B., B.D., E.T., Ö.T., Concept: S.B., C.K., B.D., E.T., G.E., S.B., Design: S.B., C.K., B.D., G.E., Ö.T., Data Collection or Processing: C.K., E.T., G.E., S.B., Analysis or Interpretation: C.K., B.D., E.T., S.B., Literature Search: S.B., E.T., G.E., Ö.T., S.B., Writing: S.B., C.K., B.D., E.T., G.E., Ö.T., S.B.

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

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REFERENCES

1. World Health Organization. Tobacco. 2022. https://www.who.int/news-room/fact-sheets/detail/tobacco.
2. Riley C, Ladak N. Reducing pediatric exposure to environmental tobacco smoke: The effects of pediatric exposure to environmental tobacco smoke and the role of pediatric perioperative care. Paediatr Anaesth 2020;30:1199-203.
3. Pugmire J, Sweeting H, Moore L. Environmental tobacco smoke exposure among infants, children and young people: now is no time to relax. Arch Dis Child 2017;102:117-8.
4. Díez-Izquierdo A, Cassanello-Peñarroya P, Lidón-Moyano C, Matilla-Santander N, Balaguer A, Martínez-Sánchez JM. Update on thirdhand smoke: A comprehensive systematic review. Environ Res 2018;167:341-71.
5. Physicians Tobacco Advisory Group of the Royal College of. Passive smoking and children. Royal College of Physicians. 2010. https://cdn.shopify.com/s/files/1/0924/4392/files/passive-smoking-and-children.pdf?15599436013786148553.
6. Centers for Disease Control and Prevention. Health Effects of Secondhand Smoke. 2021. https://www.cdc.gov/tobacco/data_statistics/fact_sheets/secondhand_smoke/health_effects/
7. Chiswell C, Akram Y. Impact of environmental tobacco smoke exposure on anaesthetic and surgical outcomes in children: a systematic review and meta-analysis. Arch Dis Child 2017;102:123-30.
8. Pehlıvan SS, Gergın OO, Bayram A, Altay D, Arslan D, Biçer C, et al. The effect of passive smoking on the laryngospasm rate in children sedated during the esophagogastroduodenoscopy. Saudi Med J 2022;43:275-82.
9. Seyidov TH, Elemen L, Solak M, Tugay M, Toker K. Passive smoke exposure is associated with perioperative adverse effects in children. J Clin Anesth 2011;23:47-52.
10. Simsek E, Karaman Y, Gonullu M, Tekgul Z, Cakmak M. The effect of passive exposure to tobacco smoke on perioperative respiratory complications and the duration of recovery. Braz J Anesthesiol 2016;66:492-8.
11. Drongowski RA, Lee D, Reynolds PI, Malviya S, Harmon CM, Geiger J, et al. Increased respiratory symptoms following surgery in children exposed to environmental tobacco smoke. Paediatr Anaesth 2003;13:304-10.
12. Jones DT, Bhattacharyya N. Passive smoke exposure as a risk factor for airway complications during outpatient pediatric procedures. Otolaryngol Head Neck Surg 2006;135:12-6.
13. Thikkurissy S, Crawford B, Groner J, Stewart R, Smiley MK. Effect of passive smoke exposure on general anesthesia for pediatric dental patients. Anesth Prog 2012;59:143-6.
14. Bahçeci C, Özkubat G, Demİroğullari S, Üçdoğruk Ş. Türkiye'de hanelerİn sİgara tüketİm harcamalarinda yasal düzenlemelerİn etkİlerİ: 2007 ve 2019 yillari oaxaca-blinder ayrıştirmasi. Dokuz Eylul University Journal of Graduate School of Social Sciences 2022;24:961-82.
15. Eke BC, Yüce Y. Türkiye'de yeni üretilen ve geliştirilmekte olan nikotin ve tütün ürünleri ile ilgili yasal düzenlemeler. Turkish Bulletin of Hygiene & Experimental Biology/Türk Hijyen ve Deneysel Biyoloji 2022;79:567-78.
16. WHO. Global Report on Trends in Prevalence of Tobacco Use 2000-2025. 2021. https://www.who.int/publications/i/item/9789240039322
17. Lakshmipathy N, Bokesch PM, Cowen DE, Lisman SR, Schmid CH. Environmental tobacco smoke: a risk factor for pediatric laryngospasm. Anesth Analg 1996;82:724-7.
18. Lyons B, Frizelle H, Kirby F, Casey W. The effect of passive smoking on the incidence of airway complications in children undergoing general anaesthesia. Anaesthesia 1996;51:324-6.
19. Mamie C, Habre W, Delhumeau C, Argiroffo CB, Morabia A. Incidence and risk factors of perioperative respiratory adverse events in children undergoing elective surgery. Paediatr Anaesth 2004;14:218-24.
20. Mamaril ME. Preoperative Risk Factors Associated With PACU Pediatric Respiratory Complications: An Integrative Review. J Perianesth Nurs 2020;35:125-34.
21. Alalami AA, Ayoub CM, Baraka AS. Laryngospasm: review of different prevention and treatment modalities. Paediatr Anaesth 2008;18:281-8.
22. Hernández-Cortez E. Update on the management of laryngospasm. Anestesia en México 2018;30:12-9.
23. Li L, Zhang Z, Yao Z, Wang H, Wang H, An H, et al. The impact of laryngeal mask versus other airways on perioperative respiratory adverse events in children: A systematic review and meta-analysis of randomized controlled trials. Int J Surg 2019;64:40-8.
24. Greenberg RA, Bauman KE, Glover LH, Strecher VJ, Kleinbaum DG, Haley NJ, et al. Ecology of passive smoking by young infants. J Pediatr 1989;114:774-80.
25. Licht AS, Hyland A, Travers MJ, Chapman S. Secondhand smoke exposure levels in outdoor hospitality venues: a qualitative and quantitative review of the research literature. Tob Control 2013;22:172-9.

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Research

Determination of Individual Innovation Characteristics of Operating Room Nurses

Ameliyathane Hemşirelerinin Bireysel İnovasyon Özelliklerinin Belirlenmesi

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ABSTRACT

Objective: This study was conducted to determine the individual innovativeness of the operating room nurses and the individual factors affecting them. Operating room nurses, who work in operating rooms where many biomedical devices and sensitive instruments are used and are constantly changing with the developments in technology, need to lead in terms of individual innovative features and adapt quickly to change.

Methods: A descriptive and cross-sectional study was conducted between 15 November and 31 December 2021 with the participation of 153 operating room nurses in the province of Istanbul. "Individual Innovation scale (IIS)" and "Descriptive Information Form" were used as data collection tools. Data analysis was done with the SPSS 25.0 program.

Results: The operating room nurses' total IIS score was 68.7±7.7, while their opinion leadership, resistance to change, and risk-taking subscale scores were 28.4±3.4, 23.2±5.5, 17.1±1.8 respectively. It was determined that gender, marital status, education level, years of experience in the operating room, surgical department, and institution characteristics affected individual innovativeness characteristics ($p<0.05$; $p<0.01$).

Conclusion: It was determined that the innovative behavior characteristics of the operating room nurses are mostly interrogators and the need to support and develop their innovativeness characteristics.

Keywords: Individual innovativeness, nurse, operating room nurse

ÖZ

Amaç: Ameliyathane hemşirelerinin bireysel yenilikçilik özelliklerini ve etkileyen bireysel faktörleri belirlemek amacıyla yapıldı. Birçok biyomedikal cihazın ve hassas aletlerin kullanıldığı ameliyathanelerde çalışan ve teknolojideki gelişmelerle sürekli değişen ameliyathane hemşirelerinin bireysel yenilikçilik özellikler açısından öncülük etmesi ve değişime hızlı uyum sağlaması gerekmektedir.

Gereç ve Yöntem: İstanbul ilinde 153 ameliyathane hemşiresinin katılımıyla 15 Kasım-31 Aralık 2021 tarihleri arasında tanımlayıcı ve kesitsel bir çalışma olarak yapıldı. Veri toplama aracı olarak "Bireysel Yenilik ölçeği (BYÖ)" ve "Tanımlayıcı Bilgi Formu" kullanıldı. Veri analizi SPSS 25.0 programı ile yapıldı.

Bulgular: Ameliyathane hemşirelerinin toplam BYÖ puanı 68,7±7,7, fikir liderliği, değişime direnç ve risk alma alt ölçek puanları sırasıyla 28,4±3,4, 23,2±5,5, 17,1±1,8 idi. Cinsiyet, medeni durum, eğitim düzeyi, ameliyathanedeki deneyim yılı, cerrahi bölüm ve kurum özelliklerinin bireysel yenilikçilik özelliklerini etkilediği belirlendi ($p<0,05$; $p<0,01$).

Sonuç: Ameliyathane hemşirelerinin yenilikçi davranış özelliklerinin daha çok sorgulayıcı olduğu ve yenilikçilik özelliklerini destekleme ve geliştirme ihtiyacı olduğu belirlendi.

Anahtar Kelimeler: Bireysel yenilikçilik, hemşirelik, ameliyathane hemşiresi

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INTRODUCTION

Innovativeness can be defined in different ways, such as adopting innovation faster than others, acting outside what was known before, and creating an absolute change. On the other hand, individual innovativeness is expressed as an individual's willingness to innovate, adopting a positive attitude, and adopting it as a behavior (1-3).

In line with the developments in diagnosis, treatment, and care services, change management is stated as the most important organizational vision for health institutions. Organizational change in the field of health services requires a vision understanding of "the basic functions of the system and those that support these functions". With this understanding, there is a need for a highly qualified workforce that performs regulations and functions professionally (4). Operating rooms appear as service areas where innovative approaches are most needed with the effect of rapidly developing technology (5).

There are studies in the literature on the innovativeness of nursing students and nurses working in internal medicine and surgery clinics (1-5). However, only two studies were found that included operating room nurses, who were most affected by the developments in science and technology and therefore had to adapt to a constant change and development.

Therefore, with the view that more research is needed on operating room nurses; in order to determine the distribution of innovative behavior level categories of operating room nurses, the relationship between innovative behavior level and sociodemographic and descriptive characteristics (age, gender, marital status, education level, operating room experience years, surgical department and institution characteristics).

This research was carried out to determine the individual innovativeness of the operating room nurses, who are most affected by the developments in science and technology and therefore have to adapt to a constant change and development, and the individual factors that affect them. Studies examining the innovative characteristics of operating room nurses could not be found. For this reason, it is aimed to make suggestions to institutions and leaders in determining, supporting, and developing the innovative characteristics of operating room nurses and to contribute to the literature.

The research questions were determined:

1) In which category are the individual innovativeness characteristics of the operating room nurses?

2) What are the individual factors affecting the individual innovativeness of the operating room nurses?

METHODS

Study Design

It was planned as a descriptive and cross-sectional study.

Sample and Setting

The study population consisted of nurses working as operating room nurses in Istanbul. The sample of the study was carried out with 153 operating room nurses who were actively working in any health institution in Istanbul between November 15 and December 31, 2021 who agreed to participate in the research and met the inclusion criteria of the study.

The snowball sampling technique, one of the nonprobability sampling methods, was used. The suggested analysis for relational studies, which is used to determine the factors decisive in calculating the sample size, was used. Considering the number of independent variables, the study was planned to be completed with the participation of 149 operating room nurses according to the 0.05 significance value, 95% power, and 0.15 effect size parameters (https://www.danielsoper.com/statcalc/calculator.aspx?id=1). The study was completed with the participation of 153 operating room nurses.

Inclusion Criteria

Operating room nurses working as operating room nurses in any institution in the province of İstanbul who reached and voluntarily agreed to participate in the research were included in the study.

Data Collecting Tools

The data were collected in the studyusing the online data collection tools "Descriptive Information Form" and "Individual Innovation scale (IIS)", which were prepared by the researchers in line with the literature (5).

Descriptive Information Form

It consists of 7 items that include the sociodemographic characteristics of the operating room nurses (age, gender, marital status, educational status, operating room working years, surgical department and institution information).

Individual Innovation Scale

It was developed by Hurt, Joseph, and Cook in 1977 to measure the innovativeness level of individuals, and its Turkish validity and reliability study was carried out by Sarıoğlu Kemer and Yıldız in 2014 (6). A total of 20 items in

the original scale were arranged as 18 items in the Turkish validity and the reliability study. The answers in the scale are 5-point Likert type; it is scored between "strongly disagree: 1 point and strongly agree: 5 points". In IIS there are 11 directs (1st, 2nd, 3rd, 4th, 7th, 8th, 10th, 11th, 14th, 16th and 17th items) and 7 reverses (18th, 15th 13th, 12th, 9th, 6th, 5th items) items. The scale has three subscale scores. 7 items (1st, 3rd, 4th, 7th, 8th, 10th, 11th items) reflecting the "Opinion Leadership subscales score" and 7 items that reflect the "Resistance to Change subscales score" (5th, 6th, 9th, 12th, 13th, 15th, 18th items) and 4 items (2nd, 14th, 16th, 17th items) reflecting the "Risk Taking subscales score" are evaluated. The lowest score that can be obtained from the scale is 18 and the highest is 90 points. The evaluation of the scale is based on the total score. In the evaluation, 82 points and above are accepted as "Innovators", between 75 and 82 points as "Pioneers", between 66 and 74 points as "Interrogators", between 58 and 65 points as "Skeptical", 57 points and below as "Traditionalists". The "Opinion Leadership subscales score" refers to the characteristics that make the individual ahead of the others according to the group characteristics; "Resistance to Change subscales score" refers to individuals' concerns about change and innovation; and the "Risk Taking subscales score" reflects the characteristics of coping with uncertainties. The related feature increases linearly with the increase in scores in all dimensions. The Cronbach's alpha coefficient of IIS 0.82 is reported as 0.80 in the Opinion Leadership subscale score, 0.78 in the Resistance to Change subscale score, and 0.72 in the Risk-Taking subscale score (1-3,6-8). In the research, the Cronbach's alpha coefficient of IIS 0.82 was 0.80 in the Opinion Leadership subscales score, 0.85 in the Resistance to Change subscales score, and 0.71 in the Risk-taking subscales score. When Cronbach's alpha reliability coefficients were examined on the basis of the total and subscale scores of the IIS, it was determined that it varied between 0.851 and 0.715, and the internal consistency of the scale was reliable according to the coefficients.

Data Collection

The data collection form was sent online to the nurses who would participate in the study. In the data collection form, information was given about the purpose of the study and the essentiality of voluntary participation, and their consent was obtained. Filling out the data collection form takes approximately 5-10 minutes.

Statistical Analysis

Data analysis was performed using SPSS 25.0 (Statistical Packages for the Social Sciences, Armonk, NY: IBM Corp. 2017) program. Within the scope of the research, the participants' sociodemographic information and IIS responses were evaluated. Since the expressions of the scale's Resistance to Change dimension consisted of opposite expressions, the expressions were reversed before the evaluations were made. In the evaluation of the data; the standard deviation, median, frequency, percentage, lowest value, and highest value were used from descriptive statistics. Scores related to the total and subscale scores of the scale were obtained from the total scores of the responses given to the statements under the dimension. Before examining the differences according to demographic variables, their conformity to the normal distribution was examined with the Kolmogorov-Smirnov test. Among the tests, Mann-Whitney U test and Kruskal-Wallis test were applied. After the Kruskal-Wallis test, the Dunn-Bonferroni test was applied as the post hoc test. In the analysis of the data, $p<0.05$ values were considered statistically significant.

Ethical Permissions

Ethical permission (no: 2021/11-733, date: 01.11.2021) for the study was obtained from the İstanbul Yeni Yüzyıl University Science, Social and Non-Interventional Health Sciences Research Ethics Committee. Permission to use the scale and written informed consent from the nurses participating in the study were obtained from the authors who conducted the validity and reliability study for the use of the scale.

RESULTS

According to the total IIS scores of the operating room nurses, individual innovativeness levels were determined to be mostly questioning (45.75%), skeptic (28.75%), pioneering (16.99%), innovative (4.57%), and least traditional (3.92%). The sociodemographic and working life characteristics of the participants are shown in (Table 1).

According to age groups, the 26-33 age group was perceived as more opinion leaders than the 18-25 age group ($p<0.05$). According to gender, men are perceived as more opinion leaders than women, while women are less anxious about change and innovation than men ($p<0.05$; $p<0.01$). In compliance with marital status, married people show a more innovative attitude and opinion leadership and are more open to change than singles ($p<0.05$; $p<0.01$). As per educational status, undergraduate and graduate graduates are more competent in terms of individual innovation and less resistant to change than associate degree graduates. Health vocational high school graduates report the ability to cope with uncertainties and take risks compared to both associate degree and undergraduate and higher graduates ($p<0.05$; $p<0.001$). According to the years of operating room experience, individual innovativeness and opinion

leadership were higher in participants with 10 or more years of experience ($p<0.05$; $p<0.001$). In accordance with the characteristics of the institution, employees working in private institutions show the ability to cope with uncertainties and opinion leadership compared with those working in public institutions ($p<0.05$). As reported by the Surgical Intervention List to be Applied in the Surgical Intervention Units of the Ministry of Health, Annex 1 group (Ministry of Health 2009/42), operating room nurses working in the surgical departments where major surgeries are performed show less resistance to change ($p<0.05$). The total scores of the operating room nurses' IIS/subscales score and items are given in (Table 2).

DISCUSSION

Due to the limited number of studies describing the individual innovative characteristics of operating room nurses, studies conducted with sample groups including nurses working in other units (medical/surgical/intensive care) were included in the discussion. Innovation in the delivery of health services and patient care is expressed as the process of transferring a new idea to the development of patient care and improving outcomes (9). It is emphasized that operating room workers, who are most affected by the rapid technological developments in recent years, should support their innovative features in order to adapt quickly to changes and developments (10). In the results of a study conducted in 2021 to determine the factors affecting the individual innovativeness of operating room staff, including operating room nurses, it has been reported that individual innovativeness levels are affected by gender, marital status, type of occupation (physician, nurse, operating room technician), age, and working year (5). In line with the results of the research, it was determined that among the operating room nurses, men are perceived as more opinion leaders than women, and women show less resistance to change than men. Married people are more competent in terms of individual innovation, more opinion leaders, and less resistant to change than singles. Although not as a professional group, in terms of the level of education that may correspond to this, it was determined that undergraduate and higher graduates were more competent in terms of individual innovativeness and less resistant to change than associate degree graduates. It was found that the graduates of health vocational high schools had higher scores in terms of risk taking compared to both associate degree and university and higher graduates, and they were more inclined to take risks. In a study, it was reported that the X generation was more innovative than the Y generation, but this result may be related to the sample characteristics in which the physicians are majority (11). In another study conducted with nurses and nursing students, it was found that the Y generation is more innovative than the X generation (7). In some studies, there is no relationship between age and innovativeness characteristics (8,12). According to the research findings, opinion leadership behavior was observed more in the 26-33 age group than in the 18-25 age group. There was no difference in the age groups of 34 years and above, indicating that the level of individual innovativeness was positively and weakly correlated with age increase. According to the different results reported in the literature, it is thought that these results can be explained by the fact that the sample group in the study consisted of operating room nurses, age ranges were determined, and comparisons of the subscales scores in the scale were made, and there is no possibility of comparison. It can be said that this result supports the view that there is a need for more research with operating room nurses, including comparisons of scale subscales scores, as

Table 1. Sociodemographic and professional experience characteristics of the participants (n=153)

Characteristics		n	%
Gender	Male	26	17.0
	Female	127	**83.0**
Age (range)	18-25 years old	66	**43.1**
	26-33 years old	34	22.2
	34-41 years old	38	24.8
	42 years and older	15	9.8
Education	Health vocational high school	30	19.6
	Associate degree	56	36.6
	Bachelor's and above	67	**43.8**
Marital status	Single	88	**57.5**
	Married	65	42.5
Operating room experience	0-1 year	38	24.8
	2-4 years	32	20.9
	5-10 years	30	19.6
	10 years and above	53	**34.6**
Institution of employment	Private hospital	101	**66.0**
	*Public hospitals	52	34.0
**Surgical group	Minor surgeries surgical group	34	22.2
	Middle surgeries surgical group	75	**49.0**
	Major surgeries surgical group	44	28.8

*Public hospitals: State Hospital (8), Education and Research Hospital (16), City Hospital (8), University Hospital (20); **Surgical group: List of Surgical Interventions to Be Applied in Surgical Intervention Units of the Ministry of Health according to Annex. 1 group (Ministry of Health 2009/42)

Table 2. Comparison of individual innovativeness levels of operating room nurses according to sociodemographic and descriptive characteristics (n=153)

Characteristics	Mean ± SD Median (lower-upper)				Test			
Age range	**18-25 years (a) (n=66)**	**26-33 years (b) (n=34)**	**34-41 years (c) (n=38)**	**42 years and above (d) (n=15)**	**H value**	**Df**	**p-value**	**Differences**
IIS total score	66.67±7.71 67 (51-87)	69.76±5.87 69 (62-80)	70.26±8.37 71 (58-86)	71.07±7.59 69 (60-86)	7.205	3	0.066	
Opinion Leadership Subscales score	27.7±3.51 28 (17-34)	29.59±2.79 30 (22-34)	28.79±3.44 28 (23-35)	28.2±3.28 28 (22-33)	8.717	3	**0.033***	b>a (p=0.024)
Risk-Taking Subscales score	16.73±2.12 17 (13-20)	17.41±1.26 17 (16-20)	17.16±1.75 17 (14-20)	17.33±1.54 16 (16-20)	3.256	3	0.354	
Resistance Change Subscales score	22.24±5.64 24 (9-33)	22.76±5.77 23 (13-34)	24.32±5.29 26 (14-33)	25.53±3.62 25 (22-33)	5.347	3	0.148	
Gender	**Male (n=26)**		**Female (n=127)**		**U**	**z**	**p-value**	
IIS total score	67±5.73 68 (58-76)		69.02±7.96 69 (51-87)		1426	-1.094	0.274	
Opinion Leadership Subscales score	29.69±1.76 29 (27-32)		28.18±3.57 28 (17-35)		1180	-2.306	**0.021***	
Risk-Taking Subscales score	17.08±2.24 17 (13-20)		17.04±1.73 17 (13-20)		1527	-0.615	0.539	
Resistance Change Subscales score	20.23±4.42 20 (14-28)		23.8±5.5 24 (9-34)		994	-3.199	**0.001****	
Marital status	**Single (n=88)**		**Married (n=65)**		**U**	**z**	**p**	
IIS total score	67.18±6.91 67 (51-87)		70.71±8.17 72 (51-86)		2048	-3.001	**0.003****	
Opinion Leadership Subscales score	28.02±3.1 28 (21-34)		29±3.67 29 (17-35)		2292	-2.113	**0.035***	
Risk-Taking Subscales score	16.84±1.87 17 (13-20)		17.32±1.73 17 (14-20)		2538	-1.213	0.225	
Resistance Change Subscales score	22.32±5.27 23.5 (9-33)		24.38±5.59 26 (13-34)		2249	-2.260	**0.024***	
Education	**Health vocational high school (a) (n=30)**		**Associate degree (b) (n=56)**	**Bachelor's and above (c) (n=67)**	**H value**	**Df**	**p-value**	**Differences**
IIS total score	69.87±6.4 71 (58-80)		66.46±7.69 66 (51-87)	70±7.8 70 (58-86)	8.278	2	**0.016***	c>b (p=0.037)
Opinion Leadership Subscales score	29.53±2.62 29 (23-34)		28±3.64 27 (17-34)	28.31±3.39 28 (21-35)	5.852	2	0.054	
Risk-Taking Subscales score	18.2±1.19 18 (16-20)		16.46±1.95 16.5 (13-20)	17.01±1.72 17 (13-20)	18.979	2	**0.0001*****	a>b (p=0.000) a>c (p=0.002)
Resistance Change Subscales score	22.13±5.05 23 (13-29)		22±6.04 22 (9-34)	24.67±4.88 25 (14-33)	8.181	2	**0.017***	c>b (p=0.029)
Operating room experience	**0-1 year (a) (n=38)**	**2-4 years (b) (n=32)**	**5-10 years (c) (n=30)**	**10 years and above (d) (n=53)**	**H value**	**Df**	**p-value**	**Differences**

Table 2. Continued

IIS total score	65.95±6.6 68 (51-78)	66.88±8.13 66.5 (51-87)	69.27±6.63 69 (59-80)	71.4±7.79 73 (58-86)	12.657	3	**0.005****	d>a (p=0.01) d>b (p=0.04)
Opinion Leadership Subscales score	27.32±2.59 28 (21-32)	27.94±4.09 27.5 (17-34)	28.93±2.86 29 (22-33)	29.26±3.48 29 (22-35)	10.288	3	**0.016***	d>a (p=0.03)
Risk-Taking Subscales score	16.58±1.84 16 (13-20)	16.63±2.18 17 (13-20)	17.2±1.06 17 (16-19)	17.55±1.81 18 (14-20)	7.039	3	0.071	
Resistance Change Subscales score	22.05±5.9 24 (9-30)	22.31±5.09 23 (15-33)	23.13±6.02 24 (14-34)	24.58±4.92 26 (13-33)	5.240	3	0.155	
Instution	**Public (n=52)**		**Private (n=101)**		**U**	**z**	**p**	
IIS total score	67.73±7.77 67.5 (51-86)		69.17±7.57 69 (51-87)		2367	-0.999	0.318	
Opinion Leadership Subscales score	27.77±3.21 28 (21-34)		28.78±3.43 29 (17-35)		2115	-1.984	**0.047***	
Risk-Taking Subscales score	16.62±1.73 16 (13-20)		17.27±1.84 17 (13-20)		2020	-2.382	**0.017***	
Resistance Change Subscales score	23.35±6.22 24.5 (9-34)		23.12±5.1 24 (13-33)		2499	-0.490	0.624	
Department of employment/surgical group	**Minor surgeries surgical group (a) (n=34)**	**Middle surgeries surgical group (b) (n=75)**	**Major surgeries surgical group (c) (n=44)**		**H value**	**Df**	**p-value**	**Differences**
IIS total score	67.65±8.13 68 (51-86)	68.16±6.71 67 (51-86)	70.36±8.62 72 (57-87)		3.178	2	0.204	
Opinion Leadership Subscales score	28.88±3.19 29 (21-34)	28.28±3.62 28 (17-35)	28.36±3.13 28 (22-34)		1.490	2	0.475	
Risk-Taking Subscales score	17.06±1.98 17 (13-20)	17.09±1.85 17 (13-20)	16.95±1.68 16 (14-20)		1.219	2	0.544	
Resistance Change Subscales score	21.71±6.47 24 (9-33)	22.79±4.68 23 (13-33)	25.05±5.57 26.5 (14-34)		8.655	2	**0.013***	c>a (p=0.031) c>b (p=0.03)

Mean ± SD: Mean ± standard deviation; *p<0.05; **p<0.01; ***p<0.001; U: Mann-Whitney U test, p: The value of signiability, Df ; Degree of freedom, H value: Kruskal-Wallis test
a: Eye surgery (8), Ear Nose Throat surgery (2), Pediatric Surgery (2), Other surgeries (26).
b: General surgery (14), Other surgeries (61).
c: Neurosurgery (6), Cardiovascular surgery (22), Orthopedics and Traumatology surgery (8), Obstetric surgery (8)

stated in the research purpose. In a qualitative study conducted with nurses (13) and in another study conducted with operating room workers (physicians, nurses, surgery technicians) (11), it has been reported that there is a linear relationship between years of experience and innovation level. In some studies, it has been reported that the year of professional experience is not related to the level of innovation (8,12,14). Individuals with 10 or more years of experience in the operating room have higher individual innovativeness levels than those with 0-1 years or 2-4 years of experience, and there is no difference between them and those with 5-10 years of experience. In terms of the Opinion Leadership subscale score, those with 10 years or more of experience state that they are perceived as more opinion leaders than those with 0-1 years of experience. Consistent with the literature, it was claimed that after the first working year, which included the inexperience and learning process, the innovativeness level of the operating room nurses increased as the years of experience increased. It is thought that this result can be explained by the development of the professionalism of operating room nurses in determining the requirements for surgical intervention and patient safety,

being aware of and eliminating inadequacies, in line with their experience in surgical intervention procedures. Among the factors hindering innovation are institutional barriers and inadequacy of resources, as well as the attitudes of members of the profession. In addition, workload and employees' feeling of pressure are also expressed as negative factors affecting the level of innovation (2). In the research conducted by Bilik et al. (5), the participants reported the attitudes of managers and institutional approaches as barriers to innovation. It was claimed in the research that the employees in private institutions showed more ability to cope with uncertainties and opinion leadership than those working in public institutions. It is thought that operating room nurses do not prefer to take risks with innovative ideas and initiatives due to the corporate culture brought by the legal regulations in public institutions, the management approach, and the approaches of the members of the profession, and prefer to continue their defined duties in the current order. For the implementation of innovations, the support of nurse leaders and the establishment of an institutional culture that adopts and values evidence-based practice standards are extremely important (15-17). As emphasized in the literature (18,19), it is recommended to know the factors that negatively affect the level of innovation, to accept and make the necessary arrangements, to increase the awareness of the leading decision-makers, and to ensure cooperation in supporting innovation and change. Those working in Major Surgeries Surgery Group departments showed less resistance to change than those working in Minor and Middle Surgeries Surgery Group departments. This result can be interpreted as the change and development observed in surgical departments that use special tools, equipment, methods, and technology that positively affect and support individual innovative features. In addition to the limited number of studies in the scientific literature that included operating room nurses in the sample group, an analysis related to the total score and subscales scores of the operating room nurses and the surgical departments they were working with could not be reached. In two studies conducted with operating room workers, in which the operating room nurses were also in the sample group, it was reported that the individual innovativeness level of the health workers in the operating room was mostly in the "traditional" category (5,14). The data obtained from another study conducted with internal medicine, surgical and intensive care nurses apart from operating room nurses was evaluated as the result that 40.7% of the nurses and in another study 42.1% of the nurses were "skeptical" (6,14). This result, which is inconsistent with the literature, is related to the fact that most participants in the sample group have a bachelor's degree or higher, have 10 years or more experience working in private institutions, and are thought to be limited to group characteristics. In a study conducted to define the individual innovativeness characteristics of intensive care, internal and surgical nurses, the total score of the nurses' IIS was 70.71±9.79, the total score of the opinion leadership subscales was 25.85±4.77, and the total score of the resistance to change subscales was 18. 57±5.81, and the Risk-Taking Subscales score total score was 15.93±3.18. In the study, although the total score of the operating room nurses' IIS (68.7±7.7) was lower than the values reported in the literature, and the total score of the Risk-Taking Subscales score (17.1±1.8) was similar, the total score of the Resistance to Change subscales score (23.2±5.5) was found to be significantly higher. Accordingly, it can be said that operating room nurses show less resistance to change and are more open to change compared with intensive care, medical, and surgical nurses. When the expressions in which the operating room nurses have an average of 4 and above among the expressions in the subscales scores, it can be concluded that they are sensitive to the problems encountered, support innovative ideas and initiatives to find solutions, and enjoy using new things and leading the use of innovations. Since no analysis was found in the literature regarding the statements containing the answers to the subscales scores, no evaluation could be made. It is predicted that because of supporting the innovativeness of the operating room nurses, who are mostly in the questioning category with their individual innovativeness, they will contribute positively to the development of intraoperative nursing care with innovative and evidence-based practices and to increase the quality of care.

Study Limitations

This research reveals the need for research on defining, supporting, and developing the innovativeness of operating room nurses by accepting that the innovativeness of operating room nurses may show different characteristics with different factors in different geographies and cultures. There are limitations to this research that should be acknowledged. The results obtained may vary according to other countries and cities in terms of geography, city, cultural structure, nursing education system, and structuring of health services. For this reason, it can be stated that the research results are limited to the sample and cannon be generalized.

CONCLUSION

It has been determined that the individual innovativeness of the operating room nurses is mostly in the inquiring category,

women are more open to change than men, men and those with more than ten years of experience are perceived as more opinion leaders, and married people are perceived as both more open to change and opinion leaders. It was found that as the level of education and years of experience increased, the innovativeness level was positively affected, while the risk-taking feature decreased. While those working in private institutions report that they are perceived as more opinion leaders than those working in public institutions, operating room nurses working in departments where major surgical operations are performed, regardless of institution, state that they are less resistant to change. Operating room nurses state that they research and develop new solution methods to the problems they encounter and that they like to lead innovations with an attitude that supports innovative ideas and initiatives. The fact that very few operating room nurses who undertake important responsibilities during surgical intervention in operating rooms where different and rapidly developing technologies are used are in the "innovative" category shows the need to develop their innovative features. Innovative behaviors in operating room nurses are thought to be one of the most important factors in the development of evidence-based patient care and safety practices in the surgical intervention process. In line with the results obtained, the institutions and leaders working together should encourage their participation in in-service training or similar programs, where they will be informed about scientific and technological developments that will support the innovative features of operating room nurses and enable them to be an opinion leader, review institutional policies, and make arrangements according to the needs. Conducting this research with including different geography and cultures; It can obtain important information about identifying and supporting the innovative characteristics of operating room nurses.

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ETHICS

Ethics Committee Approval: Ethical permission (no: 2021/11-733, date: 01.11.2021) for the study was obtained from the İstanbul Yeni Yüzyıl University Science, Social and Non-Interventional Health Sciences Research Ethics Committee.

Informed Consent: Permission to use the scale and written informed consent from the nurses participating in the study were obtained from the authors who conducted the validity and reliability study for the use of the scale.

Authorship Contributions

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

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REFERENCES

1. Kemer AS, Altuntaş S. Adaptation of the individual innovativeness scale in nursing profesion: Turkish validity reliability study. JERN 2017;14:52-62.
2. Özpulat F, Karakuzu S. Yenilikçi davranışları etkileyen faktörler: Devlet hastanesi örneği. Anadolu Kültürel Araştırmalar Dergisi 2018;2:46-58.
3. Nelson R. Nursing Innovation. Am J Nurs 2020;120:18-9.
4. Milella F, Minelli EA, Strozzi F, Croce D. Change and Innovation in Healthcare: Findings from Literature. Clinicoecon Outcomes Res 2021;13:395-408.
5. Bilik Ö, Duran M, Damar HT, Kaynar GÖ. Ameliyathane çalışanlarında bireysel yenilikçilik davranışlarının, etkileyen ve engelleyen etmenlerin belirlenmesi. SHYD 2021;8:303-13
6. Sarıoğlu Kemer A, Yıldız İ. Hemşirelerin Bireysel Yenilikçilik Özelliklerinin Belirlenmesi. SHYD 2020;3:363-70.
7. Başoğlu M, Edeer AD. X ve Y kuşağındaki hemşirelerin ve hemşirelik öğrencilerinin bireysel yenilikçilik farkındalıklarının karşılaştırılması. GÜSBD 2017;6:77-84.
8. Zengin H, Tiryaki Ö, Çınar N. Hemşirelikte yenilikçilik ve ilişkili faktörler. Sağlık ve Hemşirelik Yönetimi Dergisi 2019;6:207-17.
9. Quality ID. Delivering quality, serving communities: Nurses leading care innovations. International Council of Nurses. Geneva. 2009.
10. Ushimaru Y, Takahashi T, Souma Y, Yanagimoto Y, Nagase H, Tanaka K, et al. Innovation in surgery/operating room driven by Internet of Things on medical devices. Surg Endosc 2019;33:3469-77.
11. Yiğit S, Aksay K. A comparison between generation X and generation Y in terms of individual innovativeness behavior: the case of Turkish health professionals. International Journal of Business Administration 2015;6:106-17.
12. Baksi A, Sürücü HA, Kurt G. Hemşirelerin bireysel yenilikçilik davranışları ve bu davranışları etkileyen faktörlerin incelenmesi. ACU Sağlık Bil Derg 2020;2:310-5.
13. Sönmez B, Yıldırım A. Bir üniversite hastanesinde çalışan hemşirelerin yenilikçi davranışları ve yenilikçi davranışlarını etkileyen faktörlere ilişkin görüşlerinin belirlenmesi: Niteliksel bir çalışma. Sağlık ve Hemşirelik Yönetimi Dergisi 2014;1:49-59.
14. Gök Uğur H, Aksu D, Hakyemez A. Hemşirelerin inovasyona bakış açıları ile bireysel yenilikçilik durumları arasındaki ilişkinin incelenmesi. Samsun Sağ Bil Der 2020;5:128-4.
15. Clement-O'Brien K, Polit DF, Fitzpatrick JJ. Innovativeness of nurse leaders. J Nurs Manag 2011;19:431-8.
16. Kazmi SAZ, Naaranoja M. Healthcare transformation through change management process for innovation. International Conference on Applied Human Factors and Ergonomics 2018:380-9.
17. Qi L, Liu B, Wei X, Hu Y. Impact of inclusive leadership on employee innovative behavior: Perceived organizational support as a mediator. PLoS One 2019;14:e0212091.
18. Bagheri A, Akbari M. The Impact of Entrepreneurial Leadership on Nurses' Innovation Behavior. J Nurs Scholarsh 2018;50:28-35.
19. Sönmez B, Yıldırım A. The mediating role of autonomy in the effect of pro-innovation climate and supervisor supportiveness on innovative behavior of nurses. EJIM 2018;22:41-58.

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Research

The Surgical Results of Cholangiocarcinomas, Single Center Experience

Kolanjiokarsinomların Cerrahi Sonuçları, Tek Merkez Deneyimi

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ABSTRACT

Objective: Cholangiocarcinomas (CC) are rare tumors that develop from the biliary tract and surgery is the gold standard for them. All efforts have been made by surgeons from past to present to obtain R0 resection. The aim of the study was to examine the surgical therapy of CCs, which we have applied various surgical treatments in our clinic in the last three years.

Methods: Patients whose pathological examination yielded Hiler CC and underwent surgical operation at our clinic between February 2019 and February 2022 were retrospectively evaluated.

Results: Twenty five patients were found suitable for the study. Nine were male and 16 were female, with a mean age of 61.72±11.12 (minimum-maximum: 29-76) years. The overall morbidity rate in the postoperative period was 52%, and liver failure in the postoperative period was seen in 4 patients. Bile leakage developed in 2 patients. Portal vein thrombosis was detected in 2 patients and surgical site infection was detected in 5 patients. No mortality was seen in the intraoperative and postoperative periods. In the follow-up period, recurrence was observed in 3 patients and mortality was observed in 3 patients.

Conclusion: Advanced surgical techniques have induced extended indications in surgery and reduced mortality and morbidity ratios, and oncologic outcomes were more acceptable than before. The most significant purpose is to perform R0 resection to maintain adequate remnant liver volume. Such complex surgeries require multidisciplinary treatment in specialized hepatopancreaticobiliary and liver transplant services to optimize surgical and oncological outcomes.

Keywords: Cholangiocarcinomas, surgical results, morbidity, mortality

ÖZ

Amaç: Kolanjiokarsinomlar (KK) safra yollarından gelişen nadir tümörlerdir. KK'lerin tedavisinde cerrahi altın standarttır. Cerrahlar tarafından geçmişten günümüze R0 rezeksiyonunun elde edilmesi için her türlü çaba gösterilmiştir. Bu çalışmanın amacı, kliniğimizde son üç yılda çeşitli cerrahi tedaviler uyguladığımız KK'lerin sonuçlarını incelemektir.

Gereç ve Yöntem: Kliniğimizde Şubat 2019-Şubat 2022 tarihleri arasında Hiler KK tanısı ile cerrahi operasyon geçiren hastalarımızın tıbbi kayıtları retrospektif olarak incelendi.

Bulgular: Bu çalışmaya toplam 25 hasta dahil edildi. Çalışmada 16 kadın ve 9 erkek hasta olup, ortalama yaş 61,72±11,12 (minimum-maksimum: 29-76) yıl idi. Ameliyat sonrası dönemde genel morbidite oranı %52 idi ve 4 hastada 50:50 tanımına göre hepatektomi sonrası karaciğer yetmezliği görüldü. İki hastada safra kaçağı görüldü. İki hastada portal ven trombozu, 5 hastada cerrahi alan enfeksiyonu görüldü. İntraoperatif ve postoperatif dönemde mortalite görülmedi. Takip döneminde 3 hastada nüks ve 3 hastada mortalite görüldü.

Sonuç: Gelişen cerrahi teknik, cerrahi endikasyonları genişletmiş ve morbidite, mortalite oranı ve onkolojik sonuçlar eskisinden daha kabul edilebilir olmasına yol açmıştır. En önemli amaç, R0 rezeksiyonu yapmak ve kalacak yeterli karaciğer hacmini korumaktır. Bu tür karmaşık ameliyatlar, cerrahi ve onkolojik sonuçları optimize etmek için son derece uzmanlaşmış hepato-pankreatiko-biliyer ve karaciğer nakli ünitelerinde multidisipliner bir tedavi gerektirmektedir.

Anahtar Kelimeler: Kolanjiyokarsinomlar, cerrahi sonuçlar, morbidite, mortalite

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INTRODUCTION

Cholangiocarcinomas (CCs) are rare tumors that develop from the biliary tract. There are three different subtypes: intrahepatic, hilar, and distal CCs. CC is the second most common malignant primary liver tumor after hepatocellular carcinoma (1). Hilar CCs are also named as Klatskin tumors, which occur within 2 cm of the confluence of the bile ducts and generates for 50-70% of all CCs (2). Previously, surgical treatment for this tumor was detected as a high morbidity and mortality rate and with a low resectability ratio (up to 50%) and there is a high recurrence rate in this tumor (50% to 70%) (3,4). The diagnosis of CCs can be technically difficult and requires a high suspicion in order to detect lesions (5,6). CCs show firm biliary infiltration and vascular invasion due to a longitudinal and expansive growth pattern, and this growth pattern causes difficulty during a radical surgical intervention (6,7).

All efforts have been made by surgeons from past to present to obtain R0 resection. Because of these efforts, the surgical treatment of CCs includes extended hepatectomies, staged hepatectomy (portal vein ligation or embolization), vascular resections, and liver transplantations.

Our aim is to examine the results of CCs, which we have applied various surgical treatments in our clinic in the last three years.

METHODS

All procedures carried out in this study involving human participants were in accordance with the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki. This study was approved by the Ethics Committee of Ankara City Hospital (decision no: E2-22-2192, date: 20.07.2022).

Patients whose pathological examination yielded Hiler CC and underwent surgical operation at our clinic between February 2019 and February 2022 were retrospectively evaluated. Demographic features, preoperative factors, a type of surgery, intraoperative results, and postoperative outcomes were evaluated.

Statistical Analysis

IBM Statistical Package for Social Sciences (SPSS) ver 20.0 (IBM Corporation, Armonk, NY, USA) was used. According to the distribution of normality, Student t-test and Mann-Whitney U test was used to evaluate numerical data. Chi-square test was used for the categorical data. Numerical data were given as mean ± standard deviation and median [minimum-maximum (min-max) values] according to the normality test; categorical values were given as count (n) and percentage (%). A $p>0.05$ value was statistically significant. Kaplan-Meier test was used for survival analysis.

RESULTS

A total of 25 patients were included in this study. Nine were male and 16 were female, with a mean age of 61.72±11.12 (min-max: 29-76) years. All patients were treated surgically. The final histopathological examination revealed perihilar cholangiocarcinoma in all patients. The surgical approach was based on preoperative evaluation. In the pre-operative period, the most common complaints of the patients were jaundice (19 patients) and abdominal pain was the second most common. Preoperative percutaneous transhepatic or endoscopic biliary stenting was performed for managing obstructive jaundice in 17 patients. Bile duct resection with right hepatectomy was performed in 15 patients. Resection of the bile duct with left hepatectomy was performed in 4 patients and only bile duct resection was performed in 6 patients. R0 resection was achieved in 88% of patients and R1 resection was achieved in the other 3 patients. The median operative time of the patients was 420 minutes and median blood loss was 400 mL during the operation. The median postoperative hospital stay was 18 days (min-max: 3-91 days) (Table 1).

The overall morbidity rate in the postoperative period was 52%, and according to the 50:50 definition; liver failure in the post-hepatectomy period was seen in 4 patients. Bile leakage to the abdomen was seen in 2 patients. Portal vein thrombosis was detected in 2 patients and surgical site infection was detected in 5 patients (Table 2). No mortality was seen in the intra- and postoperative periods, which

Table 1. Demographic and clinical characteristics of the patients

Parameters	Surgery group (n=25)
Mean age ± SD (years) (min-max)	61.72±11.12 29-76
Gender (mean, %)	
Male	9
Female	16
Median value of the perop blood loss (mL) (min-max)	400 (200-600)
Median operation time (minute) (min-max)	420 (350-540)
First 30 day mortality n, (%)	0
Median hospital stay (min-max) days	18 (3-91)

SD: Standard deviation, min-max: Minimum-maximum

were defined as the first 90 days after the day of surgery In the follow-up period, recurrence was observed in 3 patients and mortality was observed in 3 patients.

Table 2. Postoperative complications of the patients

Complications	n, (%)
Surgical site infection	5 (20%)
Posthepatectomy liver failure	4 (16%)
Bile leakage	2 (8%)
Portal vein thrombosis	2 (8%)

DISCUSSION

CC is a malignant tumor that can be treated surely only by radical surgery. In the last decade, the treatment of CC was improved. By this improvment, surgical morbidity and mortality were decreased, and so indications for surgery were expanded (8). Our results in this study are encouraging and similar to previous results (9,10). There were only 3 recurrences in 25 patients in our study group and zero postoperative mortality. In the follow-up period, mortality was seen only in 3 patients.

Most papers reported that the purpose of surgery of CCs must be R0 resection; therefore, the principle surgical treatment, especially for type III and IV tumors, should include resection of the main bile duct with regional lymphadenectomy of the hepatoduodenal ligament and hepatic artery plus hemihepatectomy (right or left) and caudate lobe resection. The surgical treatment of type I or II tumors is hilar resection alone if the he R0 resection margin is achieved (11). In our study, bile duct resection with right hepatectomy was performed in 15 patients. Bile duct resection with left hepatectomy was performed in 4 patients, and only bile duct resection was performed in 6 patients. R0 resection was achieved in 88% of patients, and R1 resection was performed in 3 patients.

The surgical treatment of CC is very difficult and should be treated in an experient center. In the literature, the mortality ratio is reported as 7.5-18% and the complication rate is 19-85% (4,12-14). In our study, no mortality was seen in the intra- and postoperative periods, and the complication ratio was 52 (posthepatectomy liver failure was detected in 4 patients. Bile leakage was detected in 2 patients. Portal vein thrombosis was detected in 2 patients and surgical site infection was detected in 5 patients).

The peak prevalence of the CCs is in the seventh decade, and male predominance (1.5:1) was detected in a previous study (15). In our study, nine were male and 16 were female, with a mean age of 61.72±11.12 (min-max: 29-76) years. There is a slight female predominance in our study. In the pre-operative period, especially in CCs requiring major liver resection, biliary drainage is recommended in many publications. In our study, preoperative percutaneous transhepatic or endoscopic stenting was performed for managing obstructive jaundice in 17 patients.

Liver transplantation is also used in selected patient groups for treating CC in current literature (16,17). Today, liver transplantation is also used in selected patient groups for treating CC. In our study, liver transplantation was not applied to any patient.

Limitations of our study are a retrospective study and a single center experience, and the number of cases is low.

CONCLUSION

Advanced surgical techniques have induced extended indications in surgery and reduced mortality and morbidity ratio, and oncologic outcomes were more acceptable than before. The most significant purpose is to perform R0 resection to maintain adequate remnant liver volume. Such complex surgeries require multidisciplinary treatment in specialized hepatopancreaticobiliary and liver transplant services to optimize surgical and oncological outcomes.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of Ankara City Hospital (decision no: E2-22-2192, date: 20.07.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: O.A., V.Ö., A.G., Y.M.Ö., M.K.Ç., E.P., E.B.B., Concept: O.A., V.Ö., M.K.Ç., Design: O.A., V.Ö., M.K.Ç., Data Collection or Processing: V.Ö., A.G., Y.M.Ö., E.P., Analysis or Interpretation: V.Ö., Y.M.Ö., E.B.B., Literature Search: O.A., V.Ö., A.G., E.P., Writing: V.Ö., M.K.Ç., E.B.B.

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REFERENCES

1. Hennedige TP, Neo WT, Venkatesh SK. Imaging of malignancies of the biliary tract- an update. Cancer Imaging 2014;14:14.
2. Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD. Cholangiocarcinoma. Lancet 2005;366:1303-14.
3. Zhang W, Yan LN. Perihilar cholangiocarcinoma: Current therapy. World J Gastrointest Pathophysiol 2014;5:344-54.

4. Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BSJ, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234:507-19.
5. Hayashi S, Miyazaki M, Kondo Y, Nakajima N. Invasive growth patterns of hepatic hilar ductal carcinoma. A histologic analysis of 18 surgical cases. Cancer 1994;73:2922-9.
6. Lauterio A, De Carlis R, Centonze L, Buscemi V, Incarbone N, Vella I, et al. Current Surgical Management of Peri-Hilar and Intra-Hepatic Cholangiocarcinoma. Cancers (Basel) 2021;13:3657.
7. Ebata T, Mizuno T, Yokoyama Y, Igami T, Sugawara G, Nagino M. Surgical resection for Bismuth type IV perihilar cholangiocarcinoma. Br J Surg 2018;105:829-38.
8. Kosuge T, Yamamoto J, Shimada K, Yamasaki S, Makuuchi M. Improved surgical results for hilar cholangiocarcinoma with procedures including major hepatic resection. Ann Surg 1999;230:663-71.
9. Hu HJ, Mao H, Shrestha A, Tan YQ, Ma WJ, Yang Q, et al. Prognostic factors and long-term outcomes of hilar cholangiocarcinoma: A single-institution experience in China. World J Gastroenterol 2016;22:2601-10.
10. Romic I, Petrovic I, Golem AZ, Kinda E, Kekez T, Augustin G, et al. Surgical treatment of perihilar cholangiocarcinoma: 10-year experience at a single institution. Acta Chirurgica Croatica 2019;16:11-6.
11. Kow AW, Wook CD, Song SC, Kim WS, Kim MJ, Park HJ, et al. Role of caudate lobectomy in type III A and III B perihilar cholangiocarcinoma: a 15-year experience in a tertiary institution. World J Surg 2012;36:1112-21.
12. Kawasaki S, Imamura H, Kobayashi A, Noike T, Miwa S, Miyagawa S. Results of surgical resection for patients with hilar bile duct cancer: application of extended hepatectomy after biliary drainage and hemihepatic portal vein embolization. Ann Surg 2003;238:84-92.
13. Pichlmayr R, Weimann A, Klempnauer J, Oldhafer KJ, Maschek H, Tusch G, et al. Surgical treatment in proximal bile duct cancer. A single center experience. Ann Surg 1996;224:628-38.
14. Neuhaus P, Jonas S, Bechstein WO, Lohmann R, Radke C, Kling N, et al. Extended resections for hilar cholangiocarcinoma. Ann Surg 1999;230:808-18.
15. Zani S Jr, Pappas TN. Management of cholangiocarcinoma. In: Cameron JL, Cameron AM, editors. Current surgical therapy. 11th ed. Philadelphia: Elsevier Inc.; 2014. p. 414-9.
16. Knoefel WT, Prenzel KL, Peiper M, Hosch SB, Gundlach M, Eisenberger CF, et al. Klatskin tumors and Klatskin mimicking lesions of the biliary tree. Eur J Surg Oncol 2003;29:658-61.
17. Tsalis K, Parpoudi S, Kyziridis D, Ioannidis O, Savvala NA, Antoniou N, et al. Klatskin tumors and "Klatskin-mimicking lesions": our 22-year experience. Rev Esp Enferm Dig 2019;111:121-8.

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Research

Comparison of Facial Palsy Cases before and during the Pandemic Coronavirus Disease-2019

Koronavirüs Hastalığı-2019 Pandemisi Öncesi ve Sırasında Fasiyal Paralizi Olgularının Karşılaştırılması

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ABSTRACT

Objective: The pandemic coronavirus disease-2019 (COVID-19) is caused by a novel type of coronavirus named severe acute respiratory syndrome coronavirus-2 and is rapidly spreading all over the world. In addition to various neurological symptoms, acute facial palsy was diagnosed as the main neurological symptom in some COVID-19 patients. The current study aimed to analyze the variation and any possible association in the case numbers or medical symptoms of patients with facial palsy before and during the COVID-19 pandemic.

Methods: The clinical files of patients who were diagnosed with facial palsy in the Neurology Department of Medicalpoint Hospital, University of Economics Faculty of Medicine, İzmir were retrospectively investigated. To compare the facial palsy cases according to different periods, two patient groups were formed: before the COVID-19 pandemic and during the COVID-19 pandemic. The pandemic group was further divided into two subgroups as COVID-19-positive and COVID-19-negative patients to compare the effects of COVID-19 on facial palsy.

Results: During the specified COVID-19 period (May 2020-January 2021) of the study, 38 patients were admitted to the hospital for facial palsy; 34 facial palsy patients were admitted in the same calendar period as the two previous years (May 2018-January 2019). There was no significant difference in the frequency of facial palsy between these two time periods. There were significant differences between before and during the COVID-19 pandemic groups regarding response to cortisone therapy ($p<0.001$), facial palsy grade ($p<0.001$), electromyography findings ($p=0.005$), denervation ($p<0.001$), and 6 months recovery ($p<0.001$) data. There were also significant differences between the COVID-19-positive and COVID-19-negative subgroups regarding response to cortisone therapy ($p=0.015$) and facial palsy grade ($p=0.001$).

Conclusion: The current study findings support the possible association between the severity of the clinical course of facial palsy and COVID-19. Further studies are needed to prove a direct association between facial palsy and COVID-19.

Keywords: Severe acute respiratory syndrome, facial palsy, electromyography, COVID-19 pandemic, SARS-CoV-2, neurologic symptoms

ÖZ

Amaç: Koronavirüs hastalığı-2019 (COVİD-19) pandemisi, şiddetli akut solunum sendromu koronavirüs-2 adı verilen yeni bir koronavirüs türünden kaynaklıdır ve hızla tüm dünyaya yayılmıştır. Çeşitli nörolojik semptomlara ek olarak, COVİD-19 hastalarında bazı olgularda ana nörolojik semptom olarak akut fasiyal paralizi tanısı konulmuştur. Bu çalışma, COVİD-19 pandemisi öncesi ve sırasında fasiyal paralizi olan hastaların olgu sayılarındaki veya tıbbi semptomlarındaki varyasyonları ve olası ilişkileri analiz etmeyi amaçlamıştır.

Metot: Medicalpoint Hastanesi Nöroloji Kliniği, Ekonomi Üniversitesi Tıp Fakültesi, İzmir'de fasiyal paralizi tanısı alan hastaların klinik dosyaları retrospektif olarak incelenmiştir. Fasiyal paralizi olgularını farklı dönemlere göre karşılaştırmak için COVİD-19 pandemisinden önce ve COVİD-19 pandemisi sırasında olmak üzere iki hasta grubu oluşturulmuştur. İkinci grup (COVİD-19 pandemi sürecindeki grup), COVİD-19'un fasiyal paralizi üzerindeki etkilerini karşılaştırmak için COVİD-19 pozitif ve COVİD-19 negatif hastalar olarak iki alt gruba ayrılmıştır.

Bulgular: Çalışmanın belirlenen COVİD-19 döneminde (Mayıs 2020-Ocak 2021) 38 hasta fasiyal paralizi için hastaneye başvurmuştur; önceki iki yılın aynı takvim döneminde (Mayıs 2018-Ocak 2019) ise 34 fasiyal paralizi hastası başvurmuştur. Bu iki dönem arasında fasiyal paralizi görülme sıklığında anlamlı bir fark saptanmamıştır. Çalışma grupları (COVİD-19 pandemisi öncesi ve COVİD-19 pandemisi sırasında) arasında kortizon tedavisine yanıt ($p<0,001$), fasiyal paralizi derecesi ($p<0,001$), elektromiyografi bulguları ($p=0,005$), sinir blokajı (denervasyon) ($p<0,001$) ve 6 aylık iyileşme ($p<0,001$) verileri açısından anlamlı farklılıklar bulunmuştur. Ayrıca COVİD-19 pozitif ve COVİD-19 negatif alt gruplar arasında kortizon tedavisine yanıt ($p=0,015$) ve fasiyal paralizi derecesi ($p=0,001$) bakımından anlamlı farklılıklar saptanmıştır.

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Sonuç: Mevcut çalışma bulguları, fasiyal paralizinin klinik seyrinin şiddeti ile COVİD-19 arasındaki olası ilişkiyi desteklemektedir. Fasiyal paralizi ve COVİD-19 arasında doğrudan bir ilişki olduğunu kanıtlamak için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Şiddetli akut solunum sendromu, fasiyal paralizi, elektromiyografi, COVİD-19 pandemisi, SARS-CoV-2, nörolojik semptomlar

INTRODUCTION

The pandemic coronavirus disease-2019 (COVID-19) is caused by a novel type of coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and has rapidly spread all over the world since its first report in December 2019 in China (1). This virus primarily affects the respiratory system but can penetrate many other organs of the body. Neurological system symptoms are generally the first indication of the disease or they accompany respiratory abnormalities and include headaches, hyposmia, dizziness, confusion, cerebrovascular diseases, and encephalopathies (2). In addition to these neurological symptoms, acute facial palsy was diagnosed in COVID-19 patients as the main neurological symptom in some of the cases and was observed as unilateral or bilateral and idiopathic (Bell's palsy) (3,4). This condition has also been reported in children (5) and pregnant women (6). Facial palsy implies lower motor neuron failure of the facial nerve and can occur because of various medical conditions and events such as trauma, malignancy, autoimmune disorders, vaccination, surgery, and viral infections just as in the COVID-19 cases (7,8). Although the exact pathogenesis of viral infection-related facial palsy is still unclear, it is suggested to be associated with axonal transmission and viral reproduction leading to inflammation and demyelination (9). Some physicians noticed that facial nerve palsy cases increased after the COVID-19 pandemic compared to previous years and consistently reported literature increased recently; however, broad analysis and further research are required to reveal the exact interaction between them (2,10).

The current study aimed to analyze the variation and any possible association in the case numbers or medical symptoms of patients with facial palsy before and during the COVID-19 pandemic.

METHODS

The clinical files of patients who were diagnosed with facial palsy in the Neurology Department of Medicalpoint Hospital, University of Economics Faculty of Medicine, İzmir were retrospectively investigated. To compare the facial palsy cases according to different periods, two patient groups were formed: before the COVID-19 pandemic and during the COVID-19 pandemic. Before the COVID-19 pandemic group consisted of 34 facial palsy patients (collected data from hospital visits only between May 2018-January 2019) and during the COVID-19 pandemic group consisted of 38 facial palsy patients (collected data from hospital visits only between May 2020-January 2021). The pandemic group was further divided into two subgroups as COVID-19-positive and COVID-19-negative patients, and only cases with confirmatory tests (SARS-CoV-2 reverse transcriptase-polymerase chain reaction test) at first admission were included. Patients with inadequate clinical data or who could not be followed up for 6 months after diagnosis were excluded. In these groups, patients were compared concerning their demographic data (age and sex) and several clinical features [pregnancy, having diabetes mellitus (DM), presence of an autoimmune disease, presence of any other comorbidity, immunosuppressive therapy, corticosteroid therapy, facial palsy side and grade, electromyography (EMG) recordings, denervation, and recovery level on the control visit after 6 months]. Electrophysiological studies were conducted using the Nihon Kohden (Japan) MEB-9400K Neuropack S1 EMG/EP measuring system. Facial palsy was graded using the House-Brackmann scale (11). The study was approved by the Non-Interventional Clinical Research Ethics Committee of İzmir Bakırçay University (decision no: 634, date: 15.06.2022). All patients provided written informed consent. The research process is in accordance with the ethical standards of the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using PASW Statistics for Windows, Version 18.0. (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was set as statistically significant. The descriptive statistical data were expressed as numbers and percentiles for categorical variables and as mean, standard deviation, median, and minimum-maximum (range) for numerical variables. The normal distributions of variables were tested by visual (histograms and probability graphics) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk) test methods. For categorical variables, in two group comparisons, the Pearson chi-square test was used when applicable (expected value >5) and when not, Fisher's Exact test was used, and for ordinal variables, the Mantel-Haenszel test was used. For numerical variables in two group comparisons, the Mann-Whitney U test was used when data were not normally distributed.

RESULTS

During the specified COVID-19 period (May 2020-January 2021) of the study, 38 patients accessed the hospital for facial palsy (median age 37.0 years, range 22-60 years) and 34 facial palsy patients (median age 38.5 years, range 26-61 years) were found in the same calendar period of two previous years (May 2018-January 2019). There was no significant difference in facial palsy incidence between these two time periods. Pregnancy was in only two (9.5%) patients in the during COVID-19 group and in one (6.3%) patient in the before COVID-19 group.

Demographic data and clinical features and the comparison of these parameters between the two groups (during COVID-19 and before COVID-19) are summarized in Table 1. According to the data, there were no significant differences between these two groups regarding sex (p=0.487), age (p=0.433), facial palsy side (p=0.718), presence of comorbidity (except DM and autoimmune disease) (p=0.649), presence of DM (p=0.898), presence of autoimmune disease (p=0.463), receiving immunosuppressive therapy (p=0.599), and receiving steroid therapy (p=0.063). On the other hand, there were significant differences between the two groups regarding response to cortisone therapy (p<0.001), facial palsy grade (p<0.001), EMG findings (p=0.005), denervation (p<0.001), and 6 months recovery (p<0.001) data. In terms of cortisone therapy, in the during COVID-19 group, the full response ratio was 13.2%; partial response ratio was 52.6%; non-response ratio was 15.8%, and 18.4% of the patients did not receive the therapy, and in the before COVID-19 group, these values were 70.6%; 20.6%; 2.9%; and 5.9%, respectively. In terms of facial palsy grade, in the during COVID-19 group, mild grade ratio was 10.5%; moderate grade ratio was 39.5%; moderately severe grade ratio was 28.9%; severe grade ratio was 18.4%, and total paralysis ratio was 2.6%, and in the before COVID-19 group, these values were 52.9%; 35.3%; 8.8%; 2.9%, and 0%, respectively. In terms of EMG recordings, in the during COVID-19 group, the ratio of axonal findings was 31.6%; the ratio of demyelinating findings was 10.5%, and the ratio of mixed patterns was 57.9%, and in the before COVID-19 group, these values were 64.7%; 14.7%; and 20.6%, respectively. The denervation ratio of the patients in the during COVID-19 group was 78.9%, whereas this ratio was 38.2% in the before COVID-19 group. In terms of 6 months recovery, in the during COVID-19 group, the full recovery ratio was 28.9%; partial recovery ratio was 63.2%, and non-recovery ratio was 7.9%, and in the before COVID-19 group, these values were 88.2%; 11.8%; and 0%, respectively.

Table 2 shows the comparison of demographic and clinical data between the COVID-19-positive and COVID-19-negative subgroups within the COVID-19 group. Accordingly, of 38 patients, 9 were COVID-19-positive (2 of them were diagnosed at the admission to the hospital for facial palsy and 7 of them had COVID-19 before) and 29 were COVID-19-negative. The results were similar in these two subgroups regarding sex (p=0.984), age (p=0.345), facial palsy side (p=0.634), presence of comorbidity (except DM and autoimmune disease) (p=0.578), presence of DM (p=0.559), presence of autoimmune disease (p=0.134), receiving immunosuppressive therapy (p=0.237), receiving steroid therapy (p=0.650), EMG findings (p=0.055), denervation rate (p=0.650) and 6 months recovery rate (p=0.056). However, there were significant differences between the two subgroups regarding response to cortisone therapy (p=0.015) and facial palsy grade (p=0.001). In terms of cortisone therapy, in the COVID-19-positive subgroup, the full response ratio was 11.1%; partial response ratio was 33.3%; non-response ratio was 55.6%, and none of the patients received the therapy, and in the COVID-19-negative subgroup, these values were 13.8%; 58.6%; 3.4%; and 24.1%, respectively. In terms of facial palsy grade, COVID-19-positive subgroup, mild grade ratio was 10.5%; moderate grade ratio was 39.5%; moderately severe grade ratio was 28.9%; severe grade ratio was 18.4%, and total paralysis ratio was 2.6%, and in the COVID-19-negative subgroup, these values were 13.8%; 48.3%; 27.6%; 10.3%, and 0%, respectively.

DISCUSSION

The comparison of the clinical results revealed that the cases during the COVID-19 period had a significantly lower response to cortisone therapy, worse facial palsy grades, higher denervation ratios (almost 2-folds), worse EMG findings with a higher mixed pattern, and worse 6 months recovery than those before the COVID-19 period. Consistently, in the subgroup comparisons, significantly lower response to cortisone therapy and worse facial palsy levels were seen in COVID-19-positive patients than in COVID-19-negative patients; however, denervation, EMG findings, and 6 months recovery data were similar. These findings may support the association between facial palsy and COVID-19, especially from the aspect of the clinical course of facial palsy. On the other hand, the current study showed that the number of peripheral facial paralysis cases during the COVID-19 pandemic was similar to previous years' data from the same center. This result is in line with other similar studies where no significant difference was

Table 1. Demographic and clinical characteristics of the two patient groups: during the COVID-19 pandemic and before the COVID-19 pandemic

	During COVID-19 n=38	Before COVID-19 n=34	p
Sex, n (%)			
Female	21 (55.3)	16 (47.1)	0.487*
Male	17 (44.7)	18 (52.9)	
Age, median (range)	37.0 (22-60)	38.5 (26-61)	0.433**
Facial palsy side, n (%)			
Left	18 (47.4)	18 (52.9)	
Right	19 (50.0)	16 (47.1)	0.718*
Bilateral	1 (2.6)	0 (0.0)	
Comorbidity (except DM and autoimmune disease), n (%)	2 (5.3)	2 (5.9)	0.649†
DM, n (%)	6 (15.8)	5 (14.7)	0.898*
Autoimmune disease, n (%)	3 (7.9)	5 (14.7)	0.463†
Immunosuppressant therapy, n (%)	1 (2.6)	2 (5.9)	0.599†
Steroid therapy, n (%)	30 (78.9)	32 (94.1)	0.063*
Cortisone therapy response, n (%)			
Total	5 (13.2)	24 (70.6)	
Partial	20 (52.6)	7 (20.6)	**<0.001‡**
Non-response	6 (15.8)	1 (2.9)	
Not-received	7 (18.4)	2 (5.9)	
Facial palsy grade, n (%)			
Mild	4 (10.5)	18 (52.9)	
Moderate	15 (39.5)	12 (35.3)	
Moderate severe	11 (28.9)	3 (8.8)	**<0.001‡**
Severe	7 (18.4)	1 (2.9)	
Total paralysis	1 (2.6)	0 (0.0)	
EMG, n (%)			
Axonal	12 (31.6)	22 (64.7)	
Demyelinating	4 (10.5)	5 (14.7)	0.005*
Mixed	22 (57.9)	7 (20.6)	
Denervation, n (%)	30 (78.9)	13 (38.2)	<0.001*
6-months recovery, n (%)			
Full	11 (28.9)	30 (88.2)	
Partial	24 (63.2)	4 (11.8)	**<0.001‡**
Non-recovery	3 (7.9)	0 (0.0)	

COVID-19: Coronavirus disease-2019, DM: Diabetes mellitus, EMG: Electromyography
*Pearson chi-square test, **Mann-Whitney U test, †Fisher's Exact test, ‡Mantel-Haenszel test

Table 2. Demographic and clinical characteristics of the two patient subgroups during the COVID-19 pandemic as COVID-19 positive and COVID-19 negative

	COVID-19 positive n=9	COVID-19 negative n=29	p
Sex, n (%)			
Female	5 (55.6)	16 (55.2)	0.984*
Male	4 (44.4)	13 (44.8)	
Age, median (range)	41.0 (23-51)	35.0 (22-60)	0.345**
Facial palsy side, n (%)			
Left	5 (55.6)	13 (44.8)	0.634*
Right	4 (44.4)	15 (51.7)	
Bilateral	0 (0.0)	1 (3.4)	
Comorbidity (except DM and autoimmune disease), n (%)	0 (0.0)	2 (5.3)	0.578†
DM, n (%)	1 (11.1)	5 (17.2)	0.559†
Autoimmune disease, n (%)	2 (22.2)	1 (3.4)	0.134†
Immunosuppressant therapy, n (%)	1 (11.1)	0 (0.0)	0.237†
Steroid therapy, n (%)	8 (88.9)	22 (75.9)	0.650†
Cortisone therapy response, n (%)			
Total	1 (11.1)	4 (13.8)	**0.015‡**
Partial	3 (33.3)	17 (58.6)	
Non-response	5 (55.6)	1 (3.4)	
Not-received	0 (0.0)	7 (24.1)	
Facial palsy grade, n (%)			
Mild	0 (0.0)	4 (13.8)	**0.001‡**
Moderate	1 (11.1)	14 (48.3)	
Moderate severe	3 (33.3)	8 (27.6)	
Severe	4 (44.4)	3 (10.3)	
Total paralysis	1 (11.1)	0 (0.0)	
EMG, n (%)			
Axonal	1 (11.1)	11 (37.9)	0.055*
Demyelinating	0 (0.0)	4 (13.8)	
Mixed	8 (88.9)	14 (48.3)	
Denervation, n (%)	8 (88.9)	22 (75.9)	0.650†
6-months recovery, n (%)			
Full	1 (11.1)	10 (34.5)	0.056‡
Partial	6 (66.7)	18 (62.1)	
Non-recovery	2 (22.2)	1 (3.4)	

COVID-19: Coronavirus disease-2019, DM: Diabetes mellitus, EMG: Electromyography *Pearson chi-square test, **Mann-Whitney U test, †Fisher's Exact test, ‡Mantel-Haenszel test

found in the occurrence of the cases between the pandemic period and previous years (10,12). In contrast, Codeluppi et al. (4) reported higher incidence rates of facial palsy in the pandemic period compared with the previous year. There are a few studies on the effect of COVID-19 on facial palsy incidence comparisons, and further analyses with more comprehensive and wider samples could help to clarify any possible significant variation.

In the current study, facial palsy was the first clinical symptom of COVID-19 in 2 of 9 COVID-19-positive patients. Similarly, in another study from Türkiye, 5 of 8 COVID-19 patients (9) and in a case study, 3 of 8 patients had facial palsy as the first symptom (12). Several studies have reported facial palsy as the initial symptom of COVID-19, which have been presented in detail in literature reviews (2,3). In addition, several studies have demonstrated facial palsy as the only main symptom of COVID-19 (3,13). Furthermore, in a cohort study in Singapore, facial neuropathy was found to be the most common (71.4%) COVID-associated mononeuropathy (14). These results support the suggestion that facial palsy should be added to the COVID-19-associated neurological manifestations as a nonspecific symptom (10,12).

Neurological issues in COVID-19 are unfolding as one of the most prominent clinical outcomes of this pandemic (8,9). The most common are anosmia/ageusia, encephalitis, encephalopathy, cerebrovascular complications, myelitis, Guillain-Barré syndrome, myalgia, and facial palsy/Belly's palsy (3,12). Although there are several approaches to the possible effects of SARS-CoV-2 on the nervous system, the exact mechanism remains unclear. These approaches can be classified as hypoxia, angiotensin-converting enzyme 2 receptor downregulation, immune injury, or direct involvement via infection, and by these ways, SARS-CoV-2 can induce cytokine storms (2,15). Meticulous clinical, diagnostic and epidemiological research is required to identify the neurological disorder manifestations of COVID-19 (16). Potential mechanisms suggested for nerve damage in facial palsy include vasa nervorum ischemia and demyelination induced by viral replication and inflammation (12,17). Microthrombi and other vascular changes, through viral damage or an autoimmune reaction, may also be contributing mechanisms to dysfunction (12).

The clinical findings of facial palsy in the current study suggested a highly noticeable worse outcome when occurred in the COVID-19 period compared to a previous period for the clinical parameters stated above. Even though the parameters with significant differences were less in the subgroup comparisons, the two parameters were

still significantly worse in COVID-19-positive patients than in COVID-19-negative, reflecting the association between facial palsy and COVID-19. These alterations may be due to patients who were deemed COVID-19-negative but had previously had asymptomatic COVID-19. fears during a pandemic lead individuals to delay or avoid accessing hospitals, even for COVID-19 tests. In another comparison study, although it was reported that higher incidence rates of facial palsy were found during the pandemic period, the evaluated clinical results were similar between the pandemic group and the previous year In a case study with 8 COVID-19-positive patients with facial palsy, complete recovery was observed in 5 patients, and the facial palsy grades were mild for 5 and moderate for 3 patients (12). In the current study, the ratio of mild grade facial palsy in the before COVID-19 group (52.9%) was significantly higher than that in the during COVID-19 group (10.5%), whereas there was a slight difference in moderate grade facial palsy ratios between these two groups (35,3% and 39.5%, respectively). In addition, the complete recovery ratio in the before COVID-19 group (88.2%) was significantly higher than that in the during COVID-19 group (28.9%). In parallel, in another study from Türkiye, the complete recovery rate was reported to be 37.5% in COVID-19-positive patients with facial palsy (9). Furthermore, in subgroup comparisons of the present study, the overall complete recovery ratio was quite low (28.9%), which may support the negative clinical effects of COVID-19 on facial palsy.

As far as it is concerned, this is the first facial palsy comparison study for COVID-19 that includes not only data from different periods but also detailed clinical data including information such as EMG findings and denervation. Few works of literature restrict the exact comparison of all the current findings. Other limitations are the small sample size and performing the study in only one center.

CONCLUSION

The recent literature reveals that SARS-CoV-2 can cause several neurological symptoms and disorders, and facial palsy seems to be one of these issues. The current study findings support the possible association between the severity of the clinical course of facial palsy and COVID-19. Large-scale and postmortem studies are needed to prove a direct association between facial palsy and COVID-19.

ETHICS

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of İzmir Bakırçay University (decision no: 634, date: 15.06.2022).

Informed Consent: All patients provided written informed consent.

Authorship Contributions

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

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

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REFERENCES

1. Ullah H, Ullah A, Gul A, Mousavi T, Khan MW. Novel coronavirus 2019 (COVID-19) pandemic outbreak: A comprehensive review of the current literature. Vacunas 2021;22:106-13.
2. Estakhr M, Tabrizi R, Ghotbi Z, Shahabi S, Habibzadeh A, Bashi A, et al. Is facial nerve palsy an early manifestation of COVID-19? A literature review. Am J Med Sci 2022;364:264-73.
3. Gupta S, Jawanda MK, Taneja N, Taneja T. A systematic review of Bell's Palsy as the only major neurological manifestation in COVID-19 patients. J Clin Neurosci 2021;90:284-92.
4. Codeluppi L, Venturelli F, Rossi J, Fasano A, Toschi G, Pacillo F, et al. Facial palsy during the COVID-19 pandemic. Brain Behav 2021;11:e01939.
5. Ferreira EF, Portugal D, Silva N, Peixoto C, Matos C, Pereira I, et al. Rehabilitation of peripheral facial palsy associated with COVID-19 in a child: A case report. Ann Phys Rehabil Med 2022;65:101600.
6. Figueiredo R, Falcão V, Pinto MJ, Ramalho C. Peripheral facial paralysis as presenting symptom of COVID-19 in a pregnant woman. BMJ Case Rep 2020;13:e237146.
7. Kim SJ, Lee HY. Acute Peripheral Facial Palsy: Recent Guidelines and a Systematic Review of the Literature. J Korean Med Sci 2020;35:e245.
8. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. J Neurol 2021;268:1133-70.
9. Egilmez OK, Gündoğan ME, Yılmaz MS, Güven M. Can COVID-19 Cause Peripheral Facial Nerve Palsy? SN Compr Clin Med 2021;3:1707-13.
10. Mutlu A, Kalcioglu MT, Gunduz AY, Bakici B, Yilmaz U, Cag Y. Does the SARS-CoV-2 pandemic really increase the frequency of peripheral facial palsy? Am J Otolaryngol 2021;42:103032.
11. House JW, Brackmann DE. Facial nerve grading system. Otolaryngol Head Neck Surg 1985;93:146-7.
12. Lima MA, Silva MTT, Soares CN, Coutinho R, Oliveira HS, Afonso L, et al. Peripheral facial nerve palsy associated with COVID-19. J Neurovirol 2020;26:941-4.
13. Islamoglu Y, Celik B, Kiris M. Facial paralysis as the only symptom of COVID-19: A prospective study. Am J Otolaryngol 2021;42:102956.
14. Koh JS, De Silva DA, Quek AML, Chiew HJ, Tu TM, Seet CYH, et al. Corrigendum to 'Neurology of COVID-19 in Singapore'

[Journal of the Neurological Sciences Volume 418, 15 November 2020, 117118]. J Neurol Sci 2021;424:117406.

15. Amruta N, Chastain WH, Paz M, Solch RJ, Murray-Brown IC, Befeler JB, et al. SARS-CoV-2 mediated neuroinflammation and the impact of COVID-19 in neurological disorders. Cytokine Growth Factor Rev 2021;58:1-15.
16. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol 2020;19:767-83.
17. Goh Y, Beh DLL, Makmur A, Somani J, Chan ACY. Pearls & Oysters: Facial nerve palsy in COVID-19 infection. Neurology 2020;95:364-7.

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Research

The Influence of Sildenafil Versus Resveratrol on the Healing of Colonic Anastomosis: An Experimental Study

Sildenafil ve Resveratrolün Sol Kolon Anastomozunun İyileşmesi Üzerine Etkisi

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ABSTRACT

Objective: The prevention of colonic anastomosis leakage is a subject of ongoing surgical investigation. The present experimental study was performed to investigate whether the administration of resveratrol (R) and sildenafil (S) to rats could improve the strength of intestinal anastomosis without obvious interference with other vital components of the repair process.

Methods: Thirty-six rats were randomly divided into four groups as follows: control (C), S, R, and combined (S&R). All rats underwent left colon resection plus anastomosis. After surgery, the C group received 10 mg/kg of tap water, while the S and R groups received S (10 mg/kg) and R (10 mg/kg), respectively, via an orogastric tube for 7 days. The S&R group received both S and R in the same dosages. All rats were euthanized on postoperative day 7. Anastomotic bursting pressure (ABP) was measured, and tissue samples were taken for histopathological examination and hydroxyproline (T.H.) level assessment.

Results: The ABP was significantly higher in the S&R group than in the C group (p=0.021). When evaluated histopathologically in terms of edema, the significant difference was due to the S&R group. Tissue edema was lower in the S&R group than in the C, S, and R groups (p=0.004). There were no significant differences between the groups when analyzed for polymorphonuclear lymphocyte increase, lymphocyte increase, macrophage increase, mucosa-epithelial status, and submucosal bridge. There were also no significant differences in hydroxyproline levels between the groups (p=0.222).

Conclusion: The results suggest that the combination of R and S significantly increased the bursting pressure in rats with left-sided colonic anastomosis, with S potentially being the key driver in this outcome. The current results are encouraging; however, additional studies will be needed for confirmation.

Keywords: Resveratrol, sildenafil, colon, anastomosis, wound healing

ÖZ

Amaç: Kolon anastomoz kaçağının önlenmesi halen araştırmaları devam eden önemli bir cerrahi problemdir. Bu deneysel çalışma resveratrol (R) ve sildenafilin (S) sıçanlarda uygulanmasının anastomoz iyileşme sürecinin diğer etkenler ile belirgin etkileşim olmaksızın anastomoz sağlamlığına katkısını araştırmak için gerçekleştirilmiştir.

Gereç ve Yöntem: Otuz altı sıçan rastgele olarak aşağıdaki şekilde dört gruba ayrıldı: Kontrol (K), S, R ve kombine (S&R). Tüm sıçanlara sol kolon rezeksiyonu ve sonrasında kolokolonik anatomoz uç uca anastomoz yapıldı. Ameliyattan sonra K grubuna 7 gün boyunca orogastrik tüp yoluyla sırasıyla S (10 mg/kg) ve R (10 mg/kg) verilirken K grubuna 10 mg/kg musluk suyu verildi. S&R grup, aynı dozajlarda hem S hem de R aldı. Tüm

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sıçanlara postoperatif 7. günde ötenazi yapıldı. Anastomoz patlama basıncı (APB) ölçüldü ve histopatolojik inceleme ve hidroksiprolin (T.H.) seviyesi değerlendirmesi için doku örnekleri alındı.

Bulgular: APB, S&R grupta K grubuna göre anlamlı olarak daha yüksekti (p=0,021). Histopatolojik olarak ödem açısından değerlendirildiğinde aradaki anlamlı fark S&R gruba bağlıydı. Doku ödemi S&R grupta K, S ve R gruplarına göre daha düşüktü (p=0,004). Polimorfonükleer lenfosit artışı, lenfosit artışı, makrofaj artışı, mukoza-epitelyal durum ve submukozal köprüleşme için analiz edildiğinde gruplar arasında anlamlı fark yoktu. Gruplar arasında hidroksiprolin seviyelerinde de anlamlı farklılıklar yoktu (p=0,222).

Sonuç: Sonuçlar, R ve S kombinasyonunun, sol kolonik anastomozlu sıçanlarda patlama basıncını önemli ölçüde artırdığını ve S'nin bu sonuçta potansiyel olarak anahtar rol oynadığını göstermektedir. Mevcut sonuçlar umut vericidir, ancak doğrulama için ek çalışmalara ihtiyaç duyulacaktır.

Anahtar Kelimeler: Resveratrol, sildenafil, kolon, anastomoz, yara iyileşmesi

INTRODUCTION

Colorectal surgery is a common occurrence in the modern surgical era, but the long-standing problem of anastomotic leakage (AL) remains a challenging complication for surgeons to overcome. The incidence of this complication is reported at 3-19% and is still the leading cause of high morbidity and mortality among patients undergoing this procedure (1-3).

Although AL has multifactorial aetiology, adherence to surgical principles plays a crucial role in constructing a safe colonic anastomosis. Among these principles, the perfusion of the anastomosis is probably the most significant and overlooked condition. It is well documented that the healing process of colonic anastomosis is significantly enhanced by improving the microcirculation, thereby regulating tissue oxygenation (1-5).

Sildenafil is a selective phosphodiesterase type 5 (PDE-5) inhibitor. It is a water-soluble compound and is found in several parts of the body. Sildenafil protects cyclic guanosine monophosphate (cGMP) from degradation by cGMP-specific PDE-5. Nitric oxide (NO) is a well-known mechanism that binds to guanylate cyclase receptors, resulting in increased levels of cGMP, leading to muscle relaxation and vasodilatation of vessels, and thereby improving microcirculation (4,5).

Resveratrol (3, 5, 40-trihydroxytrans-stilbene) is a natural polyphenolic compound known from ancient times that is present in grapes and red wine and possesses anti-inflammatory, cardioprotective and neuroprotective properties. It has been shown that resveratrol reduces the damage in experimentally induced colitis by alleviating oxidative stress and stimulating apoptosis (6). Its chemopreventive efficacy through inhibition of cyclooxygenase (COX) and ornithine decarboxylase (ODC) enzymes have been well researched. Resveratrol has demonstrated decreases in oxidative stress while inducing NO synthesis in ischemia-reperfusion (6-8).

The effects of sildenafil and resveratrol individually were previously researched in ischemic colon anastomosis, ulcerative colitis, and ischemic colitis models by the present authors and other researchers (6,9-14). The combined effects of the two compounds on left-sided colon anastomosis have not been previously studied. Considering the pharmacological effects mentioned above, the present experimental study was performed to investigate whether administering a combination of resveratrol and sildenafil to rats could improve the strength of colon anastomosis without obvious interference with other vital components of the repair process.

METHODS

Animal Ethical Considerations

Ethical committee approval of the Kahramanmaraş Sütçü İmam University Faculty Medicine (decision no: 06, date: 08.05.2019) was received and then this study was carried out at the Experimental Animal Research Center of Kahramanmaraş Sütçü İmam University Faculty Medicine, Kahramanmaras, Türkiye. This research was also conducted following the Guide for the Care and Use of Laboratory Animals (NIH, 1985).

Thirty-six Wistar-albino male rats weighing 191 to 310 g were used in this study. The animals were kept in polycarbonic cages at a room temperature of 20±2 °C with 50±10% humidity in a 12-hour (h) light and dark cycle. The rats were allowed to take rat food (Purina®) in the form of standardized dry pellets.

Study Design, Anesthesia and Surgical Procedure

The thirty-six rats were divided into four groups as follows:

Control group (C): Left colon resection plus end-to-end anastomosis created; 10 cc of tap water per day was given via an orogastric tube for postoperative 7 days.

Sildenafil group (S): Left colon resection plus end- to-end anastomosis created; sildenafil was given at a dose of 10 mg/kg per day via an orogastric tube for postoperative 7 days.

Resveratrol group (R): Left colon resection plus end- to-end anastomosis created; resveratrol was given at a dose of 10 mg/kg per day via an orogastric tube for postoperative 7 days.

Combined resveratrol and sildenafil group: Left colon resection plus end- to-end anastomosis was created; both sildenafil and resveratrol were given at a dose of 10 mg/kg per day via an orogastric tube for postoperative 7 days.

Feeding of rats was discontinued 12 h before surgery. Sedation was administered by intramuscular injection of ketamine 50 mg/kg (Ketalar: Parke Davis, Eczacıbaşı, Istanbul, Türkiye) and xylazine 10 mg/kg (Rompun: Bayer AG, Leverkusen, Germany). Animals were left to breathe unassisted, and their body temperature was fixed at 37 °C by a heater during the operation (10-14).

All operations were performed by the same surgeon for the standard technique. After shaving the abdominal skin of the animals, it was stained with povidone-iodine. The table was set at a 30-degree angle to prevent the risk of aspiration. Subsequently, a 4 cm upper midline incision was rendered, and this was the entry point of the abdomen in all groups. The full-thickness colon segment was accessed 3 cm proximal to the peritoneal reflection. The transected colon segments were individually anastomosed end-to-end with 5/0 prolene sutures. The anterior abdominal wall was closed with a single-layer continuous absorbable 3/0 suture (Vicryl, Johnson & Johnson), and the skin was closed with an interrupted 3/0 silk suture (Figure 1) (11-13).

The postoperative condition was assessed 6 h within the first 48 h and every 10 h thereafter for 7 days. Diclofenac sodium (2 mg/kg, intravenous) was used twice, just after surgery and on postoperative day 1 to reduce pain in the wound area. Esomeprazole was concomitantly administered by intragastric gavage at a dose of 50 micromol/kg to prevent gastropathy (9-15).

All rats were euthanized on postoperative day 7 by administering 2 mL pentobarbital sodium (200 mg/mL, K.U. Life, Copenhagen) intraperitoneally. Anastomotic burst pressure was measured, and then the anastomosis site was resected leaving at least 3 cm space from the proximal and distal edges to evaluate tissue hydroxyproline levels and perform histopathological examination (10-14).

Anastomotic Bursting Pressure (ABP) Measurement

Evaluation of burst pressure, tissue hydroxyproline levels, and histopathological examination were performed using the same methods as previous similar studies (10-22). Intestinal pressure was measured using a pressure monitoring system. After cleaning the lumen of the anastomosis line resected by relaparotomy, the manometer (Pressure Gauge with Erka Profi Cuff) was connected with an airtight 3/0 silk suture at a distance of 3 cm from the proximal end of the anastomosis. The distal end of the anastomosis was also connected with an airtight 3/0 silk suture. An anastomosis line was placed in a bowl filled with water (Figure 2). Progressively higher pressure was applied and the pressure at which the air bubbles emerged was recorded as bursting pressure in millimeters of mercury (mmHg) (10-22).

Histopathological Examination

After measuring the anastomotic burst pressure, the 1 cm portion containing the anastomosis region was excised to be 1 cm proximal and 1 cm distal. Some tissue samples were used for the biochemical examination while the remainder were fixed in 10% formaldehyde. The samples were then parafinized, and 5 µm sections were cut and stained with hematoxylin-eosin to determine the collagen content. The samples were assessed blindly by an experienced pathologist. The results were obtained using the Verhofstad scale (15). Parameters including necrosis, edema, polymorphonuclear lymphocytes (PMNL) increase, lymphocyte increase, macrophage increase, mucosa-

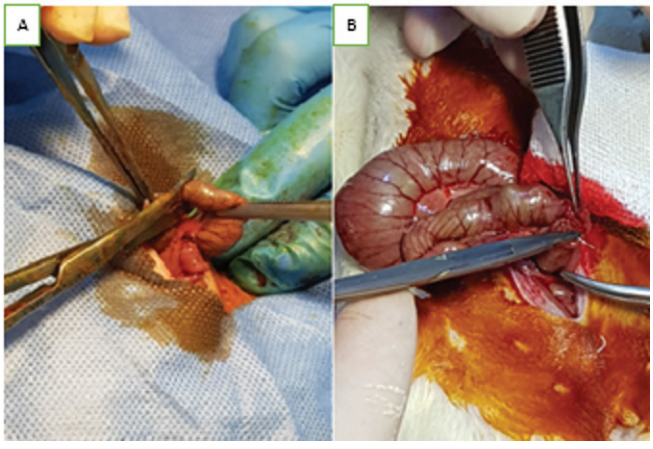

Figure 1. A) Left colon transection, B) End-to-end anastomosis of transected segments

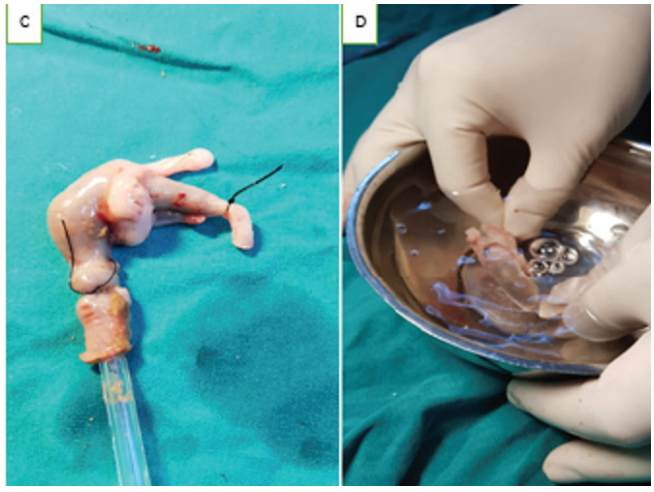

Figure 2. C) Measurement of burst pressure, D) Bursting moment of anastomosis line in pressure measurement

epithelial status, and submucosal bridge at the anastomosis line were examined with the help of this scale (15,22).

Hydroxyproline Level Measurement

The hydroxyproline level was measured as previously described. After measuring ABP, the anastomosis line was removed from the adherent tissue. 1 cm of the anastomotic line was excised. The sample harvested from the anastomosis line was submitted to the biochemistry laboratory. Acid digestion was performed in the oven for approximately 48 h by adding 1 mL of distilled water and 1 mL of 12 N hydrochloric acid (HCL) per 100 mg of tissue. It was vortexed using 0.6 mL of 50% isopropyl alcohol and dissolved by adding a further 0.6 mL of 50% isopropyl alcohol. Additionally, 0.2 mL of chloramine-T was added and then the solution was allowed to rest for 10 minutes (min). Subsequently, 1 mL of Erlich reagent was added and vortexed. It was kept in a 50 °C water bath for 90 min and was scanned against water at 560 nm wavelength. Tissue hydroxyproline values were calculated as micrograms/gram (µg/g) dry tissue (16). Hydroxyproline measurements were completed blindly by a biochemist who was unaware of the groupings.

Statistical Analysis

All statistical analyses were performed using the IBM SPSS 21.0 package program. Values were presented as mean ± standard deviation. The normality of burst pressure and hydroxyproline level measurements according to groups were evaluated with Kolmogorov-Smirnov test statistics (Table 1).

The data for ABP and tissue hydroxyproline were evaluated using One-Way analysis of variance (ANOVA). The data for histological score were evaluated using the chi-square test. Post-hoc analyses were performed with Tukey's HSD. The values were accepted as statistically significant when $p<0.05$.

RESULTS

No complications occurred that would affect the results of the study. No local or systemic side effects were observed after the administration of resveratrol or sildenafil. Anastomosis burst pressures were measured individually and compared between groups. Regarding the group means, the anastomotic burst pressure was 192.22±84.07 mmHg in the C, 247.77±53.80 mmHg in the S, 208.88±81.46 mmHg in the R, and 312.22±112 mmHg in the combined group. The results showed that there was a significant difference between the burst pressures of the control and combined groups (p=0.021). There was also a significant difference in burst pressures between the resveratrol and combined groups (p=0.004). However, no statistically significant difference existed between the sildenafil and combined groups (Table 2).

When hydroxyproline levels were analysed, the mean values were 1566.17±126.77 µg/g in the C, 1554.60±96.99 µg/g in the S, 1634.15±132.2 µg/g in the R and 1527.86±68.68 µg/g in the combined group. There were no significant differences found in hydroxyproline levels during group comparisons (p=0.222) (Table 3).

Table 1. Normality evaluation

	Burst pressure			Hydroxyproline level		
	K-S	df	p	K-S	Df	p
Control group	0.197	9	0.200*	0.202	9	0.200*
Sildenafil group	0.170	9	0.200*	0.230	9	0.185
Resveratrol group	0.249	9	0.115	0.204	9	0.200*
Combined group	0.221	9	0.200*	0.242	9	0.135

p: Kolmogorov-Smirnov (K-S). *This is a lower bound of the true significance

Table 2. Mean difference evaluation of anastomotic burst pressures (mmHg)

	Mean ± SD	Min-max		F	Df	p
Control group	192.22±84.07	80-300	28.02			
Sildenafil group	247.77±53.80	140-300	17.93	3.511	35	0.021
Resveratrol group	208.88±81.46	100-300	27.15			
Combined group	312.22±112	160-480	37.33			

p: One-Way analysis of variance (ANOVA). Min-max: Minimum-maximum, SD: Standard deviation

Histopathological examination was performed using the Verhofstad scale (15) to evaluate the inflammatory process and anastomotic healing. When all groups were evaluated in terms of edema, a statistically significant difference was found (p=0.004). When comparing the groups in pairs, this difference was found to be due to the combined group in which the level of edema was lowest. A second result after comparing the groups in pairs is that there were significant differences between the combined and Cs, between the combined and Ss, and between the combined and Rs. When all groups were evaluated in terms of necrosis, a statistically significant difference was found (p=0.037) When the groups were analyzed according to PMNL increase, lymphocyte increase, macrophage increase, mucosa–epithelial status, and submucosal bridge, there were no significant differences found (Table 4) (Figure 3).

Table 3. Mean difference evaluation of anastomotic tissue hydroxyproline levels (µg/g)

	Mean ± SD	Min-max	F	Df	p
Control group	1566.17±126.77	1338.10±1715.08			
Sildenafil group	1554.60±96.99	1370.30±1670.42	1.545	35	0.222
Resveratrol group	1634.15±132.2	1504.99±1916.38			
Combined group	1527.86±68.68	1397.39±1657.98			

p: One-Way analysis of variance (ANOVA). Min-max: Minimum-maximum, SD: Standard deviation

Table 4. Relationship evaluation of groups with histopathological findings

		Control group		Sildenafil group		Resveratrol group		Combined group		Total		Pearson chi-square	Df	p
		n	%	n	%	n	%	n	%	n	%			
Necrose	Low	7	77.8	5	55.6	1	11.1	6	66.7	19	52.8	13.426	6	0.037
	Prominent	0	0.0	1	11.1	3	33.3	3	33.3	7	19.4			
	Serious	2	22.2	3	33.3	5	55.6	0	0.0	10	27.8			
Oedema	Low	1	11.1	3	33.3	4	44.4	9	100.0	17	47.2	19.176	6	0.004
	Prominent	5	55.6	5	55.6	5	55.6	0	0.0	15	41.7			
	Serious	3	33.3	1	11.1	0	0.0	0	0.0	4	11.1			
PMNL	Little increase	1	11.1	2	22.2	1	11.1	3	33.3	7	19.4	3.200	6	0.783
	Significant increase	4	44.4	4	44.4	3	33.3	4	44.4	15	41.7			
	Diffuse infiltration	4	44.4	3	33.3	5	55.6	2	22.2	14	38.9			
Lymphocytes	Little increase	4	44.4	5	55.6	6	66.7	8	88.9	23	63.9	4.214	3	0.239
	Significant increase	5	55.6	4	44.4	3	33.3	1	11.1	13	36.1			
Macrophages	Little increase	3	33.3	5	55.6	3	33.3	6	66.7	17	47.2	3.588	6	0.732
	Significant increase	5	55.6	3	33.3	5	55.6	3	33.3	16	44.4			
	Diffuse infiltration	1	11.1	1	11.1	1	11.1	0	0.0	3	8.3			
Mucosa-epithelium	Normal glandular	0	0.0	0	0.0	3	33.3	0	0.0	3	8.3	13.600	9	0.137
	Normal cubic	3	33.3	1	11.1	1	11.1	3	33.3	8	22.2			
	Incomplete cubic	5	55.6	6	66.7	5	55.6	4	44.4	20	55.6			
	No	1	11.1	2	22.2	0	0.0	2	22.2	5	13.9			
Submucosal bridge	Good bridge	0	0.0	1	11.1	0	0.0	0	0.0	1	2.8	5.004	9	0.834
	Moderate bridge	4	44.4	2	22.2	3	33.3	4	44.4	13	36.1			
	Poor bridge	5	55.6	5	55.6	5	55.6	4	44.4	19	52.8			
	No bridge	0	0.0	1	11.1	1	11.1	1	11.1	3	8.3			

Likelihood chi-square test. PMNL: Polymorphonuclear lymphocytes

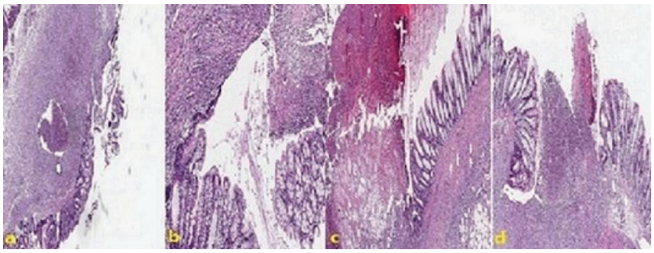

Figure 3. a. Control group, b. Sildenafil group, c. Resveratrol group, d. Combined group. Light microscopic examination (H&E staining) (400x magnification)

DISCUSSION

AL is a significant problem in terms of mortality and morbidity in patients undergoing colorectal surgery (1-3). Studies have shown that anastomotic leaks prolong hospital stays and increase medical costs (14-22). The individual effects of sildenafil and resveratrol were previously researched separately in ischemic colon anastomosis, ulcerative colitis, and ischemic colitis by some of the present authors and other researchers (6,9-14,20). The present experimental study was performed to investigate whether combined administration of resveratrol and sildenafil to rats could improve the strength of standard intestinal anastomosis without obvious interference with other vital components of the related healing process. To the authors' knowledge, this is the first study to investigate the effects of a combination of resveratrol and sildenafil on left-sided colonic anastomosis.

Before discussing the results, some important properties of sildenafil and resveratrol should be highlighted briefly to understand why anastomosis with these agents was chosen as the focus of the study. Sildenafil is a potent, selective PDE-5 inhibitor that was initially studied as an antianginal medication and is currently marketed to treat erectile dysfunction. Its effectiveness is due to the enhancement of vasodilatation by inducing muscle relaxation in the vessels and improving microcirculatory blood supply. Sildenafil also inhibits platelet aggregation, thus avoiding small-vessel obstruction (9-14). It is a water-soluble compound and is found in several parts of the body. It protects cGMP from degradation by PDE-5. NO binds to guanylate cyclase receptors, resulting in increased cGMP levels and leading to muscle relaxation in the vessels (9-12). The other agent resveratrol (3,5,40-trihydroxytrans-stilbene) is a naturally occurring polyphenolic possessing anti-inflammatory, cardioprotective and neuroprotective properties. Its preventative efficacy has recently been shown through inhibition of COX and ODC enzymes. Resveratrol reduces oxidative stress and induces apoptosis, thereby reducing damage in experimentally induced colitis (6,9-14,20). Some studies have shown that resveratrol decreased oxidative stress while inducing NO synthesis in ischemia-reperfusion (7,8,20).

Consistent with the above studies, the present study hypothesized that the synergistic effect of resveratrol and sildenafil and their antioxidant, antiplatelet, and anti-inflammatory effects could improve anastomotic healing due to its vasorelaxation, angiogenic, and antiapoptotic properties (6-15). The results showed that the C's mean anastomotic burst pressure was 192.22±84.07 mmHg. It was 247.77±53.80 mmHg in the S and 208.88±81.46 mmHg in the R. The mean burst pressure in the combined group was 312.22±112 mmHg. The results revealed a significant difference between the control and combined groups in terms of burst pressure (p=0.021). It was observed that the combination of sildenafil and resveratrol had a positive synergistic effect on the ABP and improved the strength of the intestinal anastomosis without adverse effects on other components of the associated healing process.

As a result, the answers to the following questions were highlighted by the authors. 1) Do both sildenafil and resveratrol have effects individually on anastomotic strength? Yes, but although bursting pressure increased by administering the agents individually, the results in this respect did not reach statistical significance. 2) Does the combination of these two potent drugs potentially have a synergistic effect on anastomotic strength? The answer is yes, and the results showed that when using the combination treatment, the increase in anastomotic strength was statistically significant compared with the C (p=0.021). The burst pressure was significantly higher in the combined group than in the control and Rs. Similarly, when the combined group was compared to the S, the bursting pressure was higher in the combined group. However, this difference did not reach statistical significance and may be due to the low sample size. These results showed that a combination of sildenafil and resveratrol was effective in increasing the ABP. 3) Does the combination treatment usage have obvious interference with other vital components of the repair process? The answer is no, and when the histopathological analysis was performed of PMNL increase, lymphocyte increase, macrophage increase, mucosa-epithelial status, and submucosal bridge, there were no significant differences between the groups. Tissue edema was lower in the combined group than in the control, sildenafil, and Rs (p=0.004). Necrosis was lower in the combined group than in the control, sildenafil, and Rs (p=0.004) When hydroxyproline levels were compared between groups, there were no significant differences found (p=0.222).

In summary, it is worth emphasizing that there were no adverse effects of the agents on anastomotic healing parameters neither individually nor in combined usage. Alternatively, although an increase in anastomotic strength was evident, no other positive histopathological effects were detected other than decreased edema. This may be because the animals were euthanized on day 7, which is late in the healing process. We chose the 7th postoperative day for euthanizing the rats as this was parallel to previous studies. Some of the literature regarding the effects of these agents on histopathological parameters and hydroxyproline levels is controversial. In some studies, the observed hydroxyproline levels were increased by the above-mentioned agents, while in others there was no change. Additionally, in some studies histopathological parameters improved, while in other studies there were no improvements (6,9-14,20). The key result, which is consistent with the literature, is that these two agents individually or in combined usage do not have negative effects on hydroxyproline levels and histopathological healing parameters, while their combined usage increases ABP with a synergistic effect.

In this study, a left colon anastomosis model was used in rats because experimental research on anastomotic healing has been exclusively performed in rats since the basic repair patterns are believed to be similar to those in humans. We constructed a left colonic anastomosis because lower colorectal surgery is more prone to complications due to fecal load and technical difficulties, and the effects of these complications are more problematic (6-23).

As in all studies, there were some weaknesses evident in this study. First, NO levels in the colonic tissue were not determined in this study. Second, although the sample size is enough for an experimental study, it is not a sufficient basis on which to generalise. Third, the precise cellular mechanisms by which these agents enhance anastomotic wound healing are not clear, and this warrants further research.

CONCLUSION

AL is a significant problem in terms of mortality and morbidity in patients undergoing colorectal surgery. The results of this experimental study show that a combination of sildenafil and resveratrol increased the ABP without obvious interference with other vital components of the repair process. Additionally, it is likely that sildenafil was the key agent in these outcomes. Although the results are encouraging, additional studies are needed.

ETHICS

Ethics Committee Approval: Ethical committee approval of the Kahramanmaraş Sütçü İmam University Faculty of Medicine (decision no: 06, date: 08.05.2019) was received and then this study was carried out at the Experimental Animal Research Center of Kahramanmaraş Sütçü İmam University Faculty Medicine, Kahramanmaraş, Türkiye.

Informed Consent: Experimental study.

Authorship Contributions

Surgical and Medical Practices: M.K.Y., A.Y., H.K., Concept: M.K.Y., E.R., A.S., Design: M.K.Y., E.R., A.S., A.Yo., O.I., Data Collection or Processing: M.K.Y., A.Y., H.K., Z.A.T., A.Yo., Analysis or Interpretation: M.K.Y., E.R., A.Y., Z.A.T., O.I., Literature Search: M.K.Y., A.Y., Writing: M.K.Y., A.Y., H.K., O.I.

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

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REFERENCES

1. Tanaka J, Nishikawa T, Tanaka T, Kiyomatsu T, Hata K, Kawai K, et al. Analysis of anastomotic leakage after rectal surgery: A case-control study. Ann Med Surg (Lond) 2015;4:183-6.
2. Wang ZJ, Liu Q. A Retrospective Study of Risk Factors for Symptomatic Anastomotic Leakage after Laparoscopic Anterior Resection of the Rectal Cancer without a Diverting Stoma. Gastroenterol Res Pract 2020;2020:4863542.
3. Rullier E, Laurent C, Garrelon JL, Michel P, Saric J, Parneix M. Risk factors for anastomotic leakage after resection of rectal cancer. Br J Surg 1998;85:355-8.
4. Kotera J, Mochida H, Inoue H, Noto T, Fujishige K, Sasaki T, et al. Avanafil, a potent and highly selective phosphodiesterase-5 inhibitor for erectile dysfunction. J Urol 2012;188:668-74.
5. Zhang L, Zhang RL, Wang Y, Zhang C, Zhang ZG, Meng H, et al. Functional recovery in aged and young rats after embolic stroke: treatment with a phosphodiesterase type 5 inhibitor. Stroke 2005;36:847-52.
6. Samsami-Kor M, Daryani NE, Asl PR, Hekmatdoost A. Anti-Inflammatory Effects of Resveratrol in Patients with Ulcerative Colitis: A Randomized, Double-Blind, Placebo-controlled Pilot Study. Arch Med Res 2015;46:280-5.
7. Shishodia S, Aggrawal BB. Resveratrol: A polyphenol for all season. Resveratrol in Health and Disease 1 st ed. Newyork: CRC, Taylor and Francis Group, 2006. p. 1-17.
8. de la Lastra CA, Villegas I. Resveratrol as an anti-inflammatory and anti-aging agent: mechanisms and clinical implications. Mol Nutr Food Res 2005;49:405-30.
9. Irkorucu O, Ucan BH, Cakmak GK, Emre AU, Tascilar O, Ofluoglu E, et al. Does sildenafil reverse the adverse effects of ischemia on ischemic colon anastomosis: yes, 'no'. Int J Surg 2009;7:39-43.
10. Irkorucu O, Taşcilar O, Cakmak GK, Karakaya K, Emre AU, Ucan BH, et al. The effect of sildenafil on an animal model for ischemic colitis. Dig Dis Sci 2008;53:1618-23.
11. Irkorucu O, Comert M. Effects of sildenafil citrate on ischemic colonic anastomotic healing in rats: its relationship between nitric oxide and oxidative stress. World J Surg 2009;33:160.

12. Irkorucu O, Ucan BH, Cakmak GK, Tascilar O, Emre AU, Ofluoglu E, et al. Effect of 2-octyl-cyanoacrylate on ischemic anastomosis of the left colon. J Invest Surg 2009;22:188-94.
13. Aziret M, Irkorucu O, Reyhan E, Erdem H, Das K, Ozkara S, et al. The effects of vardenafil and pentoxifylline administration in an animal model of ischemic colitis. Clinics (Sao Paulo) 2014;69:763-9.
14. Cakir T, Ozer I, Bostanci EB, Keklik TT, Ercin U, Bilgihan A, et al. Increased collagen maturity with sildenafil citrate: experimental high risk colonic anastomosis model. Int J Surg 2015;13:152-6.
15. Verhofstad MH, Lange WP, van der Laak JA, Verhofstad AA, Hendriks T. Microscopic analysis of anastomotic healing in the intestine of normal and diabetic rats. Dis Colon Rectum 2001;44:423-31.
16. Jamall IS, Finelli VN, Que Hee SS. A simple method to determine nanogram levels of 4-hydroxyproline in biological tissues. Anal Biochem 1981;112:70-5.
17. Ersoz N, Ozler M, Topal T, Uysal B, Poyrazoglu K, Simsek K, Gocgeldi E, et al. The effect of ozone treatment on experimental colon anastomosis in rats. European Surgery 2016;48:122-8.
18. Neutzling CB, Lustosa SA, Proenca IM, da Silva EM, Matos D. Stapled versus handsewn methods for colorectal anastomosis surgery. Cochrane Database Syst Rev 2012:CD003144.
19. Ayten R, Cetinkaya Z, Girgin M, Ozercan I, Ustundag B, Aygen E. The effects of intraperitoneal sildenafil administration on healing of left colonic anastomoses and intra-abdominal adhesion formation in the presence of intra-abdominal infection. Dis Colon Rectum 2008;51:1837-41.
20. Cakmak GK, Irkorucu O, Ucan BH, Tascilar O, Emre AU, Karakaya K, et al. The effects of resveratrol on the healing of left colonic anastomosis. J Invest Surg 2009;22:353-61.
21. Bedirli A, Salman B, Pasaoglu H, Ofluoglu E, Sakrak O. Effects of nuclear factor-κB inhibitors on colon anastomotic healing in rats. J Surg Res 2011;171:355-60.
22. Gorur M, Sozutek A, Irkorucu O, Karakaya B. The influence of platelet-rich plasma (PRP) on colonic anastomosis healing impaired by intraperitoneal 5-flourouracil application. An experimental study. Acta Cir Bras 2020;35:e202000504.
23. Reyhan E, Irkorucu O, Surmelioglu A, Ozkara S, Deger KC, Aziret M, et al. Efficacy of pentoxifylline and tadalafil in rat model of ischemic colitis. J Invest Surg 2014;27:349-53.

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Research

Effects of the COVID-19 Pandemic in Unvaccinated Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis Patients Using Disease-modifying Antirheumatic Drugs

Romatizmal Hastalık Nedeniyle Hastalığı Modifiye Edici Antiromatizmal İlaç Kullanan Hastaların COVİD-19 Pandemisi Dönemindeki Sağlık Durumları

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ABSTRACT

Objective: To investigate the health status, experiences, and status of contracting or being affected poorly by coronavirus disease-2019 (COVID-19) in patients using disease-modifying antirheumatic drugs (DMARD).

Methods: Patients using DMARD for rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis registered in our rheumatic diseases outpatient clinic were assessed during their routine follow-up control between July 2020 and January 2021. Their health status between March and June 2020 was also registered in the first evaluation. A follow-up form was used in which demographic data, systemic diseases and drugs, rheumatic diseases and treatments, and changes in treatment and complaints during the pandemic period were questioned.

Results: One hundred fifty six (95 female, 61 male) patients were included in the study, the mean age was 43.4. There was no relationship between age, gender, body mass index, occupation, rheumatic disease group, and DMARD groups, with conditions of getting or being affected severely by COVID-19. Statistically significant relationships were found between having a chronic respiratory disease or having more than one comorbid disease and severe COVID-19 outcomes and between having moderate/high rheumatic disease activity and contracting COVID-19 ($p<0.05$ for all). The rate of getting COVID-19 in smokers was significantly lower than in non-smokers ($p=0.039$). There was a significant increase in disease activity during the pandemic period compared with the pre-pandemic period ($p<0.001$). A statistically significant relationship was found between making changes for treating rheumatic disease and an increase in disease activity ($p=0.003$).

Conclusion: Those with multiple comorbid diseases have an increased risk of severe COVID-19, and those with moderate- tohigh disease activity have an increased risk of developing COVID-19. The decrease in compliance with routine follow-up and drug treatment during the pandemic increases the risk of increased rheumatic disease activity.

Keywords: Biologic drugs, COVID-19, DMARD, hydroxychloroquine

ÖZ

Amaç: Romatizmal hastalıkları nedeniyle hastalığı modifiye edici antiromatizmal ilaç (DMARD) kullanan hastaların koronavirüs hastalığı-2019 (COVİD-19) pandemisi döneminde sağlık durumlarını, romatizmal hastalıkları ve DMARD kullanımları açısından deneyimlerini ve COVİD-19'a yakalanma/ağır geçirme durumlarını araştırmaktır.

Gereç ve Yöntem: Romatizmal hastalıklar polikliniğimizde takipli olan ve tedavisinde DMARD kullanan romatoid artrit, ankilozan spondilit ve psöriatik artrit hastaları Haziran 2020-Ocak 2021 arasında rutin takipleri sırasında değerlendirildi. Hastaların demografik verileri, sistemik hastalıkları ve ilaçları, romatizmal hastalıkları ve tedavileri, tedavide ve şikayetlerdeki değişimleri bir takip formu kullanılarak kaydedildi.

Bulgular: Çalışmaya dahil edilen 156 (95 kadın, 61 erkek) hastanın yaş ortalaması 43,4'tü. Hastaların %25'i randevularına düzenli gelirken, %67'si tedavisinde değişiklik yapmamıştı. Yaş, cinsiyet, vücut kitle indeksi, meslek, romatizmal hastalık grubu ve DMARD grupları ile COVİD-

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19'a yakalanma/ağır geçirme durumları arasında ilişki saptanmadı. Bir kronik respiratuvar hastalığa sahip olma veya birden fazla komorbid hastalığa sahip olma ile COVİD-19'u ağır geçirme arasındaki ilişki istatistiksel olarak anlamlıydı (hepsi için p<0,05). Romatizmal hastalık aktivitesi orta/yüksek olanlarda, hastalık aktivitesi düşük/remisyonda olanlara göre COVİD-19'a yakalanma oranı anlamlı olarak daha yüksekti (hepsi için p<0,05). Sigara içenlerde COVİD-19'a yakalanma oranı, içmeyenlere göre anlamlı olarak daha düşüktü (p=0,039). Hastaların pandemi öncesine göre pandemi döneminde hastalık aktivitesinde anlamlı bir artış görüldü (p<0,001). Bu süreçte romatizmal hastalığının tedavisinde değişiklik yapma ile hastalık aktivitesinde artış durumu arasında istatistiksel olarak anlamlı bir ilişki bulundu (p=0,003).

Sonuç: Komorbid hastalıkları olanlarda COVİD-19'u ağır geçirme riski ve hastalık aktivitesi orta-yüksek olanlarda COVİD-19'a yakalanma riski artmıştır. Pandemi sürecinde rutin takibe ve ilaç tedavisine uyumun azalması, romatizmal hastalık aktivitesinde artış riskini artırmaktadır.

Anahtar Kelimeler: Biyolojik ilaçlar, COVİD-19, DMARD, hidroksiklorokin

INTRODUCTION

Inflammatory rheumatic diseases cause a predisposition to routine and opportunistic infections due to disease-related factors and immunosuppressive drugs used in the treatment (1). For this reason, both patients and doctors wondered whether inflammatory rheumatic diseases and immunosuppressive drugs used in the treatment increase the risk of getting or being severely affected by coronavirus disease-2019 (COVID-19). In the first period of the epidemic, patients tended to discontinue their immunosuppressive treatments due to the risk of contracting COVID-19 and the fear of severe illness, and they believed that stopping the treatment would reduce this risk (2-4). In addition, the risk of infection increases as the severity of rheumatic disease increases (5,6).

During the COVID-19 pandemic, conflicting results have been published regarding the risk of getting or being affected severely by COVID-19 for those with rheumatic diseases. There are studies reporting an increased risk of hospitalization and death due to COVID-19 in certain rheumatic disease groups or those using certain immunosuppressive drugs (7-9). On the other hand, some studies state that there is no increase in the risk of getting COVID-19 infection or severe course in rheumatic disease patients compared with the healthy population (10,11). The risk of hospitalization due to COVID-19 was associated with age, presence of comorbid diseases, and high prednisone dose (≥10 mg/day) in patients with rheumatic diseases (12). According to the results of studies evaluating the relationship between the use of disease-modifying antirheumatic drugs (DMARD) and poor outcomes of COVID-19, conventional synthetic DMARD (csDMARD), biological DMARD (bDMARD), and targeted synthetic DMARD (tsDMARD) groups are not associated with high risk; however, specific drugs such as sulfasalazine (SSZ), rituximab (RTX), and Janus kinase inhibitors may be associated with adverse outcomes (9,13,14). In this study, we evaluated the patients followed up in our rheumatic diseases outpatient clinic between July 2020 and January 2021, recorded their health status between March 2020 and January 2021, and questioned them again at each examination. This study aimed to investigate the health status of patients using DMARD for rheumatic diseases during the COVID-19 pandemic and to evaluate the relationship between demographic data, rheumatic disease, and DMARD use and COVID-19-related outcomes.

METHODS

We obtained the Clinical Research Ethics Committee approval from University of Health Sciences Türkiye, İstanbul Fatih Sultan Mehmet Training and Research Hospital (no: FSM EAH-KAEK 2020/95, date: 09.07.2020) for this study. Among the patients followed up in our rheumatic diseases outpatient clinic with the diagnosis of rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA), those older than 18 years of age, using DMARD for treatment, and volunteering to participate were included. Those under the age of 18 years and individuals who refused to participate were not included Exclusion criteria were being under 18 years of age and not agreeing to participate in the study. Written informed consent was obtained from all participants.

We used a follow-up form to evaluate the health status of the patients. In this form; age, gender, height, weight, smoking status (active smoker/ex-smoker/never smoker), systemic diseases, rheumatic disease type and treatment, COVID-19-related conditions [reason for polymerase chain reaction (PCR) test if performed, computed tomography (CT) result if taken, COVID-19 treatment if received], COVID-19 risk perceptions (with Likert scale), routine follow-up and treatment compliance, changes in the complaints of those who made changes in rheumatic disease treatment, and rheumatic disease activity (last control before the pandemic and the first control during the pandemic period) were recorded. Conditions associated with COVID-19, including March-June 2020, were recorded at the initial evaluation and were re-questioned at each subsequent follow-up, and recorded if there was a change in the patient's status. When comparing the data, we divided the patients into two groups in terms of getting or not getting

COVID-19 and into three groups in terms of COVID severity as not infected, mild, or severe illness. The presence of pneumonia (confirmed by CT) or the hospitalization need, as accepted by the American College of Rheumatology, was determined as criteria for severe COVID-19 (15). According to this; cases with CT-confirmed pneumonia or requiring hospitalization for treating COVID-19 were classified as severe COVID-19. Cases with neither of these two conditions (i.e. confirmed by PCR only and treated at home) were classified as mild COVID-19. In the comparison of DMARD groups, we evaluated patients in three groups as csDMARD (monotherapy or combinations), b/tsDMARD, and combined DMARD (csDMARD + b/tsDMARD) users. In terms of rheumatic disease diagnoses, comparisons were made as RA, AS, and PsA groups separately and as RA and spondyloarthritis (SpA) (AS and PsA) groups.

Statistical Analysis

Categorical variables were summarized with frequencies and percentages. Numerical variables were summarized with mean and standard deviation or median and quartiles according to their distribution. The distribution of numerical variables was evaluated using the Kolmogorov-Smirnov test. Comparisons of numerical variables between dual COVID groups (getting/not getting) were made using t-test or Mann-Whitney U test according to their distribution. Comparisons of numerical variables between triple COVID groups (did not get/mild/severe) were made by ANOVA or Kruskal-Wallis test, according to their distribution. The relationship between categorical variables was examined using the chi-square test. The McNemar test was used to compare the disease activities before and during pandemics. $P<0.05$ was considered statistically significant. The R version 4.0.4 (2021-02-15) program was used for statistical analysis.

RESULTS

Patient Characteristics and Comorbid Diseases

A total of 156 patients (95 female, 61 male) were included in the study. The mean age of the patients was 43.4. Since vaccination did not start in our country at that time, none of the patients were vaccinated for COVID-19. The most common comorbid diseases in patients were hypertension (27.6%), diabetes mellitus (14.1%), cardiovascular diseases (15.4%), and chronic respiratory diseases (CRD) (15.4%), and others were hypothyroidism (n=17), chronic renal failure (n=2), focal nodular hyperplasia of the liver (n=2), familial Mediterranean fever (n=2), and benign prostatic hyperplasia (n=2). When we grouped the patients according to the number of comorbidities, we found that the rate of those with zero, one, and more than one comorbid disease was 57%, 26.9%, and 15.4%, respectively. Age, gender, body mass index (BMI), smoking status, comorbid diseases, and COVID-19 results are presented in Table 1.

No statistically significant relationship was found between age, gender, BMI, and occupational status of patients and COVID-19 or COVID-19 severity ($p>0.05$ for all). There was a significant association between smoking status and not getting COVID-19 ($p=0.039$). Those who had COVID-19 had a lower smoking rate than those who had never had COVID-19 (16.7% and 42.4%, respectively). No significant association was found between getting COVID-19 and any comorbid disease or the number of comorbid diseases ($p>0.05$ for all). A statistically significant correlation was found between having severe COVID-19 and having CRD ($p<0.05$). The relationship between the number of comorbid diseases and severe COVID-19 was also statistically significant ($p<0.05$).

Rheumatic Diseases and DMARD Treatments

The rheumatic disease diagnoses of the patients were RA in 71 (45.5%), AS in 71 (45.4%), and PsA in 14 (9%). Diagnoses of rheumatic diseases, DMARD used in treatment, and COVID-19 status are given in Table 2.

No significant relationship was found between the diagnosis and duration of rheumatic disease and the severity of COVID-19 or COVID-19 ($p>0.05$ for all). There were no statistically significant differences between the DMARD groups in terms of getting COVID-19 or COVID-19 severity ($p>0.05$ for all). Although not statistically significant ($p=0.078$), the relationship between leflunomide use and COVID-19 severity was closer than for other csDMARDs.

Characteristics of Patients with COVID-19

Of the 156 patients included, 24 (23 with a positive PCR result and 1 with typical findings seen on thorax CT although the PCR result was negative) were diagnosed with COVID-19. Of the 24 patients diagnosed with COVID-19, 16 were treated with mild symptoms, while 8 had severe COVID-19 findings [pneumonia/hospitalization and need for oxygenation/intensive care unit (ICU)]. One patient with severe disease symptoms required ICU admission and intubation, but was subsequently extubated, and discharged with recovery. None of the patients died. Demographic data, rheumatic disease diagnoses, DMARD treatments, PCR and CT findings, and treatments for COVID-19 in patients with COVID-19 are listed in Table 3.

COVID-19 Risk Perceptions and Adherence to Follow-up and Treatment

COVID-19 risk perceptions of patients, depending on their rheumatic diseases and the DMARD they use, are presented

Table 1. Demographic data, smoking status, comorbid diseases, and COVID-19 results

	COVID-19 situation							
	Getting COVID-19			COVID-19 severity				
	Yes (n=24)	No (n=132)	p	Mild (n=16)	Severe (n=8)	Did not get (n=132)	Total (n=156)	p
Age								
Mean ± SD	49.5±11.82	49.36±13.09	0.908[1]	46.06±10.79	56.38±11.34	49.36±13.09	49.39±12.87	0.159[2]
Gender								
Male	6 (25%)	55 (41.7%)	0.124[3]	5 (31.2%)	1 (12.5%)	55 (41.7%)	61 (39.1%)	0.206[3]
Female	18 (75%)	77 (58.3%)		11 (68.8%)	7 (87.5%)	77 (58.3%)	95 (60.9%)	
BMI (kg/m²)								
Mean ± SD	28.98±5.99	28.69±5.43	0.928[1]	27.89±4.73	31.15±7.87	28.69±5.43	28.74±5.50	0.783[2]
Smoking								
Active	4 (16.7%)	56 (42.4%)	0.039[3]	2 (12.5%)	2 (25%)	56 (42.4%)	60 (38.5%)	0.063[3]
Ex	4 (16.7%)	22 (16.7%)		4 (25%)	0	22 (16.7%)	26 (16.7%)	
Never	16 (66.7%)	54 (40.9%)		10 (62.5%)	6 (75%)	54 (40.9%)	70 (44.9%)	
Comorbidity								
HT	7 (29.2%)	36 (27.3%)	0.266[3]	3 (18.8%)	4 (50%)	36 (27.3%)	43 (27.6%)	0.266[3]
DM	2 (8.3%)	20 (15.2%)	0.621[3]	1 (6.2%)	1 (12.5%)	20 (15.2%)	22 (14.1%)	0.621[3]
CVD	8 (33.3%)	19 (14.4%)	0.201[3]	2(12.5%)	3 (37.5%)	19 (14.4%)	24 (15.4%)	0.201[3]
CLD	5 (20.8%)	8 (6.1%)	0.05[3]	1 (6.2%)	3 (37.5%)	8 (6.1%)	24 (15.4%)	0.005[3]
Number of comorbidities								
0	10 (41.7%)	80 (60.6%)	0.075[3]	9 (56.2%)	1 (12.5%)	80 (60.6%)	90 (57.7%)	0.018[3]
1	11 (45.8%)	31 (23.5%)		7 (43.8%)	4 (50%)	31 (23.5%)	42 (26.9%)	
>1	3 (12.5%)	21 (15.9%)		0	3 (37.5%)	21 (15.9%)	24 (15.4%)	

[1]Student's t-test; [2]ANOVA; [3]Chi-square
SD: Standard deviation, COVID-19: Coronavirus disease-2019, BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, CVD: Cardiovascular diseases, CLD: Chronic lung diseases

in Figure 1. Accordingly, 70.5% of the patients thought that they were in the risk group for COVID-19 because of their rheumatic disease and 53% because of the DMARD they used in the treatment.

Only 39 (25%) of the patients had come to their follow-up regularly during this period. Reasons for not attending were as follows; no complaints (13.7%), hesitation to come to the hospital (58.1%), and reaching the doctor by phone (43.6%). Forty-two (26.9%) of the patients made changes for treating their rheumatic disease on their own, 8 (5.1%) made a temporary change in the treatment, and then continued as before.

As expected, those who made changes in their rheumatic disease treatment were more likely to have increased rheumatic disease activity than those who did not change their treatment. An increase in rheumatic disease activity was observed in 52% of patients who changed their treatment, this rate was 27.4% in patients who continued their treatment with the same regimen, and this was statistically significant (p=0.003). Adherence to DMARD treatment was higher in the RA group than in the SpA group. The rates of continuing routine treatment were 83.1% in the RA group and 55.3% in the SpA group, which was statistically significant (p=0.001).

Rheumatic Disease Activities and COVID-19 Outcomes

When the rheumatic disease activities (Disease Activity score-28 for RA, Bath Ankylosing Spondylitis Disease Activity index for AS, Disease Activity in Psoriatic Arthritis for PsA) of the patients before and during the pandemic period (Table 4) were compared, an increase in disease activity was observed in 55 patients. Disease activity changes between the first evaluation during the pandemic period and the last evaluation before the pandemic were significant (p<0.001). It was observed that patients in remission progressed to low and moderate disease activity groups, and patients with low disease activity progressed to high disease activity groups.

When patients with rheumatic disease activity in remission or low were compared with patients with moderate or high activity (Table 5); a statistically significant relationship was found between having moderate or high rheumatic disease activity and getting COVID-19, but not in terms of COVID-19 severity.

DISCUSSION

In this study, we evaluated patients using DMARD for rheumatic diseases in terms of the relationship between demographic and clinical characteristics and COVID-19 or

Table 2. Diagnoses, DMARD treatments and COVID-19 results

	COVID-19 situation							
	Getting COVID-19			COVID-19 severity				
	Yes (n=24)	No (n=132)	p	Mild (n=16)	Severe (n=8)	Did not get (n=132)	Total (n=156)	p
Disease								
RA	14 (58.3%)	57 (43.2%)	0.340[1]	8 (50.0%)	6 (75.0%)	57 (43.2%)	71 (45.5%)	0.473[1]
AS	9 (37.5%)	62 (47.0%)		7 (43.8%)	2 (25.0%)	62 (47.0%)	71 (45.5%)	
PsA	1 (4.2%)	13 (9.8%)		1 (6.2%)	0	13 (9.8%)	14 (9.0%)	
Disease duration Mean ± SD	116.92±84.94	125.27±72.62	0.764[2]	123.88±91.9	103±72.62	125.27±95.37	123.99±93.63	0.854[2]
csDMARD								
MTX	6 (25%)	42 (31.8%)	0.506[1]	4 (25%)	2 (25%)	42 (31.8%)	48 (30.8%)	0,801[1]
SSZ	4 (16.7%)	22 (16.7%)	1[1]	2 (12.5%)	2 (25%)	22 (16.7%)	26(16.7%)	0,741[1]
LEF	5 (20.8%)	14 (10.6%)	0.159[1]	2 (12.5%)	3 (37.5%)	14 (10.6%)	19 (12.2%)	0,078[1]
HCQ	3 (12.5%)	9 (6.8%)	0.337[1]	3(18.8%)	0	9 (6.8%)	12 (7.7%)	0,168[1]
b/tsDMARD								
ADA	2 (20%)	21 (30.4%)		2 (25%)	0	21 (30.4%)	23 (29.1%)	
ETN	2 (20%)	16 (23.2%)		2 (25%)	0	16 (23.2%)	18 (22.8%)	
GOL	1 (10%)	16 (23.2%)		1 (12.5%)	0	16 (23.2%)	17 (21.5%)	
IFX	1 (10%)	5 (7.2%)	0.387[1]	1 (12.5%)	0	5 (7.2%)	6 (7.6%)	0.002[1]
CTZ	1 (10%)	3 (4.3%)		1 (12.5%)	0	3 (4.3%)	4 (5.1%)	
RTX	1 (10%)	1 (1.4%)		0	1 (50%)	1 (1.4%)	2 (2.5%)	
SEC	0	4 (5.8%)		0	0	4 (5.8%)	4 (5.1%)	
TOC	1 (10%)	2 (2.9%)		0	1 (50%)	2 (2.9%)	3 (3.8%)	
TOF	1 (10%)	1 (1.4%)		1 (12.5%)	0	1 (1.4%)	2 (2.5%)	
DMARD groups								
csDMARD	14 (58.3%)	63 (47.7%)	0.633[1]	8 (50%)	6 (75%)	63 (47.7%)	77 (49.4%)	**0.544[1]**
b/tsDMARD	8 (33.3%)	55 (41.7%)		7 (43.8%)	1 (12.5%)	55 (41.7%)	63 (40.4%)	
combined	2 (8.3%)	14 (10.6%)		1 (6.2%)	1 (12.5%)	14 (10.6)	**16 (10.3%)**	

[1]Student's t-test; [2]ANOVA
SD: standard deviation, COVID-19: Coronavirus disease-2019, RA: Rheumatoid arthritis, AS: Ankylosing spondylitis, PsA: Psoriatic arthritis, DMARD: Disease modifying anti-rheumatic drugs, csDMARD: Conventional synthetic disease modifying anti-rheumatic drugs, b/tsDMARD: Biologic or targeted synthetic disease modifying anti-rheumatic drugs, MTX: Methotrexate, SSZ: Sulfasalasine, LEF: Leflunomide, HCQ: Hydroxychloroquine, ADA: Adalimumab; ETN: Etanercept, GOL: Golimumab, IFX: Infliximab, CTZ: Certolizumab pegol, RTX: Rituximab, SEC: Secukinumab, TOC: Tocilizumab, TOF: Tofacitinib

COVID-19 severity. We found that severe COVID-19 is more common in patients with CRD or with one or more comorbid diseases. We also found a higher rate of getting COVID-19 in those with moderate or high rheumatic disease activity. We showed that during the pandemic period, patients' compliance with their follow-up and treatment was low, and that rheumatic disease activity increased more frequently in those who made changes in their rheumatic disease treatment.

Two studies have been published from the COVID-19 Global Rheumatology Alliance (GRA) registry data on the factors affecting the risk of hospitalization and death from COVID-19 in those with rheumatic diseases (12,16). Among these, in the study evaluating the risk of hospitalization, advanced age, presence of comorbidities, and prednisone use (≥10 mg/day) were associated with a higher rate of hospitalization. Monotherapy with b/tsDMARD is associated with lower odds of hospitalization, largely due to the effect of anti-TNF treatments (12). In the study about COVID-19-related death, advanced age, male gender, specific comorbidities, and moderate/high disease activity were associated with higher risk (16). Similarly, we found a significant association between having a CRD or having more than one comorbid disease and COVID-19 severity. We did not find any difference between the patient groups using csDMARD, b/tsDMARD, and combined DMARD (cDMARD + b/tsDMARD) in terms of COVID-19-related outcomes. In a review of patients with autoimmune diseases, baseline glucocorticoid use and some specific drugs such as RTX and SSZ are associated with adverse COVID-19 outcomes, but no increased risk is observed for DMARD classes (13). In line with the COVID-19 GRA results reporting a protective effect with bDMARD use (mainly attributed to TNFis), a lower risk of COVID-19 related hospitalization is reported in patients with inflammatory bowel disease

Table 3. Demographic data, rheumatic diseases and treatments, PCR test & CT results, and COVID-19 treatments of patients with COVID-19

No	Age	Gender	Disease	DMARD	PCR	CT	COVID-19 treatment
1	53	F	AS	CTZ	Pos	No	Home, favipiravir
2	58	F	RA	LEF	Pos	No	Home, favipiravir
3	51	F	RA	MTX	Pos	Yes, typical	PLQ at home first, then favipiravir at hospital
4	47	F	RA	LEF	Pos	Yes, typical	Hospital, lopinavir-ritonavir and oseltamivir
5	66	F	RA	RTX	Pos	Yes, typical	Hospital, lopinavir-ritonavir, oseltamivir, azithromycin
6	66	M	RA	MTX	Neg	Yes, typical	Home, favipiravir
7	48	M	RA	SSZ	Pos	No	Home, HCQ and favipiravir
8	48	F	AS	IFX	Pos	No	Home, favipiravir
9	52	F	AS	SSZ	Pos	Yes, typical	Home, HCQ and favipiravir
10	60	F	RA	MTX	Pos	No	Home, favipiravir
11	61	F	RA	HCQ	Pos	No	Home, with increased HCQ dose
12	28	M	AS	ADA	Pos	No	Home, favipiravir
13	52	F	RA	HCQ	Pos	No	Home, favipiravir
14	63	F	RA	TOC+LEF	Pos	Yes, typical	Hospital, remdesivir and dexamethasone
15	27	F	RA	TOF+MTX	Pos	No	Home, favipiravir
16	54	F	RA	LEF	Pos	No	Home, favipiravir
17	46	F	AS	GOL	Pos	No	Home, favipiravir
18	37	F	AS	SSZ	Pos	Yes, typical	Hospital, HCQ, azithromycin, oseltamivir, favipiravir
19	40	M	AS	ADA	Pos	No	Home, favipiravir
20	35	F	RA	MTX+SSZ+HCQ	Pos	No	Home, favipiravir
21	38	F	AS	ETN	Pos	No	Home, favipiravir
22	52	M	PsA	MTX	Pos	No	Home, HCQ and favipiravir
23	69	F	RA	LEF	Pos	Yes, typical	ICU, favipiravir, methylprednisolone, high dose vitamin C, mechanical ventilation
24	37	M	AS	ETN	Pos	No	Home, favipiravir

F: Female, M: Male, COVID-19: Coronavirus disease-2019, RA: Rheumatoid arthritis, AS: Ankylosing spondylitis, PsA: Psoriatic arthritis, DMARD: Disease modifying anti-rheumatic drugs, MTX: Methotrexate, SSZ: Sulfasalasine, LEF: Leflunomide, HCQ: Hydroxychloroquine, ADA: Adalimumab, ETN: Etanercept, GOL: Golimumab, IFX: Infliximab, CTZ: Certolizumab pegol, RTX: Rituximab, TOC: Tocilizumab, TOF: Tofacitinib, PCR: Polymerase chain reaction, Pos: Positive, Neg: Negative, CT: Computed tomography, ICU: Intensive care unit

using TNFi monotherapy (17) and in patients with psoriasis using bDMARD (compared to non-bDMARD) (18). In addition to the risk factors mentioned above, the delayed diagnosis of COVID-19 was found to be a risk factor for hospitalization (19). Although there was no difference in COVID-19-related outcomes between DMARD classes in our study, the relationship between leflunomide use and severe COVID-19 findings was remarkable, although not statistically significant. In a study evaluating the risk of COVID-19 in patients using DMARD, a positive association was found between the use of leflunomide and the risk of COVID-19 infection (20). On the other hand, another study highlights the potential antiviral effects of leflunomide, noting that it provides faster recovery and reduced viral clearance time in patients with COVID-19 (21).

Another remarkable finding is the opposite relationship between smoking and COVID-19 in our study. 16.7% of the patients who got COVID-19 and 42.4% of those who did not were active smokers. A study supporting this finding found lower probability of testing positive for Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in active smokers than in non-smokers (22). In the study, this was explained by nicotine down-regulation of ACE-2 receptors, which SARS-CoV-2 uses to enter the cell, but the authors emphasized that this should not be interpreted as a protective effect of smoking against COVID-19 (22). In

addition, another study reported that smoking is associated with negative progression and adverse outcomes of COVID-19 (23).

A significant portion of the patients in this study thought that they were in the risk group for COVID-19 because of their rheumatic diseases and the DMARD they used. A similar finding is seen in a study from Australia, where 41% and 55.7% of patients expressed concern about the increased risk of getting COVID-19 due to their rheumatological diseases and medications, respectively. In the same study, in terms of severe COVID-19 results, 52.3% of the patients had a perception of increased risk due to rheumatological diseases and 76.1% due to their medications (2). As a predictable consequence of this situation, patients' compliance with follow-up and treatment decreased. In a study of individuals with RA in the United States, 30% of patients reported a change in treatment, and the proportion who canceled or postponed their appointments (varying in different DMARD groups) was between 28% and 35% (24). In this study, 25% of the patients attended their appointments regularly, and 67% continued their treatment as before. Similar results were observed in other studies in our country. In a study evaluating 330 patients with inflammatory rheumatic diseases in Ankara, it was observed that 27.2% of the patients continued their follow-up regularly and 11.9% changed their treatment without a doctor's advice. In a web-based survey study from İstanbul, these rates for adherence were as follows; 14.4% for follow-up and 77% for treatment. In the latter, similar to our study, there was a significant difference between the RA (81.3%) and SpA (46.3%) patient groups who continued the treatment as before. Similarly, in the study of Kalyoncu et al. (25) evaluating the preferences of patients using bDMARD for the treatment of inflammatory arthritis, the proportion of patients who discontinued bDMARD therapy was significantly higher in the SpA group (20.5%) than in the RA group (13.8%). They also showed lower disease activity in SpA patients who continued bDMARD therapy, in line with the higher incidence of increased disease activity in patients who discontinued DMARD therapy in our study. In our study, the rates of continuing routine treatment were 83.1% in the RA group and 55.3% in the SpA group, which was statistically significant. In addition, the results of a survey study in Spain are similar to our results both in terms of treatment adherence, of which 79.7% of patients continued their treatment as before and in terms of the relationship between spacing-stopping treatment and worsening disease activity (26).

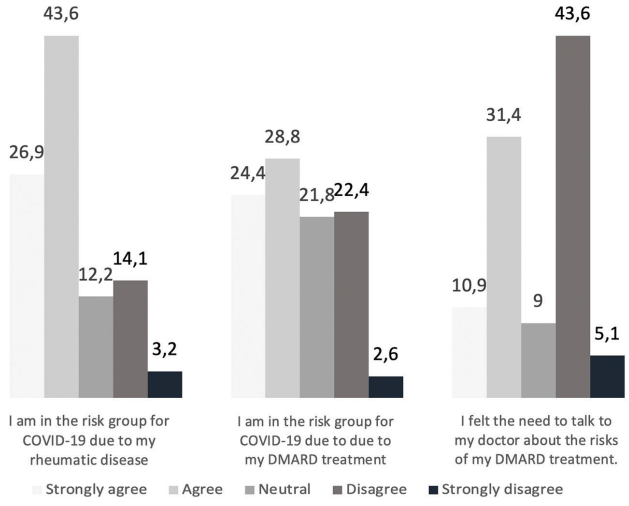

Figure 1. COVID-19 risk perceptions
COVID-19: Coronavirus disease-2019

Table 4. Rheumatic disease activities of the patients before and during the pandemic

Disease activity	After (During pandemic)				P[1]
	<0.001				
Before	**R**	**L**	**M**	**H**	
R	40	12	13	2	
L	1	41	1	27	
M	3	7	3	0	
H	0	1	1	4	

[1]McNemar's test
R: Remission, L: Low, M: Moderate, H: High

Table 5. COVID-19 status and changes in rheumatic disease activity

	COVID-19 situation							
	Getting COVID-19			COVID-19 severity				
	Yes (n=24)	No (n=132)	p	Mild (n=16)	Severe (n=8)	Did not get (n=132)	Total (n=156)	p
Disease activity								
R/L	12 (50%)	93 (70.5%)	**0.049**[1]	9 (56.2%)	3 (37.5%)	93 (70.5%)	105 (67.3%)	0.095[1]
M/H	12 (50%)	39 (29.5%)		7 (43.8%)	5 (62.5%)	39 (29.5%)	51 (32.7%)	

[1]Chi-square test
COVID-19: Coronavirus disease-2019, R: remission, L: Low, M: Moderate, H: High

The most important limitation of our study is the absence of a control group consisting of patients with rheumatic disease who did not use DMARD. Therefore, COVID-19-related outcomes in patients with rheumatic diseases and using DMARD for treatment could not be compared with patients who did not use DMARD. Another limitation is the small number of patients compared with similar studies in the literature. Patients' hesitance to come to the hospital may have caused this situation.

CONCLUSION

There is no difference in COVID-19-related outcomes between DMARD classes in patients with rheumatic diseases. Having a CRD or one or more comorbid diseases may increase the risk of severe COVID-19 manifestations. Patients with moderate or high rheumatic disease activity may get COVID-19 more frequently. Patients' perception of risk for COVID-19 has reduced compliance with follow-up and treatment, making it difficult to maintain remission or low disease activity.

ETHICS

Ethics Committee Approval: We obtained the Clinical Research Ethics Committee approval from University of Health Sciences Türkiye, İstanbul Fatih Sultan Mehmet Training and Research Hospital (no: FSM EAH-KAEK 2020/95, date: 09.07.2020) for this study.

Informed Consent: Written informed consent was obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: K.S., F.Ü.Ö., İ.A., Concept: K.S., F.Ü.Ö., İ.A., P.A., Design: K.S., F.Ü.Ö., İ.A., P.A., Data Collection or Processing: K.S., Analysis or Interpretation: K.S., F.Ü.Ö., İ.A., Literature Search: K.S., Writing: K.S., F.Ü.Ö., İ.A., P.A.

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REFERENCES

1. Hsu CY, Ko CH, Wang JL, Hsu TC, Lin CY. Comparing the burdens of opportunistic infections among patients with systemic rheumatic diseases: a nationally representative cohort study. Arthritis Res Ther 2019;21:211.
2. Antony A, Connelly K, De Silva T, Eades L, Tillett W, Ayoub S, et al. Perspectives of Patients With Rheumatic Diseases in the Early Phase of COVID-19. Arthritis Care Res (Hoboken) 2020;72:1189-95.
3. Ceribelli A, Motta F, De Santis M, Ansari AA, Ridgway WM, Gershwin ME, et al. Recommendations for coronavirus infection in rheumatic diseases treated with biologic therapy. J Autoimmun 2020;109:102442.
4. Michaud K, Wipfler K, Shaw Y, Simon TA, Cornish A, England BR, et al. Experiences of Patients With Rheumatic Diseases in the United States During Early Days of the COVID-19 Pandemic. ACR Open Rheumatol 2020;2:335-43.
5. Accortt NA, Lesperance T, Liu M, Rebello S, Trivedi M, Li Y, et al. Impact of Sustained Remission on the Risk of Serious Infection in Patients With Rheumatoid Arthritis. Arthritis Care Res (Hoboken) 2018;70:679-84.
6. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis Rheum 2002;46:2294-300.
7. Pablos JL, Galindo M, Carmona L, Lledó A, Retuerto M, Blanco R, et al. Clinical outcomes of hospitalised patients with COVID-19 and chronic inflammatory and autoimmune rheumatic diseases: a multicentric matched cohort study. Ann Rheum Dis 2020;79:1544-9.
8. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430-6.
9. Bachiller-Corral J, Boteanu A, Garcia-Villanueva MJ, de la Puente C, Revenga M, Diaz-Miguel MC, et al. Risk of Severe COVID-19 Infection in Patients With Inflammatory Rheumatic Diseases. J Rheumatol 2021;48:1098-102.
10. Haberman R, Axelrad J, Chen A, Castillo R, Yan D, Izmirly P, et al. Covid-19 in Immune-Mediated Inflammatory Diseases - Case Series from New York. N Engl J Med 2020;383:85-88.
11. Stradner MH, Dejaco C, Zwerina J, Fritsch-Stork RD. Rheumatic Musculoskeletal Diseases and COVID-19 A Review of the First 6 Months of the Pandemic. Front Med (Lausanne) 2020;7:562142.
12. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2020;79:859-66.
13. D'Silva KM, Wallace ZS. COVID-19 and Disease-Modifying Anti-rheumatic Drugs. Curr Rheumatol Rep 2021;23:28.
14. Sparks JA, Wallace ZS, Seet AM, Gianfrancesco MA, Izadi Z, Hyrich KL, et al. Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: Results from the COVID-19 Global Rheumatology Alliance physician registry. Ann Rheum Dis 2021;80:1137-46.
15. Mikuls TR, Johnson SR, Fraenkel L, Arasaratnam RJ, Baden LR, Bermas BL, et al. American College of Rheumatology Guidance for the Management of Rheumatic Disease in Adult Patients During the COVID-19 Pandemic: Version 3. Arthritis Rheumatol 2021;73:e1-12.
16. Strangfeld A, Schäfer M, Gianfrancesco MA, Lawson-Tovey S, Liew JW, Ljung L, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2021;80:930-42.
17. Brenner EJ, Ungaro RC, Gearry RB, Kaplan GG, Kissous-Hunt M, Lewis JD, et al. Corticosteroids, But Not TNF Antagonists, Are Associated With Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results From an International Registry. Gastroenterology 2020;159:481-91.
18. Mahil SK, Dand N, Mason KJ, Yiu ZZN, Tsakok T, Meynell F, et al. Factors associated with adverse COVID-19 outcomes in patients with psoriasis-insights from a global registry-based study. J Allergy Clin Immunol 2021;147:60-71.
19. Gamboa-Cárdenas RV, Barzola-Cerrón S, Toledo-Neira D, Reátegui-Sokolova C, Pimentel-Quiroz V, Zevallos-Miranda F, et al. Predictors of hospitalization for COVID-19 in patients with autoimmune rheumatic diseases: results from a community cohort follow-up. Clin Rheumatol 2021;40:4725-34.
20. Yousefghahari B, Navari S, Sadeghi M, Soleimaniamiri S, Soleimaniamiri M, Heidari B, et al. Risk of COVID-19 infection in

patients with rheumatic disease taking disease-modifying anti-rheumatic drugs. Clin Rheumatol 2021;40:4309-15.

21. Hu K, Wang M, Zhao Y, Zhang Y, Wang T, Zheng Z, et al. A Small-Scale Medication of Leflunomide as a Treatment of COVID-19 in an Open-Label Blank-Controlled Clinical Trial. Virol Sin 2020;35:725-33.
22. de Lusignan S, Dorward J, Correa A, Jones N, Akinyemi O, Amirthalingam G, et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. Lancet Infect Dis 2020;20:1034-42.
23. Vardavas CI, Nikitara K. COVID-19 and smoking: A systematic review of the evidence. Tob Induc Dis 2020;18:20.
24. Michaud K, Pedro S, Wipfler K, Agarwal E, Katz P. Changes in Disease-Modifying Antirheumatic Drug Treatment for Patients With Rheumatoid Arthritis in the US During the COVID-19 Pandemic: A Three-Month Observational Study. Arthritis Care Res (Hoboken) 2021;73:1322-31.
25. Kalyoncu U, Pehlivan Y, Akar S, Kaşifoğlu T, Kimyon G, Karadağ Ö, et al. Preferences of inflammatory arthritis patients for biological disease-modifying antirheumatic drugs in the first 100 days of the COVID-19 pandemic. Turk J Med Sci 2021;51:1615-23.
26. López-Medina C, Ladehesa-Pineda L, Gómez-García I, Puche-Larrubia MÁ, Sequí-Sabater JM, Armenteros-Ortiz P, et al. Treatment adherence during the COVID-19 pandemic and the impact of confinement on disease activity and emotional status: A survey in 644 rheumatic patients. Joint Bone Spine 2021;88:105085.

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Research

Effects of Dexmetatomidine and Midazolam on Immunity in Sepsis-induced Rats

Deksmedetomidin ve Midazolam'ın Sepsis Oluşturulmuş Sıçanlarda Bağışıklık Üzerine Etkileri

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ABSTRACT

Objective: Intensive care patients may need sedation for many reasons. The anti-inflammatory effects of different sedation options in sepsis were compared. Although the anti-inflammatory effects of some agents in sepsis have been investigated, there is insufficient evidence about the effects of alpha 2 agonists, especially dexmetatomidine. In this study, the anti-inflammatory effects of midazolam and dexmetatomidine in septic rats were investigated and compared.

Methods: Wistar Albino-type male rats with an experimental sepsis model were used in this study. Thirty-two male rats, which had no renal disease or hepatic insufficiency, were randomly divided into 4 groups. Simple laparotomy and placebo surgery were performed in the control group. After laparotomy, cecal ligation and puncture were performed in the septic group. Cecal ligation perforation (CLP) procedure was also applied to the other two groups, but 8 hours after the procedure, dexmetatomidine was given at a dose of 0.01 mg/kg to group dex rats, while midazolam was given 0.01 mg/kg to group midazolam rats. After 24 hours, blood samples were taken from all groups to measure the levels of IL-1, IL-6, and TNF-α, which were considered sepsis precursors, at the end of CLP. In addition, a histopathological examination of liver and kidney tissue was performed.

Results: When compared with the control group, TNF-α, IL-1, and IL-6 levels were found to be high in the sepsis group (p=0.002, p=0.027, p=0.017). Significant decreases were observed in both serum and tissue in these parameters in all groups. When these two agents were compared, it was seen that the anti-inflammatory effect was higher in the dexmedetomidine-administered group than in the midazolam administered rats.

Conclusion: It has been concluded that dexmedetomidine and midazolam reduce the pro-inflammatory markers that have an important role in the pathophysiology of sepsis. Also, they have immunomodulatory effects. Besides these features, it is seen that dexmetatomidine is superior to midazolam in this respect.

Keywords: Systemic inflammatory response syndrome, dexmedetomidine, midazolam, intensive care units, immunity, rats

ÖZ

Amaç: Yoğun bakım hastaları birçok nedenden dolayı sedasyona ihtiyaç duyabilir. Sepsiste farklı sedasyon seçeneklerinin anti-enflamatuvar etkileri karşılaştırıldı. Sepsiste bazı ajanların anti-enflamatuvar etkileri araştırılmış olsada, alfa 2 agonistlerinin, özellikle deksmedetomidinin etkileri hakkında yeterli kanıt yoktur. Bu çalışmada midazolam ve deksmedetomidinin septik sıçanlarda anti-enflamatuvar etkileri araştırılmış ve birbirleriyle karşılaştırılmıştır.

Gereç ve Yöntem: Bu çalışmada deneysel sepsis modeline sahip Wistar Albino tipi erkek sıçanlar kullanıldı. Renal veya hepatik disfonksiyonu olmayan 32 erkek sıçan rastgele 4 gruba ayrıldı. Kontrol grubuna basit laparotomi ve plasebo ameliyatı yapıldı. Septik grupta sadece çekal ligasyon ve ponksiyon yapıldı. Çekal ligasyon perforasyonundan (CLP) 8 saat sonra deksmedetomidin grubuna 0,01 mg/kg deksmedetomidin verilirken, midazolam grubuna 0,01 mg/kg midazolam verildi. CLP'den 24 saat sonra, IL-1, IL-6 ve TNF-α düzeylerini ölçmek için tüm gruplardan kan örnekleri alındı. Ayrıca karaciğer ve böbrek dokuları histopatolojik olarak incelendi.

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Bulgular: Kontrol grubu ile karşılaştırıldığında sepsis grubunda TNF-α, IL-1 ve IL-6 seviyeleri yüksek bulundu. Hem deksmedetomidin grubunda hem de midazolam grubunda bu parametreler hem serumda hem de dokuda anlamlı düşüş gösterdi. Bu iki ajan karşılaştırıldığında, deksmedetomidin uygulanan grupta anti-enflamatuvar etkinin midazolam uygulanan sıçanlara göre daha yüksek olduğu görüldü.

Sonuç: Deksmedetomidin ve midazolamın sepsis patofizyolojisinde önemli rolü olduğu, immünomodülatör etkileri olan proenflamatuvar belirteçleri azalttığı ve bu açıdan deksmedetomidinin midazolamdan üstün olduğu sonucuna varılmıştır (p=0,002, p=0,027, p=0,017).

Anahtar Kelimeler: Sistemik enflamatuvar yanıt sendromu, deksmedetomidin, midazolam, yoğun bakım ünitesi, immünite, sıçanlar

INTRODUCTION

Sepsis; describes the systemic inflammatory response to infection and has been one of the life-threatening problems in the history of medicine. Sepsis and septic shock are clinical pictures that require urgent treatment and they still have a high level of morbidity and mortality, which has more than 40% mortality rate today (1). Despite our increasing knowledge and treatment options, sepsis is still one of the leading causes of mortality in intensive care units. One of the most important factors that can reduce mortality is a fast, appropriate, and intensive treatment approach. Mortality is related to the underlying medical conditions, infectious agents, ability to respond to infection, appropriate antimicrobial therapy, and the development process of septic shock. There is not enough information about the actual number of sepsis cases in the world, and the existing data are mostly estimated. However, it can be seen in many clinical pictures, It is thought that sepsis is greater than the number of patients diagnosed with it (2).

Septic patients are frequently treated in intensive care units, and the use of sedation in septic patients is one of the most confusing issues, as in all intensive care patients. The indications of sedative agents and their effects on mechanical ventilation durations, hospital stay, and mortality have been the subject of many studies (3). However, there are limited studies on its effects on prognosis in sepsis (4).

Midazolam is a short-acting benzodiazepine derivative containing an imidazole ring. It acts by increasing the effect of the GABA neurotransmitter, which is involved in nerve conduction in many parts of the central nervous system especially in the cortex (5-7). Dexmetatomidine is a very potent and selective α2 adrenoreceptor agonist (6). It is used as an anesthetic adjuvant that creates analgesia and sedation. It reduces the need for anesthetics and tremors after anesthesia as well as the consumption of perioperatively used rocuronium and inhalation agents, moreover, it creates hemodynamic stability dexmedetomidine (5). Dexmetatomidine suppresses the stress response to surgery (8,9).

On the other hand, excessive secretion of inflammatory cytokines such as TNF-α, IL-8, and IL-6 was observed in the pathophysiological sepsis process. Recent studies have shown that midazolam decreases the plasma IL-1β, 6, 8 and TNF-α levels in critically ill patients (10). Therefore, midazolam was shown to inhibit the proliferation of CD3 + T-cells and the T helper 1 (Th1) cellular immune response in a rat model (11). These studies suggest that midazolam may be beneficial for septic patients with uncontrolled immuno-inflammatory responses. Dexmedetomidine, which is used for similar purposes, has been shown to help improve the outcome in animal models of sepsis by enhancing macrophage phagocytosis and bacterial clearance with its α-2 agonistic feature as well as its sedative effects (12). The anti-inflammatory effect may also need to be considered as a factor in the selection of sedation agencies in septic patients. However, it is not known which agent is more effective than the other in this respect.

In this study, a sepsis model was created in rats using the cecal ligation perforation (CLP) method, and the anti-inflammatory effects of dexmetatomidine and midazolam were examined and their superiority to each other was compared.

METHODS

All animal procedures were approved by an ethics committee (Kırıkkale University Animal Experiments Local Ethics Committee-decision no: 17/07, date: 01.03.2017) and conducted in accordance with international guidelines for the care and use of animals. For this study, 32 Wistar Albino-type male rats, which weigh 200-300 g, were used. The number of rats was determined by calculating the effect size in the power analysis and considering the number of animals in similar articles (13). The total sample size was calculated with 0.86 power and 0.5 effect size, with the least animal waste. All animals were acclimatized for 7 days before experimentation in the laboratory of the institute, where all animals were kept at 22±2 °C and 55±10% relative humidity on a constant 12-hour (h) dark/light cycle. All animals were kept in standard cages and fed the same rodent chow and water. The number of animals to be included in the study was determined by the power analysis performed with similar studies in the literature (14). Rats with mortality between the creation of the sepsis model and the collection of blood

samples were determined as the criteria for exclusion from the study.

CLP method: Surgery was initiated after 2 h of fasting. The modified cecal ligation and the puncture method was used to create sepsis in rats. Although this method is uncertain for clinical sepsis, its inflammatory markers and clinical outcomes are similar to sepsis. As it is used in many studies, it is accepted as one of the most suitable models for creating sepsis model (14). Anesthesia was completed by injecting 50 mg/kg ketamine hydrochloride (KetalarR) and 10 mg/kg xylazine hydrochloride (RometarR). The surgical area was shaved and the skin was antisepsised with betadine, and the whole process was performed under sterile conditions. The abdomen was opened with a 2-3 cm incision from the midline. The cecum was tied with 3/0 silk of the rats in this group so that the intestinal continuity was not disturbed and some of the cecum contents were removed by piercing 2-3 times with an 18 gauche needle. Then, the cecum was placed in the abdomen and sutured with 3/0 silk.

The animals were randomly divided into 4 groups of 8 animals each. The groups were, respectively, named as the "control" group, the "sepsis" group, the Dex" group (sepsis model + dexmedetomidine), and the "midazolam" group (sepsis model + midazolam).

Rats that underwent the CLP procedure were considered as the sepsis group. In addition to the sepsis model, dexmetatomidine - administered rats were determined as the "dex" group, and midazolam - administered rats were determined as the "midazolam" group. The same anesthesia and CLP procedures were applied in the "sepsis", "dex" and "midazolam" groups. In the control group, after the anesthesia procedure, the abdomen was opened and the cecum was observed to be intact and resutured.

In the dex and midazolam groups, dexmetatomidine or midazolam was administered intravenously at a dose of 0.01 mg/kg at the postoperative 8th h. According to the CLP procedure, we decided to administer the anesthetic drugs at the 8th h because the animals started to show symptoms of fever, malaise, and diarrhea between 8 and 12 h postoperatively (15). In the other two groups, normal saline was given via the tail vein at the same time and in the same volume. The chosen doses of these drugs were based on previous studies and our preliminary experiments (11,16).

At the postoperative 24th h, the incision line was widened to include the chest cavity by opening from the old incision line. Severe sepsis symptoms and hypothermia can be seen in rats 24 h after CLP, and there are literature studies recommending euthanasia for this reason (15). Taking into account the half-lives of the drugs given at the postoperative 24th h, it was predicted as the earliest time they could have an effect. Approximately 3-4 mL of blood samples were taken intracardiac and placed in biochemistry tubes. Following the blood samples, liver and kidney tissue samples were collected and placed in formaldehyde tubes. The commercially available enzyme-linked immune sorbent assay (ELISA) kits were used according to the manufacturers' recommendations: Rat TNF-alpha ELISA Kit (Elabscience, Cat: E-EL-R0019), Rat IL-1-beta ELISA Kit (Elabscience, Cat: E-EL-R0012), and Rat IL-6 ELISA Kit (Elabscience, Cat: E-EL-R0015). The collected tissues were homogenized for 5 minutes (min) at 4 °C using an electric blender. The homogenate was centrifuged at 4000 rpm at 4 °C. TNF-α, IL-1, and IL-6 analyses were performed from the obtained solution with rapid kits.

From the obtained results, inflammatory marker levels among the groups were analyzed statistically in terms of anti-inflammatory effects in both plasma and tissues.

Statistical Analysis

The normal distribution of the data's developmental parameters, which were obtained at the end of the study, was evaluated with the Kolmogorov-Smirnov test. Since the data did not show a normal distribution ($p<0.05$), the Kruskal-Wallis H test was used. The Mann-Whitney U test with Bonferroni correction was used for multiple comparisons. A $p<0.05$ was considered statistically significant. In the Shapiro-Wilk test for biochemical data, which were normally distributed, were expressed as mean ($\bar{X}$) ± standard deviation and the data that were not normally distributed were expressed as median (minimum-maximum). One-Way analysis of variance (ANOVA) was used for comparisons between groups for normally distributed data, and Tamhane and Tukey's HSD test was used for multiple comparisons between groups.

Power Analysis

t-tests - Means: Difference between two dependent means (matched pairs)
Analysis:A priori: Compute required sample size
Input: Tail(s) = One
Effect size dz = 0.5
α err prob = 0.05
Power (1-β err prob) = 0.86
Output: Noncentrality parameter δ= 2.8284271
Critical t = 1.6955188
Df = 31
Total sample size = 32
Actual power = 0.8688531

RESULTS

In this study, 32 Wistar Albino-type male rats, which weigh 200-300 g, were used. Neither mortality nor exclusion requirement was observed in the study animals. In this study, TNF-α, IL-1, and IL-6 were used as indicators for sepsis, and there was a significant difference in these values between the control and sepsis groups. It was concluded that the sepsis model was successfully created. In all three plasma, kidney and liver samples, inflammatory markers were significantly higher in the sepsis group than in the control group ($p<0.001$). The comparison between the groups is presented in Table 1. When the IL-1β values were examined, a significant decrease was observed in the dex and midazolam groups compared to the sepsis group ($p<0.001$). In addition, in the dex group plasma IL-1β values were lower than in the midazolam group ($p=0.002$). IL-1β values in kidney and liver tissues were similar in the dex and midazolam groups but these values were significantly lower than in the septic group ($p<0.001$). TNF-α values were also significantly higher in the septic group than in the control, dex and midazolam groups ($p<0.001$). Plasma TNF values were significantly lower in the dex group ($p=0.027$), whereas TNF values in the liver ($p=0.360$) and kidney ($p=0.579$) tissues were similar in the dex and midazolam groups. IL-6 levels were significantly higher in the septic group compared to the control group, and significantly lower in the dexmetatomidine and midazolam applied groups compared to the sepsis group ($p<0.001$). IL-6 levels in both serum and tissues were similar in the dex and midazolam groups ($p=0.098$). The comparison of the groups is presented in Table 1.

DISCUSSION

The significant difference in inflammatory markers between the sepsis and control groups in our study showed that the sepsis model was successfully established. In the dex and midazolam groups, inflammatory markers were significantly reduced compared with the sepsis group. This showed that both of these agents have anti-inflammatory effects. Similar to serum, inflammatory markers were significantly decreased in liver and kidney tissue samples. When dexmetatomidine and midazolam were compared, it was observed that serum TNF-α, IL-1, and IL-6 levels were significantly decreased in the dex group, which was compared with the midazolam group; therefore, dexmetatomidine had a greater anti-inflammatory effect than midazolam.

Midazolam and dexmetatomidine are commonly used sedation agents in intensive care units (17). Septic patients may need sedation with or without mechanical ventilation support. In these patients, hemodynamic and cognitive effects usually our first concerns in the selection of sedation agents. Decreased systemic vascular resistance and increased permeability present hypotension as an important problem in these patients. It is desired that the sedation agents applied minimally contribute to hypotension or even fix it.

In a meta-analysis, sedation agents were examined in sepsis patients and it was found that dexmetatomidine caused 51% less 28-day mortality compared to other sedative agents (18). Dexmetatomidine has anxiolytic and sedative effects but does not have a respiratory depressant effect. With this advantage, it is widely used in intensive care units and clinical anesthesia. Two hundred forty two patients were included in the aforementioned analysis, which compares dexmetatomidine with propofol, lorazepam and midazolam.

Table 1. The p-value was given for the total comparison of the four groups, and the comparison of the 4 groups with each other was shown

Parameters	Control n=8	Sepsis n=8	Sepsis + Dex n=8	Sepsis + Midazol n=8	p
IL-1β of serum (pg/mL)	27.19±1.75	140.38±17.35	75.62±8.75	96.59±5.73	**<0.05**
IL-1β of liver (pg/mg)	108.39±10.04	489.90±71.75	213.47±23.53	262.28±16.29	**<0.05**
IL-1β of kidney (pg/mg)	36.51±5.24	175.23±30.28	78.07±8.11	90.81±5.91	**<0.05**
TNF-α of serum (pg/mL)	43.13±4.61	319.84±24.21	160.68±16.22	185.45±12.57	**<0.05**
TNF-α of liver (pg/mg)	100.34±7.49	693.09±69.39	350.16±35.55	390.94±28.11	**<0.05**
TNF-α of kidney (pg/mg)	68.02±4.67	458.17±48.82	232.26±23.50	256.97±18.64	**<0.05**
IL-6 of serum (pg/mL)	193.57±15.88	1093.20±188.54	565.26±62.34	572.39±47.93	**<0.05**
IL-6 of liver (pg/mg)	454.24±52.90	2377.19±467.77	1235.70±144.51	1211.43±106.90	**<0.05**
IL-6 of kidney (pg/mg)	314.57±38.43	1163.12±69.74	830.02±95.44	810.52±69.99	**<0.05**

As the most important benefit in increasing survival, it was concluded that dexmetatomidine is more hemodynamically stable than other sedatives. In fact, no hypotension or bradycardia was reported in the 214 studies reviewed in this meta-analysis (19). However, when we look at the literature, it is seen that the most common side effects are hypotension and bradycardia. In the same study, after 24 h of treatment, TNF-α levels, IL-1β, and IL-6 were significantly lower in patients treated with dexmetatomidine. This led the authors to conclude that the anti-inflammatory effect of dexmetatomidine may also have affected survival in septic patients (19,20). In sepsis, the catabolic process is the precursor, and sedative drugs can be useful for treating sepsis by stopping this destruction. When we evaluated many studies in the literature, we predicted that sedative drugs may be beneficial in our study.

In our study, a significant difference was observed in plasma TNF-α, IL-1β, and IL-6 levels in rats treated with dex compared with the sepsis group. In some similar studies, it was observed that it decreased the levels of proinflammatory cytokines, and mortality decreased in rats with sepsis (21). It was noted that the effect was dose dependent. In our study group, only a single dose of dexmetatomidine and midazolam was tried to reduce the number of subjects used, and the effects of increasing doses were not analyzed. Dexmetatomidine is most commonly used for sedation in intensive care by infusion at a dose of 1 mcg/kg and maintenance doses of 0.2-0.7 mcg/kg after loading (22). According to our study, even a single dose of sedation showed an anti-inflammatory effect. Besides, new studies on more animals or subjects are needed for the effect of different doses (23).

Midazolam is one of the agents frequently used in intensive care sedation. Its anti-inflammatory effects and its effects on mortality in sepsis patients have been the subject of some studies before (24). Midazolam binds to specific receptors on macrophages, reducing the production of TNF-α, IL-1β, and IL-6. Similar to midazolam, remimidazolam also showed anti-inflammatory effects, the mechanism of which is thought to be the activation of benzodiazepine receptors and a decrease in p98 level (25). However, opposing studies have suggested that midazolam does not alter the lipopolysaccharide-stimulated cytokine response (26). Therefore, the anti-inflammatory effect of midazolam still seems controversial. In our study, TNF-α, IL-1β, and IL-6 were significantly decreased in rats using midazolam. Similarly, in a study using sedative agents, midazolam was shown to reduce inflammatory markers in peritoneal lavage fluid (27).

Infection-induced sepsis can lead to organ failure because of both cytokine responses and hemodynamic disorders. The effects of inflammatory mediators, especially in the liver, kidney, and brain, increase mortality (28). In our study, it was observed that both midazolam and dexmetatomidine had anti-inflammatory effects in the liver and kidney compared to the sepsis group. In Koca et al. (29) on 21 rats, dexmetatomidine reduced sepsis-induced lung and kidney injuries and apoptosis in septic rat models of intra-abdominal sepsis . In the study of Qui et al. (30), dexmetatomidine decreased IL-1β, IL-6 and TNF-α, NF-κB activity, and TLR4 expression, acted on the rat kidney tissues and provided a protective effect on the renal tissues.

An important point of our study is that dexmetatomidine is more effective than midazolam on serum anti-inflammatory markers, however, there is no difference between midazolam and dex in terms of TNF-α, IL-1β, and IL-6 levels in kidney and liver tissue. These two sedative agents showed similar anti-inflammatory effects in liver and kidney. This finding suggests that dexmetatomidine may be more beneficial in patients with sepsis without organ dysfunction or hemodynamic stability. We think that dexmetatomidine is more effective than midazolam because its hypotension-producing effect is less than that of other sedatives and because it affects hemodynamic stability less. Further comparison is needed for these two agents in terms of their effects on organs.

First, our study was conducted on animal models, and the results may not be certain for septic intensive care patients. When the literature is examined, it is observed that many studies have been carried out in this area in rats and the results have been adapted to humans (31). Another limitation is that both midazolam and dexmetatomidine were given in a single dose in our study. However, sedation is often used as an infusion in the intensive care unit. Different doses were not used to reduce the number of animals used. In this study, the anti-inflammatory effects of dexmetatomidine and midazolam were proven in both plasma and liver-kidney tissues, and it was concluded that more studies are required for the effects of different doses.

CONCLUSION

Our study results show that both midazolam and dexmetatomidine have an anti-inflammatory effect by causing a decrease in TNF-α, IL-1β, and IL-6 levels in rats in the sepsis model. Dexmedetomidine provides a significant decrease in serum anti-inflammatory levels compared to midazolam, and the effects of these two sedative agents are similar in the liver and kidney.

*Our article was written by producing from the thesis study.

ETHICS

Ethics Committee Approval: All animal procedures were approved by an ethics committee (Kırıkkale University Animal Experiments Local Ethics Committee-decision no: 17/07, date: 01.03.2017) and conducted in accordance with international guidelines for the care and use of animals.

Informed Consent: Experimental study.

Authorship Contributions

Surgical and Medical Practices: F.Ö., A.Y., A.D., Ç.K., Concept: F.Ö., Ç.K., Design: F.Ö., Ç.K., Data Collection or Processing: F.Ö., A.Y., A.D., Analysis or Interpretation: F.Ö., A.Y., A.D., Literature Search: F.Ö., A.Y., Writing: F.Ö., A.Y., A.D.

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REFERENCES

1. Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019- results from a systematic review and meta-analysis. Crit Care 2020;24:239.
2. Bone RC, Grodzin CJ, Balk RA. Sepsis: a new hypothesis for pathogenesis of the disease process. Chest 1997;112:235-43.
3. Train SE, Dieffenbach PB, Massaro AF, Devlin JW. Sedation, Neuromuscular Blockade, and Mortality in Acute Respiratory Distress Syndrome: Important Questions Remain. Crit Care Med 2022;50:e89-90.
4. Shehabi Y, Murfin B, James A, Al-Bassam W, Bellomo R. Trials of dexmedetomidine sedation in ventilated critically ill septic patients: Challenges, limitations and opportunities. Anaesth Crit Care Pain Med 2021;40:100925.
5. Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. Drugs 2000;59:263-8; discussion 269-70.
6. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. Proc (Bayl Univ Med Cent) 2001;14:13-21.
7. Mo Y, Zimmermann AE. Role of dexmedetomidine for the prevention and treatment of delirium in intensive care unit patients. Ann Pharmacother 2013;47:869-76.
8. Bajwa S, Kulshrestha A. Dexmedetomidine: an adjuvant making large inroads into clinical practice. Ann Med Health Sci Res 2013;3:475-83.
9. Zheng L, Zhao J, Zheng L, Jing S, Wang X. Effect of Dexmedetomidine on Perioperative Stress Response and Immune Function in Patients With Tumors. Technol Cancer Res Treat 2020;19:1533033820977542.
10. Helmy SA, Al-Attiyah RJ. The immunomodulatory effects of prolonged intravenous infusion of propofol versus midazolam in critically ill surgical patients. Anaesthesia 2001;56:4-8.
11. Ohta N, Ohashi Y, Takayama C, Mashimo T, Fujino Y. Midazolam suppresses maturation of murine dendritic cells and priming of lipopolysaccharide-induced t helper 1-type immune response. Anesthesiology 2011;114:355-62.
12. Li Y, Wu B, Hu C, Hu J, Lian Q, Li J, et al. The role of the vagus nerve on dexmedetomidine promoting survival and lung protection in a sepsis model in rats. Eur J Pharmacol 2022;914:174668.
13. Uludag O. Effect of Sugammadex and Rocuronium Combination on Cranial Neurotoxicity in Rats: Experimental Study. Kafkas Univ Vet Fak Derg 2019;25:793-9.
14. Zhang J, Wang Z, Wang Y, Zhou G, Li H. The effect of dexmedetomidine on inflammatory response of septic rats. BMC Anesthesiol 2015;15:68.
15. Toscano MG, Ganea D, Gamero AM. Cecal ligation puncture procedure. J Vis Exp 2011;(51):2860.
16. Zhang J, Zhang H, Zhao L, Zhao Z, Liu Y. Effect and Mechanism of Lidocaine Pretreatment Combined with Dexmedetomidine on Oxidative Stress in Patients with Intracranial Aneurysm Clipping. J Healthc Eng 2021;2021:4293900.
17. Sandeep Sharma,Muhammad F. Hashmi,Dominic J. Valentino III , Sedation Vacation in the ICU,In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. 2021 Sep 18. Bookshelf ID: NBK513327
18. Zamani MM, Keshavarz-Fathi M, Fakhri-Bafghi MS, Hirbod-Mobarakeh A, Rezaei N, Nader ND. Survival benefits of dexmedetomidine used for sedating septic patients in intensive care setting: A systematic review. J Crit Care 2016;32:93-100.
19. Arcangeli A, D'Alò C, Gaspari R. Dexmedetomidine use in general anaesthesia. Curr Drug Targets. 2009;10:687-95.
20. Zamani MM, Keshavarz-Fathi M, Fakhri-Bafghi MS, Hirbod-Mobarakeh A, Rezaei N, Bahrami A, et al. Survival benefits of dexmedetomidine used for sedating septic patients in intensive care setting: A systematic review. J Crit Care 2016;32:93-100.
21. Afonso J, Reis F. Dexmedetomidine: current role in anesthesia and intensive care. Rev Bras Anestesiol 2012;62:118-33.
22. Naaz S, Ozair E. Dexmedetomidine in current anaesthesia practice-a review. J Clin Diagn Res. 2014;8:GE01-4. Erratum in: J Clin Diagn Res 2022;16:ZZ01.
23. Taniguchi T, Kurita A, Kobayashi K, Yamamoto K, Inaba H. Dose- and time-related effects of dexmedetomidine on mortality and inflammatory responses to endotoxin-induced shock in rats. J Anesth 2008;22:221-8.
24. O'Donnell NG, McSharry CP, Wilkinson PC, Asbury AJ. Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarization in vitro in the presence or absence of human serum albumin. Br J Anaesth 1992;69:70-4.
25. Fang H, Zhang Y, Wang J, Li L, An S, Huang Q, et al. Remimazolam reduces sepsis-associated acute liver injury by activation of peripheral benzodiazepine receptors and p38 inhibition of macrophages. Int Immunopharmacol 2021;101:108331.
26. Takaono M, Yogosawa T, Okawa-Takatsuji M, Aotsuka S. Effects of intravenous anesthetics on interleukin (IL)-6 and IL-10 production by lipopolysaccharide-stimulated mononuclear cells from healthy volunteers. Acta Anaesthesiol Scand 2002;46:176-9.
27. Xiao D, Zhang D, Xiang D, Liu QI, Liu Y, Lv L, et al. Effects of fentanyl, midazolam and their combination on immune function and mortality in mice with sepsis. Exp Ther Med 2015;9:1494-500.
28. Sezer A, Memiş D, Usta U, Süt N. The effect of dexmedetomidine on liver histopathology in a rat sepsis model: an experimental pilot study. Ulus Travma Acil Cerrahi Derg 2010;16:108-12.
29. Koca U, Olguner ÇG, Ergür BU, Altekin E, Taşdöğen A, Duru S, et al. The effects of dexmedetomidine on secondary acute lung and kidney injuries in the rat model of intra-abdominal sepsis. ScientificWorldJournal 2013;2013:292687.
30. Qiu R, Yao W, Ji H, Yuan D, Gao X, Sha W, et al. Dexmedetomidine restores septic renal function via promoting inflammation resolution in a rat sepsis model. Life Sci 2018;204:1-8.
31. Dardalas I, Stamoula E, Rigopoulos P, Malliou F, Tsaousi G, Aidoni Z, et al. Dexmedetomidine effects in different experimental sepsis in vivo models. Eur J Pharmacol 2019;856:172401.

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Research

Is Subcutaneous Rifamycin Application Superior to Saline Application in Hip Hemiarthroplasty?

Kalça Hemiartroplastisinde Subkütan Rifamisin Uygulaması Salin Uygulamasına Üstün mü?

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ABSTRACT

Objective: The effect of subcutaneous rifampicin administration on postoperative early wound discharge in patients undergoing hemiarthroplasty after femoral neck fracture was investigated.

Methods: Between 2013 and 2015, 58 (36 female, 22 male) patients aged 65-94 (mean 79.29±7.99 years) who underwent hemiarthroplasty for hip fracture were included in the study. Two of the patients were Garden type 2, 21 were Garden type 3 and 35 were Garden type 4. The patients were followed from the postoperative period until discharge, and the length of stay was recorded. The subcutaneous rifamycin-administered group (group 1), saline irrigation-only group (group 2), and saline solution-added rifamycin group (group 3) were examined in 3 groups.

Results: The duration of discharge was statistically significant according to age ($p<0.05$). The mean duration of wound discharge was significantly higher in patients older than 75 years ($p=0.02$). The operation duration of RIF + SF irrigation was significantly higher than that of SF irrigation ($p=0.037$). There was no statistically significant relationship between operation duration, incision length and additional diseases, and discharge time ($p>0.05$).

Conclusion: There was no significant difference between the groups in terms of postoperative discharge times. The operative time was longer in patients who received subcutaneous rifamycin and were older than 75 years. Additional or isolated rifamycin application for hip hemiarthroplasty irrigation has no superiority over the saline solution.

Keywords: Hemiarthroplasty, hip fracture, rifamycin, surgical wound infection, collum femoris fracture

ÖZ

Amaç: Femur boyun kırığı sonrası hemiartroplasti uygulanan hastalarda subkütan rifamisin uygulamasının postoperatif erken yara iyileşmesine etkisi araştırıldı.

Gereç ve Yöntem: 2013-2015 yılları arasında kalça kırığı nedeniyle hemiartroplasti yapılan, yaşları 65-94 (ortalama 79,29±7,99 yıl) olan 58 (36 kadın, 22 erkek) hasta çalışmaya dahil edildi. Hastaların ikisi Garden tip 2, 21'i Garden tip 3 ve 35'i Garden tip 4 idi. Hastalar postoperatif dönemden taburcu oluncaya kadar takip edildi ve hastanede yatış süreleri kaydedildi. Deri altı rifamisin verilen grup (grup 1), sadece salin irrigasyon yapılan grup (grup 2) ve salin solüsyon eklenen rifamisin grubu (grup 3) olarak 3 grupta incelendi.

Bulgular: Taburculuk süresi yaşa göre istatistiksel olarak anlamlıydı ($p<0,05$). Ortalama yara akıntı süresi 75 yaş üstü hastalarda anlamlı olarak daha yüksekti ($p=0,02$). RIF + SF irrigasyonunun operasyon süresi, SF irrigasyonundan anlamlı derecede yüksekti ($p=0,037$). Ameliyat süresi, insizyon uzunluğu ve ek hastalıklar ile taburculuk süresi arasında istatistiksel olarak anlamlı bir ilişki yoktu ($p>0,05$).

Sonuç: Ameliyat sonrası taburculuk süreleri açısından gruplar arasında anlamlı fark yoktu. Subkütan rifamisin alan ve 75 yaşından büyük hastalarda ameliyat süresi daha uzundu. Kalça hemiartroplastisi irrigasyonu için ek veya izole rifamisin uygulamasının salin solüsyona üstünlüğü yoktur.

Anahtar Kelimeler: Hemiartroplasti, kalça kırığı, rifamisin, cerrahi yara enfeksiyonu, femur boyun kırığı

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INTRODUCTION

Surgical wound infections are one of the most important postoperative problems that change the course of the disease after surgery and prevent healing (1). Surgical wound infections, especially in elderly patients with osteoporotic hemiarthroplasty, have emerged as the cause of more problematic cases. Mortality rate increases in elderly patients due to the presence of comorbidities, low physical capacity, prolonged hospital stay, and recurrent surgeries (2). In addition, decreased blood supply, additional diseases, and biofilm formation of implants in the elderly may facilitate the development of infection in the postoperative period (3). Antibiotic prophylaxis reduces the incidence of infection (4). In a study performed by Kërveshi et al. (5), they reported that infection rates decreased when they used amikacin sulfate by diluting in patients who underwent disc herniation operation. Cordero-Ampuero and de Dios (6) reported that prolonged wound discharge may lead to infection in the future. After orthopedic surgeries, irrigation is performed by applying various antibiotics such as rifamyicin to washing fluids (7,8). Irrigation with saline is the most common form of irrigation. In this study, we aimed to reduce the risk of discharge and infection in the postoperative period by adding rifamycin (RIF) to the saline solution during irrigation or by applying RIF subcutaneously after fascial closure in patients undergoing hemiarthroplasty. The effect of RIF administration on wound discharge in the early postoperative period in patients who underwent hemiarthroplasty due to femoral neck fracture was investigated.

METHODS

After University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee approval (decision no: 2015-16/08, date: 12.10.2015), medical records of patients who underwent hemiarthroplasty after femoral neck fracture between 2013 and 2015 were retrospectively reviewed. Patients who underwent osteosynthesis with cannulated or dynamic hip screws, who underwent total hip arthroplasty, who underwent irrigation due to infection after hemiarthroplasty, revision surgeries, and patients with insufficient medical knowledge were excluded from the study. Fifty eight patients (36 females, 22 males) who met the inclusion criteria were included in the study. Femoral neck fractures of the patients were classified according to the Garden classification.

Surgical Technique and Postoperative Care

A standard posterolateral incision approach was applied to the patients after general or regional anesthesia. After passing through the skin, subcutaneous, and fascia, the trochanteric bursa was excised. The external rotators were suspended, and the capsule was reached and opened by a T-shaped incision. The femoral head was removed and the femoral canal and neck were prepared. After deciding on the appropriate size of the prosthesis, cemented hemiarthroplasty was performed. Soft tissue repair was performed anatomically. First-generation cephalosporins were administered 3x1 g in 24 hours postoperatively. Drains were removed once the drainage stopped or became less than about 25 mL/day. During the postoperative period, the discharge of the patients was monitored. Three groups were evaluated according to RIF administration or not during hemiarthroplasty. Subcutaneous RIF was treated in group 1 (Figure 1), saline alone (SF) in group 2, and RIF was added to the irrigation fluid in group 3 (SF + RIF). RIF is used only in perioperative. Group 1 was irrigated with saline and after the closure of the facia, 500 mg RIF was added subcutaneously. Group 2 was irrigated with saline. Group 3 was irrigated with saline and added 500-mg RIF. Postoperative discharge time and discharge types of the patients in three groups were evaluated.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (NCSS, LLC Kaysville, Utah, USA) was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, and ratio) as well as quantitative data showing normal distribution were used to evaluate the study data. Kruskal-Wallis test and Mann-Whitney U test were used in the comparison of the groups that did not show the normal distribution and in the determination of the group causing the difference and in the evaluation of the two groups. Fisher-Freeman-Halton test was used to compare qualitative data. The results were evaluated with 95% confidence interval and $p<0.05$ significance level.

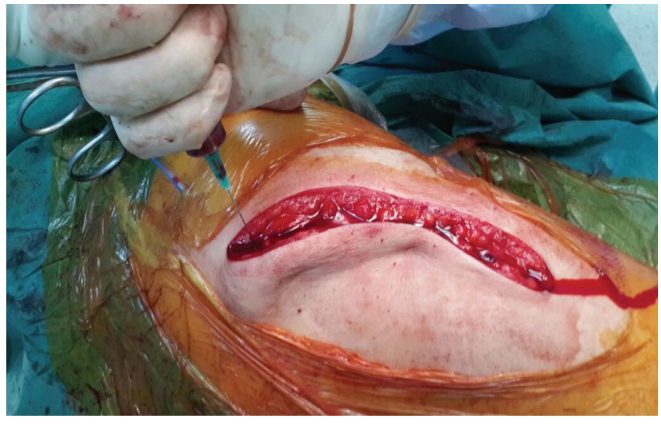

Figure 1. Application of subcutaneous rifamycin

Table 1. Demographic and clinical characteristics of patients

		Min-max	Mean ± SD
Age (years)		65-94	79.29±7.99
Hospitalization (days)		5-33	16.94±6.71
Duration of operation (minutes)		55-135	94.48±23.20
Drain withdrawal time (hours)		20-48	26.86±5.88
Postop wound discharge time		1-9	3.31±2.02
Length of skin incision		8-23	17.03±2.61
		n	%
Irrigation type	RIF + SF	10	17.2
	Subcutaneous RIF	12	20.7
	Only SF	36	62.1
Age group	≤75 age	20	34.5
	>75 age	38	65.5
Gender	Female	36	62.1
	Male	22	37.9
Length of skin incision	≤16 cm	21	36.2
	17-18 cm	23	39.7
	>18 cm	14	24.1
DM	Yes	10	17.2
	No	48	82.8
Other additional diseases	Yes	42	72.4
	No	16	27.6

RIF: Rifamycin, SF: Saline, DM: Diabetes mellitus, Min-max: Minimum-maximum, SD: Standard deviation

RESULTS

Demographic and clinical characteristics of the patients are presented in Table 1. 17.2% (n=10) of the patients had RIF + SF irrigation, 20.7% (n=12) had subcutaneous RIF application, 62.1% (n=36) had SF irrigation. 17.2% (n=10) of the patients had diabetes mellitus (DM). There was a statistically significant difference between the age distributions of the groups ($p<0.05$). This is because the age of the patients who underwent subcutaneous RIF application was significantly higher than the RIF + SF irrigation group ($p=0.012$). There was no significant difference between the ages of the other groups ($p>0.05$). There was no statistically significant difference between the groups in terms of the hospitalization period ($p>0.05$).

The mean operation duration was 101.66±15.27 minutes in patients with subcutaneous RIF application, 88.19±25.24 minutes in patients with SF irrigation, and 107.68±14.15 minutes in patients with RIF + SF irrigation There was a statistically significant difference between the groups in terms of operation duration ($p<0.05$) (Table 2). The operation duration of RIF + SF irrigation was significantly higher than that of SF irrigation ($p=0.037$). There was no statistically significant difference between the groups in terms of drain removal time, incision length, postoperative discharge time, comorbidities, and hospital stay ($p>0.05$) (Table 2). The duration of discharge was statistically significant according to age ($p <0.05$). The mean age of surgical wound discharge was significantly higher in patients older than 75 years ($p=0.02$) (Table 3). There was no statistically significant relationship between operation duration, incision length and additional diseases, and discharge time ($p>0.05$). It was observed that 75% of the patients did not contaminate the dressings after the 4th postoperative day.

DISCUSSION

Different antibiotics such as RIF have been used in the literature to prevent postoperative infections (9). Gentamicin, fusidic acid, and povidone-iodine are other known agents (10,11). RIF, gentamicin, fusidic acid, and high-pressure irrigation were applied against methicillin-sensitive Staf. In the study of Kaya et al. (9) consisting of 55 fresh frozen femoral head specimens specimens (12). They found that RIF was more effective among the groups. RIF is a bactericidal agent that affects the beta subunit of RNA polymerase (13). To the best of our knowledge, this is the first study in the literature to compare RIF administration with SF and irrigation in patients with hemiarthroplasty due to femoral neck fracture. Wound infections after surgical incisions significantly affect the morbidity and mortality of the patient in the postoperative period (14). In our study, age was the most important criterion affecting discharge time. The duration of discharge was found to be more significant in patients over 75 years of age. There are different outcomes in the literature between age and sex and postoperative infection rates. Kurtz et al. (15) found that the infection rate was higher in males in their study, while Ridgeway et al. (16) found that the infection rate was higher in females and older ages. In our study, no difference was found between the genders in terms of the infection rate. There was no statistically significant difference in the postoperative discharge time of patients with additional disease.

In the present study, no significant difference was found between the duration of hospitalization, drain withdrawal time, incision length, and additional diseases such as DM and postoperative discharge time. Previous studies stated that prolonged surgical time increases surgical wound

Table 2. Comparison of perioperative parameters between groups

RIF + SF irrigation (n=10)		Groups			p
		Subcutaneous RIF (n=12)	Only SF irrigation (n=36)		
Age (years)	Mean ± SD	74.4±7.47	83.83±7.46	79.13±7.63	[a]**0.016***
	Min-max (median)	65-85 (73)	65-94 (85)	65-92 (77)	
Hospitalization	Mean ± SD	17.70±6.79	16.50±6.80	16.88±6.83	[a]0.916
	Min-max (median)	6-27 (19)	8-32 (159	5-33 (17,50)	
Duration of operation	Mean ± SD	107.68±14.15	101.66±15.27	88.19±25.24	[a]**0.048***
	Min-max (median)	90-135 (110)	65-120 (100)	55-135 (95)	
Drain withdrawal	Mean ± SD	27.40±6.25	26.25±7.55	26.91±5.29	[b]0.667
	Min-max (median)	22-40 (25)	20-48 (24)	20-40 (26)	
Postop wound discharge time	Mean ± SD	2.77±1.48	3.25±2.00	3.47±2.17	[a]0.658
	Min-max (median)	1-6 (2)	1-7 (3)	1-9 (3)	
Length of skin incision	Mean ± SD	17.70±3.05	15.50±3.58	17.36±1.91	[a]0.067
	Min-max (median)	12-23 (18)	8-20 (16)	13-22 (17)	
DM	No	7 (70.0%)	9 (75.0%)	32 (88.9%)	[c]0.254
	Yes	3 (30.0%)	3 (25.0%)	4 (11.1%)	
Another additional disease	No	2 (20.0%)	2 (16.7%)	12 (33.3%)	[c]0.587
	Yes	8 (80.0%)	10 (83.3%)	24 (66.7%)	

[a]One-Way ANOVA test, [b]Kruskal-Wallis test, [c]Fisher-Freeman-Halton test, *p<0.05
RIF: Rifamycin, SF: Saline, DM: Diabetes mellitus, Min-max: Minimum-maximum, SD: Standard deviation

Table 3. The relationship between postop wound discharge time and other variables

Mean ± SD		Postop wound discharge time		p
		Median		
Age (years)	≤75 age	2.36±1.01	2.0	[d]**0.020***
	>75 age	3.78±2.24	3.5	
Length of skin incision	≤16 cm	3.33±2.33	2	[b]0.828
	17-18 cm	3.48±2.06	3	
	>18 cm	3.00±1.47	2	
DM	Yes	2.50±1.58	2.5	[d]0.161
	No	3.49±2.08	3	

[b]Kruskal-Wallis test, [d]Mann-Whitney U test, *p<0.05
DM: Diabetes mellitus, SD: Standard deviation

infections (2,14). In our study, no correlation was found between operation duration and discharge time. Although it has been reported in many papers that additional diseases such as DM increase the infection rate, the mean discharge time of patients with and without DM was similar (17-19). Kerveshi et al. (5) reported that DM did not affect infection rates in postoperative lumbar disk hernias. In the current study, it was found that DM did not affect the discharge time between the groups. In our study, no effect of DM on discharge time was found between the groups. There may not have been a statistically significant change, as there were 10 patients distributed across three subgroups, accounting for only 17.2% of patients. In addition, regulated DM and blood glucose levels under control may not increase the risk of infection, as supported by the literature. It is known that long-term wound discharge may lead to infection in the future and that discharges exceeding 10 days require infection parameters and/or culture follow-up (6,20,21). In this study, no significant difference was found between the wound discharge period. The mean operation duration of the RIF + SF irrigation group was longer. It was determined that surgeons preferred to add RIF to irrigation fluid during prolonged surgeries. The limitations of the study include the retrospective nature of the study, lack of randomization, non-homogenized subgroups (comorbidities, obesity, smoking history, etc.), lack of standardization during surgery (primary surgeon, surgical approach, team size, etc.), and small sample size. On the other hand, the strength of this study is that it is the first study to compare the RIF administration method with SF and irrigation in patients undergoing hemiarthroplasty for femoral neck fractures.

CONCLUSION

Additional and isolated RIF applications do not provide superiority in hip hemiarthroplasty. In addition, the duration of surgery was found to be longer in the RIF + SF group, and it was observed that surgeons tend to add RIF to SF in cases with longer operating times. Prospective randomized studies with larger patient groups are needed.

ETHICS

Ethics Committee Approval: After University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee approval (decision no: 2015-16/08, date: 12.10.2015).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.Ç., N.Z., A.B., Concept: M.Ç., Design: M.Ç., N.Z., Data Collection or Processing: M.Ç., A.B., Analysis or Interpretation: M.Ç., A.B., Literature Search: M.Ç., A.B., Writing: M.Ç., N.Z.

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REFERENCES

1. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol 1992;13:606-8.
2. Lau AC, Neo GH, Lee HC. Risk factors of surgical site infections in hip hemiarthroplasty: a single-institution experience over nine years. Singapore Med J 2014;55:535-8.
3. Jettoo P, Jeavons R, Siddiqui B, O'Brien S. Antibiotic prophylaxis for hip fracture surgery: three-dose cefuroxime versus single-dose gentamicin and amoxicillin. J Orthop Surg (Hong Kong) 2013;21:323-6.
4. Gillespie WJ, Walenkamp GH. Antibiotic prophylaxis for surgery for proximal femoral and other closed long bone fractures. Cochrane Database Syst Rev 2010;2010:CD000244.
5. Kërveshi A, Halili N, Kastrati B, Qosja F, Kabashi S, Muçaj S. Local irrigation of the surgical field with antibiotics in the end of procedure reduces the infection rate in herniated lumbar disc surgery. Mater Sociomed 2014;26:398-400.
6. Cordero-Ampuero J, de Dios M. What are the risk factors for infection in hemiarthroplasties and total hip arthroplasties? Clin Orthop Relat Res 2010;468:3268-77.
7. Fiaux E, Titecat M, Robineau O, Lora-Tamayo J, El Samad Y, Etienne M, et al. Outcome of patients with streptococcal prosthetic joint infections with special reference to rifampicin combinations. BMC Infect Dis 2016;16:568.
8. Caviglia HA, Osorio PQ, Comando D. Classification and diagnosis of intracapsular fractures of the proximal femur. Clin Orthop Relat Res 2002:17-27.
9. Kaya I, Sungur I, Yılmaz M, Pehlivanoğlu F, Kartyaşar K, Sengöz G. Comparison of the efficiency of different antibiotic irrigation solutions in decontamination of allografts contaminated with Staphylococcus aureus. Acta Orthop Traumatol Turc 2013;47:281-5.
10. Soyer J, Rouil M, Castel O. The effect of 10% povidone-iodine solution on contaminated bone allografts. J Hosp Infect 2002;50:183-7.
11. Johnson JP, Cohen EM, Antoci V. Treatment of a periprosthetic femur fracture around an antibiotic spacer with revision and an antibiotic plate. Arthroplast Today. 2019;5:401-6.
12. Owens BD, White DW, Wenke JC. Comparison of irrigation solutions and devices in a contaminated musculoskeletal wound survival model. J Bone Joint Surg Am 2009;91:92-8.
13. Calfee DP. Rifamycins. In: Mandell GL, Bennet JE, Dolin R, editors. Mendell, Douglas and Bennet's principells and proktices of infektious disseases. 7th ed. Philadelphia: Churchill Livingstone; 2010.p. 403-17.
14. Shiga T, Wajima Z, Ohe Y. Is operative delay associated with increased mortality of hip fracture patients? Systematic review, meta-analysis, and meta-regression. Can J Anaesth 2008;55:146-54.
15. Kurtz SM, Lau E, Schmier J, Ong KL, Zhao K, Parvizi J. Infection burden for hip and knee arthroplasty in the United States. J Arthroplasty 2008;23:984-91.
16. Ridgeway S, Wilson J, Charlet A, Kafatos G, Pearson A, Coello R. Infection of the surgical site after arthroplasty of the hip. J Bone Joint Surg Br 2005;87:844-50.
17. Jain NB, Guller U, Pietrobon R, Bond TK, Higgins LD. Comorbidities increase complication rates in patients having arthroplasty. Clin Orthop Relat Res 2005:232-8.
18. Lai K, Bohm ER, Burnell C, Hedden DR. Presence of medical comorbidities in patients with infected primary hip or knee arthroplasties. J Arthroplasty 2007;22:651-6.
19. Park BY, Lim KP, Shon WY, Shetty YN, Heo KS. Comparison of Functional Outcomes and Associated Complications in Patients Who Underwent Total Hip Arthroplasty for Femoral Neck Fracture in Relation to Their Underlying Medical Comorbidities. Hip Pelvis 2019;31:232-7.
20. Rogmark C, Carlsson A, Johnell O, Sernbo I. Primary hemiarthroplasty in old patients with displaced femoral neck fracture: a 1-year follow-up of 103 patients aged 80 years or more. Acta Orthop Scand 2002;73:605-10.
21. Parvizi J, Tan TL, Goswami K, Higuera C, Della Valle C, Chen AF, et al. The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria. J Arthroplasty 2018;33:1309-14.

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Research

The Correlation of Cystic Fibrosis Screening Test Results with Ultrasonographically Detected Fetal Anomalies in Prenatal Diagnosis

Prenatal Tanıda Kistik Fibroz Tarama Testi Sonuçlarının Ultrasonografik Olarak Saptanan Fetal Anomalilerle Korelasyonu

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ABSTRACT

Objective: In a multiethnic community, our goal was to assess the applicability of this method. Here we offer a collection of 112 diagnostic prenatal samples for which a comprehensive study of exons, exons/intron boundaries, and major rearrangements has been investigated in prenatal samples of fetuses with suspected cystic fibrosis over the past decade.

Methods: For the CFTR mutation study, 112 prenatal samples (amniotic fluid, chorionic villi, or cultured cells from amniotic fluid or chorionic villi) were brought into our lab. QIAseq Targeted NGS DNA Panel (Qiagen, Hilden, Germany) was performed to analyze the *CFTR* gene (27 exons).

Results: The pathogenic variation NM000492.4(CFTR):c.3454G>C was the most often found (p.Asp1152His), which accounted for 50% of the classic pathogenic CF variants in the study population. Compound heterozygous CFTR pathogenic variations were detected in one of our patients. NM000492.3(CFTR):c.2620-15C>G and NM000492.3(CFTR):c.2756A>G Two variants, one of which was reported as VUS and the other as pathogenic, were detected in a 17-week - old fetus (0.89%). Fetus inherited the NM000492.3(CFTR):c.2756A>G variant from mother and the NM000492.3(CFTR):c.2620-15C>G variant from father. There is an isolated hyperechoic bowel sign at 17 weeks of pregnancy.

Conclusion: In our case series, genetic analyzes suggest that an affected child may be heterozygous for CFTR mutations, compound heterozygous for two clinically significant recessive mutations inherited from healthy carrier parents. Early prenatal genetic testing pretesting and posttesting genetic counseling is crucial in the management of future pregnancies in heterozygous couples which are healthy carriers for CFTR mutations.

Keywords: Cystic fibrosis, genetic testing, CFTR mutations

ÖZ

Amaç: Çok ırklı bir popülasyonda kistik fibrozun prenatal dönemde genetik açıdan analizini ve sonuç olarak varyant sıklığını belirlemeyi amaçladık. Son on yılda kistik fibrozdan şüphelenilen fetüslerin doğum öncesi örneklerinden ekzonlar, ekzonlar/intron sınırları ve yeniden düzenlemeler hakkında kapsamlı bir çalışmanın araştırıldığı 112 doğum öncesi tanı örneğinden oluşan bir hasta popülasyon verisini sunuyoruz.

Gereç ve Yöntem: CFTR mutasyon analizi için 112 prenatal örneğin (amniyotik sıvı, koryonik villus veya amniyotik sıvı veya koryonik villustan kültüre edilmiş hücrelerin) laboratuvarımızda analizleri yapıldı. CFTR genini (27 ekzon) analiz etmek için QIAseq Hedefli NGS DNA Paneli (Qiagen, Hilden, Almanya) kullanılmıştır.

Bulgular: En yaygın olarak tanımlanan patojenik varyantımız, çalışma popülasyonundaki klasik patojenik varyantların %50'sini oluşturan NM000492.4(CFTR):c.3454G>C (p.Asp1152His) idi. Hastalarımızdan birinde bileşik heterozigot CFTR patojenik varyasyonu tespit edildi. NM000492.3(CFTR):c.2620-15C>G ve NM000492.3(CFTR):c.2756A>G olmak üzere, 17 haftalık fetüste sırayla ilki VUS diğeri patojenik olarak bildirilen iki varyant tespit edildi (%0,89). Fetus, NM000492.3(CFTR):c.2756A>G varyantını anneden ve NM000492.3(CFTR):c.2620-15C>G varyantını babadan kalıtım olarak almıştır. Gebeliğin 17. haftasında izole hiperekojen bağırsak bulgusu mevcuttur.

Sonuç: Bizim olgu serimizde, genetik analizler, etkilenen bir çocuğun CFTR mutasyonları için heterozigot olabileceğini, sağlıklı taşıyıcı ebeveynlerden kalıtılan klinik olarak anlamlı iki resesif mutasyon için bileşik heterozigot olabileceğini düşündürmektedir. Erken doğum öncesi genetik testler, ön test ve test sonrası genetik danışmanlık, CFTR mutasyonları için sağlıklı taşıyıcılar olan heterozigot bir çiftte gelecekteki gebeliklerin yönetiminde çok önemlidir.

Anahtar Kelimeler: Kistik fibrozis, genetik test, CFTR mutasyonları

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INTRODUCTION

One of the most prevalent autosomal recessive disorders in Caucasians is cystic fibrosis (CF). The condition is marked by progressive lung damage brought on by chronic infection, pancreatic exocrine insufficiency, male infertility, and excessive sweat chloride levels, although individuals with CF have an average life expectancy of approximately 33 years. Data from registries show that more than 72,000 people worldwide are living with CF (1). The CF gene was located on chromosome 7 in 1989. Phosphorylation of a transport protein activates the gene product's chloride channel activity, cAMP-dependent protein kinase A, referred to as the transmembrane conductance regulator in cystic fibrosis (CFTR). Different aspects of the *CFTR* protein synthesis (mRNA and protein), maturation, and channel function are impacted by pathogenic variations of the *CFTR* gene. Ion flow in epithelial cells of different organs is disturbed by the absence or malfunctioning of the CFTR protein. *CFTR* gene, which is inherited from one parent, has these mutations in both alleles, which causes CF (2).

The phenotype of each patient is the consequence of the combination two (or more) than 2,000 CFTR variations that have been discovered, which are dispersed across the gene structure and have various clinical ramifications. When CF-causing mutations are coupled, severe CF clinical characteristics result. CFTR-related abnormalities, which are single organ disorders, are associated with moderate or mild variations (CFTR-RD: diffuse bronchiectasis, congenital bilateral vas deferens absence in male infertility, pancreatitis). While some people with this condition experience severe pulmonary and/or gastrointestinal symptoms, others only experience moderate symptoms during adolescence and early adulthood. Regarding pancreatic function, genotype and phenotype are closely correlated; however, it has not been established that the discovery of certain CFTR mutations may more accurately predict the severity of pulmonary illness. There is no doubt that modifier genes and environmental variables contribute to this variety of expressions. Recently, CFTR2 research has produced incredibly helpful descriptions of the specific clinical indications and symptoms that might be anticipated with mutations (3).

Women with CF are at risk of fertility. They might signify a delayed beginning of menarche; anovulatory cycles with secondary amenorrhea are common in those with severe lung illness and malnutrition. Sperm entry of the cervical os may also be physically impeded by dehydrated and thicker cervical secretions. However, as more CF patients reach reproductive age, they need to be properly informed about contraception, pregnancy, and any potential elevated hazards related to CF (4).

Although the *CFTR* gene has more than 2,000 known mutations, only around 10% of them results in the illness, as previously indicated. Although the relative frequency of the F508del mutation varies depending on the region, it is found in all populations. Particularly among the white population of Northern European heritage, which makes up between 70 and 75 percent of the CF alleles, F508del is found at the highest frequency (3,5). The significance of the varying rates of mutation detection among different populations is the number of couples whose definitive prenatal diagnosis (PND) becomes possible when both partners are indeed identified as CF carriers.

There are a few CFTR polymorphisms that are linked to various phenotypes, from CF to CFTR-RD or CFTR-RD to the asymptomatic group. Finally, due to their rarity and lack of functional research, there are many clinical spectrum variations that are unknown (6).

Because of the outstanding development achieved regarding molecular biology, PND of genetic abnormalities is rapidly advancing. For couples who are both known to be CF mutation carriers, PND of CF is now advised. Additionally, hyperechogenic bowel and dilatation are ultrasound-detected digestive anomalies in babies that may lead to CF. This occurs primarily in the second trimester of pregnancy. CF affects approximately 1 newborn in 3500, and approximately one in 30 individuals are carriers of CF with marked regional variations (7,8).

When the fetal echogenic bowel is thought to be present, testing the fetus for CF mutations is also beneficial. Data on the incidence of additional CF prenatal diagnostic indicators and the implications of carrier screening recommendations are few (9-11). The American College of Obstetricians and Gynecologists the American College of Medical Genetics (ACMG), and the National Institutes of Health released guidelines for CF screening in the general population in 2001 (12,13). When both parents have a CF mutation, guidelines recommend prenatal testing for that pregnancy as screening is most successful when done before conception. In terms of regional demography, they also advise that laboratories providing CF screening include a minimum of 25 particular mutation sites in their panel in addition to other variants (14-16).

When individuals have a severe mutation in trans, clinical categorization based on how severe the most prevalent accompanying manifestation is: Classical CF with pancreatic insufficiency is predominantly caused by CF mutations, whereas CFTR-RD variations have residual function and

are linked to monosymptomatic illness. Variations of unclear clinical significance (VUS), which have not yet been characterized, and benign variants, which have no clinical repercussions, are present in the milder phenotype (6). In recent times, intermediate variations have been classed as variations with variable clinical outcomes, and they can occasionally cause the more typical but typically pancreatic adequate form of CF, which can have a significant impact on some people's health status and CFTR-related disorders in others (17). It remains a dangerous condition in which a PND is possible when both parents carry the disease for the genes that cause CF, despite significant advancements in treatment techniques in recent years, notably with focused therapy for specific mutations (18). It remains a dangerous condition in which a PND is possible when both parents carry the disease for the genes that cause CF, despite significant advancements in treatment techniques in recent years, notably with focused therapy for specific mutations (9,10,18-26).

The rate of asymptomatic heterozygous carriers of CF is reported to be approximately 1/30 and has long been considered predominate among Caucasians with substantial regional differences (http://www.genet.sickkids.on.ca/cftr) (7,27). Molecular biology techniques have made great strides in genetic analysis and recent years are routinely much quicker now than it was a decade ago. We have the chance in our lab to detect variations according to the geographic history of our patient base.

The objective of this systematic review was to assess the efficacy of prenatal genetic testing for identifying pathogenic CFTR mutations in pregnancies with a high risk of CF. The choice of acceptable endpoints to assess the clinical value of a prenatal diagnostic is a significant assessment difficulty. To help the interpretation of clinical findings, we also address the ethical issues surrounding genetic testing.

Therefore, we chose to perform a full CFTR analysis if CF was suspected on prenatal ultrasound. Our goal was to evaluate the applicability of this method in a multiethnic community. Here we provide a collection of 112 prenatal diagnostic samples for which a thorough analysis of exons, exon/intron boundaries, and significant rearrangements in prenatal samples of babies with suspected CF during the last ten years has been explored. By focusing on the three digestive symptoms of CF, we explain the genotype/phenotype link in a CF fetus and offer fresh information on the regional distribution of CFTR variations. Finally, we recommend that a comprehensive CFTR study be performed in all parents, regardless of their ethnic origin, in the case of a ultrasonography (USG) abnormality such as fetal bowel abnormalities.

METHODS

Patients who underwent chromosomal microarray analysis (CMA) in addition to karyotype analysis were included in the study. Invasive test indications, fetal ultrasonographic screening reports, karyotype analysis, CMA, and next-generation sequencing (NGS) results of the patients were retrospectively obtained from the electronic data system of the genetic unit.

Depending on the results of the fetal USG, only karyotype analysis or both karyotype analysis and CMA are carried out in the initial step. All invasive testing begins with speedy diagnostic procedures like fluorescence *in situ* hybridization or quantitative fluorescence polymerase chain reaction (QF-PCR), and once aneuploidy is found during these quick procedures, CMA is not recommended. Additionally, in cases where structural abnormalities are seen by USG, CMA and karyotype analysis are frequently performed.

In the second step, NGS is recommended based on ultrasonographic findings in patients whose karyotype and CMA results are reported as normal.

Between January 2012 and February 2022, for the CFTR mutation study, 112 prenatal samples (amniotic fluid, chorionic villi, or cultured cells from amniotic fluid or chorionic villi) were supplied to our lab. Dilated intestinal loops, unable to see the fetal gallbladder Non-visualization of the fetal gallbladder, and sonographic intensity more than or equal to that of the surrounding bone during ultrasound were all considered to be Digestive Ultrasound Signs; each mark was either solitary or related with other traits (Table 1).

During a genetic counseling session, the parents provided their informed permission for genetic analysis in line with Turkish law. After a thorough discussion of the research methodology, all individuals provided written authorization with notice. The Ethical Committee of the Trakya University Faculty of Medicine (decision no: 03/11, date: 27.02.2023) and the Declaration of Helsinki were followed for all procedures in the study that included people.

Following the manufacturer's instructions, BioRobot EZ1 equipment (Qiagen Hilden, Germany) was used to extract DNA from samples of amniotic fluid, chorionic villi, or cultivated cells from these tissues. Before building libraries, isolated DNA samples were checked for quantity and quality using a Qubit 2.0 fluorometer (Invitrogen, Life Technologies). Based on GenBank accession NM 000492.3, the variant nomenclature (CFTR). For exonic variations, we

Table 1. Different genotypes finding in the 112 pregnancies analyzed

Fetus genotype	Inh.	Considerations for variant classification	Fetus phenotype
NM_000492.3(CFTR):c.2620-15C>G /NM_000492.3(CFTR): c.2756A>G(p.Tyr919Cys),	Com. Het	VUS Likely pathogenic (LP)	Hyperechogenic bowel
NM_000492.4(CFTR):c.2991G>C (p.Leu997Phe)	Het	VUS	Hyperechogenic bowel
NM_000492.3(CFTR):c.2991G>C (p.Leu997Phe)	Het	VUS	Double bubble, input VSD, PEV
NM_000492.3(CFTR):c.125C>T (p.Ser42Phe)	Het	VUS	Hyperechogenic cardiac focus, PEV
NM_000492.3(CFTR):c.3485G>T (p.R1162L)	Het	VUS	Age risk (double screening test), Grade 1 Hyperechogenic bowel
NM_000492.3(CFTR):c.3659C>T (p.Thr1220Ile)	Het	VUS	Hyperechogenic focus in left ventricle, Grade 1 hyperechoic bowel
NM_000492.3(CFTR):c.2354G>A (p.Arg785Gln), NM_000492.3(CFTR):c.224G>A (p.Arg75Gln)	Com. Het	VUS	Drug use during pregnancy, Grade 1 hyperechoic bowel
NM_000492.4(CFTR):c.3038C>T (p.Pro1013Leu)	Het	VUS	Hyperechoic bowel, triple TT: T21 risk 1/97
NM_000492.3(CFTR):c.202A>G (p.Lys68Glu)	Het	VUS	Hyperechogenic bowel
NM_000492.4(CFTR):c.1519A>G (p.Ile507Val)	Het	VUS	Grade 1 Hyperechogenic bowel
NM_000492.4(CFTR):c.3454G>C (p.Asp1152His)	Het	LP	Hyperechogenic bowel
NM_000492.4(CFTR):c.4333G>A(p.Asp1445Asn)	Het	VUS	Choroid plexus cyst (Bilateral), hyperechogenic bowel
NM_000492.4(CFTR):c.3038C>T, (p.Pro1013Leu)	Het	VUS	Age risk in double TT: 1/308 (high risk), Hyperechogenic bowel (Grade 1)
NM_000492.4(CFTR):c.650A>G, (p.Glu217Gly)	Het	VUS	Age risk in double TT: 1/308 (high risk), hyperechogenic bowel (Grade 1)
NM_000492.3(CFTR): c.1521_1523delCTT (p.F508del)	Het	LP	Hyperechogenic bowel + Bilateral Pelviectasis
NM_000492.4(CFTR):c.2991G>C (p.Leu997Phe)	Het	VUS	Dextrocardia, muscular VSD, Right ectopic kidney, Hyperechogenic bowel
NM_000492.4(CFTR):c.3454G>C (p.Asp1152His)	Het	LP	Age risk:1/168, Grade 1 Hyperechogenic bowel
NM_000492.4(CFTR):c.2991G>C (p.Leu997Phe)	Het	VUS	Hyperechogenic bowel

Inh.: Inhertitance, Het.: Heterozygous, Com.Het.: Compound heterozygous

employed the HGVS nomenclature at the protein level. To examine the *CFTR* gene, the QIAseq Targeted DNA Panel (Qiagen, Hilden, Germany) was used (27 exons). According to the manufacturer's instructions, libraries were set up. With the use of the Qubit dsDNA BR Assay system, the quality of the created libraries was checked (Invitrogen, Carlsbad, CA). Illumina NextSeq550 performed Fastq files (Illumina Inc., San Diego, CA, ABD). According to the QIAseq Targeted DNA Panel procedure, libraries encompassing the target genes were created (Qiagen, Hilden, Germany). Libraries were sequenced on the Illumina NextSeq 550 after target enrichment (Illumina Inc., San Diego, CA, ABD). Variant Call Format file ordering and quality control were performed using QCI analysis (Qiagen, Hilden, Germany). Using Ingenuity software, variation analysis was carried out (Qiagen, Hilden, Germany).

Primer sets were created for all required areas to execute Sanger sequencing on an ABI 3130 (Applied Biosystems, USA) capillary electrophoresis machine and validate the variations and segregation analyses.

The classification of all the variations was done in accordance with ACMG-2015 (28) rules, and the descriptions of the variants were done in accordance with the Human Genome Variation Society (29) recommendations (30). The following bioinformatics tools were used to evaluate the variants once they had been annotated by wANNOVAR: SIFT (http://sift.jcvi.org/), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), MutationTaster (http://www.mutationtaster.org/), ClinVar Miner (https://clinvarminer.genetics.utah.edu/), CADD score (https://cadd.gs.washington.edu/snv), CFTR2 (https://cftr2.org/), CYSMA (https://cftr.iurc.montp.inserm.

fr/cysma/), Human Splicing Finder3.1 (HSF3.0) (http://www.umd.be/HSF/).

Statistical Analysis

The SPSS software version 21 (SPSS Inc., Chicago, IL, USA) package program was used to analyze the data. The format for descriptive data was number (%), mean standard deviation. To examine the distribution of continuous variables, the Kolmogorov-Smirnov test was performed. Continuous variables were compared using Student's t-test because they were regularly distributed. To ascertain the statistical significance of the categorical variables, the chi-square test was used. Fetal structural deformities related to pathogenic copy number variants (pCNVs) were examined by univariate analysis, and CMA results of fetuses with normal karyotypes were categorized as pCNVs and benign copy number variations/variants of unknown clinical significance. Possible fetal structural abnormalities linked to pCNVs discovered in univariate analysis were considered in logistic regression analysis. The threshold for statistical significance was set at $p<0.05$.

RESULTS

All 112 fetuses were screened for CF throughout the research period, three of which were twin pregnancies that had an echogenic bowel on a thorough ultrasound inspection. The mean gestational week of our patients was determined to be 19+6. Hyperechoic bowel is a common USG finding in all pregnancies. Table 1 provides an overview of the distribution of detected CF variations. The most frequently found pathogenic variation was NM000492.4(CFTR):c.3454G>C (p. Asp1152His), which was responsible for 50% of the research population's classic pathogenic CF variants. Compound heterozygous CFTR pathogenic variations were detected in one of our patients. NM000492.3(CFTR):c.2620-15C>G ve NM000492.3(CFTR):c.2756A>G two variants, one of which was reported as VUS and the other as pathogenic, were detected in a 17-week-old fetus (0.89%). Fetus inherited the NM000492.3(CFTR):c.2756A>G variant from mother and the NM000492.3(CFTR):c.2620-15C>G variant from father. There is an isolated hyperechoic bowel sign at 17 weeks of pregnancy.

Among the variants evaluated as VUS, the most detected variation was NM000492.3(CFTR):c.2991G>C (p. Leu997Phe). This VUS variant, which was detected most frequently, was encountered in the amniocentesis material of five patients.

Variations evaluated as VUS were detected in 12 patients. The total number of detected VUS was determined as 17. All of these variants, which were evaluated as VUS, had data toward likely pathogenicity according to the information obtained from different databases (ClinVar, VarSome, Franklin, HGMD-DM). All of these VUS variants detected in patients were heterozygous, except for one patient. A compound heterozygous VUS pattern was observed in one of our patients, including NM000492.3(CFTR):c.2354G>A (p. Arg785Gln) and NM000492.3(CFTR):c.224G>A (p. Arg75Gln). In the USG scan of this patient, there was a history of Grade I hyperechoic bowel and drug use during pregnancy. Except for all detected variations, only one NM000492.3(CFTR):c.1666A>g(p. Ile566Val) variation, which was reported as benign, was detected in only one of our patients (Table 1).

DISCUSSION

The risk of CF diagnosis associated with gastrointestinal abnormalities on ultrasonographic scans varies based on research from 0.5% to 9% (24,25). Since the *CFTR* gene was identified in 1989, technological developments have allowed for a deeper understanding of this gene. Current applications for CFTR analysis in the context of heterozygote co-analysis or ultrasonographic the possibility of CF serves to identify the most common mutations by geographic origin. However, these procedures have not been modified for people descended from broad areas where mutations are yet unknown. A thorough CFTR investigation, however, also entails finding uncommon variations that could be challenging to interpret. Most of the rare variants we discovered were categorized in our research as having uncertain therapeutic significance (77%). VUS should not be used in clinical decision-making, according to ACMG recommendations. However, regular variant updates are recommended if information has changed in any VUS. It is likely that under these situations, measuring the amniotic fluid containing fetal digestive enzymes may be beneficial. However, for this invasive surgery to be effective, it must be done before 22 weeks of gestation because digestive disorders are typically noticed beyond this point. Interpretation of VUS is particularly complex in the case of ultrasound intestinal abnormalities as the specificity of fetal findings is not always significant: the CFTR variants identified are not necessarily associated with CF.

We believe that the present study is important because it includes patients with positive prenatal screening test results, evaluates the entire *CFTR* gene using new generation sequencing, and provides data, for the first time to the best of our knowledge, from the Northwest Anatolian Region of Türkiye.

In summary, we present the first comprehensive study showing the distribution of *CFTR* gene variation in the Northwest Anatolian Region of Türkiye. In this study, the mutation distribution was highly heterogeneous, and we believe that analysis of the entire *CFTR* gene is necessary and will increase the diagnosis rates for the Turkish population.

The analytical step for thorough CFTR analysis is available to many laboratories in the context of mass sequencing that is now available. However, although bioinformatics databases and tools have been created to support correct clinical interpretation, proper molecular diagnosis requires thorough understanding of variations, their penetrations, and known complex alleles (31,32). Experience and expertize in this area are especially crucial when dealing with extremely uncommon or unidentified varieties where clinical observations are insufficient and in ultrasound scans where the phenotype is not specific. In this study, the incidence of CF was close to that reported from previous studies as 0.9% to 2.3% (0.89%) (23,33,34). Inheritance patterns for the CFTR variation of parents in prenatally diagnosed pregnancies were unknown. Maternal and paternal genotypes were determined by retrospective analysis, especially for our patient in whom we detected only compound heterozygous variants.

The NM000492.3(CFTR):c.2991G>C (p. Leu997Phe) variation, which we detected the most among the variations we evaluated as VUS, has been reported to increase the susceptibility to pancreatic ductular obstruction in patients with CF (Table 2) (35).

The transmembrane domain of the encoded protein sequence, ABC transporter type 1, experiences a non-conservative amino acid mutation because of CFTR c.2991G>C (p. Leu997Phe). A negative impact of variation on protein function was identified in four out of five distinct *in silico* vehicles. According to these findings, it is unlikely that the mutation would cause CF or any of the illness phenotypes that are related to it and have a variable expression. Most databases such as CFTR2 state that this variant does not cause disease (3). In addition, functional studies have also reported that the variant may have a role in organ bicarbonate permeability, in which CFTR is used for bicarbonate secretion and significantly reduces chloride conductance; however, the effect of these functional defects in vivo is unknown (36,37). However, evidence from the literature combined with allele frequency data from public databases when available was insufficient to determine whether this variant causes disease. This mutation is therefore categorized as a variant of uncertain significance.

The NM000492.4(CFTR):c.3454G>C (p. Asp1152His) variant is the variant evaluated as pathogenic. In our cases, this mutation was discovered to be heterozygous. This sequence change converts aspartic acid to the amino acid histidine at codon 1152 of the CFTR protein (p. Asp1152His). The residue

Table 2. **CFTR variants identified in the 112 patients**

Location	cDNA change	Protein change	dbSNP138	HGMD	Variant type	gnomAD Popmax Filtering AF (95% confidence interval)
Intron 15	c.2620-15C>G	p.(?)	rs139379077	CS004690	Definitely pathogenic	0.002618
Exon 17	c.2756A>G	p.(Y919C)	rs397508430	-	Uncertain significance	0.0002506
Exon 19	c.2991G>C	p.(L997F)	rs1800111	CM920171	Uncertain significance	0.003646
Exon 2	c.125C>T	p.(S42F)	rs143456784	-	Uncertain significance	0.0001750
Exon 22	c.3485G>T	p.(R1162L)	rs1800120	-	Uncertain significance	0.001111
Exon 22	c.3659C>T	p.(T1220I)	rs1800123		Uncertain significance	0.0004605
Exon 14	c.2354G>A	p.(R785Q)	rs141880790		Uncertain significance	0.00001439
Exon 03	c.224G>A	p.(R75Q)	rs1800076	CM980331	Uncertain significance	0.02769
Exon 19	c.3038C>T	p.(P1013L)	rs193922516		Uncertain significance	0.0001298
Exon 03	c.202A>G	p.(K68E)	rs397508332	CM972935	Uncertain significance	0.0005404
Exon 11	c.1519A>G	p.(I507V)	rs1801178		Uncertain significance	0.00008816
Exon 21	c.3454G>C	p.(D1152H)	rs75541969		Likely pathogenic	0.0006254
Exon 27	c.4333G>A	p.(D1445N)	rs148783445	CM962488	Uncertain significance	0.001486
Exon 06	c.650A>G	p.(E217G)	rs121909046	CM972939	Uncertain significance	0.008363
Exon 11	c.1521_1523del	p.(F508del)	rs113993960	CD890142	Likely pathogenic	-

of aspartic acid remains moderately unchanged, and there is a moderate physicochemical difference between aspartic acid and histidine. This variant is available in population databases (rs75541969, ExAC 0.05%). Although this variant can be reported in most individuals affected by congenital absence of the vas deferens, chronic pancreatitis (CP), atypical CF, and bronchiectasis, it has rarely been reported in individuals with classical CF. Experimental studies have shown that this missense change does not affect protein stability or maturation but has a negative effect on the function of CFTR in cell culture. Because of these results, the variant has been classified as pathogenic (38).

A 17-week-old fetus with isolated hyperechogenic bowel carries 2 variants detected as compounds, NM000492.3(CFTR):c.2620-15C>G, NM000492.3(CFTR):c.2756A>G. The NM000492.3(CFTR):c.2620-15C>G variant has entries in different databases as benign and VUS conflict criteria [Conflicting interpretations of pathogenicity, Uncertain significance (2); Benign (2); Likely benign (2) (Last evaluated: Sep 5, 2022)] (39,40).

The encoded protein sequence has a nonconservative amino acid change in the ABC transporter type 1 transmembrane domain (IPR011527) caused by the CFTR mutation c.2756A>G (p. Tyr919Cys). All five in-silicon vehicles showed that the mutation had a negative impact on protein function. The variation was discovered in the control chromosome 251398 with a frequency of 7.6e-05 (gnomAD). This ratio is not significantly higher than would be expected for a pathogenic variant causing CF in CFTR (7.6e-05 vs 0.013) and does not allow conclusions about the significance of the variant. c.2756A>G has been reported in the literature in individuals affected by CF, however, no second mutation was identified in these patients, and at least one of these individuals had a truncated mutation on the same allele. These investigations do not offer any firm conclusions about the link between variation and CF. These and other transmembrane 8 variations have an impact on channel transition according to at least one study, but the data is insufficient to draw firm conclusions about how the variants affect CFTR protein function (41).

In another compound heterozygous patient, 2 VUS (NM000492.3(CFTR):c.2354G>A (p. Arg785Gln) and NM000492.3(CFTR):c.224G>A (p. Arg75Gln)) was inherited as heterozygous. NM000492.3(CFTR):c.2354G>A (p. Arg785Gln), in this sequence change, it replaces arginine with glutamine at codon 785 of the CFTR protein (p. Arg785Gln). The arginine residue is poorly conserved and there is a small physicochemical difference between arginine and glutamine. This variation is available in population databases (rs141880790, ExAC 0.01%). This variation has been reported in an individual suffering from pancreatitis (PMID:17003641). This variation has a record in ClinVar (Variation ID: 573871). The following outcomes were obtained from algorithms designed to forecast how missense mutations may affect protein structure and function: Align-GVGD is "Class C0," PolyPhen-2 is "Benign," and SIFT is "Tolerated."

In the presence of an SPINK1 mutation, the CFTR p. R75Q variation has been linked to an increased risk of pancreatitis and has also been observed in more CP patients in several other studies. Researchers have discovered that CFTR p. R75Q is processed and developed in cells like CFTR WT, and physiological experiments demonstrate no gate or Cl- channel malfunction, although this variation has previously been examined for producing CF. Such data strengthen the argument that the sequence variation pR75Q does not affect the autosomal recessive condition CF. However, repeated reporting of CFTR p. R75Q as a CFTR variant in some patients with atypical CF and CF-related disorders, such as sarcoidosis, chronic obstructive pulmonary disease, and CP, suggests that normal function is somewhat impaired. Schneider et al. (42) showed for the first time that p. R75Q changes bicarbonate but not chloride conductivity. This prompts the development of the CP model, which identifies CFTR as the bicarbonate channel in the cells of the pancreatic duct and predicts that CFTR mutations that impair bicarbonate conductance will significantly raise the risk of developing pancreatic disease by completely disrupting protein synthesis or altering duct characteristics. This discovery also raises the possibility that there are other CFTR mutations that particularly affect bicarbonate conductivity and are risk factors for CP but not CF. According to data from Schneider et al. (42), heterozygous CFTR p. R75Q or CFTR p. F508del variants are inconsequential in the presence of an SPINK1 WT, while multiplying CP denotes an elevated risk. The relatively frequent CFTR variation p. R75Q corresponds to an SPINK1 mutant. This suggests that SPINK1 variations should also be investigated in patients with suspected CP (42).

The F508del variant was detected in one patient in our patient group. This is less than the rate reported in the literature for the variant. When the studies were investigated; Heltshe et al. (43). According to the US Cystic Fibrosis Foundation Patient Registry, the pregnancy rate in women with the F508del heterozygous variant has been reported as 31-34%. The second important point; in individuals carrying the F508del heterozygous variant, the rate of achieving a live birth is between 72-74%. These two conditions can be seen as the reason for the low F508del variant rate in our study (43,44).

Because our patient group was evaluated over a ten-year period. At the time of writing this article, current variant statuses have been checked and final classifications have been reported.

CONCLUSION

In our case series, genetic analyzes suggest that an affected child may be heterozygous for CFTR mutations, compound heterozygous for two clinically significant recessive mutations inherited from healthy carrier parents. Early prenatal genetic testing pretesting and posttesting genetic counseling is crucial in the management of future pregnancies in heterozygous couples which are healthy carriers for CFTR mutations. Less CF-affected babies are born because of CF testing. It is difficult to determine if this indicates that the test is worthwhile because patients may not value maternal or fetal health outcomes in their primary motivations, whether psychologically or otherwise. It might be argued that rather than health, the value of testing should be evaluated in terms of increasing patient autonomy.

In view of these findings, CF carrier screening should be made available to all couples who have a confirmed CF family history. This applies to all spouses of people with CF and to all Caucasian couples who are trying to get pregnant or seeking prenatal treatment and who are of European or Ashkenazi Jewish origin. Screening should ideally occur either before conception or during the first or early second trimester. Patients from other ethnic and racial groups should be informed about screening for CF. In addition, those in lower risk categories should be able to obtain counseling and screening upon need. Based on family history and the identification of the spouses' racial and ethnic backgrounds at the time of the initial research, the doctor should select couples who should be examined. When necessary, the obstetrician should perform CF screening and may decide to offer or request pretest counseling. It takes specialized understanding of elements and calculation of genetic risk to provide post-test counseling for couples with positive/negative, positive/untested, or positive/positive screening findings, CF severity, prognosis, treatment choices, etc. In this situation, a geneticist or physician with specialized knowledge in CF testing must be consulted. If there is a family history of CF, if carriers have been found with CF mutations that may be linked to congenital absence of the vas deferens in male offspring, if an affected adult or affected fetus has been identified, or if any of these situations apply, referral to a geneticist or person with specific expertize in CF testing should also be considered.

ETHICS

Ethics Committee Approval: The institutional review committee (Trakya University Faculty of Medicine, TUMF Scientific Research Ethics Committee Directive TUTF-BAEK, decision no: 03/11, date: 27.02.2023) approved the study.

Informed Consent: During a genetic counseling session, the parents provided their informed permission for genetic analysis in line with Turkish law.

Authorship Contributions

Surgical and Medical Practices: S.Y., H.G., Concept: E.A., H.G., Design: E.A., Data Collection or Processing: E.İ.A., H.G., Analysis or Interpretation: E.İ.A., S.D., Literature Search: E.İ.A., S.D., S.Y., Writing: E.İ.A.

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REFERENCES

1. Jackson AD, Goss CH. Epidemiology of CF: How registries can be used to advance our understanding of the CF population. J Cyst Fibros 2018;17:297-305.
2. Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, Buchwald M, Tsui LC. Identification of the cystic fibrosis gene: genetic analysis. Science 1989;245:1073-80.
3. Sosnay PR, Siklosi KR, Van Goor F, Kaniecki K, Yu H, Sharma N, et al. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. Nat Genet 2013;45:1160-7.
4. Frangolias DD, Nakielna EM, Wilcox PG. Pregnancy and cystic fibrosis: a case-controlled study. Chest 1997;111:963-9.
5. Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr 2017;181S:S4-15.
6. Castellani C, Cuppens H, Macek M Jr, Cassiman JJ, Kerem E, Durie P, et al. Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. J Cyst Fibros 2008;7:179-96.
7. Bobadilla JL, Macek M Jr, Fine JP, Farrell PM. Cystic fibrosis: a worldwide analysis of CFTR mutations--correlation with incidence data and application to screening. Hum Mutat 2002;19:575-606.
8. Hadj Fredj S, Ouali F, Siala H, Bibi A, Othmani R, Dakhlaoui B, et al. Prenatal diagnosis of cystic fibrosis: 10-years experience. Pathol Biol (Paris) 2015;63:126-9.
9. Muller F, Simon-Bouy B, Girodon E, Monnier N, Malinge MC, Serre JL, et al. Predicting the risk of cystic fibrosis with abnormal ultrasound signs of fetal bowel: results of a French molecular collaborative study based on 641 prospective cases. Am J Med Genet 2002;110:109-15.
10. Slotnick RN, Abuhamad AZ. Prognostic implications of fetal echogenic bowel. Lancet 1996;347:85-7.
11. Monaghan KG, Feldman GL. The risk of cystic fibrosis with prenatally detected echogenic bowel in an ethnically and racially diverse North American population. Prenat Diagn 1999;19:604-9.
12. Strom CM, Crossley B, Redman JB, Buller A, Quan F, Peng M, et al. Cystic fibrosis screening: lessons learned from the first 320,000 patients. Genet Med 2004;6:136-40.
13. Grody WW, Cutting GR, Klinger KW, Richards CS, Watson MS, Desnick RJ, et al. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. Genet Med 2001;3:149-54.

14. ACOG. Preconception and prenatal carrier screening for CF: Clinical and laboratory guidelines. Gynecologists, Washington, D.C. American College of Obstetricians, 2001.
15. Richards CS, Bradley LA, Amos J, Allitto B, Grody WW, Maddalena A, et al. Standards and guidelines for CFTR mutation testing. Genet Med 2002;4:379-91.
16. Watson MS, Cutting GR, Desnick RJ, Driscoll DA, Klinger K, Mennuti M, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genet Med 2004;6:387-91. Erratum in: Genet Med 2004;6:548. Erratum in: Genet Med 2005;7:286.
17. Raynal C, Corvol H. Variant classifications, databases and genotype-phenotype correlations. Arch Pediatr 2020;27 Suppl 1:eS13-8.
18. Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, et al. The future of cystic fibrosis care: a global perspective. Lancet Respir Med 2020;8:65-124. Erratum in: Lancet Respir Med 2019;7:e40.
19. Corteville JE, Gray DL, Langer JC. Bowel abnormalities in the fetus--correlation of prenatal ultrasonographic findings with outcome. Am J Obstet Gynecol 1996;175:724-9.
20. Ghose I, Mason GC, Martinez D, Harrison KL, Evans JA, Ferriman EL, et al. Hyperechogenic fetal bowel: a prospective analysis of sixty consecutive cases. BJOG 2000;107:426-9.
21. Muller F, Dommergues M, Simon-Bouy B, Ferec C, Oury JF, Aubry MC, et al. Cystic fibrosis screening: a fetus with hyperechogenic bowel may be the index case. J Med Genet 1998;35:657-60.
22. Scotet V, De Braekeleer M, Audrézet MP, Quéré I, Mercier B, Duguépéroux I, et al. Prenatal detection of cystic fibrosis by ultrasonography: a retrospective study of more than 346 000 pregnancies. J Med Genet 2002;39:443-8.
23. Ameratunga DM, Said JM, Reidy K, Palma-Dias R. Perinatal outcomes following the ultrasound diagnosis of echogenic bowel: an Australian perspective. Fetal Diagn Ther 2012;31:179-84.
24. D'Amico A, Buca D, Rizzo G, Khalil A, Silvi C, Makatsariya A, et al. Outcome of fetal echogenic bowel: A systematic review and meta-analysis. Prenat Diagn 2021;41:391-9.
25. Masini G, Maggio L, Marchi L, Cavalli I, Ledda C, Trotta M, et al. Isolated fetal echogenic bowel in a retrospective cohort: The role of infection screening. Eur J Obstet Gynecol Reprod Biol 2018;231:136-41.
26. de Becdelièvre A, Costa C, Jouannic JM, LeFloch A, Giurgea I, Martin J, et al. Comprehensive description of CFTR genotypes and ultrasound patterns in 694 cases of fetal bowel anomalies: a revised strategy. Hum Genet 2011;129:387-96.
27. Estivill X, Bancells C, Ramos C. Geographic distribution and regional origin of 272 cystic fibrosis mutations in European populations. The Biomed CF Mutation Analysis Consortium. Hum Mutat 1997;10:135-54.
28. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-24.
29. den Dunnen JT, Dalgleish R, Maglott DR, Hart RK, Greenblatt MS, McGowan-Jordan J, et al. HGVS Recommendations for the Description of Sequence Variants: 2016 Update. Hum Mutat 2016;37:564-9.
30. Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018;46:D1062-7.
31. The Clinical and Functional TRanslation of CFTR (CFTR2). Available online: https://cftr2.org/ (accessed on 17 February 2021).
32. Claustres M, Thèze C, des Georges M, Baux D, Girodon E, Bienvenu T, et al. CFTR-France, a national relational patient database for sharing genetic and phenotypic data associated with rare CFTR variants. Hum Mutat 2017;38:1297-315.
33. Goetzinger KR, Cahill AG, Macones GA, Odibo AO. Echogenic bowel on second-trimester ultrasonography: evaluating the risk of adverse pregnancy outcome. Obstet Gynecol 2011;117:1341-8.
34. Buiter HD, Holswilder-Olde Scholtenhuis MA, Bouman K, van Baren R, Bilardo CM, Bos AF. Outcome of infants presenting with echogenic bowel in the second trimester of pregnancy. Arch Dis Child Fetal Neonatal Ed 2013;98:F256-9.
35. Gomez Lira M, Benetazzo MG, Marzari MG, Bombieri C, Belpinati F, Castellani C, et al. High frequency of cystic fibrosis transmembrane regulator mutation L997F in patients with recurrent idiopathic pancreatitis and in newborns with hypertrypsinemia. Am J Hum Genet 2000;66:2013-4.
36. LaRusch J, Jung J, General IJ, Lewis MD, Park HW, Brand RE, et al. Mechanisms of CFTR functional variants that impair regulated bicarbonate permeation and increase risk for pancreatitis but not for cystic fibrosis. PLoS Genet 2014;10:e1004376. Erratum in: PLoS Genet 2014;10:e1004778.
37. Van Goor F, Yu H, Burton B, Hoffman BJ. Effect of ivacaftor on CFTR forms with missense mutations associated with defects in protein processing or function. J Cyst Fibros 2014;13:29-36.
38. Henrie A, Hemphill SE, Ruiz-Schultz N, Cushman B, DiStefano MT, Azzariti D, et al. ClinVar Miner: Demonstrating utility of a Web-based tool for viewing and filtering ClinVar data. Hum Mutat 2018;39:1051-60.
39. National Center for Biotechnology Information. ClinVar; [VCV000035844.19], https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000035844.19 (accessed March 29, 2022).
40. https://www.ncbi.nlm.nih.gov/clinvar/RCV000029499/
41. Negoda A, Hogan MS, Cowley EA, Linsdell P. Contribution of the eighth transmembrane segment to the function of the CFTR chloride channel pore. Cell Mol Life Sci 2019;76:2411-23.
42. Schneider A, Larusch J, Sun X, Aloe A, Lamb J, Hawes R, et al. Combined bicarbonate conductance-impairing variants in CFTR and SPINK1 variants are associated with chronic pancreatitis in patients without cystic fibrosis. Gastroenterology 2011;140:162-71.
43. Heltshe SL, Khan U, Beckett V, Baines A, Emerson J, Sanders DB, et al. Longitudinal development of initial, chronic and mucoid Pseudomonas aeruginosa infection in young children with cystic fibrosis. J Cyst Fibros 2018;17:341-7.
44. Cystic Fibrosis Foundation Patient Registry Annual Data Report 2021. Available from: URL: https://www.cff.org/medical-professionals/patient-registry

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Research

The Influence of Metropolis Life in the Etiology and Symptoms of Conversion Disorder

Metropol Yaşantısının Konversiyon Bozukluğunun Etiyolojisi ve Semptomalojisi Üzerindeki Etkisi

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ABSTRACT

Objective: The study examined the clinical symptoms and lifetime traumatic experience in female patients with conversion disorder (CD).

Methods: The study sample consisted of patients from a metropolis (CD-metropolis group, n=60), patients from a non-metropolis city (CD-NMC group, n=60), and healthy controls (n=60). The study was completed with 180 women. The Dissociative Events scale (DES), Childhood Trauma questionnaire-28 (CTQ-28), Traumatic Experiences checklist (TEC), and a data form were used to evaluate the participants.

Results: Some specific symptoms (inability to speak, numbness in hands and arms, pseudoseizures, paralysis in hands and arms, and fatigue) and coexisting suicide attempts and dissociation symptoms were more common, CTQ-28, DES, and TEC scores were higher, and TEC Family Support scores were lower in the CD-metropolis group than in the CD-NMC group ($p<0.05$ for all).

Conclusion: Metropolitan life is associated with a different clinical symptomatology, more frequent coexisting problems of attempted suicide and/or dissociation symptoms, and more frequent lifetime trauma compared with NMC life in the context of CD.

Keywords: Conversion disorder, metropolis life, lifetime traumatic experience, suicidal attempt, dissociative symptom

ÖZ

Amaç: Bu çalışmanın amacı, konversiyon bozukluğu (KB) olan kadın hastalarda klinik semptomatoloji ve yaşam boyu travma maruziyetini incelemektir.

Gereç ve Yöntem: Çalışma örneklemi bir metropolden (KB-metropol grubu, n=60), metropol olmayan bir kentten (KB-MOK grubu, n=60) gelen hastalar ve sağlıklı kontrollerden (n=60) oluşmaktadır. Çalışmaya 180 kadın hasta dahil edildi. Katılımcıları değerlendirmek için Dissosiyatif Yaşantılar ölçeği (DES), Çocukluk Çağı Ruhsal Travma ölçeği-28 (CTQ-28), Travmatik Yaşantılar ölçeği (TEC) ve veri formu kullanılmıştır.

Bulgular: KB-metropol grubunda KB-MOK grubuna göre bazı spesifik semptomlar (konuşamama, ellerde ve kollarda uyuşma, yalancı nöbetler, ellerde ve kollarda felç ve yorgunluk), eşlik eden intihar girişimleri ve dissosiyasyon semptomları daha yaygın bulunmuştur. Ayrıca KB-metropol grubunda KB-MOK grubuna göre CTQ-28, DES ve TEC puanları daha yüksekti ve TEC-Aile Desteği puanları ise daha düşük idi (tümü için $p<0,05$).

Sonuç: KB'de, metropol yaşamı metropol olmayan kent yaşamına göre farklı klinik semptomatoloji, daha sık intihar girişimi ve/veya dissosiyasyon semptomları ve daha sık yaşam boyu travmaya maruziyeti ile ilişkilendirilmiştir.

Anahtar Kelimeler: Konversiyon bozukluğu, metropol yaşamı, yaşam boyu travma maruziyeti, intihar girişimi, dissosiyasyon semptomları

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INTRODUCTION

Conversion disorder (CD) is characterized by the loss or alteration of motor, sensory, and neurovegetative system functions in the absence of any specific organic etiology (1,2). It is one of the most common diagnoses among new patient referrals to neurological clinics (16% of all new referrals) (3). It is estimated that 20-25% of all patients in general hospital settings have at least one symptom of conversion, while 5% meet the criteria for the full disorder (4). CD has a very rich and diverse clinical symptoms. Blindness, deafness, pseudoseizures, dystonia, paralysis, syncope or other neurological symptoms are among the most frequent symptoms (2,5). Dissociation and suicidal behavior are common coexisting problems. Suicide rates among patients with CD are estimated to range from 19.6% to 34.2% (5).

The etiology of CD is not fully understood. However, the reported risk factors include female gender, rural life, low socioeconomic status, low educational level, insufficient insight, and low mental capacity (6). A stressful or traumatic life event generally precedes the emergence of symptoms (7). Numerous studies have noted an association between CD and childhood trauma, especially sexual abuse (8,9). In one recent study, 70% of patients diagnosed with CD reported emotional neglect, 59% emotional abuse, 27% physical abuse, 65% sexual harassment, and 23.5% sexual abuse (10).

Numerous studies have examined the symptoms and childhood trauma in CD patients. However, to the best of our knowledge, the relationships between suicidal behavior and traumatic experiences and dissociation symptoms have not yet been studied in the context of the characteristics of the patient's urban place of residence. Similar to rural and urban areas, cities with different socioeconomic and sociocultural backgrounds are associated with different advantages and difficulties, which may lead to variable outcomes in terms of individuals' psychosocial living practices (11). Since the cultural background affects the clinical symptoms in CD (6,12), the sociocultural and socioeconomic characteristics of the metropolis or city in which the patient lives may be significant in the clinical setting.

The purpose of this study was to examine the clinical symptoms (including suicidal behavior and dissociation symptoms) and its association with the sociodemographic characteristics and lifetime traumatic experiences of female patients diagnosed with CD, considering the characteristics of the metropolis or city of residence. Female patients with CD living in a metropolis were compared with healthy controls and with female patients with CD living in a non-metropolis city (NMC). We hypothesized that metropolitan life would be associated with higher rates of suicide attempts, dissociation symptoms, and lifetime traumatic experiences compared with life in NMCs among patients with CD.

METHODS

Study design: This descriptive cross-sectional study was conducted simultaneously in two cities in Türkiye, one a metropolis and the other an NMC. It included a clinical sample of patients diagnosed with CD and healthy controls.

Setting and participants: Three groups of participants were established-CD patients living in the metropolis (CD-metropolis group), CD patients living in the NMC (CD-NMC group), and healthy controls. Members of the CD-metropolis group were recruited from the psychiatric outpatient clinic of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital in İstanbul, Türkiye's major metropolis. The healthy controls with no psychiatric, chronic medical or genetic illness were recruited from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital internal medicine outpatient clinics and lived in the same metropolis. Members of the CD-NMC group were recruited from the Elazığ Training and Research Hospital psychiatric Outpatient Clinic in Elazığ, an NMC with a much lower population density, immigration rate, and female employment (13). These features indicate that Elazığ possesses more rural life characteristics than the metropolis. All patients were evaluated by clinical psychiatric assessment based on DSM-5. Patients with any neurological disease, mental disability, alcohol and/or substance dependence, bipolar disorder, schizophrenia, other psychotic disorders, or tardive dyskinesia were excluded from the study. The Dissociative Events scale (DES), Childhood Trauma questionnaire-28 (CTQ-28), Traumatic Experiences checklist (TEC), and a data form were applied face to face to the participants.

Data Measurement

Data form: This 39-item semi-structured questionnaire was developed by the researchers to collect information concerning participants' demographic characteristics, clinical history, life events and traumatic experiences, family burdens, and clinical presentation of CD.

DES: This 11-point Likert-type self-report scale consists of 28 items. It was developed by Bernstein and Putnam (14) to screen dissociative events. The validity and reliability of the Turkish-language version have previously been established (15). Higher scores indicate higher dissociative symptoms.

CTQ: This self-report scale consists 28-item concerning different traumatic events. It is suitable for individuals over 12 years of age and is used to screen emotional and physical neglect and abuse as well as sexual abuse before the age of 20. In the adaptation, validity and reliability study of the 28-item form of the scale, over 5 points for sexual and physical abuse, above 7 points for physical neglect and emotional abuse, above 12 points for emotional neglect, and over 35 points for the total score were suggested as cut-off points. It was developed by Bernstein et al. (16). The validity and reliability of the Turkish-language version were investigated by Aslan and Alparslan (17).

TEC: This self-report scale was originally developed by Nijenhuis et al. (18). It is used to assess the presence of childhood traumatic experiences. It includes 29 items concerning exposure to a different traumatic experience in childhood. Its subscales include emotional neglect, emotional abuse, sexual harassment, sexual abuse and physical abuse/bodily threat (range 0-21).

Study size: When the mean was 36 and 23 (with 21.89 and 18.13 standard deviations) with 95% confidence level (1-α), 80% test pover (1-β), the number of samples to be taken in each group was determined as 37 (5).

Statistical Analysis

NCSS software (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) were used in the evaluation of the study data. The normal distribution of quantitative data was tested using the Shapiro-Wilk test and graphical evaluations. One-way ANOVA was used for comparisons of three or more normally distributed groups, and the Bonferroni test was used for paired comparisons. The Kruskal-Wallis test was applied for comparisons of three or more groups not exhibiting a normal distribution, and the Bonferroni-Dunn test was used for paired comparisons. Pearson's chi-square test and the Fisher-Freeman-Halton test were used to compare qualitative data. Significance was evaluated at the $p<0.05$ level.

Ethical Approval: Ethical approval of the study was taken from Local Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital on 18.03.2019 with 2019/105 protocol and 2019-06-02 approval numbers. The study was conducted in accordance with the ethical standards established in the Declaration of Helsinki. All participants were informed about the study, and their written and verbal consent were obtained.

RESULTS

Sample Characteristics

The study was completed with 180 female participants. The CD-metropolis group, CD-NMC group, and the healthy control group all consisted of 60 members each. The participants' ages ranged from 16 to 63 years, with a mean of 33.67±10.50 years. Educational level, monthly family income, and employment rates were statistically significantly lower in the patient groups than in the healthy control group ($p=0.001$ and $p<0.01$, respectively). The participants' sociodemographic characteristics are shown in Table 1.

Symptoms in CD Patients

The most common CD symptoms in the CD-metropolis group were fatigue (96%), crying-involuntary muscle contraction (95%), inability to speak (91.7%), numbness in the hands and arms (88.3%), loss of consciousness-falling (80%), pseudoseizures (53.3%), and paralysis in the hands and arms (51.7%). The most common symptoms in the CD-NMC group were crying-involuntary muscle contraction (93.3%), loss of consciousness-falling (76.7%), inability to speak (45%), and numbness in the hands and arms (30%). Inability to speak ($p=0.001$ and $p<0.01$, respectively), numbness in the hands and arms ($p=0.001$ and $p<0.01$), pseudoseizures ($p=0.001$ and $p<0.01$), paralysis in the hands and arms ($p=0.001$ and $p<0.01$), and fatigue ($p=0.001$ and $p<0.01$) were significantly more common in the CD-metropolis group compared to the CD-NMC group. The groups also differed significantly in terms of the presence of pseudopsychotic symptoms (50% in the CD-metropolis group compared to 30% in the CD-NMC group) ($p=0.001$ and $p<0.01$, respectively).

Suicidal Behavior in the Study Groups

Attempted suicide and suicidal ideation rates differed significantly between the groups ($p=0.001$ and $p<0.01$, respectively). The CD-metropolis group had the highest attempted suicide rate (38.3%), while the highest rate of suicidal ideation was in the CD-NMC group (40%). No difference was observed between the groups in terms of methods employed for suicide ($p>0.05$) (Table 2).

Life-time Trauma Exposure and Its Association with DES in the Study Groups

A history of domestic violence in childhood (both witnessing and being a target of violence) was much more common in both patient groups than in the control group ($p<0.05$). The main perpetrator of violence in the CD-metropolis group was the mother, while in the CD-NMC group the perpetrator was generally the father (Table 3).

Table 1. Comparison of groups in terms of sociodemographic characteristics

		CD-metropolis group (n=60) n (%)	CD-city group (n=60) n (%)	Healthy controls (n=60) n (%)	p
Marital status	Married	42 (70.0)	31 (51.7)	40 (66.7)	[b]0.089
	Single	18 (30.0)	29 (48.3)	20 (33.3)	
Educational level	Illiterate	4 (6.7)	5 (8.3)	0 (0)	[a]0.001**
	Primary school graduate	2 (3.3)	34 (56.7)	10 (16.7)	
	Middle school graduate	39 (65.0)	14 (23.3)	10 (16.7)	
	High school graduate	14 (23.3)	5 (8.3)	12 (20.0)	
	University gradaute	1 (1.7)	2 (3.3)	28 (46.6)	
Employment status	Employment	13 (21.7)	6 (10.0)	54 (90.0)	[b]0.001**
	Non-employment	47 (78.3)	54 (90.0)	6 (10.0)	
Monthly family income	≤2500 TL	41 (68.3)	53 (88.3)	4 (6.7)	[b]0.001**
	2500-5000 TL	13 (21.7)	4 (6.7)	38 (63.3)	
	≥5000 TL	6 (10.0)	3 (5.0)	18 (30.0)	

CD: Conversion disorder, TL: Turkish liras, [a]Fisher-Freeman-Halton test, [b]Pearson chi-square test, *p<0.05, **p<0.01

Table 2. Comparison of groups in terms of suicidal behaviour

		CD-metropolis group (n=60) n (%)	CD-city group (n=60) n (%)	Healthy controls (n=60) n (%)	p
Suicide attempt	Present	23 (38.3)	11 (18.3)	0 (0)	[b]0.001**
	Absent	37 (61.7)	49 (81.7)	60 (100)	
Suicide methods	Oral drug intake	16 (69.6)	9 (81.8)	-	[a]1.000
	Hanging	3 (13.0)	1 (9.1)	-	
	Jumping from hight	1 (4.3)	0 (0)	-	
	Self mutilation	3 (13.0)	1 (9.1)	-	
Suicide thoughts	Present	9 (15.0)	24 (40.0)	1 (1.7)	[b]0.001**
	Absent	51 (85.0)	36 (60.0)	59 (98.3)	

CD: Conversion disorder, [a]Fisher-Freeman-Halton test, [b]Pearson chi-square test, *p<0.05, **p<0.01

The groups differed significantly in terms of CTQ-28, DES, and TEC scores and parameters (p<0.05). The CD-metropolis group exhibited the highest CTQ-28 subscale, DES, and TEC scores. The CD-NMC group exhibited higher CTQ-28-Emotional abuse and CTQ-28-Physical abuse/neglect (at a statistically insignificant level) scores and higher TEC-Physical abuse values than the control group (p=0.001 and p<0.01 respectively). The groups also differed in terms of family support levels, the lowest being observed in the CD-metropolis group, followed by the CD-NMC group (Table 4).

Examination of correlations between CTQ-28 and DES revealed that in the CD-metropolis group, DES scores were statistically significantly correlated with those of three CTQ-28 subscales (Emotional neglect/abuse, physical neglect/abuse, and sexual abuse) (p<0.01). However, these associations were not observed in the CD-NMC group (p>0.05) (Table 5).

Association of Suicide Attempt with the DES, CTQ, and TEC Parameters

In the CD-metropolis group, attempted suicide was significantly associated with DES scores (p<0.01) (Figure 1) and with two of the CTQ subscale scores (physical neglect and physical abuse) (p<0.05) (Figure 2). However, these associations were not observed in the CD-NMC group (p>0.05) (Figure 1).

Table 3. Comparison of groups in terms of domestic violence history in childhood

		CD-metropolis group (n=60) n (%)	CD-city group (n=60) n (%)	Healthy controls (n=60) n (%)	p
Being the target of domestic violence	None	28 (46.7)	35 (58.3)	52 (86.7)	[a]0.001**
	Rare	3 (5.0)	11 (18.3)	0 (0)	
	Occasional	9 (15.0)	7 (11.7)	5 (8.3)	
	Frequent	20 (33.3)	7 (11.7)	3 (5.0)	
Perpetrator of the violence	Father	9 (28.1)	11 (44.0)	1 (12.5)	[a]0.231
	Mother	17 (53.1)	8 (32.0)	5 (62.5)	[a]0.195
	Brother	4 (12.5)	2 (8.0)	2 (25.0)	[a]0.432
	Sister	0 (0)	5 (20.0)	1 (12.5)	[a]0.015*
	Others	6 (18.8)	1 (4.0)	2 (25.0)	[a]0.107
Witnessing the domestic violence (from father to mother)	Absent	24 (40.0)	17 (28.3)	8 (13.3)	[b]0.005**
	Present	36 (60.0)	43 (71.7)	52 (86.7)	

CD: Conversion disorder, [a]Fisher-Freeman-Halton test, [b]Pearson chi-square test, *p<0.05, **p<0.01

Table 4. Comparison of groups in terms of scores of Childhood Trauma Questionnaire (CTQ), DES and Traumatic Experiences Checklist (TEC)

		CD-metropolis group (n=60)	CD-city group (n=60)	Healthy controls (n=60)	p
CTQ-28-Emotional neglect score	Min-max (median)	5-25 (12)	5-21 (6.5)	5-21 (9)	[c]0.001**
	Mean ± SD	13.17±5.82	8.38±4.23	9.85±4.01	
CTQ-28-Physical neglect score	Min-max (median)	5-17 (10)	5-25 (6)	5-20 (5)	[c]0.001**
	Mean ± SD	10.67±2.98	8.50±5.71	6.43±2.58	
CTQ-28-Emotional abuse score	Min-max (median)	5-24 (9)	5-20 (6)	5-22 (5)	[c]0.001**
	Mean ± SD	11.35±5.46	8.22±4.45	6.07±2.43	
CTQ-28-Physical abuse score	Min-max (median)	5-25 (6)	5-16 (5)	5-21 (5)	[c]0.001**
	Mean ± SD	9.17±5.84	5.85±2.20	5.35±2.10	
CTQ-28-Sexual abuse score	Min-max (median)	5-17 (5)	5-15 (5)	5-25 (5)	[c]0.001**
	Mean ± SD	7.07±3.61	5.35±1.49	5.42±2.60	
DES score	Min-max (median) Mean ± SD	3-46 (20) 23.47±14.21	1-30 (10) 9.97±6.12	1-22 (6) 7.07±5.46	[c]0.001**
TEC-Total scores	Min-max (median) Mean ± SD	1-14 (6) 6.25±3.03	0-24 (2) 3.32±3.60	0-21 (1,5) 2.42±3.60	[c]0.001**
		n (%)	n (%)	n (%)	
TEC-Family support	Absent Present	46 (76.7) 14 (23.3)	40 (66.7) 20 (33.3)	23 (38.3) 37 (61.7)	[b]0.001**
TEC-Emotional neglect/abuse	Absent Present	9 (15.0) 51 (85.0)	38 (63.3) 22 (36.7)	36 (60.0) 24 (40.0)	[b]0.001**
TEC-Physical abuse	Absent Present	20 (33.3) 40 (66.7)	46 (76.7) 14 (23.3)	55 (91.7) 5 (8.3)	[b]0.001**
TEC-Sexual harassment	Absent Present	43 (71.7) 17 (28.3)	57 (95.0) 3 (5.0)	57 (95.0) 3 (5.0)	[b]0.001**
TEC-Sexual abuse	Absent Present	43 (71.7) 17 (28.3)	57 (95.0) 3 (5.0)	57 (95.0) 3 (5.0)	[b]0.001**

CD: Conversion disorder, DES: Dissociative Events scale, CTQ-28: Childhood Trauma questionnaire, TEC: Traumatic Experiences Checklist, SD: Standard deviation, min-max: Minimum-maximum, [b]Pearson chi-square test, [c]Kruskal-Wallis test, **p<0.01

Table 5. The relationships between DES and CTQ-28 scores in patient groups

	DES score			
	CD-metropolis group (n=60)		CD-city group (n=60)	
	r	p	r	p
CTQ-28-Emotional neglect score	0.339	0.008**	0.140	0.286
CTQ-28-Physical neglect score	0.507	0.001**	0.189	0.149
CTQ-28-Emotional abuse score	0.345	0.007**	-0.005	0.971
CTQ-28-Physical abuse score	0.437	0.001**	0.161	0.219
CTQ-28-Sexual abuse score	0.455	0.001**	0.164	0.210

CD: Conversion disorder, DES: Dissociative Events scale, CTQ-28: Childhood Trauma questionnaire, r: Spearman's Rho test, *p<0.05, **p<0.01

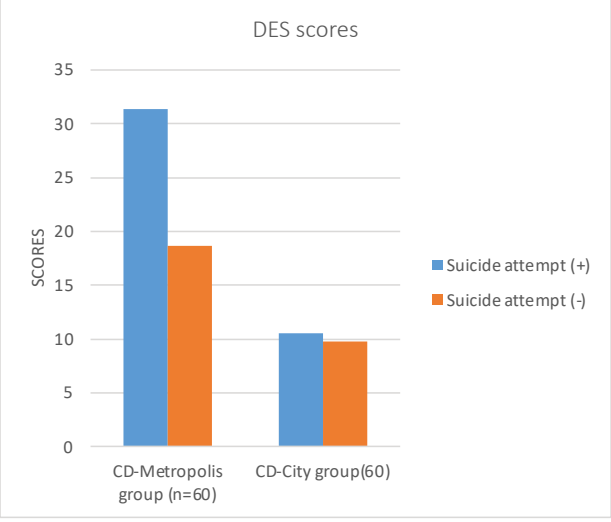

Figure 1. Correlation of suicide attempt with DES scores in patient groups
DES: Dissociative Events scale, CD: Conversion disorder

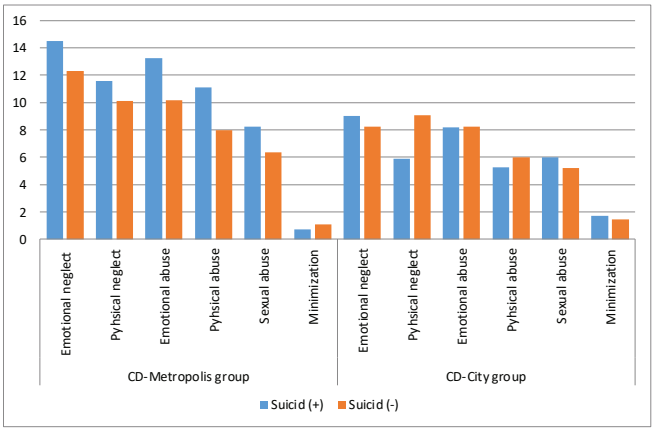

Figure 2. Correlation of suicide attempt with CTQ-28 scores in patient groups
CD: Conversion disorder, CTQ-28: Childhood Trauma questionnaire

Attempted suicide was associated with total TEC scores in the CD-NMC group and with the presence of TEC-Sexual harassment and TEC-Sexual abuse in the CD-metropolis group (p<0.05).

DISCUSSION

Consistent with the previous literature, this cross-sectional study confirms that CD is associated with a low socioeconomic level, low education level, unemployment, traumatic experiences, suicide attempts, and dissociation. However, the original feature of this study is that it examined the clinical symptoms and the relationship between coexisting suicide, dissociative symptoms, and traumatic experiences in terms of the type of city in which the participants lived. Our findings show that metropolitan life is associated with a different clinical symptoms in CD, with more frequent coexisting problems of suicide attempts and/or dissociation symptoms and more frequent traumatic experiences compared to non-NMC life. The study results also showed that suicide attempts, traumatic experiences, and dissociation symptoms were interrelated in CD patients, and that these relationships were also moderated by the type of city in which they lived. Exposure to childhood trauma and dissociative symptoms were important determinants of suicide in CD patients from the metropolis but not in those from the NMC. Based on these findings, both study hypotheses were confirmed.

The study findings are discussed under three subheadings; etiological risk factors of CD, the effects of the city of residence on the clinical symptoms and etiology of CD, and relationships between suicidal and traumatic experiences and dissociation in CD.

Etiological Risk Factors for CD

Low socioeconomic and sociocultural levels (19,20) and traumatic experiences, including those occurring in childhood (8,21-23), are two important etiological risk factors for CD. A study from Pakistan reported that emotional and sexual abuse was frequently observed in female patients with CD (24). In a study from Türkiye, 53.3% of CD patients

reported a history of physical trauma and 25% reported sexual trauma during childhood. Similarly to these previous studies, socioeconomic and educational levels were lower and lifetime traumatic experiences and childhood traumas, including exposure to domestic violence, were more common in patients with CD than in healthy controls in the present research.

An important associated risk factor in this study was the lower level of family support among patients with CD. The family is also an important source of social support (25). It protects against stressors and plays an important role for treating many psychiatric disorders. Low levels of social support have been reported in patients with CD (24). Weak family childhood ties have also been observed in these patients (26), while family members exhibit weak emotional reciprocity (19). Şar et al. (27) reported that poor reciprocal relationships with parents during childhood can lead to CD by causing problems in the development of the child's protective and stress-regulating systems. Considering that social support is an important factor in seeking treatment among individuals with CD (28), we think that investigating family support in these patients will be a useful step both in evaluation and treatment.

The Moderator Role of the City Type in Symptoms and Etiological Risk Factors

Aphasia, loss of consciousness, paresthesia, convulsions, dyspnea, paralysis, psychogenic pain, and astasia-abasia are among the most common symptoms in CD patients (2). Associated suicidality is also common, with suicide rates ranging from 19.6% to 34.2% (5). Dissociative symptoms are reported in approximately 50% of female cases (24). Crying, involuntary muscle contraction, loss of consciousness, falling, inability to speak, and numbness in the hands and arms were among the most common symptoms in both patient groups in the present study. Consistent with the previous literature, CD patients were at risk of attempted suicide and dissociative symptoms. Approximately one-third of all our CD patients, regardless of their city type, attempted suicide, and one quarter exhibited dissociation symptoms.

The clinical symptoms of the disorder varies depending on the developmental level of the country concerned. While symptoms of paralysis, loss of consciousness, blindness or aphonia are seldom observed in Western countries, they are common in developing countries (2,20,22). A study involving a sample from a rural area reported that patients with lower socioeconomic status exhibited more complex and exaggerated symptoms, while in patients with high education and economic levels CD manifests with symptoms similar to a known medical disease (20). Similarly, we found that CD manifests with a higher frequency of various specific symptoms (including an inability to speak, pseudoseizures, numbness in the hands and arms, paralysis in the hands and arms, and fatigue) and pseudopsychotic symptoms, dissociation, and attempted suicide in metropolitan life compared with NMC life. These results indicate the importance of city characteristics in the clinical presentation of the disorder.

Another factor that exhibited intercity differences in cases of CD in this study was related to the frequency of traumatic experiences. Familial problems (more frequent domestic violence and less family support) and lifetime/childhood traumatic experiences were significantly more common in patients living in the metropolis than in those living in the NMC. Although metropolises provide significant cultural and educational opportunities, they are also associated with busy and hectic daily lives (29). Working in shifts in factories and business centers may provide financial security but can also lead to differentiation in nuclear family structures and ties. These adverse outcomes may in turn result in further adverse life experiences for patients with CD living in the metropolis compared with those in less crowded cities where traditional family life still prevails.

Changes in social conditions such as crowding, migration-urbanization, and insufficient social support are among the environmental risk factors for suicide (30). Childhood trauma is reported to be associated with factors such as low socioeconomic status as well as low social support, social isolation, the mother's need to work and work at night, unemployment, debt and overcrowded city life (31). In developing countries such as Türkiye, urbanization is occurring rapidly and unbalanced, and cities are evolving into places with large mass populations. This version of urbanization has recently exacerbated environmental pollution, noise pollution, traffic problems, health problems, and security problems as well as problems such as employment, leading to increased difficulties for people living in such cities (31,32). Due to all these features, metropolitan life may be associated with increased suicidality and traumatic experiences. Based on our current finding, it may be suggested that individuals living in a metropolis among patients diagnosed with CD should receive extra attention in terms of identifying traumatic experiences during clinical evaluations.

The Moderator Effect of City Types on the Relationships Between Suicide Attempts, Traumatic Experiences, and Dissociation

Exposure to traumatic life events (such as child abuse and neglect, domestic violence, bullying, peer violence, dating

violence, sexual violence, and intimate partner violence) is reported to be associated with successful and attempted suicide (33-35). Roy described exposure to childhood trauma as among the major risk factors for suicide (36). Experiencing conflict, disaster, violence, abuse, or loss and a sense of isolation are strongly associated with suicidal behavior. In addition, sexual abuse and dissociation are reported to be independently associated with risk-taking behavior and suicidality (27,35). Specifically, sexual and physical abuse as well as physical neglect have been reported in patients with dissociative symptoms (9,20). Although associations between suicide and childhood trauma and dissociation have been investigated in many studies, the literature regarding patients with CD is limited (34). Güleç et al. (5) demonstrated a strong relationship between suicide and childhood trauma and dissociation in patients with CD. These authors concluded that comorbid dissociative disorder and exposure to childhood trauma are the two predictors of suicide in patients with CD. Similarly, a strong relationship has been demonstrated between emotional/sexual abuse and dissociation in patients with CD (24).

Consistent with previous studies, in the present research dissociation was associated with childhood trauma, specifically emotional neglect/abuse, physical neglect/abuse, and sexual abuse, while attempted suicide was related to childhood trauma (specifically physical neglect and abuse), lifetime sexual trauma, and dissociative symptoms in women diagnosed with CD. However, these associations only applied to patients living in the metropolis. None of these associations were in patients living in the NMC. In contrast, attempted suicide in patients living in the NMC was associated with the level of exposure to overall lifetime trauma. Our results indicated that attempted suicide, trauma, and dissociation symptoms in patients with CD were interrelated, although the type of city involved moderated these relationships. It may be concluded that childhood trauma and lifetime traumatic experiences are important risk factors not only for CD but also for comorbid dissociative symptoms and suicidal behavior, especially in metropolitan life.

The major limitation of this study is its cross-sectional design. Information about traumatic experiences was collected retrospectively from the participants. This might have led to memory bias. It will now be useful to examine traumatic experiences through prospective and longitudinal studies. Other limitations include the relatively small sample size and the absence of a healthy control group drawn from the NMC.

CONCLUSION

The results show that CD is associated with traumatic experiences, suicide attempts, and dissociation, and that this association is particularly prominent in metropolitan life. Since this is the first study to compare patients with CD living in a metropolis with those from an NMC, we think that our research will make an important contribution to the existing literature. Based on our findings, we conclude that the characteristics of the city in which a patient with CD lives are an important determinant of clinical symptomatology, including coexisting suicidality and dissociation and a history of exposure to trauma.

We suggest that in routine follow-ups, patients with CD, especially those living in a metropolis, should be evaluated regularly in terms of coexisting dissociative symptoms and lifetime traumatic experiences, particularly those occurring during childhood, in order to identify patients at a higher risk of suicide.

Acknowledgment: The authors would like to thank all the participants who kindly agreed to participate in the study.

ETHICS

Ethics Committee Approval: Ethical approval of the study was taken from Local Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital on 18.03.2019 with 2019/105 protocol and 2019-06-02 approval numbers.

Informed Consent: All participants were informed about the study, and their written and verbal consent were obtained.

Authorship Contributions

Surgical and Medical Practices: F.A.K., O.K., Concept: F.A.K., S.Y., P.G.G., Design: F.A.K., S.Y., P.G.G., G.D., Data Collection or Processing: F.A.K., S.Y., O.K., P.G.G., Analysis or Interpretation: F.A.K., S.Y., P.G.G., G.D., Literature Search: F.A.K., S.Y., O.K., G.D., Writing: F.A.K., S.Y., P.G.G., G.D.

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

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REFERENCES

1. Breuer J, Freud S. (original article 1893-1895). Studies on hysteria, in The Standard Edition of the Complete Psychological Works of Sigmund Freud, Vol. II. Edited and translated by Strachey J, Strachey A. London, Hogarth Press and the Institute of Psycho-Analysis, 1955, pp vii–xxxi, 1-311 (original article 1893-1895).
2. Akyüz F, Gökalp PG, Erdiman S, Oflaz S, Karşidağ Ç. Conversion Disorder Comorbidity and Childhood Trauma. Noro Psikiyatr Ars 2017;54:15-20.
3. Stone J, Carson A, Duncan R, Roberts R, Warlow C, Hibberd C, et al. Who is referred to neurology clinics?--the diagnoses made in 3781 new patients. Clin Neurol Neurosurg 2010;112:747-51.

4. Feinstein A. Conversion disorder: advances in our understanding. CMAJ 2011;183:915-20.
5. Güleç MY, Ýnanç L, Yanartaþ Ö, Üzer A, Güleç H. Predictors of suicide in patients with conversion disorder. Compr Psychiatry 2014;55:457-62.
6. Kuloglu M, Atmaca M, Tezcan E, Gecici O, Bulut S. Sociodemographic and clinical characteristics of patients with conversion disorder in Eastern Turkey. Soc Psychiatry Psychiatr Epidemiol 2003;38:88-93.
7. Ludwig L, Pasman JA, Nicholson T, Aybek S, David AS, Tuck S, et al. Stressful life events and maltreatment in conversion (functional neurological) disorder: systematic review and meta-analysis of case-control studies. Lancet Psychiatry 2018;5:307-20.
8. Mulder RT, Beautrais AL, Joyce PR, Fergusson DM. Relationship between dissociation, childhood sexual abuse, childhood physical abuse, and mental illness in a general population sample. Am J Psychiatry 1998;155:806-11.
9. Sobot V, Ivanovic-Kovacevic S, Markovic J, Misic-Pavkov G, Novovic Z. Role of sexual abuse in development of conversion disorder: case report. Eur Rev Med Pharmacol Sci 2012;16:276-9.
10. Dar LK, Hasan S. Traumatic experiences and dissociation in patients with conversion disorder. J Pak Med Assoc 2018;68:1776-81.
11. Şahan B, Akbaş T. Counseling with Culturally Different Families and Role of Culture in Turkish Family Structure. Buca F Edu J 2018;46:214-39.
12. Srinath S, Bharat S, Girimaji S, Seshadri S. Characteristics of a child inpatient population with hysteria in India. J Am Acad Child Adolesc Psychiatry 1993;32:822-5.
13. Socio-economic of provinces and regions development ranking survey-SEGE-2017-BEBKA. Republic of Turkey Ministry of Industry and Technology-Working report. Avaiable from URL:https://www.bebka.org.tr/admin/datas/sayfas/89/sege-2017_1581687211.pdf
14. Bernstein EM, Putnam FW. Development, reliability, and validity of a dissociation scale. J Nerv Ment Dis 1986;174:727-35.
15. Sar V, Kundakci T, Kiziltan E, Bakim B, Yargic LI, Tutkun H. The reliability and validity of the Turkish version of the Dissociative Experiences Scale (DES-II). Proceedings of the 33rd National Congress of Psychiatry, Antalya, Turkey. Ankara, Psychiatric Association of Turkey. 1997. p.55-64.
16. Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, Wenzel K, et al. Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am J Psychiatry 1994;151:1132-6.
17. Aslan SH, Alparslan ZN. Reliability, validity and factor structure of the Childhood Trauma Scale in a sample of university students. Turkish J Psychiatry 199;10:275-85.
18. Nijenhuis ERS, Van der Hart O, Kruger K. The psychometric characteristics of the Traumatic Experiences Checklist (TEC): First findings among psychiatric outpatients. Clin. Psychol Psychother 2022;9:200-10.
19. Liakopoulou-Kairis M, Alifieraki T, Protagora D, Korpa T, Kondyli K, Dimosthenous E, et al. Recurrent abdominal pain and headache--psychopathology, life events and family functioning. Eur Child Adolesc Psychiatry 2002;11:115-22.
20. Deveci A, Özmen E, Demet M, İçelli İ. Sociodemographic and clinical features outpatients with conversion disorder in the psychiatry department of a university hospital. Anadolu Psikiyatr Derg 2002;3:28-33.
21. Draijer N, Langeland W. Childhood trauma and perceived parental dysfunction in the etiology of dissociative symptoms in psychiatric inpatients. Am J Psychiatry 1999;156:379-85.
22. Roelofs K, Spinhoven P, Sandijck P, Moene FC, Hoogduin KA. The impact of early trauma and recent life-events on symptom severity in patients with conversion disorder. J Nerv Ment Dis 2005;193:508-14.
23. Karamustafalıoğlu OK, Özçelik B, Gönenli Toker S, Bakım B, Cengiz Ceylan Y, Akpınar A, et al. Comorbid Bipolar Disorder Among Patients with Conversion Disorder. Journal of Mood Disorders 2013;3:58-63.
24. Volkmar FR, Poll J, Lewis M. Conversion reactions in childhood and adolescence. J Am Acad Child Psychiatry 1984;23:424-30.
25. Kozlowska K, Williams LM. Self-protective organization in children with conversion and somatoform disorders. J Psychosom Res 2009;67:223-33.
26. Kozlowska K, Brown KJ, Palmer DM, Williams LM. Specific biases for identifying facial expression of emotion in children and adolescents with conversion disorders. Psychosom Med 2013;75:272-80.
27. Sar V, Onder C, Kilincaslan A, Zoroglu SS, Alyanak B. Dissociative identity disorder among adolescents: prevalence in a university psychiatric outpatient unit. J Trauma Dissociation 2014;15:402-19.
28. Dar MM, Amin R, Wani ZA, Paul MA. Sociodemogaphic and clinic profile of patients suffering from severe depressive disorders in Kashmir Valley. IJCMR 2016;3:3389-92.
29. Brown RJ, Schrag A, Trimble MR. Dissociation, childhood interpersonal trauma, and family functioning in patients with somatization disorder. Am J Psychiatry 2005;162:899-905.
30. Bachmann S. Epidemiology of Suicide and the Psychiatric Perspective. Int J Environ Res Public Health 2018;15:1425.
31. Çelik S. Overurbanizations: its problems and solutions. J Int Soc Res 2019;12:312-20.
32. Helvacı-Çelik FG, Hocaoğlu Ç. Childhood Traumas: A Review. Sakarya Medical J 2018;8:695-711.
33. Singh S, Manjula M, Philip M. Suicidal risk and childhood adversity: a study of Indian college students. Asian J Psychiatr 2012;5:154-9.
34. Saraçlı Ö, Atasoy N, Şenormancı Ö, Atik L, Açıkgöz HO, Doğan V, et al. Childhood trauma and suicide risk in the population living in Zonguldak Province. Asia Pac Psychiatry 2016;8:136-44.
35. Sar V, Akyüz G, Kundakçi T, Kiziltan E, Dogan O. Childhood trauma, dissociation, and psychiatric comorbidity in patients with conversion disorder. Am J Psychiatry 2004;161:2271-6.
36. Roy A. Combination of family history of suicidal behavior and childhood trauma may represent correlate of increased suicide risk. J Affect Disord 2011;130:205-8.

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Research

Frequency of Eating Disorders and Associated Factors in Type 1 Diabetic Adolescents

Tip 1 Diyabetik Ergenlerde Yeme Bozukluklarının Sıklığı ve İlişkili Faktörler

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ABSTRACT

Objective: Examine the relationship between eating problems, emotional problems, behavioral attitudes about treatment, and adherence to diet in adolescents.

Methods: The study was conducted with 132 participants, 60 of whom were in the healthy control group and 72 in the type 1 diabetes mellitus (T1DM) group. Participants were assessed using Children's Depression inventory (CDI), Screen for Child Anxiety Related Disorders (SCARED), and the Eating Attitude test (EAT) self-report scales and a data form.

Results: Significant scores for CDI, SCARED, and EAT were higher in the T1DM group than in the control group ($p<0.01$). Patients with lower parent education, separated parents, irregular outpatient follow-up, history of diabetes complications and refusal of insulin injections, and hospitalization in the last 3 months had higher rates of have significant outcomes for CDI and SCARED ($p<0.05$). A significant correlation was found between the person who injected insulin ($p<0.05$) and the child's adherence to diet ($p<0.01$) and the EAT scores being significant. There was a positive correlation between CDI and EAT scores ($p<0.01$).

Conclusion: Low parent education, increasing age, strict adherence to a diabetic diet, lack of responsibility for insulin therapy, and depressive symptoms have been associated with an increased risk of eating problems in adolescents. The clinical outcome will improve with identifying risky cases.

Keywords: Type 1 diabetes mellitus, adolescent, eating problems, emotional problems

ÖZ

Amaç: Ergenlerde yeme sorunları, duygusal sorunlar, tedaviye yönelik davranışsal tutumlar ve diyete bağlılık arasındaki ilişkiyi incelemeyi amaçladık.

Gereç ve Yöntem: Çalışma sağlıklı kontrol grubunda 60, tip 1 diabetes mellitus (T1DM) grubunda 72 olmak üzere toplam 132 katılımcı ile gerçekleştirilmiştir. Katılımcılar Çocuk Depresyon ölçeği (CDI), Çocuk Anksiyete İlişkili Bozukluklar için Tarama (SCARED) ve Yeme Tutum testi (EAT) kişisel bildirim ölçekleri ve veri formu kullanılarak değerlendirildi.

Bulgular: CDI, SCARED ve EAT için anlamlı puanlar T1DM grubunda kontrol grubuna göre daha yüksekti ($p<0,01$). Düşük ebeveyn eğitimi, ayrı ebeveynler, düzensiz ayakta tedavi takibi, diyabet komplikasyonları öyküsü ve insülin enjeksiyonlarını reddetme ve son 3 ayda hastaneye yatış olan hastalarda CDI ve SCARED için anlamlı sonuçlara sahip olma oranları daha yüksekti ($p<0,05$). İnsülin enjekte eden kişi ($p<0,05$) ile çocuğun diyete uyumu ($p<0,01$) ve EAT puanlarının anlamlı olması arasında anlamlı bir ilişki bulundu. CDI ve EAT puanları arasında pozitif korelasyon vardı ($p<0,01$).

Sonuç: Düşük ebeveyn eğitimi, artan yaş, diyabetik diyete sıkı bağlılık, insülin tedavisi için sorumluluk eksikliği ve depresif semptomatoloji, ergenlerde artan yeme sorunları riski ile ilişkilendirilmiştir. Riskli olguların belirlenmesi ile klinik sonuç iyileşecektir.

Anahtar Kelimeler: Tip 1 diabetes mellitus, adölesan, yeme problemleri, duygusal problemler

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is characterized by insufficient endogenous insulin production. Today, with its increasing prevalence, T1DM is defined as a public health problem in children and adolescents (1). According to the 9th edition of the International Diabetes Federation's Diabetes Atlas, 1.1 million children and adolescents worldwide have a diagnosis of T1DM (2). Because it causes serious complications and leads to a serious reduction in life quality, effective treatment is essential. Treatment of T1DM includes exogenous insulin usage, physical exercise, and a restrictive diabetic diet (3,4). Today, despite advances in T1DM treatment, at least two-thirds of adolescents and young adults have insufficient treatment adherence (3). Besides biological determinants, psychosocial factors have important roles in adherence to the nutritional regimen during adolescence, and stress and psychophysiological processes may result in impaired disease control (5).

Studies on adolescents with T1DM demonstrate that these patients have poorer psychosocial adjustment and higher rates of psychiatric disorders such as anxiety, depression, and eating disorders (ED) compared to healthy peers (6,7). The disease's psychological burden is associated with its chronic course and its treatment requiring frequent invasive procedures and restrictive diet. A restrictive diet in terms of content and timing is a challenging stressor, especially in adolescence, which is characterized by increased autonomy, withdrawal from parental authority, suboptimal impulse control, and increased self-focus in body appearance (8,9).

ED are behavioral conditions characterized by severe and persistent ailments in eating behaviors and associated distressing thoughts and emotions about eating, weight, and shape or their control. The major risk factors associated with ED are; shape and weight related concerns, family history of ED, dietary restraint, adolescence period, female gender, low self-esteem, and concerns about being underweight (10,11). In T1DM, the standard treatment regimen requires focusing on eating habits that can cause eating concerns.

It has been reported that these factors along with the psychological burden of chronic disease management and depression may lead to ED in adolescents with T1DM (12,13). Commissariat et al. (14) reported that problems in psychosocial adjustment are important causes of eating problems in adolescents with T1DM. However, studies on ED frequency specifically in the adolescence period are limited in number and existing studies show inconsistent results in terms of the association of ED with emotional problems and treatment attitudes in T1DM. Our study examined the frequency of emotional and eating problems in adolescents diagnosed with T1DM.

METHODS

Our study is a cross-sectional descriptive study conducted with adolescents diagnosed with T1DM in the Pediatric Endocrinology Outpatient Clinic. Inclusion criteria were; being at 13-18 years of age, using insulin treatment for at least 6 months, and being volunteered to participate in the study (both participants and their parents). Patients with another chronic disease, genetic/syndromic disease, or severe psychiatric disease (such as autism spectrum disorders, magnetic resonance imaging, psychotic disorder, bipolar affective disorder, substance use disorder) leading to cognitive impairment were not included in the study. Adolescents the ages of 13-18 who applied to the general pediatric outpatient clinics of the same hospital, did not have any chronic diseases and agreed to participate in the study were included as the control group. The study was conducted with 132 participants, 72 in the T1DM group and 60 in the control group. Participants were assessed using a data form and self-report scales which were Children's Depression inventory (CDI), Screen for Child Anxiety Related Disorders (SCARED), and the Eating Attitude test (EAT).

Data Collection Tools

1. Data form: It contains questions related to sociodemographic information including the age, gender, education level of the parents, socioeconomic level of the adolescent, as well as questions about the disease and its treatment. The duration of the disease diagnosis, the presence of complications, hospitalization, who administered the insulin, adherence to the diet, insulin rejection, and inability to make insulin were asked. During the patient's clinical interview, information was recorded on the data form.

2. CDI: It is a self-assessment scale with 27 items developed by Kovacs (15). Each item is scored between 0 and 2. Higher scores indicate high levels of depression. Its Turkish validity and the reliability study was done by Oy (16). Scores of at least 19 indicate significant scores for depression.

3. SCARED-Child form: This self-report scale consisting of 41 items was developed by Birmaher et al. (17) to screen childhood anxiety disorders. Its Turkish validity and the reliability study was conducted by Cakmakcı (18). The total anxiety score is also obtained from the scale, which has different subscales such as phobic anxiety, social anxiety, separation anxiety, pervasive anxiety, and school-related anxiety. Higher scores on the scale indicate higher anxiety

symptom levels. Scores of at least 25 indicate significant scores for anxiety.

4. EAT: It is a six-point likert-type self-report scale developed to evaluate possible eating behavior in individuals with and without EDs. It was developed by Garner and Garfinkel (19). It includes 40 items. It is thought to be a good screening tool for eating behavior disorders. The total score is directly related to the level of psychopathology. In other words, EAT can determine individuals who can be considered "patients" at the clinical level, as well as an indicator of how susceptible they are to this disorder. Significant scores for EDs are those above 30. A Turkish validity and reliability study of the scale was conducted by Savasir and Erol (20).

Ethics Statement: The questionnaire and methodology for this study the decision number 2020-22-32 (date: 02.11.2020) were obtained from the Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital. Written and verbal consent was obtained from all participants and their parents. The authors assert that all procedures contributing to this work comply with the ethical standards in University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital and the Helsinki Decleration of 1975, as revised in 2008. The participants' consent to participate in the study was requested personally from each individual.

Statistical Analysis

The Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used while evaluating the study data. The suitability of quantitative data to a normal distribution was tested by Kolmogorov-Smirnov, Shapiro-Wilk test and graphical evaluations. Student's t-test was used for two-group comparisons of quantitative data with normal distribution, and Mann-Whitney U test was used for two-group comparisons of data that did not show normal distribution. In comparison of qualitative data, Pearson chi-square test, Fisher's Exact test, Fisher-Freeman-Halton Exact test were used. Spearman's correlation analysis was used to evaluate the relationships between variables. Significance was assessed at least at $p<0.05$ level.

RESULTS

The study was completed with 132 participants with 13-18 years of age, of whom 60 were healthy controls and 72 were with T1DM. In the T1DM group, the average age was 14.72 years and 61.1% were girls. Groups were similar in terms of age, gender, and familial characteristics of the participants. The demographic characteristics of the groups about themselves and their families are presented in Table 1.

Findings related to clinical characteristics of the participants in the T1DM group showed that; 36.1% (n=26) had irregular outpatient clinic follow-up, 16.7% (n=12) had no diet adherence at all, and 30.5% refused insulin injections at least rarely. In 27.8% (n=20) of participant, insulin injections were being done by only parents. The distribution of characteristics of the participants in the DM group regarding the disease and its treatment is presented in Table 2.

In the DM-group; examination of the relationship between sociodemographic data and the obtaining significant scores from scales showed that there were statistically significant relationships between SCARED and family type ($p=0.003$); between CDI and family type ($p=0.001$) and paternal education ($p=0.036$); between EAT and age ($p=0.037$), maternal education ($p=0.011$) and paternal education ($p=0.025$) (Table 3).

In the DM group participants, the ratios of getting significant scores from SCARED and CDI were higher in patients who rejected insulin injections, who had irregular outpatient follow-ups, and who were hospitalized for diabetes in the previous 3 months ($p<0.05$). In addition, the ratio of getting significant scores from CDI was higher in those with diabetes complications compared to others ($p=0.023$; $p<0.05$). In the DM group, getting significant scores from EAT was related to the person who made the insulin injections ($p=0.017$; $p<0.05$) and the child's diet adherence ($p=0.001$; $p<0.01$). The ratio of getting significant scores from EAT was lower among the participants who made their own insulin injections and higher among those who always adhered to a diabetic diet (Table 4).

The groups were compared according to the scores of the scales. In the T1DM group, scores of all scales (except for SCARED-PA and SCARED-SA) and rates of getting significant scores from all scales were significantly higher compared to the control group ($p<0.05$). In the DM group, EAT scores showed a weak statistically significant positive correlation with CDI scores ($r=0.309$; $p=0.008$; $p<0.01$) but not with SCARED scores ($p>0.05$).

DISCUSSION

We examined emotional and eating problems in adolescents with T1DM diagnosis and found that compared to their healthy peers, these adolescents had more emotional and eating problems. Refusing insulin injections and having irregular outpatient follow-up, recent hospitalization, and

Table 1. Evaluation of demographic characteristics according to groups

		T1DM-group (n=72)	Control group (n=60)	p
		n (%)	n (%)	
Age (year)	Min-max (median)	13-17 (14.5)	13-18 (14)	[a]0.808
	Mean ± SD	14.72±1.25	14.78±1.57	
Gender	Girl	44 (61.1)	30 (50.0)	[b]0.200
	Boy	28 (38.9)	30 (50.0)	
Family type	Nuclear	62 (86.1)	44 (73.3)	[b]0.102
	Extended	4 (5.6)	10 (16.7)	
	Parental seperation	6 (8.3)	6 (10.0)	
Monthly family income	At minimum wage	16 (22.2)	16 (26.7)	[b]0.876
	Minimum wage-4000 TL	26 (36.1)	21 (35.0)	
	4000-5000 TL	18 (25.0)	12 (20.0)	
	≥5000 TL	12 (16.7)	11 (18.3)	
Maternal educational level	At or below primary school	36 (50.0)	25 (41.7)	[b]0.369
	Secondary education	32 (44.4)	28 (46.7)	
	University	4 (5.6)	7 (11.7)	
Paternal educational level	At or below primary school	38 (52.8)	29 (48.3)	[b]0.867
	Secondary education	28 (38.9)	26 (43.3)	
	University	6 (8.3)	5 (8.3)	

[a]Student's t-test, [b]Pearson chi-square test, Min-max: Minimum-maximum, SD: Standard deviation, TL: Turkish liras, T1DM: Type 1 diabetes mellitus

diabetes complications, which indicated lower disease management, were associated with increased emotional problems. Besides increasing age, lower parent education, lack of responsibility for insulin therapy, strict adherence to diabetic diet and depressive symptoms were associated with increased risk for eating problems in these adolescent patients.

Khandelwal et al. (5), in their case-control study showed that the prevalence of psychosocial problems in children and adolescents (6-14 years) with T1DM was 55.95%, and this rate was almost three times higher than their healthy peers. The authors report that among patients 36.9% had a depression; 32.1% had anxiety. Another cross-sectional study involving adolescents and young adults (11-25 years) similarly showed higher ratios of depression (11.3%) and anxiety (21.3%) compared with healthy controls (21). In a recent review, 14 studies on children and adolescents were examined and confirmed that T1DM is associated with high depression and anxiety symptoms (22). It is estimated that T1DM in adolescents is associated with a twice risk of depression (7). Similar to these studies, we showed higher anxiety (52.8%) and depression (36.1%) ratios in T1DM adolescents compared to healthy controls (21.7%, 8.3%, respectively).

Table 2. Distribution of disease characteristics in the diabetes mellitus-group

Disease characteristics (n=72)		n (%)
Complications	Absent	64 (88.9)
	Present	8 (11.1)
Hospitalization due to diabetes in the previous 3 months	Absent	60 (83.3)
	Present	12 (16.7)
Regular follow-up	Absent	26 (36.1)
	Present	46 (63.9)
Person who makes he insulin injections	Patient himself/ herself	44 (61.1)
	Parents	20 (27.8)
	Mixed	8 (11.1)
Child's diet adherence (depending on parental report)	Never	12 (16.7)
	Sometimes	34 (47.2)
	Generally	18 (25.0)
	Always	8 (11.1)
Adolescents' rejection of the insulin injections (depending on parental report)	Never happens	50 (69.4)
	Rarely	8 (11.1)
	Sometimes	14 (19.4)

Table 3. In DM-group: Examination of the relationship between demographic characteristics and the status of having significant scores of SCARED, CDI and EAT

		T1DM-group (n=72)					
		Significant score for SCARED		Significant score for CDI		Significant score for EAT	
		Present	Absent	Present	Absent	Present	Absent
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age (year)	Mean ± SD	14.89±1.31	14.53±1.16	15.00±1.13	14.57±1.29	15.18±1.14	14.52±1.25
	p	[a]0.217		[a]0.157		[a]0.037*	
Gender	Girl	26 (59.1)	18 (40.9)	18 (40.9)	26 (59.1)	14 (31.8)	30 (68.2)
	Boy	12 (42.9)	16 (57.1)	8 (28.6)	20 (71.4)	8 (28.6)	20 (71.4)
	p	**[b]0.228**		**[b]0.288**		**[b]0.774**	
Family type	Nuclear	32 (51.6)	30 (48.4)	20 (32.3)	42 (67.7)	22 (35.5)	40 (64.5)
	Extended	0 (0)	4 (100)	0 (0)	4 (100)	0 (0)	4 (100)
	Parental seperation	6 (100)	0 (0)	6 (100)	0 (0)	0 (0)	6 (100)
	p	**[d]0.003****		**[d]0.001****		**[d]0.087**	
Family income	At minimum wage	6 (37.5)	10 (62.5)	2 (12.5)	14 (87.5)	6 (37.5)	10 (62.5)
	Minimum wage-4000 TL	16 (61.5)	10 (38.5)	10 (38.5)	16 (61.5)	4 (15.4)	22 (84.6)
	4000-5000 TL	10 (55.6)	8 (44.4)	8 (44.4)	10 (55.6)	6 (33.3)	12 (66.7)
	≥5000 TL	6 (50.0)	6 (50.0)	6 (50.0)	6 (50.0)	6 (50.0)	6 (50.0)
	p	**[b]0.495**		**[b]0.140**		**[d]0.128**	
Maternal education	At or below primary education	18 (50)	18 (50.0)	12 (33.3)	24 (66.7)	16 (44.4)	20 (55.6)
	At or above secondary education	20 (55.6)	16 (44.4)	14 (38.9)	22 (61.1)	6 (16.7)	30 (83.3)
	p	**[b]0.637**		**[b]0.624**		**[b]0.011***	
Maternal education	At or below primary education	22 (57.9)	16 (42.1)	18 (47.4)	20 (52.6)	16 (42.1)	22 (57.9)
	At or above secondary education	16 (47.1)	18 (52.9)	8 (23.5)	26 (76.5)	6 (17.6)	28 (82.4)
	p	**[b]0.358**		**[b]0.036***		**[b]0.025***	

[a]Student's t-test, [b]Pearson chi-square test, [d]Fisher-Freeman-Halton Exact test, *p<0.05, **p<0.01, SD: Standard deviation, TL: Turkish liras, T1DM: Type 1 diabetes mellitus, CDI: Children's Depression inventory, SCARED: Screen for Child Anxiety Related Disorders, EAT: Eating Attitude test

These ratios are even higher than those reported in previous studies. We think that the most important reason for these higher rates are because our study included only adolescents, not the children. Adolescence is the last period of childhood; in which the child has weaker impulse control, more oppositional behavior, and refuses external parental control. Therefore, diabetes management becomes more difficult and deterioration in treatment adherence is more evident in the adolescence period. As a matter of fact, we found that a significant portion of the patients participating in our study had no regular clinic follow-ups and in a significant portion diet adherence was poor, which indicates their poor disease management. Disease management is important for the prognosis of the disease. Any difficulty in adaptation to disease and its treatment leads to deterioration in this process. In T1DM, disease management itself is reported to cause additional problems in the form of emotional and psychological difficulties (3). Managing T1DM in the presence of anxiety is challenging. In our study, we found that emotional problems were more common in adolescents with T1DM. Moreover, those who refused insulin injections, had irregular follow-ups, diabetes complications, and were recently hospitalized had higher emotional problems. In other words, we showed that those with poor diabetes

Table 4. In the patient group; examination of the relationship between disease characteristics and the status of having significant scores of SCARED, CDI and EAT

		DM-group (n=72)					
		Significant score for SCARED		Significant score for CDI		Significant score for EAT	
		Present	Absent	Present	Present	Absent	Present
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Person who makes he insulin injections	Patient himself/ herself	22 (50.0)	22 (50.0)	16 (36.4)	28 (63.6)	8 (18.2)	36 (81.8)
	Parents	12 (60.0)	8 (40.0)	4 (20.0)	16 (80.0)	10 (50.0)	10 (50.0)
	Mixed	4 (50.0)	4 (50.0)	6 (75.0)	2 (25.0)	4 (50.0)	4 (50.0)
	p	[d]**0.781**		[b]**0.024***		[b]**0.017***	
Child's diet adherence (depending on parental report)	Never	8 (66.7)	4 (33.3)	8 (66.7)	4 (33.3)	2 (16.7)	10 (83.3)
	Sometimes	16 (47.1)	18 (52.9)	10 (29.4)	24 (70.6)	6 (17.6)	28 (82.4)
	Generally	12 (66.7)	6 (33.3)	6 (33.3)	12 (66.7)	6 (33.3)	12 (66.7)
	Always	2 (25.0)	6 (75.0)	2 (25.0)	6 (75.0)	8 (100)	0 (0)
	p	[d]**0.162**		[d]**0.134**		[d]**0.001****	
Adolescents' rejection of the insulin injections (depending on parental report)	Never happens	18 (36.0)	32 (64.0)	12 (24.0)	38 (76.0)	18 (36.0)	32 (64.0)
	Rarely	8 (100)	0 (0)	6 (75.0)	2 (25.0)	0 (0)	8 (100)
	Sometimes	12 (85.7)	2 (14.3)	8 (57.1)	6 (42.9)	4 (28.6)	10 (71.4)
	p	[b]**0.001****		[d]**0.004****		[d]**0.113**	
Regular follow-up	Absent	18 (69.2)	8 (30.8)	16 (61.5)	10 (38.5)	6 (23.1)	20 (76.9)
	Present	20 (43.5)	26 (56.5)	10 (21.7)	36 (78.3)	16 (34.8)	30 (65.2)
	p	[b]**0.036***		[b]**0.001****		[b]**0.300**	
Coplications	Absent	32 (50.0)	32 (50.0)	20 (31.3)	44 (68.8)	18 (28.1)	46 (71.9)
	Present	6 (75.0)	2 (25.0)	6 (75.0)	2 (25.0)	4 (50.0)	4 (50.0)
	p	[e]**0.267**		[e]**0.023***		[e]**0.237**	
Hospitalization due to diabetes in the previous 3 months	Absent	28 (46.7)	32 (53.3)	14 (23.3)	46 (76.7)	20 (33.3)	40 (66.7)
	Present	10 (83.3)	2 (16.7)	12 (100)	0 (0)	2 (16.7)	10 (83.3)
	p	[b]**0.020***		[e]**0.001****		[e]**0.322**	

[a]Student's t-test, [b]Pearson chi-square test, [d]Fisher-Freeman-Halton Exact test, [e]Fisher's Exact test, *p<0.05, **p<0.01
CDI: Children's Depression inventory, SCARED: Screen for Child Anxiety Related Disorders, EAT: Eating Attitude test

management had a higher risk of emotional problems. This finding, which shows the relationship between emotional problems and poor disease management, supports the literature knowledge. Another important finding on the emotional state of these adolescents was that those with separate parents and low parental education had more emotional problems. Childhood adversities are important risk factors for psychopathology. Our findings related to family characteristics drew attention to the importance of the evaluation of adolescents with their families, not alone, in their clinical follow-ups. If negative familial factors are identified, early interventions will be valuable for the psychosocial and so for the physical health of the adolescent.

Eating problems are increased in T1DM patients (12,13). Bernstein et al. (21) reported that among T1DM patients 20.7% had irregular eating attitudes. Scheuing et al. (23) demonstrated that among 52,215 patients with diabetes 467 had clinical ED diagnosis. In our study, the eating problem was significantly higher in adolescents diagnosed with T1DM compared with their healthy peers. Almost one-third of the cases had eaten problems. Our finding related to the association of eating problems with some sociodemographic factors was striking. Eating problems

were similar to ratio in both genders but were increasing in frequency with age and were associated with low parental education level. In general, disordered eating symptoms are more common in girls, especially between the ages of 13 and 14 for girls and over 16 for boys (13,24). In T1DM, female gender and increasing age have been reported to be associated with increased risk of irregular eating behavior (25). In the presence of T1DM, there is an excessive family focus on food and weight (12). This excessive mental focus on food and feeding and weight is among the major risk factors for EDs. Our finding related to parental education level is contrary to the literature. In the general population, ED is more common in patients with higher educational levels. In particular, poorer communication with parents and poorer trust relationships were reported among girls with T1DM than those with EDs (26). We thought that the relationship between low parental education and eating problems may be due to an indirect link; low parental educational level may cause negative consequences such as problems in parent-adolescent communication, conflict, and low parental involvement in the care of adolescents, which further lead to eating problems in our participants.

The last important finding of this study showed that adolescents with T1DM had a higher risk for eating problems compared with their healthy peers. Besides, depressive mood, strict adherence to diet, and not taking the primary responsibility for insulin injections were the associated factors for this increased risk. We think that there may be various reasons why T1DM carries an extra risk in terms of EDs in adolescence. T1DM management requires focusing on timing and content of meals and calori monitoring. Inappropriate approaches in this, by health services or parents, may predispose the patient to malfunctioning eating patterns. Because in the etiopathogenesis of ED there is over focusing on body image and appearance and preoccupations with content and calori of meals are the main symptoms. It has been shown that higher levels of health and food-related anxiety may lead to ED. Similarly, psychiatric disorders such as depression and anxiety are risk factors for ED in T1DM-diagnosed adolescents (13,24). In particular, early recognization and treatment of emotional problems will enable early handling of EDs, which makes diabetes management more difficult. The fact that eating problems are higher in those with strict diet compliance draws attention to the presence of food and diet-related concerns that these patients and their parents frequently experience.

There are certain limitations to our study. Not evaluating the height, weight, and body mass indexes of the adolescents included in the study and the eating behaviors of their families can be stated as a limitation.

CONCLUSION

Treatment of T1DM requires adherence to medication and diet. However, the chronic course of T1DM, including a restricted diet and frequent interventional procedures, may cause difficulties for the patient in a psychosocial context. This study demonstrated that T1DM adolescents are at high risk for EDs and emotional problems. Further analysis showed that increasing age, lower parent education, lack of responsibility for insulin therapy, strict adherence to diabetic diet and depressive symptoms were the associated risks for ED in T1DM. EDs should be given extra attention for T1DM because its treatment is diet dependent and any difficulty in the diet will worsen the patients clinic. Therefore, the awareness of these factors in clinical settings is important. In the clinical follow-up of adolescents with T1DM, it is important to assess their emotional state, eating habits, and attitudes apart from physical well-being and laboratory findings. Besides pediatric professionals, primary healthcare providers can provide close monitoring and support to adolescents with diabetes. Early screening for psychiatric comorbidity in chronic diseases and regular follow-up from diagnosis is necessary for the clinical outcome of the disease. In T1DM adolescents, it is important to direct the cases at risk in terms of emotional and eating problems to mental health specialists as soon as possible.

ETHICS

Ethics Committee Approval: The questionnaire and methodology for this study the decision number 2020-22-32 (date: 02.11.2020) were obtained from the Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital.

Informed Consent: Written and verbal consent was obtained from all participants and their parents.

Authorship Contributions

Surgical and Medical Practices: Ö.P., S.Y., E.P.Ç., Concept: Ö.P., S.Y., E.P.Ç., Design: Ö.P., S.Y., E.P.Ç., Data Collection or Processing: Ö.P., S.Y., E.P.Ç., Analysis or Interpretation: Ö.P., S.Y., E.P.Ç., Literature Search: Ö.P., S.Y., E.P.Ç., Writing: Ö.P., S.Y., E.P.Ç.

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REFERENCES

1. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet 2014;383:69-82.
2. International Diabetes Federation. IDF Diabetes Atlas, 9th ed. Brussels, Belgium: 2019. Accessed on: 01.02.2020. Available from: https://www.diabetesatlas.org.
3. McGrady ME, Peugh JL, Hood KK. Illness representations predict adherence in adolescents and young adults with type 1 diabetes. Psychol Health 2014;29:985-98.
4. McCall AL, Farhy LS. Treating type 1 diabetes: from strategies for insulin delivery to dual hormonal control. Minerva Endocrinol 2013;38:145-63.
5. Khandelwal S, Sengar GS, Sharma M, Choudhary S, Nagaraj N. Psychosocial Illness in Children with Type 1 Diabetes Mellitus: Prevalence, Pattern and Risk Factors. J Clin Diagn Res 2016;10:SC05-8.
6. Goad K. Examining the Mental Health Issues Prevalent in Adolescent Type-1 Diabetics: An Evidence-Based Review to Improve Health. J Diabetes Metab 2015;6:599.
7. McGrady ME, Hood KK. Depressive symptoms in adolescents with type 1 diabetes: associations with longitudinal outcomes. Diabetes Res Clin Pract 2010;88:e35-7.
8. Fritsch SL, Overton MW, Robbins DR. The interface of child mental health and juvenile diabetes mellitus. Child Adolesc Psychiatr Clin N Am 2010;19:335-52.
9. Almeida MC, Claudino DA, Grigolon RB, Fleitlich-Bilyk B, Claudino AM. Psychiatric disorders in adolescents with type 1 diabetes: a case-control study. Braz J Psychiatry 2018;40:284-9.
10. Hilbert A, Pike KM, Goldschmidt AB, Wilfley DE, Fairburn CG, Dohm FA, et al. Risk factors across the eating disorders. Psychiatry Res 2014;220:500-6.
11. Colton PA, Olmsted MP, Daneman D, Rodin GM. Depression, disturbed eating behavior, and metabolic control in teenage girls with type 1 diabetes. Pediatr Diabetes 2013;14:372-6.
12. Pinhas-Hamiel O, Hamiel U, Levy-Shraga Y. Eating disorders in adolescents with type 1 diabetes: Challenges in diagnosis and treatment. World J Diabetes 2015;6:517-26.
13. Toni G, Berioli MG, Cerquiglini L, Ceccarini G, Grohmann U, Principi N, et al. Eating Disorders and Disordered Eating Symptoms in Adolescents with Type 1 Diabetes. Nutrients 2017;9:906.
14. Commissariat PV, Laffel LM, Gonzalez JS. Identity and treatment adherence in predominantly ethnic minority teens and young adults with type 1 diabetes. Pediatr Diabetes 2020;21:53-60.
15. Kovacs M. Rating scales to assess depression in school-aged children. Acta Paedopsychiatr 1981;46:305-15.
16. Oy B. Çocukluk depresyonu; Tarihçe, sınıflandırma ve tanı ölçütleri. Türk Psikiyatri Dergisi 1990;1:21-4.
17. Birmaher B, Brent DA, Chiappetta L, Bridge J, Monga S, Baugher M. Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study. J Am Acad Child Adolesc Psychiatry 1999;38:1230-6.
18. Cakmakcı FK. Çocuklarda anksiyete bozukluklarını tarama ölçeği geçerlik ve güvenirlik çalışması. Çocuk ve Gençlik Ruh Sağlığı Dergisi, 11(2).
19. Garner DM, Garfinkel PE. The Eating Attitudes Test: an index of the symptoms of anorexia nervosa. Psychol Med 1979;9:273-9.
20. Savasir I, Erol N. Yeme tutum testi: anoreksiyanervoza belirtileri indeksi. Türk Psikoloji Dergisi 1989;7:19–25.
21. Bernstein CM, Stockwell MS, Gallagher MP, Rosenthal SL, Soren K. Mental health issues in adolescents and young adults with type 1 diabetes: prevalence and impact on glycemic control. Clin Pediatr (Phila) 2013;52:10-5.
22. Buchberger B, Huppertz H, Krabbe L, Lux B, Mattivi JT, Siafarikas A. Symptoms of depression and anxiety in youth with type 1 diabetes: A systematic review and meta-analysis. Psychoneuroendocrinology 2016;70:70-84.
23. Scheuing N, Bartus B, Berger G, Haberland H, Icks A, Knauth B, et al. Clinical characteristics and outcome of 467 patients with a clinically recognized eating disorder identified among 52,215 patients with type 1 diabetes: a multicenter german/austrian study. Diabetes Care 2014;37:1581-9.
24. Calcaterra V, Mazzoni C, Ballardini D, Tomba E, Zuccotti GV, Mameli C, et al. Disturbed Eating Behaviors in Youth with Type 1 Diabetes: An Exploratory Study about Challenges in Diagnosis. Diagnostics (Basel) 2020;10:1044.
25. Tokatly Latzer I, Rachmiel M, Zuckerman Levin N, Mazor-Aronovitch K, Landau Z, Ben-David RF, et al. Increased prevalence of disordered eating in the dual diagnosis of type 1 diabetes mellitus and celiac disease. Pediatr Diabetes 2018;19:749-55.
26. Maharaj SI, Rodin GM, Olmsted MP, Daneman D. Eating disturbances, diabetes and the family: an empirical study. J Psychosom Res 1998;44:479-90.

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Research

Erysipelas-like Erythema: A Pathognomonic Rash in Children with Familial Mediterranean Fever

Erizipel Benzeri Eritem: Ailevi Akdeniz Ateşi Tanılı Çocuklarda Patognomonik Bir Döküntü

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ABSTRACT

Objective: Familial Mediterranean fever (FMF) is the most common genetic autoinflammatory disease presenting as recurrent fever episodes, and inflammation of serosal surfaces, joints, and skin. During attacks, erysipelas-like erythema (ELE) may occur on the dorsum of the foot, ankle, or lower leg. Although the skin involvement is less common, ELE is pathognomonic. We aimed to review the frequency and characteristics of ELE in children diagnosed with FMF and to identify genotypic and phenotypic differences between patients with and without ELE, if any.

Methods: This study included children aged 0-18 years diagnosed with FMF followed up by two tertiary pediatric rheumatology units. The data were collected by two pediatric rheumatology fellows from the patients' files and electronic records. We divided the cohort into two groups according to whether they had ELE. Those with ELE were included in group 1 and those without ELE were in group 2.

Results: Two thousand-three patients participated in the study. There were 197 (9.8%) patients with ELE in group 1 and 1806 (90.1%) patients without ELE in group 2. The mean age of onset of symptoms in group 1 was significantly lower than in group 2 [4.85 (minimum-maximum: 0.1-17) vs. 5.98 (minimum-maximum: 0.1-17) years, p<0.001]. The median age at diagnosis was significantly higher in group 1 [8 (0.6-18) vs. 6 (0.5-18) p<0.001]. The diagnostic delay time was 24 months in group 1, 13 months in group 2, and the duration was significantly longer in group 1 [24 (0-150) vs. 13 (0-192) p<0.001]. M694V homozygosity was more frequent in group 1 [n=116 (58.9%), n=484 (26.8%), p<0.001].

Conclusion: Because ELE is an uncommon clinical presentation, clinicians should be alert. The clinical course of patients presenting with ELE may have a more severe disease course.

Keywords: Familial Mediterranean fever, erysipelas-like erythema, genotype

ÖZ

Amaç: Ailevi Akdeniz ateşi (AAA), periyodik ateş atakları ile karakterize, ataklarda serozal yüzeyler, eklemler ve deride enflamasyonun görüldüğü, en yaygın monogenik otoenflamatuvar hastalıktır. Ataklar sırasında ayak sırtında, ayak bileğinde veya alt bacakta erizipel benzeri eritem (ELE) oluşabilir. Deri bulguları daha nadir görülmekle birlikte, ELE AAA atağı için patognomonik bir bulgudur. Bu çalışma ile, pediatrik AAA hastalarından oluşan geniş bir kohortta ELE'nin sıklığını ve özelliklerini gözden geçirmeyi, ELE bulgusu olan ve olmayan hastalar arasındaki genotipik ve fenotipik farklılıkları belirlemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya iki üçüncü basamak pediatrik romatoloji ünitesinde izlenen AAA tanısı ile takip edilen, 0-18 yaş aralığındaki çocuklar dahil edildi. Veriler, iki pediatrik romatoloji uzmanı tarafından hasta dosyalarından ve elektronik kayıtlardan toplandı. Hastalar ELE bulgusu olan ve olmayanlar şeklinde iki ana gruba ayrılarak değerlendirildi.

Bulgular: İki bin üç hasta çalışmaya dahil edildi. Grup 1'de ELE bulgusu olan 197 (%9,8) hasta varken grup 2'de ELE bulgusu olmayan 1806 (%90,1) hasta vardı. Grup 1'de ortalama semptom başlama yaşı daha küçük iken, ortanca tanı yaşı anlamlı olarak daha büyüktü [4,85 (minimum-maksimum: 0,1-17) vs. 5,98 (minimum-maksimum: 0,1-17) yaş, p<0,001; 8'e (0,6-18) karşı 6 (0,5-18) p<0,001]. Tanı gecikme süresi grup 1'de 24 ay, grup 2'de 13 ay ve grup 1'de anlamlı olarak daha uzundu [24 (0-150) vs. 13 (0-192) p<0,001]. Gruplar genotip açısından karşılaştırıldığında M694V homozigotluğu grup 1'de anlamlı olarak daha fazlaydı [n=116 (%58,9), n=484 (%26,8), p<0,001].

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Sonuç: ELE nadir görülen bir klinik bulgu olduğu için, klinisyenlerin farkındalığının yüksek olması önemlidir. ELE ile başvuran hastalar daha şiddetli bir hastalık seyrine sahip olabilir ve erken tanı önem arz etmektedir.

Anahtar Kelimeler: Ailevi Akdeniz ateşi, erizipel benzeri eritem, genotip

INTRODUCTION

Familial Mediterranean fever (FMF) is one of the most common inherited periodic fever syndromes among people of Mediterranean and Middle Eastern descent. The main features of the disease are fever, abdominal pain, and arthritis or erysipelas-like skin disease (1). The major features of FMF are recurrent fever, abdominal pain, and arthritis or erysipelas-like skin disease (2). Abdominal pain may occur abruptly before the fever, mimic appendicitis, and is accompanied by diarrhea. Monoarthritis is asymmetrical, comprises the ankle, knee, or wrist joint, and usually resolves within 5 to 14 days. An erysipelas-like erythema (ELE) is found on approximately 25% of the affected joint, and sometimes clinicians misdiagnose it as septic arthritis. The rash is especially unilateral and disappears in almost 2 to 3 days (3).

Various cutaneous manifestations have been noted in the literature in 25% to 47% of cases during attacks (4). Several types of skin lesions were associated with FMF, although ELE is an unusual but well-known pathognomonic and characteristic finding of FMF. Lesions are characterized by erythematous, tender, and warm plaques with bounded borders, usually triggered by physical effort. They may be mainly located on the dorsum of the foot, lower legs, and the medial malleolus (5). Fever and leukocytosis may accompany ELE and spontaneously subsides within 48 to 72 hours of bed rest. Apart from ELE, several skin manifestations have been described. These include diffuse erythema, urticaria, angioneurotic edema, mild desquamation, pyoderma, Raynaud phenomenon, subcutaneous nodules, and vasculitic skin lesions (6).

There is a remarkable lack of information about the characteristics of ELE in children with FMF. Since it is a pathognomonic skin lesion, it is crucial to define it in clinical practice and diagnostic approaches. We aimed to review the frequency and characteristics of ELE in a large pediatric FMF cohort and to identify genotypic and phenotypic differences between patients with and without ELE, if any.

METHODS

The study included children 0-18 years of age diagnosed with FMF who met at least one Tel-Hashomer or Eurofever/PRINTO 2019 diagnostic criteria and carried at least one mutation in exon 2, 3, 5, or 10 in the MEFV gene (7). We obtained data from the archives of two tertiary pediatric rheumatology units.

Patients' files and electronic records were evaluated by two pediatric rheumatology fellows. Clinical manifestations and laboratory features during attacks, attack-free periods, attack frequency, colchicine dose, family history of FMF and amyloidosis, parental consanguinity, genetic test results, treatments used, and presence of colchicine resistance were evaluated in detail.

All patients were receiving colchicine treatment. The dose of the colchicine regimen was 0.5 mg/day in patients <5 years, 1 mg/day in patients >5, <10 years, and 1.5 mg/day in patients >10 years. Children with prior complications (e.g., amyloidosis) or higher disease activity were given 2 mg of colchicine daily. Patients with subclinical inflammation and having one or more attacks per month (for at least three months) despite treatment with the maximum tolerable colchicine dose (for at least six months) were defined as colchicine-resistant (8). In colchicine-resistant children, anti-IL1 (anakinra, canakinumab) treatments were added to the existing treatment.

In the cohort, group 1 had patients who had experienced ELE during attacks and group 2 had patients who had never experienced ELE.

The study was approved by the Local Ethical Committee of İstanbul University, İstanbul Faculty of Medicine (decision no: 19, date: 21.08.2020).

Statistical Analysis

Microsoft Excel (Microsoft Corporation, Redmond, WA) and SPSS 28.0 (IBM, Armonk, NY) were used while collecting and analyzing the data. Visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) were used to determine whether the variables were normally distributed. Descriptive analysis was presented using proportions, medians, minimum (min), and maximum (max) values. Categorical data were statistically analyzed by chi-square analysis. Mann-Whitney U test was used to compare the non-normally distributed variables between the two independent groups. P values <0.05 were considered statistically significant.

RESULTS

A total of 2003 children were enrolled in the study. Nine hundred eighty-seven (49.2%) patients were male and 1016 (50.7%) were female. The median age at symptom onset was 4 (min-max: 0.1-17) years and the median age of diagnosis was 6 (0.5-18) years. Six hundred fifty (32.5%) patients had parental consanguinity. A family history of FMF was present in 1216 (60.6%) patients and a history of amyloidosis in 153 (7.6%) patients.

In the cohort, 197 (9.8%) patients were in group 1 and 1806 (90.1%) patients were in group 2. Demographic and clinical data of the groups were depicted in Table 1. There were 112 (56.9%) females in group 1 and 904 (50.1%) females in group 2, and the gender distribution was similar in both groups (female n=56.9 vs. 50.1%; male n=43.1 vs. 49.9% p=0.07). The mean age at onset of symptoms in group 1 was significantly lower than in group 2 [4.85 (min-max: 0.1-17) vs. 5.98 (min-max: 0.1-17) years, p<0.001]. The median age at diagnosis was significantly higher in group 1 [8 (0.6-18) vs. 6 (0.5-18) p<0.001]. The diagnostic delay duration was 24 months in group 1 and 13 months in group 2, and the duration was significantly longer in group 1 [24 (0-150) vs. 13 (0-192) p<0.001]. The prevalence of family history of amyloidosis and FMF was similar between the groups.

The annual number of attacks was evaluated and it was similar in both groups (12 vs. 12, p=0.76). When attack symptoms were evaluated; fever and abdominal pain were more frequent in group 2 [n=149 (75.6%) vs. n=1663 (92.1%), p<0.001; n=1153 (77.7%) vs. n=1672 (92.6%), p<0.001 respectively]. Chest pain, arthralgia, arthritis, persistent febrile myalgia, exercise-induced leg pain, and myalgia were significantly more frequent in group 1 [n=47 (23.9%) vs. n=318 (17.6%), p=0.03; n=164 (83.2%) vs. n=639 (35.4%), p<0.001;

Table 1. The demograhic and clinical characteristics of the patients

		Patients with erysipelas-like erythema (n=197)	Patients without erysipelas-like erythema (n=1806)	p-value
Demographic features				
Gender Female Male		112 (56.9) 85 (43.1)	904 (50.1) 902 (49.9)	0.07
Age of onset (years)	Min-max (mean)	0.1-17 (4.85)	0.1-17 (5.98)	<0.001
Age of diagnosis (years)	Min-max (median)	0.6-18 (8)	0.5-18 (6)	<0.001
Delay in diagnosis (months)	Min-max (median)	0-150 (24)	0-192 (13)	<0.001
Diagnosis of FMF in family	n (%)	118 (59.9)	1096 (60.7)	0.83
Diagnosis of amyloidosis in family	n (%)	21 (10.7)	132 (7.3)	0.93
Clinical features				
The annual number of attacks	Min-max (median)	0-48 (12)	0-48 (12)	0.76
Fever	n (%)	149 (75.6)	1663 (92.1)	<0.001
Abdominal pain	n (%)	153 (77.7)	1672 (92.6)	<0.001
Chest pain	n (%)	47 (23.9)	318 (17.6)	0.031
Arthralgia	n (%)	164 (83.2)	639 (35.4)	<0.001
Arthritis	n (%)	142 (72.1)	296 (16.4)	<0.001
Persistant febril myalgia	n (%)	9 (4.6)	24 (1.3)	0.01
Pericarditis	n (%)	4 (2)	11 (0.6)	0.052
Exertional leg pain	n (%)	81 (41.1)	288 (15.9)	<0.001
Myalgia	n (%)	81 (41.1)	366 (20.3)	<0.001
Amyloidosis	n (%)	1 (0.5)	5 (0.3)	0.46
Colchicine resistance	n (%)	18 (9.1%)	89 (4.9%)	0.013

FMF: Familial Mediterranean fever, Min-max: Minimum-maximum

n=142 (72.1%) vs. n=296 (16.4%), p<0.001; n=9 (4.6%), n=24 (1.3%) p=0.01; n=81 (41.1%), n=288 (15.9%), p<0.001; n=81 (41.1%), n=366 (20.3%), p<0.001; respectively]. Pericarditis was observed with similar frequency in both groups [n=4 (2%) vs. n=11 (0.6%), p=0.052].

All patients received colchicine therapy, and colchicine resistance was significantly more common in group 1 [n=18 (9.1%) vs. n=89 (4.9%), p=0.013]. When the genotype of patients was compared, M694V homozygosity was more common in group 1 [n=116 (58.9%), n= 484 (26.8%), p<0.001].

DISCUSSION

In this study, ELE was detected as a relatively uncommon finding in a large cohort of FMF, but it was a distinctive presentation. While the most common findings in typical FMF attacks were abdominal pain and fever, they were less frequent in those with ELE compared with others. The age of the onset of symptoms was lower and the age of diagnosis was higher in the ELE group. Since the diagnostic delay is longer, we can assume that it is more challenging to diagnose FMF in the ELE group. Exertional leg pain, arthralgia, myalgia, and persistent febrile myalgia, which are not among the classification criteria, were more common in the ELE group. The reason for the delay in diagnosis may be attributed to the fact that the patients presenting with these findings did not fulfill the diagnostic criteria. Since M694V homozygosity is more common in the ELE group, a delay in diagnosis is definitely not desired because homozygous cases have a more severe clinical course (9). It is crucial to reveal the phenotypic and genotypic characteristics of patients with ELE in terms of difficulty in diagnosis, delay in diagnosis, and prevention of morbidity.

In previous reports, ELE is notably associated with a more severe FMF clinical phenotype, M694V homozygosity, and even amyloidosis (6,10,11). Avar-Aydın et al. (10) revealed higher frequencies of biallelic exon 10 and homozygous M694V mutations in patients with ELE. They also reported that subclinical inflammation was more common in the ELE group and that patients presenting with ELE received higher doses of colchicine (10). Gezgin Yildirim et al. (12) evaluated the genotype in both groups with or without ELE and reported that M694V homozygosity was more common in the ELE group, similar to our study. They also revealed that the median colchicine dose and PRAS activity scores were higher at the final visit in patients with ELE (12). The fact that genotypic correlations associated with severe clinical courses are more common in patients presenting with ELE indicates that this patient group is a candidate for a more severe disease course. For this reason, it is essential to be vigilant in the diagnosis and follow-up of these patients. In a recent study, a novel model was built, and ELE was scored as 2 points in the scoring system to predict colchicine resistance in children with FMF (13).

ELE is an unusual but well-known pathognomonic skin manifestation of FMF (5). ELE is more common in the Turkish population and in the early phase of the disease course (11). In our cohort, the median age at diagnosis was 8 years in patients with ELE. Lesions resemble erysipelas or cellulitis, and differential diagnosis may be difficult in patients without unique clinical findings during an attack. Some features that distinguish ELE from other infectious diseases are as follows; the duration is shorter (average 4 days), it is not always accompanied by fever, it can be seen in both feet at the same time and heals spontaneously (14). When the lesion can not be distinguished from a lesion of infectious origin erysipelas, family history of FMF, detailed history of the patient, and recurrent course of the disease gain importance. In our cohort, nearly 60% of patients presenting with ELE had a family history of FMF. Being able to recognize clues during follow-up enables an early diagnosis and appropriate treatment. The delay in diagnosis was longer in the group presenting with ELE in our cohort. If we raise the awareness of pediatricians, it may influence timely diagnosis.

In this cohort, we found a similar rate of ELE (9.8%) compared to pediatric studies in our country (9,10,12,15). Öztürk et al. (15) reported abdominal pain and fever as the most common attack symptoms in their cohort. In our cohort, the rates of these symptoms were slightly higher in patients not presenting with ELE and lower in patients presenting with ELE. As reported in the literature, arthritis was more common in patients presenting with ELE in our study (10,12). In addition, arthralgia, myalgia, and prolonged febrile myalgia were also more common in the ELE group in the current study.

The retrospective design was the major limitation. There were missing data on disease severity assessment tools and acute phase reactants. Despite these, it was the largest cohort of pediatric FMF patients assessed for the presence of ELE.

CONCLUSION

ELE is an uncommon clinical presentation, and patients presenting with ELE may have different phenotypic and genotypic characteristics. We should be alert and keep in mind that the clinical course of patients presenting with ELE may have a more severe disease course. A detailed history and comprehensive physical examination are required for an accurate and timely diagnosis.

ETHICS

Ethics Committee Approval: The study was approved by the Local Ethical Committee of İstanbul University, İstanbul Faculty of Medicine (decision no: 19, date: 21.08.2020).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: F.Ç., S.D.A., G.K.K., Ş.Ç., K.U., T.C., A.T., B.S., N.A.A., Concept: F.Ç., B.S., N.A.A., Design: F.Ç., N.A.A., Data Collection or Processing: F.Ç., S.D.A., G.K.K., Ş.Ç., K.U., T.C., A.T., Analysis or Interpretation: F.Ç., S.D.A., G.K.K., Ş.Ç., K.U., T.C., Literature Search: F.Ç., Writing: F.Ç., N.A.A.

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REFERENCES

1. Krainer J, Siebenhandl S, Weinhäusel A. Systemic autoinflammatory diseases. J Autoimmun 2020;109:102421.
2. Lachmann HJ. Periodic fever syndromes. Best Pract Res Clin Rheumatol 2017;31:596-609.
3. Long SS. Distinguishing among prolonged, recurrent, and periodic fever syndromes: approach of a pediatric infectious diseases subspecialist. Pediatr Clin North Am 2005;52:811-35.
4. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine (Baltimore) 2005;84:1-11.
5. Barzilai A, Langevitz P, Goldberg I, Kopolovic J, Livneh A, Pras M, et al. Erysipelas-like erythema of familial Mediterranean fever: clinicopathologic correlation. J Am Acad Dermatol 2000;42:791-5.
6. Koné Paut I, Dubuc M, Sportouch J, Minodier P, Garnier JM, Touitou I. Phenotype-genotype correlation in 91 patients with familial Mediterranean fever reveals a high frequency of cutaneomucous features. Rheumatology (Oxford) 2000;39:1275-9.
7. Gattorno M, Hofer M, Federici S, Vanoni F, Bovis F, Aksentijevich I, et al. Classification criteria for autoinflammatory recurrent fevers. Ann Rheum Dis 2019;78:1025-32.
8. Ozen S, Demirkaya E, Erer B, Livneh A, Ben-Chetrit E, Giancane G, et al. EULAR recommendations for the management of familial Mediterranean fever. Ann Rheum Dis 2016;75:644-51.
9. Ayaz NA, Tanatar A, Karadağ ŞG, Çakan M, Keskindemirci G, Sönmez HE. Comorbidities and phenotype-genotype correlation in children with familial Mediterranean fever. Rheumatol Int 2021;41:113-20.
10. Avar-Aydın PÖ, Ozcakar ZB, Aydın F, Karakaş HD, Çakar N, Yalçınkaya F. Erysipelas-Like Erythema: A Manifestation of Severe Disease Phenotype in Pediatric Patients with Familial Mediterranean Fever. Turk Arch Pediatr 2022;57:599-602.
11. Ureten K, Gönülalan G, Akbal E, Güneş F, Akyürek O, Ozbek M, et al. Demographic, clinical and mutational characteristics of Turkish familial Mediterranean fever patients: results of a single center in Central Anatolia. Rheumatol Int 2010;30:911-5.
12. Gezgin Yildirim D, Seven MB, Gönen S, Söylemezoğlu O. Erysipelas-like erythema in children with familial Mediterranean fever. Clin Exp Rheumatol 2020;127:101-4.
13. Ayaz NA, Demirkan FG, Coşkuner T, Demir F, Tanatar A, Çakan M, et al. PREDICT-crFMF score: a novel model for predicting colchicine resistance in children with familial Mediterranean fever. Mod Rheumatol 2023:road008.
14. Mengi A, Özdolap Ş. Familial Mediterranean fever with recurrent erysipelas-like erythema and myalgia: A case report. Turk J Phys Med Rehabil 2018;64:366-8.
15. Öztürk K, Coşkuner T, Baglan E, Sönmez HE, Yener GO, Çakmak F, et al. Real-Life Data From the Largest Pediatric Familial Mediterranean Fever Cohort. Front Pediatr 2022;9:805919.

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Research

Clinical and Molecular Findings of Nine Cases with Tay-Sachs Disease From Türkiye

Tay-Sachs Hastalığı Olan Türkiye'den Dokuz Olgunun Klinik ve Moleküler Bulguları

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ABSTRACT

Objective: Tay-Sachs disease is a fatal inherited lysosomal storage disease that mostly has an early infantile onset. We presented a case series of Tay-Sachs disease, describe the clinical and molecular findings, and compare the genetic spectrum with previously reported mutations from Türkiye.

Methods: Patients with Tay-Sachs disease who were referred to the İstanbul University, İstanbul Faculty of Medicine, Department of Medical Genetics between January 2016 and December 2021 were included in this study. The diagnosis was confirmed by determining the level of serum β-hexosaminidase activity and the detection of a biallelic related variant upon Sanger sequencing of the *HEXA* gene. The clinical and molecular findings of nine cases were re-evaluated.

Results: Three disease-causing variants in the *HEXA* gene including c.78G>A (p.(Trp26Ter)) in three cases, c.1177C>T (p.(Arg393Ter)) in two cases, and c.1100_1111del (p.(Gly367_Tyr370del)) in three cases were determined. Moreover, a novel c.786C>G (p.(His262Gln)) variant was detected in one case. All of the stated variants were identified in the homozygous state.

Conclusion: Our study both reassessed and expanded the known mutation spectrum of Tay-Sachs disease in Türkiye. Given the expanding horizon of newborn screening and population carrier testing, understanding the spectrum of population-specific disease-causing variants will facilitate early diagnosis of patients and carriers.

Keywords: *HEXA* gene, Tay-Sachs disease, neurometabolic diseases

ÖZ

Amaç: Tay-Sachs hastalığı, çoğunlukla erken infantil başlangıçlı, ölümcül kalıtsal bir lizozomal depo hastalığıdır. Tay-Sachs hastalığı olan bir olgu serisini sunmayı, klinik ve moleküler bulguları tanımlamayı ve Türkiye'den daha önce bildirilen mutasyonlarla genetik spektrumu karşılaştırmayı amaçladık.

Gereç ve Yöntem: Bu çalışmaya Ocak 2016-Aralık 2021 tarihleri arasında İstanbul Üniversitesi, İstanbul Tıp Fakültesi, Tıbbi Genetik Anabilim Dalı'na refere edilen Tay-Sachs hastalığı olan olgular dahil edildi. Tanı, serum β-hekzosaminidaz enzim aktivitesi ve *HEXA* geni Sanger dizi analizinde biallelik hastalıkla ilişkili varyant saptanması ile doğrulandı. Tay-Sachs hastalığı olan dokuz olgunun klinik ve moleküler bulguları yeniden değerlendirildi.

Bulgular: *HEXA* geninde üç olguda c.78G>A (p.(Trp26Ter)), iki olguda c.1177C>T c.1177C>T (p.(Arg393Ter)) ve üç olguda c.1100_1111del (p.(Gly367_Tyr370del)) varyantları tespit edildi. Ayrıca bir olguda daha önce literatürde bildirilmeyen novel c.786C>G (p.(His262Gln)) değişimi saptandı. Tüm varyantlar olgularda homozigot olarak bulunmaktaydı.

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Sonuç: Çalışmamız, Türkiye'de Tay-Sachs hastalığının bilinen mutasyon spektrumunu hem gözden geçirmiş hem de genişletmiştir. Yenidoğan taraması ve popülasyon taşıyıcılık testinin genişleyen ufku göz önüne alındığında, popülasyona özgü hastalığa neden olan mutasyonların anlaşılması hastaların ve taşıyıcıların erken tespitini kolaylaştıracaktır.

Anahtar Kelimeler: *HEXA* geni, Tay-Sachs hastalığı, nörometabolik hastalıklar

INTRODUCTION

Tay-Sachs disease (TSD), a type of GM2-gangliosidosis, is an autosomal recessive, progressive neurodegenerative disease caused by β-hexosaminidase A (HEXA) deficiency. This lysosomal enzyme, necessary for degradation of gangliosides, is a heterodimer comprising α and β subunits encoded by the *HEXA* and *HEXB* genes, respectively. Biallelic mutations in the *HEXA* gene located at 15q23 are responsible for TSD disease in which only the β-hexosaminidase A isoenzyme becomes deficient. TSD is characterized by abnormal accumulation of gangliosides in neurons and retinal ganglion cells. Neuronal accumulation of GM2 gangliosides causes progressive loss of function in the central nervous system, whereas accumulation of GM2 in retinal ganglion cells leads to blindness (1).

The spectrum of TSD is classified into lethal infantile, juvenile, and adult forms based on the clinical presentation age (2). The most common form, generally known as the classic or acute-infantile form, results from a complete absence or extremely low level of enzyme activity and is characterized by onset before 6 months and rapidly progressive neurodegenerative clinical findings. Affected children show progressive weakness, loss of motor skills, hypotonia, increased or exaggerated startle response to loud sounds or other sudden stimuli, and myoclonic jerks between 3 and 6 months. Between 8 and 10 months, neuromotor regression, hypotonia with pyramidal findings, apathy, and decreased attentiveness is observed. Seizures and progressive macrocephaly occur in children after one year of age. The cases died in the first 4-5 years of their lives due of respiratory complications. Juvenile (subacute) and adult (late onset) forms are very rare with slower progression on a clinical course. The juvenile form is characterized by ataxia, dysarthria, and loss of independent ambulation starting after two years of age, following normal development. Tremor, psychiatric symptoms, or progressive neurogenic weakness are more common in the late-onset form, beginning in older teens or young adults.

The appearance of fundus -cherry red spot-refers to a reddish area of macula is characteristic for infantile form (3). Cranial magnetic resonance imaging (MRI) of infantile TSD shows symmetrical T2-weighted (T2W) hypointense and T1W hyperintense signals in the thalami, diffuse-progressive T2W hyperintensity in the cerebral white matter suggestive of demyelinating disorder, and cerebral atrophy in the later phase of disease (4,5).

The diagnosis of TSD is established with low HEXA activity on enzyme testing in serum or leukocytes (6). This can be confirmed by molecular genetic testing for mutations in the *HEXA* gene. The *HEXA* gene consists of 14 exons. To date, 182 mutations in the *HEXA* gene have been reported in the Human Genome Mutation Database (HGMD Professional 2021.2). In this study, the clinical, biochemical, and molecular results of nine patients were evaluated. Furthermore, the mutation spectrum profile of previously reported cases from Türkiye will be discussed.

METHODS

Cases with a definite diagnosis of TSD who were referred to the İstanbul University, İstanbul Faculty of Medicine, Department of Medical Genetics clinic between 2016 and 2021 were included in the study. The study was reviewed and approved by the İstanbul University, İstanbul Faculty of Medicine, Clinical Research Ethics Committee (decision no: 18, date: 07.10.2022) and written informed consent was obtained from all parents of the patients included in the study (no: 07.10.2022/1316113). Clinical, biochemical, and molecular findings of the patients were retrospectively reviewed. Low beta-beta-hexosaminidase A activity was demonstrated in all cases. DNA isolation (DNA Isolation Kit for Mammalian Blood, Roche Diagnostics/Elips-İstanbul) was performed from EDTA blood samples taken from nine cases and their parents. All encoded exons and exon-intron regions of the *HEXA* gene were Sanger sequenced (ABI 3500). Variants were cross-checked with ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and HGMD (http://www.hgmd.cf.ac.uk/ac/) databases. The novel variant was assessed using dbSNP, gnomAD (https://gnomad.broadinstitute.org), and Turkish Variome (TRV) (7). *In silico* prediction software, Mutation Taster (https://www.mutationtaster.org/), Sorting Intolerant From Tolerant (SIFT, https://sift.bii.a-star.edu.sg), and PolyPhen-2 HumVar (http://genetics.bwh.harvard.edu/pph2/) were used to predict

the pathogenicity. The American College of Medical Genetics and Genomics (ACMG 2015) classification was used for evaluation (8). The low activity of the HEXA enzyme in patients' plasma was consistent with TSD. Enzyme activity was determined as nmol/mL/h in cases 1 and 6 (İstanbul University, İstanbul Faculty of Medicine, Department of Medical Biochemistry) and as µmol/L/h in the remaining cases (Duzen Laboratory Group, Ankara, Türkiye). Diagnoses were determined by reduced HEXA activity characteristic clinical and molecular findings. We did not perform statistical analysis because we only had nine patients.

RESULTS

Clinical Findings

A total of nine patients (6 females and 3 males) from unrelated families diagnosed with infantile form-TSD were included in this study. There was a history of consanguineous marriage between the parents in eight cases. The remaining one family came from the same village. Also, a positive family history (affected siblings and/or cousins) was found in seven cases. All the families came from Türkiye the following cities; Tokat, Siirt, Nevşehir, Adana, Hakkari, Urfa and Sivas. The mean age of symptom onset was 7 months (range 3-9 months). Neuromotor regression was noted in seven of the nine cases (mean age of neuromotor regression is 8 months) and startle in the remaining 2 cases at 3 and 4 months. The age of definitive diagnosis, determined by low enzyme levels, ranged between 6 months and 20 months (mean age: 12.7 months). The delay between the first presentation signs and definitive diagnosis ranged from 1 month to 16 months in this case series (mean age: 5.7 months). While eight of nine patients had macrocephaly, head circumference was normal in the remaining one patient. All the cases except case 3 had cherry-red eye findings. All cases suffered from epilepsy as the disease progressed. Available cranial MRI from four cases (case 3-6) revealed T2 thalamic hypointensity, hyperintense signal changes in the basal ganglia and periventricular white matter (Figure 1). The patient demographics and clinical and molecular findings are summarized in Table 1.

Molecular Findings

Molecular genetic findings are presented in Table 1. Sequencing of the HEXA gene revealed three formerly known variants, including c.78G>A, c.1177C>T, and c.1100_1111del, in eight patients. In case 9, previously unreported c.786C>G variant was detected in homozygous form (Figure 2). The same variant was found to be homozygous in his similarly affected brother and heterozygous in his parents. According to ACMG criteria, variants received scores for PM2, PP2 and PP3 and were determined as Variants of Uncertain Significance. The functional effect was predicted to be disease causing by MutationTaster with a score of 0.9999, deleterious by SIFT with a score of 0.00 (<0.05 is predicted to be deleterious), and harmful by PolyPhen-2 HumVar with a score of 1 (1.0 is predicted to be deleterious).

DISCUSSION

In this study, we evaluated the clinical and molecular characteristics of nine cases of infantile TSD. The estimated incidence of TSD in Ashkenazi Jews was 1 in 3,600 compared to 1 in 360,000 in other populations, with carrier frequencies of 1 in 30 in Ashkenazi Jews and 1 in 300 in non-Jews, respectively (9). For our country, the incidence of TSD was calculated as 0.23 per 100,000 (10). The families in this case series come from the Black Sea, Mediterranean, Central Anatolia, and Southeastern Anatolia regions of our country. The absence of any cases in the Marmara, Aegean, and Eastern Anatolian regions can be explained by the distribution of consanguineous marriages in our country, rather than the low carrier rate of this disease in these regions. As in all autosomal recessive diseases, the incidence of this disease increases in places where consanguineous marriage is common. According to recent studies, the prevalence of consanguineous marriages in Türkiye is highest in the Southern Anatolian Region (44.8%) and least in the West Marmara Region (6.4%) (11), which follows the regional distribution in our case series.

All cases in our study had a history of consanguineous marriage between their parents, except one whose parents were from the same village. A positive family history (affected siblings and/or cousins) was also found in seven cases. Considering the families with a family history of TSD, the total number of confirmed cases of TSD in nine families was 12 (Figure 1). According to this finding, it can be predicted that the number of affected cases will decrease if appropriate genetic counseling and carrier screening are performed when TSD is diagnosed for the first time in the family. While evaluating the family pedigree in our case series, we encountered that the number of affected cases in nine families was so high -in total 21 cases-, including index cases. Because this disease has a fatal prognosis, it is essential to recognize it in countries like Türkiye with a high rate of consanguineous marriages. Although the diagnosis is made by the enzyme level, carriers of childbearing age can be detected only in the family by clarifying the molecular pathogenesis. In this case series, although four families had children with TSD before, they did not prefer prenatal

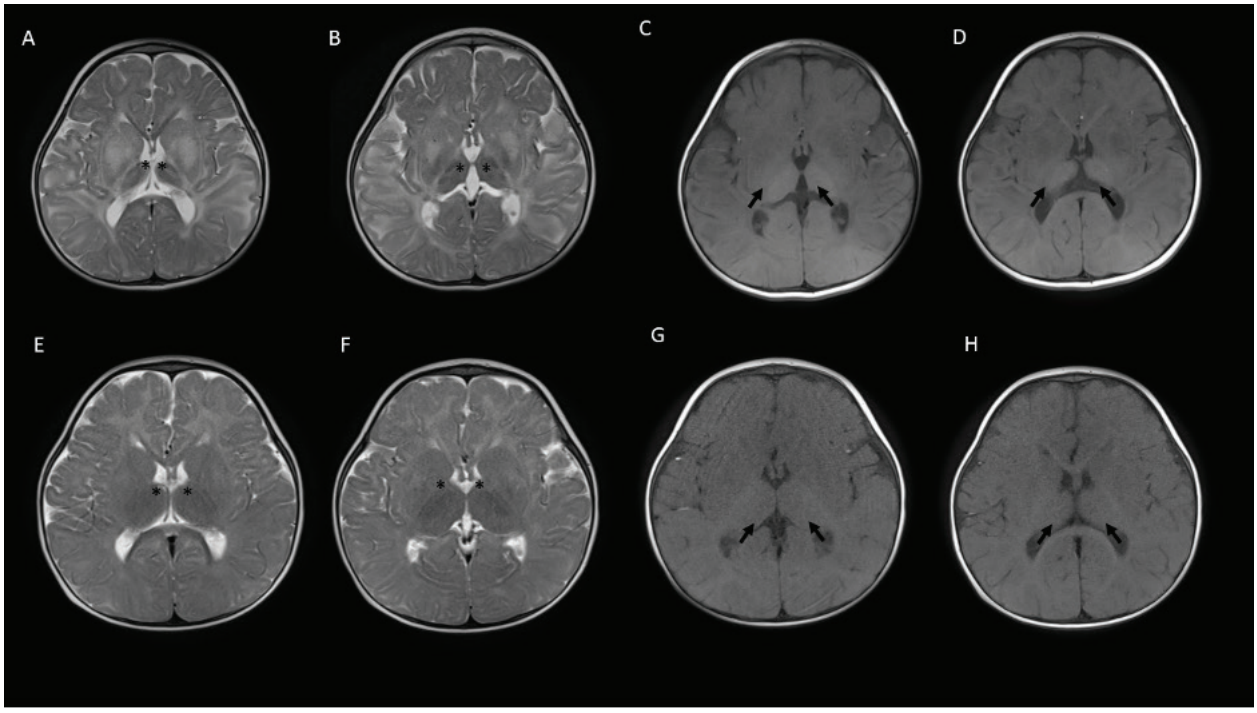

Figure 1. Cranial MRI findings in case 5 with TSD. At the age of 13 months (A-D), sagittal T2-weighted (T2W) images showed hyperintense signal changes in thalami in **A,B** (black asterisk) and sagittal T1W images showed hypointense signal changes in thalami in **C,D** (black arrow). At the age of 8 months (E-H), sagittal T2W images showed minimal hyperintense signal changes in thalami in **E,F** (black asteriskblack asterisk) and sagittal T1W images showed minimal hypointense signal changes in thalami in **G,H** (black arrow)

MRI: Magnetic resonance imaging, TSD: Tay-Sachs disease

diagnosis or preimplantation diagnosis. Even though there was a positive family history in seven cases, none of the cases were diagnosed before the symptoms.

The infantile form of TSD begins to manifest before six months of age, with neuromotor regression, hypotonia, and increased startle response (12). Smith et al. (13) reported that the mean age of first symptoms in 33 individuals with infantile TSD was 6.2 months (range 3-11), while according to a case series from Türkiye, the first symptoms began at 8.6 months of age (range 4-14 months for 8 cases) (14). As in the literature, the mean age at the first symptoms was 7 months (range 3-9 months) in our study. Neuromotor regression as the first symptom was observed in 7 of our 9 cases. The mean age of neuromotor regression was 15 and 12.3 months in cases from Iran and Türkiye, respectively (15,14). In this case series, the mean age of developmental regression was eight months, which is earlier than the literature.

TSD, like other sphingolipidoses, presents with neurodegenerative findings. While some clues or initial hallmarks may help in early diagnosis, ignoring these important symptoms may delay the diagnosis. Hypersensitivity to auditory stimuli and an exaggerated startle response are considered initial hallmarks for diagnosis. Positive family history can also increase the awareness of startle, which is an important helpful sign in the early diagnosis of cases. In the two cases (case 3 and case 4), the initial symptom was startle, noticed by the family, which started at four and three months, respectively. The earliest diagnosed case had a history of an affected brother, and the family had noticed the startle sign when he was three months old, and his diagnosed age five months. Another helpful clue is the doll face, which appears in six of our case series. This sign, typical for type 1 glycogen storage, can also be seen in Sandhoff disease (SD), another GM2 gangliosidosis associated with deficiencies in both HEXA and HEXB enzyme activity caused by mutations in the HEXB gene with neurodegenerative manifestations. Although SD is indistinguishable from TSD in terms of clinical course and ocular findings, hepatosplenomegaly seen in SD is typically absent in TSD (12). Because the cherry-red spot is found in lysosomal storage diseases, including TSD, SD, GM1 gangliosidoses, Niemann-Pick disease, Farber disease, metachromatic leukodystrophy, and sialidosis, all children with neuromotor regression require eye examination by an experienced ophthalmologist (16).

It has been reported in the literature that less than 10% of the cases does not have cherry red spots, as in this case series. This may be caused by poor technique or the loss of cherry-red appearance because of the wear of retinal ganglion

Table 1. Clinical, radiological, and molecular findings of our TSD cases

Case	Demographic findings consanguinity family history region	Presentation history age of onset presentation symptoms	Clinical findings	Cherry red sign	Diagnosis determined by biochemical results Age of diagnosis HEXA enzyme level	Mutation results
Case 1 [♀]	1.5° cousin one affected brother Tokat	7 months neuromotor regression	Hypotonia spasticity macrocephaly doll-like face	+	11 months 46.6 nmol/mL/h (n=163-527)	Homozygous c.78G>A (p. Trp26Ter)
Case 2 [♂]	2° cousin two affected siblings Siirt	9 months neuromotor regression	Hypotonia spasticity macrocephaly doll-like face	+	10 months 21.5 µmol/L/h (n=140-250)	Homozygous c.1177C>T (p.(Arg393Ter))
Case 3 [♂]	1.5° cousin no family history Nevşehir	4 months startle	Hypotonia macrocephaly doll-like face	-	20 months 10.9 µmol/L/h (n=140-250)	Homozygous c.78G>A (p.(Trp26Ter))
Case 4 [♀]	1° cousin one affected brother two affected cousins Adana	3 months startle	Hypotonia normocephaly doll-like face	+	6 months 2.3 µmol/L/h (n=140-250)	Homozygous c.1100_1111del12 (p.(Gly367_Tyr370del))
Case 5 [♀]	The same village one affected cousin Tokat	8 months neuromotor regression	Hypotonia spasticity macrocephaly doll-like face	+	14 months 6.10 µmol/L/h (n=140-250)	Homozygous c.78G>A (p.(Trp26Ter))
Case 6 [♀]	1.5° cousin two affected cousins Hakkari	7 months neuromotor regression	Hypotonia spasticity macrocephaly doll-like face	+	13 months 67 nmol/mL/h (n=140-250)	Homozygous c.1177C>T (p.(Arg393Ter))
Case 7 [♀]	1° cousin no family history Urfa	8 months neuromotor regression startle	Hypotonia macrocephaly spasticity	+	18 months 2.4 µmol/L/h (n=140-250)	Homozygous c. c.1100_1111del12 (p. Gly367_Tyr370del)
Case 8 [♀]	1° cousin two affected cousins Tokat	9 months neuromotor regression	Hypotonia macrocephaly spasticity	+	14 months 2.4 µmol/L/h (n=140-250)	Homozygous c. c.1100_1111del12 (p.(Gly367_Tyr370del))
Case 9 [♂]	1.5° cousin one affected brother Sivas	8 months neuromotor regression	Hypotonia macrocephaly	+	9 months 2.4 µmol/L/h (n=50-250)	Homozygous c.786C>G (p. (His262Gly))

cells in the advanced stage of the disease. Although almost all children with the infantile disease have a characteristic cherry-red macula, the last diagnosed case (case 3) had a normal 12-month-old eye examination. In case 3, the absence of cherry-red sign in eye examination at 12 months of age and the delay of the cranial MRI examination for up to 22 months due to the necessity of anesthesia led to a diagnostic delay for this case. His diagnosis was made by lysosomal scanning, with cranial MRI detecting symmetrical T2W hypointense and T1W hyperintense signals in the thalamus, diffuse progressive T2W hyperintensity suggesting demyelinating disorder in cerebral white matter (13). As in this case, cranial MRI findings are helpful in making the diagnosis. Although cranial imaging findings in TSD may vary during the clinical course of the disease process, especially in the early period of the disease, thalami may be hypointense on T2W images and hyperintense on T1W images due to the deposition of calcium. The combination of hyperdensity on T2W and hypointense signal involving bilateral thalami suggests TSD.

The definitive diagnosis of TSD in a clinically affected individual is established by demonstrating low HEXA activity and/or biallelic HEXA gene mutations. Gort et al. (12) reported that the age at diagnosis for 34 TSD cases was between 7 and 36 months. Similarly, in the case series reported from Türkiye, the mean age at diagnosis was 13.4 months (range 2-23) for nine TSD cases and 14.5 months for eight TSD cases (range 8-36) (14,17). The age of definitive diagnosis, determined by low enzyme levels, ranged

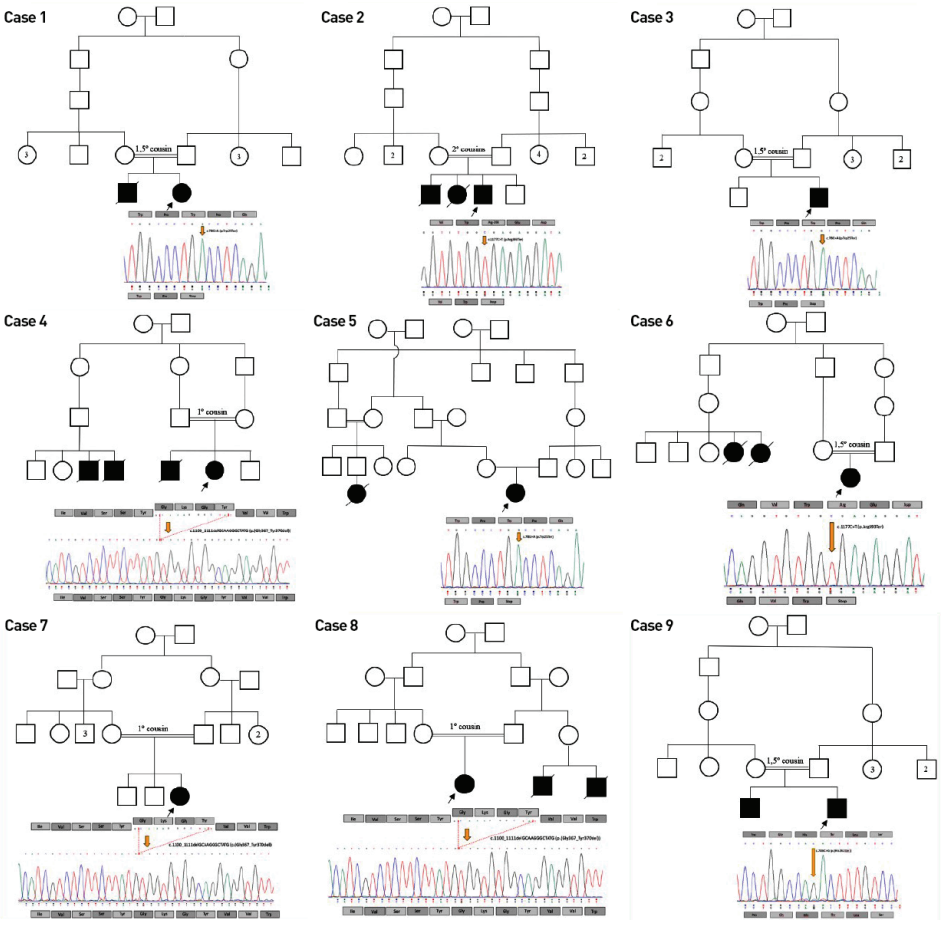

Figure 2. Pedigree analysis and molecular results of our cases

between 6 months and 20 months (mean age: 12.7 months) in our study compatible with the literature.

Since Ozkara et al. (18) described a homozygous mutation at the donor junction of intron 5 c.570+1G>A in the first Turkish patient with TSD in 1995, the following mutations have been reported, c.409C>T (p.(Arg137Term)), c.1177C>T (p.(Arg393Ter)), c.1100_1111del (p.(Gly367_Tyr370del)), c.1361G>A (p.(Gly454Asp)), c.412+1G>T (p.(*)), c.1510C>T (p. Arg504Cys)), c.78G>A (p.(Trp26Ter)), c.798G>C (p. Trp266Cys)), c.902T>G (p.(Met301Arg)) (14,17,19-24).

In our study, we identified three known variants, c.78G>A, c.1177C>T, and c.1100_1111del, and one novel variant, c.786C>G predicted pathogenic. According to the literature of cases from Türkiye, the most common associated variant in patients from Türkiye was found to be c.1100_1111del (p.(Gly367_Tyr370del)), a 12-bp deletion in exon 10 predicted to result in an in-frame deletion of four residues. This variant has been reported as c.1133_1144del or c.1096_1107del in previous publications. This variant has been corrected from publications to conform to the Human Genome Structural Variation nomenclature. The novel variant c.786C>G in case 9 was found to be compatible with the inheritance model, and clinical findings with in silico predictions supported that the c.786C>G variant is a novel disease-causing variant.

CONCLUSION

Because TSD is a well-known disease, cases with low beta-hexosaminidase A activity are often referred to genetic diagnosis centers for molecular genetic tests, and the diagnosis is confirmed by determining the mutation status. After the diagnosis of the case, families may not be able to receive genetic counseling because they deal with the medical needs of their children with severe disease.

In addition, parents of cases with homozygous mutations are not usually tested for carrier conditions. However, it is very important to prove that they are carriers in order to better explain to parents that the disease is hereditary. For this reason, it is important to provide genetic counseling to the family of each diagnosed case. For national premarital screening programs, it may be recommended that consanguineous parents seek genetic counseling before having children. It is also very useful to draw a family

tree by the genetic counselor to explain the autosomal recessive inheritance pattern of a family receiving genetic counseling and to give information that fertile siblings and cousins of the parents may also carry the disease. Giving the prenatal diagnosis/preimplantation option by giving genetic counseling to the family will prevent the emergence of new cases of this disease in the family. In neurometabolic diseases diagnosed with enzymes such as TSD, knowing the mutation that causes the disease in the family allows the carriers to be screened and the families to be given accurate genetic counseling.

ETHICS

Ethics Committee Approval: The study was reviewed and approved by the İstanbul University, İstanbul Faculty of Medicine, Clinical Research Ethics Committee (decision no: 18, date: 07.10.2022).

Informed Consent: Written informed consent was obtained from all parents of the patients included in the study.

Authorship Contributions

Surgical and Medical Practices: A.D.A., Ç.G., T.K., E.Ş., Ş.A., U.A., V.K., G.T., M.K., A.İ., G.G., G.Y., O.U., Concept: A.D.A., Ç.G., T.K., E.Ş., Ş.A., U.A., V.K., G.T., M.K., A.İ., G.G., G.Y., O.U., Design: A.D.A., Ç.G., V.K., M.K., G.Y., O.U., Data Collection or Processing: A.D.A., Ç.G., T.K., E.Ş., Ş.A., U.A., V.K., G.T., M.K., G.Y., Analysis or Interpretation: A.D.A., Ç.G., U.A., V.K., G.T., G.G., G.Y., O.U., Literature Search: A.D.A., Ç.G., U.A., V.K., G.T., G.G., G.Y., O.U., Writing: A.D.A., Ç.G., A.İ., G.G., G.Y., O.U.

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REFERENCES

1. Gravel RA, Kaback MM, Proia RL, Sandhoff K, Suzuki K, Suzuki K. The GM2 gangliosidoses. In: Scriver C, Beaudet A, Sly W, Valle D, editors. Metabolic and Molecular Bases of Inherited Diseases. New York, NY: McGraw-Hill; 2001. p. 3827-76.
2. Bley AE, Giannikopoulos OA, Hayden D, Kubilus K, Tifft CJ, Eichler FS. Natural history of infantile G(M2) gangliosidosis. Pediatrics 2011;128:1233-41.
3. Leavitt JA, Kotagal S. The "cherry red" spot. Pediatr Neurol 2007;37:74-5.
4. Mugikura S, Takahashi S, Higano S, Kurihara N, Kon K, Sakamoto K. MR findings in Tay-Sachs disease. J Comput Assist Tomogr 1996;20:551-5.
5. Aydin K, Bakir B, Tatli B, Terzibasioglu E, Ozmen M. Proton MR spectroscopy in three children with Tay-Sachs disease. Pediatr Radiol 2005;35:1081-5.
6. Hall P, Minnich S, Teigen C, Raymond K. Diagnosing Lysosomal Storage Disorders: The GM2 Gangliosidoses. Curr Protoc Hum Genet 2014;83:17.
7. Kars ME, Basak AN, Onat OE, Bilguvar K, Choi J, Itan Y, et al. The genetic structure of the Turkish population reveals high levels of variation and admixture. Proc Natl Acad Sci U S A 2021;118:e2026076118.
8. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24.
9. Kaback M, Lim-Steele J, Dabholkar D, Brown D, Levy N, Zeiger K. Tay-Sachs disease--carrier screening, prenatal diagnosis, and the molecular era. An international perspective, 1970 to 1993. The International TSD Data Collection Network. JAMA 1993;270:2307-15.
10. Ozkara HA, Topcu M. Sphingolipidoses in Turkiye. Brain Dev 2004;26:363-6.
11. Kaplan S, Pinar G, Kaplan B, Aslantekin F, Karabulut E, Ayar B, et al. The prevalence of cansaguineous marriages and affecting factors in Turkiye: A national survey. J Biosoc Sci 2016;48:616-30.
12. Gort L, de Olano N, Macías-Vidal J, Coll MA; Spanish GM2 Working Group. GM2 gangliosidoses in Spain: analysis of the HEXA and HEXB genes in 34 Tay-Sachs and 14 Sandhoff patients. Gene 2012;506:25-30.
13. Smith NJ, Winstone AM, Stellitano L, Cox TM, Verity CM. GM2 gangliosidosis in a UK study of children with progressive neurodegeneration: 73 cases reviewed. Dev Med Child Neurol 2012;54:176-82.
14. Er E, Canda E, Yazıcı H, Eraslan C, Sözmen EY, Uçar SK, et al. Evalution of demographic and clinical characterictics of patients with GM2 Gangliosidosis. J Pediatr Res 2018;5:12-6.
15. Karimzadeh P, Jafari N, Nejad Biglari H, Jabbeh Dari S, Ahmad Abadi F, Alaee MR, et al. GM2- gangliosidosis (Sandhoff and Tay Sachs disease): Diagnosis and neuroimaging findings (an Iranian pediatric case series). Iran J Child Neurol 2014;8:55-60.
16. Gupta L, Mirza A, Gulati A, Gulati P. Magnetic resonance imaging findings in Tay-Sachs disease. Neurol India 2018;66:1201-2.
17. Bilginer-Gürbüz B, Bulut FD, Koç Uçar H, Sarıgeçili E, Sarıkepe B, Özalp Yüreğir Ö. GM2 gangliosidoses: evaluation of clinical, biochemical, and genetic findings of patients with three novel mutations. Cukurova Med J 2021;46:1201-7.
18. Ozkara HA, Akerman BR, Ciliv G, Topçu M, Renda Y, Gravel RA. Donor splice site mutation in intron 5 of the HEXA gene in a Turkish infant with Tay-Sachs disease. Hum Mutat 1995;5:186-7.
19. Ozkara HA, Navon R. At least six different mutations in HEXA gene cause Tay-Sachs disease among the Turkish population. Mol Genet Metab 1998;65:250-3.
20. Ozkara HA, Sandhoff K. Characterization of two Turkish beta-hexosaminidase mutations causing Tay-Sachs disease. Brain Dev 2003;25:191-4.
21. Sinici I, Ozkara HA, Topçu M, Ciliv G. Biochemical and molecular characterization of mutant hexosaminidase A in a Turkish family. Pediatr Int. Pediatr Int 2003;45:16-22.
22. Ozkara HA, Sandhoff K. A new point mutation (G412 to A) at the last nucleotide of exon 3 of hexosaminidase alpha-subunit gene affects splicing. Brain Dev 2003;25:203-6.
23. Sinici I, Onder E, Topçu M, Ozkara HA. Identification of 7th hexosaminidase A mutation of Tay-Sachs disease in the Turkish population. Turk J Pediatr 2007;49:337-8.
24. Arslan M, Unay B, Vurucu S, Gül D, Akın R. Tay-Sachs disease in a Turkish patient due to c.78G> A HEXA mutation: a case report. Eur J Paediatr Neurol 2013;17:41.

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Research

Occupational Health Literacy Level and Related Factors in Casting Factory Workers

Bir Döküm Fabrikası Çalışanlarında İş Sağlığı Okuryazarlık Düzeyi ve İlişkili Faktörler

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ABSTRACT

Objective: Occupational health literacy (OHL) is associated with the actions and decisions of employees in the workplace and with various occupational health outcomes. Prior studies specific to OHL are limited. The aim of this study was to determine the level of OHL and related factors.

Methods: A descriptive cross-sectional study was performed among the employees in a metal foundry factory operating as a supplier of steel castings, steel forgings, and machined parts to several industries. All employees over the age of 18 were invited to participate. Data were collected through a web-based questionnaire including demographic characteristics of the employees and the OHL scale. Independent sample t-test, One-Way ANOVA, and Tukey multiple comparison tests were performed for data analysis. A p-value of <0.05 was considered statistically significant.

Results: Among the 860 employees, 334 participated in the survey (38.9%). The mean age of participants was 35.60±8.96 (range: 21-67 years). 98.5% were male; 57.8% were married, 21.6% were working for over 16 years. Most participants were high school graduates (71.1%). The participants' mean OHL scale score was 84.27±15.46 (range: 49-114). The mean scores of OHL significantly differed by participants' age, educational level, working time in the factory, number of Occupational Health and Safety (OHS) training sessions received, job collar type, presence of occupational accident history in the past 3 years, and age at first work in an income generating job (p<0.05).

Conclusion: The study results contribute to our understanding of the factors that influence OHL and can guide OHS providers and employers, factory management, and union representations in planning intervention points for healthy and safe workplaces. More studies are needed to close the gap in the field.

Keywords: Occupational health literacy, employees, occupational health, casting factory

ÖZ

Amaç: İş sağlığı okuryazarlığı (İSO), çalışanların iş yerindeki eylem ve kararlarıyla ve çeşitli iş sağlığı sonuçlarıyla ilişkilidir. İSO'ya özgü önceki araştırmalar sınırlıdır. Bu çalışmanın amacı, İSO düzeyini ve ilişkili faktörleri belirlemektir.

Gereç ve Yöntem: Tanımlayıcı kesitsel tipte planlanmış olan çalışma, çeşitli endüstrilere çelik döküm, çelik dövme ve işlenmiş parça tedarikçisi olarak faaliyet gösteren bir metal döküm fabrikasında çalışanlar arasında gerçekleştirilmiştir. Çalışmaya 18 yaş üstü tüm çalışanlar davet edilmiştir. Veriler, çalışanların demografik özelliklerini ve İSO ölçeğini içeren çevrimiçi bir anket aracılığıyla toplanmıştır. Veri analizi t-testi, Tek-Yönlü ANOVA ve Tukey çoklu karşılaştırma testleriyle yapılmıştır.

Bulgular: Sekiz yüz altmış çalışandan 334'ü ankete katılmıştır (%38,9). Katılımcıların yaş ortalaması 35,60±8,96 (aralık: 21-67 yıl), 98,5'i erkek; %57,8'i evli ve %21,6'sı 16 yıldan uzun süredir çalışmaktadır. Katılımcıların çoğu lise mezunudur (%71,1). Katılımcıların OHL ölçek ortalama puanı 84,27±15,46 (aralık: 49-114). ISO ortalama puanları katılımcıların yaşı, eğitim düzeyi, fabrikada çalışma süresi, alınan İş Sağlığı ve Güvenliği (İSG) eğitimi sayısı, iş yaka tipi, son 3 yılda iş kazası öyküsü varlığı ve gelir getirici bir işte ilk çalışma yaşına göre istatistiksel olarak anlamlı farklılık göstermiştir (p<0,05).

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Sonuç: Çalışma sonuçları, İSG'yi etkileyen faktörleri anlamamıza katkıda bulunmakta ve sağlıklı ve güvenli işyerleri için müdahale noktalarının planlanmasında İSG profesyonellerine, işverenlere, fabrika yönetimlerine ve sendika temsilciliklerine rehberlik edebilmektedir. Alandaki daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: İş sağlığı okuryazarlığı, çalışanlar, iş sağlığı, döküm fabrikası

INTRODUCTION

Since the proposition of the concept "health literacy" in 1974, different definitions have been proposed. Most were limited to health literacy within the health care context, and their focus was on understanding health information and acting accordingly. Nowadays, the concept and means to measure have considerably evolved (1). The World Health Organization (WHO) defined health literacy as "the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good health" and placed the concept in the context of health promotion which is the process of enabling people, individually and collectively, to increase control over the determinants of health and thereby improve their health (2,3). WHO recently modified the definition of health literacy and stated that personal knowledge and competencies are mediated by organizational structures and availability of resources (4). Health literacy is influenced and shaped by individual, situational, cultural, and social factors. As a social factor influencing the health of a large proportion of the adult population worldwide, work environment and occupation represent important settings for determinants of health literacy (2,5).

Occupational health is defined as "the promotion and maintenance of the highest degree of physical, mental and social well-being of workers in all occupations" (6). Health promotion is increasingly gaining ground in occupational safety and health (7). WHO called on countries to develop policies and institutions to promote occupational health, to intervene more in the workplace to prevent accidents at work and work-related diseases (8).

Health literacy can be assigned to both occupational health and safety and workplace health promotion because workers are often confronted with health information from occupational health professionals about occupational hazards, occupational injuries/diseases (9,10). Safety and health skills and knowledge are key qualifications in occupational health and safety and workplace health promotion. The extent to which employees possess these competencies has a significant influence on their behavior in the workplace. Increasing workers' individual health literacy can enable them to independently shape their working conditions as a behavioral preventive measure and thus contribute to the implementation of structural preventive measures. Improving literacy skills in the workplace is a tool to empower individuals to make safe choices. Employees with higher literacy skills can better understand instructions for using equipment and materials, and they are more likely to comprehend and practice workplace health and safety procedures (11,12).

Occupational health literacy (OHL) has emerged as a part of health literacy, with the concept of Occupational Health and Safety (OHS) gaining more importance as a result of increasing industrialization, expanding business lines, developing technology, and increasing worker population worldwide (13). OHL refers to the degree to which individuals have the capacity to receive, process, and understand basic OHS information and services necessary to make appropriate decisions regarding health and safety in the workplace. It is specifically an important aspect in the prevention of work-related diseases and injuries (13-15).

Studies among the working population regarding occupational health issues and literacy are available in the literature. However, literacy studies conducted with employees in different business lines are mostly based on the concept of health literacy (16-19). Researchers state "lack of attention to factors affecting prevention" as one of the reasons for the high prevalence of occupational diseases and accidents. One of the factors affecting the prevention of occupational diseases and accidents is the ability of employees to adequately understand and implement measures and interventions related to OHS, that is, their OHL (13). Prior studies addressing OHL are limited (13,20), thereby creating an important gap regarding studies that evaluate OHL and influencing factors in the literature.

The primary aim of this study was to evaluate OHL levels and related factors among employees of a metal foundry factory. As there is a gap in the literature, the secondary aim is to contribute to the literature in the field.

METHODS

Study Design, Study Population

A descriptive cross-sectional study was conducted among the employees of a metal foundry factory in Mersin, Türkiye, which operates as a supplier of steel castings, steel forgings,

and machined parts to the automotive, construction equipment, and railway industries. For data collection, all 860 employees of the factory over the age of 18 were invited to participate in the web-based survey. Participation was voluntary, and informed consent was obtained from the participants at the beginning of the survey.

Data Collection

Data were collected in cooperation with factory management and union representation between March 20-31, 2022. The link of the web-based survey was first announced to the employees via official e-mails with invitations to participate in the survey. The day after, reminder messages with sms were sent to all employees by the human resources department. Then, the survey link was shared twice with a reminder message through WhatsApp groups in cooperation with the union representative. The structured web-based questionnaire consists of two parts. The first part of the questionnaire included demographic information and the second part included the OHL scale.

Sociodemographic Information Form

The first part of the questionnaire included demographic information (sex, age, the highest level of education, marital status, presence of chronic disease) and additional questions that are thought to be decisive age at first work in an income generating job, work length time at current factory, presence of occupational accident and occupational disease history in the past 3 years, number of OHS training sessions, and sources of information on OHS.

OHL Scale

To assess OHL, the OHL scale (21) was used for which Turkish validity and reliability studies were conducted. The Turkish form of the scale has been reported as a highly valid and reliable measurement tool to determine the OHL levels of employees (Cronbach's alpha =0.93) (22).

The OHL scale consists of 38 items within 4 dimensions: Ability to gain access, understanding, evaluation, and use of OHS information. Each item is evaluated on a 3 point scale (1 point = "not relevant", 2 point = "somewhat relevant", 3 point = "high relevant").Evaluation is made on the total score. The lowest score that can be obtained from the scale is 38, and the highest score is 114. A high score is considered a high level of OHL.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). The consistency of OHL scale scores with normal distribution was examined with the skewness and kurtosis values of the dataset. Both values varied between -1 and +1, so it was assumed that data is normally distributed (23). The sample characteristics were described by performing descriptive analyses. Variables were defined by number (n), percentage (%), mean, standard deviation, and median (minimum:maximum) values. For comparison of mean OHL score between the groups of each independent variable, depending on the number of independent variable groups compared, independent sample t-test and One-Way ANOVA were performed for statistical analyses. For multiple comparisons between groups, the Tukey HSD test was used for further analysis. A p-value of <0.05 was considered statistically significant for all statistical comparisons.

Ethics Committee Approval

The study was approved by the Bahçeşehir University Clinical Research Ethics Committee (decision no: 2023-06/05, date: 15.03.2023).

RESULTS

Characteristics of Participants

The survey was completed by 334 employees, with an overall response rate of 38.8%. The mean age of the participants was 35.60±8.96 years (range: 21-67 years). Of the respondents 98.5% (n=329) were male; 57.8% (n=193) were married, 21.6% (n=90) were working for over 11 years, and 15.6% (n=52) were in their first working year in the factory. In terms of education level, 71.1% (n=237) of the participants had completed high school, 13.8% (n=46) had completed secondary school or less, and 15.3% (n=51) had completed bachelor's or higher education. Participants reporting occupational accident and occupational disease history in the past three years were 39.2% (n=131) and 1.5% (n=5) respectively. Characteristics of the participants are presented in Table 1.

Regarding the source of information about OHS in which the participants could give multiple answers, 282 participants stated occupational safety specialist, 268 OHS trainings, 187 safety signs in the workplace, 162 occupational physicians, 106 co-workers/friends, 101 internet, 91 managers/supervisors as their main sources of information. As presented in Table 2 the occupational safety specialist (23.6%), OHS training at workplace (22.4%), health and safety signs at workplace (15.6%) and workplace physician (13.5%) were the most relevant sources of OHS information among participants.

Associations Between the OHL Score

The participants' mean OHL score was 84.27±15.46 (range: 49-114). One-Way ANOVA was performed to compare

Table 1. Characteristics of the study population and relationship between the study variables and the occupational health literacy through bivariate analyses

Variables	n	%	Mean ± SD	test	p
Age group (years)					
20-29	109	32.6	79.88±13.78	4.87	**0.002***
30-39	120	35.9	85.45±16.18		
40-49	76	22.8	87.17±16.36		
50+	29	8.7	88.31±12.63		
Gender					
Female	5	1.5	91.60±0.34	1.06	0.268**
Male	329	98.5	84.16±15.51		
Marital status					
Single	141	42.2	86.72±15.93	-2.48	**0.013****
Married	193	57.8	82.49±14.86		
Level of education					
Secondary school or less	46	13.8	71.81±13.42	21.42	**0.000***
High school	237	71.0	85.08±15.33		
Bachelor's or higher	51	15.3	90.98±11.62		
Presence of chronic disease					
Yes	66	19.8	82.91±15.24	0.79	0.425**
No	268	80.2	84.61±16.35		
Type of job collars					
White-collar	48	14.4	90.52±13.35	3.06	**0.002****
Blue-collar	286	85.6	83.22±15.56		
Age at first work in an income generating job					
10-14	31	9.3	91.58±12.75	4.65	**0.010***
15-17	80	24.0	85.33±15.94		
≥18	223	66.8	82.88±15.37		
Working time in the factory (years)					
≤1	52	15.6	86.35±15.89	7.06	**0.000***
2-5	112	33.5	80.35±15.50		
6-10	80	24.0	82.40±15.05		
≥11	90	26.9	89.62±13.95		
Occupational accident history in past 3 years					
Yes	131	39.2	89.40±13.69	5.188	**0.000****
No	203	60.8	80.97±15.66		
Occupational disease history in past 3 years					
Yes	5	1.5	84.20±9.41	-0.01	0.992**
No	329	98.5	84.27±15.54		
Number of OHS trainings received					
1	94	28.1	78.81±12.68	11.17	**0.000***
2	65	19.5	82.17±15.48		
3	57	17.1	83.33±16.11		
≥4	118	35.3	90.24±15.30		

SD: Standard deviation, OHS: Occupational Health and Safety, *One-Way ANOVA test; **independent sample Student's t-test

Table 2. Source of information about Occupational Safety and Health*

Source of information about Occupational Safety and Health*	n	%
OHS trainings	268	22.4
Workplace physician	162	13.5
Occupational safety specialist	282	23.6
Health and safety signs at workplace	187	15.6
Co-workers/friends	101	8.4
Internet	106	8.9
Managers/supervisors	91	7.6

*Multiple responses. OHS: Occupational Health and Safety

the effect of education, age group, age at first work in an income generating job, and number of OHS training sessions received on the total OHL score. As presented in Table 1 One-Way ANOVA test revealed that there is a statistically significant difference in mean OHL between at least two groups for age groups (F=4.87, p=0.002), for level of education (F=21, 42), p=0.000), for working time in the factory (F=7.06, p=0.000), for number of OHS training sessions received (F=11.17, p=0.000), and for age group at first work in an income generating job (F=4.65, p=0.01). The mean scores of OHL does not differed statistically with the presence of chronic disease, presence of occupational disease history in the past three years, and gender (p>0.05).

In further analysis according to the results of Tukey's HSD test for multiple comparisons, the mean value of OHL was significantly different between bachelors' degree or higher education and secondary school or less education [p=0.000, 95% confidence interval (CI) = (12.05, 26.28)]. There was no significant difference in means of OHL between secondary school or less education and high school education (p>0.05). OHL was significantly higher for participants who were working for at least 11 years in the factory compared to the participants working for 2-5 years [p=0.000, 95% CI = (3.77, 14.78)] and 6-10 years [p=0.011, 95% CI = (1.25, 13.20)]. There was no significant difference in OHL between participants who were working for at least 11 years in the factory compared to the participants who were within their first year in the factory (p=0.596). OHL was significantly lower in the age group 20-29 compared to the age groups 30-39, 40-49 and 50 and higher [(p=0.030, 95% CI = (-10.76, 10.38); (p=0.008, 95% CI = (-13.16, -1.43)] and [p=0.041, 95% CI = (-16.63, -0.23) respectively]. There was no significant difference in mean value of OHL between the age groups 30-39, 40-49 and 50 and higher (p>0.05). OHL was significantly higher in 10-14 age group at first work in an income generating job and ≥18 age group [p=0.009, 95% CI = (1.80, 16.60)]. There was no statistically significant difference in mean OHL between age group 10-14 and age group 15-17 (p=0.131) or between age group 15-17 and ≥18 age group (p=0.438). OHL among participants who received at least four OHS trainings was significantly higher compared to those who received less OHS trainings (p<0.05). There was no significant difference in the mean value of OHL between the other three groups who received less than 4 OHS trainings (p>0.05).

DISCUSSION

As mentioned earlier, prior international and national studies specific to OHL are limited. Also, there is a lack of reliable and valid measurement instruments for OHL. As far as is known, this is the first study addressing the OHL and related factors among workers with reliable and valid measurement instruments in our country. The use of the recently developed and adapted OHL scale makes it difficult to compare and relate the results of the study to other national and international studies.

Considering that the range that can be obtained from the OHL scale is between 38 and 114, the OHL level among the participants was moderate to high with a mean score of 84.27±15.46 (range: 49 -114). The most relevant sources of OHS information among participants are OHS trainings, occupational safety specialists, and workplace physicians. Thereason why the participants' OHL was moderate to high may be explained by the effects of mandatory OHS training. Also, assignment of occupational safety specialist and workplace physician may provide a communication way to receive information on OHS they need. The assignment of occupational safety specialist and workplace physician in the factory and OHS training at workplace is thought to be the impact of the legal regulations. In Türkiye, workplaces are categorized into three hazard classes: very hazardous, hazardous, and less hazardous. This classification is based on the type of work performed, the materials used or produced at each step, work equipment, types and methods of production, as well as other aspects related to the working environment and working conditions. Many issues such as employee training hours and frequency on OHS, assignment and working hours of OHS professionals, and risk assessment are determined according to the hazard class of the workplace. According to this classification, the factory in which the study is conducted (the metal casting industry) is considered very hazardous (24). The law 6331 (25) mandates employers to inform employees about the health and safety risks of the workplace, the rights

and obligations of employees, take protective measures against the workplace risks, provide workplace doctors and occupational safety professionals, medical examinations for their employees on a routine basis etc. The principles and procedures (e.g. the subjects, hours and frequency) of OSH training to be provided to employees are set out by the regulation (26).

As expected in the metal manufacturing industry, most participants (98.5%) were male. Gender segregation is an expected finding in the metal manufacturing industry. The labor market is highly gender-segregated by industry and occupation in most countries of the world, with men dominating the industrial sector in every region of the world (27).

The data showed that OHL was significantly associated with some factors. OHL was significantly higher in participants with a bachelors degree or higher education compared with participants with a lower degree education. The influence of educational level is proven in many health literacy studies (16,17,19,28). Therefore, it is reasonable to assume that the educational level of employees will have significant effects on their OHL.

The finding that the OHL was significantly high in participants who were white-collar workers compared to blue-collar workers is most likely related to the educational attainment of the participants. OECD reports that across all counties the percentage of adults with tertiary education is higher among occupations requiring advanced skills (white-collars) (29).

Participants who received at least four OHS trainings had a significantly higher mean value of OHL compared with those who received less OHS trainings. This result agrees with studies reporting that regular OHS education increases knowledge regarding OSH (30,31).

The OHL level of the participants who had been working in the factory for at least 11 years was significantly higher compared to the participants who had been working for 2-5 years and 6-10 years, while no difference was found when compared to the participants who were in their first year in the factory. Also, no statistical difference was found when the OHL level of the participants who were in their first year in the factory was compared with the participants who had been working for 2-5 years and 6-10 years. This result agrees with the results of a study conducted with 150 sasirangan workers in South Calitmantan on OHL, which reported that a longer period of working is related to good OHL (20).

Another result of the study is that the participants with an occupational accident history in the past three years have higher OHL. The unexpected result of the positive association between the presence of a work accident history and higher OHL may be due to the possibility that injured workers were provided with OHS information after they had an occupational accident. Another explanation could be that respondents with a history of occupational accidents tend to seek more OHS information by themselves than those without a history of occupational accidents

In the study where the concept of OHL was first introduced, it was reported that there was a positive association between OHL and occupational accidents among US adolescents (13). They explained this result with the possibility of inappropriate, incomplete or inadequately delivered safety training, thereby limiting its ability to have a preventative impact.

Considering that workers' OHL of the employees needs to be assessed with appropriate, reliable and validated tools to contribute and guide OSH professionals, employers, factory managements and union representatives when deciding on the method, content and level of measures and/or interventions to be taken to protect workers from health hazards they are exposed to at work, this study is one of the pioneering studies highlighting occupational health-specific literacy and contributing to our understanding of some of the factors that influence OHL.

This study should be interpreted in the context of its limitations. First, the cross-sectional design of the current study only offers information on association and cannon provide any information about causality. The second limitation concerns that the study was conducted online and employees participated voluntarily. Although the precise characteristics of a sample (i.e. number of target employees, their possibilities of accessing the web-based survey) were well known by the researcher previously, the employees who participated in the survey may have responded in the desired way, misrepresenting their true status about the content of the survey, and a respondent bias might have occurred. In addition, an online data collection may have led to selection bias in which employees with low literacy levels may have participated less than those with high literacy levels. The third limitation might be the participation rate in the study, which may lead to a non-response bias. Finally, since all participants were employees of the same factory, the results of the research may be unique to that factory, and the results of this study may not necessarily be generalized to other employees or industries.

CONCLUSION

Despite its limitations, the study found that the OHL of factory employees is influenced by factors such as employee

educational level, job collar type, number of OHS trainings, and presence of occupational accident history in the last three years. Interventions based on influencing factors of OHL can be more effective in improving the OHL of employees. Evaluating and understanding the level of OHL and influencing factors is the first step to develop evidence-based interventions to protect workers from workplace hazards and promote their health.To identify more factors influencing OHL of employees, future studies conducted in different workplaces and appropriate evaluation instruments are suggested.

ETHICS

Ethics Committee Approval: The study was approved by the Bahçeşehir University Clinical Research Ethics Committee (decision no: 2023-06/05, date: 15.03.2023).

Informed Consent: Participation was voluntary, and informed consent was obtained from the participants at the beginning of the survey.

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REFERENCES

1. Batterham R, Beauchamp A, Osborne R. Health literacy. In: Quah SR, Cockerham W, editors. The International Encyclopedia of Public Health. 2nd ed. Academic Press; 2017. p.428-37.
2. Sørensen K, Van den Broucke S, Fullam J, Doyle G, Pelikan J, Slonska Z, et al. Health literacy and public health: a systematic review and integration of definitions and models. BMC Public Health 2012;12:80.
3. Nutbeam D. Health promotion glossary. Health Promot Int 1998:13:349–64.
4. Health promotion glossary of terms 2021. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.
5. Jørgensen MB, Larsen AK. Occupational health literacy: Healthy decisions at work. Okan, O, Bauer U, Levin-Zamir D, Pinheiro P, Sørensen K, editors. In: International Handbook of Health Literacy: Research, Practice and Policy across the Lifespan. Policy Press: 2019. P.347–58.
6. World Health Organization. Occupational health. https://www.who.int/health-topics/occupational-health
7. Eickholt C, Hamacher W, Lenartz N. Gesundheitskompetenz im Betrieb fördern - aber wie? [How to promote health competence at work]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2015;58:976-82.
8. World Health Organization. Health Literacy: The Solid Facts; WHO Regional Office for Europe: Copenhagen, Denmark, 2013; Available from: https://apps.who.int/iris/handle/10665/326432
9. Rollin L, Ladner J, Gislard A, Monfrin F, Larchevesque JY, Deslandes P, et al. Hazard information needs and information seeking in French workers. Occup Med (Lond) 2013;63:473-8.
10. Rhebergen MD, Lenderink AF, van Dijk FJ, Hulshof CT. Do Dutch workers seek and find information on occupational safety and health? Am J Ind Med 2012;55:250-9.
11. The Conference Board of Canada. Campbell A. All signs point to yes literacy's impact on workplace health and safety; 2008. Available from: https://www.brantskillscentre.org/wp-content/uploads/2012/05/All-Signs-Point-to-Yes-Literacys-Impact-on-Workplace-Health-Safety.pdf
12. The Conference Board of Canada. Campbell A. What you don't know can hurt you: Literacy's impact on workplace health and safety; 2010. Available from: http://en.copian.ca/library/research/cboc/whatyoudontknow/whatyoudontknow.pdf
13. Rauscher KJ, Myers DJ. Occupational health literacy and work-related injury among U.S. adolescents. Int J Inj Contr Saf Promot 2014;21:81-9.
14. Wong BK. Building a health literate workplace. Workplace Health Saf 2012;60:363-9; quiz 70.
15. Ehmann AT,Ög E, Rieger MA, Siegel A. Work-Related Health Literacy: A Scoping Review to Clarify the Concept. Int J Environ Res Public Health 2021;18:9945.
16. Güner MD, Ekmekci PE. Health Literacy Level of Casting Factory Workers and Its Relationship With Occupational Health and Safety Training. Workplace Health Saf 2019;67:452-60.
17. Acar GA, Baltacı K, Acımış KM, Orhan O. Health Literacy Level and Related Factors Among Employees of a Textile Factory. Karaelmas Journal of Occupational Health and Safety 2021;3:209-17.
18. Karl JI, McDaniel JC. Health Literacy Deficits Found Among Educated, Insured University Employees. Workplace Health Saf 2018;66:419-27.
19. İbrahimoglu O, Kilic H, Mersin S. Health Literacy Levels of Factory Employees and Affecting Factors: Bilecik Case. Sağlık ve Toplum 2019;29:3:26-32.
20. Yusida H, Suwandi T, Yusuf A, Sholihah Q. Relationship individual factors with occupational health literacy (observational study on industrial workers of Sasirangan in South Kalimantan). Int J Sci Res Publ 2016;6:1:481-4.
21. Suthakorn W, Songkham W, Tantranont K, Srisuphan W, Sakarinkhul P, Dhatsuwan J. Scale Development and Validation to Measure Occupational Health Literacy Among Thai Informal Workers. Saf Health Work 2020;11:526-32.
22. Uskun E, Güclü M, Evcil FY, Kalayci O, Kartal FM, Onal O, et al. Turkish Validity and Reliability of the Occupational Health Literacy Scale: A Methodological Study. Turkiye Klinikleri J Med Sci 2022;42:3:191-203.
23. George D, Mallery M. IBM SPSS Statistics 25 Step by Step: A Simple Guide And Reference. 15th ed. New York Taylor & Francis; 2019.
24. Ministry of Labour and Social Security. Communiqué on Workplace Occupational Health and Safety Related Hazard Classes. Resmi Gazete, 2012-12-26, No. 28509. Available from: http://www.resmigazete.gov.tr/eskiler/2017/02/20170227M1-1-1.pdf
25. Occupational Health and Safety Law, No: 6331. 30-06-2012 Official Gazette No: 28339. Available from: http://www.resmigazete.gov.tr/eskiler/2012/06/20120630-1.htm.
26. Ministry of Labour and Social Security Principles and Regulations for Occupational Health and Safety Training of Employees. Resmi Gazete, 2013-05-15, No. 28648. Available from: http://www.resmigazete.gov.tr/eskiler/2013/05/20130515-1.htm
27. Das S, Kotikula A. Gender-Based Employment Segregation: Understanding Causes and Policy Interventions. 2019. Available from: www.worldbank.org
28. Gyekye SA, Salminen S. Educational status and organizational safety climate: does educational attainment influence workers' perceptions of work- place safety? Saf Sci 2009;47:1: 20–28.
29. OECD. Education at a Glance 2022: OECD Indicators, OECD Publishing, Paris. https://doi.org/10.1787/3197152b-en
30. Boini S, Colin R, Grzebyk M. Effect of occupational safety and health education received during schooling on the incidence of workplace injuries in the first 2 years of occupational life: a prospective study. BMJ Open 2017;7:e015100.
31. Şenkal O, Kanık R, Sezgin, ME, Şenkal ÖA. Occupational Health and Safety Education at Inclusive Vocational Schools in Turkey. SAGE Open 2021;11:4.