Ahi Evran Medical Journal

Ahi Evran Tıp Dergisi

Year/Yıl:2024 Volume/Cilt: 8 Issue/Sayı:1

Ahi Evran Medical Journal

Year: 2024 Volume: 8 Issue: 1
e-ISSN: : 2619-9203

Ahi Evran Medical journal is indexed in ULAKBIM, TRdizin, DOAJ, Index Copernicus Master List, EBSCO, Türk Medline, Türkiye Atıf Dizini (Turkiye Citation Index)

AHİ EVRAN MEDİCAL JOURNAL 2024;8(1)

HAKEM LİSTESİ / REVIEWER LIST

Adem TOKPINAR, Ordu Üniversitesi, Tıp Fakültesi.

Ahmed Ramiz BAYKAN, Sağlık Bilimleri Üniversitesi, Erzurum Bölge Sağlık Uygulama ve Araştırma Merkezi.

Akif ERBİN, Sağlık Bilimleri Üniversitesi, İstanbul Haseki Sağlık Uygulama Ve Araştırma Merkezi, Cerrahi Tıp Bilimleri Bölümü, Üroloji Anabilim Dalı.

Aslı KARAKILIÇ, Balıkesir Üniversitesi.

Asrın NALBANT, Izmır Bakırcay Unıversıty, School Of Medıcıne.

Atalay DOĞRU, Süleyman Demirel Üniversitesi, Tıp Fakültesi.

Ayhan ÇETİNKAYA, Bolu Abant Izzet Baysal Unıversıty, School Of Medıcıne.

Aziz KARA, Afyonkarahısar Health Scıences Unıversıty.

Burcu YAĞIZ, Bursa Uludağ Üniversitesi.

Deniz Deniz ÖZTURAN, Ordu Üniversitesi.

Elif POLAT, Faculty Of Medıcıne.

Ender ŞİMŞEK, Yıldırım Beyazıt Üniversitesi, Tıp Fakültesi.

Ezgi Işıl TURHAN, Bursa Şehir Hastanesi, Tıbbi Patoloji.

Fatih KAR, Kütahya Sağlık Bilimleri Üniversitesi.

Fatih ÖZDAĞ, Sağlık Bilimleri Üniversitesi, Hamidiye Tıp Fakültesi, Hamidiye Tıp Pr.

Fatma ÇELİK, Fırat Üniversitesi Tıp Fakültesi Anesteziyoloji Ve Reanimasyon.

Fettah EREN, Selcuk Unıversıty.

Funda CANAZ, Eskısehır Osmangazı Unıversıty, School Of Medıcıne.

Fırat AKAT, Ankara Üniversitesi.

Hatice HARMANCI, Konya.

Hüseyin İLTER, Kırşehir Ahi Evran Üniversitesi.

Lut TAMAM, Çukurova Üniversitesi, Tıp Fakültesi.

Mehmet Reşit ÖNCÜ, Van Yüzüncü Yıl Üniversitesi Tıp Fak. Acil Tıp Ad.

Memiş Hilmi ATAY, Ondokuz Mayıs Üniversitesi.

Muhammet Okay ÖRÜN, Sağlık Bilimleri Üniversitesi Van Eğitim Ve Araştırma Hastanesi.

Murat KAÇMAZ, Hatay Mustafa Kemal Üniversitesi, Tayfur Ata Sökmen Tıp Fakültesi, Dahili Tıp Bilimleri Bölümü, İç Hastalıkları Anabilim Dalı, Hematoloji Bilim Dalı.

Neşe ÇÖLÇİMEN, Van Yüzüncü Yıl Üniversitesi, Tıp Fakültesi.

Orhan MERAL, İzmir Bakırçay Üniversitesi, Tıp Fakültesi.

Ozan CENGİZ, Dokuz Eylül Üniversitesi.

Oğuz GÜNDOĞDU, Sivas Cumhuriyet Üniversitesi.

Oğuz EKMEKÇİOĞLU, Kayseri.

Rabia Burcin GİRGİN, İnönü Üniversitesi.

Ramazan ÜSTÜN, Van Yüzüncü Yıl Üniversitesi Tıp Fakültesi Fizyoloji Anabilim Dalı.

Reyhan KÖSE ÇOBANOĞLU, Aydın Adnan Menderes Üniversitesi, Tıp Fakültesi, Dahili Tıp Bilimleri Bölümü, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı.

Salih TOKMAK, Duzce Unıversıty, Faculty Of Medıcıne.

Sanem SARIBAŞ, Kırşehir Ahi Evran Üniversitesi.

Selcen DURAN, Kırşehir Ahi Evran Üniversitesi, Tıp Fakültesi.

Sevcan UĞUR, Alanya Alaaddin Keykubat Üniversitesi, Tıp Fakültesi.

Sibel OYMAK YALÇIN, Çanakkale Onsekiz Mart Üniversitesi, Tıp Fakültesi, Dahili Tıp Bilimleri Bölümü, Halk Sağlığı Anabilim Dalı.

Sinan KARACABEY, Marmara University Training and Research Hospital.

Turgay BÖRK, Fırat Üniversitesi.

Yusuf KOÇAK, Tokat Gaziosmanpaşa Üniversitesi Tıp Fakültesi.

Zeynep KÖYLÜ MIZRAK, Sağlık Bakanlığı.

Zeynep KÖYLÜ MIZRAK, Sağlık Bakanlığı.

Şadiye KUM, Aydın Adnan Menderes Üniversitesi Veteriner Fakültesi.

Şamil ÖZTÜRK, Çanakkale Onsekiz Mart Üniversitesi, Sağlık Hizmetleri Meslek Yüksekokulu.

AHİ EVRAN MEDİCAL JOURNAL 2024;8(1)
AHİ EVRAN TIP DERGİSİ 2024;8(1)

İÇİNDEKİLER/CONTENTS

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Cancer Screenings in Primary Care in Türkiye

Türkiye'de Birinci Basamakta Kanser Taramaları

İzzet FİDANCI[1]

Received: 08.03.2023; Accepted: 05.07.2023

[1]Hacettepe University, Faculty of Medicine, Department of Family Medicine, Ankara, Türkiye.
Corresponding Author: İzzet Fidancı, Hacettepe University, Faculty of Medicine, Department of Family Medicine, Ankara, Türkiye.
e-mail: izzetfidanci@gmail.com

How to cite: Fidancı İ. Cancer screenings in primary care in turkey. Ahi Evran Med J. 2024;8(1):1-3. DOI: 10.46332/aemj.1262057

Dear Editor,

According to the World Health Organization (WHO), cancer has become a significant global health issue. In 2020, there were approximately 19.3 million new cases of cancer worldwide, representing an increase compared to the 18.1 million cases reported in 2018. Cancer is one of the leading causes of death globally, with approximately 10 million people dying from it in 2020. The most common types of cancer worldwide are lung cancer, breast cancer, colorectal cancer, prostate cancer, and stomach cancer.[1]

For up-to-date data on cancer incidence in Türkiye, they can consult the Turkish Cancer Statistics report. According to the 2018 report, 165.093 new cancer cases were detected in Türkiye. The incidence of cancer in Türkiye varies depending on factors such as gender, age, geographical region, and others. Therefore, cancer control and early diagnosis programs are of paramount importance.[2] Table 1 presents the percentage rates and incidences of common cancer types worldwide and in Türkiye.[1,3]

Table 1. The percentage rates and incidences of common cancer types worldwide and in Türkiye.[1,3]

Worldwide		**Türkiye**	
Type of cancer	**Percentage Ratio**	**Type of cancer**	**Percentage Ratio**
Lung cancer	11.6%	Breast cancer	21.8%
Breast cancer	11.7%	Lung cancer	10.5%
Colorectal cancer	10.0%	Colorectal cancer	8.6%
Prostate cancer	7.1%	Gastric cancer	6.5%

Cancer screening is performed at all levels of the health system in many countries. It is also carried out in secondary and third-tier health facilities, along with family medicine, which is the basic unit of the first-tier medical facilities. According to the Family Medicine Practice Regulation in Türkiye, cancer screenings are among the duties, authorities, and responsibilities of family physicians.[4-6]

It is aimed to reduce carcinogen exposure and cancer burden in residential areas and cancer screening programs have been implemented with the joint efforts of all health institutions. The primary objective of cancer screening programs is to ensure early diagnosis and treatment. In terms of primary health care services, 3 main cancer screening programs are actively and widely practiced in Türkiye. These are breast, cervical and colorectal cancer screening programs. Table 2 shows the information brochure published by the Ministry of Health of the Republic of Türkiye.[5]

Table 2. Cancer Screenings in Primary Health Care Organizations in Türkiye (Brochure obtained from the Ministry of Health, General Directorate of Public Health, Department of Cancer).[7]

Breast cancer	Cervical cancer	Colorectal cancer
20 and above *Breast self-examination once a month *Breast examination at a healthcare organization every 2 years **40-69 years:** *Breast self-examination once a month *Breast examination at a healthcare organization once a year *Mammography once in 2 years	**Women aged 30-65 (every 5 years):** *HPV - DNA Test *Smear Test	**Men and women aged 50-70:** *Fecal Occult Blood Test once in 2 years *Colonoscopy once in 10 years

Breast Cancer Screening Program

Women aged between 20 and 40 years are required to undergo self-examination for breast cancer, the most common type of cancer in women, as well as medical examinations once a year for those with a history of breast cancer and twice a year to those with history of cancer. For all women between the ages of 40 and 69, physician examinations should be performed once a year and mammography should be performed once every two years.[5,6]

The cancer screening programs in Türkiye are organized by District Health Directorates (DHS) in cooperation with Family Health Centers (FHC) and Cancer Early Diagnosis, Screening, and Education Centers (KETEM). Patients determined in accordance with the criteria are selected by family physicians and their transportation is organized by the FHC or KETEM on certain days and hours.[5-7]

Cervical Cancer Screening Program

Cervical cancer screening is widely used for early diagnosis due to its simplicity and lack of invasive procedures. As with all screening programs, the main objective is early diagnosis and treatment of the target population. The Papanicolaou test (PAP Smear test) or Human Papilloma Virus test (HPV test) is performed in women aged 30-65 years. Positive results are referred to a gynecologist and the treatment process is planned. If the test is negative, the test must be repeated every 5 years. Women with at least the last two scans with normal results are removed from the scan program after they reach the age of 65.[5,8]

Colorectal Cancer Screening Program

Colorectal cancers are rare under the age of 40, but the greatest risk factor for sporadic cancers is older age. After turning 40, the incidence starts to increase significantly.[9,10] The primary screening with a fecal occult blood test (FOBT) in Türkiye is initiated at the age of 50 and patients with two negative FOBT tests are excluded from the screening program.[5]

A single result is not sufficient for this test, which is why it is more suitable to assess on 3 consecutive days. Family physicians engage in this part of the screening, and the results of a single FOBT are entered into the patient's examination data and the results are submitted to the Ministry of Health. Colonoscopy every 10 years, another screening method, is recommended for all individuals over the age of 50, and a biopsy can be conducted in suspicious cases.[5,9]

In Türkiye, a study of 5,204 people found that a significant proportion of the general population suffers from a lack of knowledge about early diagnosis of cancer. The study findings showed a positive correlation between individuals with a familial history of cancer and their enhanced understanding of cancer screening tests, as well as their increased frequency of undergoing these screenings.[10]

To enhance public engagement in cancer screening, various strategies can be employed. These include organizing awareness campaigns, providing accurate and comprehensive information through educational programs, motivating celebrities and community leaders to support the cause, facilitating easy accessibility to screening services, implementing incentivizing approaches, expanding health insurance coverage, establishing social support groups, fostering collaborations at

local levels, employing personalized communication strategies, offering financial assistance, and ensuring continuous monitoring and evaluation. These efforts aim to actively involve the public in screening programs, foster public interest in cancer screening through health education and mobile outreach tools, and promote active cancer registry for obtaining reliable and comprehensive cancer statistics from the Ministry of Health, as well as data for the International Cancer Research Institute (ICAR). Encouraging participation in cancer screening programs is crucial in achieving these objectives.

As a result, in Türkiye, although cancer screening is carried out at all levels of healthcare, it will be possible to do and increase the number of these screening at the basic health services where the public has the easiest and most convenient access to the health system. Screenings for 3 types of cancer are commonly performed in primary healthcare services in Türkiye, and efforts should be made to increase the number of these screening programs and to increase public participation.

Conflicts of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Authors' Contributions

Concept/Design: İF. Data Collection and/or Processing: İF. Data analysis and interpretation: İF. Literature Search: İF. Drafting manuscript: İF.

REFERENCES

1. World Health Organization (WHO). (2021). Cancer. https://www.who.int/news-room/fact-sheets/detail/cancer. Accessed 11 June, 2023.
2. Turkish Ministry of Health. (2018). Cancer Statistics in Turkey 2018. Retrieved from https://kanser.gov.tr/Dosya/ca2018.pdf. Accessed 11 June, 2023.
3. Türkiye Halk Sağlığı Kurumu (TÜRKHAS). (2022). Türkiye Kanser İstatistikleri 2021. https://kanser.gov.tr/Dosya/turkkanseristatistikleri-2021.pdf. Accessed 11 June, 2023.
4. Aile Hekimliği Uygulama Yönetmeliği. Resmî Gazete Tarihi: 25.01.2013 Resmî Gazete Sayısı: 28539. https://www.resmigazete.gov.tr/eskiler/2013/01/20130125-26.htm. Accessed 15 October, 2022.
5. Ulusal Kanser Tarama Standartları. T.C.Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü Kanser Dairesi Başkanlığı. https://hsgm.saglik.gov.tr/tr/kanser-tarama-standartlari/listesi.html. Accessed 15 October, 2022.
6. Kozan R, Tokgöz VY. Türkiye'de Meme Kanseri Farkındalığı ve Tarama Programı. Acıbadem Üniv. Sağlık Bilim. Derg. 2016;7(4);185-188.
7. Kayhan A, Arıbal E. Meme kanseri taraması: Neden yapıyoruz? Ne zaman? Değerlendirmede yaşanan sorunlar. Trd Sem. 2014;2(2):230-240.
8. Göksalan H, Uyar EE. Pap smear ile servikal kanser taraması. Türk Aile Hek Derg. 2004;8(3):105-110.
9. Kanser Taramaları Yaptırmak. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü Kanser Dairesi Başkanlığı. https://hsgm.saglik.gov.tr/tr/kanserden-korunma/kanserden-korunmalist/kanser-taramalarını-yaptırmak.html. Accessed 15 October, 2022.
10. Bayçelebi G, Aydın F, Gökosmanoğlu F, Tat TS, Varım C. Trabzon'da Kanser Tarama Testleri Farkındalığı. Journal of Human Rhythm. 2015;1(3):90-94.

ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Deaths associated with Methanol Poisoning in Şanlıurfa

Şanlıurfa'da Metanol Zehirlenmesine Bağlı Ölümler

İsmail ALTIN[1] Ahmet Sedat DÜNDAR[1]

ÖZ

Amaç: Metanol, odunun destrüktif distilasyonundan elde edilen berrak, renksiz ve yüksek derecede toksik bir maddedir. COVID-19 pandemi döneminde özellik kronik alkol kullanıcılarının ucuz alkollü içecek ve kolonya gibi alternatif içecekler tükettiği ve toksikolojik analizlerde alkollü sıvılarda etanolün yerine daha ucuz olan metanol kullanılmasına bağlı metanol intoksikasyonlarında artış olmuştur. Bu çalışmada, Şanlıurfa Adli Tıp Şube Müdürlüğü'nde otopsisi yapılan ve ölüm nedeni metanol zehirlenmesi olarak belirlenen olguların değerlendirilmesi amaçlanmıştır.
Araçlar ve Yöntem: 1 Ocak 2016- 1 Kasım 2022 yıllar arasındaki Şanlıurfa Adli Tıp Şube Müdürlüğü'nde ölüm nedeni metil alkol intoksikasyonu olarak belirlenen 15 olgu incelenmiştir. Olguların sosyodemografik verileri, olay yeri bilgileri, klinik bulgular ve hastane yatış verileri ile, olayların yıllara göre dağılımı, alınan içecek türü ve toksikolojik & patolojik veriler değerlendirilmiştir.
Bulgular: Olguların tümü erkekti. Yaş ortalaması 52.1 olarak hesaplandı. Tüketilen içeceklerin 8'inde kolonya, 4'ünde sahte rakı, viski ve votka olduğu belirlenirken, 3'ünde içeceğin türü belirlenemedi.
Sonuç: Alkollü sıvı tüketiminin arttığı dönemlerde sıvılara etanol yerine metanol karıştırılabileceği unutulmamalı ve intoksikasyonlara karşı halkı bilinçlendirici çalışmalar yapılmalıdır. Metanol intoksikasyonuna karşı alkollü içecek ve kolonya gibi alkollü antiseptiklerin üretim ve satışı aşamasında kontroller arttırılarak gerekli yaptırımlar uygulanmalıdır.

Anahtar Kelimeler: adli tıp; otopsi; ölüm; metanol zehirlenmesi

ABSTRACT

Purpose: Methanol, is a clear, colourless, highly toxic substance obtained from the destructive distillation of wood. During the COVID-19 pandemic, chronic alcohol users consumed alternatives such as cologne and cheap alcohol, the toxicology analyses showed that there was an increase in methanol poisoning due to the use of cheaper methanol instead of ethanol in alcoholic liquids. The aim of this study was to evaluate autopsy cases in the Şanlıurfa Forensic Medicine Branch Directorate that were recorded as cause of death from methanol poisoning.
Materials and Methods: 15 cases whose cause of death was determined to be methyl alcohol intoxication were examined at Şanlıurfa Forensic Medicine Branch Directorate between 1 January 2016 and 1 November 2022. Sociodemographic data of the cases, crime scene information, clinical findings and hospitalization data, distribution of events according to years, type of beverage consumed toxicological and pathological data were evaluated.
Results: All of the cases were male. The mean age was calculated as 52.1. The drinks consumed were determined to be cologne in 8 cases, fake raki, whisky and vodka in 4, and the type of drink could not be determined in 3 cases.
Conclusion: It should not be forgotten that in times of increased alcohol consumption, methanol can be mixed with liquids in place of ethanol, and programs should be implemented to inform the public about intoxications. The necessary precautions against methanol intoxication should be taken by increasing control at the production and sales stages of alcoholic drinks and antiseptics containing alcohol, such as cologne.

Keywords: autopsy; death; forensic medicine; methanol poisoning

Received: 05.04.2023; Accepted: 04.07.2023

[1]Şanlıurfa Forensic Medicine Branch Office, Şanlıurfa, Türkiye.

Corresponding Author: İsmail Altın, Şanlıurfa Forensic Medicine Branch Office, Şanlıurfa, Türkiye. e-mail: drsmltn@gmail.com

How to cite: Altın İ, Dündar AS. Deaths associated with methanol poisoning in şanlıurfa. Ahi Evran Med J. 2024;8(1):4-10. DOI: 10.46332/aemj.1277010

INTRODUCTION

Methanol is a clear, colourless, volatile, light, combustible, aliphatic alcohol with a specific smell, which is obtained from the destructive distillation of wood, and is a highly toxic substance.[1] In addition to use as a solvent in industry, there are synthetic organic components in its structure. As methanol is cheap, it is used in the production of fake alcohol, and as poisoning and death can result from the consumption of readily available solutions such as cologne, it is important in respect of forensic medicine.[1, 2]

Methanol can cause severe metabolic disorders, blindness, permanent neurological dysfunctions and death.[3] Methanol manifests toxic effects with formic acid metabolites and formaldehyde that are released when broken down.[4] The toxic effects of methanol are seen in the body through the digestive system, and it can also be spread and have an effect on the body by absorption from the skin and via the respiratory system.[5] Methanol poisoning causes high morbidity and mortality even at low doses. A lethal dose of methanol can show individual differences according to age, gender, and metabolic rate. It is estimated that a lethal dose of methanol that can be taken orally is 30 – 240 mL, and the minimum toxic dose is 100 mg/kg. There are data in literature that even a methanol level of <20 mg/dL is dangerous.[6,7]

The majority of cases of methanol intoxication are accidental, and only occasionally of suicide origin. Adults with chronic alcoholism may consume solutions containing methanol either knowingly or accidentally, and accidental deaths of children, although rare, can also be seen.[2,8] Many cases of poisoning and death can be seen associated with an increase in illegal alcohol production. In Turkey, many deaths have been reported following the consumption of illegally produced alcohol.[2] Reports have shown that the majority of methanol intoxications in Tunisia, Turkey, and India are related to the drinking of cologne and perfume.[9]

The illegal production of alcoholic drinks and their consumption is a signiificant problem in Turkey and around the world. The consumption of illegally produced alcohol varies from region to region and constitutes approximately 30% of all alcohol consumption worldwide. The highest levels of consumption of illegal alcohol are in Eastern Europe, South America, and Africa. It has been reported that 50% of the alcohol consumed in Ukraine in 2005 was unrecorded or illegal.[10] According to the 2010 World Health Organisation Global Information System of Alcohol and Health (WHO-GISAH), approximately 30% of the alcohol consumed in Turkey was illegally produced.[11]

Alcohol is the most frequently encountered psychoactive substance in forensic toxicology. It is known that alcohol abuse can lead to alcohol-related diseases, and trigger alcohol consumption at a younger age and violent behaviours.[12] Individuals with high blood alcohol concentrations are likely to injure themselves through accidental falls or experience blunt trauma.[13] Alcohol abuse can cause death. According to WHO reports, 3.3 million people per year worldwide die because of alcohol consumption, and this constituted 5.9% of all deaths in 2012.[12,13]

The aim of the study is to evaluate the socio-demographic, clinical and autopsy findings of the phenomena of methanol poisoning, which were autopsied at the Sanliurfa Division of Forensic Medicine and identified as the cause of death.

MATERIALS and METHODS

The study was approved by the Ministry of Justice Forensic Medicine Institute Education and Scientific Research Commission (Date: 22/02/2023 and number 2023/102). A total of 4,650 cases of autopsy carried out between 1 January 2016 and 1 November 2022 were examined by the Directorate of Forensic Medicine in SanlIurfa. From these, 15 (0.32%) cases were determined which were recorded as death resulting from methanol intoxication. For each of these cases a retrospective examination was made of the hospital records, autopsy reports, histopathology reports, autopsy photographs, scene of incident reports prepared by the police or armed forces, witness statements, and expert opinion reports. The cases were evaluated in respect of sociodemographic data, findings from the environment of the incident, information related to the incident, the content of the drink consumed,

cause of death, clinical findings, and toxicology and histopathology examination results.

The samples were analyzed using a GC/MS system (Hewlette Packard (Palo Alto, CA)) consisting of HP-6890 gas chromatograph, HP-5972 mass selective detector (MSD), and HP-6890 automatic liquid sampler. Separations of compounds as methanol, ethanol, formic acid, formamide, acetaldehytde, methyl amine, methyl formate, acetic acid, iso-amyl alcohol, trans-anethole, propionic acid, 1-butanol, 1-propanol, ethyl acetate, 2-propanol and trioxan were performed using HP-FFAP (25 m, 0.2 mm i.d., with 0.33 mm film thicknesses) cross-linked capillary column (Hewlette Packard, Palo Alto, CA).

RESULTS

In 15 cases on which autopsy was performed in the Şanlıurfa Forensic Medicine Branch Directorate in a 6-year period, the cause of death was determined to be methanol intoxication. All the cases were male with a mean age of 52.1 years (range, 32-68 years). The deaths occurred in the city centre in 11 cases and in a rural location in 4 cases. All the locations of the incident were the home. The cases comprised 13 Turks and 2 Syrians. Distribution of the cases by year is shown in Table 1.

Table-1 Sociodemographic Data.

Case	Gender	Age (years)	Location of incident	Year	Month	Season	Place of residence
1.	Male	50	Home	2016	11	Autumn	City centre
2.	Male	51	Home	2016	10	Autumn	City centre
3.	Male	59	Home	2016	11	Autumn	Rural
4.	Male	41	Home	2017	2	Winter	City centre
5.	Male	32	Home	2017	2	Winter	City centre
6.	Male	42	Home	2017	1	Winter	City centre
7.	Male	53	Home	2020	6	Summer	City centre
8.	Male	49	Home	2020	5	Spring	Rural
9.	Male	68	Home	2020	11	Autumn	City centre
10.	Male	53	Home	2020	12	Winter	Rural
11.	Male	52	Home	2021	5	Spring	City centre
12.	Male	57	Home	2021	6	Summer	City centre
13.	Male	58	Home	2021	12	Winter	City centre
14.	Male	62	Home	2021	12	Winter	Rural
15.	Male	55	Home	2022	8	Summer	City centre

The most common clinical findings were clouded consciousness with respiratory problems, and there were visual impairment and coma symptoms in few cases. The drink causing the intoxication was most often cologne (n: 8), and these cases were seen to be within the last 3 years (2020-2022). In the post-poisoning trial, the other drinks consumed were raki, whiskey and vodka, while in three cases the type of the drink could not be determined. (Table 2). No methyl alcohol was detected in the toxicology analysis of body fluids taken from long-lasting events (n:2) in the hospital, while in all other phenomena, methyll alcohol was found. (Table 2). No traces of trauma were determined in any case in the external examination of the medicolegal autopsies performed. The histopathological and toxicology findings of the body samples taken in the medicolegal autopsies are shown in Table 2.

From the anamneses taken from close relatives it was learned that some cases (#7, 8, 10, 12, 14, 15) had chronic alcohol dependence and drank cologne when they could not obtain alcohol for economic reasons. The man, registered as case number seven in the hospital records, died in a hospital from drinking two glasses of cologne. Case no. 10 felt ill after drinking cologne and died after presenting at hospital. The person with case number 12 have been drinking cologne for the past two weeks after previously drinking only alcohol. Case no. 14 was stated to have drunk cologne regularly for the last 6 months with no previous history of drinking cologne. Case no.15 was reported to have chronic alcohol and cologne dependency.

Table 2. Type of Drink, Toxicological and Histopathological Data of the Cases.

Case	Clinical findings	Drink consumed	Methyl alcohol level blood/intra-ocular (mg/dL)	Ethyl alcohol level blood/intra-ocular (mg/dL)	Histopathological findings
1.	Visual impairment	Raki	238/263	-	Liver: diffuse macrovesicular fattiness in parenchyma cells and cirrhosis Heart: calcified atheroma plaque narrowing the lumen by 50% in coronary artery samples
2.	Visual impairment	Illegal drink of indeterminate type	159/256	-	Liver: advanced stage macro and micro vesicular fattiness, Heart: widespread scar areas, advanced degree of perivascular and interstitial fibrosis, advanced degree of obstruction in coronary vessels
3.	Clouded consciousness and respiratory problems	Illegal drink of indeterminate type	0	-	Liver: advanced stage macro and micro vesicular fattiness and cirrhosis, Lungs: bronchopneumonia Heart: Mild fibrosis in the heart, advanced degree of obstruction in coronary vessels and ischaemia consistent with 3-7 days
4.	Clouded consciousness and respiratory problems	Whisky and vodka	46/62	64/28	Liver: advanced stage macro and micro vesicular fattiness Heart: mild fibrosis, moderate obstruction in coronary vessels
5.	Visual impairment	Illegal drink of indeterminate type	520/624	-	Liver: advanced stage macro and micro vesicular fattiness, hepatosteatosis, Eyes: severe congestion and bleeding below the retina
6.	Clouded consciousness and respiratory problems	Vodka	128/154	173/171	Liver: Steatosis, Lungs: pneumonia,
7.	Clouded consciousness and respiratory problems	Cologne	119/166	-	Liver: Cirrhosis,
8.	Clouded consciousness and respiratory problems	Cologne	342/477	-	Liver: mild macro and micro vesicular fattiness, Heart: mild obstruction in coronary vessels
9.	Clouded consciousness and respiratory problems	Whisky	239	-	Liver: advanced stage macro and micro vesicular fattiness and cirrhosis, Lungs: interstitial fibrosis, oedema, congestion, Heart: mild fibrosis
10.	Visual impairment	Cologne	-	-	Liver: mild macro and micro vesicular fattiness, Lungs: lobular pneumonia, purulent bronchitis, Heart: mild fibrosis
11.	Clouded consciousness and respiratory problems	Cologne	386/505	-	Liver: cirrhosis, Heart: scarring and almost complete obstruction in coronary vessels
12.	Coma	Cologne	274/360	-	Liver: advanced stage macrovesicular fattiness and cirrhosis, Kidneys: Acute tubular necrosis, Heart: mild fibrosis
13.	No information	Cologne	216/314	-	Liver: moderate macrovesicular steatosis in hepatocytes, congestion, Heart: mild obstruction in coronary vessels
14.	Clouded consciousness and respiratory problems	Cologne	143/202	25/15	Liver: an increase in connective tissue in portal areas with expansion, widespread macrovesicular and microvesicular steatosis, Heart: scarring and advanced degree of obstruction in coronary vessels
15.	Clouded consciousness and respiratory problems	Cologne	98/143	-	Heart: mild obstruction in coronary vessels

DISCUSSION

Excessive alcohol consumption can cause death by drowning, traffic accidents, or violence. Previous studies have shown that deaths related to acute alcohol poisoning (AAP) constitute a significant proportion of all alcohol-related deaths.[12] There was reported to be a significant increase in morbidity and mortality due to methanol in Iran during the COVID-19 pandemic. As methanol is cheaper and can be found more easily than ethanol, some fraudsters in Iran used methanol instead of ethanol in home-produced alcohol and a serious increase in deaths has been reported in recent times.[9,14] Similarly in the current study, 60% (n:9) of the victims were determined to have died during the COVID-19 pandemic, all died at home as a result of methanol poisoning, and no traumatic findings were determined in the autopsies. This suggests that as a result of the economic problems that emerged during the pandemic, chronic alcoholics in particular voluntarily searched for cheap alcohol and turned to alternatives such as cologne.

Previous studies have shown that the majority of cases of methanol toxicity in Tunisia, Turkey, and India were related to drinking cologne and perfume.[9] Research in Turkey has shown that the majority of deaths related to methanol poisoning originate from the drinking of illegally and home-produced alcohol. Pectolytic enzymes in many fermentation products such as in fruit (grapes, plums)-based alcoholic drinks and apple wine can increase the methanol levels in illegal home-produced drinks. In addition, methanol can be used instead of ethyl alcohol during the illegal production of alcohol. As a result of this, sporadic outbreaks are encountered with cases of death related to methanol poisoning.[15,16] In the present study, the majority of the victims (8/15) were determined to have died after drinking cologne. All of the deaths from cologne consumption occurred during the outbreak of COVID-19. This suggests that this is due to the use of cheaper methanol instead of ethanol in illegal production, which is linked to the large antiseptic increase of cologne production.

Previous studies reported that methanol poisoning is generally seen in males, usually in the 4^{th} -5^{th} decades of life.[14,15] It has also been stated that hospital presentations may be delayed in places where alcohol consumption is not acceptable to society or for religious reasons.[14] Consistent with the literature, all the cases in the current study were male with a mean age of 52.1 years. This was thought to be due to alcohol consumption just being among males because of the traditional cultural characteristics of Şanlıurfa.

The clinical symptoms of methanol intoxication resemble the symptoms of normal alcohol intake, such as sleepiness, headache, nausea and vomiting. However, it can subsequently cause much more serious symptoms such as kidney failure, respiratory failure, convulsions, and central nervous system depression extending to coma. Visual impairments occur in approximately 50% of patients, and these may develop as diplopia, blurred vision, decreased visual acuity, photophobia, decreased visual field, and blindness.[3,17] In the current study, clouded consciousness and respiratory problems were observed in 9 cases, and 4 presented at the Emergency Department with visual disorders and 1 in a state of coma.

Varying ranges of blood concentration at a toxic level in methanol poisoning have been reported in literature. The widest range reported is 15-500 mg/dl.[18] The morbidity and mortality limits for methanol have been seen to be in extremely broad ranges in studies in literature.[19,20] The lethal dose of alcohol is related to age, gender, and genetic factors, and the rate of alcohol consumption, the type of drink, and drinking habits may also have an effect.[12] In the current study, the blood toxicology levels showed variability of 46-520 mg/dl, and the intra-ocular fluid toxicology levels of 62-624 mg/dl. In the toxicology examinations of the bodily fluids of 2 cases, no methanol or metabolites were determined as they were hospitalised or a long time. Therefore, in cases of intoxication, sending the first blood sample taken in hospital to a centre that can analyze methanol and metabolites would make a significant contribution to the autopsy procedure.

Alcohol can inhibit the central nervous system, can cause respiratory depression, and ultimately can lead to death because of asphyxia.[13] Pulmonary oedema, pulmonary congestion, alveolar spaces filled with hemorrhagic oedema, gastric mucosal damage, cardiac findings, obstructions related to foreign bodies in the trachea,

bronchi or bronchioles associated with vomiting, and changes in organs and tissues due to chronic alcohol use can be seen in the autopsies of deaths related to alcohol intoxication.[12] Acute and chronic changes were determined in the tissues of all the present study cases, which was supportive of methanol intoxication and consistent with the literature (Table 2). When performing an autopsy, other causes of suspicious death must be discounted and non-specific autopsy findings must be supported by forensic investigation data.

From 4650 medicolegal autopsies performed in our centre in the last 7 years, 0.32% (n:15) were determined to have died as a result of methanol intoxication. There was seen to be an increase in methanol poisonings as a result of consuming alternative drinks such as drinks with cheap alcohol or cologne, especially by those with chronic alcohol use during the COVID-19 pandemic. Toxicology analyses determined that cheaper methanol had been used in alcoholic liquids instead of ethanol. All the victims were male, and the majority were chronic alcoholics in the 5^{th} and 6^{th} decades of life who died at home. In the autopsies, there were seen to be non-specific histopathological findings and no signs of trauma. In the toxicology analysis, the methanol level in the intra-ocular fluid was higher, and analysis of the first blood samples taken at the hospital, especially for those treated for a long period provided significant support in clarification of the event. In conclusion, there is a need for programs to be implemented to inform the public about intoxications developing after the consumption of liquids containing methanol, and early treatment should be started. In addition, there is a need to take precautions against methanol intoxication by increasing control at the production and sales stages of alcoholic drinks and antiseptics containing alcohol, such as cologne.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Acknowledgments

We thank the Forensic Medicine Institute for their contribution to the study.

Ethics Committee Permission

The study was approved by the Ministry of Justice Forensic Medicine Institute Education and Scientific Research Commission (Date: 22/02/2023 and number 2023/102).

Authors' Contributions

Concept/Design: ASD, İA. Data Collection and/or Processing: ASD, İA. Data analysis and interpretation ASD, İA. Literature Search: ASD, İA. Drafting manuscript: ASD, İA.

REFERENCES

1. Koca T, Hilal A. Metil Alkol (Metanol) İntoksikasyonu. Adli Tıp Bülteni. 2020;25(2):128-138.
2. Mutlu E, Balcı Y, Seçkin Ç Muğla'da Metanol Zehirlenmesine Bağlı Ölümler: Olgu Serisi. Adli Tıp Bülteni. 2022;27(2):150-156.
3. Taşkın Ö, Akpınar AA, Dişel NR. Metil Alkol Zehirlenmeleri. Anatolian J Emerg Med. 2022;5(1):37-42.
4. Pohanish RP. Sittig's Handbook of Toxic and Hazardous Chemicals and Carcinogens. USA: Elsevier; 2012.
5. Vural S. Transdermal Methanol Intoxication Via Folk Medicine. J Emerg Med Case Rep. 2019;10(2):50-52.
6. Patil AM, Meshram SK, Kharat RD et al. Profile of Fatal Methyl Alcohol Poisoning Outbreak-A Medicolegal Autopsy Case Study. Indian J Med Forensic Med Toxicol. 2013;7(1):16-20.
7. Gautam M, Dandu H, Siddiqui SS, Atam V, Kumari S, Rathore S. Acute Methanol Toxicity: Clinical Correlation with Autopsy Findings, a Descriptive Study. J Assoc Physicians India. 2022;70(6):11-12.
8. Kim H-J, Na J-Y, Lee Y-J, Park J-T, Kim H-S. An autopsy case of methanol induced intracranial hemorrhage. Int J Clin Exp Pathol. 2015;8(10):13643.
9. Wang LL, Zhang M, Zhang W et al. A retrospective study of poisoning deaths from forensic autopsy cases in northeast China (Liaoning). J Forensic Leg Med. 2019;63:7-10.
10. Lachenmeier DW, Samokhvalov AV, Leitz J et al. The composition of unrecorded alcohol from eastern Ukraine: is there a toxicological concern beyond ethanol alone? Food Chem Toxicol. 2010;48(10): 2842-2847.
11. Global Information System on Alcohol and Health (GISAH). Available from: http://apps.who.int/gho/data/node.main.GISAH?lang ¼en Erişim tarihi 13 December, 2022.
12. Arslan MM, Zeren C, Aydin Z, et al. Analysis of methanol and its derivatives in illegally produced alcoholic beverages. J Forensic Leg Med. 2015;33:56-60.
13. Zeren C, Aydin Z, Yonden Z, Bucak S. Composition of bogma raki, Turkish traditional alcoholic beverage. J Food Technol. 2012;10(3):87-89.
14. Kurtaş Ö, Imre KY, Özer E, et al. The evaluation of deaths due to methyl alcohol intoxication. Biomed. Res. 2017;28(8):3680-3687.
15. Azmak D. Methanol related deaths in Edirne. Leg Med. 2006;8(1):39-42.

16. Hovda KE, Lao YE, Gadeholt G, et al. Formate test for bedside diagnosis of methanol poisoning. Basic Clin. Pharmacol. Toxicol. 2021;129(1):86-88.
17. DJ D. DiMaio VJM: Forensic Pathology. CRC Press. BOCa Raton, l993:507-547.
18. Mittal B, Desai A, Khade K. Methyl alcohol poisoning: an autopsy study of 28 cases. J Postgrad Med. 1991;37(1):9-13.
19. Graw M, Haffner H-T, Althaus L, Besserer K, Voges S. Invasion and distribution of methanol. Arch Toxicol. 2000;74(6):313-321.
20. Zakharov S, Kurcova I, Navratil T, Salek T, Komarc M, Pelclova D. Is the measurement of serum formate concentration useful in the diagnostics of acute methanol poisoning? A prospective study of 38 patients. Basic Clin Pharmacol Toxicol. 2015;116(5): 445-451.

ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Extramedullary Hematopoiesis with Atypical Localization in Patients with Hemolytic Anemia

Hemolitik Anemili Hastalarda Atipik Lokalizasyonlu Ekstramedüller Hematopoez

Şerife LEBLEBİSATAN[1] Metin ÇİL[2] Adnan BARUTÇU[3]

ÖZ

Amaç: Bu çalışmada bölgemizde takip edilmekte olup çoğunluğu hemoglobinopati tanısı almış hemolitik anemili hastalarda ekstramedüller hematopoez (EMH) atipik lokalizasyonlarını saptamak amaçlanmıştır.
Araçlar ve Yöntem: 01.07.2020-28.02.2022 tarihleri arasında hastanemiz Çocuk Hematoloji Kliniğinde takip edilen hemolitik anemili hastaların dosyaları ve görüntüleme tetkikleri retrospektif olarak tarandı. Hastalardan şikayetleri nedeniyle ya da başka nedenlerle görüntüleme yapılıp lezyonlar saptananlar değerlendirildi. Hastaların bir kısmı 18 yaş üzerindeydi ve olgular daha çok bu yaşlarda saptandı.
Bulgular: Çalışmada toplam 247 hasta tarandı.Görüntüleme tetkiklerinde öncelikle akciğer filmleri ve sonrasında gerekli görülen daha ileri yöntemlerle (toraks bilgisayarlı tomografisi, manyetik resonans görüntüleme gibi) tarama yapıldığında 5 hastada atipik lokalizasyonda EMH saptandı. Hastalarda tek veya çift taraflı torakal paraspinal EMH saptandı. Bir hastada ek olarak sağ böbrek EMH odağı mevcuttu.
Sonuç: Hemolitik anemili hastalarda saptanan kitle lezyonunun atipik lokalizasyonda EMH olma olasılığının klinisyen ve radyolog tarafından değerlendirilmesi hastayı gereksiz tanısal ve girişimsel işlemlerden koruyacaktır. Hastaların düzenli takip ve tedavileri esnasında bu lezyonların varlığı açısından da öngörülü olunmalıdır.

Anahtar Kelimeler: anemi; görüntüleme; hemoglobinopati; hematopoez

ABSTRACT

Purpose:This study aimed to determine the atypical localizations of extramedullary hematopoiesis (EMH) in patients with hemolytic anemia, most of whom were diagnosed with hemoglobinopathy and are followed in our region.
Materials and Methods: The files and imaging examinations of hemolytic anemia patients in the Pediatric Hematology Clinic of our hospital between 01.07.2020-28.02.2022 were retrospectively scannedPatients who were imaged for complaints or for other reasons were evaluated for lesions. Some of the patients were over the age of 18 and the cases were mostly detected at this age.
Results: A total of 247 patients were scanned in the study, and EMH was detected in atypical localization in 5 patients as a result of imaging studies, firstly with lung films and then with more advanced methods (such as chest computed tomography, magnetic resonance imaging) when necessary. Unilateral or bilateral thoracic paraspinal EMH was detected in the patients. One patient had an additional right kidney EMH focus.
Conclusion: Clinical and radiological evaluation of the probability of a mass lesion detected in patients with hemolytic anemia to be EMH at atypical localization will protect the patient from unnecessary diagnostic and interventional procedures. During the regular follow-up and treatment of the patients, the presence of these lesions should also be predicted.

Keywords: anemia; hemoglobinopathy; hematopoiesis; imaging

Received: 25.10.2022; Accepted: 10.07.2023

[1]Adana City Training and Research Hospital, Department of Radiology, Adana, Türkiye.
[2]Adana City Training and Research Hospital, Department of Pediatric Hematology, Adana, Türkiye.
[3]Çukurova University Medical Faculty, Department of Pediatrics, Adana, Türkiye.
Corresponding Author: Adnan Barutçu, Çukurova University Medical Faculty, Department of Pediatrics, Adana, Türkiye. e-mail: adnan_barutcu@hotmail.com

How to cite: Leblebisatan Ş, Çil M, Barutçu A. Extramedullary hematopoiesis with atypical localization in patients with hemolytic anemia. Ahi Evran Med J. 2024;8(1):11-15. DOI: 10.46332/aemj.1194238

INTRODUCTION

The presence of hematopoietic tissue except bone marrow in order to increase hemoglobin value while causing growth, shape change and even structural changes in tissue is called Extramedullary hematopoiesis (EMH).[1] It is seen mostly where low hemoglobin levels due to insufficient erythrocyte production or transfusion policy cannot prevent tissue hypoxia in diseases like hemolytic anemias or rarely in the bone marrow myeloproliferative diseases.[2]

It can be observed under even physiological situations that the main location of fetal hematopoiesis are in liver and the spleen as EMH at embryonic and fetal life.[3] However, pathologic EMH is observed when normal hematopoiesis in the bone marrow cannot function properly, and it may be interrupted by myelofibrosis, thalassemias, or other conditions affecting the hematopoietic system. Therefore-pathological EMH regions may be associated with the reactivation of the embryonic hematopoietic structure in many organs where they are observed.

The correct interpretation of mass lesions that are unexpectedly detected in radiological examinations performed for other purposes in patients with hematological anemia who receive either transfusion or other other treatments, is of a great importance both for the patient and the clinician. Since non-benign diagnostic interpretations may lead to unnecessary diagnostic and even surgical interventions keeping extramedullary hematopoiesis (EMH) in mind even though they are in atypical localizations.

Here we intended to summarize our EMH cases with with their clinical and radiological imagings while discussing clinical variations and management.

MATERIALS and METHODS

The files of the 247 patients in the Pediatric Hematology Clinic of our hospital with the diagnosis of hemolytic anemia between July 2020 and February 2022 were reviewed retrospectively. All of the patients were scanned for their previous Chest X rays and abdominal ultrasonography if performed. Patients without previous X-ray were excluded. Patients with congenital anemia can be followed in the pediatric hematology department at this age. In radiological examinations, EMH foci in rare localizations such as paraspinal, kidney, adrenal and mesentery were investigated, except for common localizations such as spleen, liver, thymus and lymph nodes.

The study was approved by Adana City Training and Research Hospital Clinical Research Ethics Committee (Date: 27.01.2022, Session No: 98, Decision No: 1763).

Statistical Analysis

The data was analyzed using SPSS 20.0 software package for windows. Categorical variables were summarized as numbers and percentages while continuous variables were summarized as mean and standard deviation (median and minimum-maximum if necessary).

RESULTS

Of the patients included in the study, 6 were being followed with a diagnosis of pyruvate kinase deficiency, 120 with sickle cell anemia, and 121 with β thalassemia. Some of the patients were over the age of 18 and the five EMH cases were mostly detected at this age group. EMH in atypical localization was detected in 5 patients. Unilateral or bilateral thoracic paraspinal EMH was detected in all patients. One patient had an additional right kidney EMH focus. Their disease diagnosis distribution were mostly hemoglobinopathies as in Table 1. The details of patients were given below with their treatments and transfusion schedules. EMH patients were older and have higher platelet levels. Diagnostic distributions, some hemogram values and demographic data of the patients are shown in Table 1.

Case 1: A 23-year-old female patient with hemolytic anemia, is being followed up in a chronic transfusion regimen, and receives 1-2 Units of erythrocyte suspension every 2 months. A few years ago, the patient underwent abdominal USG during gallstone/hypersplenism investigations and was diagnosed with a right renal mass, and a CT scan was recommended for mass characterization. Splenomegaly and cholelithiasis were observed in axial abdominal CT scans with oral and IV contrast (Figure 1). In the sections

passing through the lower thoracic level, there were bilateral paravertebral masses of 23x13 mm at the level of the T9 vertebra on the right and 23x10 mm at the level of the T8-T9 vertebrae on the left in the posterior thoracic section. A mass lesion with a size of 12x9 cm, well-circumscribed, solid and heterogeneous internal structure, developed from the right kidney, which was observed to compress the liver (Figure 1) was observed. Surgery was recommended with the diagnosis of malignant lesion of renal origin in the initial evaluations; however, a diagnosis of EMH was considered after a comprehensive evaluation of the images and the patient's clinical picture. In the follow-up images, the diagnosis was confirmed as the mass began to shrink with regular erythrocyte transfusions and elevation of basal hemoglobin.

Table 1. Diagnostic distributions, some hemogram values and demographic data of the patients.

	All patients n=247 (100%)	**EMH (-)**	**EMH(+)**
Male sex, n (%)	110 (44%)	108 (44%)	2 (40%)
Diagnosis, n(%)			
PKD	6 (2%)	4 (2%)	2 (40%)
SCA	120 (49%)	120 (50%)	-
β Thal	121 (49%)	118 (48%)	3 (60%)
		Mean±SD Median (min-max)	**Mean±SD Median (min-max)**
Age (months)	175.6±83.9 184.0 (7.0-348.0)	171.4±83.1 181.0 (7.0 – 348.0)	271.6±22.6 282.0 (242.0-296.0)
Hg (gr/dL)	9.9±2.2 9.3 (4.9-15.5)	9.9±2.2 9.3 (4.9-15.5)	8.6±0.9 8.4 (7.9-10.2)
Platelet (/μL)	454100±241190 (201000-1123000)	445000±242690 (210000-1123000)	647800±57070 (566000- 709000)

PKD; Pyruvate Kinase Deficiency, SCA; Sickle Cell Anemia, β Thal; Beta Thalassemia

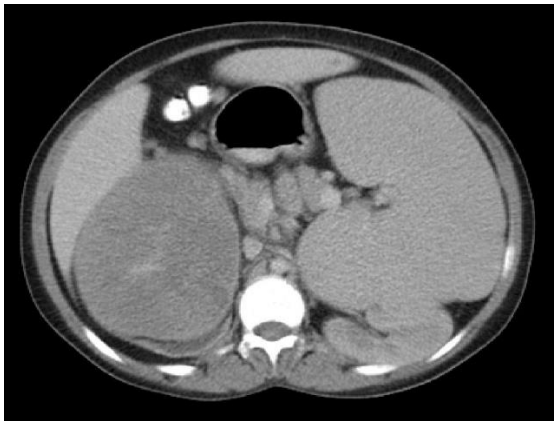


Figure 1. Contrast-enhanced axial CT scan shows a smooth-circumscribed slightly enhanced hypodense mass originating from the right kidney.

Case 2: A 25-year-old female patient with hemolytic anemia (with a preliminary diagnosis of membranopathy) was out of follow-up because she started working in another province after her graduation. After being followed for a long time without blood transfusion, she was referred to the clinic where she was followed up before, due to mediastinal enlargement in the chest X-ray. In her new genetic evaluation, she was diagnosed with Pyruvate Kinase deficiency. In the thoracic vertebra MR examination, an oval, well-circumscribed, EMH focus was found in the right paravertebral localization in the axial T2W section (Figure 2).

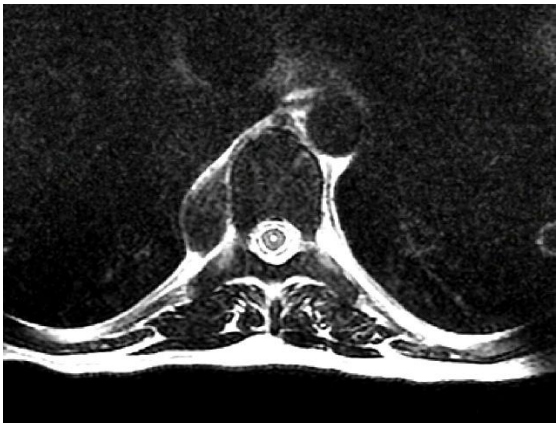


Figure 2. Axial T2W thoracic vertebra MRI scan shows well-circumscribed EMH in the right paraspinal area.

Case 3: A 24-year-old female patient with a diagnosis of thalassemia intermedia who was not transfused because she was out of follow-up for a long time presented with respiratory symptoms. EMH was detected with thorax CT taken after chest X-ray. On CT imaging, a mass extending between T2-T4 vertebral corpus levels in the left paraspinal area and measuring 46x36 mm at T4 vertebral corpus level was observed . At the level of the T5 vertebra corpus, a separate 46x17 mm mass with lobulated contours was measured in the left paraspinal area. Mass lesions were observed extending bilaterally in the paraspinal area along the T6-T11 vertebrae, and their axial dimensions were

69x28 mm on the right and 48x12 mm on the left at the level of the T10 vertebral body (Figure 3).

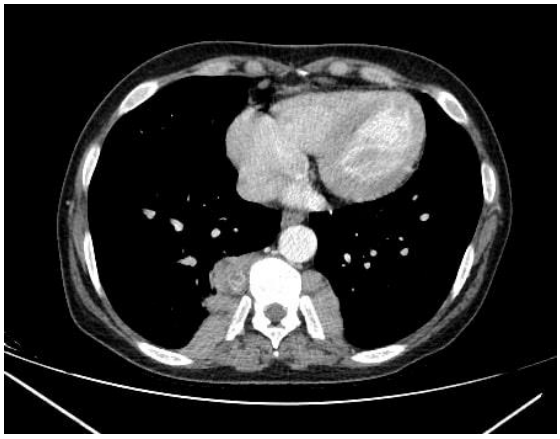


Figure 3. Axial contrast-enhanced thoracic CT scan shows bilateral paravertebral lobulated contoured EMH.

Case 4: A 20-year-old Thalassemia Major patient was on a regular transfusion regimen and had thoracic paraspinal EMH on CT examination.

Case 5: A 21-year-old thalassemia intermedia patient was alive with transfusion-free subnormal hemoglobin levels, and bilateral paravertebral EMH foci were present in the MRI images of the thoracic vertebrae.

DISCUSSION

When we examine the literature, there are over 3000 articles and we see that the number of publications has increased every year since the 1980s and has reached more than a hundred per year in recent years. This may be related to the increase in complications as a result of the increasing survival rates of these congenital hemolytic anemia patients as ß thalassemia and sickle cell anemia in recent years. The total number of publications in these two disease groups is around one third of all publications. In general, case reports have been reported and, rarely, studies and reviews have been included.[4-6]. In screening for this group of diseases, as in our thalassemia patients, non-transfusional thalassaemia patients had higher EMH rates than those who had transfusions, whereas in sickle cell anemia patients the EMH rate was higher, which we couldn't detect in our study.The fact that Pyruvate Kinase deficiency patients, which are detected in very few numbers in the literature, are seen in 40% of the patients we screened, this may be due to the difficulties in diagnosis of this disease group, as well as the difficulties in detecting EMH.

As the literature revealed, EMH can also be caused by also ineffective erythropoietic conditions (such as pernicious anemia, hypochromic anemia, erythroblastosis fetalis, folate or vitamin B12 deficiency), loss of stem cell differentiation (such as in myelosclerosis, myelofibrosis, and polycythemia rubra vera); or non-myeloid neoplastic diseases with bone marrow myelophysical effects (such as leukemia, lymphoma, carcinomatosis). Hematologically normal individuals also may present with EMH.[7] Also, it has been widely reported in the literature to occur in places that are not expected to include hematopoiesis.[8-11] EMH tends to develop in serous membranes such as the pleura, pericardium, mesentery, and omentum, as well as in tissues such as the adrenal glands, gastrointestinal tract, epididymis, uterus, peripheral nerves, thoracic cavity, breast, heart, adipose tissue, cartilage, brain, and spinal cord.[7] Although it is most commonly seen in the posterior mediastinum, it has also been reported in the retroperitoneum and kidneys.[7] EMH is very rare in the kidney parenchyma, as in one of our patients.

In X-ray examination, they are observed as well-circumscribed masses in the paraspinal areas.[12-13] On CT scans, they are observed as paravertebral lesions of muscle density, which do not cause destruction in the adjacent bone, with smooth borders and lobulation at the edges. Contrast enhancement is homogeneous. However, in chronic lesions, iron accumulation and fat deposition may lead to a heterogeneous appearance in the lesion.[12] Paravertebral masses show intermediate signal intensity on both T1- and T2-weighted MR images. Enhancement with IV Gadolinium agents is minimal or absent. Chronic inactive lesions are observed heterogeneously. If fat deposition has developed, areas with high signal intensity are observed on both T1 and T2-weighted MR images. Treating the patients with blood transfusion reduces the sizes of the lesions, and low signal intensity can be observed in both T1 and T2-weighted MR images of the mass due to massive iron deposition on MRI.[13]

In renal involvement, EMH may be located in the renal parenchyma or renal pelvis, or it may be located perirenal.[14] Generally, EMH has a diffuse appearance and it is rare to

present as a focal mass-like lesion. EMH as a solitary renal mass has been reported in only a few cases in the literature. In all these cases, renal cell carcinoma or other secondary malignancies were the initial diagnosis.[15] It has been reported that the lesions were hypodense on non-contrast CT and showed mild enhancement with contrast in the patient who had EMH foci that filled and enlarged the pelvicalyceal system of both kidneys.[16]

As the treatment concerned, blood transfusions are typically used to treat such situations, which can lessen the hematopoietic drive for EMH. Other alternatives include surgery, radiation, hydroxyurea, or a case-by-case mix of these.

The small number of patients and the retrospective design are limitations of the study. Considering the relative rarity of the disease process and the time required to collect sufficient number of patients, it is unfortunately not possible to conduct a prospective study.

In conclusion, EMH can occur in a variety of locations, familiar or unfamiliar to the clinician, with expected and unexpected sites. Especially in hematologic diseases, the evaluation of these lesions should include benign hematopoiesis efforts of the hematopoietic system. Thus, unnecessary evaluation and interventions can be avoided.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

The study was approved by Adana City Training and Research Hospital Clinical Research Ethics Committee (Date: 27.01.2022, Session No: 98, Decision No: 1763).

Authors' Contributions

Concept/Design: ŞL, MÇ. Data Collection and/or Processing: ŞL, MÇ, AB. Data analysis and interpretation: ŞL, AB. Literature Search: ŞL, MÇ, AB. Drafting manuscript: ŞL, MÇ, AB. Critical revision of manuscript: ŞL, MÇ, AB.

REFERENCES

1. Yang X, Chen D, Long H, Zhu B. The mechanisms of pathological extramedullary hematopoiesis in diseases. Cell Mol Life Sci. 2020;77(14):2723-2738.
2. Malla S, Razik A, Das CJ, Naranje P, Kandasamy D, Kumar R. Marrow outside marrow: imaging of extramedullary haematopoiesis. Clin Radiol. 2020;75(8): 565-578.
3. Kapatia G, Kaur A, Rastogi P, et al. Extramedullary hematopoiesis: Clinical and cytological features. Diagn Cytopathol. 2020;48(3):191-196.
4. Kalchiem-Dekel O, Greenbaum U. Extramedullary Hematopoiesis in β-Thalassemia. Mayo Clin Proc. 2015;90(11):1591-1592.
5. Ata F, Subahi EA, Choudry H, Yassin MA. Protocol for extramedullary hematopoiesis in patients with transfusion-dependent β-thalassemia (TDT): A systematic review. Health Sci Rep. 2021;4(4): 429.
6. A Subahi E, Ata F, Choudry H, et al. Extramedullary haematopoiesis in patients with transfusion dependent β-thalassaemia (TDT): a systematic review. Ann Med. 2022;54(1):764-774.
7. Rajiah P, Hayashi R, Bauer TW, Sundaram M. Extramedullary hematopoiesis in unusual locations in hematologically compromised and noncompromised patients. Skeletal Radiol. 2011;40(7):947-953.
8. Ch'en IY, Lynch DA, Shroyer KR, Schwarz MI. Gaucher's disease. An unusual cause of intrathoracic extramedullary hematopoiesis. Chest. 1993;104(6): 1923-1924.
9. Li R, Reddy VV, Palmer CA. Extramedullary hematopoiesis: an unusual finding in subdural hematomas. Case Rep Pathol. 2011; 718585.
10. Ginzel AW, Kransdorf MJ, Peterson JJ, Garner HW, Murphey MD. Mass-like extramedullary hematopoiesis: imaging features. Skeletal Radiol. 2012;41(8): 911-916.
11. Vardareli E, Entok E, Ak I, Bayhan H. An unusual localization of extramedullary hematopoiesis. Clin Nucl Med. 1996;21(3):256-257.
12. Sohawon D, Lau KK, Lau T, Bowden DK. Extra-medullary haematopoiesis: a pictorial review of its typical and atypical locations. J Med Imaging Radiat Oncol. 2012;56(5):538-544.
13. Haidar R, Mhaidli H, Taher AT. Paraspinal extramedullary hematopoiesis in patients with thalassemia intermedia. Eur Spine J. 2010;19(6):871-878.
14. Ricci D, Mandreoli M, Valentino M, Sabattini E, Santoro A. Extramedullary haematopoiesis in the kidney. Clin Kidney J. 2012;5(2):143-145.
15. Ahuja S, Grover G, Jha AK, Sodhi K, Bansal D, Dey P. Extramedullary hematopoiesis presented as solitary renal mass: a case report with review of literature. Diagn Cytopathol. 2011;39(6):435-437.
16. Kim YK, Kwak HS, Kim CS, Chung GH, Han YM, Lee JM. Hepatocellular carcinoma in patients with chronic liver disease: comparison of SPIO-enhanced MR imaging and 16-detector row CT. Radiology. 2006;238(2):531-541.

ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Evaluation of Patients Presenting to the Emergency Department in terms of Sociodemographic Characteristics, Diagnosis Codes and COVID-19 Diagnosis

Acil Servise Başvuran Hastaların Sosyodemografik Özellikler, Tanı Kodları ve COVID-19 Tanısı Açısından Değerlendirilmesi

Özlem TEKİR[1] Ali Kamil BAYRAKTAR[2]

ÖZ

Amaç: Acil serviste COVID-19 tanısı alan hastaların sosyodemografik özellikleri ve tanı kodları açısından değerlendirilerek COVID-19 pandemisinin acil servis başvurularına ve işleyişine olan etkisini incelemek amaçlandı.
Araçlar ve Yöntem: Retrospektif, tanımlayıcı tipte olan bu çalışma, 1100 yataklı bir hastanenin acil servisinde 11.03.2020-31.03.2021 tarihleri arasında yapıldı.
Bulgular: Acil servis başvuruların yıl içerisindeki dağılımına göre; pandemi polikliniğine kabul edilen hasta sayıları haziran ayında en düşük seviyede, kasım ayında ise en yüksek seviyededir. Aylık başvuru sayılarının yaşa göre dağılımında en çok başvuru 15-29 yaş grubu ile 30-44 yaş gurubunda; en az başvuru ise 0-14 yaş gurubundadır. Hastanede yatarak tedavi edilen COVID-19 tanılı kişi sayıları nisan ve kasım aylarında en yüksek seyiyededir.Toplam başvuruya oranla test sonucu pozitif çıkma oranlarının en yüksek olduğu aylar; ekim (%15.3), ocak (%15.5) ve mart (%17.1) aylardır. Pozitiflik oranının cinsiyet bazlı dağılımında değerler genel olarak birbirine yakın olmakla birlikte 13 aylık ortalama değere bakıldığında kadınlarda ortalama değer %4.40, erkeklerde ortalama değer %4.45'tir.
Sonuç: Çalışmanın sağladığı veriler, COVID-19 pandemisinin acil servis başvurularına ve işleyişine olan etkisini göstermekle beraber; benzer durumlara yönelik olarak, gerekli eğitim, planlama ve organizasyon süreçlerine katkı sağlayacaktır.

Anahtar Kelimeler: acil servis; covid-19; retrospektif çalışma; tanı; triyaj

ABSTRACT

Purpose: This study was conducted to evaluate patients diagnosed with COVID-19 in the emergency department in terms of their sociodemographic characteristics and diagnosis codes and to examine the effect of the COVID-19 pandemic on presentations to the emergency department and its functioning.
Materials and Methods: This retrospective, descriptive study was conducted in the emergency department of an 1100-bed hospital between March 11, 2020 and March 31, 2021.
Results: According to the distribution of emergency service admissions during the year, the number of patients admitted to the pandemic outpatient clinic was the lowest in June and the highest in November. Considering the distribution of monthly presentation figures by age, the highest number of admissions were in the 15-29 and 30-44 age groups, and the least number of admissions was in the 0-14 age group. The number of patients diagnosed with COVID-19 was the highest in April and November. The months with the highest rate of positive test results compared to the total admissions were October (15.3%), January (15.5%), and March (17.1%). In the gender-based distribution of the COVID-19 positive cases, the values were generally close to each other; however, when the 13-month average was considered, it was found 4.40% in females and 4.45% in males.
Conclusion: Data provided by our study showed that the effect of the COVID-19 pandemic on emergency service admissions and functioning. Besides, they will contribute to the necessary education, planning, and organization processes for similar situations.

Keywords: covid-19; diagnosis; emergency department; retrospective study; triage

Received: 30.03.2023; Accepted: 14.07.2023

[1]İzmir Demokrasi University, Faculty of Health Sciences Department of Nursing, Internal Medicine Nursing, İzmir, Türkiye.
[2]Balıkesir Atatürk City Hospital, Emergency Department, Balıkesir, Türkiye.

Corresponding Author: Özlem Tekir, İzmir Demokrasi University, Faculty of Health Sciences Department of Nursing, Internal Medicine Nursing, İzmir, Türkiye.
e-mail: ozlemtekir_10@hotmail.com

How to cite: Tekir Ö, Bayraktar AK. Evaluation of patients presenting to the emergency department in terms of sociodemographic characteristics, diagnosis codes and covid-19 diagnosis. Ahi Evran Med J. 2024;8(1):16-21. DOI: 10.46332/aemj.1273360

INTRODUCTION

Emergency departments are units that provide uninterrupted health services and have been designed for the implementation of primary medical and surgical interventions required by individuals with health problems, such as accidents, trauma, and life-threatening diseases, which require rapid intervention.[1] Since emergency departments are the first application and intervention unit for many health problems, they are of great significance in terms of individual and public health and are like the showcase of the hospitals they are affiliated with.[2,3] It is very important to evaluate the number of presentations to the emergency department and the characteristics of the patients beforehand so that necessary planning and organization can be provided for the patient.[4]

In the new coronavirus (COVID-19) pandemic with high morbidity and mortality rates, emergency departments have been at the forefront of hospital and community care. They are of great significance in terms of both identifying and treating suspected COVID-19 cases and continuing to diagnose and treat other medical emergencies.[5,6,7,8] The most important issue in this process is the provision of high-quality and effective care. Therefore, it is of great significance to reorganize and restructure emergency departments to meet changing needs.[9,10,11,12]

In the light of this information, this study was conducted to evaluate patients who were diagnosed with COVID-19 in the emergency department in terms of their socio-demographic characteristics and diagnosis codes and to examine the effect of the COVID-19 pandemic on presentations to the emergency department and its functioning.

MATERIALS and METHODS

Design and Setting

In this retrospective, descriptive study, patients presenting to the emergency department of a 1100-bed hospital in a province in Türkiye between March 11, 2020 and March 31, 2021 were evaluated in terms of their sociodemographic characteristics, diagnosis codes, and COVID-19 diagnosis.

The data used in this study were obtained by retrospectively searching the hospital information management system (HIMS) records, which were anonymized by the IT department of the hospital where the research was conducted. First, the distribution of the number of emergency department admissions according to the adult emergency outpatient clinic and the pandemic outpatient clinic was determined. Afterward, the distribution of all patients admitted to both outpatient clinics according to triage codes, gender, age groups, and treatment type and the distribution of the individuals according to the services where they were admitted were examined. In addition, the diagnostic procedures of the patients admitted to the emergency department pandemic outpatient clinic, their distribution according to the diagnosis codes, the rates of starting antiviral drugs, and their distribution according to polymerase chain reaction (PCR) test results (negative or positive) were examined.

The diagnosis coding system of the International Classification of Diseases-10 (ICD-10) was used as the basis for determining the distribution according to the diagnosis codes, and the diagnoses were categorized according to the systems.

Analysis of Data

Data obtained from HIMS records were transferred to Microsoft Excel 2016 office software. Grouping of data, creation of charts, and calculation of mean and percentage distributions were performed on this software.

Ethical Dimension of Research

At the outset, the approval of Balıkesir University Faculty of Medicine Clinical Research Ethics Committee (decision no: 2021/126, date: 26.05.2021) was obtained for the study.

RESULTS

Considering the distribution of emergency service presentations throughout the year, the highest number of presentations in the adult emergency polyclinic in a ten-day period was in the last period of July 2020. The number of patients admitted to the pandemic outpatient clinic was the highest in the second period of November 2020 and the

lowest in the last period of June 2020 (Figure 1).

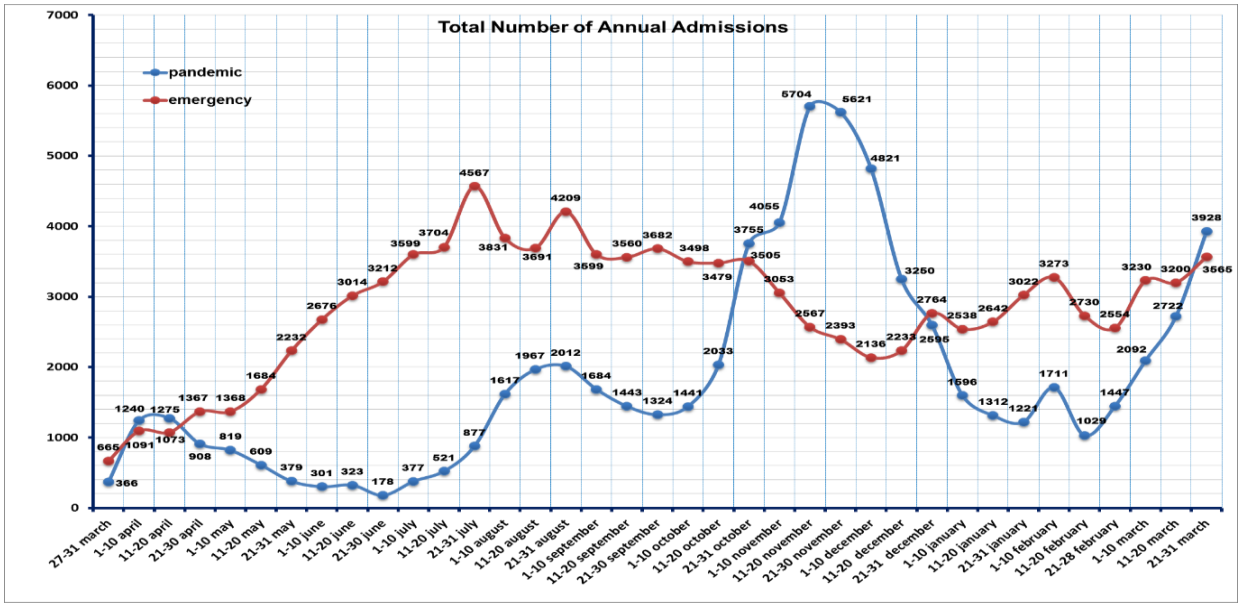


Figure 1. Annual distribution of the number of emergency service admissions in 10-day periods.

The examination of the distribution of emergency department admissions by gender indicated that the rates of male patient admissions were higher in both the pandemic outpatient clinic and the emergency outpatient clinic. It was seen that the majority of admissions in both polyclinics were in the yellow triage area. Presentation rates with the red triage code were higher in both outpatient clinics in March and April compared to other months (Supplement Table 1).

When the distribution of admissions to the pandemic outpatient clinic according to age groups was examined, it was determined that the highest number of admissions was in the 15-29 and 30-44 age groups, and the lowest number of admissions was in the 0-14 age group (Figure 2).

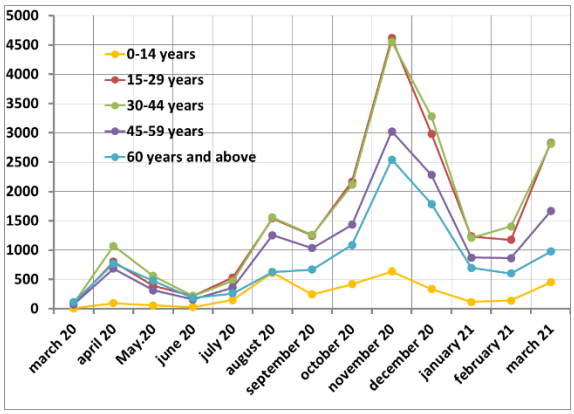


Figure 2. Distribution of emergency department pandemic outpatient clinic admissions by age groups.

It was observed that the rates of chest X-ray and thoracic computed tomography (CT) requests for diagnosis were high in the first months in the pandemic outpatient clinic (Supplement Table 2). The data of the number of people whose throat and nose swab samples were taken for diagnostic purposes in the first three months and a part of June could not be reached in the hospital database. Swab samples had been taken from all individuals admitted to the pandemic outpatient clinic in February 2021. The highest number of swab samples had been taken in November 2020. The rate of COVID-19 positive samples was the lowest in August 2020 and the highest in January 2021 and March 2021 (Supplement Table 2). Antiviral medication treatment as a result of examinations in the pandemic outpatient clinic was first initiated in May 2020.

The first data on PCR tests were available as of June. The highest rates of positive test results compared to the total admissions were observed in 2020 October, 2021 January, and 2021 March. Although the values for the gender-based distribution of positive test rates were generally close to each other, the 13-month average value was 4.40% for females and 4.45% for males (Figure 3).

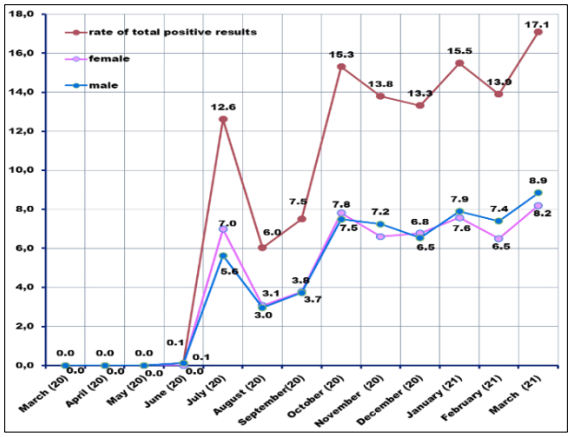


Figure 3. The rate of positive PCR test results of emergency service pandemic outpatient clinic admissions.

The highest number of patients who were deemed suitable for hospitalization after their presentation to the pandemic outpatient clinic was observed in November 2020 and December 2020. The highest rate of COVID intensive care admissions referred from the pandemic outpatient clinic was observed in March 2021. The highest number of patients admitted to the COVID service from the pandemic outpatient clinic was in April 2020 and November 2020.

The highest admission rates from the emergency outpatient clinic to the COVID service and the COVID intensive care unit were in April 2020 (Supplement Table 3).

The diagnosis codes that were most often used in the diagnosis of individuals who presented to the pandemic outpatient clinic were Z03, Z03.8, and Z03.9 (observation and evaluation for suspected diseases and conditions). The most frequently used diagnosis codes following those used for the diagnosis of suspected diseases were in the range of J00–J99, which were used for the diagnosis of respiratory system diseases (Supplement Table 4).

DISCUSSION

Emergency departments have an important role in the identification and treatment of suspected cases of COVID-19, which has high morbidity and mortality rates, as well as the uninterrupted delivery of healthcare for other medical emergencies.[5] Accordingly, this study provides important data in terms of protecting emergency department resources and increasing service efficiency.

In this study, the examination of the distribution of emergency department admissions during the year indicated that the number of admissions increased in April, May, and June in the emergency outpatient clinic and decreased in the pandemic outpatient clinic. It was seen that the number of admissions to the pandemic outpatient clinic in October, November, and December was higher than the number of admissions to the emergency outpatient clinic. In their study on patterns of emergency department visits and procedures during the COVID-19 pandemic, Baugh et al.[13] found a significant decline in emergency department presentations during 8 weeks of the early COVID-19 wave between March and April 2020 compared to the same weeks in 2019. It was determined that the mean level of severity of presentations to the emergency department was higher during 2020 and that it was accompanied by a rise in the number of critical care procedures performed in the emergency department and a fall in the number of low severity emergency department procedures. Jeffery et al.[14] found that there were small increases in emergency department presentations in 3 states, (Massachusetts, Colorado, and North Carolina) in late April 2020 while the trends in emergency department admissions and hospital admissions in health systems of 5 states in the first months of the COVID-19 pandemic in the USA in April 2020 was investigated. Also, they reported that the rates of hospitalizations from the emergency department were associated with the number of state-level new COVID-19 cases. Wee et al.[15] reported that 1,841 individuals presented to the emergency department in a 3-month time between January 1, 2020 and April 1, 2020 with respiratory syndromes that required admission or met the criteria for COVID-19 suspicion and that all of the cases tested positive for COVID-19 while they reseraced on containing COVID-19 in the emergency department.

When the distribution of presentations to the pandemic outpatient clinic according to age groups was examined, it was found that the highest number of presentations was in the 15-29 and 30-44 age groups, and the least number of presentations was in the 0-14 age group. These results were found to be consistent with similar studies in the literature.[16,17] One study stated that the mean age of all patients who applied to the emergency department with the suspicion of COVID-19 was 45.15, and the mean age of

confirmed COVID-19 cases was 47.55.[18] In their study on 1,099 confirmed COVID-19 cases, Güneysu et al. (2020) stated that the average age was 49.50 years.[19]

The distribution of emergency department admissions by gender in this study indicated that rates of male patient admissions were higher in both the pandemic outpatient clinic and the emergency outpatient clinic. Similarly study of Açıksarı and Kınık,[16] stated that 52.5% of the patients who presented to the emergency department in March and April 2020 were male. In some similar studies searching emergency department admissions observed that the rate of female patients was higher in emergency department admissions, unlike the findings of this study.[1,17,20]

Some studies have shown that COVID-19 infection is more common in males.[18,19,21,22] In this study, while the rates of positive cases were higher in females in some months, they were observed higher in males in other months. Considering the monthly average value over a 13-month period,the rates of positive cases were higher in males than in females with the neglected difference (0.045%).

Triage is very important in terms of distinguishing patients who are likely to be infected with the pathogen causing the disease during pandemics.[11] As a result of this study, We observed that 65.7% of emergency department presentations in November and 59.9% in December were referred to the pandemic outpatient clinic. This result was important in that it showed that the contact of individuals with suspected COVID 19 symptoms with other areas were cut off. Similarly, Wee et al. (2020) stated that most COVID-19 cases (84.2%, 59/70) were identified at emergency department triage since they met the criteria for suspected cases.[15]

In our study, we observed that the rates of chest X-ray and thoracic CT requests for diagnostic purposes were high in the first months in the pandemic outpatient clinic but that they gradually decreased afterward. The widespread utilization of PCR tests and their use as the main criterion in diagnosis was thought to be the reason for this decrease. İt was observed that the supply of medications to people who were deemed suitable for antiviral drug treatment was first started in May and that there was a decrease in medication initiation rates in the last months within the scope of the study according to the results of the PCR test. It was thought this might have been related to the new developments in the effectiveness of the drug used.[23]

According to the results of the study, the number of COVID service and COVID intensive care unit hospitalizations in October 2020, November 2020, and December 2020 was high. In addition, the number of hospitalizations referred from the emergency outpatient clinic to the COVID intensive care unit was higher than the number of patients referred from the pandemic outpatient clinic. This was considered to be due to the admission of severe COVID-19 cases to the red zone of the emergency department and the addition of these patients in the emergency outpatient clinic records on the HIMS database.

In this study, the most frequently used codes in the diagnosis of patients admitted to the pandemic outpatient clinic were Z03, Z03.8, and Z03.9 (observation and evaluation for suspicious diseases and conditions). This showed that the majority of patients referred to the pandemic outpatient clinic were identified as COVID-19 suspects. This result is an indication that triage is conducted effectively and that individuals are directed to the right area. It was determined that the number of people admitted to the pandemic outpatient clinic with the diagnosis code U07.3 (COVID-19) was high in April (177) and May (164) but decreased in other months. The reason for the falling numbers of COVID-19 diagnoses after these months was thought to be due to the widespread use of home follow-up system. After observation and evaluation for suspected diseases and conditions, the most frequently used diagnosis codes were in the range of J00–J99 used for the diagnosis of respiratory system diseases. In a study on the evaluation of patients presented to the emergency department, it was stated that respiratory system and pain complaints were the most common reasons for patient presentations.[24] On the other hand, in their meta-analysis study, Khan et al. (2020) stated that the most common co-morbidities in COVID-19 patients were HT, DM, and cardiovascular diseases, respectively.[25]

In conclusion, this study was conducted to evaluate patients who were diagnosed with COVID-19 in the emergency department in terms of their socio-demographic

characteristics and diagnosis codes and to examine the effect of the COVID-19 pandemic on presentations to the emergency department and its functioning. The study data showed the effect of the COVID-19 pandemic on emergency service admissions and functioning. Besides, they will contribute to the necessary education, planning, and organization processes for similar situations.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

Approval for this study was received from Balıkesir University Clinical Research Ethics Committee (date 26.05.2021 and number 2021/126).

Authors' Contributions

Concept/Design: ÖT. Data Collection and/or Pro-cessing: AKB. Data analysis and interpretation: AKB, ÖT. Literature Search: ÖT, AKB. Drafting manuscript: ÖT, AKB. Critical revision of manuscript: ÖT, AKB.

REFERENCES

1. Çevik C, Tekir Ö. Emergency service admission evaluation of diagnosis codes, triage and socio-demographic. BAUN Health Sci J. 2014;3(2):102-107.
2. Aydın T, Aydın ŞA, Köksal Ö, Özdemir F, Kulaç S, Bulut M. Evaluation of features of patients attending the emergency department of Uludag University Medicine. JAEM. 2010;9:163-168.
3. Söyük S, Kurtuluş SA. The evaluation of the problems' emergency services from staff perspectives. GUJHS. 2017;6(4):44-56.
4. Köse A, Köse B, Öncü MR, Tuğrul F. Admission appropriateness and profile of the patients attended to a state hospital emergency department. Gaziantep Med J. 2011;17(2):57-62.
5. Türk M, Dursun R, Güloğlu C. Emergency Service, Patient Evaluation and Management During COVID-19. Dicle Med J. 2021;48(Special Issue):23-28.
6. Sanliturk D, Yilmaz A. Evaluation of Covid-19 Triage Assessment Scale in Patients Attending the Emergency Department. J Basic Clin Health Sci. 2022;6(1):55-65.
7. Tokem Y, Turhan S, Çelik GO. Emergency approach strategies in COVID-19 adult patients with definitive and possible diagnosis. IKCUSBFD. 2020;5(2):203-209.
8. Shen Y, Cui Y, Li N, et al. Emergency responses to Covid-19 outbreak: Experiences and lessons from a General Hospital in Nanjing, China. Cardiovasc Intervent Radiol. 2020;43:810–819.
9. Whiteside T, Kane E, Aljohani B, Alsamman M, Pourmand A. Redesigning emergency department operations amidst a viral pandemic. Am. J. Emerg. Med. 2020;38(7):1448-1453.
10. Giamello JD, Abram S, Bernardi S, Lauria G. The emergency department in the COVID-19 era. Who are we missing? Eur J Emergency Med. 2020; 27(4): 305–306.
11. Kunt MM, Karaca MA. COVID 19 pandemic and emergency service triage. Anatolian J Emerg Med. 2020;3(3):96-98.
12. Atilla ÖD, Kılıç TY. Emergency department organization, patient assessment and management processes in COVID-19 Pandemic. J Tepecik Educ Res Hosp. 2020;30(Additional number):183-194.
13. Baugh JJ, White BA, McEvoy D, et al. The cases not seen: Patterns of emergency department visits and procedures in the era of COVID-19. Am. J. Emerg. Med. 2021;46:476-481.
14. Jeffery MM, D'Onofrio G, Paek H, et al. Trends in emergency department visits and hospital admissions in health care systems in 5 States in the first months of the COVID-19 pandemic in the US. JAMA Intern Med. 2020;180(10):1328-1333.
15. Wee LE, Fua T-P, Chua YY, et al. Containing COVID-19 in the emergency department: The role of improved case detection and segregation of suspect cases. AEM. 2020;27(5):379-387.
16. Açıksarı K, Kınık K. Process management and outcomes of the emergency department of a training and research hospital in Turkey during the Coronavirus Disease 2019 pandemic. Anatol Clin. 2020;25(Special Issue 1):263-283.
17. Yüksel A. Evaluation of patient profile presenting to emergency department in terms of diagnostic codes and triage. Anatolian J Emerg Med. 2020;3(2):37-41.
18. Güneysu F, Durmuş E, Yürümez Y. Evaluation of the blood parameters success in predicting the COVID-19 patients applying to the emergency room in the COVID-19 pandemic. Sakarya Med J. 2021;11(3): 479-488.
19. Guneysu F, Yurumez Y, Guclu E, et al. The diagnostic process of COVID-19 in the emergency department: laboratory and ımaging methods. Rev Assoc Med Bras. 2020;66(2):58-64.
20. Şimşek DÖ. General overview of triage scales and determination of factors affecting emergency service applications in Turkey by logistic regression. TSJJ.2018;7(13):84-115.
21. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E. et al. Latin American Network of Coronavirus Disease 2019-COVID-19 Research (LANCOVID-19) Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623.
22. Jin J-M, Bai P, He W, et al. Gender differences in patients with COVID-19: Focus on severity and mortality. Front Public Health. 2020;29(8):152.
23. Hassanipour S, Arab-Zozani M, Amani B, Heidarzad F, Fathalipour M, Martinez-de-Hoyo R. The efficacy and safety of Favipiravir in treatment of COVID-19: A systematic review and meta-analysis of clinical trials. Scientific Reports. 2021;11(1):11022.
24. Kayhan Tetik B, Tetik B, Karaoğlan A, Alpağan C, Mete B, Paksoy N. Evaluation of patients admissing emergency care services from the point of view of family medicine. Ankara Med J. 2020;20(2):281-289.
25. Khan MMA, Khan MN, Mustagir MG, Rana J, Islam MS, Kabir MI. Effects of underlying morbidities on the occurrence of deaths in COVID-19 patients: A systematic review and meta-analysis. J Glob Health. 2020;10(2):020503.

ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

The Investigation of the Effects of Calcitriol on Human Ovarian Carcinoma Cells

Kalsitriol'ün İnsan Ovaryum Kanser Hücrelerine Etkisinin Araştırılması

***Bahar KARTAL*[1] *Ebru ALIMOGULLARI*[1]**

ÖZ

Amaç: Over kanseri jinekolojik malignitelerden ölümlerin önde gelen nedenlerindendir. Kadınlarda kansere bağlı ölümlerde beşinci sırada yer almaktadır. D Vitaminin aktif formu olan kalsitirol, vitamin D reseptörüne (VDR) bağlanarak fonksiyon göstermektedir. Kalsitriol, proliferasyon, apoptoz, diferansiasyon, inflamasyon, invazyon, anjiyogenez ve metastaz ile ilgili çoklu sinyal yollarını düzenleyerek kanser gelişimini ve büyümesini etkileme potansiyeline sahiptir. Kolon, meme ve prostat kanseri büyümesini sağlayan spesifik sinyal yollarının kalsitriol ile düzenlemesi incelendiğinde kalsitriolün birçok farklı kanser türünde kanser hücreleri üzerinde geniş bir etkiye sahip olduğu görülmüştür. Çalışmamızın amacı kalsitriolün ovaryum kanser hücrelerine karşı etkisini araştırmaktır.
Araçlar ve Yöntem: Çalışmamızda MDAH-2774 insan ovaryum kanseri hücre hattı kullanılmıştır. Hücreler farklı dozlarda kalsitriole 24 ve 48 saat maruz bırakıldıktan sonra MTT testi ve kantitatif gerçek zamanlı PCR yöntemi uygulanmıştır.
Bulgular: MTT testi sonucunda, kalsitirolün ovaryum kanser hücrelerinin canlılığını azalttığı tespit edildi. Kalsitriol uygulanan grupta kontrol grubuna kıyasla VDR ve p53 gen ekspresyonlarında artış saptandı. Bunlara ek olarak, kalsitriol uygulamasının proapoptotik belirteç Bax'ın gen expresyonunda artışa ve anti-apoptotik Bcl-2 ekspresyonunda azalmaya neden olduğu tespit edildi.
Sonuç: Sonuç olarak kalsitriol tedavisinin, ovaryum kanser hücrelerinin proliferasyonunu azalttığı ve apoptozu indüklediği saptanmış olup, kasitriolün tek başına veya kemoterapi ilaçlarıyla kombinasyon halinde kullanılmasının ovaryum kanser tedavilerinde potansiyel bir rolü olabileceği düşünülmektedir.

Anahtar Kelimeler: apoptoz; kalsitriol; mtt analizi; ovaryum kanseri; qrt-pcr

ABSTRACT

Purpose: Ovarian cancer is the fifth leading cause of cancer death in women, leading cause of death from gynecologic malignancies, and the second most commonly diagnosed gynecologic malignancy, however the underlying pathophysiology is not clearly understood. Calcitriol, the active form of vitamin D serves its activity by binding to the vitamin D receptor (VDR). Calcitriol regulates multiple signaling pathways such as proliferation, apoptosis, differentiation, inflammation, invasion, angiogenesis and metastasis. It has been found to have a broad effect on several cancer types such as colon, breast and prostate cancer. Therefore, the study aimed to investigate the effects of calcitriol on human ovarian cancer cells.
Material and Methods: The human MDAH-2774 ovarian carcinoma cells were exposed to different dose ranges of calcitriol for 24 and 48 hours. Cultured cells were evaluated in terms of MTT assay and quantitative Real time PCR.
Results: As evidenced by the MTT assay, calcitriol treatment resulted in the reduction of cell viability in human MDAH-2774 cells. The gene expressions of VDR and p53 were increased with the calcitriol treatment compared to control. Additionally the gene expression of proapoptotic marker Bax increased and the anti-apoptotic marker Bcl-2 decreased with the presence of the calcitriol.
Conclusion: In conclusion calcitriol treatment decreased cell proliferation and induced apoptosis in ovarian cancer cells, therefore we can suggest that calcitriol, either by itself or in combination with chemotherapy drugs, may be effective in treating ovarian cancer.

Keywords: apoptosis; calcitriol; mtt assay; ovarian cancer; qrt-pcr

Received: 02.01.2023; Accepted: 06.07.2023

[1]Ankara Yıldırım Beyazıt University, Medical Faculty, Department of Histology and Embryology, Ankara,Türkiye.

Corresponding Author: Bahar Kartal, Ankara Yıldırım Beyazıt University, Medical Faculty, Department of Histology and Embryology, Ankara,Türkiye. e-mail: bahar.kartal@outlook.com

How to cite: Kartal B, Alimoğulları E. The investigation of the effects of calcitriol on human ovarian carcinoma cells. Ahi Evran Med J. 2024;8(1):22-28.
DOI: 10.46332/aemj.1228216

INTRODUCTION

The process of ovarian carcinogenesis is complex. Obvious symptoms including weight loss, bloating, and discomfort are not present in ovarian cancer.[1] It frequently occurs just before or after menopause and is associated with breast, cervical, colorectal, lung, stomach, and endometrial cancer.[2] Progression and metastasis of ovarian cancer are equal to those of other solid tumors require additional processes, such as the destruction of intercellular structures, changes in cellular adhesion, cell migration and invasion.[3] Patients with ovarian cancer receive treatment that combines surgery and chemotherapy. The main surgical procedure's objectives are to confirm the diagnosis, establish the lesion's stage, and reduce the tumor.[4] A lipid-soluble hormone called vitamin D is typically produced by exposure to sunshine. Vitamin D comes in two different forms: vitamin D3 and vitamin D2.[5] The primary form of vitamin D that is stored and circulated is 25-hydroxyvitamin D, which is produced by the liver from both forms of the vitamin. The serum levels of this form are thought to be the best indicator of the vitamin D status of the entire body.[6] Kidney receives it after the initial hydroxylation and transforms it into calcitriol, the active form of vitamin D.[7]

Calcitriol regulates a wide range of biological activities, mostly via the nuclear vitamin D receptor (VDR).[8] In Additionally, to modulating biological processes like cell proliferation, wound healing, neuromuscular activity, and immunological response, calcitriol is essential for preserving the body's calcium balance. Additionally, through controlling signaling pathways involved in cell proliferation, differentiation, apoptosis, inflammation, invasion, and metastasis, calcitriol may have an anti-cancer effect.[9,10]

While calcitriol's anti-tumor effects have been extensively studied in a number of in vitro and in vivo human and murine tumor models, including leukemia,[11] squamous cell carcinoma,[12] prostate,[13] breast,[14] and colon cancer,[15] there is little information on ovarian cancer. As a result, the current study's objective is to assess how calcitriol affects the human ovarian cancer cell line.

MATERIALS and METHODS

Cell Culture

MDAH-2774 ovarian cancer cells (CRL No: 10303; ATCC, USA) were grown in RPMI-1640 media (Biological Industries, Israel) with 10% fetal calf serum (GIBCO, Invitrogen Co.,UK), 100 units/mL penicillin and 100 g/mL streptomycin (Sigma Chemical Co., MO, USA).

After adding RPMI-1640 to inactivate the trypsin and harvesting semi-confluent cells from flasks with 0.05% trypsin (Sigma Chemical Co., MO, USA), the cells were resuspended in culture media**.**

MTT Assay

MDAH cells were seeded in 96-well plates at a density of (2×10^3 cells/well) and maintained for 24 and 48 hours with calcitriol (71820, Cayman ChemicalCo, USA) at concentrations of 0.5nM, 1nM, 10nM, 50nM, 100nM, 200nM, 500nM and 1000nM.[16] GroupI(control): nontreated, groupII: (0.5nM, 1nM, 10nM, 50nM, 100nM, 200nM, 500nM and 1000nM) calcitriol treatment for 24h and group III: (0.5nM, 1nM, 10nM, 50nM, 100nM, 200nM, 500nM and 1000 nM) calcitriol treatment for 48 hours. Following incubation, cell viability was assessed using the MTT assay (Sigma-Aldrich, St. Louis, USA), in compliance with the guidelines provided by the manufacturer. On a microplate reader (Enspire, PerkinElmer, USA), the absorbance was measured between 570 and 630 nanometers. Cell viability was evaluated as a percentage of untreated cells.

Quantitative Real-Time PCR

qRT-PCR was utilized to assess the levels of VDR expression for the evaluation of calcitriol's genomic effect, BAX expression levels for its pro-apoptotic effects, BCL2 expression levels for its anti-apoptotic and. P53 expression levels for its antitumor impact.

The cultured MDAH-2774 cells were treated with 1nM, 100nM and 1000nM calcitriol for 24h. RNeasy Mini Kit (QIAGEN Brand Cat.No.74104) was utilized to perform mRNA isolation according to defined guidelines. 1 mg of

RNA and 2mL of 5xPrimerScript RT Master Mix (TaKaRa, Japan) made up the reverse transcription reactions, which had 10 mL total in volume. RNA primer sequences were given in Table 1. The C100 PCR System (Bio-Rad, CA, USA) was used to conduct reactions for 15 minutes at 37°C. The internal control was GAPDH. On the ABI 7500 PCR equipment, the qPCR was carried out using the SYBR Green (Roche, Basel, Switzerland) dye detection method.

Table 1. The primer sequences of RNA.

GAPDH	**F:**GAAGGTGAAGGTCGGAGTCAAC	**R:**CAGAGTTAAAAGCAGCCCTGGT
VDR	**F:**TCTCCTGCCTACTCACGATAA	**R:**GCTACTGCCCGTGAGAATATAA
BCL-2	**F:**TTCTTTGAGTTCGGTGGGGTC	**R:**TGCATATTTGTTTGGGGCAGG
BAX	**F:**ATGGACGGGTCCGGGGAG	**R:**TCAGAAAACATGTCAGCTGCC
P53	**F:**TTCTCATCACCGGCATCACG	**R:**GCTATCACAAACTGCAAGACG

Statistical Analysis

The statistical analyzes were done by applying two-tailed student's t-test and analysis of variance (ANOVA) by using GraphPad Prism® V.5.00 software (GraphPadsoftware Inc., La Jolla, USA). The data was presented as means ± SEM. The free Relative Expression Software Tool (REST 2009, Qiagen) was used to determine fold changes in gene expression, the comparative CT technique, and statistical analysis. The tests considered significance level of $p<0.05$.

RESULTS

MTT Assay Results

We examined the potential of calcitriol at various concentrations 0.5nM, 1nM, 10nM, 50nM, 100nM, 200nM, 500nM and 1000 nM for 24, and 48 hours. The MTT assay data analysis revealed that 50nM, 200nM and 500nMcalcitiriol treatment for 24 hours reduced the cell proliferation at %90, %93, and %94 respectively, compared to control. 1nM, 100nM and 1000nM doses of calcitriol treatment for 24h reduced the MDAH cell proliferation at %82,%86 and %94 respectively (Figure 1A).

On the other hand, treatment with the same amounts of calcitriol, particularly 100nM and 1000nM for 48 hours led to an increase in cell proliferation (Figure 1B). According to these observations, calcitriol showed its inhibitory effects for 24 hours.

For the ensuing studies, the concentrations of 1 nM, 100 nM, and 1000 nM were chosen because they had the best inhibitory effects on both cell viability and proliferation.

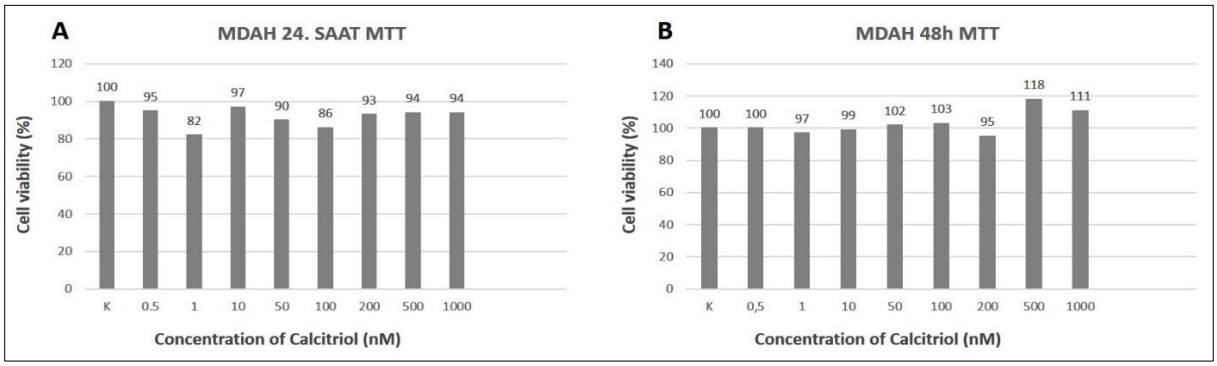


Figure 1. Analyses of cell viability.

QRT-PCR Results

The gene expressions of the human MDAH-2274 ovarian cancer cells treated with calcitriol at 1 nM, 100 nM and 1000 nM were presented in (Figure 2). This translated to the up-regulated expression of VDR, P53, and proapoptotic protein Bax and down-regulated antiapoptotic protein Bcl-2 due to culturing in the presence of 1000 nM calcitriol for 24 hours (Figure 2).

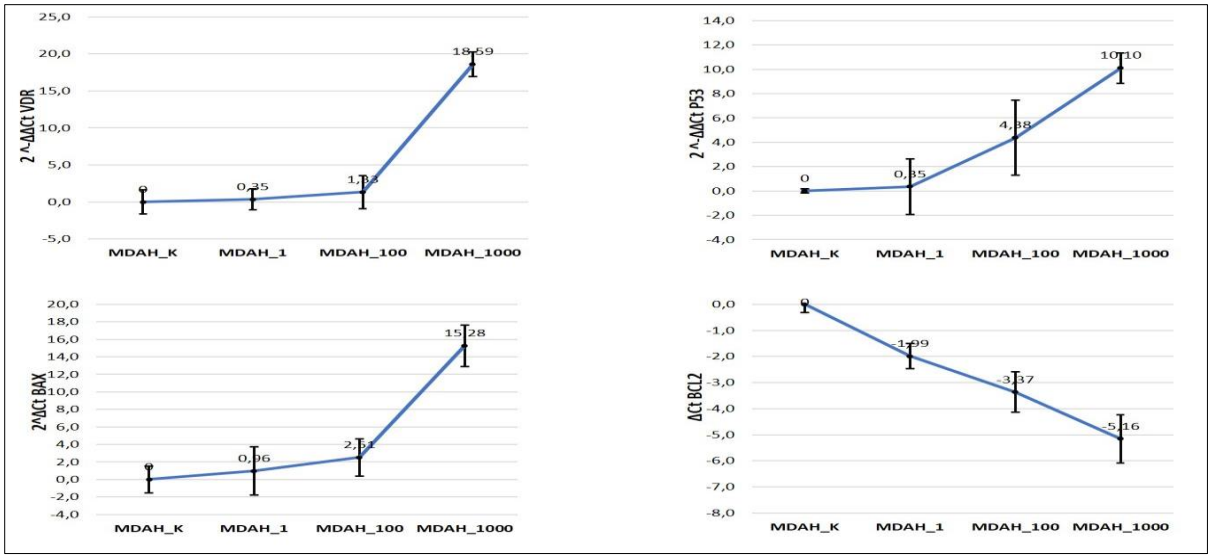


Figure 2. Quantitative RT-PCR Analyses.

DISCUSSION

A powerful steroid hormone, calcitriol is an active metabolite of vitamin D. By controlling numerous signaling pathways, calcitriol has demonstrated anti-tumor benefits in a variety of malignancies. It is crucial in prostate and other malignancies and is biologically active. According to studies, populations residing at higher latitudes have greater risks of various malignancies due to low vitamin D levels.[17]

Calcitriol, the biologically active derivative of vitamin D, has anticancer properties both independently and in conjunction with chemotherapeutic medicines, in a variety of cell types. The aggressive tumor known as malignant pleural mesothelioma (MPM) is uncommon. It has a poor prognosis and few therapies are available. The researchers investigated calcitriol's potential anticancer function. The findings demonstrated calcitriol decreased cell survival and proliferation in human MPM cells.[18]

Numerous cancer cell models have been used in studies to show the effects of calcitriol on cell differentiation and anti-proliferation. In addition, in cancer animal models, calcitriol and its analogs demonstrated the capacity to postpone tumor development and suppress tumor progression, either alone or in combination with anticancer medicines.[19,20,21]

Sunlight exposure, nutrition, and supplements all affect vitamin D levels. There was mounting evidence that ovarian cancer risk was elevated in people with low vitamin D levels. Yin et al.'s meta-analysis of 10 cohort studies on the incidence of ovarian cancer discovered an average rise in 25(OH)2D3 of 20 ng/ml.[22] Higher 25(OH)D concentrations are linked to prolonged survival rates, according to a case-control study of 1631 women with epithelial ovarian cancer (adjusted HR: 0.93; 95%CI: 0.88-0.99 per 10 nmol/L).[23]

Wong et al. researched into the connection between postmenopausal women's serum 25(OH)D) concentrations and cancer-specific mortality. Women who had lower serum concentrations of 25 (OH) D is less than the average value of 64 nmol/L; had a greater risk of dying from cancer. For every 30 nmol/L drop in serum 25 (OH) D level, resulted in a 30% increase in the overall risk of cancer-related death.[24] According to epidemiological data, vitamin D supplementation is linked to a lower cancer mortality rate and lower circulating vitamin D levels are linked to to a higher chance of developing ovarian cancer.[25]

In Lagos, Nigeria, women were studied by E Sajo et al. to ascertain the connection between the risk of ovarian cancer and serum vitamin D levels. Each participant's venous blood was taken to measure the serum 25-hydroxyvitamin D [25(OH)D] level using a vitamin D ELISA kit. Researchers discovered that the vitamin D levels in ovarian

cancer patients were lower than those in healthy individuals. Epithelial ovarian cancer risk was four times higher in people with vitamin D deficiency.[26]

In one study, the impact of calcitriol and calcidiol on the growth of melanoma cells and the way they responded to radiation from proton beams was evaluated. Melanoma cell lines (human SKMEL-188, hamster BHM Ma, and hamster BHM Ab) were given calcitriol as pretreatment at graduated doses (0, 10, and 100 nM) and then exposed to radiation of 0 to 5 Gy. They discovered that that at 10 nM, calcitriol inhibited the growth of human melanoma, yet just calcidiol did the same at 10 and 100 nM levels for hamster lines. Melanoma cells were made more sensitive to modest doses of proton beam radiation after receiving either 1.25(OH)2D3 or 25(OH)D3.[27]

We used the MTT test to analyze different calcitriol concentrations and treatment durations to identify the effects of calcitriol on cell viability. The MTT assay showed that treatment with calcitriol decreased the viability of human MDAH-2774 ovarian cancer cells in a concentration- and time-dependent manner.The MTT assay data analysis revealed that calcitriol therapy at concentrations of 1 nM, 100 nM, and 1000 nM for 24 hours reduced the proliferation of MDAH-2774 cells.

Virtually every type of human cell contains VDR, but it is primarily found in metabolic organs. Recent research has identified VDR as a mitochondrial localization, and it has been discovered that in cancer cell lines, keratinocytes, and adipocytes, calcitriol suppresses mitochondrial respiration. This has an impact on lipid metabolism, cell differentiation, and proliferation.[28] Being a fat-soluble substance, calcitriol easily interacts with VDR, where it has an impact on biological processes.[29]

Reduced fibrosis and inflammation in both acute and chronic murine pancreatitis are two advantages of VDR-directed treatment. Genomic investigations have also revealed a link between tumor growth and shorter disease-free life periods and low-to-absent expression of VDR and cytochrome p450.[30]

Tumor suppressor gene (TSG) inactivation is a molecular target for the emergence of neoplasia. One of the TSGs in a range of malignant tumors is p53. Advanced-stage and high grade tumors have been linked to endometrial cancer that expresses mutant P53 protein strongly.[31]

Bcl-2, an anti-apoptotic protein, prevents cell death by controlling the activity of the mitochondrial membrane. The pro-apoptotic proteins that are responsible for causing cell death are encoded by the Bcl-2-associated X protein (BAX). Excessive Bcl-2 expression suppresses apoptosis while excess of Bax causes cell death. It has been hypothesized that the P53/BCL2/BAX apoptotic signaling pathway is dysfunctional during the development and progression of tumors.[32]

A melanoma cell line was utilized in one study to investigate the anti-proliferative impact of calcitriol using a cell viability assay. PCR, expression of apoptosis-related genes, and western blot analysis of apoptosis protein levels. They discovered that the apoptosis-related proteins caspase-3, caspase-8, and caspase-9 could all be activated by calcitriol. These calcitriol side effects highlight the drug's potential as a strong adjuvant therapy for melanoma.[33,34]

By using qRT-PCR, we examined the gene expression of VDR, p53, Bax, and Bcl-2. We discovered that treatment of MDAH-2274 ovarian cancer cells for 24 hours with 1000nM calcitriol raised the expression of VDR, p53, and Bax and decreased Bcl-2.

Ohnishi et al. demonstrated that vitamin D-induced cell cycle arrest is caused by the inhibition of numerous essential proteins that control the G1/S phase and up-regulate the expression of P53.[35] In accordance with the literature, we discovered enhanced p53 expression. The current study's findings further demonstrated that the decreased expression of Bcl-2 and elevated Bax expression in calcitriol-treated MDAH cells are necessary for calcitriol's anti-apoptotic and anti-proliferative actions.

In addition to inhibiting the epithelial-to-mesenchymal transition, calcitriol has been demonstrated to enhance VDR expression in a variety of cancer cells such as bronchial epithelial and peritoneal mesothelial cells.[36]

In the current study, we also discovered elevated VDR expression in MDAH cells that had received calcitriol treatment. We demonstrated the antiproliferative and apoptotic effects of calcitriol on human ovarian cancer cells. Thus, we can propose that vitamin D might be helpful as an adjunctive therapy for ovarian cancer.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

Since a cell line was used in this study, ethics committee approval is not required.

Authors' Contributions

Concept/Design: BK. Data Collection and/or Processing: EA. Data analysis and interpretation: EA. Literature Search: BK. Drafting manuscript: BK. Critical revision of manuscript: EA. Supervisor: BK.

REFERENCES

1. Marczak A, Denel M. Trabectedin as a single agent and in combination with pegylated liposomal doxorubicin – activity against ovarian cancer cells. Contemp Oncol. 2014;18(3):149-152.
2. Mersch J, Jackson MA, Park M, et al. Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian. Cancer.2015;121(2):269-275.
3. Liotta LA, Steeg PS, Stetler-Stevenson WG. Cancer metastasis and angiogenesis: an imbalance of positive and negative regulation. Cell.1991;64(2):327-336.
4. Harter P, Bois A, Hahmann M, et al. Surgery in recurrent ovarian cancer. Ann Sur Oncol. 2006;13(12): 1702-1710.
5. Elangovan H, Chahal S, Gunton JE. Vitamin D in Liver Disease: Current Evidence and Potential Directions. Biochim Biophys Acta Mol Basis Dis. 2017;1863(4):907-916.
6. Wacker M, Holick MF. Vitamin D Effects on skeletal and extraskeletal health and the need for supplementation. Nutrients. 2013;5(1):111-148.
7. Christakos S, Dhawan P, Verstuyf A, et al.Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects Vitamin D Analogs. Physiol Rev. 2016; 96(1):365-408.
8. Feldman D, Krishnan AV, Swami S, et al.The role of vitamin D in reducing cancer risk and progression. Nat Rev Cancer. 2014;14(5):342-357.
9. Wang Y, Zhu J,De Luca HF. Where is the vitamin D receptor? Arch Biochem Biophys. 2012;523(1):123-133.
10. Sintov AC, Rarmolinsky L, Dahan A, et al. Pharmacological effects of vitamin D and its analogs: recent developments. Drug Discov Today. 2014;19(11):1769-1774.
11. Koeffle HF, Hirji K, Itri L. 1,25-Dihydroxyvitamin D3: in vivo and in vitro effects on human preleukemic and leukemic cells. Cancer Treat Rep. 1985;69(2): 1399-1407.
12. Hershberger PA, Modzelewski RA, Shurin ZR, et al. 1,25-Dihydroxycholecalciferol (1,25-D3) inhibits the growth of squamous cell carcinoma and down-modulates p21(Waf1/Cip1) in vitro and in vivo. Cancer Res. 1999;59(11):2644-2649.
13. Lokeshwar BL, Schwartz GG, Selzer MG,et al. Inhibition of prostate cancer metastasis *in vivo*: a comparison of 1,23-dihydroxyvitamin D (calcitriol) and EB1089. Cancer Epidemiol Biomarkers Prev. 1999;8(3):241-248.
14. Welsh J. Vitamin D and breast cancer: insights from animal models. Am J Clin Nutr. 2004;80(6):1721-1724.
15. Diaz GD, Paraskeva C,Thomas MG,et al. Apoptosis is induced by the active metabolite of vitamin D3 and its analogue EB1089 in colorectal adenoma and carcinoma cells: possible implications for prevention and therapy. Cancer Res. 2000;60(8):2304-2312.
16. Fatsa T, Hoşbul T, Elçi MP, et al. Antiproliferative, anti-inflammatory, antitumoral and proapoptotic effects of calcitriol on MCF-7 and MCF-10A cell lines. Indian J. Exp. Biol. 2023;61(5):320-328
17. Ricciardi CJ, Bae J, Esposito D, et al. 1,25-dihydroxyvitamin D3/vitamin D receptor suppresses brown adipocyte differentiation and mitochondrial respiration. Eur J Nutr. 2015;54(6):1001-1012.
18. Gesmundo I, Silvagno F, Banfi D, et al. Calcitriol Inhibits Viability and Proliferation in Human Malignant Pleural Mesothelioma Cells. Front. Endocrinol. 2020;11:559-586.
19. Feldman D, Krishnan AV, Swami S,et al. The role of vitamin D in reducing cancer risk and progression. Nat Rev Cancer. 2014;14(5):342-357.
20. Bandera Merchan B, Morcillo S, Martin-Nunez G, et al. The role of vitamin D and VDR in carcinogenesis: through epidemiology and basic sciences. J Steroid Biochem Mol Biol. 2017;167:203-220.
21. Carlberg C, Munoz A. An update on vitamin D signaling and cancer. Semin Cancer Biol. 2020;79:217-230.
22. Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: circulating vitamin D and ovarian cancer risk. Gynecol Oncol. 2011;121(2):369-375.
23. Webb PM, de Fazio A, Protani MM, et al. Circulating 25-hydroxyvitamin D and survival in women with ovarian cancer. Am J Clin Nutr. 2015;102(1):109-114.
24. Wong G, Lim WH, Lewis J, et al. Vitamin D and cancer mortality in elderly women. BMC Cancer. 2015;15:106.
25. Andraž D,Nina Fokter D. Vitamin D and Ovarian Cancer: Systematic Review of the Literature with a Focus on Molecular Mechanisms. Cells. 2020;9:335.
26. Sajo E, Okunade K, Olorunfemi G, Rabiu K, Anorlu R. Serum Vıtamın D Deficıency And Rısk Of Epıthelıal Ovarıan Cancer In Lagos, Nigeria. ecancer. 2020;14:1078.
27. Ewa P, Agnieszka D, Zenon M, et.al. Calcitriol and Calcidiol Can Sensitize Melanoma Cells to Low–LET Proton Beam Irradiation. Int J Mol Sci. 2018;19(8): 2236.
28. Consiglio M, Destefanis M, Morena D, et al.The vitamin D receptor inhibits the respiratory chain, contributing to the metabolic switch that is essential for cancer cell proliferation. PLoS ONE. 2014;9(12):e115816.
29. Ricca C , Aillon A, Bergandi L, et al. Vitamin D receptor is necessary for mitochondrial function and cell health. Int J Mol Sci. 2018;19(6):1672.
30. Slominski AT, Brożyna AA, Zmijewski MA, et al. Vitamin D signaling and melanoma: Role of vitamin D and its receptors in melanoma progression and management. Lab Investig. 2017;97(6):706-724.
31. Consiglio M, Viano W, Casarin S, et al. Mitochondrial and lipogenic effects of vitamin D on differentiating

and proliferating human keratinocytes. Exp Dermatol. 2015;24(10):748-753.
32. Argiris A, Cohen E, Karrison T, et al. A phase II trial of perifosine, an oral alkylphospholipid, in recurrent or metastatic head and neck cancer. Cancer Biol Ther. 2006;5(7):766-770.
33. Bao A, Li Y, Tong Y. 1,25-Dihydroxyvitamin D3 and cisplatin synergistically induce apoptosis and cell cycle arrest in gastric cancer cells. Int J Mol Med. 2014;33(5):1177-1184.
34. Chaitanya GV, Alexander JS, Babu PP. PARP-1 cleavage fragments: Signatures of cell-death proteases in neurodegeneration. Cell Commun Signal. 2010;8:31.
35. Ohnishi T,Takahashi A, Ohnishi K. Studies about space radiation promote new fields in radiation biology. J Radiat Res. 2002;43:7-12.
36. Campbell MJ, Trump DL. Vitamin D receptor signaling and cancer. Endocrinol Metab Clin North Am. 2017; 46:1009-1038.

BİLİMSEL ARAŞTIRMA MAKALESİ

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Normal Servikal Sitolojili Kadınlarda Yüksek Riskli Human Papillomavirus Sıklığı ve Tip 16/18 Dağılımı: Tek Merkez Çalışma

The Prevalence and Distribution of High Risk Human Papilloma Virus İnfection from Turkish Women with Normal Cytology: A Single Center Study

Hatice ŞENELDİR[1] Beyda GÜMÜŞTAŞ[2] Gülsüm GÜNHAN[2] Feride Ebrar KILLI[2]

Berivan OZAN[2] İsmail CANBAŞ[2] Deryagül SEVİNDİ[2]

ÖZ

Amaç: Serviks kanseri, kadınlarda en yaygın görülen kanser türlerinden biridir. Serviks kanserinin Human Papilloma virüs (HPV) ile ilişkisi kanıtlanmış olup hastaların tamamına yakınında HPV DNA varlığı gösterilmiştir.
Çalışmadaki amacımız; normal servikal sitolojili kadınlarda yaşlara göre yüksek riskli HPV (hrHPV) sıklığını ve tip 16/18 dağılımını araştırmak ve diğer çalışmalarla karşılaştırmasını yapmaktır.
Araçlar ve Yöntem: Çalışmamızda İstanbul Medeniyet Üniversitesi Prof. Dr. Süleyman Yalçın Şehir Hastanesi Tıbbi Patoloji Anabilim Dalı'nda 01.10.2018-01.10.2020 tarihleri arasında, servikal sitolojisi malignite açısından negatif ve hrHPV DNA incelemesi yapılmış 4212 servikal sitolojik materyal retrospektif olarak değerlendirildi. Olgular, yaşlarına göre 21-24 yaş, 25-29 yaş, 30-44 yaş, 45-54 ve 55-65 yaş olmak üzere 5 gruba ayrıldı. Gruplar hrHPV pozitifliği ve tip 16/18 dağılımı açısından analiz edildi.
Bulgular: Toplam 4212 olgunun 494'ünde (%11.73) hrHPV pozitifliği saptandı. Grup 1 (21-24 yaş), grup 2 (25-29 yaş), grup 3 (30-44 yaş), grup 4 (45-54 yaş) ve grup 5 (55-65 yaş) hrHPV pozitiflik oranı sırası ile %31.97, %16.83, %18.34, %11.29, %8.73 ve % 10.18 olarak bulundu.
HrHPV pozitifliği açısından Grup 1 ve 2 ile diğer gruplar arasında istatistiksel olarak anlamlı farklılık bulunmaktadır ($p<0.05$).
HPV tip 16 pozitifliği açısından Grup 1 ve diğer gruplar arasında istatistiksel olarak anlamlı farklılık bulunmaktadır ($p<0.05$), grup 2, 3, 4 ve 5 arasında anlamlı bir farklılık bulunmamaktadır ($p>0.05$).
Sonuç: Meta analiz çalışmalarına göre; normal sitolojili kadınlarda yaklaşık %6.6 oranında hrHPV pozitifliği bildirilmiştir. Bu oran düşük-orta sosyoekonomik düzeydeki toplumlarda daha sık olmak üzere %1.4 ile %25.6 arasında değişmektedir. Bu çalışmada da yaş gruplarından bağımsız bu oran %11.73 olarak saptanmış literatür ile uyumlu olarak bulunmuştur.

Anahtar Kelimeler: hrHPV; normal sitoloji; serviks; tip16/18

ABSTRACT

Purpose: The aim of this study was to investigate the prevalence and age distribution of high risk human papilloma virus (hrHPV) infection from Turkish women with normal cytology.
Materials and Methods: Our study population consisted of 4212 women with normal cytology and adequate hrHPV molecular testing. The cases were divided into 5 groups according to their age ranges as 21-25 years old, 25-29 years old, 30-44 years old, 45-54, and 55-65 years old. Groups were compared with hrHPV positivity and type 16/18 positivity.
Results: Hr HPV was detected in 494 (11.73 %) of 4212 cases. The positivity of hr HPV were 31.97% in group 1 (21-24 years), 18.34% in group 2 (25-29 years), 11.29% in group 3 (30-44 years), 8.73% in group 4 (45-54 years), and 10.18% in group 5 (55-65 years) . There was statistically significant difference in the rates of hrHPV between group 1 and the other groups ($p<0.05$). There was statistically significant difference in the rates of hrHPV of group 2 and the other groups ($p<0.05$) . There was statistically significant difference in the rates of type 16 between groups 1 and the other groups ($p<0.05$) .
Conclusion: According to meta-analysis studies, hrHPV positivity has been reported in approximately 6.6% of women with normal cytology. This rate varies between 1.4% and 25.6%, being more frequent in societies with low-middle socioeconomic status. In this study, this rate was found to be 11.73% independent of age groups and was found to be consistent with the literature.

Keywords: cervix; hrHPV; normal cytology; type 16/18

Gönderilme tarihi: 12.01.2023; Kabul edilme tarihi: 10.08.2023

[1]İstanbul Medeniyet Üniversitesi Tıp Fakültesi, Tıbbi Patoloji Anabilim Dalı, İstanbul, Türkiye.
[2]İstanbul Medeniyet Üniversitesi Tıp Fakültesi, İstanbul, Türkiye.

Sorumlu Yazar: Hatice Şeneldir, İstanbul Medeniyet Üniversitesi Tıp Fakültesi, Tıbbi Patoloji Anabilim Dalı, İstanbul, Türkiye.
e-posta: hkodabas@yahoo.com

Makaleye atıf için: Şeneldir H, Gümüştaş B, Günhan G, Kıllı FE, Ozan B, Canbaş İ, Sevindi D. Normal servikal sitolojili kadınlarda yüksek riskli human papillomavirus sıklığı ve tip 16/18 dağılımı: tek merkez çalışma. Ahi Evran Med J. 2024;8(1):29-34. DOI: 10.46332/aemj.1232937

GİRİŞ

Serviks kanseri, tüm dünyada kadınlarda görülme sıklığı ve mortalite açısından dördüncü sırada yer alan bir kanser türüdür. Her yıl yaklaşık 600.000 yeni vaka tanımlanmakta ve 300.000'den fazla kadın da bu sebeple hayatını kaybetmektedir.[1-2] Yeni servikal kanser vakalarının %90'dan fazlası gelişmekte olan ülkelerde ortaya çıkmakta ve vakaların yaklaşık % 50'si kaybedilmektedir.[2]

Epidemiyolojik çalışmalar serviks kanseri için majör risk faktörünün human papilloma virüs (HPV) enfeksiyonu olduğunu göstermiştir.[2] Serviks kanseri olgularının neredeyse tümünden (% 95'den fazlası) HPV DNA/RNA'sı izole edilebilmektedir. Bu nedenle serviks kanseri sıklığında azalma HPV enfeksiyonunun tanınması, önlenmesi ve tedavi edilmesi ile mümkündür.[2] Özellikle tarama programları ile sıklıkla asemptomatik olan prekürsör lezyonlar tanınmakta ve etkili bir şekilde tedavi edilebilmektedir.[2]

Bununla birlikte prekürsör lezyonlar henüz oluşmadan normal servikal sitolojili kadınlarda da HPV pozitifliği saptanabilmektedir. Güncel Amerikan Kolposkopi ve Servikal Patoloji Derneği (ASCCP) kılavuzlarına göre yüksek riskli HPV (hrHPV) pozitifliği olan sitolojisi normal olan hastaların yönetimi farklılık gösterebilmektedir. Olgular, hrHPV test sonuçlarına göre kolposkopiye yönlendirilebilir veya bir yıl sonra hrHPV testi tekrar istenebilir.[3] Türkiye'de hrHPV pozitifliği olan normal sitolojili kadınların sıklığı ile ilgili veri sağlayan bazı çalışmalar mevcuttur. HrHPV prevelansını, İnal ve ark. %1.5,4 Akçalı ve ark. %8.5,5 Tezcan ve ark %18.9,6 Şahiner ve ark. %19.7,7 Yüce ve ark. %21.48 olarak bildirmişlerdir. Katalan Onkoloji Enstitüsü ve Uluslararası Kanser Araştırma Ajansı, HPV ve Kanser Bilgi Merkezi (ICO/IARC) 2023 verilerine göre, normal sitolojiye sahip Türk kadınları arasında hrHPV prevelansı %1.5 ila %32.1, HPV tip 16/18 prevalansı ise %4.2 olarak rapor edilmiştir.[9]

Bu çalışmadaki amacımız; bölgemizde servikal sitolojisi normal olan kadınlarda hrHPV sıklığını ve tip 16/18 dağılımını yaşlara göre araştırmak ve benzer diğer çalışmalarla karşılaştırmasını yapmaktır.

ARAÇLAR ve YÖNTEM

Çalışmamızda İstanbul Medeniyet Üniversitesi Göztepe Prof. Dr. Süleyman Yalçın Şehir Hastanesi Tıbbi Patoloji Anabilim Dalı'nda 01.10.2018-01.10.2020 tarihleri arasında, servikal sitolojisi malignite açısından negatif olan ve hrHPV DNA inceleme-si yapılmış toplam 4447 adet servikal sitolojik materyal patoloji raporları üzerinden retrospektif olarak değerlendirildi.

Çalışmaya 21-65 yaş arası, 2014 Bethesda Sistemine göre yeterlilik kriterlerine uyan ve malignite açısından negatif tanısı alan, hrHPV DNA incelemesi yapılmış ve yeterli sonuç elde edilmiş olgular dahil edildi. Yaşı 21'den küçük, 65'den büyük, yeterlilik kriterlerine uymayan yetersiz sitolojili ve hrHPV DNA çalışması yapılmış ancak yeterli sonuç elde edilememiş olan olgular dışlandı. Sonuç olarak 4212 adet servikal sitolojik materyal çalışmaya alındı.

Servikal sitolojik örnekler, sıvı bazlı sitoloji (ThinPrep Pap Test) yöntemi ile değerlendirilmiştir. Kalan koruyucu solüsyonlarından Roche marka Cobas4800 System Liquid Cytlogy Preparation Kit kullanılarak DNA izolasyonu ve Real Time PCR yöntemiyle HPV DNA genotiplendirmesi yapılmıştır. Bu test HPV DNA genotip 16, Genotip 18 ve "diğer" başlığı altında HPV DNA HR (yüksek risk) Genotiplerini (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 ve 68) saptamaktadır. Olgular, yaşlarına göre 21-24, 25-29, 30-44, 45-54 ve 55-65 olmak üzere 5 gruba ayrıldı. Gruplar hrHPV pozitifliği ve tip 16/18 dağılımı açısından analiz edilerek karşılaştırıldı.

Çalışmamız için S. B. İstanbul Medeniyet Üniversitesi Göztepe Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulundan onay alınmıştır (tarih 02.12.2020 ve sayı 2020/0723).

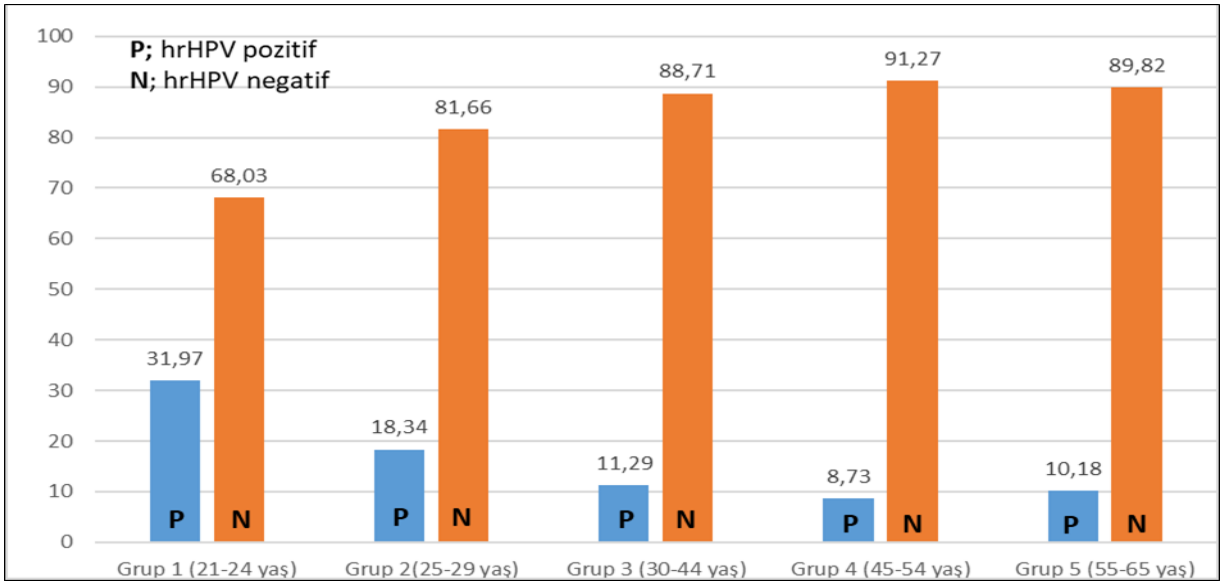
İstatiksel Analiz

İstatiksel analiz için SPSS versiyon 22 yazılımı (IBM, New York City, New York), çalışma verileri değerlendirilirken tanımlayıcı istatistiksel metodlar (ortalama, ortanca değer, grup dağılım ve yüzdelikleri) ve niteliksel verilerin karşılaştırılmasında "Pearson Chi-Square" Ki-Kare testi kullanıldı. Anlamlılık $p<0.05$ olarak değerlendirildi (Şekil 1).

BULGULAR

Olguların yaşları 21 ile 65 arasında değişmekte olup, ortalama değer 51.50, ortanca değer 43 olarak bulundu. Toplam 4212 olgunun 147'si (%3.50) 21-24, 338'i (%8.02) 25-29, 2072'si (%49.19) 30-44, 1203'ü (%28.56) 45-54, 452'si (%10.73) 55-65 yaş aralığında idi (Tablo 1).

Olguların 494'ünde (%11.73) hrHPV pozitifliği saptandı. Grup 1 (21-24 yaş), grup 2 (25-29 yaş), grup 3 (30-44 yaş), grup 4 (45-54 yaş) ve grup 5'in (55-65 yaş) hrHPV pozitiflik oranı sırası ile %31.97, %18.34, %11.29, %8.73 ve %10.18 olarak bulundu (Şekil 1). Genel HPV durumları, tip 16 ve 18 dağılımları Tablo 2'de belirtilmiştir.



Şekil 1. Yaş gruplarına göre pozitif ve negatif hrHPV dağılımı.

Tablo 1. Yaş gruplarına göre olgu sayılarının dağılımı.

Grup	Olgu Sayısı (n/%)
Grup 1 (21-24)	147 (%3.50)
Grup 2 (25-29)	338 (%8.02)
Grup 3 (30-44)	2072 (%49.19)
Grup 4 (45-54)	1203 (%28.56)
Grup 5 (55-65)	452 (%10.73)
Toplam	**4212 (%100)**

HrHPV pozitifliği açısından Grup 1 ile diğer tüm gruplar (2,3,4,5) arasında istatistiksel olarak anlamlı farklılık bulunmaktadır (p=.00095, p<0.00001, p<0.00001, p<0.00001 sırasıyla).

HrHPV pozitifliği açısından Grup 2 ile diğer tüm gruplar (1,3,4,5) arasında istatistiksel olarak anlamlı farklılık bulunmaktadır (p=.00095, p=0.000251, p<0.00001, p=0.000948 sırasıyla).

HrHPV pozitifliği açısından grup 3 ile 5 arasında ve grup 4 ile 5 arasında ise istatistiksel olarak anlamlı bir farklılık bulunmamaktadır (p=0.493478, p=0. 361762 sırasıyla).

HPV tip 16 pozitifliği açısından Grup 1 ve diğer tüm gruplar (2,3,4,5) arasında istatistiksel olarak anlamlı farklılık bulunmakta (p=0.000105, p<0.00001, p<0.00001, p<0.00001 sırasıyla), grup 2, 3, 4 ve 5 arasında anlamlı bir farklılık bulunmamaktadır (p>0.05).

HPV tip 18 pozitifliği açısından Grup 1 ve diğer tüm gruplar (2,3,4,5) arasında istatistiksel olarak anlamlı farklılık bulunmakta (p=0.005002, p<0.00001, p<0.00001, p=0.001229), grup 2, 3, 4 ve 5 arasında anlamlı bir farklılık bulunmamaktadır (p>0.05).

Tablo 2. Yaş gruplarına göre genel hr HPV durumları, tip 16 ve 18 dağılımları.

Gruplar (yaş aralığı)	HPV (genel) Pozitif n (%)	HPV (genel) Negatif n (%)	HPV Other Pozitif n (%)	HPV Other Negatif n (%)	Tip 16 Pozitif n (%)	Tip 16 Negatif n (%)	Tip 18 Pozitif n (%)	Tip 18 Negatif n (%)
Grup 1 (21-24)	47/147 (%31.97)	100/147 (%68.03)	33/147 (%22.45)	114/147 (%77.55)	19/147 (%12.93)	128/147 (%87.07)	9/147 (%6.12)	138/147 (%93.88)
Grup 2 (25-29)	62/338 (%18.34)	276/338 (%81.66)	54/338 (%15.98)	284/338 (%84.02)	12/338 (%3.55)	326/338 (%96.45)	5/338 (%1.48)	333/338 (%98.52)
Grup 3 (30-44)	234/2072 (%11.29)	1838/2072 (%88.71)	195/2072 (%9.41)	1877/2072 (%90.59)	59/2072 (%2.85)	2013/2072 (%97.15)	17/2072 (%0.82)	2055/2072 (%99.18)
Grup 4 (45-54)	105/1203 (%8.73)	1098/1203 (%91.27)	86/1203 (%7.15)	1117/1203 (%92.85)	24/1203 (%1.9)	1179/1203 (%98)	9/1203 (%0.75)	1194/1203 (%99.25)
Grup 5 (55-65)	46/452 (%10.18)	406/452 (%89.82)	34/452 (%7.52)	418/452 (%92.48)	14/452 (%3.1)	438/452 (%96.9)	6/452 (%1.33)	446/452 (%98.67)
Toplam	494/4212 (%11.73)	3718/4212 (%88.27)	401/4212 (%9.54)	3811/4212 (%90.46)	127/4212 (%3.04)	4085/4212 (%96.96)	46/4212 (%1.09)	4166/4212 (%98.91)

HrHPV; High risk human papilloma virüs.

TARTIŞMA

Serviks kanserinin insidans ve mortalite oranları tüm dünyada coğrafi farklılıklar göstermektedir.[1-2] En yüksek bölgesel insidans ve ölüm oranı Güney ve Doğu Afrika, Güneydoğu Asya ve Güney Amerika ülkelerinde görülmektedir.[1] Kuzey Amerika, Avustralya ve Batı Asya ise 7 ila 10 kat daha düşük insidans oranına sahiptir.[1] Türkiye, serviks kanseri açısından kadınlarda görülen kanserler arasında yaklaşık dokuzuncu sırada olması nedeni ile düşük insidanslı ülkeler grubunda yer almaktadır.[10]

Yüksek riskli HPV enfeksiyonu servikal kanser gelişimindeki ana etiyolojik ajandır.[2] Özellikle yüksek riskli HPV tipleri olarak bilinen 16, 18, 31, 45 tüm serviks kanseri hastalarının %80'inde bulunmaktadır.[11] HPV enfeksiyonunun başlangıcı ile kanser gelişimi arasında uzun bir latent dönemin bulunması nedeniyle öncül lezyonlar veya kanserler tarama programlarıyla erken evrelerde saptanabilmektedir. Bu nedenle servikal kanser taramasında temel olarak servikal sitoloji incelemesi yapılmakta ve HPV testleri kullanılmaktadır. Hasta yönetimi; olgunun yaşına, sitolojik inceleme, hrHPV ve tip 16/18 sonuçlarına göre planlanmaktadır.[12]

On bir farklı ülkenin (Nijerya, Hindistan, Vietnam, Tayland, Kore, Kolombiya, Arjantin, Şili, Hollanda, İtalya ve İspanya) 13 ayrı bölgesindeki genel popülasyondaki kadınlardan rastgele seçilerek yapılan meta analiz çalışmalarına göre normal sitolojili kadınlarda yaklaşık % 6.6 oranında hrHPV pozitifliği bildirilmiştir. Bu oran düşük-orta sosyoekonomik düzeydeki toplumlarda daha sık olmak üzere %1.4 ile % 25.6 arasında farklılık göstermektedir.[11] Bu çalışmada da yaş gruplarından bağımsız olarak bu oran %11.73 olarak saptanmış olup literatür ile uyumlu olarak bulunmuştur.

Literatürde yaş gruplarına göre olan dağılımda 25 yaş altı kadınlarda en yüksek hrHPV pozitifliği saptanırken 35 yaş altındaki kadınlarda da yüksek hrHPV pozitifliği görülmüştür.[11] HrHPV prevalansı 35-44 yaş grubunda azalmış, 45-54 yaş ve daha ileri yaş grubunda ise tekrar artış göstermiştir.[11] Bu çalışmada da yaş gruplarına göre; 25 yaş altı kadınlarda en yüksek hrHPV pozi-tifliği, 29 yaş altı kadınlarda yüksek hrHPV pozitifliği, 45-54 yaş arasında en düşük hrHPV pozitifliği saptanmış olup 54-65 yaş arasında tekrar hafif bir artış gözlenmiştir.

Sanjose ve arkadaşlarının yaptığı meta analiz çalışmasına göre hrHPV ile enfekte olan kadınların %23.3'ünün tip 16, %8.5'inin tip 18 ile enfekte olduğu bildirilmiştir.[11] Bu çalışmada da literatüre benzer şekilde 494 hrHPV pozitif olgunun %25.70'i tip 16, %9.31'i tip 18 pozitifliği göstermiştir. Ayrıca 21-24 yaş arası kadınlarda tip 16 ve 18 pozitifliği diğer yaş gruplarına göre anlamlı derecede yüksek bulunmuştur.

Türkiye'de 2014 yılından itibaren hrHPV tabanlı organize tarama programları uygulanmaya başlanmış ve bu verilerden elde edilen ilk sonuçlara göre bir milyon kadın taramaya alınmıştır. Bu çalışmada hrHPV pozitif olguların % 66.7'sinde sitolojik olarak benign özellikler saptandığı

gösterilmiştir.[10] Türk popülasyonunda normal sitolojili olgularda HPV oranı Dursun ve arkadaşlarının çok merkezli ve 6388 vakalık çalışmasında %27, 2013'te Akyar ve arkadaşlarının çalışmasında %17.7, Eren F. ve arkadaşlarının çalışmasında % 34, Erdoğdu tarafından yapılan çalışmada %16.7 olarak bulunmuştur.[13-16] Bu çalışmadaki sonuçlar da ulusal çalışmalara benzer şekilde toplumumuzda sanıldığının aksine yüksek oranda HPV taşıyıcılığı olduğunu, nüfus dağılımının heterojenitesini göstermekte ve tarama yöntemlerinin önemini ortaya koymaktadır.

Çalışmamızda bazı kısıtlılıklar sözkonusudur. Tek merkezli ve hastane bazlı bir çalışma olması, nisbeten sosyoekonomik düzeyi yüksek bir çevreye ait hasta popülasyonun olması toplumun tümünü temsil edebilme açısından sınırlılık oluşturmuş olabilir. Veriler hastane kayıtlarından oluşturulmuştur. Bu kişiler sağlık sorunu olan veya benzeri bir sebeple hastaneye başvuran kişilerdir. Bu nedenle çalışma toplum taraması niteliğinde değildir.

HPV enfeksiyonu açısından en önemli risk faktörü seksüel aktivitedir. Erkek ve kadınlarda HPV bulaşma riskinin partner sayısı, ilk seksüel ilişkinin erken yaşta olması, seksüel temasla bulaşan diğer hastalıkların varlığı ile arttığı bilinmektedir.[2] Aynı zamanda düşük sosyoekonomik durum, kötü hijyenik koşullar, sigara içilmesi, ilk gebelik yaşının erken olması, ırk, immunsupresyon, oral kontraseptif kullanımı gibi faktörlerin de servikal neoplazi riskini arttırdığı bildirilmiştir.[2] Bu çalışmada da genç kadınlarda daha yüksek olarak saptanan HPV prevelansının başta partner çeşitliliği olmak üzere yaşam şekillerindeki ve tercihlerdeki değişiklikler ile birlikte, tarama ya da erken tanı için sağlık kuruluşlarına başvurma oranının artışı ile açıklanabileceğini düşünmekteyiz.[17] Ayrıca bu çalışmadaki gibi hrHPV ve tip 16 için, 55-65 yaş arasında görülen ikinci pikin nedeninin de kadınlarda gebe kalma endişesinin azalması veya ortadan kalkması olarak değerlendirilebileceğini öngörmekteyiz.[17]

HPV enfeksiyonundan korunmayı sağlayacak profilaktik HPV aşılarının topluma sunulması ve bu konuda toplumun bilgilendirilmesi büyük önem taşımaktadır.[12] Ülkemizde, HPV için ulusal bir aşılama programı bulunmamaktadır. Türk Jinekolojik Onkoloji Derneği HPV aşısını önermektedir. Türkiye'de yapılan çalışmalar daha çok HPV aşısı farkındalık oluşturma ve genel tutum çalışmalarıdır.[16]

Sonuç olarak, ülkemizdeki hrHPV sıklığının ve yaş dağılımının diğer toplumlardakine benzer olduğunu düşünmekteyiz. Ülkemizdeki gerçek HPV prevalansı ve tiplerinin belirlenebilmesi için toplum tabanlı geniş sayıda hasta içeren serilere ve bilinçlenme çalışmalarına ihtiyaç duyulmaktadır. Dünya Sağlık Örgütü'nün önerisinde olduğu gibi, ülkemizde de aşılama çalışmaları, tarama testlerinin yaygınlaştırılması ve prekanseröz lezyonların tanınması ile serviks kanserinin elimine edilmesinin mümkün olabileceğini öngörmekteyiz.

Çıkar Beyannamesi

Herhangi bir çıkar çatışmasının olmadığını yazarlar beyan etmektedirler.

Bilgilendirme

Çalışmamız 20-21 Mart 2021 tarihinde gerçekleşen 2021 MEDJR CONGRESS'de çevrim içi sözlü sunum olarak sunulmuştur.

Etik Kurul İzni

Bu çalışma için S. B. İstanbul Medeniyet Üniversitesi Göztepe Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulundan onay alındı (02.12.2020 tarih ve 2020/0723 sayı).

Araştırmacıların Katkı Oranı Beyanı

Ana fikir/Planlama: HŞ. Veri toplama/İşleme: HŞ, BG, GG, FEK, BO, İC, DS. Veri analizi ve yorumlama: HŞ, BG, GG, FEK, BO, İC, DS. Literatür taraması: HŞ, BG, GG, FEK, BO, İC, DS. Yazım: HŞ. Gözden geçirme ve düzeltme: HŞ.

KAYNAKÇA

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020:GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3): 209-249.
2. Arbyn M, Weiderpass E, Bruni L, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health. 2020;8(2):e191-e203.
3. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus

Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis. 2020;24(2):102-131.
4. Inal MM, Köse S, Yildirim Y, et al. The relationship between human papillomavirus infection and cervical intraepithelial neoplasia in Turkish women. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society. 2007;17(6):1266-1270.
5. Akcali S, Goker A, Ecemis T, Kandiloglu A R, Sanlidag T. Human papilloma virus frequency and genotype distribu-tion in a Turkish population. Asian Pacific journal of cancer prevention: APJCP. 2013;14(1): 503-506.
6. Tezcan S, Ozgur D, Ulger M, et al. Human papillomavirus genotype distribution and E6/E7 oncogene expression in Turkish women with cervical cytological findings. Asian Pacific journal of cancer prevention: APJCP. 2014;15(9):3997-4003.
7. Şahiner F, Kubar A, Yapar M, Şener K, Dede M, Gümral R. Detection of major HPVs by a new multiplex real-time PCR assay using type-specific primers. J. Microbiol. Methods. 2014;97:44-50.
8. Yuce K, Pinar A, Salman MC, et al. Detection and genotyping of cervical HPV with simultaneous cervical cytology in Turkish women: a hospital-based study. Arch. Gynecol. Obstet. 2012;286(1):203-208.
9. Bruni L, Albero G, Serrano B, et al. ICO/IARC HPV ve Kanser Bilgi Merkezi. Dünyada İnsan Papilloma Virüsü ve İlgili Hastalıklar. Özet raporu; 2023.
10. Gultekin M, Zayifoglu Karaca M, Kucukyildiz I, et al. Initial results of population based cervical cancer screening program using HPV testing in one million Turkish women. Int J Cancer. 2018;142(9):1952-1958.
11. De Sanjosé S, Diaz M, Castellsagué X, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a metaanalysis. The Lancet. Infect. Dis. 2007;7(7):453-459.
12. Wang Z, Liu T, Wang Y, et al. Risk of cervical lesions in high-risk HPV positive women with normal cytology: a retrospective single center study in China. Infect Agent Cancer.2020;15:34.
13. Dursun P, Ayhan A, Mutlu L, et al. HPV types in Turkey: multicenter hospital based evaluation of 6388 patients in Turkish gynecologic oncology group centers. Turk Patoloji Derg. 2013;29(3):210-216.
14. Akyar I, Aydın Ö, Yakıcıer MC, Kocagöz T, İnce Ü, Ünsal İ. Human papillomavirus prevalence and type in liquid-based cervical samples from Turkish women in a selected risk group. Turk J Med Sci. 2013;43(6):963-970.
15. Eren F, Erenus M, Bas E, Ahiskali R, Yoldemir T. Prevalence of HPV infection by cytologic diagnosis and HPV DNA extraction and prevalence of the HPV genotypes detected in urban Turkish women. Int J Gynaecol Obstet. 2010;109(3):235-238.
16. Erdoğdu İH. Moleküler Hpv Uygulanan Olgularda Hpv Sonuçları ile Patolojik Materyallerin Karşılaştırılması. Dicle Tıp Derg. 2019;46(1): 167-172.
17. Argyri, E., Papaspyridakos, S., Tsimplaki, E. et al. A cross sectional study of HPV type prevalence according to age and cytology. BMC Infect Dis. 2013;13(1): 1-8.

ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

The Relationship of Perceived Social Support with Level of Insight and Treatment Adherence in Individuals Diagnosed with Schizophrenia and Bipolar Disorder

Şizofreni ve Bipolar Bozukluk Tanılı Bireylerde Algılanan Sosyal Desteğin İçgörü Düzeyi ve Tedavi Uyumuyla İlişkisi

***Hanife KOCAKAYA*[1] *Kübra ARSLAN*[2] *Şadiye Visal BUTURAK*[3] *Ebru TURGAL*[4]**

ÖZ

Amaç: Bu çalışmada bipolar ve şizofreni tanılı hastaların algıladıkları sosyal desteğin tedavi uyumları ve içgörü düzeyleriyle ilişkisinin belirlenmesi amaçlanmıştır.
Araçlar ve Yöntem: Bu araştırma son 1 yıl içinde kliniğimizde yatarak tedavi görmüş, remisyon döneminde olan, 55 bipolar ve 55 şizofreni tanılı hasta olmak üzere 110 birey ile yürütülmüştür. Katılımcılara sosyodemografik ve klinik veri formu, Young Mani Derecelendirme Ölçeği (YMDÖ), Klinik Global İzlenim Ölçeği (CGİ), İçgörünün Üç bileşenini Değerlendirme Ölçeği (İÜBDÖ), Morisky Tedavi Uyum Ölçeği (MTUÖ) ve Çok Boyutlu Algılanan Sosyal Destek Ölçeği (ÇBASD) uygulanmıştır.
Bulgular: Bipolar hastaların yaş ortalaması 40.47±12.96, şizofreni tanılı hastaların yaş ortalaması 40.45±11.71 idi. Algılanan aile, arkadaş, özel biri desteği ve total destek puanı bipolar hastalarda anlamlı (p=0.000, p=0.000, p=0.004, p=0.000, sırasıyla) yüksek saptanmış olup, en yüksek destek aileden, ardından arkadaş ve önemli kişilerden algılanmıştır. Gruplar tedavi uyumları açısından farklılık (p=0.083) göstermemekle birlikte, iç görü puanı bipolar hastalarda anlamlı yüksekti (p=0.001). Gruplar algılanan sosyal desteği etkileyen faktörler açısından hiyerarşik regrasyon analiziyle değerlendirilmiştir. Cinsiyet, eğitim yılı, içgörü ve tedavi uyumunun sosyal destek için prediktif (p=0.04, p=0.01, p<0.001, p=0.01, sırasıyla) olduğu görülmüştür.
Sonuç: Bipolar ve şizofren hastalara bakım verenlerin (aile vb.) sosyal desteğin klinik gidişe etkisi konusunda bilgilendirilmesi içgörü ve tedavi uyumuna olumlu katkı sağlayarak bakım verenlerin yükünü azaltabilir.

Anahtar Kelimeler: algılanan aile desteği; kronik ruhsal hastalıklar; tedavi

ABSTRACT

Purpose: This study aims to examine the relationship between perceived social support, insight, and treatment adherence in patients with schizophrenia and bipolar disorder.
Materials and Methods: This study was conducted with 110 individuals, including 55 bipolar and 55 schizophrenia patients, who had been hospitalized in our clinic in the last 1 year and were in remission. Participants were administered a sociodemographic and clinical data form, Young Mania Rating Scale (YMDÖ), Clinical Global Impression Scale (CGI), Three Components of Insight Rating Scale (IÜBDÖ), Morisky Treatment Compliance Scale (MTUÖ) and Multidimensional Perceived Social Support Scale (MSPSS).
Results: The mean age was 40.47±12.96 for bipolar patients and 40.45±11.71 for schizophrenics. Perceived family, friend, significant others support, and total support was found to be higher (p=0.000, p=0.000, p=0.004, p=0.000, respectively) of bipolar patients, and the highest support was perceived from family, followed by friends and significant people. Although the groups did not differ in terms of treatment adherence (p=0.083), the insight score was significantly higher in bipolar patients (p=0.001). Groups were evaluated with hierarchical regression analysis in terms of factors affecting perceived social support. Gender, years of education, insight, and treatment adherence were found to be predictive of social support (p=0.04, p=0.01, p<0.001, p=0.01, respectively).
Conclusion: Informing caregivers (family, etc.) of bipolar and schizophrenic patients about the effect of social support on clinical outcome may reduce the burden of caregivers by contributing positively to insight and treatment compliance.

Keywords: chronic mental illness; perceived family support; treatment

Received: 06.05.2023; Accepted: 21.08.2023

[1]Kırıkkale University Faculty of Medicine Department of Psychiatry, Kırıkkale, Türkiye.
[2]Kırıkkale University Faculty of Health Sciences Department of Social Work, Kırıkkale, Türkiye.
[3]Mersin University Faculty of Medicine Department of Psychiatry, Mersin, Türkiye.
[4]Hitit University Faculty of Medicine Department of Biostatistics, Çorum, Türkiye.
Corresponding Author: Hanife Kocakaya, Kırıkkale University Faculty of Medicine Department of Psychiatry, Kırıkkale, Türkiye.
e-mail: drhanifekocakaya@gmail.com

How to cite: Kocakaya H, Arslan K, Buturak ŞV, Turgal E. The relationship of perceived social support with level of insight and treatment adherence in individuals diagnosed with schizophrenia and bipolar disorder. Ahi Evran Med J. 2024;8(1):35-42. DOI: 10.46332/aemj.1293440

INTRODUCTION

Schizophrenia and bipolar disorder are lifelong psychiatric diseases that begin at an early age and, are characterized by aggravations, remissions, and relapses. Individuals with bipolar disorder and schizophrenia have a poor quality of life due to factors such as residual symptoms, medication side effects, and lack of social support, even if they have achieved clinical remission. Social support is defined as helpful people experiencing stress or difficulties with those around them.[1] Perceived social support, on the other hand, includes how aware people are of their social support network and how satisfied they are with it, and this is considered a better psychological sign than objectively measured social support.[2] In a study evaluating social support in bipolar patients, it was reported that high-level social support decreases recurrence through increased treatment adherence.[3] Cohen et al. reported that low social support predicted the recurrence of depressive episodes. Also, the perception of social support came from friends, parents, and partners related to decreased number of depressive attacks and hospitalization.[4] Similarly, social support is one of the factors that influence symptom severity, recovery, and adherence to medication in schizophrenia patients.[5] However, social support systems for schizophrenia patients are not sufficient due to stigma, exclusion, and isolation.[6]

Insight is defined as acknowledging that one has a mental illness, being aware of their symptoms, and accepting treatment.[7] Studies evaluating the relationship between insight and clinical features in bipolar patients have associated better insight with fewer attacks, fewer hospitalizations, and a longer duration of illness.[8] In studies evaluating insight in psychotic disorders, especially schizophrenia; lack of insight has been associated with increased hospitalization rate, adverse clinical outcomes decreased psychosocial functioning and impaired adherence to treatment.[9]

Treatment adherence is the degree to which a person accepts the behaviors (medication, etc.) recommended by healthcare providers. Especially in schizophrenic patients, regular drug use and compliance with medical recommendations are of primary importance for the success of treatment. However, in studies conducted in our country, it has been reported that treatment non-compliance is common in patients with schizophrenia.[10,11] Treatment non-adherence is a common problem in bipolar patients, and it can lead to an increase in hospitalization rates, care costs, mortality, suicide attempts, and decreased functionality.[13] However, there are a limited number of studies evaluating social support, insight, and adherence to treatment in patients with bipolar disorder and schizophrenia. This study aims to determine the relationship between perceived social support, insight levels, and treatment adherence in patients with schizophrenia and bipolar disorder hospitalized in the psychiatry clinic in the last 1 year.

MATERIALS and METHODS

Approval for the study was received from Kırıkkale University Faculty of Medicine Non-Interventional Research Ethics Committee (Date: 16.09.2021 and numbered 2021.09.09). The principles of the Declaration of Helsinki were followed throughout the research. This is a cross-sectional and descriptive study. Schizophrenia and bipolar patients who were hospitalized Kırıkkale University Faculty of Medicine psychiatry service between 01.07.2020 and 01.07.2021 were included in the study. During this period, 135 patients received inpatient treatment with various diagnoses, and 125 of these patients were diagnosed with bipolar disorder and schizophrenia. Among these individuals, 110 patients (55 bipolar, 55 schizophrenia) who were in remission and had regular outpatient visits after discharge were included in our study.

Among these individuals, 110 patients (55 bipolar, 55 schizophrenic) between the ages of 18-65 who were in remission and had regular outpatient visits after discharge were included in our study. Exclusion criteria from the study include a diagnosis of alcohol and/or substance abuse disorder, a diagnosis of mental retardation, and a lack of cooperation that cannot answer questions.Data were collected between 16.09.2021 and 20.03.2022.

Sociodemographic and clinical data form, Young Mania Rating Scale (YMDS), Clinical Global Impressions Scale (CGI), Schedule for Assessment of Insight (SAI), Morisky Medication Adherence Scale (MMAS), and Multidimensional Scale of Perceived Social Support (MSPSS) were administered to the participants.

Sociodemographic and clinical data form: was prepared by the researchers. The participants' socio-demographics (gender, etc.) and clinical characteristics (application type, length of hospital stay, etc.) were recorded.

Young Mania Rating Scale (YMDS): It is a scale filled in to assess manic symptoms based on the state of the past 48 hours. Turkish reliability and validity studies were conducted.[14]

Clinical Global Impressions Scale (CGI-s): It is a three-dimensional (illness severity, recovery, and side effect) scale that evaluates the clinical course of psychiatric disorders. In this study, severity (Clinical Global Impression-Violence) and side effect (Clinical Global Impression-Side Effect) sub-dimensions were used.[15]

Schedule for Assessment of Insight (SAI): The scale has eight questions and insight is evaluated in three dimensions. These are; (a) awareness of the illness, (b) abnormal evaluation of psychotic experiences, and (c) adherence to treatment. Turkish validity and reliability study was conducted and applied by the clinician. The highest score of the first seven questions is 14, and it is left to the clinician whether to ask the eighth question. As the score obtained from the scale increases, the level of insight increases.[16]

Morisky Medication Adherence Scale (MMAS): The scale consists of four questions and the answer is “yes/no”. If all questions are answered "no", drug compliance is considered high, if one or two questions are answered "yes", drug compliance is considered medium, if three or four questions are answered "yes", drug compliance is considered low. A low score on the scale indicates high adherence to treatment. The Turkish validity and reliability study was conducted by Yılmaz.[17]

Multidimensional Perceived Social Support Scale (MPSSS): The scale consists of a total of 12 items and has sub-dimensions of family support, friend support, and special support. The scale is a 7-point Likert-type scale with the form "Absolutely no 1,2,3,4,5,6,7 Definitely yes". The score of the scale varies between 12 to 84 and there is no cut-off point. A high score on the scale means high perceived social support. The MSPSS has shown high internal reliability (Cronbach's alpha =.87, .85, and .91 respectively for the Family, Friends and Significant Others subscales).[2]

Statistical Analysis

SPSS 21 (SPSS Inc., Chicago, Ill, USA) program was used in the analysis of the data. Skewness and kurtosis tests were applied to show whether the continuous variables were normally distributed and it was seen that the data were normally distributed. Continuous variables were expressed as mean and standard deviation. Student's t-test and Chi-square were used for comparisons between groups in terms of demographic and clinical characteristics. The relationship between perceived social support, clinical characteristics, insight, and adherence to treatment in bipolar and schizophrenic patients was evaluated with the Pearson correlation coefficient. Hierarchical Regression Analysis was used to evaluate the factors affecting social support (age, years of education, number of hospitalizations, length of hospital stay, number of suicides, disease duration, insight, and treatment compliance scores). Significance level was $p<0.05$.

RESULTS

In our study, the mean age was 40.47±12.96 for bipolar patients and 40.45±11.71 for schizophrenics. Demographic and clinical characteristics were similar between the groups ($p>0.05$) (Table 1). However, long-acting injection use was significantly higher in the schizophrenics ($p=0.004$). When we evaluated with MSPSS (high/medium/low) in terms of treatment adherence, , 6 (10.6%) patients were low adherence , 34 (61.8%) patients were moderately compatible, and 15 (13%) patients were highly compatible in the bipolar group. In the schizophrenia group, 12 (21.8%) patients were low adherent, 36 (65.5%) were moderate adherent, and 7 (12.7%) were high adherent. The groups were similar in terms of treatment compliance ($p=0.083$). The SAI score was significantly higher in bipolar patients ($p=0.001$). When evaluated in terms of perceived social support; perceived family support ($p=0.000$), friend support ($p=0.000$), special person support ($p=0.004$), and perceived total support score ($p=0.000$) were statistically significantly higher in bipolar patients. When the groups were evaluated in terms of CGI

scale severity and side effect sub-dimensions, severity scores were statistically significantly higher in the schizophrenia group (p=0.00). However, there was no significant difference (p=0.87) between the groups in terms of side effect scores (Table 2).

Table 1. Socio-demographic characteristics of bipolar and schizophrenic patients.

Socio-demographic characteristics	Bipolar disorder (n=55)	Schizophrenia (n=55)	p
Age	40.47 (±12.96)	40.45 (±11.71)	0.994
Gender			
Female	32 (%8.2)	28 (% 50.9)	0.448
Male	23 (%41.8)	25 (% 49.1)	
Education Level			
Primary school	17 (%30.9)	19 (%34.5)	
Middle school	14 (%25.5)	17 (%30.9)	0.214
High schoo	12 (%21.8)	14 (%25.5)	
University	12 (%21.8)	5 (%9.1)	
Education year	9.76 (±4.26)	8.58 (±3.57)	0.118
Marital status			
Single	22 (%40)	23 (%41.8)	
Married	23 (%41.8)	23 (%41.8)	0.795
Divorced	10 (%18.2)	9 (%16.4)	
Employment			
Employee	7 (%12.7)	7 (%12.7)	
Housewife	19 (%34.5)	21 (%38.2)	0.850
Disabled	15 (%27.3)	13 (%23.6)	
Student	14 (%25.5)	14 (%25.5)	

Values; mean±standard deviation, presented as a percentage (%), *p<0.05

Table 2. Comparison of the groups in terms of Clinical features, Perceived Social Support, Insight and Adherence to Treatment.

Variables		Bipolar Disorder N (%)	Schizophrenia N (%)	p
Admission site	Policlinic	45 (%81.8)	40 (%72.7)	0.182
	Emergency	10 (%18.2)	15 (%27.3)	
Reason for admission	Attack period	35 (%63.6)	33 (%60)	0.422
	Diagnosis/treatment	20 (%36.4)	22 (%40)	
Axis 2	Yes	13 (%23.6)	6 (%10.9)	0.064
	No	42 (%76.4)	49 (%89.1)	
Physical illness	Yes	15 (%27.3)	10 (%18.2)	0.182
	No	40 (%72.7)	45 (%81.8)	
Attempted suicide	Yes	13 (%23.6)	9 (%16.4)	0.238
	No	42 (%76.4)	46 (%83.6)	
Cigarette	Yes	43 (%78.2)	45 (%81.8)	0.406
	No	12 (%21.8)	10 (%18.2)	
LAI	Yes	7 (%12.7)	20 (%36.4)	0.004*
	No	48 (%87.3)	35 (%63.6)	
MMAS	Low	6 (%10.9)	12 (%21.8)	0.083
	Medium	34 (%61.8)	36 (%65.5)	
	High	15 (%27.3)	7 (%12.7)	
Disease duration		12.42 (± 11.03)	13.25 (± 10.32)	0.682
Number of hospitalizations		4.64 (± 4.20)	4.16 (± 2.69)	0.484
Duration of hospitalization		19.18 (± 10.81)	19.85 (± 10.50)	0.741
MPSSS				
	Family	24.56 (± 3.34)	19.76 (± 6.36)	<0.001**
	Friends	13.84 (± 5.95)	8.71 (± 5.40)	<0.001**
	Significant Others	10.13 (± 6.54)	5.93 (± 4.21)	<0.001**
	Total Perceived Social Support	48.47 (± 11.01)	34.33 (±11.43)	<0.001**
CGI-S		1.49 (±.63)	2.22 (±.60)	<0.001**
CGI-SE		1.44 (±.57)	1.36 (±.52)	0.487
SAI		10.24 (± 3.39)	7.62 (± 3.24)	<0.001**
MMAS		1.45 (± 1.10)	1.85 (± 1.06)	0.05

Abbreviations: MMAS: Morisky Medication Adherence Scale, LAI: long-acting injection, MPSSS; Multidimensional Perceived Social Support Scale, CGI-S; Clinical Global Impression-ilnes severity, CGI-SE; Clinical Global Impression- side effects, SAI; Schedule for Assessment of Insight, MMAS; Morisky Medication Adherence Scale, *p<0.05, **p <.001

In bipolar patients; there was a negative correlation between perceived friend support and total support and disease severity (r=-.292, p<0.05, r=-.288, p<0.05), and a positive correlation with years of education(r=.472, p<0.001, r=.276, p<0.05). A significant negative correlation was found between MSPSS score and perceived family support (r=-.333, p<0.05), friend support (r=-.488 p<0.001), special someone support sub-dimension (r=-.432, p<0.001), and perceived total support(r=-.612, p<0.001). In addition, a significant positive correlation was found between the SAI score and all sub-dimensions of perceived social support (r=.392, p<0.001, r=.349, p<0.001, r=.416, p<0.001, r=.547, p<0.001, respectively) (Table 3).

Table 3. The relationship between schizophrenic and bipolar patients' perceived social support and other factors.

Group	Bipolar Disorder				Schizophrenia			
Variables	Family	Friends	Significant Others	Total Perceived Social Support	Fam-ily	Friends	Significant Others	Total Perceived Social Support
Age	-.172	-.243	.093	-.137	-.138	-.059	-.011	-.111
Education Year	.176	.472**	.099	.276*	.167	.255	.374**	.358**
Number of hospitalizations	.154	-.017	-.188	-.073	-.066	-.330*	-.302*	-.309*
Duration of hospitalization	.064	.067	-.108	-.003	-.089	-.280*	-.050	-.209
Number of suicides	-.021	-.088	-.047	-.079	-.085	.027	-.128	-.079
Disease duration	-.072	-.285*	-.003	-.174	-.280*	-.030	.001	-.172
CGI-S	-.142	-.292*	-.162	-.288*	-.205	-.180	-.243	-.297*
CGI-SE	-.053	-.071	-.239	-.157	-.107	-0,231	0,063	-.154
SAI	.392**	.349**	.416**	.547**	.270*	.291*	.202	.371**
MMAS	-.333*	-.488**	-.432**	-.612**	-.263*	-.334	-.201	-.391**

Abbreviations: MPSSS; Multidimensional Perceived Social Support Scale, CGI-S; Clinical Global Impression-ilnes severity, CGI-SE; Clinical Global Impression-side effects, SAI; Schedule for Assessment of Insight, MMAS; Morisky Medication Adherence Scale, Presented with Pearson Correlation Coefficients, *p<0.05, **p <.001 **p <.001,

In the schizophrenia group, a significant positive correlation was found between years of education and perceived special person support sub-dimension (r=.374, p<0.001) and perceived total support (r=.358, p<0.001). A negative relationship was found between the number of hospitalizations and the support of friends (r=-.330, p<0.05), support for a special person (r=-.302, p<0.05), and total support (r=-.309, p<0.05). A significant negative correlation was found between disease duration and perceived family support (r=-.280, p<0.05). A significant negative correlation was found between disease severity and total support (r=-.297, p<0.05). A positive correlation was found between the score of SAI and family support (r=.270, p<0.05), friend support (r=.291, p<0.05), and perceived total support (r=.371, p<0.001). A negative correlation was found between the MSPSS score and the sub-dimension of family support (r=-.263, p<0.05) and total support (r=-.391, p<0.001) (Table 3).

Hierarchical regression analyzes were performed to determine the contribution of these variables. Accordingly, gender, years of education, insight, and treatment compliance were found to predict perceived total support (p=0.04, p=0.01, p<0.001, p=0.01, respectively)(Table 4).

Table 4. Examination of the factors affecting social support by Hierarchical Regression Analysis.

Model	Predictor	B	SE B	β	p	R2	ΔR2
1	Constant	36.36	6.59		0.00		
	Gender	-12.98	2.8	-0.493	**0.04**	0.35	0.34
	Age	0.06	0.10	0.059	0.53		
	Education year	0.82	0.32	0.24	**0.01**		
2	Number of hospitalizations	-0.07	0.36	-0.01	0.85		
	Duration of hospitalization	-0.08	0.10	-0.07	0.42	0.37	0.33
	Number of suicides	-1.17	1.17	-0.08	0.32		
	Disease duration	-0.16	0.14	-0.13	0.24		
3	CGI-S	-3.24	2.3	-0.17	0.12	0.44	0.38
	CGI-SE	-0.57	2.17	-0.02	0.79		
4	SAI	1.29	0.33	0.34	**0.00**	0.52	0.46
5	MMAS	-3.16	1.20	-0.26	**0.01**	0.55	0.49

Abbreviations: MPSSS; Multidimensional Perceived Social Support Scale, CGI-S; Clinical Global Impression-ilnes severity, CGI-SE; Clinical Global Impression- side effects, SAI; Schedule for Assessment of Insight, MMAS; Morisky Medication Adherence Scale, p<0.05, p <.001

DISCUSSIONS

Social support is one of the most effective tools for coping with and adapting to difficult and stressful events and positively affects the process and results of psychiatric treatment and psychotherapy.[18] In our study, the perceived family, friend, and personal support and total support were found to be significantly higher in bipolar patients, and the family perceived the highest support, followed by friends

and important people. In addition, years of education, insight, and treatment compliance were found to be predictors of perceived social support.

In our study, perceived social support was found to be higher in bipolar patients than in schizophrenics in all areas. One study evaluating schizophrenic and bipolar patients in terms of perceived social support reported that social support was significantly higher in bipolar patients.[19] In a study evaluating schizophrenic and bipolar patients in terms of internalized stigma, self-esteem, and perceived social support, it was reported that there was no difference between the groups.[20] In the study about schizophrenia and bipolar patients in remission evaluated in terms of their perceived social support and quality of life analyzed that perceived social support is higher in the schizophrenia group.[21] Our study results were similar to the results of Singh et al. This could be explained by the fact that our patients are in remission, and our bipolar patients use mood stabilizers, which are drugs that require more frequent and regular follow-ups.

The highest level of support was perceived from family, followed by friends and important people for bipolar and schizophrenic patients. This could be explained by the fact that the majority of individuals with chronic mental illness generally live with their families. Similar results were reported in the study examining the social networks of people with chronic mental illness, and it suggested that the patients' social networks were formed by family members at a higher rate.[22] The fact that the patients received the least support from a private person can be explained by the fact that most of these patients are single and lack a special relationship, as reported in the literature. Another study reported that social support was received from family, friends, and important people, respectively about examining the relationship between suicidal behavior and perceived social support in bipolar patients in remission.[23] Similar results were reported in the study by Uygun et al.[24] In a study focused on patients diagnosed with schizophrenia, it was reported that perceived support came mostly from family and other important people after friends.[25]

When the groups were evaluated in terms of insight, it was observed that insight was high in bipolar patients. Although there is limited data on insight in bipolar patients, it was reported that patients with a diagnosis of schizophrenia showed weaker insight into a mental disorder and its social consequences in a study bipolar and schizophrenic patients in remission evaluated in terms of insight. [26]

In the bipolar group, although perceived social support decreased as the severity of the illness increased, no similar correlation was found with the duration of the illness, the number of hospitalizations, and the length of hospitalization. This may be associated with sub-threshold symptoms, which are known to have a significant impact on the course of the disease and well-being. In a study evaluating perceived social support in bipolar patients, it was reported that there was no significant relationship between social support and the number of attacks or hospitalizations. However, it was found that subthreshold depressive symptoms decreased with the increase in social support.[23] Similarly, Staner et al.showed that social support is not a risk factor for relapse[27] and our result is similar to the literature in this respect. In bipolar patients, a significant positive correlation was found between insight and the support of friends, the support of a special person sub-dimension, and total support.Another study evaluating insight and treatment adherence in bipolar patients reported that higher insight facilitated support from family and friends.[28] This situation could be explained by the fact that it is difficult to maintain social ties such as friendship and marriage due to a lack of insight, more attacks, and a decrease in psychosocial functionality. In addition, it was observed that bipolar patients with good adherence to treatment had higher perceptions of social support, and it was reported that as social support increased, therapeutic cooperation became stronger.[29,30]

In our study, we observed that as the number of hospitalizations increased in schizophrenics, perceived friend and special someone support decreased. In addition, it was determined that as the duration of the disease increased, perceived family support decreased, and as the severity of the disease increased, perceived total support decreased. This could be explained by the decrease in socialization due to the excess time spent in the hospital and the decrease in the tolerance of families due to the increase in the burden of care as the duration of illness increases. In a recent study investigating the relationship between perceived social

support and recovery in schizophrenics showed that all dimensions of perceived social support had a significant relationship with recovery.[31] The increase in hospitalizations and poor clinical course in patients with psychotic disorders may weaken or even break the social ties that patients establish with friends and special people. Although a different scale was used in our study, our result was similar to the literature. Perceived family support was higher in patients with schizophrenia who had a high insight. In a study evaluating the relationship between social support and insight in schizophrenia, it was reported that perceived social support was associated with insight graded by both the clinician and the patient. In addition, same data reported that patients with high insight have higher perceived social support, and they can seek help from other people more easily to manage their illness and life.[32] Especially in patients diagnosed with psychotic disorder, lack of insight results in difficulties in adherence to treatment, an increase in hospitalization rates, and a negative clinical course, which can lead to weakening or even breaking the social ties that patients establish with friends and a special person.[9] Another finding of our study is that perceived family support and total support are higher in schizophrenics with high adherence to treatment. Also one study evaluating adherence to antipsychotics reported that perceived family support caused a positive approach toward the drug and positively affected the treatment.[33]

In bipolar and schizophrenic patients, there was a significant positive correlation between years of education and perceived friend and special someone support. This could be explained by the fact that the individual can contribute to their social network by making different friendships during the education process, and to social support in terms of turning these friendships into permanent friendships.

When the sample is evaluated in terms of factors that predict social support; gender, years of education, insight, and treatment compliance were found to be predictors. In a cross-sectional study evaluating the relationship between perceived social support and quality of life in psychiatric patients with demographic and clinical variables, it was reported that age, education level, employment status, duration of illness, initiation of treatment, and hospitalization status significantly affect the level of social support.[34] In another study, it was shown that poor social support is associated with multiple hospitalizations in patients with schizophrenia and bipolar disorder[35] and our study results are consistent with the literature. However, longitudinal studies on this subject are needed.

Our study has some limitations. The healthy control group was not included for comparison. Second, details on residual symptoms and drug use were not included.

Conclusion

In this study, the relationship between perceived social support, insight levels, and treatment adherence of schizophrenic and bipolar patients in remission who received inpatient treatment in the psychiatry clinic in the last 1 year was evaluated. In our study, the perceived family, friend, and personal support and total support were found to be significantly higher in bipolar patients, and the family perceived the highest support, followed by friends and important people. In addition, education years, insight, and treatment adherence were found to be predictors of perceived social support. The negative impact on the clinical course of the decrease in social support combined with the decrease in perceived social support due to the chronic course of mental illnesses seems to represent a vicious circle. For this reason, informing caregivers (family, spouse, etc.) about the effect of perceived social support on the clinical course and receiving psychoeducation about coping with symptoms may contribute to reducing the burden of caregivers and increasing social support.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

The study was approved by Kırıkkale University Non-Interventional Studies Ethics Committee (date 16.09.2021 and number 2021.09.09)

Authors' Contributions

Concept/Design: HK, ŞVB. Data Collection and/or Processing: HK, KA. Data analysis and interpretation: ET,

KA. Literature Search: HK, KA. Drafting manuscript: HK, ŞVB. Critical revision of manuscript: HK, ET, ŞVB. Supervision: ŞVB, ET, KA.

REFERENCES

1. Brissos S, Dias VV, Carita AI, et al. Quality of life in bipolar type I disorder and schizophrenia in remission: clinical and neurocognitive correlates. Psychiatry Res. 2008;160(1):55-62.
2. Eker D, Arkar H, Yaldız H. Factorial structure, validity, and reliability of revised form of the multidimensional scale of perceived social support. Turkish Journal of Psychiatry. 2001;12(1):17-25.
3. Kleindienst N, Engel R, Greil W. Psychosocial and demographic factors associated with response to prophylactic lithium. A systematic review for bipolar disorders. Psychol. Med. 2005;35(12):1685-1694.
4. Cohen AN, Hammen C, Henry RM, et al. Effects of stress and social support on recurrence in bipolar disorder. J. Affect. Disord. 2004;82(1):143-147.
5. Corrigan PW, Phelan SM. Social support and recovery in people with serious mental illnesses. Community Ment. Health J. 2004;40(6):513-523.
6. Hendryx M, Green CA, Perrin NA. Social support, activities, and recovery from serious mental illness: STARS study findings. J. Behav. Health Serv. Res. 2009;36(3):320-329.
7. Reddy M. Insight and psychosis. Indian J. Psychol. Med. 2015;37(3):257-260.
8. Dias VV, Brissos S, Frey BN, et al. Insight, quality of life and cognitive functioning in euthymic patients with bipolar disorder. J. Affect. Disord. 2008;110(1-2):75-83.
9. Margariti M, Ploumpidis D, Economou M, et al. Quality of life in schizophrenia spectrum disorders: associations with insight and psychopathology. Psychiatry Res. 2015;225(3):695-701.
10. Altun ÖŞ, Karakaş SA, Olçun Z, et al. An investigation of the relationship between schizophrenic patients' strength of religious faith and adherence to treatment. Arch. Psychiatr. Nurs. 2018;32(1):62-65.
11. Yılmaz E, Okanlı A. The effect of internalized stigma on the adherence to treatment in patients with schizophrenia. Arch. Psychiatr. Nurs. 2015;29(5):297-301.
12. Sajatovic M, Chen P, Dines P, et al. Psychoeducational approaches to medication adherence in patients with bipolar disorder. Disease Management & Health Outcomes. 2007;15(3):181-192.
13. Krahn GL. WHO World Report on Disability: a review. Disabil Health J. 2011;4(3):141-142.
14. Karadağ F, Oral ET, Aran Yalçın F, et al. Young mani derecelendirme ölçeğinin Türkiye'de geçerlik ve güvenilirliği. Turk Psikiyatri Derg. 2001;13(2):107-114.
15. Guy W, ECDEU Assessment Manual for Psychopharmacology, Revised US Dept Health, Education and Welfare publication (ADM), Rockville, National Institude of Mental Health. 1976;76-338.
16. Aslan S, Kılıç BG, Karakılıç H, et al. İçgörünün üç bileşenini değerlendirme ölçeği: Güvenilirlik ve geçerlik çalışması. Türkiye'de Psikiyatri. 2001; 3(1):17-24.
17. Yılmaz S. Psikiyatri hastalarında ilaç yan etkileri ve ilaç uyumu. İstanbul Üniversitesi Sağlık Bilimleri Enstitüsü, Yüksek Lisans Tezi 2004.
18. Brüggemann BR, Garlipp P, Haltenhof H, et al. Quality of life and social support as outcome characteristics of a psychiatric day hospital. Ger. J. Psychiatry. 2007;10(3):58-68.
19. Singh NK, Chakraborty P. A comparative study of perceived social support in schizophrenia and bipolar affective disorder (Manic) cases. Indian Journal of Health & Wellbeing. 2020;11(7-9):393-397.
20. Hülya K, Demir S. Şizofreni ve bipolar bozukluğu olan hastalarda içselleştirilmiş damgalanma, benlik saygısı ve algılanan sosyal destek. Cukurova Med. J. 2018;43(1):99-106.
21. Prabhakaran S, Nagarajan P, Varadharajan N, et al. Relationship Between Quality of Life and Social Support Among Patients with Schizophrenia and Bipolar Disorder: A Cross-Sectional Study. Journal of Psychosocial Rehabilitation and Mental Health. 2021:1-9.
22. Brunt D, Hansson L. The social networks of persons with severe mental illness in in-patient settings and supported community settings. J Ment Health. 2002;11(6):611-621.
23. Kazan Kizilkurt O, Giynas FE, Yazici Gulec M, et al. Bipolar disorder and perceived social support: relation with clinical course, and the role of suicidal behaviour. Psychiatr. Clin. Psychopharmacol. 2019;29(4):787-793.
24. Uygun E, Cebeci RB, Özsoy E, et al. Investigation of the relationship between perceived social support and psychological resilience in bipolar disorder: a cross-sectional study. Anadolu Psikiyatr. Derg. 2020; 21(1):37-44.
25. Sawant NS, Jethwani KS. Understanding family functioning and social support in unremitting schizophrenia: A study in India. Indian J. Psychiatry. 2010;52 (2):145.
26. Braw Y, Sitman R, Sela T, et al. Comparison of insight among schizophrenia and bipolar disorder patients in remission of affective and positive symptoms: analysis and critique. Eur. Psychiatry. 2012;27(8):612-618.
27. Staner L, Tracy A, Dramaix M, et al. Clinical and psychosocial predictors of recurrence in recovered bipolar and unipolar depressives: a one-year controlled prospective study. Psychiatry Res. 1997;69(1):39-51.
28. Gutiérrez-Rojas L, Martínez-Ortega JM, Pérez-Costillas L, et al. Illness insight and medication adherence among patients with bipolar disorder. J. Nerv. Ment. Dis. 2020;208(6):481-487.
29. Strauss JL, Johnson SL. Role of treatment alliance in the clinical management of bipolar disorder: stronger alliances prospectively predict fewer manic symptoms. Psychiatry Res. 2006;145(2-3):215-223.
30. Kulhara P, Basu D, Mattoo SK, et al. Lithium prophylaxis of recurrent bipolar affective disorder: long-term outcome and its psychosocial correlates. J. Affect. Disord. 1999;54(1-2):87-96.
31. El-Monshed A, Amr M. Association between perceived social support and recovery among patients with schizophrenia. Int. J. Africa Nurs. Sci. 2020;13:100236.
32. Hélène T, Hélène V, Jean B, et al. Impact of interpersonal factors on insight in schizophrenia. Schizophr. Res. 2014;159(2-3):527-532.
33. Baloush-Kleinman V, Levine SZ, Roe D, et al. Adherence to antipsychotic drug treatment in early-episode schizophrenia: a six-month naturalistic follow-up study. Schizophr. Res. 2011;130(1-3):176-181.
34. Mahmoud AS, Berma AE, Gabal SAAS. Relationship between social support and the quality of life among psychiatric patients. J. psychiatry psychiatr. disord. 2017;1(2):57-75.
35. Kumar V, Singh B, Singh P, et al. Expressed Emotion and Social Support in Rehospitalized Psychiatric Patients. Social Work. 2018;9(2).

BİLİMSEL ARAŞTIRMA MAKALESİ

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Endoskopik Retrograd Kolanjiopankreatografi Sonrası Pankreatit ile Preoperatif Dönemde Bakılan Laboratuar Parametrelerinin İlişkisi

Relationships Between Post-Endoscopıc Retrograde Cholangiopancreatography Pancreatitis and Preoperative Laboratory Parameters

Soner ÖNEM[1] Süleyman DOLU[2] Mehmet CAMCI[3] Arif YÜKSEL[4]

ÖZ

Amaç: Endoskopik retrograd kolanjiopankreatografi (ERCP) öncesinde bakılan laboratuar tetkikleri ile post-ERCP pankreatit ilişkisinin araştırılması.
Araçlar ve Yöntem Mart 2015- Haziran 2016 tarihleri arasında yapılan ERCP işlemler retrospektif olarak incelendi. ERCP yapılan hastaların yaşı, cinsiyeti, ERCP endikasyonları, ERCP sırasında yapılan işlemler, işlem sonrası oluşan komplikasyonlar belirlendi. İşlem öncesinde hastaların beyaz küre, nötrofil, lenfosit, hemoglobin, trombosit, aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), alkalen fosfataz (ALP), gama glutamil transferaz (GGT), total bilirubin, albumin, laktat dehidrogenaz (LDH) değerleriyle post-ERCP pankreatit ilişkisi araştırıldı.
Bulgular: Hastaların işlem öncesi bakılan laboratuar parametrelerinden GGT ve AST seviyesi pankreatit geçiren hastalarda, geçirmeyenlere oranla düşüktü. (GGT p=0.001, AST p=0.006). Diğer parametrelerde ise anlamlı fark saptanılmadı.
Sonuç: Post-ERCP pankreatit ERCP'nin en sık görülen komplikasyonudur. Pankreatit gelişimi açısından risk faktörleri bulunan hastaların tespiti erken tanı ve tedavi açısından önem taşımaktadır. AST düzeyinin normal üst sınırından 1.5 kat ve GGT düzeyinin 4 kattan düşük olması pre-operatif pankreatit risk değerlendirmesinde kullanılabilir.

Anahtar Kelimeler: pankreatit; post-ERCP; risk faktörü

ABSTRACT

Purpose: Investigation of the relationship between post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis and laboratory tests performed before ERCP.
Materials and Methods: ERCP procedures performed between March 2015 and June 2016 were analyzed retrospectively. Patient's age, gender, ERCP indications, procedures performed during ERCP, complications after ERCP were determined. The relationship between post-ERCP pancreatitis and white blood cell, neutrophil, lymphocyte, hemoglobin, thrombocyte, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gama-glutamly transferase (GGT), total bilirubin, albumin, lactate dehydrogenase (LDH) values of the patients before the procedure was investigated.
Results: GGT and AST levels in the preoperative period were lower in patients with pancreatitis compared to those who did not (GGT p=0.001, AST p=0.006). No significant difference was found in other parameters.
Conclusion: Post-ERCP pancreatitis is the most common complication of ERCP. Detection of patients with risk factors for the development of pancreatitis is important for early diagnosis and treatment. AST level lesser than 1.5 times normal value and GGT level lesser than 4 times can be used in pre-operative pancreatitis risk assessment.

Keywords: pancreatitis; post-ERCP; risc factors

Gönderilme tarihi: 21.10.2022; Kabul edilme tarihi: 25.08.2023

[1]Kırşehir Eğitim Araştırma Hastanesi, Gastroenteroloji, Kırşehir, Türkiye.
[2]Dokuz Eylül Üniversitesi Tıp Fakültesi, Gastroenteroloji, İzmir, Türkiye.
[3]Özel Orta Doğu Hastanesi, Gastroenteroloji, Mersin, Türkiye.
[4]İzmir Bozyaka Eğitim Araştırma Hastanesi İç Hastalıkları Kliniği, İzmir, Türkiye.
Sorumlu Yazar: Soner Önem, Kırşehir Eğitim Araştırma Hastanesi, Gastroenteroloji, Kırşehir, Türkiye. e-posta: soneronem@hotmail.com

Makaleye atıf için: Önem S, Dolu S, Camcı M, Yüksel A. Endoskopik retrograd kolanjiopankreatografi sonrası pankreatit ile preoperatif dönemde bakılan laboratuar parametrelerinin ilişkisi. Ahi Evran Med J. 2024;8(1):43-47. DOI: 10.46332/aemj.1192501

GİRİŞ

Endoskopik retrograd kolanjiopankreatografi (ERCP), yandan görüşlü bir endoskop ile duodenuma geçilerek papilla vateri yoluyla kontrast madde enjekte edilerek, skopi altında safra yolları ve pankreatik kanalın görüntülenmesi işlemidir. ERCP ilk olarak 1968 yılında kullanılmaya başlanmış olup günümüzde pankreatobiliyer hastalıkların tanı ve tedavisinde yaygın olarak kullanılmaktadır.[1] Uygulamaya başlamasından beş dekattan fazla geçen ERCP ile pankreatikobiliyer hastalıkların tedavisinde oldukça ilerleme sağlanmıştır. Bununla birlikte ERCP işlemine bağlı komplikasyonlar gelişebilmektedir. En sık karşılaşılan komplikasyon pankreatit olup başlıca görülen diğer komplikasyonlar kanama, perforasyon, kolanjit, kolesistit ve kardiyopulmoner sorunlardır.[2] Post-ERCP pankreatitin erken tanınması ve önlenmesiyle hastaneye yatış ve sağlık harcamalarında azalma sağlanabilir.[3] Bu yüzden post ERCP panreatit için risk faktörlerini belirlemek önem taşır. Post-ERCP pankreatit gelişimi için hasta ve işlem ile ilişkili risk faktörleri tanımlanmıştır. Oddi sfinkter disfonksiyon şüphesi, genç yaş(<55) , normal bilirubin değerleri, daha önceden post-ERCP pankreatit (PEP) geçirmek, kadın cinsiyet, zor-uzamış kanülasyon, ön-kesi sfinkterotomi, pankreatik sfinkteromi, pankreatik kanala opak verilmesi, biliyer sfinkterin balonla dilatasyonu pankreatit gelişimi için risk faktörleridir.[4,5] Risk faktörlerini tespit edilerek koruyucu endoskopik veya farmakolojik tedaviler yapılabilir.

Bu çalışma tek merkezde, tek endoskopist tarafından 15 aylık süre içinde yapılan ERCP işlemlerinin retrosepktif incelemesinde, laboratuvar değerleri ile ERCP sonrası pankreatit ilişkisini incelemeyi amaçlamıştır. Komplikasyonların önceden tespit edilebilip edilemeyeceği bu makalenin hedefi olacaktır.

ARAÇLAR ve YÖNTEM

Çalışmada Mart 2015- Haziran 2016 tarihleri arasında endoskopi ünitesinde yaşı 18'den büyük hastalara tek bir endoskopist tarafından yapılan ERCP işlemleri retrospektif olarak incelemeye alındı. Endoskopist ERCP konusunda 5 yıllık bir deneyime sahipti ve yıllık ortalama 150 işlem yapmaktaydı. Tüm hastalardan işlem öncesinde aydınlatılmış onam formu alındı. ERCP işlemi hastalara en az 8 saatlik açlık sonrasında anestezi hekimi tarafından sedoanaljezi uygulanarak yapıldı. İşlem sırasında hastalara sürekli nazal yol ile oksijen verildi. Oksijen saturasyonları pulse oksimetri ile takip edildi. Bağırsak motilitesini önlemek için gerek halinde hiyosin butilbromür intravenöz yol ile verildi.

Çalışmada ERCP yapılan hastaların yaşı, cinsiyeti, ERCP endikasyonları, ERCP sırasında yapılan işlemler, işlem sonucu oluşan komplikasyonlar belirlendi. İşlemden bir gün önce bakılan beyaz küre, nötrofil, lenfosit, trombosit, AST, ALT, ALP, GGT, total bilirubin, albumin, LDH, CRP değeri kayıt edildi. Bu değerler ile komplikasyonlar arasındaki ilişki araştırıldı.

Post ERCP pankreatit tanımı ve derecelendirmesi ASGE (American Society of Gastrointestinal Endoscopy) kriterlerine göre yapıldı. Post-ERCP pankreatit tanısı kriterler için yeni başlayan ya da kötüleşen karın ağrısı, işlem sonrası 24 saat sonra bakılan amilaz düzeyinde 3 kattan fazla artış olması, hastaneye yatış gerektirmesi ya da planlanan sürenin en az iki gün uzaması olarak kabul edildi.[6] ERCP'lerin tümünde post-ERCP pankreatit gelişimini engellemek amacıyla profilaktik 100 mg rektal indometazin uygulandı.

Bu çalışma için İzmir Bozyaka Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulundan onay alındı (07.06.2016 tarih ve 3 sayı).

İstatistiksel Analiz

Araştırmada elde edilen veriler Statistical Package for the Social Sciences (SPSS) 18 programına aktarılarak degerlendirildi.[7] Değerler ortalama ± standart sapma olarak verildi. İki bağımsız grubun karşılaştırılmasında Student t testi kullanıldı. Sürekli olmayan değişkenlerin karşılaştırılmasında ki-kare testi kullanıldı. $p<0.05$ istatistiksel anlamlı olarak kabul edildi.

BULGULAR

Çalışmaya Mart 2015 ile Haziran 2016 tarihleri arasında İzmir Bozyaka Eğitim Araştırma Hastanesi Gastroenteroloji Endoskopi Ünitesinde, çeşitli endikasyonlar ile 187 hastaya yapılan 206 ERCP işlemi dahil edildi. Yapılan ERCP' lerin 101'i (%49) kadın, 105'ü (%51) erkekti. Yaş

ortalamaları 62.2±17.08' idi. Hastaların en küçüğü 19 yaşında ve en büyüğü 93 yaşındaydı. 14 hastaya 2 defa, 1 hastaya 3 defa ve 1 hastaya da 4 defa ERCP işlemi yapıldı. Uygulanan ERCP sayılarının dekatlara göre dağılımı şu şekildeydi (Tablo 1). En fazla işlem 54 sayıyla (%26.2) 70-80 yaş aralığındaki hastalara uygulanmıştı.

Tablo 1. Yaş aralığı ve ERCP sayısı.

Hasta yaş aralığı	Hasta sayısı(=n)
<20 yaş	2 (%1)
20-30 yaş	9 (%4.4)
30-40 yaş	20 (%9.7)
40-50 yaş	10 (%4.9)
50-60 yaş	37 (%18)
60-70 yaş	41 (%19.9)
70-80 yaş	54 (%26.2)
80-90 yaş	31 (%15)
>90 yaş	2 (%1)

ERCP öncesinde işlem endikasyonları şu şekildeydi: koledok taşı 159 tane (%77.2) , malign-benign darlık 35 tane (%17), kist hidatik 4 tane (%1.9), post-operatif kaçak 7 tane (%3.4), tekrarlayan pankreatit atakları 1 tane (%0.5).

ERCP sonrasında hasta tanılarıysa (Tablo 2) de belirtilmiştir.

Tablo 2. ERCP sonrası tanılar ve sayıları.

ERCP sonrası tanı	İşlem sayısı (=n)
Koledok taşı	109 (%52.9)
Malign-benign darlık	36 (%17.5)
Mikrolityazis	31 (%15)
Normal bulgular	20 (%9.7)
Post operatif kaçak	7 (%3.4)
Kist hidatik	1 (%0.5)
Fasciola hepatica	1 (%0.5)
Papilla açılım anomalisi	1 (%0.5)

ERCP kanülasyonunda 162 işlemde (%78.6) sfinkterotom; 16 işlemde (%7.7) iğne uçlu (needle knife) ile kanülasyon sağlandı. İşlemlerin 28 tanesi ise (%13.5) sfinkterotomiliydi.

İşlemlerde görülen komplikasyonlar ve sayıları şu şekilde saptanıldı: pankreatit 6 (%2.9), kanama 3 (%1.5), perforasyon 1 (% 0.5).

Hastaların işlem öncesi bakılan beyaz küre, nötrofil, lenfosit, platelet, AST, ALT, total bilirubin, ALP, GGT, CRP, LDH, albumin düzeyleri ile pankreatit gelişimi arasında fark olup olmadığı incelendi. GGT ve AST seviyesi ise pankreatit geçiren hastalarda, geçirmeyenlere oranla düşüktü ve istatiksel olarak anlamlı saptanıldı (Tablo 3) (GGT için p=0.001; AST için p=0.006). Pankreatit geçirenlerde ortalama GGT değeri 114±76, AST değeri ise 59±48 U/L'idi. Diğer parametrelerde ise anlamlı fark saptanmadı. Pankreatit oranı %2.9 olarak saptandı.

Hastalarda kanülasyon sırasında sfinkterotom ve iğne uçlu kullanılması pankreatit gelişimi açısından incelendi. Sfinkterotom ile kanülasyon yapılan 156 (%78) işlemde pankreatit gözlenmezken 5 işlemde pankreatit gelişti. İğne uç ile kanülasyon yapılan 16 hastadan (%7) ise 1 hastada pankreatit gelişti. Bu işlemler ile pankreatit arasında ilişki tespit edilmedi(p=0.67).

Tablo 3. Pankreatit olan ve olmayan hastalarda ortalama laboratuar parametreleri.

Parametreler	Pankreatit	Ortalama	Standart Sapma	P
WBC	Yok	9801.17	4680.814	0.4
	Var	8340.00	4680.814	
Nötrofil	Yok	7633.51	4757.415	0.3
	Var	5460.00	2881.493	
Lenfosit	Yok	1465.79	793.383	0.8
	Var	2020.00	518.507	
PLT	Yok	275220.93	97583.121	0.7
	Var	307200.00	116546.98	
AST	Yok	155.38	156.316	**0.006**
	Var	59.20	48.236	
ALT	Yok	178.81	171.258	0.3
	Var	71.40	94.996	
Total bilirubin	Yok	5.830	6.4342	0.3
	Var	2.932	5.0751	
ALP	Yok	374.28	437.096	0.2
	Var	199.50	196.198	
GGT	Yok	451.79	458.550	**0.001**
	Var	114.75	76.904	
CRP	Yok	77.327	94.5943	0.9
	Var	67.000	36.6697	
LDH	Yok	237.05	80.011	0.3
	Var	210.67	108.510	
Albumin	Yok	3.4421	.62163	0.7
	Var	3.6000	.21602	

TARTIŞMA

Akut pankreatit ERCP sonrası en sık görülen komplikasyondur. Post-ERCP pankreatit insidansı %1.6 ile %15.7 arasında değişmekle birlikte yaklaşık olarak %3.5 olarak bulunmuştur.[8] Başka bir çalışmada insidansı %9.7, mortalite oranı %0.7 olarak belirlenmiştir.[9] Bizim çalışmamızda da post-ERCP pankreatit oranı %2.9 bulunmuş olup literatüre benzerlik göstermektedir.

Akut pankreatit mekanizmasında ortak son nokta inflamasyon yolunun aktivasyonudur. Papilla ya da pankreatik sfinkterin mekanik obstruksiyonu, kontrast sırasında oluşan hidrostatik hasar, kontrast sırasında kimyasal ya da alerjik hasar ERCP sırasında oluşabilecek olası mekanizmlardır. Hasar, ödem, pankreatik sfinkterin perforasyonu,

safra yolu ya da ampullanın elektrokoter ısısıyla hasarlanması pankreatik sekresyonunun obstruksiyonuna yol açabilir. Aynı mekanizma proleotik enzimlerin lümen içi aktivasyonunu sağlayarak hasarı meydana getirebilir. Ayrıca kanallara yapılan giriş kontaminasyona yol açarak olası bir enfeksiyon payı olabilir. İnflamasyon kaskadının aktive olması zimojen enzimlerin proleotik enzimlere aktive olmasını, inflamatuar hücrelerin kemotaksisini ve bu da inflamatuar mediyatör ve sitokinlerin salınmasına yol açar. Bu kaskad lokal inflamasoyonla sınırla olabileceği gibi sistemik inflamatuar yanıt sendromunu başlatabilir.[10]

Pankreatik stentlemenin post-ERCP pankreatiti azalttığı belirtilmiştir. Ampulla ve sfinkter boyunca pankreatik kanala yerleştirilen stent yaralanma veya ödem nedeniyle pankreas salgılarının kesintiye uğramasını engelleyerek akışı sağlar.[11] Literatüre göre metalik stentler plastik stentlere göre PEP açısından daha risklidir.[12]

İnflamasyon kaskadını inhibe etmek amacıyla kullanılan rektal NSAİİ (özellikle indometazin ve diklofenak) post-ERCP pankreatiti önlemekte kullanılabilir. NSAİ ilaçlar rektal olarak işlem öncesinde veya hemen işlem sonrasında kullanılabilir.[3] Çalışmamızda tüm hastalara işlem öncesinde rektal 100 mg indometasin uygulaması yapılmıştır.

Post-ERCP pankreatit riski normal bilirubini bulunan hastalarda artmış olarak saptanmıştır.[13] İşlem öncesinde veya sonrasında bakılan bazı testlerle pankreatit riskini öngörmede prediktif etkileri araştırılmıştır. Preoperatif laboratuar değerleri ile post-ERCP pankreatit ilişkisi 1196 ERCP işleminde incelenmiştir. Hastaların ALT, ALP, bilirubin, lökosit, amilaz, sodyum, potasyum, kalsiyum değerleri ile ilişkisi saptanmamıştır.[14] Pankreatiti erken dönemde saptamak amacıyla ERCP sonrası 4.saatte bakılan serum amilaz değerinin 516 IU/l üzerinde olması belirleyici olabilmektedir.[15] ERCP işleminden 24 saat öncesinde bakılan serum sedimentasyon değerinin 30/saat üzerinde olması PEP ile ilişkili bulunmuştur.[16] Nötrofil/ lenfosit oranı, lenfosit/trombosit oranı 1000 hastalık bir seride PEP için prediktif bulunmuştur.[17] Post-ERCP pankreatitin erken göstergesi olarak öncesinde ve işlem sonrasında bakılan amilaz değerilerinin farkı beliryeciyi olabilmektedir.[18] Çalışmamızda pankreatit geçiren hastalarda AST ve GGT düzeylerinin geçirmeyen hastalara göre düşük olduğu saptanıldı. Pankreatit geçiren hastalarda ortalama AST ve GGT düzeyleri sırasıyla 59 IU/L ve 114 U/L saptanılmıştır. GGT hepatobiliyer hastalıklarda yükselebilen transport enzimidir. Sağlıklı kişilerde ortalama seviyesi 0-30 IU/L arasında değişmektedir. Çalışmamızda AST ve GGT düzeyi yüksek bulunan hastalarda kolestaza bağlı safra yollarının daha geniş olması daha kolay kanulasyon imkanı nedeniyle pankreatit riskini azaltmış olabilir.

Çalışmamızın kısıtlayıcı yanları retrospektif olarak tek merkezde yapılmış olması, az hasta içermesidir. Daha yüksek hasta sayıları içeren çalışmalarla sonuçların desteklenmesi gerekmektedir.

Sonuç olarak preoperatif dönemde AST'nin normal üst sınırından 1.5 kat ve GGT'nin 4 kat aşağıda olması post-ERCP pankreatit için risk taşımaktadır. Bu hastalar işlem sonrasında pankreatit açısından yakın takip edilmelidir. Erken tanı ile pankreatite bağlı komplikasyonlar ve hastane maliyetleri azaltılabilir.

Çıkar Beyannamesi

Herhangi bir çıkar çatışmasının olmadığını yazarlar beyan etmektedirler.

Etik Kurul İzni

Bu çalışma için İzmir Bozyaka Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulundan onay alındı (07.06.2016 tarih ve 3 sayılı).

Araştırmacıların Katkı Oranı Beyanı

Ana fikir/Planlama: SÖ. Veri toplama/İşleme: SÖ. Veri analizi ve yorumlama: SD. Literatür taraması: SÖ. Yazım: SÖ, SD, MC, AY. Gözden geçirme ve düzeltme: MC, AY. Danışmanlık: MC, AY.

KAYNAKÇA

1. McCune WS, Shorb PE, Moscovitz H. Endoscopic cannulation of the ampulla of vater: a preliminary report. Ann Surg. 1968;167(5):752-756.
2. Freeman ML. Complications of endoscopic retrograde cholangiopancreatography: avoidance and management. Gastrointest Endosc Clin N Am. 2012;22(3): 567-586.
3. Dumonceau JM, Kapral C, Aabakken L, et al. ERCP-

related adverse events: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2020;52(2):127-149.
4. ASGE Standards of Practice Committee, Anderson MA, Fisher L, et al. Complications of ERCP. Gastrointest Endosc. 2012;75(3):467-473.
5. Bhatt H. Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis: An Updated Review of Current Preventive Strategies. Clin Exp Gastroenterol. 2021;14:27-32.
6. ASGE Standards of Practice Committee, Chandrasekhara V, Khashab MA, et al. Adverse events associated with ERCP. Gastrointest Endosc. 2017;85(1):32-47.
7. IBM SPSS Statistics | IBM. Available from: https://www.ibm.com/products/spss-statistics Erişim tarihi 01 August, 2016.
8. Andriulli A, Loperfido S, Napolitano G, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. Am J Gastroenterol. 2007;102(8):1781-1788.
9. Elmunzer BJ, Scheiman JM, Lehman GA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med. 2012;366(15): 1414-1422.
10. Thaker AM, Mosko JD, Berzin TM. Post-endoscopic retrograde cholangiopancreatography pancreatitis. Gastroenterol Rep (Oxf). 2015;3(1):32-40.
11. Freeman ML. Pancreatic stents for prevention of post-ERCP pancreatitis: for everyday practice or for experts only?. Gastrointest Endosc. 2010;71(6):940-944.
12. Martinez NS, Inamdar S, Firoozan SN, et al. Evaluation of post-ERCP pancreatitis after biliary stenting with self-expandable metal stents vs. plastic stents in benign and malignant obstructions. Endosc Int Open. 2021;9(6):E888-E894.
13. Dumonceau JM, Andriulli A, Deviere J, et al. European Society of Gastrointestinal Endoscopy (ESGE) Guideline: prophylaxis of post-ERCP pancreatitis. Endoscopy. 2010;42(6):503-515.
14. Jokelainen J, Ismail S, Kylänpää L, et al. Effect And Predictive Value Of Routine Preoperative Laboratory Testing For Endoscopic Retrograde Cholangiopancreatography. Scand J Surg. 2020;109(2):115-120.
15. Jamry A. The prognostic value of serum and urine amylase levels and blood count parameters in assessing the risk of post-endoscopic pancreatitis development. Prz Gastroenterol. 2021;16(2):132-135.
16. Mohammad Alizadeh AH, Afzali ES, Behzad C, et al. Is ESR Important for Predicting Post-ERCP Pancreatitis?. Clin Med Insights Gastroenterol. 2015;8:23-27.
17. Li H, Bao J, Mei Q. Markers of immune responsiveness and post-ERCP pancreatitis?. Gastrointest Endosc. 2020;92(3):796.
18. Kusumoto K, Nakai Y, Itokawa Y, et al. Prediction of pancereatits following endoscopic retrograde cholangiopancreatography. Nihon Shokakibyo Gakkai Zasshi. 2020;117(9):788-795.

ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Effects Of Folic Acid Versus Nicotine On Bone Development

Kemik Gelişiminde Nikotine Karşı Folik Asitin Etkileri

***Kadirhan DOĞAN*[1] *Mehtap NİSARİ*[2] *Ahmet PAYAS*[3] *Tolga ERTEKİN*[4]**

***Hatice GÜLER*[2] *Özge AL*[2]**

ÖZ

Amaç: Gebelikte maruz kalınan nikotin sadece anneye değil, fetal dokulara da doğrudan veya dolaylı olarak zarar verir. Bu çalışmadaki amaç gebelik döneminde kullanılan nikotine karşı verilen folik asitin fetusların kemik gelişimine olası etkilerinin araştırılmasıdır.
Araçlar ve Yöntem: 18 yetişkin dişi sıçan kontrol, düşük doz nikotin (DDN), yüksek doz nikotin (YDN), düşük doz nikotin + folik asit (DDN + FA), yüksek doz nikotin + folik asit (YDN + FA) ve folik asit (FA) gruplarına eşit olarak ayrıldı. 20 gün boyunca 1 ml/kg serum fizyolojik (SF) solüsyonu kontrol grubuna, 3 mg/kg nikotin DDN'ye, 6 mg/kg nikotin YDN'ye, 3 mg/kg nikotin ve 400 µg/kg FA DDN+FA'ya, 6 mg/kg nikotin ve 400 µg/kg FA YDN+FA'ya, 400 µg/kg FA FA grubuna uygulandı. Gebeliğin 20. gününde sezaryen ile alınan fetüslerın kemikleri ikili iskelet boyama tekniği ile boyandı. Boyanan ön ve arka ekstremite kemikleri stereomikroskop altında fotoğraflandı. Kemik uzunluğu, kemikleşme derecesi ve kemikleşme yüzdesi ölçüldü. İstatistiki veriler R programlama dili (v. 3.2.3) kullanılarak değerlendirildi.
Bulgular: Kemik gelişimi DDN ve YDN gruplarında anlamlı derecede düşük; DDN+FA ve YDN+FA gruplarında kontrol grubuna yakındı ($p<0.05$).
Sonuç: Gebelikte kullanılan nikotin fetüslerin kemik gelişimini azaltırken, FA bu etkiyi azaltarak kemikleşmeyi arttırabilir.

Anahtar Kelimeler: boyama; iskelet; kemikleşme; sıçan

ABSTRACT

Purpose: Nicotine exposure during pregnancy directly or indirectly harms not only the mother but also the fetal tissues. The aim of this study is to investigate the possible effects of folic acid given against nicotine used during pregnancy on bone development of fetuses.
Materials and Methods: 18 adult female rats were divided into control, low-dose nicotine (LDN), high-dose nicotine (HDN), low-dose nicotine + folic acid (LDN + FA), high-dose nicotine + folic acid (HDN + FA), and folic acid (FA) group equally. During 20 days, 1 ml/kg serum physiologic (SP) solution to the control group, 3 mg/kg nicotine to LDN, 6 mg/kg nicotine to HDN, 3 mg/kg nicotine and 400 µg/kg FA to LDN+FA, 6 mg/kg nicotine and 400 µg/kg FA to HDN+FA, 400 µg/kg FA to the FA group was administered. Bones of fetuses taken by cesarean section on the 20th day of pregnancy were stained with the bilateral skeleton staining technique. The stained anterior and posterior extremity bones were photographed under a stereomicroscope. Bone length, extent of ossification and percentage of ossification were measured. Statistical data were evaluated using the R programming language (v. 3.2.3).
Results: The bone development of LDN and HDN groups was significantly lower and LDN+FA and HDN+FA groups was close to the control group ($p<0.05$).
Conclusion: While nicotine used during pregnancy decreases the bone development of fetuses, FA may decrease this effect and increase ossification.

Keywords: ossification; rats; skeleton; staining

Received: 06.04.2023; Accepted: 06.09.2023

[1]Kapadokya University, Faculty of Dentistry, Nevşehir, Türkiye.
[2]Erciyes University, Faculty of Medicine, Department of Anatomy, Kayseri Türkiye.
[3]Amasya University, Faculty of Medicine, Department of Anatomy, Amasya, Türkiye.
[4]Afyonkarahisar Health Science University, Faculty of Medicine, Department of Anatomy, Afyon, Türkiye.

Corresponding Author: Mehtap Nisari, Erciyes University, Faculty of Medicine, Department of Anatomy, Kayseri Türkiye. e-mail: mehtapnisari@gmail.com

How to cite: Doğan K, Nisari M, Payas A, Ertekin T, Susar H, Al Ö. Effects of folic acid versus nicotine on bone development. Ahi Evran Med J. 2024;8(1):48-55. DOI: 10.46332/aemj.1278167

INTRODUCTION

Pregnant women are exposed to certain chemicals due to living conditions.[1] These chemicals can lead to congenital malformations by getting into the fetal circulation and having various teratogenic effects on the embryo as well as stopping skeletal development which is an important part of somatic growth and development.[2]

One of the most important non-contagious risk factors that threaten human health is cigarette smoke which comprises more than 4800 chemicals, and nicotine is a crucial substance in it.[3] Nicotine is a toxic alkaloid found in the tobacco plant of the Solanaceae family that leads to addiction.[4]

Prenatal exposure to nicotine is an important risk factor that increases the incidence of illness and death for the newborn.[5] Nicotine prevents bone formation by decreasing osteoblast activity, increases osteoclast activity and causes osteonecrosis and periodontal bone loss.[6,7] It reduces the regeneration of fibroblasts and macrophages and delays scar tissue formation.[8] It also decreases vitamin D storage in the liver by altering the metabolism of vitamin D, which is important for bone formation and development.[9]

Folic acid (FA), also known as B9 and folate, is a water-soluble B vitamin. Humans and other mammals cannot synthesize FA in their tissues.[10] According to the World Health Organization (WHO), the daily FA intake for non-pregnant women and adults is 170 µg/kg/day while it is 370-470 µg/kg/day during pregnancy and 270 µg/kg/day during lactation. Women planning a pregnancy should be taking 400 µg/kg/day FA supplementation every day until the 12th week of pregnancy.[11] Inadequate intake of vitamin FA during pregnancy leads to megaloblastic anemia characterized by larger red blood cells stored in the bone marrow than normal.[12]

The effects of folic acid on the possible effects of nicotine on bone development have not yet been in studies. The aim of this study is to investigate role of folic acid against the nicotine on fetal bone development by means of the double staining technique

MATERIALS and METHODS

Selection and Breeding of Experimental Animals

In this study, which was initiated with the approval of Erciyes University Animal Experiments Local Ethics Committee (Date: 09.12.2015 and numbered 15/151), 18 Wistar-Albino female rats with an average weight of 150 g, obtained from Erciyes University Experimental Research and Application Center (DEKAM) were used.

During the study, the rats were kept in DEKAM at a constant temperature of 22 °C in the rooms where 12 hours of light and 12 hours of darkness were provided. The rats were fed with pellet type feed containing 21% crude protein and tap water which they could drink without restriction.

Two rats were randomly placed in the same cage with one male rat at 17.00 on the day of breeding. The following morning at 07.00, female rats underwent a vaginal smear test. Females observed with sperm under microscope were accepted as 0.5 days pregnant and 6 groups (3 rats in each group) were randomly placed in different cages.

Preparation and Application of Nicotine and Folic Acid

SP (1 ml/kg per day) was intraperitoneally (ip.) applied to the rats in the control group.

Nicotine (3 mg/kg per day) was subcutaneously (sc.) applied to LDN.

Nicotine (3 mg/kg per day) was applied subcutaneously and half-hour later FA (400 µg/kg per day) intraperitoneally to LDN+FA.

Nicotine (3 mg/kg per day)was applied subcutaneously twice per day to HDN.

Nicotine (3 mg/kg per day) was applied subcutaneously twice per day and half-hour later FA (400 µg/kg per day) intraperitoneally to HDN+FA.

FA (400 µg/kg per day) was applied intraperitoneally to FA.

In the preparation of nicotine; 19.9 ml of SP was added to 0.1 ml of Nicotine For Synthesis (Merck, M820877.0025), which contains 1000 mg of nicotine in 1 ml. From the resulting 20 ml mixture, 0.09 ml was taken and applied as low dose in the evenings, and 0.09 ml as high dose in the mornings and evenings.

FA was applied according to the recommendation of WHO, which is 400 µg/kg/day. Considering that the rats were on average 150 g, 0.1 ml SF was mixed into 60 µg FA (Sigma, F7876-10). The mixture was prepared daily.

Euthanasia of Rats and Removal of Fetuses

On the 20th day of pregnancy, euthanasia was performed using ketamine (75 mg/kg) + xylazine (10 mg/kg) as anesthetic agent. The anterior abdominal walls of the rats were removed and the fetuses were removed with their placentas. The fetuses were humanely sacrificed using high-dose anesthesia. Fifteen fetuses were taken randomly from each group for measurements.

Staining

Double staining is a technique used in teratogenic and developmental studies that is based on the coloring of the bone and cartilage, which form the skeleton with either different dyes and different colors or different shades of the same color.[13] The first publishing by Simons and Van Horn assured the staining of the bone tissue with Alizarin Red-S and the cartilage tissue with Alcian Blue, after which the double staining technique of the skeleton began to be an often preferred method in 1971.[14] In 1976, Inouye mixed Alizarin Red-S and Alcian Blue into a single solution and stained bone and cartilage tissues at the same time. This method has since been a gold standard in the double staining technique for its quickness and effectiveness.[15]

The fetuses were skinned and the internal organs and eyes were removed before staining. All fetuses were kept in 70% ethanol for 7 days for dehydration. Subsequently, they were kept in pure acetone for 3 days and then cleared of adipose tissue taken into the dye solution in glass containers.

The glass containers, which were cut off from air, were kept in a drying-oven at 37 °C for seven days and the bone and cartilage were stained. At the end of day 7, the fetuses were kept under running tap water for two hours. Then, the transparency phase was initiated. Fetuses which had been stained waited during the 4-stage transparency phase;

1 day in 1% KOH in stage 1.

5 days in a mixture of 1% KOH (80 ml) and 20% glycerin (20 ml) in stage 2.

5 days in a mixture of 1% KOH (50 ml) and 50% glycerin (50 m) in stage 3.

5 days in a solution of 1% KOH (20 ml) and 80% glycerin (80 ml) in stage 4.

The fetuses that underwent the transparency stage were placed into 100% glycerin (Figure 1).

Figure 1. The fetuses in 100% glycerin.

Measurements

The anterior and posterior extremities of the fetuses were separated by forceps and photographs were taken with a Nikon™ E5700 camera. The photographs were transferred to a computer and the bone length, extent of ossification and percentage of ossification were measured using Image J software (Figure 2).

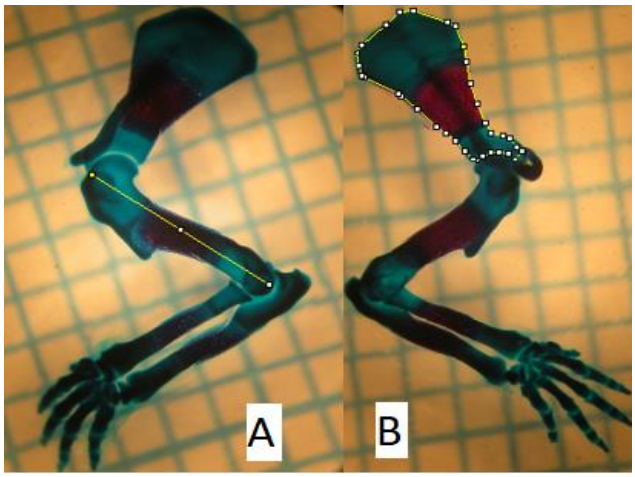


Figure 2. Measurements Using Image J Software.
A. Length Measurement. B. Area Measurement.

Statistical Analysis

Normal distribution of the data was analyzed using Shapiro-Wilk test, histogram and Q-Q plots, whereas homogeneity of variance was examined using Levene's test. One-way analysis of variance (ANOVA) was used for normally distributes intergroup comparisons, and Tamhane's T2 was used in multiple comparisons. Data were analyzed using author-written codes in R programming language version 3.2.3 (release date: December, 2015; URL: https://cran-archive.r-project.org/bin/windows/base/old/3.2.3/). $p<0.05$ was considered statistically significant.

RESULTS

The first effect in nicotine-administered rats was the stage of shock. After this phase, severe convulsions involving the whole body were observed. Following the spasms that lasted approximately 2 minutes, a sedation phase of 2-3 minutes was observed.

a. Measurement Results of Anterior Extremities

The length of scapula, humerus, radius, ulna bones; the extent of the ossification area and the percentage of ossification in the LDN and HDN groups were statistically smaller ($p<0.05$) in comparison with the control group (HDN<LDN<Control).

The length of scapula, humerus, radius, ulna bones; the extent of the ossification area and the percentage of ossification in LDN+FA were statistically bigger ($p<0.05$) in comparison with LDN.

The length of scapula, humerus, radius, ulna bones; the extent of the ossification area and the percentage of ossification in HDN+FA were statistically bigger ($p<0.05$) in comparison with HDN.

The length of scapula, humerus, radius, ulna bones; the extent of the ossification area and the percentage of ossification in FA were smaller in comparison with the control group; however, the difference between them was not statistically significant (Figure 3).

The data regarding anterior extremities bones are given in Table 1 and Table 2.

Table 1. Data regarding Scapula and Humerus Bones.

Variables	Scapula Bones			Humerus Bones		
Groups	BL (mm)	EO (mm^2)	PO (mm^2)	BL (mm)	EO (mm^2)	PO (mm^2)
Control	3.31	1.65	45.7	4.35	1.81 ^{d}	37.97
LDN	3.16 ^{a,b,c,d}	1.38 ^{a,b,c,d}	37.64 ^{a,b,c,d}	4.11 ^{a,d}	1.48 ^{a,b,d}	34.51 ^{a,d}
LDN+FA	3.33	1.66	46.13	4.18	1.74 ^{d}	38.35
HDN	3.12 ^{a,b,c,d}	0.84 ^{a,b,c,d,e}	18.86 ^{a,b,c,d,e}	4.08 ^{a,d}	0.86 ^{a,b,c,d,e}	18.34 ^{a,b,c,d,e}
HDN+FA	3.26	1.55 ^{d}	40.64 ^{a,b,d}	4.14 ^{a,d}	1.57 ^{a,b,d}	37.1 ^{d}
FA	3.3	1.71	48.38	4.34 ^{c,e}	1.9	39.68

Average values were used
BL: Bone lenght, EO: Extent of ossification, PO: Percent of ossification,
(Significant compared to) a: the Control b: the LDN+FA c: the HDN+FAd: the FA e: the LDN.

Table 2. Data regarding Radius and Ulna Bones.

Variables	Radius Bones			Ulna Bones		
Groups	BL (mm)	EO (mm^2)	PO (mm^2)	BL (mm)	EO (mm^2)	PO (mm^2)
Control	3.21	1.35	39.99 ^{b,d}	4.23	1.57	34.58 ^{b,c,d}
LDN	3.08 ^{a,d}	1.15 ^{a,b,c,d}	32.57 ^{a,b,c,d}	4.09 ^{b,d}	1.27 ^{a,b,c,d}	26.1 ^{a,b,c,d}
LDN+FA	3.2	1.31	48	4.24	1.43 ^{d}	41.25
HDN	3.05 ^{a,d}	0.6 ^{a,b,c,d,e}	17.57 ^{a,b,c,d,e}	4.05 ^{a,b,c,d}	0.71 ^{a,b,c,d,e}	14.45 ^{a,b,c,d,e}
HDN+FA	3.14	1.27 ^{d}	39.52 ^{b,d}	4.14 ^{b,d}	1.39 ^{a,d}	38.19 ^{d}
FA	3.26	1.4	47.49	4.29	1.58	42.72

Average values were used
BL: Bone lenght, EO: Extent of ossification, PO: Percent of ossification,
(Significant compared to) a: the Control b: the LDN+FA c: the HDN+FAd: the FA e: the LDN.

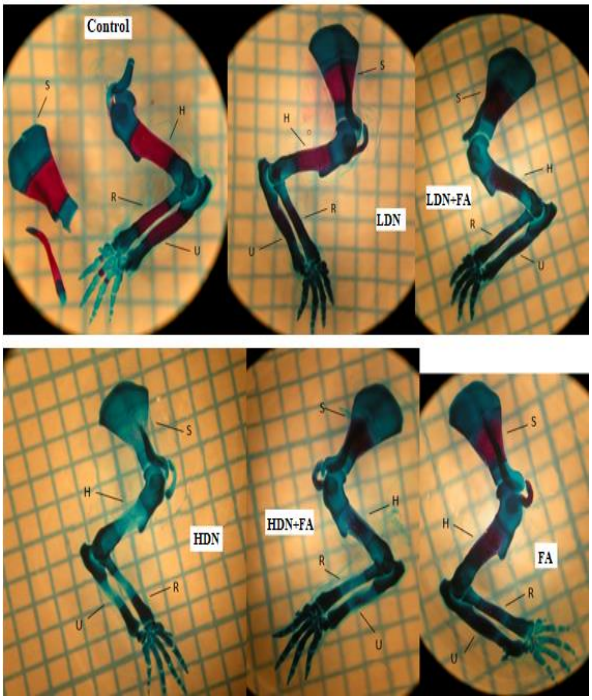


Figure 3. Anterior Extremities Bones.
S: Scapula H: Humerus R: Radius U: Ulna LDN: Low dose nicotine
HDN: High dose nicotine FA: Folic acid.

b. Measurement Results of Posterior Extremities

The length of femur, tibia, fibula bones; the extent of the ossification area and the percentage of ossification in the LDN and HDN groups were statistically smaller ($p<0.05$) in comparison with the control group (HDN<LDN<Control). Ossification in femur, tibia and fibula was not at all observed in the HDN group.

The length of femur, tibia, fibula bones; the extent of the ossification area and the percentage of ossification in LDN+FA were statistically bigger ($p<0.05$) in comparison with LDN.

The length of femur, tibia, fibula bones; the extent of the ossification area and the percentage of ossification in HDN+FA were statistically bigger ($p<0.05$) in comparison with HDN.

The length of femur, tibia, fibula bones, ulna bones; the extent of the ossification area and the percentage of ossification in FA were smaller in comparison with the control group; however, the difference between them was not statistically significant (Figure 4).

The data regarding posterior extremities bones are given in Table 3.

Table 3. Data regarding posterior extremities.

Variables	Femur Bones			Tibia Bones			Fibula Bones		
Groups	BL (mm)	EO (mm^2)	PO (mm^2)	BL (mm)	EO (mm2)	PO (mm^2)	BL (mm)	EO (mm^2)	PO (mm^2)
Control	3.77	1.34	22.54	3.72	1.35	35.29	3.68	1.26	55.77
LDN	3.55 a,d	0.86 a,b,c,d	22.86	3.49 a,d	1.03 a,b,d	22.63 a,d	3.48 a,d	1.05 a,b,c,d	30.73 a,b,c,d
LDN+FA	3.69	1.28 a,d	22.23	3.61	1.22 a,b,d	18.49 a,d,e	3.59 d	1.25	41.81 a,d
HDN	3.45 a,b,c,d	0 a,b,c,d	0 a,b,c,d	3.4 a,b,d	0 a,b,c,d,e	0 a,b,c,d,e	3.41 a,b,c,d	0 a,b,c,d,e	0 a,b,c,d,e
HDN+FA	3.63 a,d	1.2 a,b,d	21.29 a,d,e	3.47 a,d	1.15 a,d	18.3 a,d,e	3.5 a,d	1.19 a,d	36.74 a,b,d
FA	3.79	1.37	23.49	3.73	1.36	35.32	3.71	1.27	56.08

Average values were used
BL: Bone lenght, EO: Extent of ossification, PO: Percent of ossification,
(Significant compared to) a: the Control b: the LDN+FA c: the HDN+FA d: the FA e: the LDN.

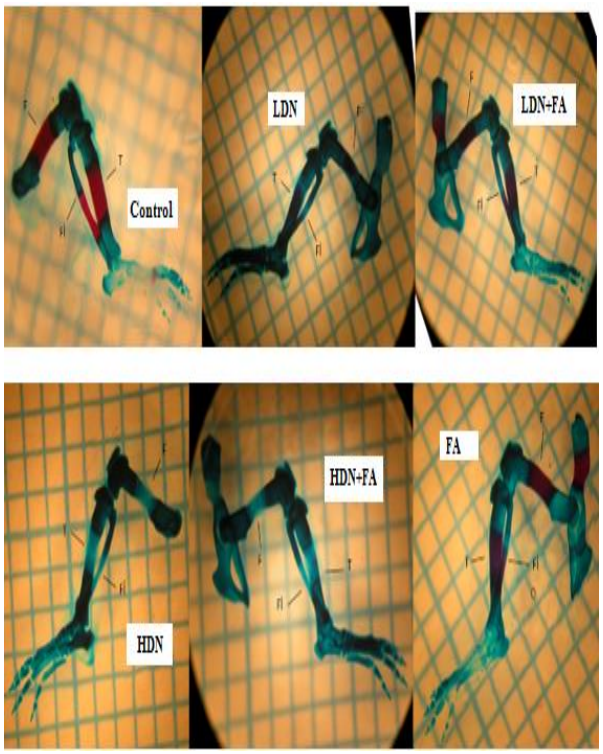


Figure 4. Posterior Extremities Bones.
F: Femur T: Tibia Fi: Fibula LDN: Low dose nicotine HDN: High dose nicotine FA: Folic acid.

DISCUSSION

The main finding of the study is that FA is a powerful antioxidant, and, it has a protective effect against the teratogenic effect of nicotine.

Bone is the basic tissue that is responsible for blood production, adjustment of mineral balance and the movement and protection of the body. It is known that teratogenic substances such as alcohol and cigarette used during pregnancy adversely affect fetal bone development.[16]

To investigate the effects of nicotine on molar teeth in neonatal period was aimed in the fasting study, which involved administering 1.67 mg/kg nicotine intraperitoneally to the mother rats between day 6-21 of pregnancy. On the 4th day after birth, 50 rat pups were weighed and a statistically significant difference between the control group (6.29±0.33 gr) and the nicotine group (4.99±0.32 gr) was found.[17] In our study, a statistically significant difference ($p<0.05$) was found that demonstrated lower weight values between the nicotine-administered LDN group (2.30±0.13 gr) with HDN group (2.13±0.09 gr) and the control group (2.50±0.13 gr).

Patel et al. (2013) conducted a systematic examination by reviewing the orthopedic studies about effects of smoking on bone healing. In their study, they scanned MEDLINE, Web of Science, The Cochrane Library, SCOPUS and EMBASE with the keywords “bone, bone healing, nicotine, tobacco, cigarette” and found that 13 of 17 studies, 9 of which are on tibia and 8 of which are on other orthopedic studies, concluded that smoking adversely affects bone development.[18] In our study analysis of the percentage of tibia bone ossification

indicated that the mean of the control group was 35.29±2.99 mm² and the mean of the LDN group was 22.63±2.46 mm². Ossification in tibia bones was not at all observed in the HDN group.

Mızrak et al. (2014) mixed 0.4 mg/kg/day LDN and 6 mg/kg/day nicotine HDN into the drinking water of rats for 12 months, and gave normal drinking water to the control group. At the end of 12 months, they found that there was no significant difference in the comparison of bone mineral density measurements of the femur and lumbar vertebrae with the control group.[19]

Susar et al. (2017) focused on the protective role of vitamin E against the teratogenic effect of nicotine in their studies. High-Dose Nicotine group they formed were given 6 mg/kg nicotine subcutaneously and the ossification percentage of the bones was examined. It was consequently found that the values were lower than those of the control group.[20] In our study, percentage of ossification in scapulae (18.86±8.12 mm²) in the HDN group was statistically significantly lower in comparison with the control group (45.70±4.57 mm²) as well as lower percentage of ossification in humeri (18.34±8.84 mm²) than that of the control group (37.97±3.41 mm²), lower percentage of ossification in ulnae (14.45±9.78 mm²) than that of the control group (34.58±3.41 mm²) and lower percentage of ossification in radii (17.57±12.89 mm²) than that of the control group (39.99±7.23 mm²).

Vitamin FA plays an important role in the synthesis of DNA and is necessary for maternal health during pregnancy and the normal development of the fetus.[21] Governments and health organizations around the world since the mid-1990s to the present day has emphasized that women should take FA supplements before and during pregnancy to reduce the likelihood of having a baby with brain and spinal tube defects.[22]

Mohammadi et al. (2012) investigated the effect of cyclosporine on bone volume and bone density and whether FA has a protective effect against bone loss. In their experimental studies, 40 Sprague-Dawley rats were randomly divided into 5 groups and for 6 weeks, gave olive oil for the rats in Group A, cyclosporine for the rats in Group B, FA for the rats in Group C, and cyclosporine+FA for the rats in Group D. Group F was designated as the control group. At the end of the study they concluded that the values of Group B (46.3±13.6 mm3) were significantly lower than Group C (80.4±15.70 mm3) and Group D (73.9±21.3 mm3) in the comparison of total volume values of the mandible. Mohammadi et al. concluded that an increase in cyclosporine decreases bone mineral density and causes bone loss; FA may have a protective effect against bone loss.[23]

This study, therefore, examines the protective role of folic acid against the teratogenic effect of nicotine on embryonic bone development. As a result of this study, it was found that nicotine use impaired bone development depending on the dose. Scapula, ulna, radius and fibula bones were most affected by LDN; and humerus, femur and tibia bones were less affected by LDN. The developmental impairment of the anterior bones was higher in HDN in comparison with LDN, and the development of posterior bones was completely prevented in HDN; whereas FA, which was administered in addition to LDN and HDN, played a protective role by increasing bone development.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Erciyes University Scientific Research Project Unit (TYL-2016-6497). The funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Ethics Committee Permission

Approval was received for this study from Erciyes University Animal Experiments Local Ethics Committee (Date: 09.12.2015 and numbered 15/151).

Authors' Contributions

Concept/Design: KD, MN, AP, TE, HG, ÖA. Data Collection and/or Processing: KD, MN, AP, TE, HG, ÖA. Data analysis and interpretation: KD, MN, AP, TE, HG, ÖA. Literature Search: KD, AP. Drafting manuscript: KD, MN. Critical revision of manuscript: KD, MN, TE. Supervisor: MN, TE, HG, ÖA.

REFERENCES

1. Yılmaz H, Ertekin T, Atay E, et al. Antioxidant role of melatonin against nicotine's teratogenic effects on embryonic bone development. Iran J Basic Med Sci. 2018;21(8):787-793.
2. Nisari M, Ulger H, Unur E, Karaca O, Ertekin T. Effect of interleukin 12 (IL-12) on embryonic development and yolk sac vascularisation. Bratisl Lek Listy. 2014;115(9):532-537.
3. Lugg ST, Scott A, Parekh D, Naidu B, Thickett DR. Cigarette smoke exposure and alveolar macrophages: mechanisms for lung disease. Thorax. 2022;77(1):94-101.
4. Callahan PM, Terry AV Jr, Peitsch MC, Hoeng J, Koshibu K. Differential effects of alkaloids on memory in rodents. Sci Rep. 2021;11(1):9843.
5. Yüce B, Tengiz Fİ. Effects of tobacco use during pregnancy on infant and child health. D J Med Sci. 2020;6(2):70-73.
6. Marinucci L, Bodo M, Balloni S, Locci P, Baroni T. Subtoxic nicotine concentrations affect extracellular matrix and growth factor signaling gene expressions in human osteoblasts. J Cell Physiol. 2014;229(12):2038-2048.
7. Kirschneck C, Proff P, Maurer M, Reicheneder C, Römer P. Orthodontic forces add to nicotine-induced loss of periodontal bone: An in vivo and in vitro study. J Orofac Orthop. 2015;76(3):195-212.
8. Payas A, Ekinci Y, Gürbüz K, et al. Vitamin B12 reduces the negative effects of nicotine on fetal bone development in the rats. Jt Dis Relat Surg. 2022;33(1):216-224.
9. Manavi KR, Alston-Mills BP, Thompson MP. History of tobacco, vitamin D and women. Int J Vitam Nutr Res. 2020;90(5-6):389-394.
10. Shulpekova Y, Nechaev V, Kardasheva S, et al. The Concept of Folic Acid in Health and Disease. Molecules. 2021;26(12):3731.
11. Vajda FJE, O'Brien TJ, Graham JE, et al. Folic Acid dose, valproate and fetal malformations. Epilepsy&Behavior. 2021;114:107569.
12. Green R. Vitamin B12 deficiency from the perspective of a practicing hematologist. Blood. 2017;129(19):2603-2611.
13. Booth M, Powell N, Corfield C, French JM. An automated technique for double staining of bone and cartilage in fetal mouse skeletal specimens using alizarin red S and Alcian blue. Biotech Histochem. 2022;97(3):222-227.
14. Dingerkus G, Uhler LD. Enzyme Clearing Of Alcian Blue Stained Whole Small Vertebrates For Demonstration Of Cartilage. Stain Technol. 1977;52(4):229-232.
15. Liao YJ, Tang PC, Chen LR, Yang JR. A protocol for differential staining of cartilages and ossified bones in fetal and adult mouse skeletons using alcian blue and alizarin red S. J Histotechnol. 2020;43(4):204-209.
16. Çetin E, Malas MA. Fetal Büyümeye Etki Eden Çevresel Faktörler. S.D.Ü. Tıp Fak. Derg. 2005;12(2):65-72.
17. Oruç Ş. Ratlarda Hamilelik Döneminde Verilen Nikotinin, Neonatal Dönemde Molar Dişler Üzerindeki Etkileri, Master Thesis, Dicle Üniversitesi; 1996. https://tez.yok.gov.tr/UlusalTezMerkezi/tezDetay.jsp?id=91qsG18yUN59V_N5VMHDKw&no=91qsG18yUN59V_N5VMHDKw. Accessed 01 April, 2023.
18. Patel RA, Wilson RF, Patel PA, Palmer RM. The Effect of Smoking On Bone Healing. Bone Joint Res. 2013;2(6):102-111.
19. Mızrak S, Turan V, Inan S, et al. Effect of Nicotine on RANKL and OPG and Bone Mineral Density. J Invest Surg. 2014;27(6)327-331.
20. Susar H, Aycan K. Nikotinin Embriyonal Kemik Gelişimi Üzerindeki Teratojenik Etkisine Karşı E Vitamininin Koruyucu Rolü, Phd Thesis, Erciyes University, 2017. https://tez.yok.gov.tr/UlusalTezMerkezi/tezDetay.jsp?id=qiHiezOEio-GiML-DvHTy9w&no=B387_zfwUqbAIMeYXZJF6A. Accessed 01 April, 2023.
21. Canever L, Alves CS, Mastella G, et al. The Evaluation of Folic Acid-Deficient or Folic Acid-Supplemented Diet in the Gestational Phase of Female Rats and in Their Adult Offspring Subjected to an Animal Model of Schizophrenia. Mol Neurobiol. 2018;55(3):2301-2319.
22. Al-Gailani S. Making birth defects 'preventable': preconceptional vitamin supplements and the politics of risk reduction. Stud Hist Philos Biol Biomed Sci. 2014;47:278-289.
23. Mohammadi A, Omrani L, Omrani LR, et al. Protective Effect of Folic Acid on Cyclosporine-Induced Bone Loss in Rats. Transpl Int. 2012;25(1):127-133.

BİLİMSEL ARAŞTIRMA MAKALESİ

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Epilepsi Hastalarında Uyku Bozuklukları: Anket Çalışması

Sleep Disorders in Epilepsy Patients: A Questionnaire Study

***Selcen DURAN*[1] *Asuman ÇELİKBİLEK*[1] *Burc Esra SAHİN*[1]**

***Aysu YETİŞ*[1] *Naime Meric KONAR*[2]**

ÖZ

Amaç: Epilepsi ve uyku bozuklukları karşılıklı olarak birbirini olumsuz etkilemektedir. Bu çalışmanın amacı takibimizde olan epilepsi hastalarında sık görülen uyku bozukluklarını ve bu bozuklukların hastalık süresi, nöbet tipi ve sıklığı, antiepileptik ilaç (AEİ) sayısı ve türü ile ilişkisini incelemektir.
Araçlar ve Yöntem: 99 epilepsi tanılı hasta bu anket çalışmamıza dahil edildi. Demografik veriler, epilepsi hastalık süresi, nöbet tipi ve sıklığı, kullanılan AEİ sayısı ve türü yüz yüze sorgulanarak kaydedildi. Tüm hastalara, Pittsburg uyku kalite indeksi (PUKİ), Epworth uykululuk ölçeği (EUÖ), Berlin uyku anketi (BUA) ve huzursuz bacaklar sendromu (HBS) anketi uygulandı.
Bulgular: Epilepsi hastalarımızda PUKİ skoru 5 puan ve üzeri olan hasta sayısı 56 (%56.6), EUÖ skoru 10 puan ve üzeri olan hasta sayısı 9 (%9.1), BUA'ne göre obstrüktif uyku apne sendromu (OUAS) için yüksek riskli hasta sayısı 53 (%53.5) idi. Hastaların 25 (%25.3)' inde HBS varlığı tespit edildi. PUKİ skoru jeneralize epilepsili hastalarda anlamlı yüksek (kötü uyku kalitesi) tespit edildi (p=0.045). PUKİ (p=0.035), EUÖ (p=0.043) ve BUA (p=0.039) skorlarının hepsi HBS var olan hastalarda, olmayanlara göre anlamlı yüksek idi.
Sonuç: Hastalarımızda yüksek oranda HBS, kötü uyku kalitesi ve artmış OUAS riski bulundu. HBS' si olan epilepsi hastalarımızda, olmayanlara göre kötü uyku kalitesi, gündüz aşırı uykululuk ve OUAS riskini anlamlı yüksek bulundu. Epileptik bireylerde uyku bozukluklarının varlığının ısrarla sorgulanması gerektiğini düşünüyoruz.

Anahtar Kelimeler: epilepsi; huzursuz bacaklar sendromu; obstrüktif uyku apne sendromu; uyku; uyku kalitesi

ABSTRACT

Purpose: Epilepsy and sleep disorders mutually affect each other negatively. The aim of this study was to investigate the common sleep disorders in epilepsy patients in our follow-up and their relationship with disease duration, seizure type and frequency, number and type of antiepileptic drugs (AEDs).
Materials and Methods: 99 patients diagnosed with epilepsy were included in this survey study. Demographic data, duration of epilepsy disease, seizure type and frequency, number and type of AEDs used were recorded by face-to-face questioning. Pittsburg sleep quality index (PSQI), Epworth sleepiness scale (ESS), Berlin sleep questionnaire (BSQ) and restless legs syndrome (RLS) questionnaire were applied to all patients.
Results: In our epilepsy patients, the number of patients with a PDQI score of 5 points or more was 56 (56.6%), the number of patients with an IQR score of 10 points or more was 9 (9.1%), and the number of patients at high risk for obstructive sleep apnea syndrome (OSAS) according to BUA was 53 (53.5%).
Conclusion: Our patients had a high rate of RLS, poor sleep quality and increased risk of OSAS. Poor sleep quality, excessive daytime sleepiness and OSAS risk were significantly higher in epilepsy patients with RLS compared to those without RLS. We think that the presence of sleep disorders in epileptic individuals should be questioned persistently.

Keywords: epilepsy; sleep; sleep quality; restless legs syndrome; obstructive sleep apnea syndrome

Gönderilme tarihi: 01.06.2023; Kabul edilme tarihi: 14.09.2023

[1]Kırşehir Ahi Evran Üniversitesi, Tıp Fakültesi, Nöroloji Anabilim Dalı, Kırşehir. Türkiye.
[2]Kırşehir Ahi Evran Üniversitesi, Tıp Fakültesi, Biyoistatistik ve Tıbbi Bilişim Anabilim Dalı, AD, Kırşehir, Türkiye.
Sorumlu Yazar: Selcen Duran, Kırşehir Ahi Evran Üniversitesi, Tıp Fakültesi, Nöroloji Anabilim Dalı, Kırşehir. Türkiye. e-posta: drselcenduran@gmail.com

Makaleye atıf için: Duran S, Çelikbilek A, Şahin BE, Yetiş A, Konar NM. Epilepsi hastalarında uyku bozuklukları: Anket çalışması.
Ahi Evran Med J. 2024;8(1):56-61. DOI: 10.46332/aemj.1308388

GİRİŞ

Epilepsi, kortikal nöronlardaki anormal elektriksel deşarj sonucu ortaya çıkan ani, tekrarlayıcı, tetiklenmemiş nöbetlerle karakterize bir klinik tablodur.[1] Epilepsi ve uyku bozuklukları karşılıklı olarak birbirini etkileyen ve epilepsi tedavisinde zorluklara yol açan bir durumdur. Uykuda nöbet geçirme, epilepsili bireylerde uyku fragmantasyonu yaparak toplam uyku süresini ve uyku kalitesini azaltmaktadır.[2] Azalan uyku kalitesi, gündüz aşırı uykululuk, dikkat ve konsantrasyon eksikliği ve yorgunluk gibi bulgulara sebebiyet vermektedir.[3] Ayrıca, kullanılan antiepileptiklerin uyku üzerine olan etkisi ve eşlik eden psikososyal komorbiditeler de, epilepsili bireyin uyku mimarisini değiştirerek uykuyu olumsuz etkilemektedir.[4]

Epilepsi hastalarında nöbetler arasındaki dönemde üretilen patolojik aktiviteler olan interiktal epileptiform deşarjların sayı ve senkronizasyonu, uykunun farklı evrelerinde değişkenlik gösterir. Deşarjlar, evre 3 Non-REM de daha belirgin olmak üzere tüm Non-REM dönemlerinde artar; bu artışta talamus anahtar rol oynamaktadır.[2] Non-REM döneminde talamokortikal nöronlarda görece hiperpolarizasyon veya senkronizasyon meydana gelmekte, bu durum epileptik nöronların uyarılabilirliğini kolaylaştırmaktadır.[5] Aksine, deşarjların uykunun REM döneminde baskılandığı bilinmektedir.[6]

Epilepsili bireylerde, eşlikçi uyku bozuklukları arasında gündüz aşırı uyku hali ve hipersomnia, insomni ve obstrüktif uyku apne sendromu (OUAS) sık görülmektedir.[2] Bu durumların varlığı da nöbet kontrolü sağlamayı zorlaştırmaktadır.[7] Sadece uykusuzluk ile tetiklenen nöbet türlerinin varlığı bile tek başına epileptik hastalarda uyku bozukluklarının ayrıntılı irdelenmesi ve tedavi edilmesi gerektiğinin yeterli bir kanıtıdır. Bu açıdan, epilepsi ve uyku bozuklukları birlikteliği hangisi sebep hangisi sonuç olduğuna bakılmaksızın klinisyenler tarafından dikkate alınmalıdır.[8] Çalışmamızın amacı takibimizde olan epilepsi hastalarında sık görülen uyku bozukluklarını ve bu bozuklukların hastalık süresi, nöbet tipi ve sıklığı, antiepileptik ilaç (AEİ) sayısı ve türü ile ilişkisini incelemektir.

ARAÇLAR ve YÖNTEM

Çalışma Tasarımı

Bu anket çalışmamıza, Şubat 2017- Ekim 2017 tarihleri arasında Kırşehir Eğitim ve Araştırma Hastanesi Nöroloji polikliniğinde takipli olan 18 yaş üzeri epilepsi tanılı hastalar dahil edilmiştir. Hastaların demografik verileri (yaş, cinsiyet, medeni durum, eğitim durumu) ve epileptik nöbete ait bilgiler (epilepsi hastalık süresi, nöbet tipi, nöbet sıklığı, rutin elektroensefalografi (EEG) bulguları, AEİ sayısı ve türü) kayıt edilmiştir. Nöbet tipi; nöbet semiyolojisi, EEG ve kranial manyetik rezonans görüntülemeden faydalanılarak The International League Against Epilepsy (ILAE) 2017 sınıflaması kullanılarak yapılmıştır.[9] Buna göre hastalar; parsiyel, jeneralize ve sınıflandırılamayan olmak üzere 3 gruba ayrılmıştır. Nöbet sıklığı; ayda 1'den fazla olanlar sık nöbet, ayda 1 den az olanlar seyrek nöbet ve 1 yıldan uzun süredir nöbetsiz olanlar kontrol altında olmak üzere 3 gruba bölünmüştür.[10] Hastalar, AEİ sayısına göre monoterapi ve/veya kombinasyon tedavisi olarak ayrıca gruplandırılmıştır. Epilepsi hastalık süresi 1 yıldan az, 1-5 yıl, 5-10 yıl ve 10 yıldan uzun süre olmak üzere 4 gruba ayrılmıştır.

Hastalara Pittsburg uyku kalite indeksi (PUKİ), Epworth uykululuk ölçeği (EUÖ), Berlin uyku anketi (BUA) ve Huzursuz bacaklar sendromu (HBS) anketi alanında uzman nörolog tarafından yüz yüze uygulandı. 1989 yılında Buyse ve ark tarafından geliştirilen PUKİ skalasının Türkçe geçerlilik ve güvenilirliği Ağargün ve ark. tarafından yapılmıştır. 21 sorudan oluşmakta ve 5 puan ve üzeri kötü uyku kalitesi varlığını göstermektedir.[11,12] EUÖ 1991 yılında tanımlanmış olup gündüz uykululuğu saptamaya yardımcı bir testtir. Türkçe geçerlilik ve güvenilirliği İzci ve ark tarafından yapılmıştır. 0-24 puan arası puanlanır; 10 puan ve üzeri gündüz aşırı uykululuğu gösterir.[13,14] BUA, OUAS için kullanılan bir tarama testi olup 3 farklı kategoride 10 sorudan oluşmaktadır. 2 veya daha fazla kategori pozitif sonuçlanırsa OUAS riski yüksek kabul edilmektedir.[15] HBS tanısı için Uluslararası Huzursuz Bacaklar Sendromu Çalışma grubu tarafından hazırlanan ve Türkçeye uyarlanan tanı kriterleri uygulandı.[16]

Sorulara yanıt veremeyecek düzeydeki kognitif bozukluğu olan, psikiyatrik tedavi alan, gebe olan, HBS sıklığını artırabilecek hastalıkları (romatolojik, diyabet, kronik böbrek yetmezliği, vb) olan ve sekonder nedenlere bağlı epilepsisi olan hastalar çalışmaya dahil edilmedi.

Tüm hastalardan çalışmaya katılım onam formu alındı. Çalışmaya Ahi Evran Üniversitesi Klinik Araştırmalar Etik Kurulundan 24/01/2017 tarih ve 2017-02/06 sayılı onay alındıktan sonra başlandı. Bu çalışma Helsinki Deklerasyonu Prensipleri'ne uygun olarak yapıldı.

İstatistiksel Analiz

Verilerin istatistiksel analizinde SPSS v.21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) kullanıldı. Normallik varsayımının testi için Kolmogorov-Smirnov Testi'nden yararlanıldı. Tanımlayıcı istatistikler, sayısal değişkenler için ortalama ± standart sapma (SS), kategorik değişkenler için sayı (n) ve yüzde (%) olarak verildi. Kategorik verilerin karşılaştırmalarında Ki-kare ve Fisher Exact testi kullanıldı. Tüm analizlerde $p<0.05$ istatistiksel anlamlılık olarak kabul edildi.

BULGULAR

Bu çalışmaya 63 (%63.6) kadın, 36 (%36.4) erkek olmak üzere 99 hasta dahil edildi. Hastaların yaş ortalaması 35.3±13.1 idi. Hastaların 27 (%27.3) parsiyel nöbet, 49 (%49.5) jeneralize nöbet, 23 (%23.2) sınıflandırılamayan nöbet idi. Hastaların rutin EEG bulguları incelendiğinde; 33 hastanın (%33.3) normal olduğu, 16 hastada (%16.2) non spesifik yavaşlama, 22 hastada (%22.2) fokal epileptik bulgu, 9 hastada jeneralize epileptik bulgu (%9.1) izlenmiştir, 19 hastanın (%19.2) ise EEG kaydı bulunamamıştır. Nöbet sıklığı incelendiğinde; 32 (%32.3) hasta nöbetsiz iken, 23 (%23.2) hastada sık nöbet, 44 (%44.4) hastada ise seyrek nöbet mevcuttu. AEİ sayısına göre; 68 (%68.7) hasta monoterapi, 31 (%31.3) hasta kombinasyon tedavisi almaktaydı. AEİ türü olarak; 44 (%31.9) hasta levetirasetam, 24 (%17.4) hasta karbamazepin ve/veya okskarbazepin, 42 (%30.4) hasta valproik asit, 12 (%8.7) hasta lamotrijin ve 16 (%11.6) hasta ise diğer ilaç tedavilerini kullanılıyordu. Epilepsi hastalarımızda PUKİ skoru ortalaması 5.64±3.4 olup skoru 5 puan ve üzeri olan hasta sayısı 56 (%56.6) idi. EUÖ skoru ortalaması 4.31±3.6 olup skoru 10 puan ve üzeri olan hasta sayısı 9 (%9.1) idi. BUA sonucuna göre OUAS için yüksek riskli hasta sayısı 53 (%53.5) idi. Ayrıca tüm epilepsili hastaların 25 (%25.3)' inde HBS varlığı tespit edildi. Epilepsi hastalarının demografik verileri Tablo 1'de özetlenmiştir. (Tablo 1).

Tablo 1. Epilepsi hastalarında demografik ve klinik veriler (n=99).

Değişkenler	Kategori	n (%)
Cinsiyet	Erkek	36 (36.4)
	Kadın	63 (63.6)
Medeni durum	Evli	66 (66.7)
	Bekar	30 (30.3)
	Boşanmış/dul	3 (3)
Öğrenim durumu	Okuryazar değil	2 (2)
	İlkokul	33 (33.3)
	Ortaokul	14 (14.1)
	Lise	32 (32.3)
	Üniversite	18 (18.2)
Hastalık süresi (yıl)	1 yıldan az	2 (2)
	1-5 yıl	25 (25.3)
	5-10 yıl	26 (26.3)
	10 yıldan uzun	46 (46.5)
Nöbet tipi	Sınıflandırılamayan	23 (23.2)
	Parsiyel	27 (27.3)
	Jeneralize	49 (49.5)
Nöbet sıklığı	Nöbetsiz	32 (32.3)
	Sık nöbet	23 (23.2)
	Seyrek nöbet	44 (44.4)
AEİ sayısı	Monoterapi	68 (68.7)
	Kombinasyon	31 (31.3)
AEİ türü	Levetirasetam	44 (31.9)
	Valproik asit	42 (30.4)
	Karbamazepin/Okskarbazepin	24 (17.4)
	Lamotrijin	12 (8.7)
	Diğer	16 (11.6)
PUKİ skoru	< 5	43 (43.4)
	≥ 5	56 (56.6)
EUÖ skoru	< 10	90 (90.9)
	≥ 10	9 (9.1)
BUA skoru	Düşük risk	46 (46.5)
	Yüksek risk	53 (53.5)
HBS varlığı	Var	25(25.3)
	Yok	74(74.7)

Değerler *n* (%) olarak ifade edildi. AEİ: Antiepilepik İlaçları, PUKİ: Pittsburg Uyku Kalitesi İndeksini, EUÖ: Epworth Uykululuk Ölçeğini, BUA: Berlin Uyku Anketini, HBS: Huzursuz Bacaklar Sendromunu tanımlamaktadır.

Epilepsi hastalarında PUKİ, EUÖ, BUA skorlarının demografik verilerle karşılaştırılması Tablo 2' de verilmiştir. Buna göre; PUKİ, EUÖ ve BUA skorları cinsiyet (PUKİ için p=0.674; EUÖ için p=0.481; BUA için p=0.677), medeni durum (PUKİ için p=0.663; EUÖ için p=0.566; BUA için p=0.198), öğrenim durumu (PUKİ için p=0.929; EUÖ için p=0.249; BUA için p=0.548) hastalık süresi (PUKİ için p=0.141; EUÖ için 0.379; BUA için p=0.616), nöbet sıklığı (PUKİ için p=0.597; EUÖ için p=0.286; BUA için p=0.209), kullanılan AEİ sayısı (PUKİ için p=0.999; EUÖ için p=0.716; BUA için p=0.665) ile ilişkili bulunmadı. Nöbet tipi açısından bakıldığında; PUKİ skoru jeneralize

epilepsili hastalarda anlamlı yüksek (kötü uyku kalitesi) tespit edildi (p=0.045). PUKİ (p=0.035), EUÖ (p=0.043) ve BUA (p=0.039) skorlarının hepsi HBS var olan hastalarda, olmayanlara göre anlamlı yüksek idi (Tablo 2).

Tablo 2. Epilepsi hastalarında PUKİ, EUÖ, BUA skorlarının demografik verilerle karşılaştırılması.

Değişkenler	Kategori	PUKİ skoru < 5	PUKİ skoru ≥ 5	*p* değeri	EUÖ skoru < 10	EUÖ skoru ≥ 10	*p* değeri	BUA skoru < 2	BUA skoru ≥ 2	*p* değeri
Cinsiyet	Erkek	17 (47.2)	19 (52.8)	0.674*	34 (94.4)	2 (5.6)	0.481*	18 (50)	18 (50)	0.677*
	Kadın	26 (41.3)	37 (58.7)		56 (88.9)	7 (11.1)		28 (44.4)	35 (55.6)	
Medeni durum	Boşanmış/dul	1 (33.3)	2 (66.7)	0.663**	3 (100)	0 (0)	0.566**	1 (33.3)	2 (66.7)	0.198**
	Bekar	15 (50)	15 (50)		26 (86.7)	4 (13.3)		18 (60)	12 (40)	
	Evli	27 (40.9)	39 (59.1)		61 (92.4)	5 (7.6)		27 (40.9)	39 (59.1)	
Öğrenim durumu	Okuryazar değil	1 (50)	1 (50)	0.929**	2 (100)	0 (0)	0.249**	0 (0)	2 (100)	0.548**
	İlkokul	15 (45.5)	18 (54.5)		30 (90.9)	3 (9.1)		15 (45.5)	18 (54.5)	
	Ortaokul	6 (42.9)	8 (57.1)		13 (92.9)	1 (7.1)		5 (35.7)	9 (64.3)	
	Lise	12 (37.5)	20 (62.5)		31 (96.9)	1 (3.1)		17 (53.1)	15 (46.9)	
	Üniversite	9 (50)	9 (50)		14 (77.8)	4 (22.2)		9 (50)	9 (50)	
Hastalık süresi (yıl)	1 yıldan az	0 (0)	2 (100)	0.141**	2 (100)	0 (0)	0.379**	0 (0)	2 (100)	0.616**
	1-5 yıl	7 (28)	18 (72)		21 (84)	4 (16)		12 (48)	13 (52)	
	5-10 yıl	12 (46.2)	14 (53.8)		23 (88.5)	3 (11.5)		12 (46.2)	14 (53.8)	
	10 yıldan uzun	24 (52.2)	22 (47.8)		44 (95.7)	2 (4.3)		22 (47.8)	24 (52.2)	
Nöbet tipi	Sınıflandırılamayan	7 (30.4)	16 (69.6)	**0.045****	20 (87)	3 (13)	0.483**	7 (30.4)	16 (69.6)	0.196**
	Parsiyel	17 (63)	10 (37)		26 (96.3)	1 (3.7)		13 (48.1)	14 (51.9)	
	Jeneralize	19 (38.8)	30 (61.2)		44 (89.8)	5 (10.2)		26 (53.1)	23 (46.9)	
Nöbet sıklığı	Nöbetsiz	14 (43.8)	18 (56.3)	0.597**	30 (93.8)	2 (6.3)	0.286**	16 (50)	16 (50)	0.209**
	Sık nöbet	8 (34.8)	15 (65.2)		19 (82.6)	4 (17.4)		7 (30.4)	16 (69.6)	
	Seyrek nöbet	21 (47.7)	23 (52.3)		41 (93.2)	3 (6.8)		23 (52.3)	21 (47.7)	
AEİ sayısı	Monoterapi	30 (44.1)	38 (55.9)	0.999*	61 (89.7)	7 (10.3)	0.716*	33 (48.5)	35 (51.5)	0.665*
	Kombinasyon	13 (41.9)	18 (58.1)		29 (93.5)	2 (6.5)		13 (41.9)	18 (58.1)	
HBS varlığı	Var	6 (24)	19 (76)	**0.035***	20 (80)	5 (20)	**0.043***	7 (28)	18 (72)	**0.039***
	Yok	37 (50)	37 (50)		70 (94.6)	4 (5.4)		39 (52.7)	35 (47.3)	

Değerler *n* (%) olarak ifade edildi. AEİ: Antiepilepik İlaçları, PUKİ: Pittsburg Uyku Kalitesi İndeksini, EUÖ: Epworth Uykululuk Ölçeğini, BUA: Berlin Uyku Anketini, HBS: Huzursuz Bacaklar Sendromunu tanımlamaktadır. $p<0.05$ istatistiksel olarak anlamlı kabul edilmiştir.
*: Fisher Exact Test
**: Ki-Kare Testi

TARTIŞMA

Epilepsi ve uyku arasındaki ilişki her ne kadar çok uzun zamandır bilinse de patofizyolojisi halen tam olarak anlaşılamamıştır.[17] Sık nöbet, AEİ kullanımı, nokturnal nöbetler ve eşlikçi psikiyatrik durumlar epileptik hastalarda uyku bozukluklarına yol açan durumlardır.[4] Tersine, uyku bozukluklarının varlığı da nöbet sıklığını arttırmaktadır.[7] Nitekim, HBS epilepsi hastalarında yaygın olup, görülme sıklığı değişik serilerde %5.8-32.3 aralığındadır.[18-20] Bizim çalışmamızda HBS sıklığı literatürle uyumlu olarak %25.3 olarak bulunmuştur. Gayer ve ark. yaptığı bir çalışmada sağ temporal epilepsili olgularda HBS sıklığını %42 olarak yüksek bildirmişlerdir.[21] Epilepsi hastalarındaki HBS sıklığının farklı çalışmalarda bu kadar geniş aralıkta saptanmasının nedeni dışlama kriterlerinin değişkenlik göstermesi ile ilişkili olabilir.[20] Yapılan bir çalışmada epilepsi hastalarında HBS varlığının dirençli nöbetler ile ilişkili olduğu görülmüştür, [22] ancak bizim çalışmamızda nöbet sıklığı ile HBS varlığı arasında bir ilişki bulunamamıştır. Biyokimyasal değişkenler, yaş ve cinsiyet farklılıkları, kullanılan AEİ çeşitliliği bunu açıklayabilir. Öte yandan biriken veriler, HBS prevelansının kadınlarda daha fazla görüldüğünü ve bunun demir metabolizması ile ilişkili olabileceğini de düşündürmektedir.[23] Ayrıca, östrojenin şizofrenide dopamin antagonisti gibi davranması, ve gebelikte artan östrojen seviyesi ile beraber HBS semptomlarında artış izlenmesi de HBS' de hormonal faktörlerin etkisine işaret edebilir.[24] Dahası, HBS ile duygudurum bozukluklarının sıklıkla bir arada olması kadınlardaki yatkınlığın bir yansıması olabilir.[25]

Kullanılan antiepileptiklerin uykunun yapısını değiştirdiği uzun zamandır bilinmektedir.[26] Yapılan bir metaanalizde, lamotrijin insomni için risk oluşturuken fenobarbital gün içi uykululuğa sebep olabildiği, lakosamid, karbamezepin, levetirasetamın uyku üzerine hiç etkisi olmadığı öne sürülmüştür.[27] Farklı çalışmalarda; fenobarbital, valproik asit ve yüksek doz levetirasetamın gün içi uykululuğu arttırırken, gabapentin, pregabalin, klobozam ve karbamezepinin uyku latansını kısaltarak gece döneminde uyku etkinliğini arttırdığı bildirilmiştir.[4] Bizim çalışmamızda, tekli veya kombine tedavi rejimi uyku kalitesi ile ilişkili bulunmadı. Bununla birlikte, jeneralize nöbeti olan hastaların uyku kalitesi daha kötü saptandı. Jeneralize epilepsilerde uykuda ortaya çıkan interiktal epileptiform deşarjlar uykuda bölünmelere, uyku mimarisinde bozulmaya ve uyku kalitesinde azalmaya sebep olur.[28] Epilepsi hastalarında kötü uyku kalitesi (PUKİ skoru ≥ 5 puan) prevalansı, ülkemizde

yapılan bir çalışmada %42.5[20] iken, İspanyol bir çalışmada ise %53.6 olarak bulunmuştur.[29] Takibimizdeki epilepsi hastalarında kötü uyku kalitesine sahip hasta oranı literatürle uyumlu olarak %56 idi.

Literatürde epilepsi hastalarında gündüz aşırı uykululuk (EUÖ skoru ≥ 10 puan) prevalansı %18-47 arasında olup dirençli nöbetlerde daha yüksektir.[30] Çalışmamızda ise bu değer %9.1 olarak tespit edildi. Gün içi uykululuğu arttıran fenitoin, fenobarbital ve gabapentin gibi ilaçların çalışmamızda az sayıda hastada kullanılması bu düşüklüğü açıklayabilir. Öte yandan, bir meta-analizde epilepsi hastalarında hafif, orta ve ağır OUAS varlığının %33.4 olduğu tespit edilmiştir.[31] Pek çok çalışma, epilepsi hastalarında OUAS birlikteliğinin dirençli epilepsi, nokturnal nöbet ve status epileptikus riskini arttırdığını göstermiştir.[32] Dahası, epilepsi ve komorbid OUAS tanısı olan hastalara PAP veya oksijen tedavisi uygulanmasının EEG'de diken dalga aktivitesini azalttığının gösterilmesi, OUAS'ın epileptogenez üzerinde etkisi olabileceğini düşündürmüştür.[33] Çalışmamızda epilepsi hastalarında BUA yapılmış olup %53.5 hastada OUAS için yüksek risk saptanmıştır. Karbamazepin, okskarbazepin ve levetirasetam kullananlarda OUAS riskinin daha fazla olduğu, valproik asit gibi kilo alımına sebep olabilecek antiepileptiklerin de OUAS açısından risk oluşturabileceği, fokal epilepsilerin jeneralize epilepsilere göre daha yüksek OUAS riski taşıdığı bilinmektedir.[34] Buna dayanarak, çalışmamızda valproik asit ve levetirasetam kullanımının görece fazla olması hasta grubumuzda artmış OUAS riskini açıklayabilir. Öte yandan, BUA skorunun epilepsi hastalık süresi, nöbet tipi, nöbet sıklığı ve AEİ tedavi şekli ile ilişkili olmadığı sonucu açıklanmaya muhtaçtır. Yine de pratik bir OUAS tarama testi olan BUA' nın epilepsili bireylerde uygulanmasının, bu bireylerde tedavide optimizasyonu sağlamak için mantıklı olabileceğini düşünmekteyiz.

Çalışmamızın anket ve yüz yüze sorgulamaya dayanması, polisomnografi ve uyku deprivasyonlu EEG yapılmaması, örneklem sayısının kısıtlı olması, cinsiyet dağılımının eşit olmaması, nöbet tipine uygun ve etkin dozda antiepileptik kullanımının irdelenmemesi çalışmanın kısıtlılıklarıdır.

Sonuç olarak; epilepsi hastalarımızın yaklaşık çeyreğinde HBS, yarısında ise kötü uyku kalitesi ve yüksek OUAS riski bulduk. Kötü uyku kalitesini jeneralize epilepsili hastalarda daha sık saptadık. Ayrıca; kötü uyku kalitesi, gündüz aşırı uykululuk ve OUAS riskini HBS' si olan epilepsili hastalarımızda olmayanlara göre anlamlı yüksek bulduk. Bulgularımıza dayanarak, epileptik bireylerde uyku bozukluklarının varlığının ısrarla sorgulanması gerektiğini düşünüyoruz.

Çıkar Beyannamesi

Herhangi bir çıkar çatışmasının olmadığını yazarlar beyan etmektedirler.

Etik Kurul İzni

Bu çalışma için Ahi Evran Üniversitesi Klinik Araştırmalar Etik Kurulu'ndan onay alındı (24/01/2017 tarih ve 2017-02/06 sayı).

Araştırmacıların Katkı Oranı Beyanı

Ana fikir/Planlama: SD, AY, BEŞ. Veri toplama/İşleme: SD, AY, BEŞ. Veri analizi ve yorumlama: SD, NMK, AÇ. Literatür taraması: SD, AY, BEŞ. Yazım: SD, AÇ. Gözden geçirme ve düzeltme: SD, NMK, AÇ. Danışmanlık: AÇ, NMK.

KAYNAKÇA

1. Akdağ G, Algın D, Erdinç O. Epilepsi/epilepsy. OTD. 2016;38(1):35-41.
2. Roliz AH, Kothare S. The Interaction Between Sleep and Epilepsy. Curr Neurol Neurosci Rep. 2022;22(9): 551-563.
3. Maganti R, Hausman N, Koehn M, Sandok E, Glurich I, Mukesh BN. Excessive daytime sleepiness and sleep complaints among children with epilepsy. Epilepsy & Behavior. 2006;8(1):272-277.
4. Jain SV, Glauser TA. Effects of epilepsy treatments on sleep architecture and daytime sleepiness: an evidence-based review of objective sleep metrics. Epilepsia. 2014;55(1):26-37.
5. Steriade M, Contreras D. Relations between cortical and thalamic cellular events during transition from sleep patterns to paroxysmal activity. J. Neurosci. 1995;15(1):623-642.
6. Bazil CW. Effects of antiepileptic drugs on sleep structure: are all drugs equal? CNS drugs. 2003;17(10): 719-728.
7. Ismayilova V, Demir AU, Tezer FI. Subjective sleep disturbance in epilepsy patients at an outpatient clinic: a questionnaire-based study on prevalence. Epilepsy Res. 2015;115:119-125.
8. Manni R, Terzaghi M. Comorbidity between epilepsy and sleep disorders. Epilepsy Res. 2010;90(3):171-177.
9. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE

Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-521.
10. Acaroğlu G, Yılmaz E. Epilepsili Hastalarda İlaç Uyumunun Yaşam Kalitesine Etkisi. Epilepsi: JTES 2016;22(1):17-25.
11. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213.
12. Ağargün MY, Kara H, Anlar O. Pittsburgh uyku kalitesi indeksinin geçerliği ve güvenirliği. Turk Psikiyatri Derg. 1996;7(2):107-115.
13. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-545.
14. Izci B, Ardic S, Firat H, Sahin A, Altinors M, Karacan I. Reliability and validity studies of the Turkish version of the Epworth Sleepiness Scale. Sleep Breath. 2008;12(2):161-168.
15. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. 1999;131(7):485-491.
16. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med. 2003;4(2):101-119.
17. Derry CP, Duncan S. Sleep and epilepsy. Epilepsy & Behavior. 2013;26(3):394-404.
18. Yazdi Z, Sadeghniiat-Haghighi K, Naimian S, Zohal MA, Ghaniri M. Prevalence of Sleep Disorders and their Effects on Sleep Quality in Epileptic Patients. Basic Clin Neurosci. 2013;4(1):36-41.
19. Öztürk İ, Aslan K, Bozdemir H, Foldvary-Schaefer N. Frequency of Restless Legs Syndrome in adults with epilepsy in Turkey. Epilepsy Behav. 2016;57:192-195.
20. Öztürk O, Kabeloğlu V, Ataklı D. Restless leg syndrome prevalence in epilepsy patients and its impact on quality of sleep. Sleep Biol. Rhythms. 2022;20(3):413-420.
21. Geyer JD, Geyer EE, Fetterman Z, Carney PR. Epilepsy and restless legs syndrome. Epilepsy Behav. 2017;68:41-44.
22. Li YS, Yeh WC, Chang YH, Hsu CY. Restless Legs Syndrome in Patients with Epilepsy: Risk analysis, Polysomnography, and Quality of Life evaluation. Sleep. 2023;zsad054.
23. Manconi M, Ulfberg J, Berger K, et al. When gender matters: restless legs syndrome. Report of the "RLS and woman" workshop endorsed by the European RLS Study Group. Sleep Med Rev. 2012;16(4):297-307.
24. Seeman MV. Why Are Women Prone to Restless Legs Syndrome? Int J Environ Res Public Health. 2020;17(1):368.
25. Becker PM, Sharon D. Mood disorders in restless legs syndrome (Willis-Ekbom disease). J Clin Psychiatry. 2014;75(7):e679-694.
26. Carvalho BMS, Chaves J, da Silva AM. Effects of antiepileptic drugs on sleep architecture parameters in adults. Sleep Sci. 2022;15(2):224-244.
27. Liguori C, Toledo M, Kothare S. Effects of anti-seizure medications on sleep architecture and daytime sleepiness in patients with epilepsy: A literature review. Sleep Med Rev. 2021;60:101559.
28. Yadav V, Nanda S, Kaushik JS, Bala K. Sleep Characteristics Among Children with Idiopathic Generalized Epilepsy: A Polysomnography-Based Study. Indian J Pediatr. 2021;88(9):925-927.
29. Planas-Ballvé A, Grau-López L, Jiménez M, Ciurans J, Fumanal A, Becerra JL. Insomnia and poor sleep quality are associated with poor seizure control in patients with epilepsy. Neurologia (Engl Ed). 2022;37(8):639-646.
30. Giorelli AS, Passos P, Carnaval T, Gomes Mda M. Excessive daytime sleepiness and epilepsy: a systematic review. Epilepsy Res Treat. 2013:629469.
31. Lin Z, Si Q, Xiaoyi Z. Obstructive sleep apnoea in patients with epilepsy: a meta-analysis. Sleep Breath. 2017;21(2):263-270.
32. Sethi NK. The Relationship Between Epilepsy, Obstructive Sleep Apnea, and Treatment Outcome. Sleep Med Clin. 2022;17(4):639-645.
33. Oliveira AJ, Zamagni M, Dolso P, Bassetti MA, Gigli GL. Respiratory disorders during sleep in patients with epilepsy: effect of ventilatory therapy on EEG interictal epileptiform discharges. Clin Neurophysiol. 2000;111(2):141-145.
34. Soylemez E, Ozturk O, Baslo SA, Balcik ZE, Atakli D. Metabolic syndrome and obstructive sleep apnea syndrome among patients with epilepsy on monotherapy. Epilepsy Behav. 2020;111:107296.

ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Bibliometric Analysis of Research on "Urology and COVID-19"; Web of Science Example

"Üroloji ve COVID-19" Konulu Araştırmaların Bibliyometrik Analizi; Web of Science Örneği

İbrahim ÜNTAN[1] Mümtaz DADALI[1,2] Erol ERŞEKERCİ[1] Muhammed Şahin BAĞBANCI[1]

ÖZ

Amaç: Çalışma, pandeminin patlak vermesinden bu yana "Üroloji ve COVID-19" alanlarında yayınlanan 1616 çalışmanın bibliyometrik analiz ve trendlerini ortaya koymayı amaçlamaktadır. Böylelikle araştırmacılara bu konulardaki araştırmaların istatistiksel dağılımları hakkında temel bilgiler verilmesi amaçlanmıştır.
Araçlar ve Yöntem: Web of Science Core Collection Veritabanı kullanılarak 2020, 2021, 2022 ve 2023 yıl aralığında "Üroloji ve COVID-19" konulu bibliyometrik analiz yapılmıştır. Sonuçlar aynı dönemin "Üroloji" yayınlarıyla karşılaştırılmıştır. Trendler ayrıca ücretsiz çevrimiçi görsel yazılım (carrot[2]) kullanılarak farklı verilerle değerlendirilmiştir.
Bulgular: Toplam 5481 makale bu çalışmalara 13036 kez atıf yapmıştır. En yaygın belge türü araştırma makalesi, en sık yayınlanan alan Üroloji & Nefroloji, en çok kullanılan dil İngilizce, en çok yayınlanan dergi Journal of Urology, en çok yayın veren ülke Amerika Birleşik Devletleri ve en çok katkı sağlayan kurum Udice Üniversitesi olmuştur.
Sonuç: Dünyanın dengelerini bozan bu bulaşıcı hastalık, yayınların dengesini de kendi lehine değiştirmiştir. Ürologlar, pandemi ile mücadele ederken "Üroloji ve COVID-19" araştırmalarına izole "Üroloji" araştırmalarından daha çok önem vermiştir.

Anahtar Kelimeler: bibliyometri; covıd-19; pandemi; sars-cov-2; üroloji; yeni koronavirus

ABSTRACT

Purpose: The study aims to reveal the bibliometric analysis and trends of 1616 studies published in the fields of "Urology and COVID-19" since the outbreak of the pandemic. Thus, it is aimed to provide researchers with basic information about the statistical distribution of research on these topics. This study aims to reveal the bibliometric analyzes and trends of 1616 studies published in the "Urology and COVID-19" fields since the pandemic broke out. Thus, it was aimed to provide researchers with basic information about the field of research on these subjects, in which countries it was conducted, and in which journals it was mostly published.
Materials and Methods: A bibliometric analysis was conducted on "Urology and COVID-19" for 2020 - 2023 years using the Web of Science Core Collection Database. The results were compared with "Urology" publications of the same period. Trends were also evaluated with different data using free online visualization software (carrot2).
Results: A total of 5481 articles cited these studies 13036 times. The most common document type was research article, the most common field was Urology & Nephrology, the most common language was English, the most common journal was the Journal of Urology, the most common publishing country was the United States, and the most common contributing institution was Udice University.
Conclusion: This infectious disease, which disrupted the balance of the world, also changed the balance of publications in its favor. Urologists gave more importance to "Urology and COVID-19" research than isolated "Urology" research while fighting against the pandemic.

Keywords: bibliometrics; covıd-19; novel coronavirus; pandemics; urology; sars-cov-2

Received: 01.02.2023; Accepted: 25.10.2023

[1]Department of Urology, Training and Research Hospital, Kırşehir Ahi Evran University, Kırşehir, Turkey.
[2]Department of Medical Ethics and History, Faculty of Medicine, Hacettepe University, Ankara, Turkey.

Corresponding Author: İbrahim Üntan, Department of Urology, Training and Research Hospital, Kırşehir Ahi Evran University, Kırşehir, Turkey.
e-mail: ibrahimuntan@hotmail.com

How to cite: Üntan İ, Dadalı M, Erşekerci E, Bağbancı MŞ. Bibliometric analysis of research on "urology and covid-19"; web of science example. Ahi Evran Med J. 2024;8(1):62-68. DOI: 10.46332/aemj.1245720

INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously 2019-nCoV), has had a worldwide impact. Healthcare services in many nations have had to alter their operations due to the COVID-19 surge. Previously ongoing research trials have been suspended due to the sudden shift in resources toward managing this pandemic. Besides, surgical departments have had to prioritize and cancel surgeries, balance the safety of patients and staff, and assume the risk of operating where surgery is essential to life or limb.[1] There is ongoing research in many medical specialties in areas that relate to COVID-19, and urological research is one of these. Studies have examined not only how COVID-19 may affect bodily systems concerning pathophysiology, but also how it may impact routine care in a specialty, from an administrative and clinical practice perspective. Therefore, as in every field, COVID-19 studies in the field of urology are also quite abundant and increasing.

As a term, it is seen that statistical bibliography was used in lessons at Cambridge University by E. Wyndham Hulme in 1922, and then these courses were turned into a book.[2] Hulme counted documents with his work on the growth of modern civilization. The next use of the term statistical bibliography is seen in an article by Raisig in 1962 on citations in health sciences.[3] In order not to confuse the term with statistical bibliographies, the term bibliometry was defined by Pritchard in 1969.[4] Bibliometry according to Pritchard; It is the application of mathematics and statistical methods to books and other communication media.

The purpose of this research; is to reveal the bibliometric analysis and trends of 1616 studies published on "Urology and COVID-19". In this way, it is aimed that readers in the field of "Urology and COVID-19" can easily reach the statistics of the studies against the increasing number of works. It is aimed by the researchers to increase the awareness of the authors and the subjects who form the discipline with the least effort and to contribute to which area and how their studies will be directed.

MATERIALS and METHODS

Web of Science

Web of Science (WOS) is a website that provides subscription-based access to multiple databases that provide comprehensive citation data for many different academic disciplines.

Study Design

Using the WOS database, the subjects of "Urology and COVID-19" was searched and the obtained countries, journals, publication years, publication numbers, publication types, publication languages, and subject trends and organizations that contributed to the research were examined with bibliometric analysis. When "Urology and COVID-19"-related words are scanned in the Web of Science Core Collection database; the titles, the publications about "Urology and COVID-19" are listed by scanning (Supplementary Material 1, 2). With this scan, 1616 studies published in 2020, 2021, 2022, and 2023 when COVID-19 was effective, were accessed and analyzed.

Carrot²

Carrot² is an open-source search engine that can also be used online.[5] The clustering algorithm, offers components by dividing the searches into thematic categories. The results of open-access sources are grouped. In the study, trends were also evaluated with different data using free online visual software (carrot²).

Classification Criteria

While evaluating which country the studies were from, the authors were included in the cluster of the country from which country the study was, so studies with authors from different countries could be included in different clusters. The evaluation made according to the contributing organizations is also in the same way.

RESULTS

Tables and graphics in the findings were obtained from the WOS database.[6]

When the distribution of the studies has been examined over the years, it has been seen that there were 634 publications in 2020, 495 in 2021, 481 in 2022, and 6 in 2023. From Türkiye 43, 35 and 34 publications have taken place in WOS in 2021, 2022, and 2023 respectively. When the publications were divided according to WOS categories, it has been seen that most publications were in the Urology & Nephrology category by far. The first 5 categories have been given in Figure 1.

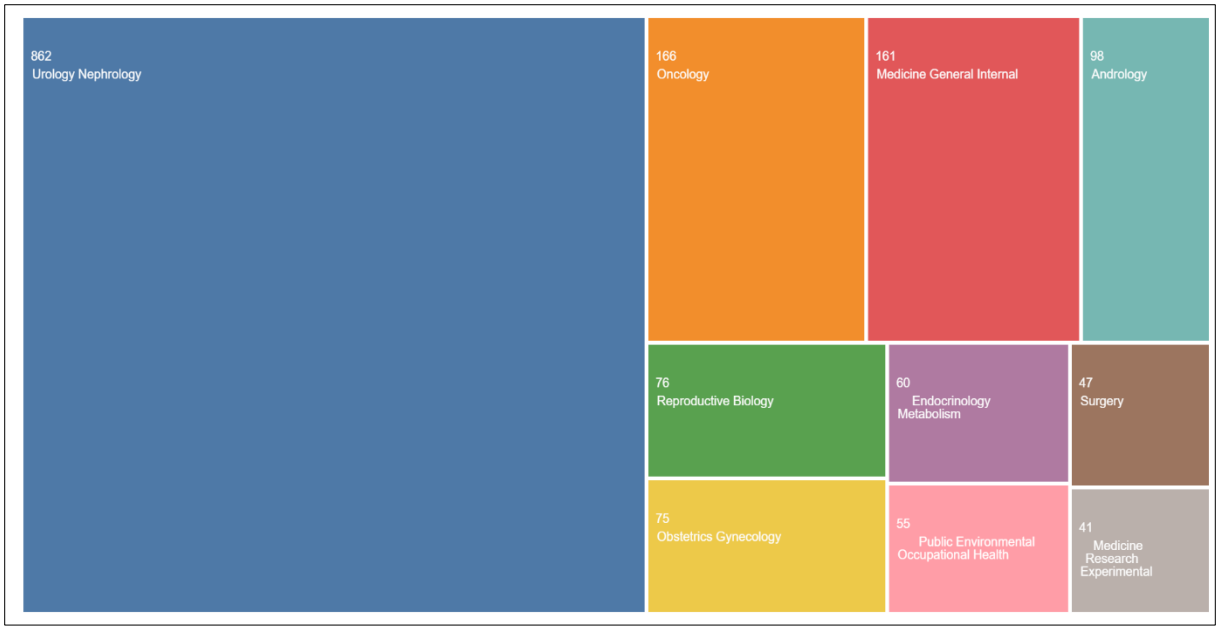


Figure 1. Studies according to WOS categories.

When the studies are evaluated according to the publication types, it is seen that there are many different types of publications and the article type comes first. The distribution of the publications according to the document type is given in Figure 2.

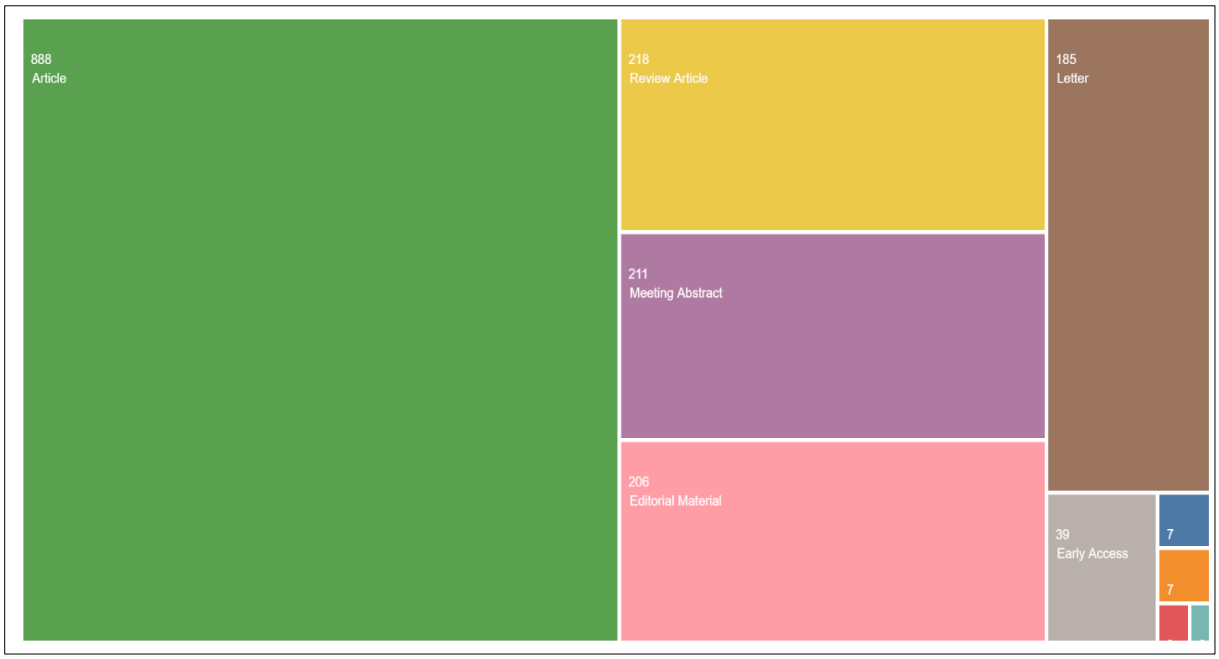


Figure 2. Studies according to document types.

Studies have been published in 7 different languages. Whereas English takes first place, there is only one study published in Turkish. The distribution of the publications by language has been given in Figure 3.

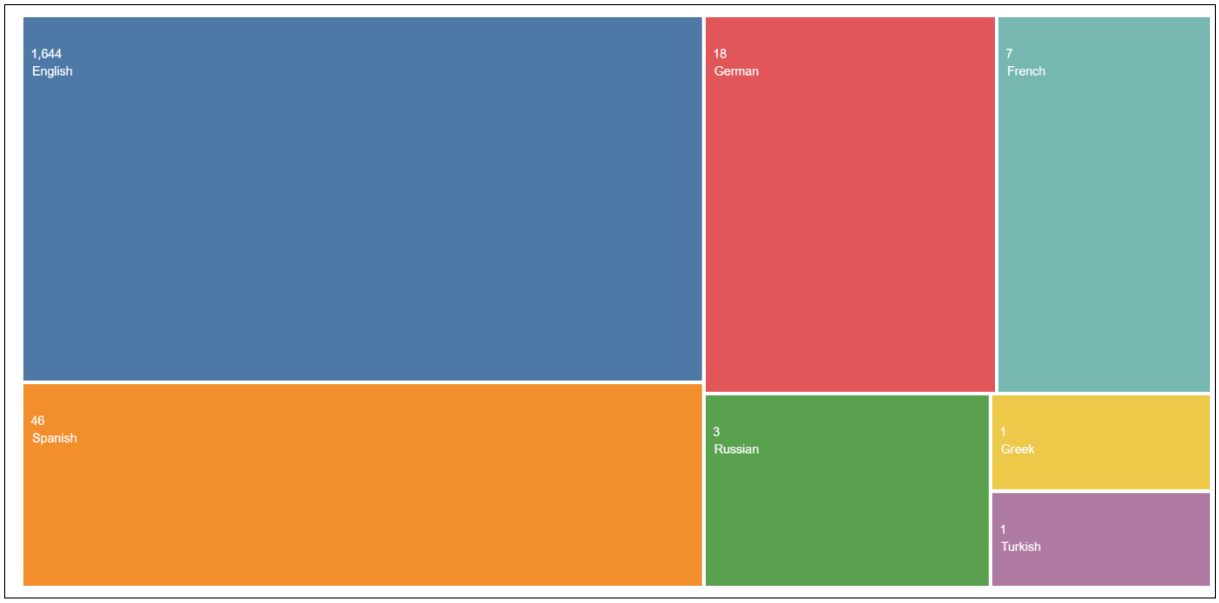


Figure 3. Studies according to languages.

Studies have been published in 459 different journals in total. Journal of Urology ranks first with 100 publications. The first 10 journals in which the studies were published have been given in Figure 4.

Figure 4. Studies according to the journals they were published in.

1616 studies have been cited a total of 13036 times, 2177 times in 2020, 5264 times in 2021, 5486 times in 2022, and 109 times in 2023. A total of 7191 citations were made without self-citation. The studies were cited to 5481 articles in total and 4482 articles were found to be cited when self-citations were removed. The average number of citations of the studies was found to be 8.07. The H index of the publications is 52. The top 5 publications with the most citations have been given in Table 1.

When the studies are classified according to which country they are from, it is seen that most studies came from the United States of America (USA). Türkiye ranks 5th, the first 10 countries where the studies are published are given in Figure 5.

The publications quoted from Türkiye have been ranked according to their citation number, the first 3 publications have been given in Table 1.

Table 1. Top 5 cited studies and 3 most cited studies overall, and from Türkiye, respectively, citations by years.

	PMID	type	journal	WOS category	2020	2021	2022	2023
overall	32387456	Article	Ann Oncol.	Oncology	102	143	74	2
	32283711	Article	Cells.	Cell Biology	108	131	77	0
	32482249	Article	Fertil Steril.	Reproductive Biology	93	114	65	1
	32379329	Letter	JAMA Netw Open	Reproductive Biology	56	109	60	1
	32650948	Article	Fertil Steril.	Urology & Nephrology	28	86	74	1
Türkiye	32507625	Article	Eur Urol.	Urology & Nephrology	15	44	34	1
	32883151	Article	Aging Male	Urology & Nephrology	1	36	24	0
	32781456	Article	Urol Int.	Urology & Nephrology	8	31	18	1

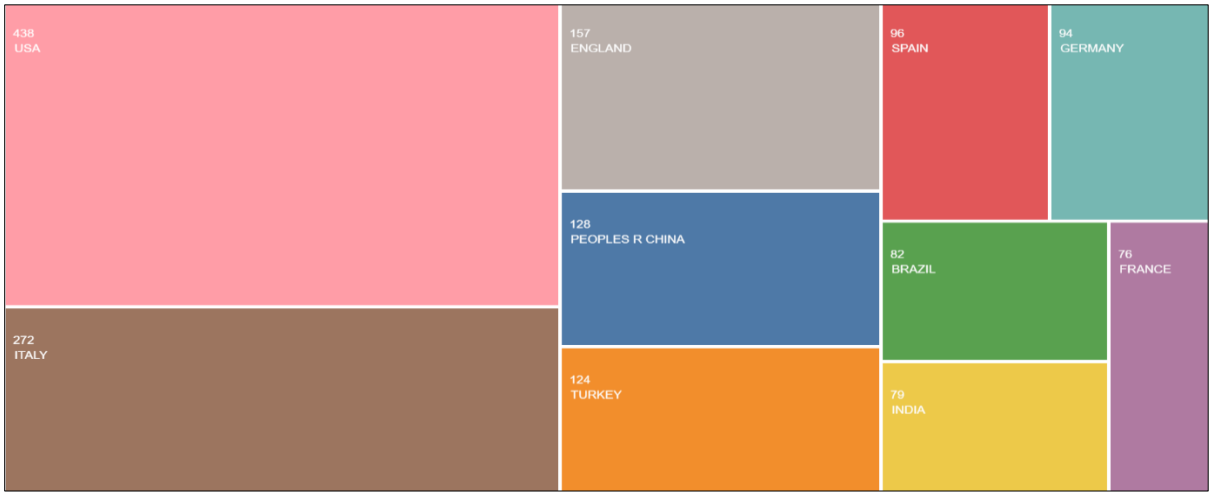


Figure 5. Studies by country of origin.

When the institutions that contributed to the studies were examined, it has been seen that there were 2717 organizations in total. The top 3 organisations are given in Table 3. The first three institutions that contribute from Türkiye can be seen in Table 2.

Table 2. Organizations contributing to studies (top 3), overall, and Türkiye respectively.

	Organizations	studies	percent
over.	Udice University	54	3.342%
	University of London	53	3.280%
	Sapienza University	49	3.032%
TR*	University of Health Sciences	20	0.012%
	Istanbul Medipol University	15	0.009%
	Istanbul University	11	0.006%

TR: Türkiye, over: overall

Studies Türkiye contributed were cited 1141 times in total. 1035 citations have been made without self-citation.

The studies were cited in 767 articles in total, and the number of publications was revised to 715 when self-citations were removed. The average number of citations of the publications is 10.19 The H index of the publications is 17.

In the Carrot² search made with the title of "Urology", the top 100 studies were reached, and according to these data, it was seen that the word "Urology" was most frequently used with the term prostate cancer, and "COVID-19" was used in the second place. The visual according to the aforementioned search was presented in Figure 6.

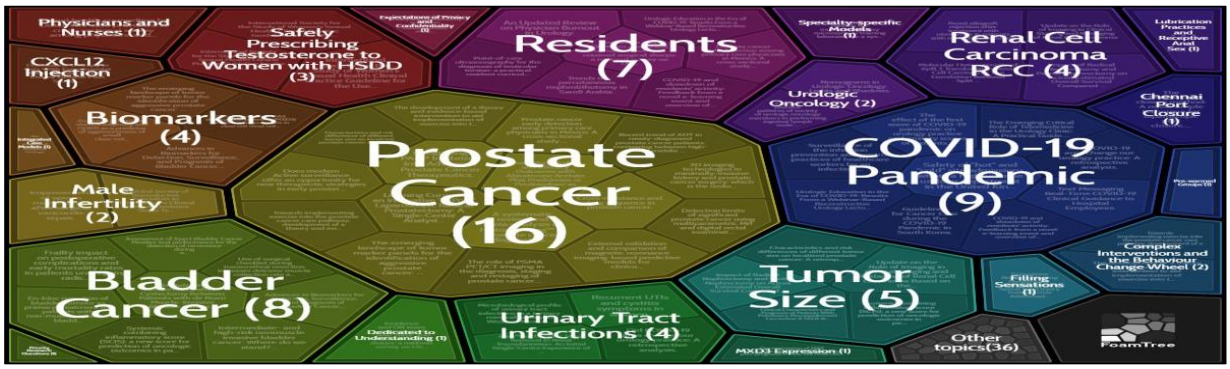


Figure 6. Visual of the Carrot² Analysis with Pubmed for the term "Urology"

DISCUSSION

Bibliometrics is a tool used to achieve quantitative research assessment exercises of academic output, teams, or even individuals in the field of scientific research. It is also important to know the basics of this method such as the impact factor, the h-index, and how journals evaluated. Bibliometric studies provide researchers the opportunity to easily examine all studies on some subjects.

Since Covid 19 erupted, healthcare workers have been having rough times. Because they have been trying to cope with the disease with insufficient information from the beginning, and also trying to collect information to recognize the disease to overcome it. Therefore, they are actively working in the field on the one hand, and on the other hand, they conduct research and publish them. For this reason, publications about COVID-19 are quite high.[7] This abundance affects the field of urology as well.[8] Our study is the only study in the literature that analyzes publications in the fields of "Urology and COVID-19" bibliometrically.

Türkiye has contributed 3.184% to literature in the field of "Urology" in the last four years, it has contributed 6.931% to the publications of "Urology and COVID-19". Türkiye participated in "Urology and COVID-19" publications at a higher rate. This can be attributed to the intense pandemic period that broke out in Türkiye. It is possible to conclude that Turkish researchers are making special efforts to overcome the pandemic. In many publications, it is mentioned that the scientific progress of urologists in their field was interrupted by the outbreak of the COVID-19 pandemic.[9]

In the last four years, publications in the field of "Urology and COVID-19" are similar to those in the field of "Urology" in terms of WOS category, but the andrology category started to appear on the scene earlier.[10] The reason for this may be that the testicular involvement of the COVID-19 disease has attracted attention and concentrated the studies on itself.[11]

Although the document type has spread in a wide range in the field of "Urology" in the last four years, types such as book and book reviews are not observed in "Urology and COVID-19"-oriented studies. We can attribute this to the lack of sufficient and deep-rooted information yet to reveal such widely attended documents.

Although most of the world languages are used in the studies in the field of "Urology", in the last four years, 97.946% of them are in English.[12] Although there are only 7 languages in "Urology and COVID-19" studies, English was limited to 95.297%. Spanish has come forward in this field among studies. This can also be attributed to the researchers' desire to reach out to large audiences and help their colleagues fight the disease by not using minor languages.[13]

Since the beginning of the pandemic, all journals have been more inclined to publish studies on COVID-19.[14] The country's ranking shows a similar ranking in "Urology and COVID-19" publications as in "Urology" publications. While Türkiye was in 12th place in the general ranking, is in 5th place in the ranking of "Urology and COVID-19" publications.

Data showed that Italian institutions constitute half of the top 10 institutions. The dramatic progress of the pandemic in Italy may have contributed to this.[15] As a matter of fact, we only see USA organizations in the first place in studies in the field of "Urology". Unfortunately, Turkish institutions are not as effective as "Urology and COVID-19" publications in the general ranking. Turkish institutions are starting to appear in the list of "Urology and COVID-19" publications in the 3rd tenspot while they are starting to appear in the list of "Urology" publications after the 11th tenspot.

However, our article has some limitations. The main limitations are that there can be publications outside the WOS database and that the publications can be included in more than one cluster at the same time in terms of the country and institution.

Conclusions

The fact that the "Urology" studies were ahead of the "Urology and COVID-19" studies in terms of proportion and order made us think of the following. Urologists, who had to leave their professions in Turkey and all over the world due to the pandemic that started suddenly and spread

rapidly, tried to reveal the unknown aspects of the disease from a urological point of view while fighting the pandemic. By doing so, Turkey has contributed more to the literature than it otherwise would have. This contribution to the disease is obvious, but time will tell how the epidemic is damaging urology

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Acknowledgments

We wish a speedy recovery to everyone suffering from this global epidemic. We would like to thank all healthcare professionals who fought the pandemic both in the research and field stages.

Ethics Committee Permission

Since this study is a bibliometric analysis, ethics committee permission is not required.

Authors' Contributions

Concept/Design: İÜ, MD. Data Collection and/or Processing: İÜ, MD. Data analysis and interpretation: İÜ, EE. Literature Search: İÜ, EE. Drafting manuscript: İÜ, MŞB. Critical revision of manuscript: İÜ, MŞB. Supervisor: İÜ, MD, EE, MŞB.

REFERENCES

1. Stensland KD, Morgan TM, Moinzadeh A, et al. Considerations in the Triage of Urologic Surgeries During the COVID-19 Pandemic. Eur Urol. 2020;77(6):663-666.
2. Statistical Bibliography in Relation to the Growth of Modern Civilization: Two Lectures delivered in the University of Cambridge in May 1922. Nature. 1923;112(2816):585-586.
3. Raisig LM. Statistical bibliography in the health sciences. Bull Med Libr Assoc. 1962;50(3):450-461.
4. Pritchard A. Statistical bibliography or bibliometrics. J. Doc. 1969;25:348-349.
5. https://search.carrot2.org/#/search/pubmed/urology/treemap. Erişim tarihi 31 Ocak, 2023.
6. https://www.webofknowledge.com. Erişim tarihi 30 Ocak, 2023.
7. Farooq RK, Rehman SU, Ashiq M, Siddique N, Ahmad S. Bibliometric analysis of coronavirus disease (COVID-19) literature published in Web of Science 2019-2020. J Family Community Med. 2021;28(1):1-7.
8. Iscaife A, Marchini GS, Srougi V, et al. The urologist's role in the fight of COVID-19 pandemic: mandatory mindset shift on the frontline. Int Braz J Urol. 2020;46(5):879-882.
9. Teoh JY, Ong WLK, Gonzalez-Padilla D, et al. A Global Survey on the Impact of COVID-19 on Urological Services. Eur Urol. 2020;78(2):265-275.
10. Simoni M, Hofmann MC. The COVID-19 pandemics: Shall we expect andrological consequences? A call for contributions to andrology. Andrology. 2020;8(3):528-529.
11. Yang M, Chen S, Huang B, et al. Pathological Findings in the Testes of COVID-19 Patients: Clinical Implications. Eur Urol Focus. 2020;6(5):1124-1129.
12. Di Bitetti MS, Ferreras JA. Publish (in English) or perish: The effect on citation rate of using languages other than English in scientific publications. Ambio. 2017;46(1):121-127.
13. Dal-Re R, Morell F. The COVID-19 Pandemic Changes the Scientific Publication System. Arch Bronconeumol. 2021;57:17-18.
14. Siddiqui S, Ahmed A, Azim A. Selecting Journal for Publication in the Era of "Haste Predatory Journals and COVID-19". Indian J Crit Care Med. 2020;24(12):1284-1285.
15. Rocco B, Sighinolfi MC, Sandri M, et al. The dramatic COVID 19 outbreak in Italy is responsible of a huge drop of urological surgical activity: a multicenter observational study. BJU Int. 2021;127(1):56-63.

ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Decision-making for Postoperative Care in Geriatric Patients Undergoing Minor Surgeries using Mini Mental State Examination, Barthel Index of Activities of Daily Living and CSHA-Clinical Frailty Scale

Minör Cerrahi Geçiren Geriatrik Hastalarda Mini Mental Durum Muayenesi, Barthel Günlük Yaşam Aktiviteleri İndeksi ve CSHA-Klinik Kırılganlık Ölçeği ile Postoperatif Bakım Kararı Verme

Fatma Nur ARSLAN[1] *Filiz ÜZÜMCÜGİL*[2] *Basak AKCA*[2]

ÖZ

Amaç: Yaşlı hastalardaki majör cerrahileri takiben postoperatif sonucun tahmini, bilişsel işlev, işlevsel durum ve kırılganlıkla ilgili verilere dayanan bir karar verme süreci gerektirir. Bu çalışmada söz konusu parametrelerin minör cerrahiler için prediktif değerlerini değerlendirmeyi amaçladık.
Araçlar ve Yöntem: Elektif minör cerrahi planlanan American society of Anesthesiologists (ASA) skoru 1-3'e sahip ≥65 yaş hastalar çalışmaya alındı. Hastaneye yatıştaki kognitif fonksiyonu, fonksiyonel durumu ve kırılganlığı değerlendirmek için Mini Mental Test (MMSE), Barthel İndeksi (BI) ve Clinical Frailty Scale (CSHA-CFS) kullanıldı. Bu parametrelerin ameliyat sonrası yatış durumu ile ilişkileri değerlendirildi.
Bulgular: Doksan dokuz hasta çalışmaya dahil edildi. MMSE puanları, Barthel Indeksleri ve CSHA-CFS puanları tüm gruplarda benzerdi. Yatan hasta sayısı tek başına MMSE <24 (n=49 (%66.2)) veya MMSE<24 ve ASA>2 (n=19 (%82.6)) olan hastalarda daha fazlaydı. Kırılganlık skoru CSHA-CFS≥4 (n=33 (%75)) (p=0.025) veya ASA >2 (n=20 (%83.3)) (p=0.023) olan hastalarda yatan hasta sayısı daha yüksekti. ASA>2 olan hastalarda kırılganlık skorundan bağımsız olarak >1 gün yatış süresi (LOS) (p=0,036) ve yoğun bakım (PACU) kalış olasılığı (p=0.042) daha yüksekti. 30 gün içinde yeniden kabul ile parametreler arasında korelasyon yoktu.
Sonuç: ASA>2 ve MMSE<24 yatarak tedavi durumu ile korelasyon göstermektedir ve minör cerrahilerden sonra yaşlılarda kalış süresinin bir günden fazla olması için bağımsız bir prediktif faktördür. CSHA-CFS ≥4 olması ayrıca bağımsız olarak yatış verilmesi ile ilişkili bulunmuştur.

Anahtar Kelimeler: barthel indeksi; kırılganlık, minor cerrahi girişimler, MMSE; yatış süresi

ABSTRACT

Purpose: Prediction of postoperative outcome following major surgery in elderly patients requires a decision-making process based on data on cognitive function, functional status and frailty. In this study, we aimed to evaluate the predictive value of these parameters for minor surgeries.
Materials and Methods: Patients aged ≥65 years with American society of Anesthesiologists (ASA) score 1-3 scheduled for elective minor surgery were included in the study. Mini Mental Test (MMSE), Barthel Index (BI) and Clinical Frailty Scale (CSHA-CFS) were used to assess cognitive function, functional status and frailty at hospitalization. The associations of these parameters with postoperative hospitalization status were evaluated.
Results: Ninety-nine patients were included in the study. MMSE scores, Barthel Indices and CSHA-CFS scores were similar in all groups. The number of inpatients was higher in patients with MMSE<24 alone (n=49 (66.2%)) or MMSE<24 and ASA>2 (n=19 (82.6%)). The number of inpatients was higher in patients with a frailty score of CSHA-CFS≥4 (n=33 (75%)) (p=0.025) or ASA >2 (n=20 (83.3%)) (p=0.023). Patients with ASA>2 were more likely to have >1 day length of stay (LOS) (p=0.036) and intensive care unit (PACU) stay (p=0.042), independent of the frailty score. Readmission within 30 days was not correlated with the parameters.
Conclusion: ASA>2 and MMSE<24 correlate with inpatient status and are independent predictive factors for length of stay of more than one day in the elderly after minor surgery. CSHA-CFS ≥4 was also independently associated with hospitalization.

Keywords: barthel index; frailty; length of stay; minor surgical procedures; MMSE

Received: 31.07.2023; Accepted: 02.11.2023

[1]Kırşehir Ahi Evran University Faculty of Medicine Anesthesiology and Reanimation Department, Kırşehir, Türkiye.
[2]Hacettepe University Faculty of Medicine Anesthesiology and Reanimation Department, Ankara, Türkiye.

Corresponding Author: Fatma Nur Arslan, Kırşehir Ahi Evran University Faculty of Medicine Anesthesiology and Reanimation Department, Kırşehir, Türkiye.
e-mail: fatma.arlan@ahievran.edu.tr

How to cite: Arslan FN, Üzümcügil F, Akca B. Decision-making for postoperative care in geriatric patients undergoing minor surgeries using mini mental state examination, barthel index of activities of daily living and CSHA-clinical frailty scale. Ahi Evran Med J. 2024;8(1):69-76. DOI: 10.46332/aemj.1335000

INTRODUCTION

As the aging population grows, several pathologies which may benefit from surgery require a decision-making process regarding the postoperative outcome in these elderly patients. The functional status pertaining to activities of daily living (ADL) and cognitive functions have gained interest in the last decades, as aging or the presence of comorbidities alone were not found sufficient to predict postoperative outcome.[1-4] In addition to the individual assessments of functional status and cognitive functions, the concept of frailty has provided beneficial for the decision-making process of elderly patients scheduled for surgery.[1,2,5]

Cognitive disorders have been shown to be an important factor to predict the outcome of hospitalized older patients, especially with comorbidities.[3,6,7] The Mini Mental State Evaluation (MMSE) is a cognitive function test which has been recommended to be used for the preoperative evaluation of elderly patients to determine the level of cognitive disorder, as the presence of dementia and cognitive impairment was reported to be related with length of stay and 30-day unscheduled readmissions in these patients.[3] The MMSE scores in elderly patients were also reported to be correlated with the functional status, which also declines with aging.[3,4] The ADL assessment using Barthel Index (BI) has been suggested to be a reliable scoring system to evaluate the functional status, as the patients with higher BI scores were found to more evidently survive their postoperative ICU stay after major abdominal surgeries.[4] Aside from these two parameters individually assessing the cognitive function and functional status, frailty, which defines the vulnerability of an individual to have more tendency to develop mortality or dependency after exposing to a physical or phycological stress, has been recommended to be used for predicting clinical outcome of elderly patients.[2,5] Clinical Frailty Scale (CFS) developed by Canadian Study of Health and Aging (CSHA) was recommended to guide patient care through decision-making process determining which intervention will be either more likely to be beneficial or harmful for the individual, as it has been reported to be a significant predictor for several clinical outcomes including mortality, disability, length of stay in hospital, readmission, and functional and cognitive decline.[8-14] Current data support the impact of these scales for decision-making after major surgeries, however, there is limited data pertaining to its impact on minor surgeries.[10-12]

As minor surgeries are expected to result in lower complication rates related to the procedure itself in the postoperative period; the cognitive functions, functional status, and frailty assessment may provide more beneficial for decision-making in terms of postoperative care compared to major surgeries. In our study, we aimed to find out the impact of frailty parameters on the outcomes to lead decision-making regarding postoperative care in geriatric patients undergoing minor surgeries. For this purpose, the cognitive functions, the functional status and the frailty were evaluated using, MMSE, Barthel Index and CSHA-CFS, respectively in geriatric patients undergoing minor surgeries.

MATERIALS and METHODS

This study was designed as prospective clinical trial. The ethical guidelines outlined in the 1964 Declaration of Helsinki and its later revisions have been followed in the conduct of this investigation. After obtaining Hacettepe University Non-Interventional Clinical Research Ethics Committee approval (GO-18/1123, 2019/01-08), the patients ≥ 65 years of age with ASA score 1-3, who were scheduled to undergo elective minor surgeries (eye surgery, urological surgery, general surgery) under general anaesthesia between 10th January-10th June 2019 were enrolled.

All patients were informed, and consent was obtained from each to perform three separate preoperative assessments for cognitive function, functional capacity and frailty. The cognitive functions were assessed using Mini Mental State Evaluation (MMSE) (Score: 0-30).[15] A cut-off score of 24 was used, as it has been suggested to differentiate MMSE≥24, normal cognition; from MMSE<24, cognitive impairment to some degree.[16] The functional status was assessed using Barthel Index (BI) of Activities of Daily Living (ADL) to determine the disability and functional dependency of the patients revealing scores of < 20, 20-39, 40-59, 60-79 and 80-100 interpreted as total dependence, very dependent, partially dependent, minimally dependent

and live independently, respectively.[17] The frailty was assessed using Canadian Study of Health and Aging-Clinical Frailty Scale (CSHA-CFS) in order to determine the severity of frailty with 7-point scale. CSHA-CFS≥4 (frail to some degree) has been suggested as the cut-off score strictly correlated with postoperative outcome, determining 'apparently vulnerable' (CFS 4), 'mildly frail' (CFS 5), 'moderately frail' (CFS 6) and 'severely frail' (CFS 7) patients, discriminating the 'very fit' (CFS 1), 'well' (CFS 2) and 'well with treated comorbid disease' (CFS 3) patients (Table 1).[1,2] Data regarding comorbidity and demographics, as well as, the parameters such as unanticipated weight loss, falling accidents, depression and drug use was obtained. Albumin and haematocrit levels were obtained from records, which were within at least 1 month prior to surgery.

In our hospital, the status of the patients in terms of postoperative care as either outpatient or inpatient following elective minor surgery was decided by a multidisciplinary team including the geriatrist, anaesthesiologist and surgeon prior to surgery considering age, co-morbidities and anticipated postoperative complications. The length of stay (LOS) in inpatient status was at the initiative of the same multidisciplinary team, as well. In this study, the primary outcome was the relationship between the cognitive functions, functional capacity and frailty with the decision-making regarding the postoperative status of the patient as being either outpatient or inpatient and also for need of Post Anaesthesia Care Unit (PACU), as well as, the length of stay and readmission within 30-days after surgery. Age, ASA scores, unanticipated weight loss, falling accidents, depression, albumin and haematocrit levels, polypharmacy were evaluated as secondary outcome parameters in terms of their impact on the decision-making regarding the postoperative status of the patient as being either outpatient or inpatient and also for need of Post Anaesthesia Care Unit (PACU), as well as, the length of stay and readmission within 30-days after surgery.

The LOS was defined by < 1 day if the patient was admitted to hospital for an overnight stay postoperatively. PACU stay was included in the inpatient group for the correlation analysis, hence, the inpatient group represented all patients other than outpatients, unless otherwise stated.

Statistical Analysis

The data was analysed by IBM SPSS statistics 17.0 (IBM Corporation, Armonk, NY, USA). The distribution of continuous numerical variables was examined by using Kolmogorov-Smirnov test, while the assumption of homogeneity of variances were investigated by Levene's test. Descriptive statistics were shown by mean ± SD or median (1^{st} quartile-3^{rd} quartile) for continuous numeric variables and by number cases and % for categorical variables.

The significance of the differences between groups in term of continuous numeric variables was evaluated using Student's t test, whereas, the significance of the differences between independent groups more than two was evaluated using One-Way ANOVA where the assumptions for parametric test were met. The significance of the differences between groups in term of continuous numeric variables was evaluated using Mann Whitney U test when the number of groups was two, whereas, the significance of the differences between independent groups of more than two was evaluated using Kruskal Wallis test where the assumptions for parametric test were not met.

The categorical data was evaluated using Fisher's exact probability test or Continuity Chi-Square test according to the expected frequency in 2 x 2 crosstabs was below 5 in least ¼ of the cells or between 5-25, respectively. Otherwise, Pearson's Chi-square test was used.

The combined effect of the parameters that may contribute to the status of the patient either as outpatient or inpatient, the length of hospital stays either < 1 day or >1 day, estimation of PACU stay and unscheduled readmission within 30-days was evaluated using multivariate logistic regression analysis. The variables revealing $p<0.25$ as a result of univariate statistical analysis were included in the regression models as candidate factors. Haematocrit levels and diagnosed depression were included in the regression model for unscheduled readmission within 30-days, in which neither of these parameters were found predictive. The only factor that can be predictive for the LOS and estimation of PACU stay was ASA, hence, multiple regression analysis was not performed. The odds ratio, 95% con-

fidence interval and Wald statistics were calculated pertaining to each variable. p<0.05 was accepted statistically significant.

RESULTS

Ninety-nine patients ≥ 65 years of age were included. The demographics and the data regarding outpatient and inpatient, as well as, the patients with postoperative PACU stay were presented in Table 1. The primary and secondary parameters related to postoperative outcomes were presented in Table 2.

Table 1. The demographics and the data regarding outpatient and inpatient status, as well as, the PACU stay postoperatively.

Variables	N=99
Age (years)	72.1 ± 5.9
Gender	
Female	59 (59.6%)
Male	40 (40.4%)
Weight (kg)	76.7 ± 15.8
BMI	27.4 (24.9-31.2)
BMI Groups (n)	
<25 kg/m2	25 (25.3%)
25.0-29.99 kg/m2	39 (39.4%)
30.0-40.0 kg/m2	30 (30.3%)
>40 kg/m2	5 (5.1%)
Outpatient group (n (%))	38 (38.4%)
Inpatient group (Including PACU stay) (n (%))	61 (61.6%)
PACU stay (n (%))	5 (5.1%)
Length of hospital stay (day)	1 (0-2)
<1 day (n (%))	25 (25.2 %)
>1 day (including PACU) (n (%))	36 (36.3%)

BMI: Body Mass Index, PACU: Post Anesthesia Care Unit (Intensive Care)

The MMSE scores, BIs and CSHA-CFS scores were similar in patients who were decided either to be at outpatient or inpatient status after minor surgery. Considering the cut-off value of 24 for MMSE, among the patients with MMSE < 24 (n=74), 23 (31%) had ASA > 2 and 82.6% (n=19) of these were inpatients (Table 3). Considering the cut-off value for CFS of ≥ 4, the number of patients revealing a score of ≥ 4 interpreted as 'frail to some degree' was higher in inpatient group (p=0.025). The number of patients who stayed > 1 day were higher among patients with CFS≥4, despite statistical insignificance (Table 3).

Table 2. The primary and secondary parameters of the study evaluated for their impact on postoperative outcome.

Parameters	
Albumin (g/dl)	4.1 (3.9-4.3)*
Haematocrit (%)	39.5* ± 4.8
	Patients (n)
Weight loss	9 (9.1%)
Falling accidents (number of events)	
0	89 (89.9%)
1	6 (6.1%)
>1	4 (4.0%)
Depression	
None	82 (82.8%)
Without diagnosis	13 (13.1%)
With diagnosis	4 (4.0%)
Polypharmacy (≥5 drugs)	18 (18.2%)
ASA physical status	
1	10 (10.1%)
2	65 (65.6%)
3	24 (24.3%)
Scores (min-max)	
MMSE Score	21.0 (16.0-24.0)*
MMSE	Patients (n)
<24	78 (79%)
≥24	21 (21%)
Barthel Score of ADL	100.0 (95.0-100.0)
CSHA-CFS	3.0 (3.0-5.0)
CSHA-CFS	Patients (n)
<4	55 (55.6%)
≥4	44 (44.4%)

*Mean (min-max), ASA: American Society of Anesthesiologists, MMSE: Mini Mental Scor-ing Examination, ADL: Activities of Daily Living, CHSA-CSF: Canadian Study of Health and Aging (CSHA) - Clinical Frailty Scale (CFS)

The secondary parameters including age, gender, BMI, albumin and haematocrit levels, weight loss, the history of falling accidents, depression and polypharmacy were similar in all patients pertaining to outpatient and inpatient status, as well as, in patients with the LOS either < 1 or > 1 day (Table 3).

The evaluation of the combined effect of ASA and CSHA-CFS revealed that patients with ASA score of > 2 had 4.9 times (95% CI: 1.108-21.614) more probability of LOS < 1 day and 3.7 times (95% CI: 1.066-13.126) more probability of LOS > 1 day irrespective of CFS (p=0.036).

PACU stay was not found to be related with any of the primary and secondary parameters. However, the parameters which revealed p<0.25 were included in regression model as a result of univariate analysis. The most predictive parameter of PACU stay was ASA score > 2. The patients with ASA score > 2 had 13.9 times (95% CI: 1.095-176.132) more probability to need PACU stay after minor surgery compared to patients with ASA score 1 - 2 irrespective of other parameters (p=0.042).

The readmission within 30-days (n=13 (13.1%)) were mostly related to surgical complications (n=8 (8.1%)), while the other related causes were cardiac (n=3 (3.0%)), respiratory (n=1 (1.0%)) and renal (n=1 (1.0%)) without any need for further intervention and none of the primary or secondary parameters were found to be related with these causes (p>0.05).

Table 3. The relationships between the primary and secondary parameters with postoperative outcomes regarding outpatient and inpatient status of the patients after minor surgery, as well as, the length of stay.

Parameters	**Outpatient (n=38)**	**Inpatient (n=61)**		**p**
		<1 day (n=25)	**>1 day (n=36) (Including PACU stay)**	
Albumin (g/dL) (min-max)	4.2 (3.9-4.3)	4.1 (3.8-4.2)	4.1 (3.8-4.2)	0.298†
Haematocrit (%) (mean±SD)	40.2 ± 5.2	39.5 ± 4.8	38.8 ± 4.4	0.447¥
Weight loss (n)	2 (5.3%)	3 (12.0%)	4 (11.1%)	0.553¶
Falling accidents (n)	3 (7.9%)	3 (12.0%)	4 (11.1%)	0.839¶
Depression (n)	1 (2.6%)	2 (8%)	1 (2.8%)	0.554¶
Polypharmacy (≥5)	5 (13.2%)	4 (16.0%)	9 (25%)	0.397‡
ASA>2	4 (10.5%) a, b, c		20 (32.8%) c	0.023#
		9 (36.0%) a	11 (30.6%) b	0.038‡
Scores (min-max)				
MMSE Score	21.0 (16.0-26.0)	20.0 (15.0-24.0)	20.0 (16.0-22.0)	0.434†
MMSE				0.167†
<24 (n=74)	25 (33.8%)		49 (66.2%)	0.082†
Barthel Score of ADL	100.0 (98.7-100.0)	100.0 (95.0-100.0)	100.0 (95.0-100.0)	0.847†
ASA ≤2 (n=51)	21 (41.2%)		30 (58.8%)	
		9 (29%)	21 (71%)	
ASA >2 (n=23)	4 (17.4%)		19 (82.6%)	
		9 (47.4%)	10 (52.6%)	
≥24 (n=25)	13 (52%)		12 (48%)	0.480‡
ASA ≤2 (n=24)	13 (54.2%)		11 (45.8%)	
		6 (60%)	4 (40%)	
ASA >2 (n=1)	0		1	
		0 (0%)	1 (100%)	
CSHA-CFS	3.0 (3.0-4.3)	4.0 (3.0-5.0)	4.0 (3.0-5.0)	0.343†
CSHA-CFS				
<4 (n)	27 (49%)		28 (51%)	
		12 (42.9%)	16 (57.1%)	0.990#
≥4 (n)	11 (25%)		33 (75%)	0.025#
		13 (39.4%)	20 (60.6%)	0.990#

Likelihood ratio, † Kruskal Wallis test, ¥One-Way Anova, ‡Pearson's chi-square test #Continu-ity correction chi-square. ASA: American Society of Anesthesiol-ogists, MMSE: Mini Mental Scoring Examination, ADL: Activities of Daily Living, CHSA-CSF: Canadian Study of Health and Aging (CSHA) - Clinical Frailty Scale (CFS)

DISCUSSION

In our study, the patients admitted to hospital at inpatient status for a LOS > 1 day postoperatively after elective minor surgeries were found to have CSHA-CFS of ≥ 4. Thus, frailty defined by CSHA-CFS revealed that it may provide useful data in decision-making regarding postoperative care in geriatric patients undergoing minor surgeries.

The cognitive disorders have been reported to predict worse outcomes in hospitalized older patients.[18,19] In a recent retrospective study by Chao et al., the hospitalized older patients were classified according the MMSE scores, and in the presence of dementia and cognitive impairment. In this study, the number and severity of comorbidities were found to be predictors of LOS and unscheduled readmission within 30-days in hospitalized older patients, whereas, the number of comorbidities was also found to predict the LOS in patients with normal cognitive function

in terms of MMSE.[3] In our study, the MMSE revealed similar scores in all patients. However, we observed that the patients with MMSE<24 were higher in inpatient group, and additionally, the patients with MMSE<24 who had an ASA physical status of > 2 were higher in inpatient group, supporting the study by Chao et al. Moreover, in our study the comorbidities revealing an ASA physical status > 2 was also an independent predictor of inpatient status after minor surgery in elderly patients.

The Activities of Daily Living (ADL), which is widely assessed using Barthel Index (BI) has been reported to reliably reflect the functional status and ability to live independently in older patients.[4] In a study by Kang et al. BI < 30 was reported to constitute a cut-off value to predict ICU-survival in patients ≥ 65 years of age, who underwent elective major abdominal surgery. In our study, the BIs revealed scores > 95 interpreted as live independently, thus it was not expected to cause difference in terms of either outpatient or inpatient status, as well as, the LOS and readmission within 30 days. However, we did not evaluate the BI at discharge, thus, we cannot deduce any relationship pertaining to the change in BI during hospitalization.

In a study by Makary et al. addressing both major and minor surgeries, frailty was found as an independent factor for predicting prolonged hospital stay, while its predictive value increased when combined with ASA assessment.[20] In our study, we used CSHA-CFS for frailty assessment and the threshold for frailty was CSHA-CFS ≥ 4, which has been suggested for being the cut-off value significantly correlated with postoperative outcome.[2,21]

In a study by Cheung et al. the CHSA-CFS revealed a 62% of frailty to some degree (CSHA-CFS ≥ 4) in patients ≥ 65 years admitted to a trauma centre, however, the authors classified the frailty as non-frail, pre-frail and frail, thus frailty incidence revealed 14.2% with patients having CHSA-CFS of 6-7.[22] The incidence of frailty (frailty to some degree according to CSHA-CFS stratification) was found to be 44.4% (n=44) in our patient group similar to 38% in the study by Artiles-Armas et al. and 62% in the study by Cheung et al., all of which constituted higher incidences than the other studies.[2,22-24] In our hospital we performed CSHA-CFS easily and found the stratification according to a threshold of ≥ 4 feasible.

It cannot be denied that major surgeries may have more deleterious effects regarding postoperative care in geriatric patient group.[13,20,25] However, minor surgeries may be expected to result in lower surgery-related postoperative complications; therefore, frailty might become a more leading parameter to decide for postoperative care compared to major surgeries. In our study, frailty was found to be an independent predictor for hospital stay and length of hospital stay after minor surgery. In our study, comorbidity, cognition, fall, haematocrit and albumin levels were not found to be related with these outcomes, individually or in combination. On the other hand, the ASA scores were found to be a factor leading to an impact on LOS in our study. The inpatient numbers were higher in patients with ASA > 2 compared to outpatients. The hospitalization either for < 1 day or > 1 day was higher in patients with ASA > 2 with probability of 4.9 times and 3.7 times compared to patients with ASA 1-2, respectively. However, there was no unanticipated hospitalization in our study, hence ASA scores can be considered safe to use as a predicting factor for hospitalization and LOS.

In our study, geriatricians, surgeons and anaesthetists decided together for patients who were admitted to PACU for postoperative care considering age, co-morbidities and anticipated complications. However, none of the parameters regarding frailty assessment including the CSHA-CFS score was found to be related with postoperative PACU stay.

Readmission to hospital within 30 days after surgery was reported to be mostly related to postoperative complications.[26] In our study, the incidence of readmission to hospital within 30 days was 14.1% and the incidence of postoperative complications regarding surgical intervention leading to readmission was 8.1%, without any correlation with any parameters regarding frailty assessment. Postoperative complications are known to be the most important cause of readmission[27] and their correlation with frailty has been reported to be significant,[28] nevertheless this correlation was not found in our study most probably due to the small patient group or the targeted surgical type which included only minor surgeries. However, similar to our study, frailty index was not found to be correlated with postoperative complications and readmission within 30-

days irrespective of the type of surgery, which was suggested to be related with the coordination between the geriatricians and surgical team on decision-making regarding the perioperative care.[29] In our hospital a similar coordination has been handled for these patients, which might constitute a beneficial approach leading to our results, as well.

The limitations of our study include, firstly, the inclusion of mostly eye surgeries and urological minor surgeries. Conducting the study with a wider surgical diversity may eliminate possible differences that may arise from differences between surgical branches. There were five patients admitted to the postoperative intensive care unit throughout the study. Although there is no statistically significant correlation between frailty parameters and intensive care admission, we believe that this finding should be reconsidered with other studies conducted only with intensive care patients, including a larger number of patients, and using other frailty scales.

As conclusion, in our study, the ASA score > 2, MMSE < 24 and the frailty score defined by CSHA-CFS ≥ 4 was found to be correlated with the decision on the postoperative care of geriatric patients after minor surgeries in favour of inpatient status. These preoperative assessments as well as the routine assessments regarding comorbidities may prove beneficial for decision-making regarding postoperative care in geriatric patients undergoing minor surgeries.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

The study was approved by Hacettepe University Non-Interventional Clinical Research Ethics Committee (2019/01-08 date and GO-18/1123 number).

Authors' Contributions

Concept/Design: FNA, FÜ. Data Collection and/or Processing: FNA, FÜ. Data analysis and interpretation: FNA, FÜ, BA. Literature Search: FNA, FÜ. Drafting manuscript: FNA, FÜ, BA. Critical revision of manuscript: FÜ, BA. Supervisor: FÜ, BA.

REFERENCES

1. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489-495.
2. Artiles-Armas M, Roque-Castellano C, Conde-Martel A, et al. The comprehensive complication index is related to frailty in elderly surgical patients. J. Surg. Res. 2019;244:218-224.
3. Chao YT, Kuo FH, Lee YS, et al. Characteristics and Outcome Determinants of Hospitalized Older Patients with Cognitive Dysfunction. Int J Environ Res Public Health. 2022;19(1):584.
4. Kang Y, Zhang G-C, Zhu J-Q, et al. Activities of daily living associated with postoperative intensive care unit survival in elderly patients following elective major abdominal surgery: An observational cohort study. Medicine. 2021;100(22):e26056.
5. Church S, Rogers E, Rockwood K, et al. Scoping review of the Clinical Frailty Scale. BMC geriatrics. 2020;20(1):1-18.
6. Mukadam N, Sampson EL. A systematic review of the prevalence, associations and outcomes of dementia in older general hospital inpatients. Int. Psychogeriatr. 2011;23(3):344-355.
7. Zekry D, Herrmann FR, Grandjean R, et al. Demented versus non-demented very old inpatients: the same comorbidities but poorer functional and nutritional status. Age Ageing. 2008;37(1):83-89.
8. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-M156.
9. Fried LP, Ferrucci L, Darer J, et al. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J. Gerontol. A Biol. Sci. Med. Sci. 2004;59(3):M255-M263.
10. Shah R, Borrebach JD, Hodges JC, et al. Validation of the Risk Analysis Index for evaluating frailty in ambulatory patients. J Am Geriatr Soc. 2020;68(8):1818-1824.
11. Varley PR, Borrebach JD, Arya S, et al. Clinical utility of the risk analysis index as a prospective frailty screening tool within a multi-practice, multi-hospital integrated healthcare system. Ann. Surg. 2021;274(6): e1230-e1237.
12. Shinall MC, Arya S, Youk A, et al. Association of preoperative patient frailty and operative stress with postoperative mortality. JAMA surgery. 2020;155(1): e194620-e194620.
13. Andreou A, Lasithiotakis K, Venianaki M, et al. A comparison of two preoperative frailty models in predicting postoperative outcomes in geriatric general surgical patients. World J. Surg. 2018;42:3897-3902.
14. Lee SY, Lee S-H, Tan JH, et al. Factors associated with prolonged length of stay for elective hepatobiliary and neurosurgery patients: a retrospective medical record review. BMC Health Serv. Res. 2018;18(1):1-9.
15. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-198.
16. Güngen C, Ertan T, Eker E, et al. [Reliability and validity of the standardized Mini Mental State Examination in the diagnosis of mild dementia in Turkish population]. Turk Psikiyatri Derg. 2002;13(4):273-281.
17. Collin C, Wade D, Davies S, et al. The Barthel ADL Index: a reliability study. Int. Disabil. Stud. 1988;10 (2):61-63.

18. Formiga F, Fort I, Robles MJ, et al. Comorbidity and clinical features in elderly patients with dementia: differences according to dementia severity. J Nutr Health Aging. 2009;13(5):423-427.
19. Duthie A, Chew D, Soiza R. Non-psychiatric comorbidity associated with Alzheimer's disease. QJM. 2011;104(11):913-920.
20. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. J. Am. Coll. Surg. 2010;210(6):901-908.
21. Okabe H, Ohsaki T, Ogawa K, et al. Frailty predicts severe postoperative complications after elective colorectal surgery. Am J Surg. 2019;217(4):677-681.
22. Cheung A, Haas B, Ringer TJ, et al. Canadian study of health and aging clinical frailty scale: does it predict adverse outcomes among geriatric trauma patients? J. Am. Coll. Surg. 2017;225(5):658-665.
23. Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. J Am Geriatr Soc. 2006;54(6):991-1001.
24. Birkelbach O, Mörgeli R, Spies C, et al. Routine frailty assessment predicts postoperative complications in elderly patients across surgical disciplines–a retrospective observational study. BMC Anesthesiol. 2019;19(1):1-10.
25. Robinson TN, Wu DS, Pointer L, et al. Simple frailty score predicts postoperative complications across surgical specialties. Am. J. Surg. 2013;206(4):544-550.
26. Merkow RP, Ju MH, Chung JW, et al. Underlying reasons associated with hospital readmission following surgery in the United States. Jama. 2015;313(5):483-495.
27. Glance LG, Kellermann AL, Osler TM, et al. Hospital readmission after noncardiac surgery: the role of major complications. JAMA Surg. 2014;149(5):439-445.
28. Lin HS, Watts JN, Peel NM, et al. Frailty and postoperative outcomes in older surgical patients: a systematic review. BMC Geriatr. 2016;16(1):157.
29. Shahrokni A, Tin A, Alexander K, et al. Development and evaluation of a new frailty index for older surgical patients with cancer. JAMA Network Open. 2019;2 (5):e193545-e193545.

ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

The Effect of Intermittent Fasting Diet and Light-Intensity Physical Activity on Serum Irisin Levels in Elderly Individuals

Aralıklı Açlık ve Hafif Yoğunluklu Fiziksel Aktivitenin Yaşlı Bireylerde Serum İrisin Düzeylerine Etkisi

Hüsniye BİLGE SERTDEMİR[1] Safiye Beyza DURSUN[1] Shaafah NAMULODI[1]

Mehmet Salih KAYA[1] Fahri BAYIROĞLU[1]

ÖZ

Amaç: Bu çalışmanın amacı, yaşlı bireylerde egzersiz ve aralıklı açlık diyetinin bazı antropometrik ölçümler ve dolaşımdaki irisin konsantrasyonu üzerindeki etkilerini değerlendirmek ve irisin ile vücut yağ yüzdesi arasındaki ilişkiyi araştırmaktı.
Araçlar ve Yöntem: Yaş ortalaması 69±9 olan 44 yaşlı gönüllü (21 erkek ve 23 kadın) rastgele 4 gruba ayrıldı; Kontrol (n=8), Bocce grubu (n=12), Aralıklı açlık grubu (n=12), Bocce ve Aralıklı açlık grubu (n=12). Kontrol grubundakiler günlük rutinlerine devam etti. Bocce grubundakiler haftanın 5 günü 2 saat boyunca Bocce Oyunu oynadı. Aralıklı açlık grubundakilere ardışık olmayan haftanın iki günü 16 saatlik besin kısıtlaması programı uygulandı. Bocce ve Aralıklı açlık grubundakilere Bocce Oyununa ilaveten besin kısıtlaması programı uygulandı. Uygulamalara 12 hafta devam edildi.
Bulgular: Uygulama öncesi ve sonrası aynı gruplar karşılaştırıldığında serum irisin değerleri arasında anlamlı bir fark bulunmadı ($p>0.05$). Vücut yağ yüzdesi, kontrol grubundaki artış dışında diğer tüm gruplarda anlamlı olarak azaldı ($p<0.05$). Vücut ağırlığı Bo ve IF gruplarında önemli ölçüde azaldı ($p<0.05$). Uygulama sonrası gruplar kontrol grubu ile karşılaştırıldığında, IF grubunun vücut yağ yüzdesinde anlamlı azalma ($p<0.05$) görülmesine rağmen, irisin seviyelerinde gözlenen benzer anlamlı farklılık muhtemelen deneysel uygulamanın sonucu olmayıp, gruplar arasındaki yaş yönünden gelişen kaçınılmaz heterojen dağılımdan kaynaklanmaktaydı. Vücut yağ yüzdesi ve vücut ağırlığı değişimi ile dolaşımdaki irisin seviyeleri arasında korelasyon bulunmadı (sırasıyla $r=0.116$, $p=0.437$; $r=-0.145$, $p=0.649$).
Sonuç: Aralıklı açlık ve Bocce müdahalesi yaşlı bireylerde vücut yağ yüzdesi ve ağırlığında azalmaya sebep olurken, serum irisin değerlerinde anlamlı bir değişikliğe yol açmadı. Bu durum, yaşlı bireylerde irisine verilen cevap süresinin daha yavaş olmasından ve/veya egzersizin süre ve yoğunluğundan kaynaklanıyor olabilir.

Anahtar Kelimeler: aralıklı açlık; bocce oyunu; irisin; yaşlı

ABSTRACT

Purpose: The aim of this study was to evaluate the effects of exercise and intermittent fasting diet on some anthropometric measurements and circulating irisin concentration and to investigate the relationship between irisin and body fat percentage in elderly subjects.
Materials and Methods: Forty-four elderly volunteers (21 men and 23 women) with a mean age of 69±9 years were randomly divided into 4 groups; Control (n=8), Bocce group (n=12), Intermittent fasting group (n=12), Bocce and Intermittent fasting group (n=12). Those in the control group continued with their normal activities. The Bocce group played Bocce for two hours five days a week. Those in the intermittent fasting group followed a 16-hour food restriction schedule on two non-consecutive days of the week. In addition to the Bocce Game, participants in the Intermittent Fasting and Bocce groups were given a food restriction regimen. The interventions were sustained for 12 weeks.
Results: There was no significant difference in serum irisin levels between the same groups before and after treatment ($p>0.05$). Body fat percentage decreased significantly in all groups except the increase in the control group ($p<0.05$). Body weight decreased significantly in Bo and IF groups ($p<0.05$). Although there was a significant decrease ($p<0.05$) in body fat percentage in the IF group compared to the control group, the similar significant difference observed in irisin levels was probably not the result of the experimental treatment, but was probably due to the inevitable heterogeneous distribution in terms of age between the groups. There was no correlation between body fat percentage and body weight change and circulating irisin levels ($r=0.116$, $p=0.437$; $r=-0.145$, $p=0.649$, respectively).
Conclusion: Intermittent fasting and Bocce intervention resulted in a decrease in body fat percentage and weight in elderly subjects, but not in serum irisin levels. This may be due to the slower response time to irisin in elderly individuals and/or the duration and intensity of exercise.

Keywords: aged; bocce game; irisin; intermittent fasting

Received: 25.07.2023; Accepted: 23.11.2023

[1]Ankara Yıldırım Beyazıt Universitesi, Ankara, Türkiye.
Corresponding Author: Hüsniye Bilge Sertdemir, Ankara Yıldırım Beyazıt Üniversitesi, Ankara, Türkiye. e-mail: hbilge@ybu.edu.tr

How to cite: Bilge Sertdemir H, Dursun SB, Namulodi S, Kaya MS, Bayıroğlu F. The effect of intermittent fasting diet and light-intensity physical activity on serum irisin levels elderly individuals. Ahi Evran Med J. 2024;8(1):77-84. DOI: 10.46332/aemj.1331280

INTRODUCTION

In the 20th century, there has been an unprecedented increase in the average human lifespan in many countries of the world. In Türkiye, the proportion of the elderly population is increasing every year. With the increase in the elderly population, the incidence of chronic and metabolic diseases has also increased.[1] Aging is associated with several biological changes that result in a progressive decline in cognitive and physical function and consequent loss of independence and an increased risk of death. These changes are accelerated by a lifestyle characterized by low levels of physical activity, and/or excessive caloric intake and excess body weight. Therefore, lifestyle changes such as physical activity and dietary modifications that improve body composition (reducing body fat and/or increasing muscle mass) can slow the development of age-related diseases and mitigate the loss of cognitive and physical function.[2]

Inactivity can lead to many chronic diseases hence accelerating the secondary aging process and leading to premature death.[3] Regular exercise protects against the development of aging-related pathologies by increasing insulin sensitivity.[2] Therefore, physical activity and exercise are protective factors for non-communicable chronic diseases such as cardiovascular diseases, stroke, metabolic diseases such as diabetes, cancer, lung diseases, immune disorders, musculoskeletal system diseases, etc.[3]

Adipose tissue is a dynamic tissue that plays an important physiological role in maintaining health and homeostasis. White adipose tissue and brown adipose tissue are considered key endocrine organs; however, they differ functionally and morphologically. The browning of white adipose tissue produces beige adipocytes. Physical exercise leads to adipose tissue browning by increasing the levels of specific molecules such as beta- aminoisobutyric acid, irisin, and fibroblast growth factor 21 (FGF21). The central roles played by hormones in the process of browning adipose tissue highlight the importance of individual lifestyle, including circadian rhythm and diet. In contrast to the pro-inflammatory and adipose tissue-impairing effects of the Western diet, certain foodstuffs, including capsaicin and n-3 polyunsaturated fatty acids, dietary interventions such as calorie restriction and intermittent fasting promote browning and metabolic activity of white adipose tissue.[4]

Intermittent fasting is a non-pharmacological dietary intervention that slows aging. Intermittent fasting is reported to increase insulin sensitivity and reduce inflammation-related diseases and oxidative stress in the cell.[5] Today, one of the most popular types of intermittent fasting diets is the 16:8 time-restricted eating model in two days, which involves total or partial restriction of food intake during the 16 hours of the day while allowing food intake in the remaining 8 hours for two non-consecutive days of the week. This model, which does not include calorie restriction, has the potential to prevent metabolic diseases.[6]

Irisin is a peptide myokine consisting of 112 amino acids. The transmembrane protein is produced from Fibronectin type III domain 5 (FNDC5) protein.[7] Irisin is secreted mainly in skeletal muscle, especially from the nuclear parts of the perimysium and endomysium.[8] Irisin was initially identified by its ability to brown white adipose tissue.[7] It has also been shown that irisin has many other positive effects on metabolism such as increased mitochondrial biogenesis, reduction of bone loss and stimulation of bone formation, reduction of inflammation, and improved glucose tolerance.[9,10]

It is reported that circulating irisin levels in older people gradually decrease as muscle tissue mass decreases each year after the age of 50.[11] As a result, keeping irisin levels stable in the elderly is critical for controlling aging-related diseases.

It is reported that exercise has different effects on irisin levels, depending on the type and intensity of exercise.[12-14] Nutrition is another factor that influences the secretion of irisin. Unfortunately, the impact of intermittent fasting on the amounts of circulating irisin has not been definitively proven. There has been a multitude of contradictory outcomes concerning these relationships. For example, while it was reported that applying the 16:8 model, which is one of the time-restricted diets, for 12 weeks caused fluctuations in serum irisin levels,[15] another study reported that Ramadan fasting reduced irisin values.[16]

The objective of this study was to assess the impact of Bocce and intermittent fasting for two days per week on the serum irisin levels and anthropometric measurements of sedantery elderly individuals. In addition, correlations between serum irisin levels and whole-body fat composition, waist circumference measurements, and waist-hip ratio in the elderly were evaluated.

MATERIALS and METHODS

The study included 44 people, 21 men and 23 women, whose mean age was 69±9, who did not have a disease that prevented their inclusion and had voluntarily agreed to participate in the study. Based on the power analysis, it is recommended that each application group consist of twelve individuals. As a result, volunteers were divided into four groups at random. The participants in the control group proceeded with their regular daily activities (n=8). The Bocce group (Bo) where volunteers played a game of-Bocce for one hour 2 times a day, 5 days a week (n=12). The Intermittent fasting group (IF) implemented a two-day food restriction practice (16 hours on Mondays and Thursdays from 18:00 in the evening to 10:00 the next day) (n=12). The Bocce and Intermittent Fasting group (BoIF) combined the Bocce game with a food restriction program, without implementing any water restriction. The applications lasted for 12 weeks. Approval for this studywas received from AYBÜ Yeni Mahalle Training andResearch Hospital Clinical Research Ethics Committee (dated 17.02.2020 and numbered 2021-02/05).

Bocce

A special Bocce module developed for the elderly was used in the study.

The field dimensions for the elderly are arranged as 3m-2m-4.25m-4.25m-2m-3m and the ground is an artificial surface. Each team in this competitive game consists of five players, with two of them serving as substitutes. Each of the three athletes participating in the game has two balls. The balls are 7-8 cm in diameter and weigh 650gr -800gr. The target ball (pallino) made of wood is 2.5 cm and the athletes try to bring the shots close to the target ball.

Measurement of Serum Irisin Levels

In both pre- and post-application, a total of 5 ml of venous blood samples were collected from the participants, and subsequently, their serums were separated.The concentrations of serum irisin were measured using assay (ELISA) kits (Bioassay Technology Laboratory) following the instructions provided by the manufacturer.Optical density measurements of the samples were read by the standard microplate reader at a 450 nm (Heales MB580 brand ELISA reader).

Body Analysis

The body weights and body fat percentages of the subjects were measured using a body analyzer both before and after the applications (Tanita BC 730).

Statistical Analysis

Results were expressed as mean ± standard deviation. SPSS (version 22.0, IBM Corp., Armonk, NY, USA) package program was used for statistical analysis of the data. Accordingly, the One Way Anova-Tukey test was used to compare the groups, and the Paired Sample T-test was used to measure the within-group variation over time. Spearman Correlation Test was used for correlation analysis.

RESULTS

Comparison of the post-application groups with the pre-application groups showed no statistically significant difference in terms of serum irisin levels ($p>0.05$, Table 1). Comparison of the serum irisin values of the post-treatment groups with the control group showed a statistically significant increase in the IF group ($p=0.014$, Table 1). No statistically significant difference in serum irisin values was found between gender groups ($p=0.212$).

It was determined that the body fat percentage decreased statistically in the Bo, IF, and BoIF groups in the post-application measurements compared to the pre-application measurements, while it increased significantly in the control group ($p=0.013$, $p=0.001$, $p=0.024$, $p=0.007$, Table 1), respectively. In addition, the body fat percentage of the

post-treatment groups was found to be statistically significantly lower in the IF group when compared to the control group (p=0.012, Table 1).

Table 1. Comparison of group data before and after application and control group (Mean ± Standard Deviation).

	Before				After			
	Control	**Bo**	**IF**	**BoIF**	**Control**	**Bo**	**IF**	**BoIF**
n	**8**	**12**	**12**	**12**				
Age (years)	75±9	70±8.9	66±6	67.3±9				
Height (cm)	160.4±12.6	159.6±10.4	164.3±8.4	163.6±9.8				
Body weight (kg)	80±17.4	79.7±10.2	82±18.5	80.8±14.9	82±17.5	74.9±12.2*	76±19*	78±13.8
Fat percentage (%)	30.6±3	37.6±4.6	31.6±6	32.1±3.7	35.6±5*	31.9±5.3**	28.4±6.1$^{*\#}$	30.5±2.9*
Waist circumference (cm)	105.8±22.6	95.1±8.1	92.3±10.8	97.5±10.7	104±21.6	94.1±9.7	94.3±8	94.3±9.3
Hip circumference (cm)	115±17.8	109.5±13.8	102.3±12.4	107.2±9.4	110.4±17.6	109.9±10.3	103.7±10.6	102.6±14
Waist-Hip Ratio	0.92±0.13	0.91±0.11	0.9±0.1	0.92±0.1	0.94±0.09	0.86±0.09	0.9±0.1	0.92±0.1
Serum irisin level (ng/ml)	3.86±1.83	6.51±2.12	6.64±2.32	5.73±1.43	3.18±1.87	5.41±1.62	6.39±1.84$^{\#}$	4.86±2.83

The One Way Anova-Tukey test was used to compare the groups, and the Paired Sample T-test was used to measure the within-group variation over time. $^{*}p<0.05$, $^{**}p<0.001$: Comparison before and after application. $^{\#}p<0.05$: Comparison with the control group. (Bo: Bocce; IF: Intermittent fasting; BoIF: Bocce+Intermittent fasting).

Body weight decreased statistically significantly in the Bo and IF groups in the post-application measurements compared to the pre-application measurements (p=0.005, p=0.016 Table 1), respectively.

The alternation of circulating irisin level was not correlated with change in body fat percentage and body weight (r=0.116, p=0.437; r=-0.145, p=0.649, Figures 1 and 2), respectively

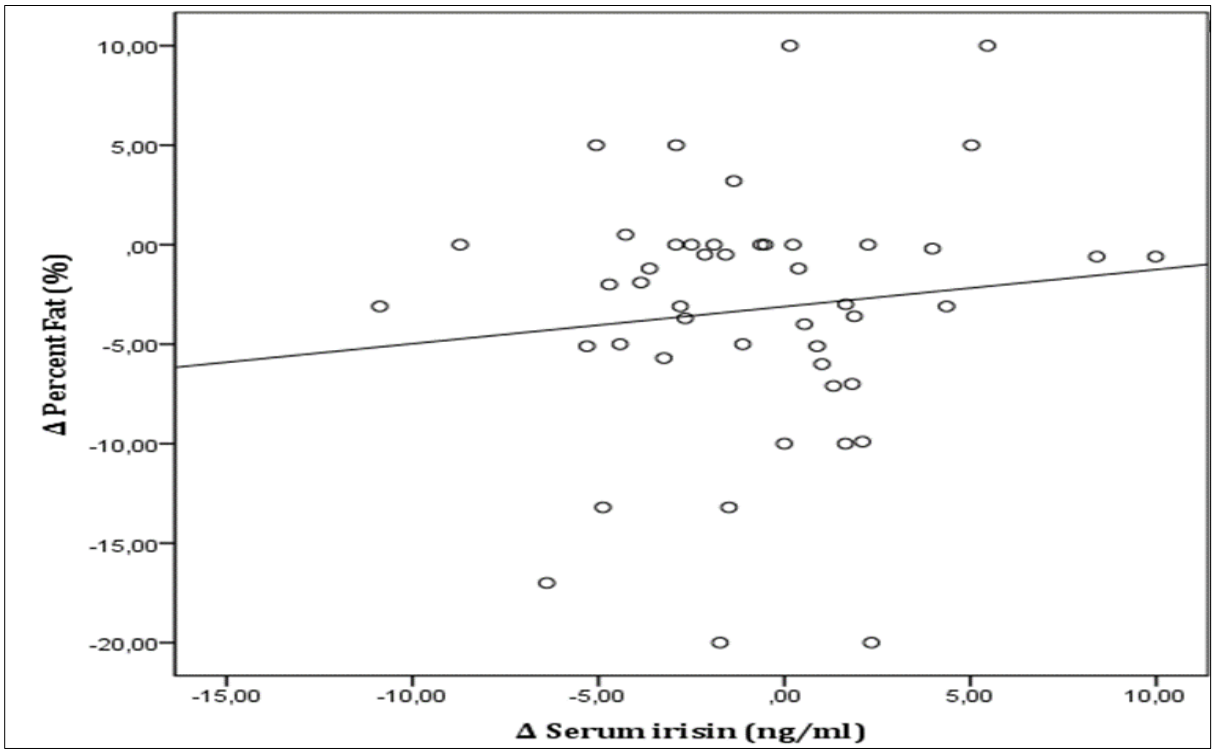


Figure 1. The relationship between circulating irisin and body fat percentage. Spearman's r=0.116, p=0.437.

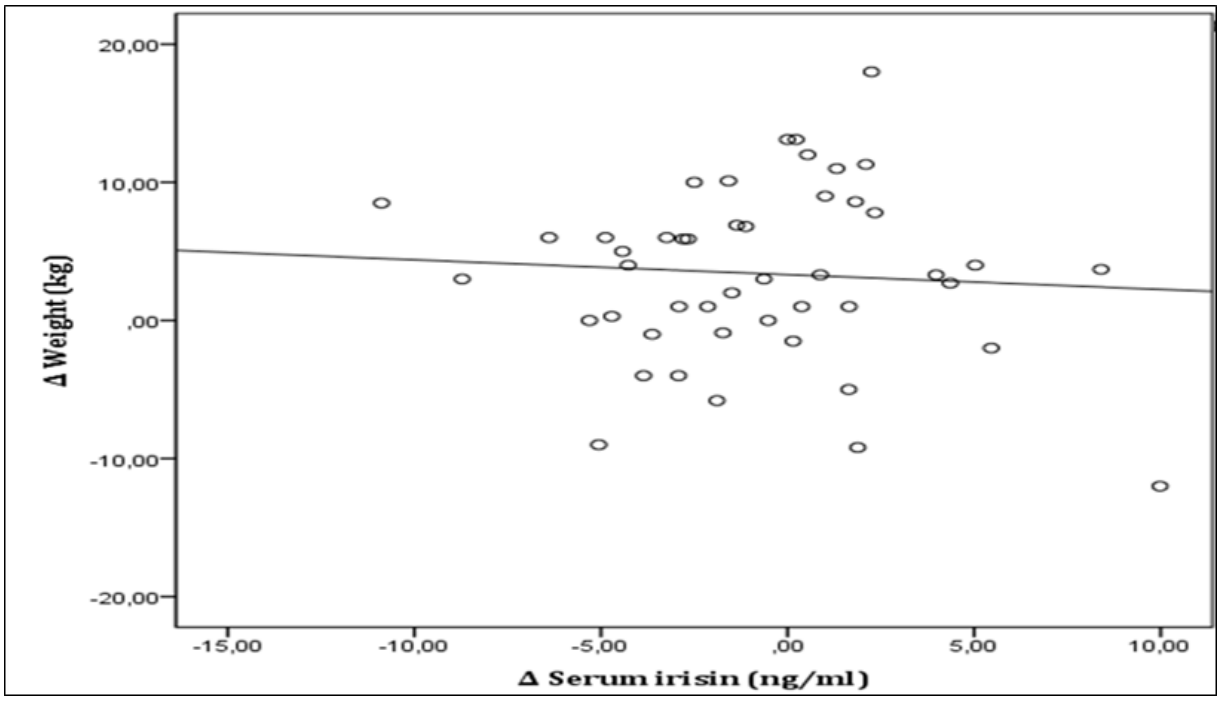


Figure 2. The relationship between circulating irisin and body weight. Spearman's r=-0.145, P=0.649.

There were no statistically significant differences seen in waist and hip circumference, as well as waist-to-hip ratio, between the groups before and after the application. Additionally, no significant differences were found between the control group and the Bo and BoIF groups after the application ($p>0.05$).

DISCUSSION

In this study, the effect of intermittent fasting and Bocce on serum irisin levels in the elderly was examined. There was no significant statistical difference observed in the irisin levels of the groups before and after treatment. It was observed that intermittent fasting and the Bocce caused a significant decrease in body fat percentage and body weight, and it was determined that the body fat percentage was significantly lower in the IF group than in the control group. No significant correlation was found between serum irisin and body fat percentages.

Despite the significant impact of diet on metabolic risk factors and the strong correlation between irisin and metabolic health, prior investigations into the potential of dietary treatments to regulate circulating irisin levels have yielded in conflicting results. A study investigating the impact of a diet's macronutrient composition on the levels of FNDC5 and irisin in mouse skeletal muscle found that a diet rich in fat and carbohydrates downregulated FNDC5 expression and resulted in a significant reduction in skeletal muscle irisin levels.[17]

A clinical study conducted on 163 patients with metabolic syndrome found a positive correlation between vegetable protein and saturated fat, and irisin levels.[18] Another study examining the effect of diet quality and diet style on irisin level found a positive correlation between the DASH (Dietary Approaches for the Prevention of Hypertension) score and irisin level. Fruit consumption has been shown to have a positive impact on the irisin levels while meat consumption is associated with a negative effect.[19] A study by Alzoughool et al. to investigate the effect of intermittent fasting on serum irisin levels reported that Ramadan fasting reduced serum irisin levels.[16] In a study by Spyridon et al., the effects of Orthodox fasting and a time-restricted diet (16:8) on irisin levels, in which daily consumption of animal foods such as meat, dairy products, and eggs are avoided during the fasting period and fish and olive oil are not consumed on certain days of the week, were examined. Orthodox fasting was reported to cause more significant increases in irisin levels than time-restricted feeding.[15]

In the present study, no significant change was observed in serum irisin values in the pre-and post-application intermittent fasting groups in the elderly, while serum irisin

values were found to be statistically higher in the post-application intermittent fasting group compared to the control group. However, it was not suggested that this difference was caused only by the intervention. The relationship between diet and irisin is influenced by various factors, including differences in diet composition, adherence to the diet, and duration of the study. The participants were given the same meals for this study to provide more conclusive evidence on the effectiveness of intermittent fasting. However, it was not recorded how much food was consumed by the participants. This particular circumstance represents one of the limitations present in the research.

Chronic exercise may cause increased circulating iris by contracting skeletal muscles[7,20] and may even offset decreases in muscle mass and strength in older adults.[21] White adipose tissue browning is an extremely dynamic process influenced by a variety of factors, including temperature, physical exercise, thyroid hormones, circadian rhythm, food components, and dietary regimens. The involvement of adipose tissue variability in the organism's metabolic health and inflammatory processes indicates that this process has a promising therapeutic effect for reducing the risk associated with many chronic diseases. It has been shown that brown and beige fat can regulate lipid metabolism with irisin in rats and humans.[22] There have been reports indicating a negative correlation between the decrease in whole body fat percentage in older persons who engage in 12 weeks of resistance exercise and the increase in serum irisin level.[23]

Due to the lower physiological serum irisin levels in older persons (>60 years), circulating irisin levels tend to rise more rapidly after training sessions compared to younger adults, particularly after intense training.24 Although exercise frequency is favorably associated with increased irisin blood levels,[25] it has been found that groups that exercise regularly do not gain equally from training.[24,26] For example, some in vivo studies using different physical exercise protocols failed to detect an association between irisin or PGC1α levels and exercise. It was observed that FNDC5 mRNA levels in the diaphragm muscles of obese Zucker rats and lean Zucker rats did not change even after 9 weeks of aerobic training on a motorized treadmill.[27]

In humans, mRNA PPARGC1A and FNDC5 levels in skeletal muscle significantly increased after 12 weeks of training. However, it was found that circulating irisin levels paradoxically decreased from 160 to 143 ng /ml.[28] In another study, it was reported that the expression of FNDC5 in human muscles did not change after an 8-week endurance training program.[29] In contrast, Morelli et al. showed higher serum irisin concentrations in individuals performing high-intensity physical activity compared to physically inactive subjects.[13] High-intensity exercise was associated with greater irisin response than low-intensity exercise at similar energy expenditure.[14] The Bocce game applied in this study did not cause significant changes in the irisin values of the subjects after the application compared to the pre-application. In the post-application values, serum irisin levels of the group playing the Bocce game were found to be higher than the control group, although not at a significant level. This could be attributed to Bocce being a low-intensity form of exercise, resulting in a slower development of the body's response to exercise in the elderly. Alternatively, it could be due to the exercise frequency not being sufficient to increase irisin levels. A study reported that irisin levels increased significantly after an 8-week resistance-training program but were not affected by aerobic training.[12] This indicates that the intensity and type of physical activity affect irisin concentrations. Therefore, to determine the impact of intermittent fasting and exercise on serum irisin levels in elderly individuals, it is important to conduct comprehensive investigations that consist of varying exercise durations based on intensity, a more limited age distribution among participants, gender-specific analysis, and a larger sample size.

The current study has a number of limitations. First, the groups formed as a result of randomization did not have a uniform age distribution because the ages of the older people in the research sample ranged widely. Furthermore, the observed disparity in irisin levels could potentially be attributed to the heterogeneous variations in daily individual activity among the groups and the differences in the mean ages of the groups, which arose as a consequence of randomization during the formation of the groups. For this reason, the after treatment values of the groups were compared with the post treatment values of the control group and the before treatment values of the same groups.

Conclusion

Lifestyle changes such as physical activity and dietary interventions in the elderly have the potential to slow the rate of development of age-related diseases by improving body composition (reducing body fat and/or increasing muscle mass). Despite the well-known benefits of physical activity, the vast majority of older adults do not engage in the minimum levels of physical activity required to stay healthy. At this time, it is critical to urge the elderly to engage in exercises other than light-intensity physical activities in order to achieve effective physiological levels.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

Approval for this study was received from AYBÜ Yeni Mahalle Training and Research Hospital Clinical Research Ethics Committee (dated 17.02.2020 and numbered 2021-02/05).

Authors' Contributions

Concept/Design: HBS, SBD, FB, MSK. Data Collection and/or Pro-cessing: HBS, SBD, SN. Data analysis and interpretation: HBS, MSK, FB. Literature Search: HBS, SBD, SN, MSK, FB. Drafting manuscript: HBS, SBD, SN. Critical revision of manuscript: MSK, FB. Supervisor: MSK, FB.

REFERENCES

1. M, Oxlund B, Jespersen A, et al. The challenges of human population aging. Age Ageing. 2015;44(2):185-187.
2. Bouchard C, Blair SN, Katzmarzyk PT. Less Sitting, More Physical Activity, or Higher Fitness? Mayo Clin Proc. 2015;90(11): 1533-1540.
3. Cartee GD, Hepple RT, Bamman MM, Zierath JR. Exercise Promotes Healthy Aging of Skeletal Muscle. Cell Metab. 2016;23(6):1034-1047.
4. Machado SA, Pasquarelli-do-Nascimento G, da Silva DS, et al. Browning of the white adipose tissue regulation: new insights into nutritional and metabolic relevance in health and diseases. Nutr Metab (Lond). 2022; 19(1):61-61.
5. Domaszewski P, Konieczny M, Pakosz P, Bączkowicz D, Sadowska-Krępa E. Effect of a Six-Week Intermittent Fasting Intervention Program on the Composition of the Human Body in Women over 60 Years of Age. Int J Environ Res Public Health. 2020;17(11):4138.
6. Hatori M, Vollmers C, Zarrinpar A, et al. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. Cell Metab. 2012; 15(6):848-860.
7. Boström P, Wu J, Jedrychowski MP, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012;481(7382):463-468.
8. Aydin S. Three new players in energy regulation: Preptin, adropin and irisin. Peptides. 2014;56:94-110.
9. Maak S, Norheim F, Drevon CA, Erickson HP. Progress and Challenges in the Biology of FNDC5 and Irisin. Endocr Rev. 2021;42(4):436-456.
10. Perakakis N, Triantafyllou GA, Fernández-Real JM, et al. Physiology and role of irisin in glucose homeostasis. Nat. Rev. Endocrinol. 2017;13(6):324-337.
11. Von Haehling S, Morley JE, Anker SD. An overview of sarcopenia: facts and numbers on prevalence and clinical impact. J Cachexia Sarcopenia Muscle. 2010;1(2): 129-133.
12. Kim HJ, Lee HJ, So B, Son JS, Yoon D, Song W. Effect of Aerobic Training and Resistance Training on Circulating Irisin Level and Their Association With Change of Body Composition in Overweight/Obese Adults: a Pilot Study. Physiol Res. 2016;65(2):271-279.
13. Morelli C, Avolio E, Galluccio A, et al. Impact of Vigorous-Intensity Physical Activity on Body Composition Parameters, Lipid Profile Markers, and Irisin Levels in Adolescents: A Cross-Sectional Study. Nutrients. 2020;12(3):742.
14. Tsuchiya Y, Ando D, Goto K, Kiuchi M, Yamakita M, Koyama K. High-Intensity Exercise Causes Greater Irisin Response Compared with Low-Intensity Exercise under Similar Energy Consumption. Tohoku J. Exp. Med. 2014;233(2):135-140.
15. Karras SN, Koufakis T, Adamidou L, et al. Effects of Christian Orthodox Fasting Versus Time-Restricted Eating on Plasma Irisin Concentrations Among Overweight Metabolically Healthy Individuals. Nutrients. 2021;13(4):1071.
16. Alzoughool F, Al Hourani H, Atoum M, Abdelgader R, Alanagreh L. Irisin, leptin and adiponectin levels are reduced significantly during fasting. Med J Nutrition Metab. 2019;12(4):389-396.
17. De Macêdo SM, Lelis DdF, Mendes KL, et al. Effects of Dietary Macronutrient Composition on FNDC5 and Irisin in Mice Skeletal Muscle. Metab Syndr Relat Disord. 2017;15(4):161-169.
18. Osella AR, Colaianni G, Correale M, et al. Irisin Serum Levels in Metabolic Syndrome Patients Treated with Three Different Diets: A Post-Hoc Analysis from a Randomized Controlled Clinical Trial. Nutrients. 2018;10(7):844.
19. Ko B-J, Park KH, Shin S, et al. Diet quality and diet patterns in relation to circulating cardiometabolic biomarkers. Clin Nutr. (Edinburgh, Scotland). 2016;35(2):484-490.
20. Qiu S, Cai X, Sun Z, Schumann U, Zügel M, Steinacker JM. Chronic Exercise Training and Circulating Irisin in Adults: A Meta-Analysis. Sports Med. 2015;45(11):1577-1588.
21. Kim H-j, So B, Choi M, Kang D, Song W. Resistance exercise training increases the expression of irisin concomitant with improvement of muscle function in aging mice and humans. Exp Gerontol. 2015;70:11-17.
22. Wu J, Boström P, Sparks LM, et al. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell. 2012;150(2):366-376.
23. Zhao J, Su Z, Qu C, Dong Y. Effects of 12 Weeks Resistance Training on Serum Irisin in Older Male Adults. Front Physiol. 2017;8:171.
24. Cosio PL, Crespo-Posadas M, Velarde-Sotres Á, Pe-

laez M. Effect of Chronic Resistance Training on Circulating Irisin: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Int J Environ Res Public Health. 2021;18(5):2476.
25. Fox J, Rioux BV, Goulet EDB, et al. Effect of an acute exercise bout on immediate post-exercise irisin concentration in adults: A meta-analysis. Scand J Med Sci Sports. 2017;28(1):16-28.
26. Huh JY, Panagiotou G, Mougios V, et al. FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise. Metabolism. 2012;61(12):1725-1738.
27. Peterson JM, Mart R, Bond CE. Effect of obesity and exercise on the expression of the novel myokines, Myonectin and Fibronectin type III domain containing 5. PeerJ. 2014;2:e605.
28. Norheim F, Langleite TM, Hjorth M, et al. The effects of acute and chronic exercise on PGC-1α, irisin and browning of subcutaneous adipose tissue in humans. FEBS J. 2013;281(3):739-749.
29. Besse-Patin A, Montastier E, Vinel C, et al. Effect of endurance training on skeletal muscle myokine expression in obese men: identification of apelin as a novel myokine. Int J Obes. 2013;38(5):707-713.

ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

The Relationship Between Physical Activity and Cognition in Kırşehir Ahi Evran University Medical Faculty Students

Kırşehir Ahi Evran Üniversitesi Tıp Fakültesi Öğrencilerinde Fiziksel Aktivite ve Biliş Arasındaki İlişki

Seda KOÇAK[1] Hasan ÇALIŞKAN[2] Serdar KARAKULLUKÇU[3] Ferhat PEKTAŞ[1]

ÖZ

Amaç: Tıp Fakültesi eğitiminin zorluğu ve yoğunluğu nedeniyle tıp öğrencilerinde sedanter yaşam görülmektedir. Farklı metodolojik çalışmalarda görüldüğü gibi, fiziksel aktivite bilişsel işlevleri etkiler. Bu çalışmaların çok azı gençlikle ilgilidir. Bu nedenle tıp fakültesi öğrencilerinin fiziksel aktivite ve bilişsel parametrelerini ve birbirleri ile olan ilişkilerini kesitsel bir çalışmada analiz etmeyi amaçlandı.
Araçlar ve Yöntem: Çalışmaya bir tıp fakültesinin tüm sınıflarından 138 öğrenci dahil edildi. Tıp öğrencileri üç ölçeği tamamladı. Fiziksel aktivite IPAQ-SF ile belirlendi. Bilişsel değişkenler otonom öğrenme ve bilişsel esneklik ölçeği ile ölçüldü.
Bulgular: Sonuçlar, toplam, şiddetli ve orta düzeyde fiziksel aktivitenin kız ve erkek öğrenciler arasında önemli ölçüde farklılık gösterdiğini ortaya koydu. Benzer şekilde, öğrenmenin bağımsızlığı da doğumda atanan cinsiyetten etkilenmiştir. İlk üç sınıf öğrencilerinin bilişsel esneklik puanları son üç sınıf öğrencilerine göre daha yüksekti (p=0.001). Bilişsel esneklik tıpta yıllar içinde azaldı.
Sonuç: Korelasyon analizine göre fiziksel aktiviteler ile bilişsel işlevler arasında anlamlı bir ilişki olmadığı sonucuna varılmıştır. Tıp eğitimi ve fiziksel aktivitelerde etkinliği çok fazla araştırmaya konu olmayan otonom öğrenme ve bilişsel esneklik gibi bilişsel işlev çalışmaları gelecekte daha fazla araştırılmalıdır.

Anahtar Kelimeler: bilişsel esneklik; egzersiz; otonom öğrenme

ABSTRACT

Purpose: Due to the difficulty and intensity of medical school education, medical students often lead a sedentary lifestyle. As seen in different methodological studies, physical activity affects cognitive functions. Few of these studies are related to youth. Therefore, we aimed to analyze medical students physical activity and cognitive parameters and their association between each other in cross sectional study.
Materials and Methods: 138 students from all classes of a medical faculty were included in the study. Medical students completed three scales. Physical activity was determined by the IPAQ-SF. Cognitive variables were measured by autonomous learning and cognitive flexibility scale.
Results: The results revealed that total, vigorous and moderate physical activity differed significantly between female and male students. Similarly independence of learning was influenced by sex assigned at birth. First three years students' cognitive flexibility scores were higher than last three year ones (p=0.001). Cognitive flexibility has decreased over the years in medicine.
Conclusion: According to the correlation analysis reported in the study, there was no conclusive link between physical activity and cognitive abilities. Cognitive function studies such as autonomous learning and cognitive flexibility, whose effectiveness has not been the subject of much research in medical education and physical activities should be investigated more in future.

Keywords: cognition; medical students; physical activity

Received: 28.05.2023; Accepted: 29.11.2023

[1]Kırşehir Ahi Evran University, School of Medicine, Physiology Department, Kırşehir, Türkiye.
[2]Balıkesir University, School of Medicine, Physiology Department, Balıkesir, Türkiye.
[3]Karadeniz Technical University, Department of Public Health Türkiye.
Corresponding Author: Seda Koçak, Kırşehir Ahi Evran University, School of Medicine, Physiology Department, Kırşehir, Türkiye.
e-mail: seda.kocak@ahievran.edu.tr

How to cite: Koçak S, Çalışkan H, Karakullukçu S, Pektaş F. The relationship between physical activity and cognition in kırşehir ahi evran university medical faculty students. Ahi Evran Med J. 2024;8(1):85-93. DOI: 10.46332/aemj.1303657

INTRODUCTION

Humans have led a life that includes compulsory physical activity alongside hunger and satiety cycles historically. Mankind encountered a less active life with the mechanization brought by the industrial revolution. Furthermore environmental conditions and lifestyle have changed dramatically with the technological revolution.[1] Physical inactivity is admitted a risk factor leading to the formation of chronic and psychological diseases in today's societies.[2] According to the WHO's 2004 report, Around 3.2 million individuals die each year from physical inactivity, the fourth most important risk factor for mortality.[3] In Turkey, sedentary lifestyle is gradually increasing. The rate of people over 19 years of age with a sedentary lifestyle is 39.9% according to the Turkey Nutrition and Health Research reports made in 2017.[4] While physical inactivity has increased in university students and medical students as there are closures worldwide during the pandemic, no different situation has been observed in Turkey.[5]

When cognitive flexibility is defined psychologically, it can be considered as the ability to change one's behavior and strategy in changing situations and conditions.[6] The neuropsychological definition of cognitive flexibility, on the other hand, can be counted as a concept in which executive functions such as problem solving skills, coping with stress for problem solving and decision making are carried out in higher brain regions such as lateral, medial prefrontal and anterior cingulate cortex, where cognitive processes are dynamically changed and activated.[7] Medical education is an integrated system consisting of many subbranches. Medicine and sub-branches of medicine, such as physiology, are called ill-structured domains. In medical education, students can be successful by combining and interpreting the information they have learned from different branches. Therefore, a medical student should have a certain cognitive flexibility in order to be successful.[8]

Autonomous learning is the process of organizing, planning and taking action for learning activities by taking control and responsibility People who have gained autonomy in learning actually develop their cognitive flexibility by questioning their methods and applying the techniques to the situation in order to overcome optimal difficulties in education.[9] Face-to-face education was discontinued during the pandemic. Therefore, autonomous learning has become a more important skill in the COVID-19 era[10] Students have the opportunity to study more autonomously with the web-based learning policies developed in this process.[11] However, during the pandemic process, distance education had disadvantages as well as advantages in terms of autonomous learning. While students with strong self-learning skills were comfortable studying from home, education was insufficient for these low-skilled students. Thus, the value of autonomous learning to promote student development in medical education was once again understood.

Research on the relationship between physical activity and cognitive abilities has been conducted in clinical populations and healthy humans.[11] In many studies, cognitive functions have been evaluated using neuropsychological tools.[12,13] Few of these studies are related to youth groups.[14] Therefore, young medical students were selected in present study. Our research was aimed to question the relevance of physical activity and cognitive functions in medical students, and to analyse the relationship between physical activity and cognitive functions.

MATERIALS and METHODS

Design

This cross-sectional study, which analysed physical activity and cognitive abilities, was carried out in a medical school in Turkey. While International Physical Activity Questionnaire Short Form (IPAQ-SF) was used for physical activity, autonomous learning and cognitive flexibility scales were used for cognitive functions.

Participants

The study included all medical students in the academic year 2021-2022 at Kırşehir Ahi Evran University. The sample of study was 138 medical students comprised of 87 female (%63) and 51 male (%37). We wanted to include all classes in faculty, therefore there were no exclusionary requirements. Our study was reviewed and approved by the Non-Interventional Clinical Research Ethics Committee of Kırşehir Ahi Evran University Faculty of Medicine

(dated 22.03.2022 and numbered 2022/06-58). Participants were included from all six classes. We used and analyzed all factors that would affect the results of the data in socio-demographic questions and scales.

G-Power 3.1 program was used to calculate the sample size. The total sample size was found to be 134 via considering the effect size as 0.3, alpha err prob as 0.05 and power as 0.95. Therefore, 138 students who volunteered to participate in the study were included.

Web-based surveys were distrubuted to the students in medical faculty via WhatsApp or e-mail for data collection using Google forms. Students were required to sign a consent form that detailed the study and stated that they were free to reject to participate. Then, students filled out demographic questionnaire as well as the other scales. Participants were given a WhatsApp and e-mail contact to use throughout the research in order to contact the study team with any questions or issues.

Ouestionnaires

Demographic Questionnaire: This questionnaire was developed for this study to gather demographic information and self-reported daily life information. The questionnaire includes factors that could affect their cognitive performance and/or physical activity like age, sex assigned at birth, classes, health and medical conditions, including the usage of mental medications and marital status. Body mass index (BMI) was calculated using height and weight values (weight in kilograms divided by height in meters squared).

International Physical Activity Questionnaire (Short Form): In our study, a The international physical activity questionnaire with Turkish validity and reliability was used.[15] The short form of questionnaire was used. The questionnaire's goal is to find out how much healthy adults and youth exercised throughout the previous seven days. The questionnaire consists of 7 questions. The questionnaire asks how much time was spent doing walking, moderate physical activity, and vigorous physical activity. Time spent sitting is considered as a separate question. Responses were translated to metabolic equivalent task minutes per week (MET-min/wk), using the IPAQ scoring method. For the analysis of IPAQ data, the following values were used: 3.3 METs for walking, 4.0 METs for moderate physical activity, and 8.0 METs for strenuous physical activity. According to the formula, the amount of physical activity was calculated using the collected data.

An average MET score was calculated for each type of activity. The formula was created by multiplying the activity's minutes, days, and METs. Physical activities were also divided into three categories: low, moderate, and high levels of physical activity. Low physical activity refers to a lack of or insufficient physical exercise to fall into categories 2 or 3. Moderate physical activity refers to moderate-intensity, or vigorous-intensity activities attaining a minimum of 600 MET-min/wk. High physical activity is defined as activities of moderate to vigorous intensity that total at least 3.000 MET-min per week. Calculation of the total score includes the sum of walking, moderate-intensity activity and vigorous activity over minutes and days.

Autonomous Learning Scale: The Autonomous scale adapted to Turkish by Arslan and Yurdakul was conducted in this study.[16] The scale measures independent learning and study habits on two separate subscales. Items are graded on a Likert scale of 1 to 5, with 1 being the most unlike me and 5 being the most like me. Two items were worded negatively to help participants avoid response bias. The range of possible scores on the scale is between 12 and 60. Higher scores indicate greater autonomy, independence, and a favorable attitude toward learning.

Cognitive Flexibility Scale: Celikkaleli conducted validity and reliability assessments on the Turkish version of Cognitive Flexibility scale.[17]There are a total of 12 items on the scale. It is a 6 point Likert scale. (1) I do not participate at all, (2) I do not participate, (3) I do not attend, (4) I participate a little, (5) I participate, and (6) I definitely participate are scale responses. The range of possible scores on the scale is between 12 and 72. Scores that are higher reflect better cognitive flexibility.

Statistical Analysis

Following the IPAQ's guidelines for measuring physical activity based on MET, we calculated the total METs equal to a week. The formula was:

Total Physical Activty: 3.3 MET for walking X minutes X days +4.0 MET for moderate activity X days X minutes + 8 MET for vigorous activity X minutes X days.

All statistical analyses were carried out using SPSS 22.0. In the descriptive statistics of the evaluation outcomes, numerical variables were expressed as mean and standard deviation, while categorical variables were expressed as number and percentage. In the analysis of the research data, descriptive data were expressed as number, percentage, mean, and standard deviation. The Mann Whitney U test was used to analyze numerical variable comparisons between two independent groups. When three or more independent groups were compared, Kruskal Wallis test was used. To compare qualitative data, chi-square analysis was performed. The correlation analysis (Spearman) was conducted to examine the extent of correlations among physical activity level, autonomous learning and cognitive flexibility. Statistical alpha significance level was accepted as $p<0.05$.

RESULTS

Sociodemographic Characteristics of Medical Students

The distribution of students across different educational years, as well as variances in demographics and body composition factors, are shown in Table 1. %63 of 138 students were female and %29.7 of 138 students' age were 21-22. %65.2 students' BMI was normal. Most of the students (%44.2) were first-year students. %37.7 students were living with family. In terms of health and medical issues, 12 of all students (%8.7) reported psychiatric disorder that could affect their cognitive performance. 8 of 138 students reported using psychiatric medication.

Assesment of Physical Activity

The distribution of the students in the study according to their physical activity levels is as follows: 43 students (%31.1) were low active, 60 students were moderate active (%43.4) and 35 students were highly active (%25.3). Figure 1 shows students by physical activity level.: The amount of physical activity for the individual was categorized as follows: Low: when MET-minutes per week are less than 600; Moderate: when the MET-minutes per week are between 600 and 1500; and High: when MET-minutes per week are greater than 1500.[18]

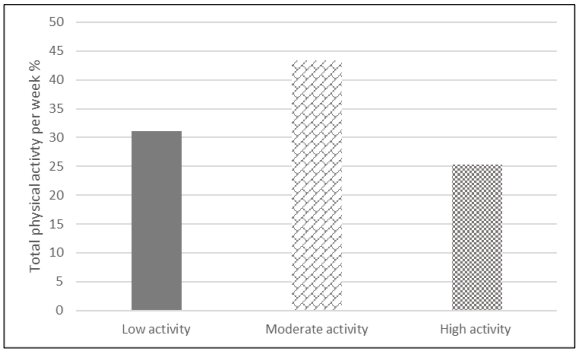


Figure 1. Total physical activity per week %.

Table 1. Sociodemographic Characteristics of Medical Students.

Sociodemographic Variable		
Age	**N**	**Percentage (%)**
17-18	17	12.3
19-20	49	35.5
21-22	41	29.7
23+	31	22.5
Gender		
Female	87	63
Male	51	37
Body Mass Index (BMI)		
Underweight	17	12.3
Normal	90	65.2
Overweight	23	16.7
Obese	8	5.8
Years		
Year 1	61	44.2
Year 2	26	18.8
Year 3	17	12.3
Year 4	10	7.2
Year 5	12	8.7
Year 6	12	8.7
Marital Status		
Single	102	73.9
Single (Partnered)	36	26.1
Monthly Allowance (Turkish lira)		
Less than 4000	98	71
4001-6000	8	5.8
6001-8000	8	5.8
8001-10000	14	10.1
10001+	10	7.2
Living situation		
Alone	16	11.6
With friends	25	18.1
With family	52	37.7
Student accomodation	45	32.6
History of a chronic disease		
Yes	12	8.7
No	126	91.3
History of a psychiatric disorder		
Yes	12	8.7
No	126	91.3
History of a psychiatric drug		
Yes	8	5.8
No	130	94.2
Smoking		
Smoking	29	21
Never smoked	93	67.4
Previously smoked	16	11.6
Alcohol Consumption		
Yes	29	21
Never	100	72.5
Withdrawn	9	6.5

*Mann-Whitney U test

Assessment of Physical Activity Parameters According to Sex Assigned at Birth and Years

Differences in physical activity were analyzed for sex assigned at birth. Total, vigorous and moderate physical activity differed significantly between female and male as Table 2 shows. Walking and sitting parameters did not change according to sex assigned at birth (p=0.519 and p=0.149 respectively). Male students' BMI was higher than female students' (p<0.001). Average BMI scores of students were normal according to the World Health Organization obesity classification.

Table 2. Physical activity parameters according to years and sex assigned at birth.

Variables	Total Group (n=138)	Female (n=87)	Male (n=51)	p*	1-3 Years (n=104)	4-6 Years (n=34)	p*
BMI	22.6±4.0	21.4±3.6	24.5±4.1	<0.001	22.4±4.0	23.2±4.2	0.222
Total Physical Activity (MET-min/wk)	1292.8±1335.6	1029.7±1002.7	1741.5±1683.0	0.003	1314.6±1394.3	1226.0±1153.9	0.676
Vigorous Physical Activity (MET-min/wk)	317.1±821.0	191.7±531.8	531.0±1134.3	0.003	313.1±883.8	329.4±600.1	0.013
Moderate Physical activity (MET-min/wk)	233.2±471.8	150.2±362.3	374.9±593.1	0.01	238.3±503.8	217.8±363.0	0.18
Walking (MET)	743.0±729.3	687.8±691.4	837.2±787.9	0.519	764.0±718.8	678.8±768.2	0.103
Sitting (hour/day)	4.7±5.2	4.2±5.0	5.5±5.4	0.149	5.0±5.4	3.7±4.4	0.228

*Mann-Whitney U test

The first three years are typically theoretical, with the following three years consisting of practical/clinical rotations in medicine. Pre-clinical years spend most of time in the classroom. No difference was seen although expecting students to be highly active during clinical rotations according to total, moderate physical activity levels, sitting and walking parameters. Vigorous physical activity levels were higher in 4-6 years (p=0.013). Table 2 indicates the reported level of students' physical activity.

Assessment of Autonomous Learning and Cognitive Flexibility According To Sex Assigned At Birth, Years, Living With Psychiatric Disorder, Terms and Marital Status

The 12-item Autonomous Learning Scale has two subscales that assess study habits and independence of learning. Sex assigned at birth did not influence autonomous learning and cognitive flexibility scores. Independence of learning was influenced by it. Male independent of learning scores were higher than female ones (p=0.045). Study habbits was not influenced by sex assigned at birth. Lectures and laboratory activities are mixed during the first three years of medical school. Medical students are preoccupied with a massive amount of knowledge that they study in 3 years. Busy syllabus in pre-clinical years can influence cognitive flexibility. First three years students' cognitive flexibility scores were higher than last three year ones (p=0.001). Medical education years effected cognitive flexibility scores. Cognitive flexibility has decreased over the years in medicine. Table 3 indicates autonomous learning and cognitive flexibility scores according to sex assigned at birth and years.

After analyzing autonomous learning scores for sex assigned at birth (p=0.096), 3- year terms (p=0.759) and years of medical students (p=0.824), there were no significant effects of these parameters on autonomous learning. Likewise, types of living situation did not effect autonomous learning (p=0.774). No relationship was found between history of a physchiatric disorder and autonomous learning (p=0.427).

Table 3. Autonomous Learning And Cognitive Flexibility according to Gender and Years.

Variables	Total (n=138)	Female (n=87)	Male (n=51)	p*	1-3 Years (n=104)	4-6 Years (n=34)	p*
Autonomous Learning	40.1±10.9	41.6±9.7	37.6±12.5	0.096	40.0±10.8	40.6±11.5	0.759
Independence of Learning	24.4±6.4	25.4±5.7	22.7±7.3	**0.045**	24.5±6.3	24.1±6.9	0.825
Study Habits	15.7±5.1	16.2±4.7	14.9±5.7	0.238	15.5±5.1	16.5±5.2	0.304
Cognitive Flexibility	47.5±10.5	48.4±10.6	46.0±10.1	0.112	49.1±10.4	42.8±9.5	**0.001**

*Mann-Whitney U test

Correlation Between Physical Activity, Autonomous Learning and Cognitive Flexibility

Data revealed the links between students' physical activity, autonomous learning and cognitive flexibility. The findings of the correlation study revealed a weak negative association between walking and autonomous learning. Similarly, there is a weak correlation between independence of learning and walking. Moreover, no correlation was found between cognitive flexibility and physical activity levels. BMI did not effect physical activity levels. Autonomous learning independence of learning and study habits were found to have positive strong relationship. There was no correlation between autonomous learning and cognitive flexibility. Total physical activity levels were positively related with vigorous and moderate physical activities and walking. Table 4 indicates correlation analysis of physical activity and cognitive functions.

Table 4. Correlation between Physical Activity, Autonomous Learning and Cognitive Flexibility.

Variables	BMI	Total Physical Activity	Vigorous Physical Activity	Moderate Physical Activity	Walking (MET)	Sitting (hour/day)	Autonomous learning	Independence of learning	Study habits
BMI	-	-	-	-	-	-	-	-	-
Total Physical Activity (MET)	r= 0.167 p= 0.050	-	-	-	-	-	-	-	-
Vigorous Physical Activity (MET)	r= 0.099 p= 0.250	**r= 0.546** **p= <0.001**	-	-	-	-	-	-	-
Moderate Physical Activity (MET)	r= 0.030 p= 0.723	**r= 0.455** **p= <0.001**	**r= 0.515** **p= <0.001**	-	-	-	-	-	-
Walking (MET)	r= 0.093 p= 0.276	**r= 0.676** **p= <0.001**	r= 0.003 p= 0.972	r= -0.092 p= 0.285	-	-	-	-	-
Sitting (hour/day)	r= -0.002 p= 0.986	**r= 0.234** **p= 0.006**	r= -0.077 p= 0.369	r= 0.028 p= 0.747	**r= 0.267** **p= 0.002**	-	-	-	-
Autonomous learning	r= 0.023 p= 0.787	r= 0.044 p= 0.611	r= -0.048 p= 0.573	**r= -0.191** **p= 0.025**	**r= 0.190** **p= 0.025**	r= 0.048 p= 0.574	-	-	-
Independence of learning	r= 0.048 p= 0.576	r= 0.061 p= 0.480	r= 0.061 p= 0.480	r= -0.149 p= 0.082	**r= 0.207** **p= 0.015**	r= 0.007 p= 0.937	**r= 0.915** **p= <0.001**	-	-
Study habits	r= 0.029 p= 0.736	r= 0.024 p= 0.779	r= -0.006 p= 0.944	**r= -0.178** **p= 0.037**	r= 0.144 p= 0.092	r= 0.037 p= 0.671	**r= 0.926** **p= <0.001**	**r= 0.725** **p= <0.001**	-
Cognitive Flexibility	r= -0.113 p= 0.188	r= 0.035 p= 0.688	r= -0.144 p= 0.093	r= -0.058 p= 0.501	r= 0.161 p= 0.059	r= 0.061 p= 0.476	r= 0.036 p= 0.672	r= 0.119 p= 0.164	r= -0.058 p= 0.500

* Spearman test.

DISCUSSION

The relationship between exercise and medical students' cognitive abilities was analysed in this study. However, research on physical activity's effect on medical students' cognition and mediating roles of demographic parameters are limited. Our results not only expand the relationship between physical activity and autonomous learning and cognitive flexibility over previous studies[19] but also provide indirect evidence by explaining some of the variables about them.

Out of all, 43 (%31.1) were inactive, 60 (%43.4) active and 35 (%25.3) more active than normal. Medical students in our sample tended to be active type. In a study conducted with Turkish medical students, the rate of active students was found to be %75.1,[20] while the rate of active students was found to be %50.3 in another study.[21] The percentage of active students in our study remains low compared to other studies.

When we evaluated the physical activity parameters according to sex assigned at birth, total physical activity, vigorous physical activity and moderate physical activity values were higher in male students. Female students were %69 less active than male ones (1029.7 and 1741.5 MET-min/wk.).Women participate in physical activity at lower rates than men. In this case, gender-specific psychosocial factors are effective like self-efficacy, social support, and motivation.[22] More studies are needed to address gender-specific psychological and social aspects of physical activity motivations in medical students.

There are studies in medicine on autonomous learning or cognitive flexibility.[23-25] To the best of our knowledge, there are no studies evaluating autonomous learning and cognitive flexibility in medical students. There may be significant individual variability in tasks related to cognitive flexibility and autonomous learning. Derrick et al. emphasized that demographic factors like gender and are crucial factors to take into account in autonomous learning.[26] When the autonomous learning and cognitive flexibility values were analyzed in our study, no statistically significant sex assigned at birth difference emerged.

One of the striking results of our research is that independence of learning scores of female students is higher than male students. Various predictors underlie the gender difference in independent learning. While only self-efficacy was a predictor for female students, these predictors were more in male students like study time, active learning strategies, performance goal and self-efficacy.[27] Although it was not measured by any scale in our study, it is thought that the self-efficacy of female students is higher.

Social and emotional changes occur in lives and young people develop mechanisms that require adaptation with the transition to a professional career in adolescence and young adulthood. Therefore, young people's cognitive flexibility may provide some advantages.[28] Some of past researches indicate that cognitive flexibility declines with age.[29,30] Some of them indicates that cognitive flexibility was not affected by age.[31] Although there is no significant difference in cognitive flexibility values between ages, a decrease is observed. This may be due to the small difference between age groups. When the pre-clinical and clinical periods were evaluated in our study, years 4-6 students were less flexible than years 1-3 students. The level of cognitive flexibility is also affected by the fact that people are experts in their subjects. The degree of specialization and cognitive flexibility are inversely correlated. As a person specializes, the ability to adapt to new situations and develop different approaches to similar problems, in short, decreases cognitive flexibility.[32] It can be predicted that the same situation may occur in the education phase. In the pre-clinical years, ideas for specialization may also be formed, and the orientation to internships in the subject of specialization may increase.

Considering other parameters affecting cognitive flexibility, psychiatric diseases come to the fore in the literature.[33] Recent studies revealed that there was a lack of cognitive flexibility in different psychiatric disorders like major depressive disorder,[34] obsessive-compulsive disorder[35] and schizophrenia.[36] Cognitive flexibility scores of students with psychiatric disorder were lower than those without, but this difference was not significant in our study. Similar results were also noted in autonomous learning in the present study. The number of students with psychiatric disorder was small. The small size of the group may affect the statistical result. Future studies about psychiatric disorders, cognitive flexibility and autonomous learning in young university students will increase further evaluations.

Emotional state is another parameter that affects cognitive flexibility. Indirect evidence suggests that emotional state influences cognitive flexibility.[37] Partnered students had lower cognitive flexibility scores than single students. The link between emotional states and cognitive processes may vary from person to person.

In our study, autonomous learning scores of students living alone and students living with other people were also compared. In this comparison, the lowest score was in the students living alone, and no statistically significant difference was found. Interaction of students with other people in their lives may affect their learning processes. Higher mental functions may have occurred as a result of students providing dynamic social interactions with their environment.[38]

There are few studies investigating the effect of physical activity on cognitive functions in university students, generally the studies were conducted with the elderly.[39] When the correlation analysis results are examined, we analyzed that there is no relationship between the physical activity levels of university students and their cognitive functions. Different exercise types don't affect cognition in a study conducted with adolescents. Reasons for this have been suggested as exercise intensity and timing of cognitive tests.[40] Another study supporting our results showed that both higher physical activity and lower sedantary behaviour have no effect on cognitive performance.[41] Uncorrelatedness between exercise and cognition has been hypothesized as an explanation that young age marks the brain's maximal development in regions associated to cognitive skills, making it impossible to acquire additional progress of these cognitive abilities.[42,43] Our results contradict a prior study conducted among university students, higher executive functions showed a correlation with physical activity.[19] Cognitive functions were better in active students and academic success was associated with cognitive decline in inactive students in another study conducted with medical and engineering students.[44] Magnon et al. emphasized that past sedantariness affects cognitive performance in university students.[45]

In present study it is unclear whether the inactivity of the physically inactive students is attributed to their lifestyle rather than their medical studies. No correlation was found between physical activity and cognition. In order to understand the inactivity of medical students, preventive interventions may be needed so that the student health problems related to inactivity can be overcome.

The present study was subjected to limitations. First, the data on physical activity and cognitive function was based on self-reports. The use of self-reports might have had an impact on the findings. Second, there may be pre-existing personal differences in cognitive and physical activity. Third, precise reasoning is difficult as we applied a cross-sectional study design.

In summary, The correlation study showed no evidence of a substantial association between physical activity and cognitive processes. Further research is needed to define the relationship between cognitive functions and physical activity in medical students.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Acknowledgments

Presented at Europhysiology 2022, Copenhagen, Denmark (Poster number is B 03-29-L).

Ethics Committee Permission

Approval for this study was received from Kırşehir Ahi Evran University Non-Interventional Research Ethics Committee (dated 22.03.2022 and numbered 2022-6/58).

Authors' Contributions

Concept/Design: SK, FP, HÇ, SK. Data Collection and/or Processing: SK, FP, HÇ, SK. Data analysis and interpretation: SK, FP, HÇ, SK. Literature Search: SK, FP, HÇ, SK. Drafting manuscript: SDK. Critical revision of manuscript: HÇ, SK. Supervisor: SK, HÇ.

REFERENCES

1. Berkhout F, Hertin J. Impacts of information and communication technologies on environmental sustainability: Speculations and evidence. OECD: Brighton, UK, 2001.
2. González K, Fuentes J, Márquez JL. Physical inactivity, sedentary behavior and chronic diseases. Korean J Fam Med. 2017;38(3):111.
3. World Health Organization. The World health report: 2004: changing history, 2004.
4. Bakanlığı, TC Sağlık. Türkiye beslenme ve sağlık araştırması (TBSA) " Beslenme durumu ve alışkanlıklarının değerlendirilmesi sonuç raporu. 2019.
5. Bağcı TAB, Kanadıkırık A, Somyürek E, et al. Impact of COVID-19 on eating habits, sleeping behaviour and physical activity status of final-year medical students in Ankara, Turkey. Public Health Nutr. 2021;24(18): 6369-6376.
6. Ionescu T. Exploring the nature of cognitive flexibility. New Ideas Psychol. 2012;30(2):190-200.
7. Dajani DR, Uddin LQ. Demystifying cognitive flexibility: Implications for clinical and developmental neuroscience. Trends Neurosci. 2015;38(9):571-578.
8. Rhodes AE, Rozell TG. Cognitive flexibility and undergraduate physiology students: increasing advanced knowledge acquisition within an ill-structured domain. Adv Physiol Educ. 2017;41(3):375-382.
9. Tam M. Constructivism, instructional design, and technology: Implications for transforming distance learning. J Educ Techno Soc. 2000;3(2):50-60.

10. Ariebowo T. Autonomous learning during COVID-19 pandemic: Students' objectives and preferences. J. Foreign Lang. Teach. 2021;6(1):56-77.
11. Maru MG, Pikirang CC, Setiawan S, Oroh EZ, Pelenkahu N. The internet use for autonomous learning during COVID-19 pandemic and its hindrances. Int. J. Interact. Mob. Technol. 2021;15(18):65-79.
12. Ruet A, Brochet B. Cognitive assessment in patients with multiple sclerosis: From neuropsychological batteries to ecological tools. Ann. Phys. Rehabil. Med. 2020;63(2):154-158.
13. Chan AS, Shum D, Cheung RW. Recent development of cognitive and neuropsychological assessment in Asian countries. Psychol. Assess. 2003;15(3):257.
14. Ruiz-Hermosa A, Álvarez-Bueno C, Cavero-Redondo I, Martínez-Vizcaíno V, Redondo-Tébar A, Sánchez-López M. Active commuting to and from school, cognitive performance, and academic achievement in children and adolescents: A systematic review and meta-analysis of observational studies. Int. J. Environ. Res. Public Health. 2019;16(10):1839.
15. Saglam M, Arikan H, Savci S, et al. International physical activity questionnaire: reliability and validity of the Turkish version. Percept. Mot. Skills. 2010;111(1):278-284.
16. Yurdakul C. An investigation of the relationship between autonomous learning and lifelong learning. Int. J. Educ. Res. 2017;2(1):15-20.
17. elikkaleli Ö. The Validity and Reliability of the Cognitive Flexibility Scale. Education & Science. 2014;176(3):339-346.
18. Schlickmann DW, Kock KS. Level of Physical Activity Knowledge of Medical Students in a Brazilian University. J Lifestyle Med. 2022;12(1):47-55.
19. Byrd-Bredbenner C, Quick V, Koenings M, Martin-Biggers J, Kattelmann KK. Relationships of cognitive load on eating and weight-related behaviors of young adults. Eat. Behav. 2016;21:89-94.
20. Dikmen AU, Altunsoy M, Koç AK, Eda K, Özkan S. Physical activity level of medical students: Is there a family effect? Arch. Med. Res. 2022;3(2):63-73.
21. Oğuzhan A, Girit Ç, Şennur K, Necdet S, Vardar SA. The relationship between chronotypes and physical activity in healthy young medical students. Turk. Med. Stud. J. 2018;5(2):24-27.
22. Edwards ES, Sackett SC. Psychosocial Variables Related to Why Women are Less Active than Men and Related Health Implications. Clin Med Insights Womens Health. 2016;9(1):47-56.
23. Meyerson SL, Odell DD, Zwischenberger JB, et al. The effect of gender on operative autonomy in general surgery residents. Surgery. 2019;166(5):738-743.
24. Coulson RL, Feltovich PJ, Spiro RJ. Cognitive Flexibility in Medicine: An Application to the Recognition and Understanding of Hypertension. Adv Health Sci Educ Theory Pract. 1997;2(2):141-161.
25. Houser MM, Worzella G, Burchsted S, Marquez C, Domack T, Acevedo Y. Wellness skills for medical learners and teachers: Perspective taking and cognitive flexibility. MedEdPORTAL. 2018;14:10674.
26. Derrick M, Rovai A, Ponton M, Confessore G, Carr P. An examination of the relationship of gender, marital status, and prior educational attainment and learner autonomy. Educ. Res. Rev. 2007;2(1):1-8.
27. Pirmohamed S, Boduszek D. Gender Differences in the Presence and Extent of Academic Motivational Attributes, Independent Study, and the Predictive Value on Achievement amongst University Students. Proceedings of International Academic Conferences.IISES.2015:2704648.
28. Crone EA, Dahl RE. Understanding adolescence as a period of social–affective engagement and goal flexibility. Nat. Rev. Neurosci. 2012;13(9):636-650.
29. Richard's MM, Krzemien D, Valentina V, et al. Cognitive flexibility in adulthood and advanced age: Evidence of internal and external validity. Applied Neuropsychology: Adult. 2021;28(4):464-478.
30. Wilson CG, Nusbaum AT, Whitney P, Hinson JM. Age-differences in cognitive flexibility when overcoming a preexisting bias through feedback. J Clin Exp Neuropsychol. 2018;40(6):586-594.
31. Fleming VB. Cognitive flexibility and spoken discourse in younger and older adults.Doctoral dissertation, University of Texas.2007.
32. Wu JS-T, Hauert C, Kremen C, Zhao J. A Framework on Polarization, Cognitive Inflexibility, and Rigid Cognitive Specialization. Front. Psychol. 2022;13:1386.
33. Snyder HR, Miyake A, Hankin BL. Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. Front. Psychol. 2015;6:328.
34. Stange JP, Alloy LB, Fresco DM. Inflexibility as a vulnerability to depression: A systematic qualitative review. Clinical Psychology: Science and Practice. 2017;24(3):245.
35. Gruner P, Pittenger C. Cognitive inflexibility in obsessive-compulsive disorder. Neurosci. 2017;345:243-255.
36. Koren D, Seidman LJ, Harrison RH, et al. Factor structure of the Wisconsin Card Sorting Test: dimensions of deficit in schizophrenia. Neurosci. 1998;12(2):289.
37. Vásquez-Rosati A, Montefusco-Siegmund R, López V, Cosmelli D. Emotional influences on cognitive flexibility depend on individual differences: A combined micro-phenomenological and psychophysiological study. Front. Psychol. 2019;10:1138.
38. Stubbé HE, Theunissen NC. Self-directed adult learning in a ubiquitous learning environment: A meta-review. Proceedings of the First Workshop on Technology Support for Self-Organized Learners.2008:5-28.
39. Erickson KI, Hillman C, Stillman CM, et al. Physical Activity, Cognition, and Brain Outcomes: A Review of the 2018 Physical Activity Guidelines. Med Sci Sports Exerc. 2019;51(6):1242-1251.
40. Van den Berg V, Saliasi E, De Groot RH, Jolles J, Chinapaw MJ, Singh AS. Physical activity in the school setting: Cognitive performance is not affected by three different types of acute exercise. Front. Psychol. 2016;7:723.
41. Golsteijn RH, Gijselaers HJ, Savelberg HH, Singh AS, de Groot RH. Differences in habitual physical activity behavior between students from different vocational education tracks and the association with cognitive performance. Int. J. Environ. Res. Public Health. 2021;18(6):3031.
42. Rezab S. Exercise and cognition in young adults. Psychological Sciences Undergraduate Publications, Presentations and Projects. 2015.
43. Salthouse TA, Davis HP. Organization of cognitive abilities and neuropsychological variables across the lifespan. Developmental Review. 2006;26(1):31-54.
44. Akram M, Ghous M, Tariq I, Khan H, Paracha M, Hussain B. The association between physical activity with cognitive and cardiovascular deconditioning in age related decline of college students. JPMA J Pakistan Med Assoc. 2018;68(12):1755-1758.
45. Magnon V, Vallet GT, Dutheil F, Auxiette C. Sedentary lifestyle matters as past sedentariness, not current sedentariness, predicts cognitive inhibition performance among college students: an exploratory study. Int. J. Environ. Res. Public Health. 2021;18(14):7649.

BİLİMSEL ARAŞTIRMA MAKALESİ

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Anti-Aquaporin 4 Ve Anti-Miyelin Oligodentrosit Glikoprotein Antikor İlişkili Nöromiyelitis Optika Spektrum Hastalığı Tanısı Alan Olguların Klinik ve Radyolojik Özellikleri

Clinical and Radiologıcal Features of Patients Diagnosed wıth Anti-Aquaporin 4 and Anti-Myelin Oligodentroside Glycoprotein Antibody-Related Neuromyelıtıs Optica Spectrum Disease

***Melike DOĞAN ÜNLÜ*[1]** **Serpil DEMİRCİ[1]**

ÖZ

Amaç: Nöromiyelitis Optika Spektrum Hastalığı (NMOSH) tanısı alan ve antikor pozitifliği eşlik eden hastaların klinik, görüntüleme ve laboratuvar bulgularını sunmayı amaçladık.
Araçlar ve Yöntem: Bu retrospektif gözlemsel çalışmaya NMOSH tanısı alan 15 hasta dahil edildi.
Bulgular: Hastalarımızın 11'i kadın, 4'ü erkekti. Hastalığın ortalama başlangıç yaşı 51.27±12.26 idi. İlk klinik atak 3 hastada eş zamanlı optik nörit (ON) ve miyelit iken, 6 hastada miyelit, 5 hastada ON idi. On hastanın aquaporin-4 (AQP-4) IgG antikoru, 5 hastanın miyelin oligodentrosit glikoprotein (MOG) IgG antikoru pozitifti. Altı hastanın beyin omirilik sıvısı (BOS) proteini yüksekti. Sekiz hastanın BOS oligoklonal bantı Tip 1 negatif, 1 hastanın Tip 2 pozitif, 1 hastanın Tip 3 pozitifti. Sekiz hastanın kranial manyetik rezonans görüntülemesi normal iken 1 hastanın multipl skleroz (MS)'a benzer lezyonları vardı. İki hastanın önceden bilinen Sjögren Sendromu (SS) tanısı vardı, 3 hastaya da kliniğimizde SS tanısı koyuldu. Atak tedavisi olarak intravenöz metilprednizolon (1000 mg/gün) ve töropatik plazma değişimi, profilaktik tedavi olarak oral steroid, azatioprin, ritüksimab ve siklofosfamid tekli veya kombinasyon tedavileri verildi.
Sonuç: NMOSH'ı prognoz olarak MS'den daha ağır seyretmektedir. Otoimmün hastalıklardan en sık SS ile birliktelik gösterir. MOG IgG antikor pozitifliği olanların AQP-4 IgG antikor pozitifliği olanlara göre atak ve profilaktik tedaviye yanıtları daha iyi olduğu görülmüştür.

Anahtar Kelimeler: aquaporin 4; miyelin oligodentrosit glikoprotein; nöromiyelitis optika; optik nörit; transvers miyelit

ABSTRACT

Purpose: We aimed to present the clinical, imaging and laboratory findings of patients which diagnosed Neuromyelitis Optica Spectrum Disease (NMOSD) and accompanied by antibody positivity.
Materials ve Metods: This retrospective observational study included 15 patients diagnosed with NMOSH.
Results: Eleven of our patients were female and four were male. The mean age at onset was 51.27±12.26 years. The first clinical attack was simultaneous optic neuritis (ON) and myelitis in 3 patients, myelitis in 6 patients and ON in 5 patients. Ten patients had positive aquaporin-4 (AQP-4) IgG antibody and 5 patients had positive myelin oligodentrocyte glycoprotein (MOG) IgG antibody. Six patients had elevated cerebrospinal fluid (CSF) protein. CSF oligoclonal band of eight patients was Type 1 negative, 1 patient was Type 2 positive, and 1 patient was Type 3 positive. Eight patients had normal cranial magnetic resonance imaging, while 1 patient had lesions similar to multiple sclerosis (MS). Two patients had a previous diagnosis of Sjögren's Syndrome (SS) and 3 patients were diagnosed with SS in our clinic. Intravenous methylprednisolone (1000 mg/day) and thoropathic plasma exchange were given as treatment for the attack, and oral steroids, azathioprine, rituximab and cyclophosphamide were given as prophylactic treatment.
Conclusion: NMOSH has a more severe prognosis than MS. It is most frequently associated with SS among autoimmune diseases. It has been observed that patients with MOG IgG antibody positivity have better response to attack and prophylactic treatment than patients with AQP-4 IgG antibody positivity.

Keywords: aquaporin 4; myelin oligodentrocyte glycoprotein; neuromyelitis optica; optic neuritis; transverse myelitis

Gönderilme tarihi: 26.05.2023; Kabul edilme tarihi: 08.12.2023

[1]Süleyman Demirel Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, Isparta, Türkiye.

Sorumlu Yazar: Melike Doğan Ünlü, Süleyman Demirel Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, Isparta, Türkiye.
e-posta: dr.melikedoganunlu@gmail.com

Makaleye atıf için: Doğan Ünlü M, Demirci S. Anti-aquaporin 4 ve anti-miyelin oligodentrosit glikoprotein antikor ilişkili nöromiyelitis optika spektrum hastalığı tanısı alan olguların klinik ve radyolojik özellikleri. Ahi Evran Med J. 2024;8(1):94-103. DOI: 10.46332/aemj.1303107

GİRİŞ

Nöromiyelitis Optika Spektrum Hastalığı (NMOSH) optik nörit (ON) ve miyelit ile karakterize santral sinir sistemi (SSS)'nin inflamatuar demiyelinizan bir hastalığıdır.[1] Kadınlarda daha sık görülür ve demiyelinizan hastalıkların %1-2'lik kısmını oluşturur.

Astrosit ayaksı çıkıntılarında bulunan Aquaporin-4'e karşı oluşan otoantikor hastalığın patogenezinden sorumlu tutulmaktadır.[2] Bu otoantikorların Aquaporin-4'e bağlanması kan beyin bariyerinde aşırı geçirgenlik yapmakta ve sonrasında perivasküler inflamasyon, astrosit hasarı, spinal kord ve optik sinirlerde demiyelinizasyonu tetiklemektedir.[3] Anti-aquaporin 4 reseptör antikoru (AQP4-IgG) %91 spesifite ve %73 sensitivite ile NMOSH için bir biyobelirteç olarak kabul edilmiştir.[4] AQP4-IgG en çok beyin, omurilik ve optik sinirde bulunur. Hastaların yaklaşık %70'inde AQP4-IgG pozitif saptanmaktadır.[4] AQP-4 IgG antikoru negatif olan bazı NMOSH olgularında 2012 yılında Miyelin Oligodendrosit Glikoprotein (MOG)'e karşı serum antikorları olan Anti-MOG İmmunglobulin G antikoru (MOG-IgG) bulunmuştur.[5] MOG, SSS'indeki oligodendrositler ve miyelin yüzeyinde eksprese edilmektedir. MOG-IgG, AQP-4 Ig G için seronegatif olan NMOS hastalarının yaklaşık %40'ında pozitif olarak saptanmaktadır.[6]

NMOSH'nin öncelikli belirtileri ON ve transvers miyelittir (TM). ON sıklıkla bilateral olma eğilimindedir, TM ise genellikle omuriliğin üçden fazla segmentini etkilemektedir.

Uzun süredir MS'in bir alt tipi olarak kabul edilmiştir. Ancak; son zamanlarda yapılan klinik, görüntüleme, nöropatolojik ve serolojik çalışmalar, NMOSH'nın ayrı bir hastalık olduğunu göstermiştir ve aralarında önemli farklar vardır. NMOSH'ı MS'e göre daha geç başlangıçlı olup kadınları daha çok etkilemekte ve daha ağır seyretmektedir.[1] Miyelit ve ON atağı NMOSH'da daha ciddidir ve kalıcı özürlülüğe neden olur. NMOSH'da sıklıkla beyin manyetik rezonans görüntüleme (MRG)'si normaldir ya da MS'nin radyolojik kriterlerini karşılamaz. Spinal kord MRG'de üç ya da daha uzun vertebral segmenti içeren longitüdinal geniş bir lezyon vardır. Beyin omurilik sıvısı (BOS) incelemesinde pleositoz ve protein yüksekliği NMOSH'de daha fazladır. En önemli özelliği ise NMO-IgG antikor pozitifliğinin eşlik etmesidir.[7,8] BOS'da oligoklonal band (OKB) pozitifliği her iki hastalıkta da gözlenirken, MS'de daha sıklıkla tespit edilmektedir. BOS'ta OKB pozitifliği MS'de %85 iken, NMO'da bu oran %15-30'dur.[7]

Eşlik eden otoimmün sendromlar NMOSH'de sık görülür. Bunlar arasında en sık otoimmün tiroidit, sistemik lupus eritematozus (SLE) ve Sjögren Sendromu (SS) görülür.[1]

Atak tedavisine 1000 mg/gün intravenöz (IV) metilprednizolon (MP) ile başlanmaktadır. Atağın ciddiyetine bağlı olarak oral steroid ile doz kademeli olarak azaltılarak devam edilmelidir. Hastanın klinik durumu yeterince düzelmezse veya nörolojik semptomlar kötüleşirse terapötik plazma değişimi (TPD) beş ila yedi seans yapılabilir. TPD ne kadar erken başlanırsa klinik yanıt daha iyi olur.[9] Ataklar MS'e göre daha uzun sürede düzeldiği ve sekel bırakma olasılığı MS'den daha fazla olduğu için NMOSH'nın MS'den ayrımı iyi yapılmalı ve mümkün olduğunca vakit kaybetmeden atak ve remisyon tedavisine başlanmalıdır.

Makalemizde demiyelinizan hastalıklar arasında en sık karşılaştığımız MS'e göre daha nadir görülen, farklı görüntüleme, klinik ve laboratuar bulguları olan seropozitif 15 NMOS hastasını retrospektif olarak değerlendirdik.

ARAÇLAR ve YÖNTEM

Bu retrospektif gözlemsel çalışmaya 2016-2021 yılları arasında Süleyman Demirel Üniversitesi Nöroloji Kliniğinde; Wingerchuk tanı kriterlerine göre NMOSH tanısı alan 15 olgu alındı. Hastalara çalışma için bilgi verildi ve yazılı onamları alındı. Her hastanın detaylı nörolojik muayenesi ve demografik bilgileri kaydedildi. Hastalığın başlangıç yaşı, Genişletilmiş Özürlülük Durum Ölçeği (EDSS), atak özellikleri, atak sayıları, ataklar arasındaki süre, atak sırasında aldıkları tedavi ve profilaktik tedavi, görüntüleme bulguları, beyin omurilik sıvısı (BOS) sonuçları, görsel uyarılmış potansiyel (VEP) bulguları ve antikor yanıtları retrospektif olarak değerlendirildi. Çalışma protokolü Süleyman Demirel Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu tarafından (06.01.2022 tarih ve 1/4 sayı) onaylandı.

BULGULAR

Hastaların 11'i (%73.3) kadın, 4'ü (%26.7) erkekti. Hastalığın ortalama başlangıç yaşı 51.27±12.26 idi. Hastaların ortalama atak sayısı 2.67±1.45 olup ilk atak ile ikinci atak arasında geçen ortalama süre 18±31.16 aydı. Hastaların ortalama EDSS skoru 3.47±1.93 idi (Tablo 1). Üç hastada ilk klinik atak eş zamanlı ON ve miyelit iken, 5 hastada ON, 6 hastada miyelit, 1 hastada ise dirençli bulantı kusma ile karakterize Area Postrema Sendromuydu. İlk atak ON olan 5 hastanın 3'ünde ON atağı tek taraflıydı ve MOG IgG antikoru pozitifti. İlk atağı bilateral ON olan 2 hastanın da AQP-4 IgG antikoru pozitifti. İlk atak miyelit olan hastaların 4'ünün AQP-4 IgG, 2'sinin MOG-IgG antikor pozitifliği vardı. Olgulardan 10 hastanın AQP-4 IgG antikoru, 5 hastanın MOG IgG antikoru pozitifdi (Tablo 1).

Tablo 1. Olguların Demografik ve Klinik Özellikleri.

Hastalar	Yaş	C	İlk atak	1. ve 2. atak arası süre	Toplam atak sayısı	OİH	AT	PT	Antikor	EDSS (atak)	Tanı
Olgu 1	39	K	Bilateral ON ve myelit	3 ay	5 (4 ON, 1 myelit)	SS	Pulse TPD	SP RTX	AQP-4 IgG	6	NMOSH
Olgu 2	53	K	ON (bilateral)	1 yıl	4 (1 ON, 3 miyelit)	SS	TPD	AZA RTX	AQP-4 IgG	4.5	NMOSH
Olgu 3	62	E	Myelit	1 yıl	3 (miyelit)	SS	Pulse	SP	AQP-4 IgG	4.5	NMOSH
Olgu 4	66	K	ON (bilateral)	4 yıl	3 (bil ON, 2 miyelit)	Yok	TPD	RTX	AQP-4 IgG	6	NMOSH
Olgu 5	47	E	Myelit	1 yıl	4 (3 miyelit 1 ON)	Yok	Pulse TPD	AZA Oral steroid	AQP-4 IgG	2.5	NMOSH
Olgu 6	60	K	Bilateral ON ve Miyelit	2 yıl	3 (2 miyelit, 1 ON)	Yok	Pulse	-	AQP-4 IgG	2	NMOSH
Olgu 7	61	K	Sağ ON	-	1	Yok	Pulse	AZA	MOG IgG	1.5	MOGAD
Olgu 8	46	K	Sol ON	-	1	RA	Pulse	Metoteraksat, oral steroid	MOG IgG	1.5	MOGAD
Olgu 9	47	K	Sol ON	1 yıl	2 (ON)	Yok	Pulse TPD	RTX	MOG IgG	2.5	MOGAD
Olgu 10	41	K	Miyelit	-	1	SS	Pulse TPD	SP RTX	AQP-4 IgG	6	NMOSH
Olgu 11	33	K	Area postrema sendromu	3 ay	3 (area postrema, 2 ON)	Yok	Pulse TPD	AZA	AQP-4 IgG	1.5	NMOSH
Olgu 12	60	K	Miyelit	2 yıl	3miyelit	Yok	Pulse TPD	-	AQP-4 IgG	4.5	NMOSH
Olgu 13	68	K	Bilateral ON ve miyelit	10 yıl	3 (2 ON, 1 myelit)	SS	Pulse	AZA Oral steroid	AQP-4 IgG	6	NMOSH
Olgu 14	28	E	Miyelit	-	1	Yok	Pulse	AZA	MOG IgG	1.5	MOGAD
Olgu 15	58	E	Miyelit	-	1	Yok	Pulse	AZA	MOG IgG	1.5	MOGAD

C:Cinsiyet, OİH:Otoimmün hastalık, AT:Atak tedavisi, PT: Profilaktik tedavi, EDSS:Genişletilmiş özürlülük durum ölçeği, ON:Optik Nörit, SS:Sjögren Sendromu, RA:Romatoid artrit, TPD:Terapötik plazma değişimi, AZA:Azatiyoprin, RTX: Ritüksimab, SP: Siklofosfamid, AQP-4: Aquaporin 4, MOG: Miyelin oligodentrositik glikoprotein, NMO: Nöromiyelitis optika, MOGAD: Miyelin Oligodentrositik glikoprotein ilişkili hastalık

Beş hastanın BOS sonucuna ulaşılamadığı için elimizde 10 hastanın BOS sonuçları mevcuttu. 6 hastanın BOS proteini yüksekti ve hiçbir hastada BOS'da pleositoz saptanmadı. 8 hastanın oligoklonal bantı Tip 1 negatif, bir hastanın da Tip 2 pozitif (olgu 10), 1 hastanın da Tip 3 pozitifdi (olgu 14) (Tablo 1).

Sekiz hastanın kranial MRG'si normal iken 6 hastanın nonspesifik iskemik değişiklikleri vardı (Tablo 2). Bir hastanın (olgu 5) kranial lezyonları MS radyolojik kriterlerini karşılamasa da MS'deki gibi periventriküler, korpus kallozuma teması olan ve U liflerini tutan özellikteydi ve torakal MRG'sinde beş vertebra boyunca kesintisiz görülen kontrast tutulumu olan demiyelinizan lezyonu vardı. Bu hastanın BOS OKB tip 1 negatif, BOS proteini normal, BOS'da pleositozu yoktu, AQP-4 IgG antikoru pozitifti.

MOG IgG pozitifliği olanlardan olgu 7-8-9'un kranial ve spinal MRG'sinde hiçbir demiyelinizan lezyonu yoktu (Tablo 2). Bu hastaların başlangıç kliniği tek taraflı ON idi. Olgu 14 ve 15'in kranial MRG'si normal iken spinal MRG'de iki vertebra boyunu geçen demiyelinizan lezyonu vardı.

Tablo 2. Olguların Manyetik Rezonans Görüntüleme (MRG), Görsel Uyarılmış Potansiyel (VEP) ve Beyin Omurilik Sıvısı (BOS) bulguları.

Hastalar	KRANİAL ve ORBİTA MRG	SPİNAL MRG	VEP	BOS
Olgu 1	Kranial MRG: Normal	Servikal: C1-7 hiperintens ekspansif demiyelinizan lezyon Torakal: T1-7 hiperintens demiyelinizan lezyon	P100 latanslarında bilateral uzama	Protein: 40 mg/dl OKB: Tip 1
Olgu 2	Kranial MRG: Periventriküler-supraventriküler beyaz cevher alanlarında nonspesifik iskemik gliotik değişiklikler	Servikal C1-2 düzeyinden başlayıp C7'ye uzanım gösteren kordda yer yer ekspansiyona neden olan T1A'da izointens, T2A'da hiperintens yer yer kontrast tutulumu olan patolojik sinyal değişikliği Torakal: Th 1-7 arasında uzanım gösteren T1A da izointens, T2A'da hiperintens heterojen kontrastlanan lezyon alanları	P100 latanslarında bilateral uzama	Yok
Olgu 3	Kranial MRG: Peri-supraventriküler düzeyde beyaz cevher alanlarında, bilateral bazal ganglionlarda, T1A da izointens, T2A ve FLAIR de hiperintens iskemik gliotik değişiklikler	dens axis apeksi hizasında spinal kord-bulbus bileşke düzeyinden başlayıp C7'ye kadar uzanım gösteren spinal kordun tamamını tutan T1A'da izointens, T2A'da hiperintens kontrast tululumu gösteren demiyelinizan lezyon	P100 latanslarında bilateral uzama	Protein: 72 mg/dl OKB: tip 1
Olgu 4	Kranial MRG: Normal	Servikal: C1'den başlayıp C7'ye uzanan spinal kordun santralinde baskın kontrast tutan demiyelinizan hiperintens lezyon Torakal: T5-6, T8-9, T9-10 bir vertebra boyunu geçmeyen, kontrast tutulumu olmayan milimetrik hiperintens odaklar	P100 latanslarında bilateral uzama	Yok
Olgu 5	Kranial MRG: Periventriküler düzeyde birkaç adet, ventriküle dik yerleşen ve her iki serebral hemisferde subkortikal düzeyde U liflerini de tutan milimetrik boyutta demiyelinizan odaklar	Servikal: C3-6 arasında spinal kord santral-posteriorunda daha belirgin izlenen, spinal kordda ekspansiyona neden olan yamalı tarzda kontrast tutulumu olan sinyal değişikliği Torakal: T2'den başlayıp T7 vertebra korpusuna kadar süreklilik gösteren, spinal kordun santralini tutan, T4-5'de kontrastlanması olan demiyelinizan lezyon	P100 latanslarında bilateral uzama	Protein: 45 mg/dl OKB: Tip 1
Olgu 6	Kranial MRG: Periventriküler supraventriküler düzeyde iskemik gliotik değişiklikler	C2-6 düzeyinde spinal kordda ekspansiyona neden olan, T1Ada hipointens, T2Ada hiperintens kontrast tutan demiyelinizan lezyon	Yok	Protein: 27 mg/dl OKB: Tip 1
Olgu 7	Kranial MRG: Normal Orbita: Demiyelinizan lezyon yok. Kontrast tutulumu yok	demiyelinizan lezyonu yok	Sağda P100 latanslarında uzama	Yok
Olgu 8	Kranial MRG: Normal Orbita MRG: Normal	Demiyelinizan lezyon yok	Solda P100 latanslarında uzama	Yok
Olgu 9	Kranial MRG: Normal Orbita MRG: Normal	Demiyelinizan lezyon yok	Solda P100 latanslarında uzama	Protein: 58 mg/dl OKB: Tip 1
Olgu 10	Kranial MRG: Normal Orbita MRG: sol optik sinirde belirgin kontrast tutulumu, optik şitte silik kontrastlanma, sağ optik sinirde intraorbital anterior kesimde hafif silik kontrastlanma	Spinal MRG: Servikomeduller bileşkeden başlayıp T10 a kadar uzanan kontrast tutan ödem etkisi oluşturan ve kordda ekspansiyona neden olan demiyelinizan lezyon	Bilateral P100 latanslarında uzama	Protein: 192 mg/dl OKB: Tip 2
Olgu 11	Kranial MRG: Normal Orbita MRG: Normal	Spinal MRG: Demiyelinizan lezyon yok	P100 latanslarında bilateral uzama	Protein: 27 mg/dl OKB: Tip 1
Olgu 12	Kranial MRG: Periventriküler iskemik gliotik odaklar	C1-4 ve T1-8 arası uzanım gösteren T2A hiperintens heterojen kontrast tutan lezyon	Solda P100 latanslarında uzama	Protein: 103 mg/dl OKB: Tip 1
Olgu 13	Kranial MRG: Periventriküler iskemik gliotik odak	Servikomeduller bileşkeden başlayıp C7 ye kadar uzanan servikal kordu ekspanse eden heterojen kontrastlanması olan demiyelinizan lezyon	Bilateral P100 latanlarında uzama	Yok
Olgu 14	Kranial MRG: normal	Servikal MRG: C5 hizasından başlayıp T1'e kadar uzanım gösteren demiyelinizan lezyon	Bilateral P100 latanlarında uzama	Protein: 110 mg/dl OKB: Tip 3
Olgu 15	Kranial MRG: Periventriküler iskemik gliotik odak	Servikal MRG: normal Torakal MRG:T2'den başlayıp T8'e kadar uzanan kordu hafif ekspanse eden demiyelinizan lezyon	Bilateral P100 latanlarında uzama	Protein: 140 mg/dl OKB: Tip 1

MRG: Manyetik rezonans görüntüleme, VEP:Görsel uyarılmış potansiyel, BOS: Beyin oirilik sıvısı, OKB: Oligoklonal bant

İki hastanın önceden bilinen SS tanısı vardı, 3 hastaya da kliniğimizde SS tanısı koyuldu. SS eşlik eden hastaların AQP-4 IgG antikoru pozitifti. SS olan hastaların ikisinin ilk atağı eş zamanlı ON ve miyelitti. Bir hastanın da eşlik eden Romatoid Artrit (RA) tanısı ve MOG IgG antikor pozitifliği vardı (Tablo 1).

VEP'de bir hasta hariç diğer hastaların P100 latansında uzama vardı.

Yedi hasta atak tedavisi olarak 1000 mg/gün IV MP (pulse steroid) tedavisi alırken 2 hasta sadece TPD, 6 hasta pulse steroid ve TPD kombine tedavisini aldı. Profilaktik tedavi olarak 4 hastaya sadece azatiyoprin (AZA), 2 hastaya sadece ritüksimab (RTX), SS tanısı olan hastalara RTX, siklofosfamid (SP), AZA tekli veya kombinasyon tedavileri, 2 hastaya oral steroid ve AZA kombinasyonu, RA eşlik eden bir hastaya da metotreksat ve oral steroid kombinasyon tedavisi verildi. İki hasta takiplere gelmedikleri için profilaktik tedavi başlanamadı (Tablo 1).

TARTIŞMA

Wingerchuk tarafından 2006 yılında NMO tanısı için kriterler belirlenmiştir. Bu kriterlere göre ON, TM ve belirtilen üç destekleyici kriterden ikisinin olması gerekir: 1-Spinal MRG'de 3 ve daha üstü segment tutulumunun olması 2- Kranial MRG bulgularının MS için tanısal olmaması 3-NMO-IgG antikor seropozitifliği.[7] Bu kriterleri tam olarak karşılamayan olgular NMOSH olarak sınıflandırılmıştır.[1,10] 2015 yılında bu kriterler tekrar revize edilmiş, NMO ve spektrum hastalıkları NMOSH adı altında tek bir antite olarak kabul edilmiştir. Yeni kriterlere göre AQP4 IgG antikor pozitifliği olan olgular için bir ana klinik bulgu tanı için yeterlidir, diğer olası tanıların da dışlanması gerekmektedir. Bu ana klinik bulgular: 1-Optik nörit, 2-Akut transvers miyelit, 3-Area postrema sendromu, 4- Akut beyinsapı sendromu, 5- Semptomatik narkolepsi veya akut klinik diansefalik sendromu, 6- NMOSH için tipik beyin lezyonlarını içeren semptomatik serebral sendrom.[11] Olgularımızın hepsi revize edilmiş yeni tanı kriterlerini karşılıyordu.

NMOSH ortalama başlangıç yaşı 35-45 yaş arasındadır ve kadınlarda daha sık görülür.[12] Hastalarımızın ortalama başlangıç yaşı 51.27±12.26 olup hastaların %73.3'ü kadındı. Hastalık %20 hastada monofazik seyir, % 80 hastada ise ataklı seyir gösterir.[3] Hastalarımızda da ataklı seyir hakimdi. Ataklar arasındaki süre değişken olmakla birlikte hastaların yaklaşık %90'ının ilk atağı takip eden 3 yıl içerisinde ikinci atağı geçirme ihtimali yüksektir.[3] Hastalarımızın ilk atak ile ikinci atak arası geçen süre ortalaması 18±31.16 aydı.

NMOSH'da hastaların %10-25'inde AQP-4 IgG antikorları saptanmaz. Bu seronegatif grubun yaklaşık %21'inde MOG'a karşı otoantikorlar saptanır.[13] Hasta grubumuzdan 10 kişinin AQP4 IgG, 5 kişinin de MOG IgG antikoru pozitifti.

MOG, SSS'inde oligodentrositler tarafından üretilen bir proteindir. Bu glikoproteinin işlevi tam olarak anlaşılamamıştır fakat hücre yüzey reseptörü veya hücre adezyon molekülü olarak hareket edebilir. Miyelin Oligodentrosit Glikoprotein İlişkili Hastalık (MOGAD) SSS'nin nadir görülen antikor ilişkili inflamatuar demiyelinizan bir hastalığıdır. ON, TM, akut dissemine ensefalomiyelit (ADEM), kortikal ensefalit gibi değişen klinik tablolar ile başlayabilir. Klinik tablo NMOSH'a benzer olsa da son yıllarda yapılan çalışmalar sonucu MOGAD immün patolojisinin diğerlerinden oldukça farklı olduğu bildirilmiştir.[14]

MOGAD'da ADEM tablosu ateş, halsizlik, baş ağrısı, bulantı, kusma, mental durum değişikliği, epileptik nöbet, motor ve duyu kayıpları, vizüel kayıplar gibi klinik bulgularla karakterizedir, özellikle çocuk hastalarda sık görülür. ADEM tanısı alan çocukların serumunda %40-62 oranında MOG antikoru saptanmıştır.[15-17] ADEM ile başlangıç MOG antikoru pozitif olan yetişkin hastaların %18'inden az görülür.[16,18]

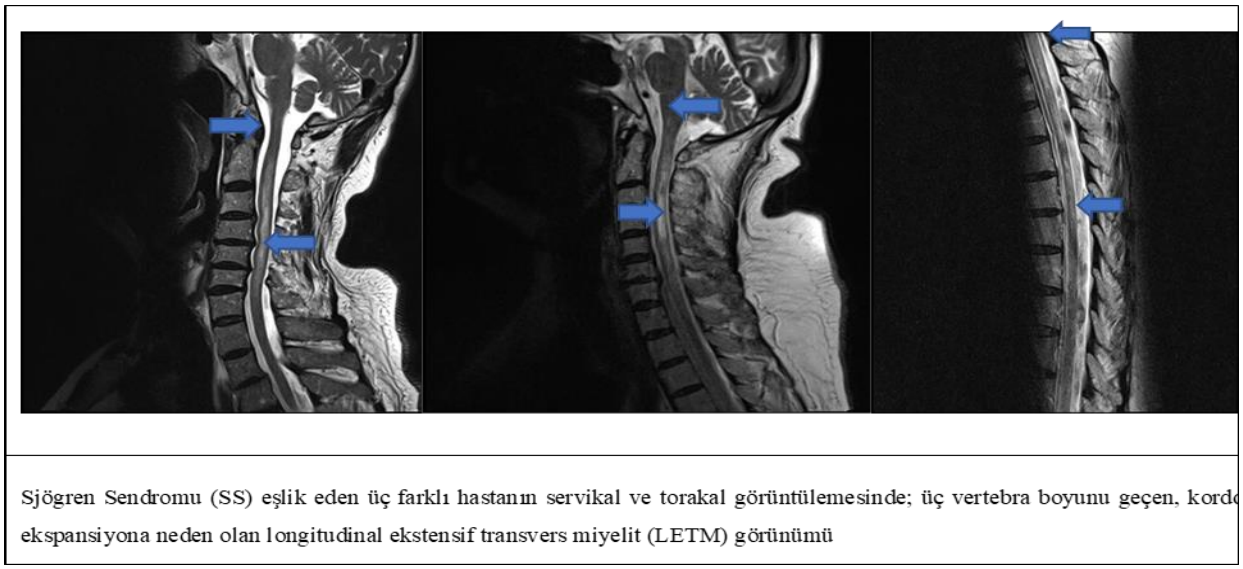
MOGAD'da ON ilk klinik atak olarak %40-60 hastada bildirilmiştir ve daha sıklıkla yaşlı hastalarda görülür. Genç olgularda daha sıklıkla tek taraflı ON görülürken geç başlangıçlı olgularda da her iki optik sinirin tutulduğu görülmüştür.[19] MOGAD hastalarının yaklaşık %20'sinde başlangıç bulgusu olarak izole TM görülür. TM ve ON birlikteliği hastaların %8-15'inde görülür.[16,18,20] Özellikle genç hastalarda NMO'ya benzer 3 vertebra boyunu geçen longitudinal ekstensif transvers miyelit (LETM) görülebilir. NMO'nun aksine spinal kordun alt kısımlarını da içine alan akut flask miyelit tarzında tutulumlar yapabilir.[21] Dorsal medulla oblongata tutulumuna bağlı inatçı bulantı kusma hıçkırık kliniği area postrema sendromu olarak bilinir, NMO'da daha sık görülür. Bir çalışmada MOGAD hastalarının yaklaşık % 15'nde bildirilmiştir ve bu hastaların yaklaşık %91'inde ilk semptom olarak görülmüştür.[16] Bir hastamızın başlangıç kliniği dirençli bulantı kusma ile karakterize area postrema semdromuydu. Bu hastanın AQP-4 IgG antikoru pozitifti.

MOGAD tanısı koyduğumuz 3 hasta kadın, 2 hasta erkekti ve başlangıç yaşı 40 yaş üstüydü. Üç hastanın başlangıç kliniği tek taraflı ON, 2'sinin ise TM'di. Başlangıç kliniği ON olan 3 hastanın da spinal, orbita ve kranial MRG'lerinde herhangi bir demiyelinizan lezyon yoktu. Başlangıcı TM olan 2 hastanın spinal MRG'sinde 3 vertebra boyunu geçen LETM vardı. Hastaların VEP'de anterior görme yollarında etkilenmesi vardı. Üç hastanın BOS proteinin yüksekti, BOS'da pleositozu yoktu ve 2 hastanın OKB Tip 1 negatif, 1 hastanın da tip 3 pozitifti.

Anti-MOG ilişkili NMOSH, daha erken başlangıçlı ve daha iyi bir klinik ile seyretme eğilimindedir.[16] MOGAD tanısı alan hastalarımızda da ON kliniğindeki düzelme AQP-4 IgG antikoru pozitif olanlara göre daha iyiydi. 2 hasta atak tedavisi olarak sadece pulse steroidden fayda görürken 1'inde pulse steroid sonrası plamaferez tedavisi ihtiyacı oldu, bu hastaya da profilaktik olarak ritüksimab tedavisi başlandı. LETM olan 2 MOGAD olgusu ise atak tedavisinde pulse steroidden fayda gördü ve profilaktik tedavi olarak AZA başlandı.

NMOSH'da BOS bulguları MS'den oldukça farklıdır. MS'de milimetre küp başına 50'nin altında ve sadece mononükleer hücre görülürken, NMOSH'de hücre sayısı 50'nin üzerinde olabilir ve polimorf hücreler görülebilir. MS'de BOS proteini normal veya ılımlı yüksek iken NMOSH'da artmış olabilir.[22] Hastalarımızdan 10 hastanın BOS bulguları değerlendirildi. Yedi hastanın BOS proteini yüksekti ve hiçbirinde milimetre küpde 50'nin üzerinde hücre saptanmadı. NMOSH'da BOS'da OKB pozitifliği MS'e göre oldukça nadirdir, %15-30 civarındadır.[7] Hastalarımızdan sadece olgu 10'nun OKB tip 2 pozitifliği, olgu 14'ün de Tip 3 OKB pozitifliği vardı.

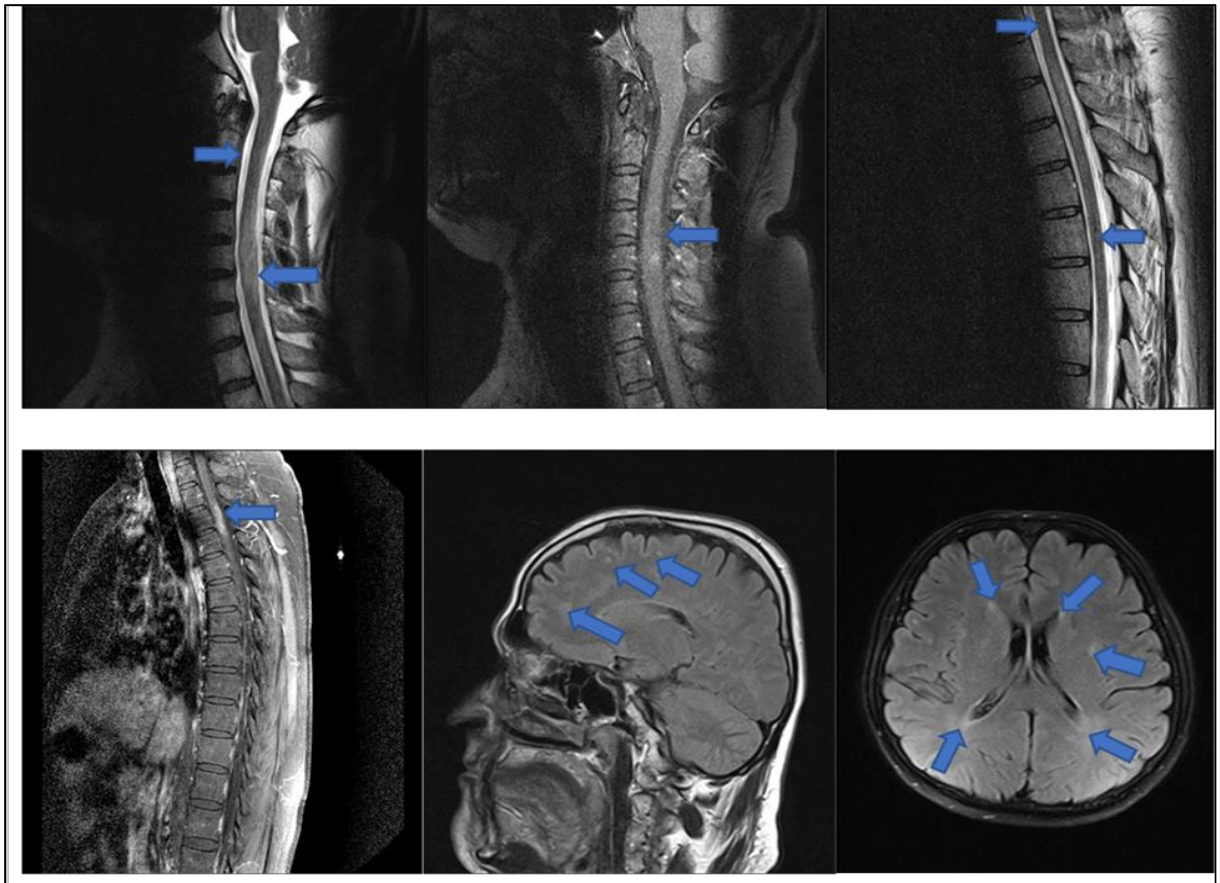
NMOSH'nin en spesifik görüntüleme özelliği 3 veya daha fazla bitişik vertebra boyunca uzanan ve ağırlıklı olarak omurilikte merkezi gri cevheri içeren LETM'dir (Resim 1). Akut dönemde gadolinyum tutulumu ve ödem görülür. Lezyonun uzun segment olması MS'den ayrıt ettiren en önemli görüntüleme bulgularından biri olsa da MS'de de birleşme eğiliminde olan uzun segment lezyonlar veya NMOSH'da da kısa segment lezyonlar görülebilir. Servikal lezyonlar medulla oblangataya kadar uzanabilir. On bir hastanın en az üç vertebra boyunca kesintisiz uzanan spinal kord lezyonu vardı. Dört hastanın spinal kordda herhangi bir lezyonu yoktu. Bu 4 hastadan 3'ünün MOG IgG pozitifliği vardı.



Resim 1. Spinal MRG'da Longitudinal Ekstensif Transvers Miyelit (LETM) Görünümü.

NMO hastalarının beyin MRG'leri çoğunda normal olsa da nonspesifik beyin lezyonları görülebilir. Lezyonların MS'in Barkoff Kriterlerini karşılaması nadirdir. NMOSH'deki beyin lezyonları, AQP4 su kanallarının yoğun olarak bulunduğu özellikle serebral aquadukta yakın olan lateral, üçüncü ve dördüncü ventriküllerin ependimal yüzeyini takiben periependimal alanlarda asimetrik olarak dağılmaktadır. Korpus kallozum, diensefalik bölge ve beyin sapının ependimal yüzeyleri özellikle area postrema ve nükleus traktus solitarius gibi alanlar beyin lezyonları için tipik yerler olarak kabul edilmektedir.[23,24]

Hastalarımızdan 8'inin beyin MRG'si normaldi. Altı hastanın periventriküler bölgede milimetrik nonspesifik beyaz cevher lezyonu vardı. Olgu 5'in beyin lezyonları MS'deki gibi periventriküler ventriküle dik yerleşen, U liflerini tutan ve korpus kallozuma teması olan demiyelinizan lezyon özelliğindeydi. Olgu 5'in kranial lezyonları MS'e benzer olsa da spinal MRG'sinde servikal ve torakalde en az 3 vertebra boyunca kesintisiz uzanan demiyelinizan lezyonu vardı (Resim 2). Serum AQP-4 IgG antikoru pozitif, BOS OKB Tip 1 negatifdi (Tablo 2).

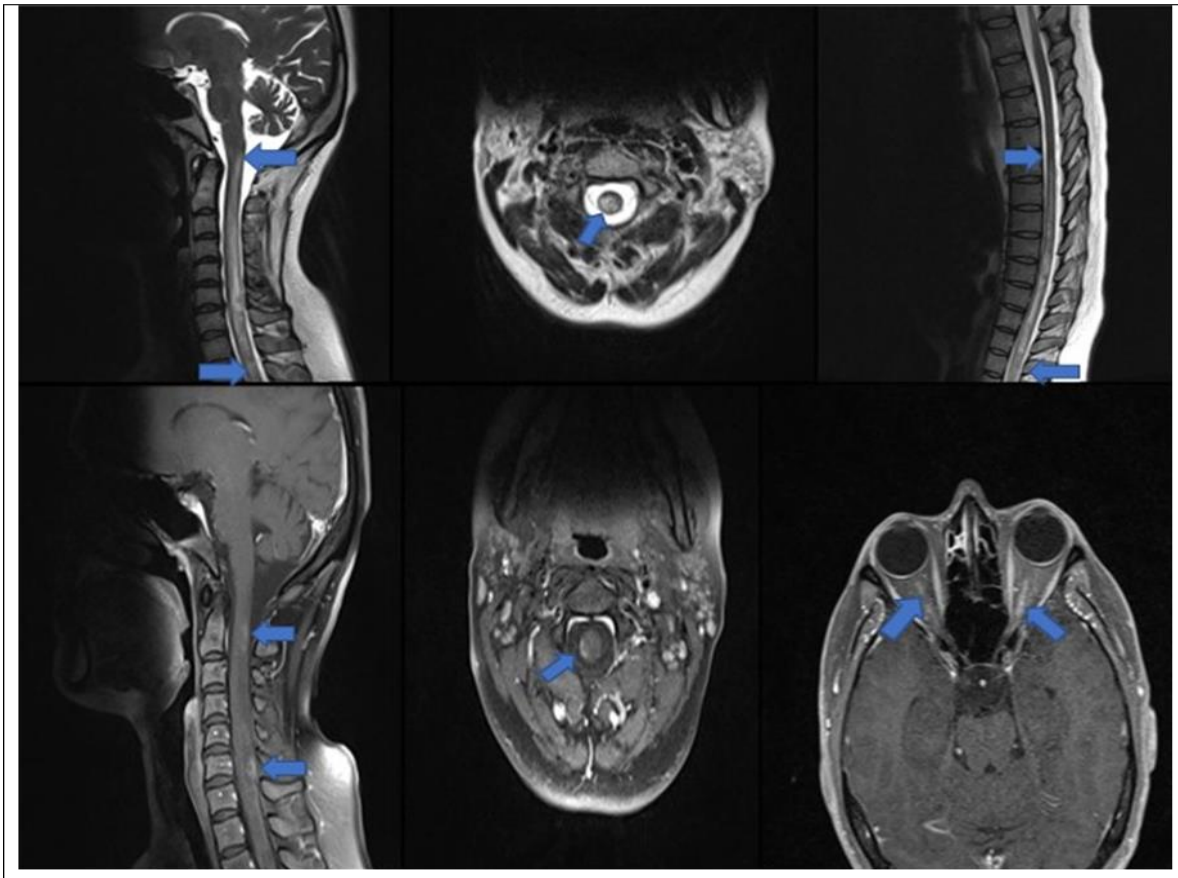


Servikal C3-6 arasında spinal kordda ekspansiyona neden olan yamalı tarzda kontrast tutulumu ve T2'den başlayıp T7 vertebra korpusuna kadar süreklilik gösteren, spinal kordun santralini tutan, T4-5'de kontrastlanması olan demiyelinizan lezyon

Periventriküler düzeyde birkaç adet, ventriküle dik yerleşen ve her iki serebral hemisferde subkortikal düzeyde U liflerini de tutan milimetrik boyutta demiyelinizan lezyonlar

Resim 2. Olgu 5'in servikal, torakal ve kranial manyetik rezonans görüntülemesi (MRG).

Optik sinir tutulumu MS'e göre NMOSH'da daha sık görülür. Optik sinirlerde kalınlaşma, kontrast tutulumunun olması, optik sinirin uzunluğunun yarısından daha uzun lezyonların olması, sinirin arka segmentinin veya optik kiyazma tutulumunun olması NMOSH'ı lehinedir. MOGAD'daki optik nörit bulguları, AQP4-IgG ilişkili NMOSH ve MS'deki optik nörit bulgularından farklı bazı özellikler gösterir. Bilateral optik sinir lezyonları MOGAD'da daha sık görülür. Kiyazma tutulumu çok nadirdir. Etraftaki orbital dokulara kadar uzanabilen perioptik kontrast artışı hastaların üçte birinden fazlasında görülmektedir.[25] Elimizde 5 hastanın orbita MRG'si mevcuttu. MOGAD tanısı alan üç hastamızın da orbita MRG'lerinde herhangi bir lezyon görülmedi. Sadece olgu 10'nun orbita MRG'sinde bilateral optik sinirlerde kontrastlanma vardı (Resim 3). Bu hastanın da AQP-4 IgG antikoru pozitifti (Tablo 2).



Servikomedüller bölgeden başlayıp T10'a kadar kesintisiz uzanım gösteren ve kontrast tutulumu olan demiyelinizan lezyon.
Orbita MRG'de solda daha belirgin olmak üzere her iki optik sinirde kontrast tutulumu

Resim 3. Olgu 10'un spinal ve orbita manyetik rezonans görüntülemeleri (MRG).

VEP incelemelerinde NMO hastalarının yaklaşık %40'ında P100 latansında uzama ve hastaların yaklaşık %25'inde amplitüdlerde azalma bulunmuştur. Hastaların biri hariç diğerlerinde P100 latanslarında tek taraflı veya iki taraflı uzama vardı.[26]

Eşlik eden otoimmün hastalıklar NMOSH'de sık görülür. Bu otoimmün hastalıklar arasında en sık otoimmün tiroidit, sistemik lupus eritematozus (SLE) ve SS görülmektedir.[1] SS'de ON ve/veya LETM görülebilir. Bu hastalarda AQP-4'e karşı antikorlar tespit edilmiştir.[27] SS ve NMO arasındaki bağlantı net bilinmese de yapılan çalışmalar SS ve NMO örtüşmesi olan hastalarda patogenezde ortak bir mekanizma olabileceğini düşündürmektedir.[28] Hastalarımızdan 5'inin SS'u, 1'inin RA tanısı vardı. SS olan 5 hastanın 3'üne kliniğimizde tanı koyuldu. Hastalarımızdan herhangi bir atak tedavisi başlanmadan önce vaskülit belirteçleri alındı. Göz hastalıkları tarafından kuru göz ve üveit sekeli gibi gözde romotolojik hastalık bulgusu olup olmadığı değerlendirildi. SS'ye yönelik antikor pozitifliği ve kuru göz bulgusu eşlik eden hastalara tükrük bezi biyopsisi yapıldı. Sonuçlar romotoloji bölümü tarafından değerlendirilerek 3 hastaya SS tanısı koyuldu. Eşlik eden otoimmün hastalığın prognozu kötüleştirdiği bilinmektedir.[29] Önceden bilinen SS ve RA tanıları olan 3 hasta kullanmakta olduğu immünsüpresif tedavi altında nörolojik atak geçirdi. SS tanısı olan hastalarımız atak tedavisinde 1000 mg/gün IV MP'dan daha az fayda gördü ve TPD'ye ihtiyaç duydu. Aynı zamanda bu hastaların profilaktik tedaviye yanıtları da diğerlerine göre daha az oldu.

NMOSH'da ataklar daha şiddetli ve sekel bırakma eğiliminde olduğu için atak tedavisine vakit kaybetmeden başlamak önemlidir. Atak tedavisinde ilk tercih 3-5 gün IV 1000 mg/gün MP (pulse)'dir. MP'den fayda görmeyen veya tolere edemeyen hastalara vakit kaybetmeden gün aşırı TPD başlanmalıdır. İntravenöz immünoglobulin

(IVIG) kullanımına ilişkin veriler sınırlıdır ve IVIG yararını değerlendiren çok merkezli randomize kontrollü bir çalışma yoktur.[30] Hastalarımızdan 7'si sadece pulse tedavisi alırken, 2 hastaya sadece TPD yapıldı. 6 hastada ise öncelikle pulse ile tedaviye başlanıp sonradan TPD ihtiyacı oldu. Tüm hastalara koruyucu tedavi başlanana kadar 1 mg/kg oral steroid tedavisi idame devam edildi.

NMOSH çoğu vakada tekrarlayan bir seyir izlediğinden, genellikle tam olmayan iyileşme ve nörolojik defisitlerin hızlı ilerlemesi nedeniyle tanı doğrulandıktan sonra uzun süreli immünosupresif tedavi başlatılmalıdır. Buna göre, AZA ve RTX şu anda NMO'da en yaygın kullanılan birinci basamak tedavilerdir. Diğer immünsüpresif tedaviler arasında mikofenolat mofetil, SP, mitoksantron, metotreksat yer alır.[9] Son yıllarda yapılan çalışmalarda interlökin 6 (IL-6)'nın NMO'lu hastalarda NMO-IgG üreten plazmablastların kalıcılığına katkıda bulunduğunu öne sürülmüştür.[31] Bu hipoteze göre IL-6 reseptör bloke edici antikor olan tocilizumabın tedavide olumlu etkisini gösteren çalışmalar ağırlık kazanmıştır. Bu nedenle, tocilizumab bu tür hastalar için başka bir tedavi seçeneği olarak düşünülebilir.[32,33] Klasik tedavi seçeneklerine yanıt alınamayan vakalarda yeni geliştirilen monoklonal antikor olan ilaçlardan eculizumab, inebilizumab, satralizumab kullanılabilmektedir.[34]

Kombinasyon tedavisi, agresif seyirli NMO hastaları için potansiyel bir seçenektir. AZA ile oral steroid, metotreksat-oral steroid, siklosporin A-oral steroid, RTX-metotreksat kombinasyon tedavilerinin de NMOSH'da etkili olduğu gösterilmiştir.[9]

Hastalarımızdan 4 hastaya AZA, 2 hastaya RTX, 1 hastaya SP, 2 hastaya SP ve RTX, 1 hastaya AZA ve RTX, 2 hastaya oral steroid ve AZA kombinasyon tedavileri başlandı. RA eşlik eden bir hastaya da metotreksat tedavisi almaktaydı, bu tedavinin yanına oral steroid eklendi. İki hasta takiplere gelmediği için tedavi başlanamadı. Profilaktik tedavi sonrası MOG IgG antikoru pozitif olan 4 hastada tekrarlayan atak görülmedi (1 hasta takiplere gelmedi). AQP-4 IgG antikor pozitifliği olan 10 hastanın 5'inde tekrarlayan optik nörit ve miyelit atakları gelişti. Profilaktik tedavi sonrası atak gelişen 5 olgunun 3'ünde SS tanısı vardı.

MS'de kullanılan interferon beta, fingolimod, natalizumab, okrelizumab, alemtazumab gibi ilaçların çoğu NMOSH'nin semptomlarını kötüleştirebilmektedir.[9]

Sonuç olarak klinik, laboratuvar ve görüntüleme bulguları olarak MS'den farklı özelliklere sahip olan NMOSH'ı prognoz olarak da daha ağır seyretmektedir. Optik nörit ve miyelit atakları MS'den daha ağır seyretmekte ve daha uzun sürede ve genellikle sekelli olarak iyileşmektedir. BOS'da OKB pozitifliği MS'e göre daha nadir görülse de klinik gidiş ve görüntüleme bulguları klinisyeni NMOSH'ı yönünde şüphelendirmeli ve antikor istemeye yönlendirmelidir. İlk kez bakılan MOG ve AQP-4 IgG antikorları negatif gelse bile klinik ve görüntüleme NMOSH'nı düşündürüyor ise antikorların 3-6 ay ara ile tekrar bakılması önerilmektedir. NMOSH'ı otoimmün hastalıklardan en sık SS ile birliktelik gösterir. NMOSH'ı tanısı alanlarda altta yatan otoimmün hastalıklar da araştırılmalı veya SS tanısı olan hastalarda SSS tutulumu açısından NMOSH'ı akla gelmelidir. Çalışmamızdaki kısıtlılık olgu sayımızın az olmasıdır. Hasta grubumuzdan MOGAD tanısı alan hastaların AQP-4 antikor pozitifliği olanlara göre atak ve profilaktik tedaviye yanıtları daha iyi olsa da kesin yorum yapabilmek için daha fazla sayıda olgunun olduğu ileri çalışmalara ihtiyaç vardır.

Çıkar Beyannamesi

Herhangi bir çıkar çatışmasının olmadığını yazarlar beyan etmektedirler.

Teşekkür

Çalışmada yer alan hastalarımıza teşekkür ederiz.

Etik Kurul İzni

Bu çalışma için Süleyman Demirel Üniversitesi Tıp Fakültesi Klinik Araştırmaları Etik Kurulundan onay alındı (06.01.2022 tarih ve 1/4 sayı).

Araştırmacıların Katkı Oranı Beyanı

Ana fikir/Planlama: MDÜ, SD. Veri toplama/İşleme: MDÜ, SD. Veri analizi ve yorumlama: MDÜ, SD. Literatür taraması: MDÜ. Yazım: MDÜ, SD. Gözden geçirme ve düzeltme: MDÜ, SD. Danışmanlık: SD.

KAYNAKÇA

1. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology. 1999;53(5): 1107-1114.
2. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med. 2005;202(4):473-477.
3. Sellner J, Boggild M, Clanet M, et al. EFNS guidelines on diagnosis and management of neuromyelitis. Eur J Neurol. 2010;17(8):1019-1032.
4. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet. 2004;364(9451):2106-2112.
5. Lee DH, Linker RA. The role of myelin oligodendrocyte glycoprotein in autoimmune demyelination: a target for multiple sclerosis therapy? Expert Opin Ther Targets. 2012;16(5):451-462.
6. Hamid SH, Whittam D, Mutch K, Linaker S, Solomon T, Das K. What proportion of AQP4- IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients. J Neurol. 2017;264(10):2088-2094.
7. Wingerchuk DM. Diagnosis and Treatment of Neuromyelitis Optica. The Neurologist. 2007;13(1):2-11.
8. Wingerchuk DM, Pittock SJ, Lennon VA, et al. Neuromyelitis optica diagnostic criteria revisited: validation and incorporation of the NMOIgG serum autoantibody. Neurology. 2006;66(10):1485-1489.
9. Trebst C, Jarius S, Berthele A, et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). J Neurol. 2014;261:11-16.
10. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. Lancet Neurol. 2007;6(9):805-815.
11. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85(2): 177-189.
12. Sahraian MA, Radue EW, Minagar A. Neuromyelitis Optica Clinical Manifestations and Neuroimaging Features. Neurol Clin. 2013;31(1):139-152.
13. Sato, DK, Callegaro D, Lana-Peixoto MA, et al. Distinction between MOG antibody positive and AQP4 antibody-positive NMO spectrum disorders. Neurology. 2014;82(6):474-481.
14. Ambrosius W, Michalak S, Kozubski W, Kalinowska A. Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease: Current Insights into the Disease Pathophysiology, Diagnosis and Management. Int. J. Mol Sci. 2021;22(1):100.
15. Brilot F, Dale RC, Selter RC, et al. Antibodies to Native Myelin Oligodendrocyte Glycoprotein in Children with Inflammatory Demyelinating Central Nervous System Disease. Ann. Neurol. 2009;66(6):833-842.
16. Jurynczyk M, Messina S, Woodhall MR, et al. Clinical Presentation and Prognosis in MOG-Antibody Disease: A UK Study. Brain. 2017;140(12):3128-3138.
17. Armangue T, Olivé-Cirera G, Martínez-Hernandez E, et al. Associations of paediatric demyelinating and encephalitic syndromes with myelin oligodendrocyte glycoprotein antibodies: A multicentre observational study. Lancet Neurol. 2020;19(3):234-246.
18. Cobo-Calvo A. Ruiz A, Maillart E, et al. Clinical Spectrum and Prognostic Value of CNS MOG Autoimmunity in Adults: The MOGADOR Study. Neurology. 2018;90(21):e1858-e1869.
19. Ciotti J, Eby N, Wu G, Naismith R, Chahin S, Cross A. Clinical and laboratory features distinguishing MOG antibody disease from multiple sclerosis and AQP4 antibody-positive neuromyelitis optica. Mult. Scler. Relat. Disord. 2020;45:102399.
20. Netravathi M, Venkappayya Holla V, Nalini A, et al. Myelin oligodendrocyte glycoprotein-antibody-associated disorder: A new inflammatory CNS demyelinating disorder. J. Neurol. 2021;269(4):1419-1433.
21. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and Related Disorders: A Multicenter Study of 50 Patients. Part 2: Epidemiology, Clinical Presentation, Radiological and Laboratory Features, Treatment Responses, and Long-Term Outcome. J. Neuroinflamm. 2016;13(1):1-45.
22. Akman Demir G. Nöromiyelitis optika: Klinik ve İmmünolojik Özellikler. Türkiye Klinikleri J Neurol-Special Topics. 2009;2(4):37-40.
23. Dutra BG, da Rocha AJ, Nunes RH, Junior AC. Neuromyelitis optica spectrum disorders: spectrum of MR imaging findings and their differential diagnosis. Radiographics. 2018;38(1):169-193.
24. Pittock SJ, Lennon VA, Krecke K, Wingerchuk DM, Lucchinetti CF, Weinshenker BG. Brain abnormalities in neuromyelitis optica. Arch Neurol. 2006;63(3):390-396.
25. Lana-Peixoto M. Talim N. Neuromyelitis optica spectrum disorder and anti-mog syndromes. Biomedicines. 2019;7(2):42.
26. Ringelstein M, Kleiter I, Ayzenberg I, et al. 2013 Visual evoked potentials in neuromyelitis optica and its spectrum disorders. Mult Scler. 2014;20(5):617-620.
27. Wandinger KP, Stangel M, Witte T, et al. Autoantibodies against aquaporin-4 in patients with neuropsychiatric systemic lupus erythematosus and primary Sjögren's syndrome. Arthritis Rheum. 2010;62(4):1198-1200.
28. Önerli Yener M. Sjögren sendromunda nörolojik manifestasyonlar. Öztekin ZN. Romatolojik Hastalıkların Nörolojik Yönleri. 1. Baskı. Ankara: Türkiye Klinikleri; 2021;48-54.
29. Wingerchuk DM, Weinshenker BG. Neuromyelitis optica: clinical predictors of a relapsing course and survival. Neurology. 2003;60(5):848-853.
30. Magraner MJ, Coret F, Casanova B. The effect of intravenous immunoglobulin on neuromyelitis optica. Neurologia. 2013;28(2):65-72.
31. Chihara N, Aranami T, Sato W, et al. Interleukin 6 signaling promotes anti-aquaporin 4 autoantibody production from plasmablasts in neuromyelitis optica. Proc Natl Acad Sci USA. 2011;108(9):3701-3706.
32. Araki M, Aranami T, Matsuoka T, Nakamura M, Miyake S, Yamamura T. Clinical improvement in a patient with neuromyelitis optica following therapy with the anti-IL-6 receptor monoclonal antibody tocilizumab. Mod Rheumatol. 2013;23:827-832.
33. Kieseier BC, Stu O, Dehmel T, et al. Disease amelioration with tocilizumab in a treatment-resistant patient with neuromyelitis optica: implication for cellular immune responses. JAMA Neurol. 2012;70(3):390-393.
34. Fitzgerald S. Three new treatment options for neuromyelitis optica spectrum disorder. Neurology Today. 2019;19(11):7-10.

ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Comparison of the Effects of Anesthesia Methods on Dynamic Thiol/Disulfide Homeostasis in Patients with Chronic Obstructive Pulmonary Disease Under Surgical Stress

Cerrahi Stres Altındaki Kronik Obstruktif Akciğer Hastalığı Olan Hastalarda Anestezi Yöntemlerinin Dinamik Tiyol/disülfid Dengesine Etkilerinin Karşılaştırılması

Fatma ÇELİK[1] Recai DAĞLI[2] Bilal İLANBEY[3]

ÖZ

Amaç: Kronik Obstrüktif Akciğer Hastalığı (KOAH), artan oksidatif stres ile bağlantılıdır. Anestezi uygulamalarına bağlı olarak değişen oksidatif stres durumu, cerrahi stresi ve postoperatif komplikasyon insidansını etkileyebilir.
Bu çalışma, inguinal herni operasyonu geçiren KOAH'lı hastalarda genel anestezi (GA) ve spinal anestezinin (SA) dinamik tiyol-disülfid dengesi üzerindeki etkilerini karşılaştırmayı amaçlamaktadır.
Araçlar ve Yöntem: KOAH'ın Teşhisi, Yönetimi ve Önlenmesi için 2017 Küresel Strateji Raporuna göre, hava akımı obstrüksiyonu (%50≤FEV 1<%79) ve FEV1/FVC<0.7 olan hastalar değerlendirildi. Bu gözlemsel çalışmaya inguinal herni cerrahisi planlanan, grup GA (n=26) ve grup SA (n=26) olmak üzere toplam 52 KOAH hastası dahil edildi. Preoperatif dönemde ve postoperatif 24. saatte kan örnekleri alındı. Tiyol/disülfid dengesinin parametreleri analiz edildi.
Bulgular: Hem grup GA hem de grup SA'da anestezi öncesine göre anestezi sonrasında total tiyol, native tiyol ve disülfid değerlerinde bir azalma gözlendi. Ancak sadece Grup SA'da anestezi sonrası total tiyol ($p<0.01$) ve nativ tiyol ($p=0.012$) değerlerinin anestezi öncesi değerlerine göre azalması istatistiksel olarak anlamlıydı. Diğer değişkenlerdeki değişim istatiksel olarak anlamlı değildi. Grup GA ve grup SA arasındaki karşılaştırmalarda anestezi öncesi ve sonrası tiyol/disülfit değişkenlerinde kayda değer bir fark gözlenmedi.
Sonuç: Cerrahi stres altındaki KOAH hastalarında genel ve spinal anestezi yöntemleri dinamik tiyol/disülfid dengesi üzerine benzer bir yanıt göstermiştir.

Anahtar Kelimeler: disülfid; KOAH; oksidatif stres; spinal anestezi; tiyol

ABSTRACT

Purpose: Chronic Obstructive Pulmonary Disease (COPD) is linked to increased oxidative stress. Changing oxidative stress status due to anesthesia applications may affect surgical stress and the incidence of postoperative complications.
This study aims to contrast the impacts of general anesthesia (GA) and spinal anesthesia (SA) on the dynamic thiol-disulfide homeostasis among patients with COPD who are undergoing inguinal hernia surgery.
Materials and Methods: According to the 2017 Global Strategy Report for the Diagnosis, Management and Prevention of COPD, patients with airflow obstruction (50%≤FEV1<79%) and FEV1/FVC<0.7% were evaluated. A total of 52 COPD patients, group GA (n=26) and group SA (n=26), scheduled for inguinal hernia surgery were included in this observational study. Blood samples were collected preoperatively and at 24 hours postoperatively. Parameters of thiol/disulfide balance were analyzed.
Results: In both group GA and group SA, a decrease in total thiol, native thiol and disulfide values was observed after anesthesia compared to pre-anesthesia. However, only in group SA, the decrease in total thiol ($p<0.01$) and native thiol ($p=0.012$) values after anesthesia was statistically significant. The change in other variables was not statistically significant. There was no significant difference between group GA and group SA in the thiol/disulfite variables before and after anesthesia.
Conclusion: General and spinal anesthesia methods demonstrated a similar response on dynamic thiol/disulfide homeostasis in COPD patients under surgical stress.

Keywords: COPD; disulfide; oxidative stress; spinal anesthesia; thiol

Received: 21.08.2023; Accepted: 12.01.2024

[1]Department of Anaesthesiology and Reanimation, Faculty of Medicine, Fırat University, Elazığ, Türkiye.
[2]Department of Anaesthesiology and Reanimation, Faculty of Medicine, Kırşehir Ahi Evran University, Kırşehir, Türkiye.
[3]Department of Medical Biochemistry, Faculty of Medicine, Kırşehir Ahi Evran University, Kırşehir, Türkiye
Corresponding Author: Fatma Çelik, Department of Anaesthesiology and Reanimation, Faculty of Medicine, Fırat University, Elazığ, Türkiye.
e-mail: fatma.celik@firat.edu.tr

How to cite: Çelik F, Dağlı R, İlanbey B. Comparison of the effects of anesthesia methods on dynamic thiol/disulfide homeostasis in patients with chronic obstructive pulmonary disease under surgical stress. Ahi Evran Med J. 2024;8(1):104-110. DOI: 10.46332/aemj.1347211

INTRODUCTION

The World Health Organization reports that the prevalence of chronic obstructive pulmonary disease (COPD) is increasing day by day worldwide and it ranks as the third leading cause of death.[1] COPD is a heterogeneous disease characterized by permanent abnormalities in the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema). Inflammation in the respiratory tract is accompanied by increased airflow resistance. Airflow obstruction, hyperinflation, ventilation/perfusion mismatch, weakening hypoxic pulmonary vasoconstriction, hypoxemia, and hypercapnia lead to respiratory failure.[2] Therefore, the perioperative anesthesia management of patients with COPD involves numerous challenges.

Oxidative stress (OS) stands as a paramount factor in the pathophysiology of COPD. Oxidative stress arises due to an excess production of reactive oxygen species (ROS) surpassing the inherent antioxidant defense mechanisms.[3-5] Oxidative stress plays a key role in proteolytic activity, gene expression of proinflammatory mediators, protein modification, signal transduction, and apoptosis mechanisms.[6,7] Existing COPD may be exacerbated by increased OS and other comorbidities may increase through systemic OS.[2,8] However, in the perioperative period, OS is associated with a complex acute phase response that includes many factors such as the severity of tissue damage caused by surgical intervention, anesthesia duration and technique, and underlying comorbidities.[4,9] It is reported that patients with COPD undergoing surgical procedures are at high risk of morbidity and mortality.[10,11] Additionally, increased OS is associated with postoperative complications.[12] Better clinical results and less postoperative complications can be seen with the application of anesthesia, which reduces exposure to OS.[4,8,13-16] The mechanism underlying this pathological link between often overlooked OS and postoperative complications remains uncertain. The main reason for this uncertainty could be the complexity of measuring ROS and oxidative stress-mediated damage.[4] Until today, OS levels have been studied using numerous complex methods. The search for more practical approaches in this regard continues. Studies on OS, particularly through the thiol/disulfide balance, are frequently addressed in the current literature.[14,17-20]

Dynamic thiol-disulfide homeostasis indicates the status of thiols and disulfides in metabolism. Thiol compounds are organic compounds that contain the sulfhydryl (-SH) group, and this group helps prevent the formation of oxidative stress. When oxidative stress is present, two thiol groups undergo oxidation, leading to the formation of reversible disulfide (-SS-) bonds. Converting disulfide bonds into thiol structures ensures the continuous equilibrium of dynamic thiol-disulfide homeostasis.[21] In the past, the bidirectional dynamic nature of thiol-disulfide homeostasis was analyzed in a unidirectional manner. Today, with the method developed by Erel and Neşelioğlu, the parameters in both directions of equilibrium can be measured separately and collectively.[18] When we reviewed the current literature, we found that there is not enough research on the effects of anesthesia applications on dynamic thiol/disulfide homeostatic status in COPD patients.

In this study, dynamic thiol/disulfide homeostatic responses of general and spinal anesthesia methods in COPD patients under surgical stress were evaluated.

MATERIALS and METHODS

Study Design and Ethical Considerations

This prospective observational study was approved by Ahi Evran University Faculty of Medicine Clinical Research Ethics Committee (date 10.10.2017 and number 2017-15/174). The study was organized in accordance with the principles set out in the Declaration of Helsinki.

Patients, Inclusion and Exclusion Criteria

The study was conducted at Kırşehir Ahi Evran University Training and Research Hospital between January 2018 and December 2018.

Patients scheduled for elective unilateral inguinal hernia surgery were evaluated according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) program's Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2017 Report. Patients defined as GOLD 2, with airflow obstruction ($50\% \leq FEV1 < 79\%$) and a forced expiratory volume

in 1. second to forced vital capacity ratio (FEV1/FVC) < 0.7, were accepted for the study.[5]

The research involved individuals aged 18 or above, diagnosed with COPD, and possessing an ASA (American Society of Anesthesiologists) physical status classification of II. Patients who stopped smoking and alcohol at least 2 years before participating in the study were accepted.

The study excluded participants who were set to undergo bilateral inguinal hernia surgery, individuals taking multivitamins, those with inflammatory conditions, cancer diagnoses, established cardiovascular issues, cerebrovascular disorders, kidney or liver ailments, metabolic or endocrine disorders, current smokers and alcohol users, patients with a body mass index (BMI) exceeding 35. Additionally, patients with other lung diseases apart from COPD (e.g., tuberculosis, bronchiectasis) were also excluded from the study.

Determining Sample Size

After the preliminary study, Priori power analysis was used to determine the sample size. In the power analysis, with α=0.05 and Power (1-β)=0.80, the total sample size was calculated as 52 for the independent t-test and 34 for the paired t-test. Following the conclusion of the research, a post hoc power analysis was performed to assess the statistical power of the study findings. According to the results of the power analysis, 52 subjects were used in the study.

Procedure

Prior to the surgery, all patients underwent monitoring using non-invasive blood pressure (NIBP), electrocardiography (EKG) and peripheral oxygen saturation (SpO2). Patients were subjected to intravenous catheterization using an 18-G catheter, and intravenous infusion of 10 ml/kg 0.9% NaCl was initiated. The type of anesthesia was determined by the anesthetists who were not included in the study, depending on whether the patients accepted spinal anesthesia or not.

The study population consisted of 52 patients who were categorized into two groups based on the administered anesthesia technique: Group GA (General anesthesia, n=26) and Group SA (Spinal anesthesia, n=26).

General Anesthesia Application

After monitoring the patients in the general anesthesia group, venous blood samples were taken 5 minutes before preoxygenation and at the postoperative 24th hour. Following preoxygenation at a rate of 4 L/min for 2 minutes, the anesthesia induction was carried out using propofol (2 mg/kg), fentanyl citrate (2 μg/kg), and rocuronium bromide (0.6 mg/kg). The patients were intubated after 2 minutes of ventilation with 100% O_2. Anesthesia was maintained with 4L/min flow (50% O_2 + 50% dry air) and 2% sevoflurane. For postoperative analgesia, a combination of tramadol hydrochloride (1 mg/kg) and paracetamol (1 g vial) infusion solution was administered. For decurarization, neostigmine methylsulfate (0.04 mg/kg) + atropine sulfate (0.5 mg) were given.

Spinal Anesthesia Application

After monitoring, venous blood samples were collected from patients in the spinal anesthesia group both before the spinal procedure and at the 24-hour mark postoperatively. With the patient in a seated position, the intrathecal space between the L4-L5 vertebrae was accessed using a 26-gauge atraumatic spinal needle (Atraucan; Braun, Germany). A single dose of 0.5% hyperbaric bupivacaine hydrochloride (10 mg) was injected. The patient was positioned lying on their back, and the extent of sensory block was assessed through the Pinprick test. The surgical procedure was initiated upon achieving the T10 dermatome level with the spinal block.

Thiol/Disulfide Laboratory Examination

Two venous blood samples taken preoperatively and postoperatively were collected in gel serum tubes. The tubes were placed in a centrifuge and spun at 1500xg for 10 minutes. The resulting supernatant serum was then preserved at -80°C until the point of analysis for thiol-disulfide parameters. Using the technique outlined by Erel and Neselioğlu, the status of thiol-disulfide homeostasis was examined via a commercial kit (Rel Assay Diagnostics,

Gaziantep, Türkiye) on the Cobas 501 autoanalyzer (Roche Diagnostics, Germany).[22] Calculations were performed to determine dynamic parameters related to thiol/disulfide homeostasis, including ratios of disulfide/native thiol (%), native thiol/total thiol (%) and disulfide/total thiol (%). The recorded data encompassed the age, body mass index (BMI), anesthesia method, and dynamic thiol/disulfide homeostasis parameters of patients diagnosed with COPD who had undergone inguinal hernia surgery.

Statistical Analysis

In this study, primarily, the dynamic thiol/disulfide homeostasis parameters of both the GA and SA groups were evaluated before and after surgical stress. Secondarily, the thiol/disulfide homeostasis statuses between the GA and SA groups were compared.

For this purpose, the data for native thiol (μmol/L), total thiol (μmol/L), disulfide (μmol/L), disulfide/native thiol (%), native thiol/total thiol (%) and disulfide/total thiol (%) were determined. The statistical analysis of the study was conducted using the Statistical Package for Social Sciences version 21.0 software for Windows (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp., USA) and power analyses were performed using G-Power 3.1.9.4. The normal distribution assumption for quantitative variables was assessed via the Shapiro-Wilk test. It was determined that the data was normally distributed. The descriptive statistics of the variables were presented as Mean ± Standard deviation. In all statistical assessments, results with a p-value lower than 0.05 were considered to indicate statistical significance.

Dependent variable comparisons were conducted using the paired sample T-test, while intergroup comparisons were executed through the utilization of Student's T-test.

RESULTS

A total of 64 patients who underwent inguinal hernia surgery within the specified date range were examined. Following the pre-test results, the data of a total of 52 male patients (GA (n=26) and SA (n=26)) were evaluated statistically.

The mean age was 63.32∓9.78 in group GA and 60.58∓8.92 in group SA. In group GA, the average BMI was 25.88±2.83, while in group SA, it was 26.25±2.08. Age and BMI exhibited resemblances across the groups. Explanatory statistics and analysis results of the variables that we evaluated the thiol/disulfide balance before and after anesthesia in group GA and group SA are given in Table 1.

Table 1. The effects of general anesthesia (Group GA) and spinal anesthesia (Group SA) applications on dynamic thiol/disulfide balance before and after surgical stress.

Variables	Group	preoperative	postopoperative	pa
Total thiol	GA	340.73∓47.97	324.95∓62.93	0.276
	SA	343.74∓57.29	317.66∓50.44	0.003*
p b		0.840	0.649	
Native thiol	GA	305.47∓43.22	290.98∓57.64	0.268
	SA	307.34∓57.54	286.59∓49.83	0.012*
p b		0.897	0.772	
Disülfid	GA	17.62∓8.13	16.98∓4.61	0.731
	SA	18.20∓6.63	15.53∓4.95	0.066
p b		0.784	0.284	
Disülfid/Total thiol	GA	5.11∓2.14	5.26∓1.15	0.752
	SA	5.46∓2.57	5.01∓1.96	0.318
p b		0.602	0.575	
Disülfid/Native thiol	GA	5.81∓2.76	5.92∓1.49	0.865
	SA	6.34∓3.66	5.66∓2.60	0.273
p b		0.564	0.677	
Native thiol/Total thiol	GA	89.76∓4.28	89.47∓2.32	0.758
	SA	89.046∓5.15	89.99∓3.90	0.296
p b		0.589	0.565	

The data is presented as mean±SD.
[a] Paired Sample T-test was used to compare dependent variables
[b] Student T test was used for comparisons between group

According to Table 1, initially, each group was evaluated both before and after anesthesia. In both the GA group and the SA group, a reduction was observed in the total thiol, native thiol, and disulfide values after anesthesia compared to before anesthesia. However, this decrease was statistically significant only in Group SA, with post-anesthesia total thiol (p=0.003) and native thiol (p=0.012) values being significantly different from their pre-anesthesia values. The changes in other variables were not statistically significant. In comparisons between Group GA and Group SA, there were no significant differences detected in relation to thiol/disulfide variables, both prior to and post anesthesia.

After the completion of the research, power analysis was conducted using Post-Hoc power. The lowest power value for Independent t-test results was 0.79, and the lowest power value for paired t-test results was found to be 0.85. These power values show that the study results are reliable and robust results.

DISCUSSION

This study was conducted with the objective of exploring the connection between the anesthesia approach and the dynamic thiol/disulfide equilibrium among COPD patients undergoing surgical stress. We observed similar levels of OS in patients received general anesthesia and spinal anesthesia. The findings of our study specifically conducted on COPD patients address the existing gap in the literature on this topic.

The effects of anesthesia methods during the perioperative period have frequently been compared in the literature. Rodgers et al.[23] evaluated 141 prospective randomized studies comparing neuraxial anesthesia with general anesthesia in the general patient population. According to this review, patients receiving neuraxial anesthesia experience reduced mortality, decreased postoperative pulmonary and cardiac complications, lower incidence of renal failure, and decreased occurrence of deep vein thrombosis. Hausman et al.[24] reported that patients with COPD undergoing surgical operations carry an increased risk of postoperative complications. The authors have demonstrated that the choice of regional anesthesia in COPD patients is associated with lower morbidity, postoperative pneumonia, prolonged mechanical ventilator requirement, and unplanned postoperative intubation. Avoiding general anesthesia in patients with COPD is considered to potentially provide benefits. Therefore, traditionally, if the patient accepts regional intervention and there is no contraindication for the procedure, regional anesthesia is preferred. In surgical patients with COPD, it is necessary to elucidate the critical importance of adding OS changes due to anesthesia application onto the existing chronic OS in this preference. In our study, we compared OS levels in COPD patients who underwent surgical procedures according to different anesthesia methods. However, we found that patients who underwent general anesthesia and those who underwent spinal anesthesia had similar OS levels. The findings of our study do not support the advantages of preoperative and postoperative spinal anesthesia in this patient group as observed in other studies.

There are studies comparing OS levels using different methods. For example, Aremu et al.[25] evaluated the OS levels of general and spinal anesthesia in orthopedic surgery patients as biomarkers (malondialdehyde, glutathione, catalase and nitrile). The authors have reported that anesthesia could lead to different effects on OS and inflammatory cytokines in patients undergoing surgery.

Thiol/disulfide hemostasis studies investigating the relationship between anesthesia methods and surgical stress and OS are generally performed on the patient population without COPD. In one of these studies, a comparison was made between spinal anesthesia and general anesthesia in laparoscopic gynecological surgery. Similar to our study, no difference was found in the evaluation of total oxidant, antioxidant levels and OS index.[26]

In another study, the effects of sevoflurane and desflurane anesthesia during laparoscopic cholecystectomy on lipid peroxidation were compared in a non-COPD patient group. It was determined that plasma malondialdehyde and superoxide dismutase concentrations increased more with desflurane administration compared to sevoflurane.[27] We also administered sevoflurane during general anesthesia. There was no statistically notable alteration detected in the thiol/disulfide balance prior to and subsequent to anesthesia within the GA group. In the study by Kulacoğlu et

al.,[28] the effects of local, spinal, and general anesthesia types on inflammatory response and OS in Lichtenstein hernia repair were compared in the general population. The total antioxidant status showed slight changes across the three anesthesia types. According to the findings of this study, local and spinal anesthesia methods are suggested as better alternatives in terms of OS compared to general anesthesia.[28] On the other hand, our study has shown similar results regarding the effects of general and spinal anesthesia on dynamic thiol/disulfide homeostasis in COPD patients under surgical stress.

Limitations

This study has some limitations. The study included COPD patients with moderate airflow obstruction (50% ≤ FEV1 < 79%) and FEV1/FVC < 0.7. It does not reflect patients with more severe COPD clinic. Severe COPD patients often have secondary comorbidities. Regional anesthesia is applied in this patient group to minimize the risk of perioperative complications. In order to reach a general conclusion about patients with COPD, a larger sample size including different surgical procedures is needed. Additionally, our study population included COPD patients who were ex-smokers. Patients who stopped smoking and alcohol at least 2 years before participating in the study were accepted.[29,30] It is a scientific fact that there is a process in which the effects of smoking on oxidative stress will be seen, even if the COPD patient is an ex-smoker. Therefore, it is important to clarify the oxidative stress status in the COPD group that has never actively smoked.

In conclusion, the OS levels of COPD patients who underwent inguinal hernia surgery were similar for both general anesthesia and spinal anesthesia applications. Based on these findings, considering the OS responses, it can be observed that both anesthesia methods can be applied in patients with mild to moderate COPD, provided there are no other contraindications.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Funding

This study was supported by the Ahi Evran University Scientific Research Projects Coordination Unit. (Project Number: TIP.A4.18.003)

Ethics Committee Permission

The study was approved by Ahi Evran University Clinical Research Ethics Committee (dated 10.10.2017 and numbered 2017-15/124).

Authors' Contributions

Concept/Design: FÇ. Data Collection and/or Processing: FÇ, RD, Bİ. Data analysis and interpretation: FÇ, RD. Literature Search: FÇ. Drafting manuscript: FÇ, RD. Critical revision of manuscript: FÇ, RD, Bİ. Supervisor: FÇ, RD, Bİ.

REFERENCES

1. Zinellu E, Zinellu A, Fois AG, Carru C, Pirina P. Circulating biomarkers of oxidative stress in chronic obstructive pulmonary disease: a systematic review. Respir Res. 2016;17(1):150.
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease: 2023 Report. Available from: www.goldcopd.org. Accessed December 13, 2022.
3. Sies H, Berndt C, Jones DP. Oxidative Stress. Annu Rev Biochem. 2017;86:715-748.
4. Stevens JL, Feelisch M, Martin DS. Perioperative Oxidative Stress: The Unseen Enemy. Anesth Analg. 2019;129(6):1749-1760.
5. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org 2017. Accessed June 15, 2017.
6. McGuinness AJA, Sapey E. Oxidative Stress in COPD: Sources, Markers, and Potential Mechanisms. J Clin Med. 2017;6(2):21.
7. Lakhdar R, Denden S, Kassab A, et al. Update in chronic obstructive pulmonary disease: role of antioxidant and metabolizing gene polymorphisms. Exp Lung Res. 2011;37(6):364-375.
8. Barnes PJ. Oxidative Stress in Chronic Obstructive Pulmonary Disease. Antioxidants (Basel). 2022;11(5): 965.
9. López-Armada MJ, Riveiro-Naveira RR, Vaamonde-García C, Valcárcel-Ares MN. Mitochondrial dysfunction and the inflammatory response. Mitochondrion. 2013;13(2):106-118.
10. Fields AC, Divino CM. Surgical outcomes in patients with chronic obstructive pulmonary disease undergoing abdominal operations: An analysis of 331,425 patients. Surgery. 2016;159(4):1210-1216.
11. Johnson AP, Altmark RE, Weinstein MS, Pitt HA, Yeo CJ, Cowan SW. Predicting the Risk of Postoperative Respiratory Failure in Elective Abdominal and Vascular Operations Using the

National Surgical Quality Improvement Program (NSQIP) Participant Use Data File. Ann Surg. 2017;266(6):968-974.
12. Senoner T, Schindler S, Stättner S, Öfner D, Troppmair J, Primavesi F. Associations of Oxidative Stress and Postoperative Outcome in Liver Surgery with an Outlook to Future Potential Therapeutic Options. Oxid Med Cell Longev. 2019;3950818.
13. Kundović SA, Rašić D, Popović L, Peraica M, Črnjar K. Oxidative stress under general intravenous and inhalation anaesthesia. Arh Hig Rada Toksikol. 2020;71(3):169-177.
14. Dağlı R, Songur Dağlı S, Nar R. Comparison of thiol/disulfide balance in elective and emergency cesarean sections: a prospective, observational study. Journal of Clinical Obstetrics Gynecology. 2019;29(2):68-76.
15. Senoner T, Velik-Salchner C, Luckner G, Tauber H. Anesthesia-Induced Oxidative Stress: Are There Differences between Intravenous and Inhaled Anesthetics? Oxid Med Cell Longev. 2021;8782387.
16. Karabayırlı S, Keskin EA, Kaya A, et al. Assessment of fetal antioxidant and oxidant status during different anesthesia techniques for elective cesarean sections. J Res Med Sci. 2015;20(8):739-744.
17. Tanyildiz M, Yetimakman AF, Yazici MU et al. Effect of cardiopulmonary bypass on thiol/disulfide homeostasis in congenital heart surgery. TGKDC. 2023;31(4):454-466.
18. Kazancioglu L, Batcik S, Arpa M, et al. The relationship between intraoperative body temperature and thiol/disulfide balance in geriatric patients undergoing elective transurethral prostate resection surgery with spinal anesthesia. Eur Rev Med Pharmacol Sci. 2023;27(18):8523-8530.
19. Gürü S, Kadı G, Yıldırım Ç, Gökhan Ş, Özhasenekler A, Gürü M, Neşelioğlu S, Erel Ö. Thiol/Disulfide Homeostasis and Ischemia-Modified Albumin Levels in 61 Patients with Hypercapnia: A Case-Control Study. Med Sci Monit. 2023;29:e940674.
20. Songur Dağlı S, Dağlı R. The Effect of Delivery Mode on Thiol-Disulfide Balance in the Umbilical Cord Blood. Ahi Evran Med. J. 2021;5(1):22-27.
21. Erel Ö, Erdoğan S. Thiol-disulfide homeostasis: an integrated approach with biochemical and clinical aspects. Turk J Med Sci. 2020;50(Si-2):1728-1738.
22. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem. 2014;47 (18):326-332.
23. Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ (Clinical research ed). 2000;321(7275):1493.
24. Hausman Jr MS, Jewell ES, Engoren M. Regional versus general anesthesia in surgical patients with chronic obstructive pulmonary disease: does avoiding general anesthesia reduce the risk of postoperative complications? Anesth Analg. 2015;120(6):1405-1412.
25. Aremu PA, Ajayi AM, Ben-Azu B, Orewole OT, Umukoro S. Spinal and general anesthesia produces differential effects on oxidative stress and inflammatory cytokines in orthopedic patients. Drug Metab Pers Ther. 2021;36(1):17-23.
26. Kaya Uğur B, Pirbudak L, Öztürk E, Balat Ö, Uğur MG. Spinal versus general anesthesia in gynecologic laparoscopy: A prospective, randomized study. Turk J Obstet Gynecol. 2020;17(3):186-195.
27. Koksal GM, Sayilgan C, Aydin S, Uzun H, Oz H. The effects of sevoflurane and desflurane on lipid peroxidation during laparoscopic cholecystectomy. Eur J Anaesthesiol. 2004;21(3):217-220.
28. Kulacoglu H, Ozdogan M, Gurer A, et al. Prospective comparison of local, spinal, and general types of anaesthesia regarding oxidative stress following Lichtenstein hernia repair. Bratisl Lek Listy. 2007;108(8):335-339.
29. Rutgers SR, Postma DS, Ten Hacken NH, et al. Ongoing airway inflammation in patients with COPD who do not currently smoke. Thorax. 2000;55(1):12-18.
30. Fratta Pasini AM, Ferrari M, Stranieri C, Vallerio P, Mozzini C, Garbin U, Zambon G, Cominacini L. Nrf2 expression is increased in peripheral blood mononuclear cells derived from mild-moderate ex-smoker COPD patients with persistent oxidative stress. Int J Chron Obstruct Pulmon Dis. 2016 28;(11):1733-1743.

REVİEW

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

New Perspectives on Obesity Related Novel Peptides

Obeziteyle İlişkili Güncel Peptitlere Yeni Yaklaşımlar

***Sümeyye KOÇ*[1] *Levent SARIYILDIZ*[2] *Esma MENEVŞE*[1]**

ÖZ

Özellikle çocukluk ve adölesan zamanlarında gelişen obezite, her yaşta önemli bir sağlık sorunu olarak karşımıza çıkmaktadır. Hipotalamusu vücudun enerji depoları hakkında uyaran hormonlar, yemek yemeyi engelleyip vücut ağırlığının belli fizyolojik sınırlar içerisinde kalmasını sağlamaktadırlar. Obezite ve obeziteyle ilişkili olan hormonların araştırılması bu kapsamda çok önemlidir. Obezite ile ilişkili hormonların günümüze kadar tespit edilmiş olan fonksiyonlarının, daha ileri çalışmalara rehberlik edebileceğini düşünmekteyiz. Bu derlemede obeziteyle ilişkili hormonlar ve onların etki mekanizmalarına değinilmiştir.

Anahtar Kelimeler: ghrelin; irisin; leptin; nesfatin-1; nöropeptid-y; oreksin

ABSTRACT

Obesity, which develops especially in childhood and adolescence, is an important health problem at all ages. Hormones that stimulate the hypothalamus about the body's energy stores prevent eating and keep body weight within certain physiological limits. Investigating obesity and the hormones associated with obesity is very important in this context. We believe that the functions of obesity-associated hormones that have been identified to date can guide further studies. In this review, obesity-related hormones and their mechanisms of action are discussed.

Keywords: ghrelin; irisin; leptin; nesfatin-1; neuropeptide-y; orexin

Received: 07.12.2022; Accepted: 04.010.2023

[1]Selçuk Üniversitesi Tıp Fakültesi, Konya, Türkiye.
[2]KTO Karatay Üniversitesi Tıp Fakültesi, Konya, Türkiye.
Corresponding Author: Levent Sarıyıldız, KTO Karatay Üniversitesi Tıp Fakültesi, Konya, Türkiye.
e-mail: leventsariyildiz@hotmail.com

How to cite: Koç S, Sarıyıldız L, Menevşe E. New perspectives on obesity related novel peptides. Ahi Evran Med J. 2024;8(1):111-120.
DOI: 10.46332/aemj.1215675

OBESITY

Obesity is a chronic condition which may lead to physical, psychological, social, and economic problems caused by the excess of energy received with nutrients over the energy expended.[1] Obesity has recently started to be a common health problem in all societies and has shown a rapid increase in all age periods, starting from childhood and adolescence in many countries.[2] On the other hand, body fat mass, which is the increase of body weight above the desired level regarding height as a result of an excessive increase in the ratio of desired mass, is closely related to adipose tissue. It is well known that another factor that attracts attention in the progress of the obesity is dependent on the way of nutrition in the first years of the life of people. In a study conducted on breastfed and non-breastfed children, the rate of obesity was found to be lower in breastfed children. In addition, this study emphasized that the duration of breastfeeding, the type and number of complementary foods, and the time of onset affect the occurrence of obesity.[3] Obesity, which is an epidemic problem, directly affects the development of many chronic diseases. Also obesity is directly related with the diseases e.g., type 2 DM hypertension, coronary heart, metabolic diseases, respiratory system diseases and cancer.[4]

When we analyze the biochemistry of nutrition, the first definitions that come to mind are peptides that regulate food intake. According to their origin, these peptides are classified as peptides produced in the CNS and peripheral peptides produced in the digestive tract. According to their effects on nutritional behavior, they are grouped as orexigenic and anorexigenic peptides. Orexigenic peptides stimulate food intake by initiating the feeling of hunger, while anorexigenics are peptides that stop food intake by creating a feeling of satiety (table 1).[5]

Table 1. Some known orexigenic and anorexigenic peptides.[5]

OREXIGENIC PEPTIDES	ANOREXIGENIC PEPTIDES
Ghrelin	Leptin
Noropeptit y (NPY)	Insulin
Arcuate-associated peptide (AGRP)	Glucagon-like peptide-1 (GLP-1)
Melanin concentrating hormone (MCH)	Cholecystokinin (CCK)
Orexin	Cocaine amphetamine regulatory transcript (CART)
Galanin	α-Melanocyte stimulating hormone (α - MSH)
Opioids	Serotonin
Nitric oxide *	Corticotropin-releasing factor (CRF)
Kannabioits *	Nesfatin- 1
	Bombesin

* A peptide is an element that is not in the structure.

HORMONES INVOLVED IN OBESITY

LEPTIN

Leptin discovered in 1994 is an important appetite-regulating hormone with a molecular weight 16 kDa and a single-chain polypeptide structure encoded by the LEP (OB) gene located on the long part of the chromosome (7q31)which is a protein product with 167 amino acids. Leptin is formed by white/brown adipose tissue, the placenta, stomach, mammary gland, ovarian follicles, heart, bone/cartilage tissue, some fetal organs, and the brain. Leptin reduces the intake of nutrients and increases the metabolic rate. It is believed that leptin shows this effect via inhibiting the synthesis of NPY, AgRP (Agouti-related peptide) and MSH which are released from the arcuate nucleus (Bound leptin reflects the energy state at rest, and free leptin reflects the body fat mass (figure1-2).[5]

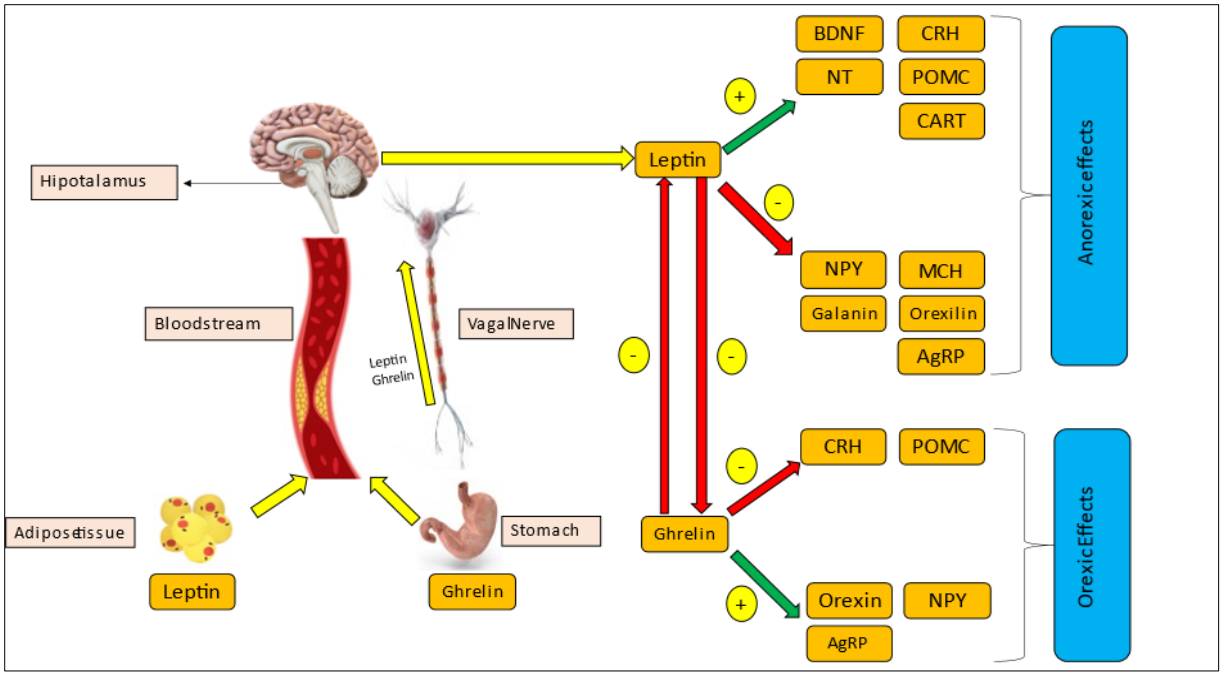


Figure 1. The physiological mechanism of leptin action.

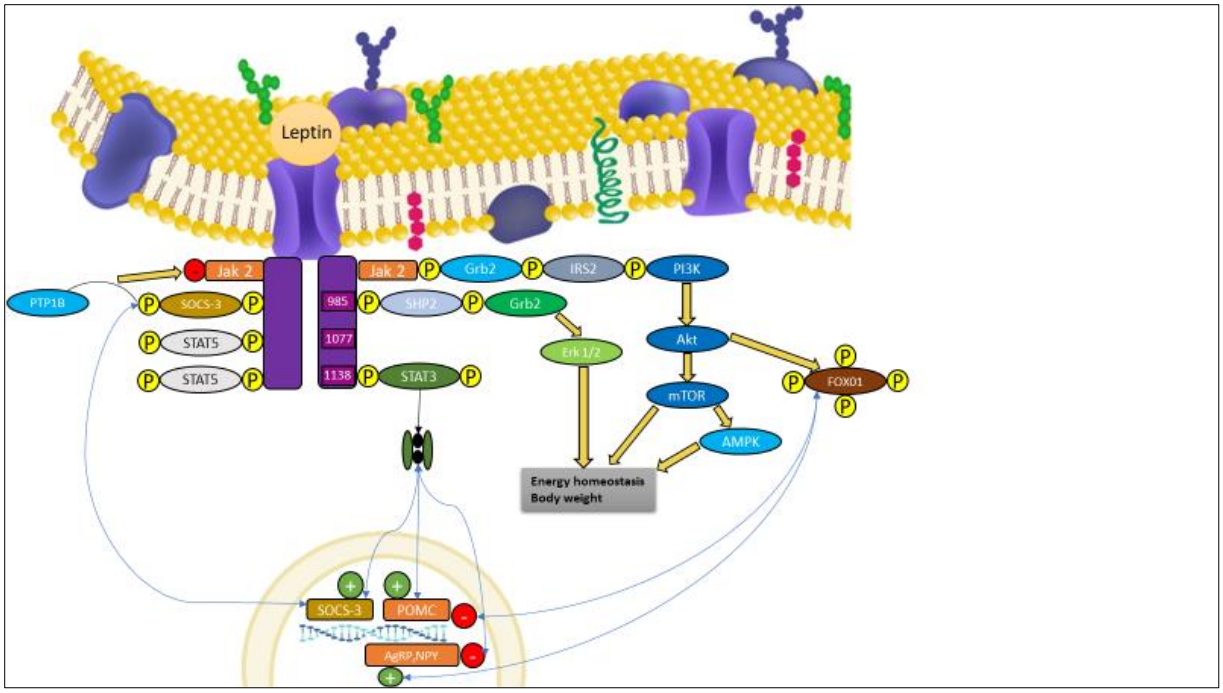


Figure 2. Leptin signaling pathway overview.

The expression of proopiomelanocortin (POMC) is induced in hypothalamic leptin, and AgRP and NPY are inhibited. Thus, these changes increase releasing of gonadotropin-releasing hormones (GnRH), thyrotropin (TRH). Leptin reduces the release of ACTH, and CRH, and inhibits insulin secretion from pancreatic β-cells.[6]

Leptin crosses the blood-brain barrier with a special active transport system. In an obese person, leptin levels in the cerebrospinal fluid are less high than their circulating amount.[7] In addition, in the absence of leptin or mild leptin fluctuations, the arcuate nucleus, paraventricular nucleus, lateral and dorsomedial hypothalamic neuronal connections of the hypothalamus are inhibited. Therefore, it causes metabolic complications and leads to obesity. There are findings that obesity caused by leptin deficiency in humans, decreased the number of circulating $CD4^{(+)}$ T cells,

impaired T cell receptor immunity, and the release of cytokine can be adjusted by recombinant leptin applications.[8]

GHRELIN

Ghrelin was extracted from the stomach by Kojima and colleagues in 1999. It is a hormone containing 28 amino acids in structure and has been identified as an endogenous ligand of the type 1a receptor. It forms the active form of ghrelin, that also provides the release of growth hormone by binding an n-octenyl group fatty acid to serine which is the 3rd amino acid of ghrelin. This form is called active or acyl ghrelin.[9]

Ghrelin shows its effect by binding to GHS-R type 1a. By binding to the receptor, it induces the secretion of growth hormone-releasing hormone (GHRH) in the hypothalamus.[10]

Anorexigenic activation of ghrelin is regulated by neurons that engage specific receptors in the hypothalamus. Ghrelin is a regulator that has very different effects on metabolism. Ghrelin is found in hypothalamic neurons that regulate satiety and food intake. At the same time, ghrelin receptors are also present in other neurons that contribute to eating behavior in brain regions. While this increases ghrelin levels, it causes a decrease in leptin levels. This state can result in obesity. NPY gene expressions stimulated and increased by ghrelin eliminate the decreases in food intake induced by leptin. On the contrary, inhibition of NPY gene expressions causes suppression of food intake mediated by leptin and is the main mechanism. Amphetamine (AMPH), is used for the treatment of obesity, was determined to be used in obese individuals for appetite suppression.[11]

NEUROPEPTIDE Y, PEPTIDE YY AND PANCREATIC POLYPEPTIDE (PP)

Neuropeptide Y (NPY), peptide YY (PYY), pancreatic polypeptide (PP) and peptide Y (PY) polypeptides are members of the Neuropeptide Y peptide family. Among them, NPY is a peptide with 36 amino acids, which is widely found in the central and peripheral nervous system along with AgRP. NPY is found mostly in the sympathetic nerves, and fewer in parasympathetic nerves. NPY blood flow rate as well as metabolic rate decreases in brown adipose tissue. The Y5 receptor, one of the five G-protein receptors of neuropeptide Y, appears to be definitively responsible for regulating food intake.[5]

NPY influences adipose tissue apart from the effect of hypothalamic NPY on food intake,.Central NPY injection causes an increase in adipose tissue by increasing the level of plasma corticosterone and insulin.[12] The level of both insulin and leptin increases with an increase in adipose tissue. The synthesis and activity of NPY are inhibited. Thus, nutrient intake is reduced. Conversely, with food restriction (for example, when insulin or leptin levels are too low in the fasting state), the level of NPY increases. As a result, an increase in food intake occurs. The physiological role of NPY in nutrition, which is the most important effect, has not been fully determined due to the complexity of the common effects of NPY on the hypothalamus. When this receptor is precisely determined, it will be quite important in the cure of obesity. The synthesis of PYY and PP is carried out only by endocrine cells in the digestive tract. NPY in the intestinal–brain and brain–intestinal axis also existed. NPY and PYY alter digestive system motility and entry to the brain through inhibition of electrolyte secretion. PYY is also affected by the gut microbiota. NPY have a pro-inflammatory effect by stimulating Y1 receptors. PP and PYY send signals to the brain. They reduce appetite, anxiety and depression in this way. The information given above shows that NPY, PYY and PP have a significant role of the NPY-Y receptor system at various grade of the intestinal–brain axis as both neural and endocrine messengers.[13]

PYY in the intestine is produced by endocrine L cells. These cells are abundant in the lower gastrointestinal tract.[14] PYY L cells contain glicentin, glucagon-like peptide-1 and glucagon-like peptide-2, a proglucagon-derived peptide.[15] It is thought that L cells containing PYY are important chemo sensors in the intestine.[16]

The function of NPY, PYY and PP is associated with the expression of different Y receptor subtypes. After eating, PP is released from the pancreas and exerts its tue via the Y4 and Y5 receptors. This mechanism of action affecting the vagus nerve prevents gastric emptying. The decrease

in appetite through vagal signaling is caused by this effect.[17] PP also has an inhibitory role on intestinal motor activity and peristalsis. This newly discovered role in glucose homeostasis makes PYY an important one for the treatment of diabetes and obesity.[13]

NESFATIN-1

Nesfatin-1, first discovered by Shimizu et al.[18] in 2006, is a neurohormone or satiety molecule derived from the nucleobindin 2 [nucleobindin 2 (NUCB2)] protein that is expressed in humans and rats, especially in the hypothalamus, adipose tissue, pancreas, gastric mucosa, and brain. Nesfatin-1, which is newly discovered and identified as one of the anorexigenic peptides, affects the centers of the brain by targeting the arcuate nucleus where the hunger and satiety regions are located in the hypothalamus or by reaching the tractus solitarius nucleus in the brainstem and crossing the blood-brain barrier with a neural network interaction.[19] Nesfatin-1 is a receptor-sensitive amino-terminal fragment activated by a peroxisome proliferator consisting of 82 amino acids (MW 9.7 kDa). As a result of the translation of NUCB2, a protein consisting of 396 amino acids is released. NUCB2, which can be divided post-translationally by the pro-hormone converting enzyme, ultimately forms three different peptide products (segments). These segments are N-terminal nesfatin-1 (amino acid 1-82), nesfatin-2 (amino acid 85-163) and C-terminal nesfatin-3 (amino acid 166-396).[19] It is synthesized from nucleobindin 2 (NUCB2), known as the satiety peptide. Besides the effects of nesfatin-1 in the nervous system, it also has roles on the appetite mechanism and nutritional status.[18] Nesfatin-1 is closely related to diabetes, obesity. It is also associated with anorexia nervosa, psychiatric disorders and neurogenic diseases (figure3).[20]

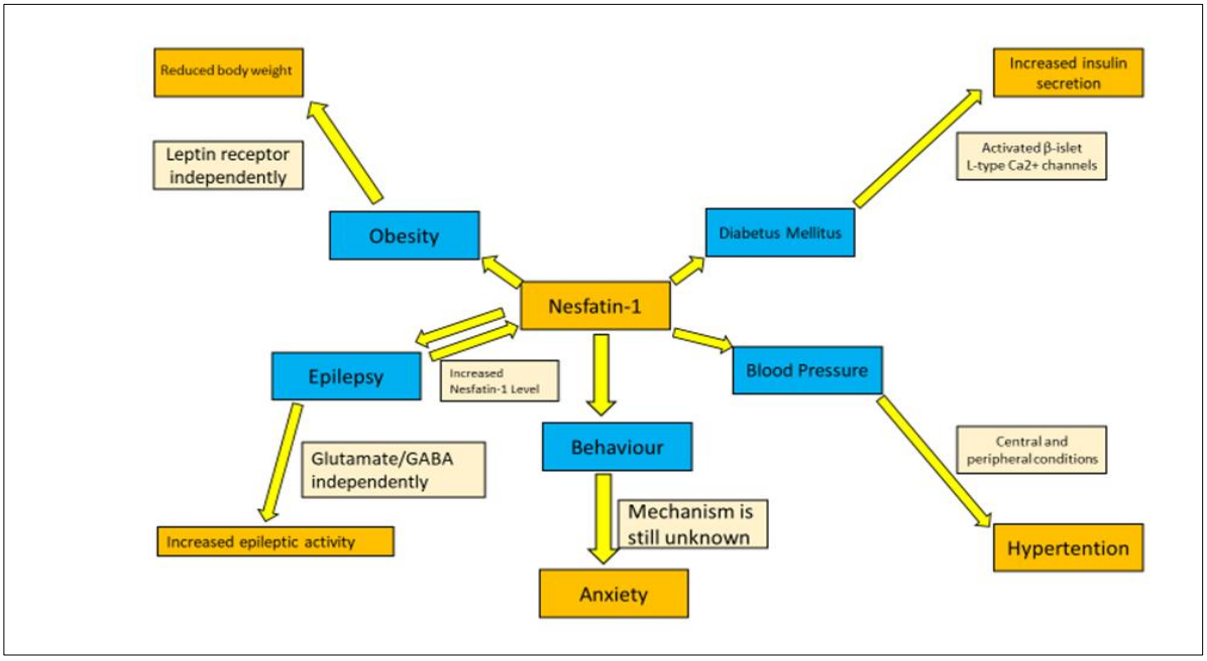


Figure 3. Common clinical state of Nesfatin-1.

In a study, it was reported that nesfatin-1 and NUCB2 levels increased 2 hours after feeding in 48 hours of fasting of rats.[21] This shows that nesfatin-1 plays a role in the regulation of energy balance, especially after eating. Nesfatin-1 is effective in the physiological control of nutrition. By suppressing the peristalsis of the digestive system, it reduces food intake. It plays a role in controlling body weight.[18] Chronic infusion of Nesfatin-1 is reported to steadily inhibit body weight gain and reduce white adipose tissue.[19] In another rat study, nesfatin-1 decrease food intake, feeding frequency on a dose-dependent basis (0.3 nmol).[20] All the data obtained show that Nesfatin-1 is an anorexigenic signaling agent. It has been found that serum nesfatin-1 is less in obese individuals. In a study which is performed on polycystic ovary syndrome (PCOS) women (n=55) showed that serum nesfatin -1 levels are negatively related with body mass index (BMI) Besides, congenital nesfatin-1 enzyme deficiency is associated with obesity.[22]

OREXIN

Orexin A contains 33 amino acids, while orexin B contains 28 amino acids. The similarity of amino acid sequence of orexin B is to 46% of orexin A.[23] Although the pharmacodynamics effects of orexin A and orexin B are relatively similar, their pharmacokinetic properties differ. Orexin A, due to its high lipophilic property, quickly enters the brain by passive diffusion. Orexin B, on the other hand, cannot enter the brain due to its low lipophilic property and is rapidly metabolized in the blood.[24] Nakabayashi et al.[25] showed that mRNA expression for pre-pro-orexin has been identified in kidney, adrenal gland, pancreas, placenta, stomach, ileum, colon and colorectal epithelial cells. This result shows that the production of orexin A also occurs in human peripheral tissues. Orexins are in the endocrine cells of the pancreas, but its functional significance has not been clearly defined.It has been suggested that orexin-A stimulates glucose uptake in adipocytes, increases lipogenesis by inhibiting hormone-sensitive lipase, and in addition to these effects, it inhibits the activation of peroxisome proliferator activated receptor gamma (PPARγ), which controls immune and inflammatory responses.[26] In addition to their triggering effects on food intake, orexins have been found to be involved in various hypothalamic control mechanisms with their effects on the continuation of wakefulness, neuroendocrine, cardiovascular and cognitive functions. Orexins synthesized by neurons located in the hypothalamus have been reported to exert neuroendocrine effects both in the hypothalamus and on the pituitary gland.[27]

It is stated that the role of orexin in energy balance is realized by inhibiting anorexinergic arcuate neurons and activating orexinergic arcuate neurons in contrast.[28] In a conducted study, there is no clear knowledge about whether orexin causes hyperphagia by directly affecting the systems in the appetite regulation or by affecting other neuropeptides. Some experts note that orexins do not cause obesity, despite the effect of increasing food intake. The reason for this state, orexins also increase metabolic rate. In a study, it postulated that orexin neurons inhibit leptin receptors, while leptin given to rats reduces the level of hypothalamic orexin A and reduces the activity of orexin neurons.[28] The results of studies show that orexin-A can act as a hormone-like substance. It does this by regulating the effects of insulin on food and glucose. Besides, there is evidence that orexin-A and leptin play a regulatory role in rodent's feeding behavior. Chronic intraperitoneal leptin administration has a weight loss effect.At the same time, a significant decrease in the orexin-A mRNA levels of the hypothalamus also occurs with this application.[29]

IRISIN

Irisin, was identified by Pontus et al.[30] in 2012, is a peptide protein consisting of 112 amino acids. Irisin is a myokine which is the proteolytic product of fibronectin type III domain 5 (FNDC5), a membrane protein in muscles.[31] It causes an increase in brown adipose tissue. Thus, it causes an increase in energy consumption. It also mediates the positive effects of exercise on metabolism.[20] It is produced in skeletal muscle and adipose tissue, heart tissue, intracranial arteries, kidney, myelin sheath, neural cells, ovaries, Purkinje cells, rectum, salivary glands, sweat glands, stomach, testes, and tongue tissues.[32]

Peroxisome proliferators are stimulated because of exercise, which leads to energy expenditure. This causes the activation of the receptor gamma (PPARy) and PGC1-A. This activation causes an increase in the expression of the FNDC5 gene. PGC1-α controls the mitochondrial biogenesis and oxidative energy metabolism of many cells as an intermediary. FNDC5 is synthesized and secreted from the muscle tissue via PGC1-α, and it regulates the gene expression of brown adipose tissue mitochondrial protein 1 (UCP1), cytochrome c oxidase 7a (COX7a) and otopetrin 1 (OTOP1). 20 nm FNDC5 added to the adipose tissue culture medium increased UCP1 expression by about 7 ratios. Increased expression of UCP1 inhibits ATP synthesis. It leads to the formation of heat. It causes energy expenditure. FNDC5 regulates thermogenesis in brown adipose tissue (figure 4).[20]

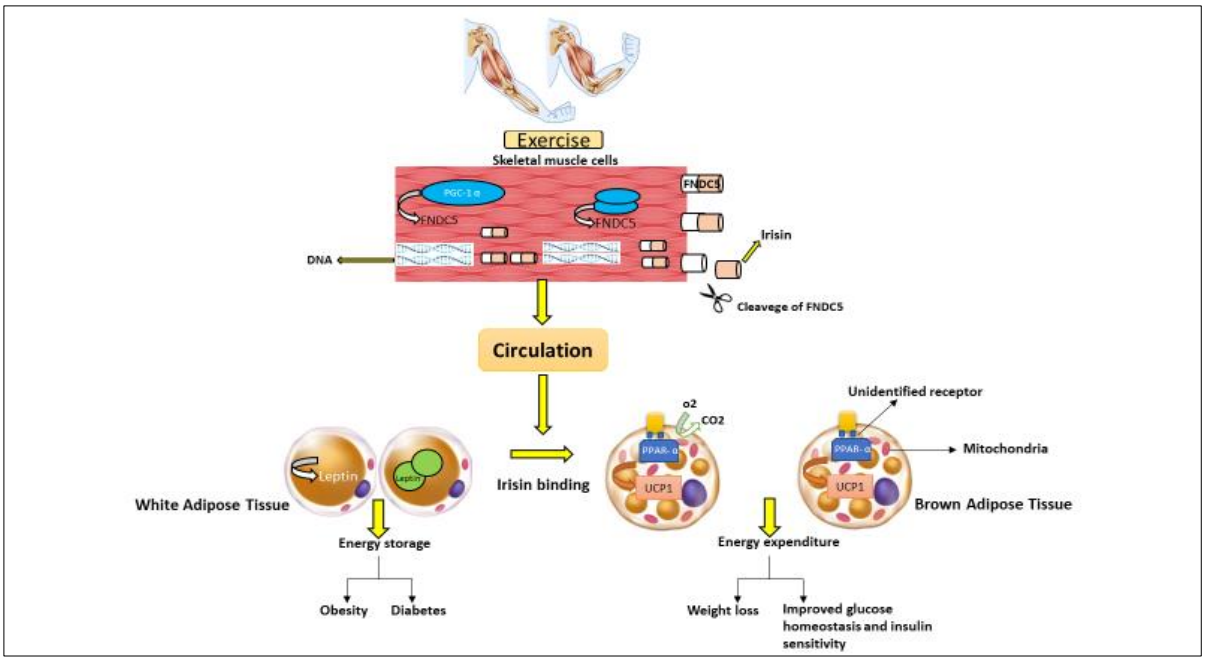


Figure 4. Exercise-induced browning of adipose tissue with irisin and PGC-1α.

Irisin which is firstly investigated in skeletal muscle, is synthesized, and secreted in many tissues. Even though there are contrary results in the studies, it is stated that irisin has many physiological properties in such as weight loss, decreasing in insulin resistance, is related with obesity, glucose regulation, and effects on lipid metabolism.[31] Although irisin is prominent with its myokine identity secreted from muscle, it is an adipokine due to its secretion from adipose tissue. When the effect of circulating irisin levels was examined, the secretion from white adipose tissue was at a lower level than that secreted from muscle.[33]

Despite studies showing that irisin levels decrease when adipose tissue increases, the level of circulating irisin increases when waist circumference and waist/hip ratio and leptin levels increase. Individuals with the normal range of BMI is and without any metabolic disorders, the majority of circulating irisin levels are secreted from muscle cells, while in obese individuals the amount of irisin is secreted because of an increase in body fat mass is excessive in adipose tissue.[33] It is believed that significantly reducing irisin levels in the blood and FNDC5 gene expression in obese people who have lost body weight by bariatric surgery method supports that mechanisms for reducing high irisin levels in obese people may be a therapeutic approach. But in a study that clarified the insulin level after bariatric surgery in obese individuals, it was also determined that the level of irisin increased in response to decreased body mass (figure 4).[31]Again, a lower irisin level in the elderly obese group is associated with age-related decreased muscle function. In obesity, the synthesis of circulating irisin levels increases as a regulatory response to the metabolic disorders such as low insulin levels and insulin resistance. The high level of irisin in obesity may benefit as a predictive factor in use for early diagnosis and treatment. Physical activity, which is very important in controlling metabolic problems such as obesity, Type 2 DM, cardiovascular diseases, is also associated with the hormone irisin that increases because of muscle contraction. In relation to the exercise performed, the levels of iris in the tissues vary.[34] In studies with long-term exercise plans, an increase in blood irisin levels is increases immediately after daily training, while a slowly decreases is observed after 30 minutes. There is no difference in circulating irisin levels after the end of the planned exercise study. Therefore, it can be concluded the acute effective elevation of the blood irisin level during exercises is due to the fact of homeostatic regulation of ATP and followed by a decrease in basal concentrations.[35]

It is believed that irisin has an important role in decrease the amount of fat in the body, since it is a thermogenic agent.[36] In previous research, irisin levels were found to be 353.1±18.6 ng/mL in obese individuals and 198.4±7.8 ng/mL in controls. Irisin were measured as 353.1±18.6

ng/mL in men and 267.6±12 ng/mL in women. This study shows that irisin levels are higher in men in relation to gender.[36] Circulating irisin increases in obesity as a compensatory response to hyperglycemia. at the same time, it has been suggested that the sensitivity of the iris to insulin and leptin decreases.[37]

An association between plasma iris concentrations of the obese and diabetic group and body mass index, age and different biochemical parameters could not be determined. Also, when all Type 2 diabetes patients were grouped separately, it was found that there was an association between circulating irisin levels and both HbA1c and urea.[38]

AMYLIN

Amylin is a polypeptide consisting of 37 Amino acids. In case of satiety, insulin is secreted from the β cells of the pancreas as a signal of satiety. It exerts its effect by acting on cortical homeostatic and hedonic brain regions. It prolongs the emptying process of the stomach and suppresses the secretion of glucagon. It plays a primary role in regulating glucose levels after childbirth by creating an anorectic signal. Therefore, synthetic amylin analogues can take part in the treatment process of obese individuals as anti-obesity drugs.[39]

Amylin plays an important role in regulating post-meal satiety. It activates proopiomelanocortin neurons through amylin kinase signaling. This pathway is regulated by extracellular signaling. This arrangement is made independently of leptin.[40] It seems that amylin will be very useful for losing weight and regulating glucose levels. Due to the short duration of action of amylin and its tendency to self-cluster, it makes it difficult to show the above-mentioned effects for a long time.[41]

The use of analogues of amylin in the treatment of obesity seems to be a reliable option that increases the likelihood of obtaining results. It is stated that administration of amylin analogues in combination with GLP-1 (glucagon such as peptide-1) agonists for more weight loss is more beneficial compared to monotherapy. For these therapeutic agents to be used effectively in the treatment of obesity, conducting studies in which more examples are included is important in terms of effectiveness and reliability.[42]

OBESTATIN

Injection of a newly discovered hormone, obestatin, prolongs the residence time of food in the stomach. It is revealed in new studies that the feeding and contraction stimuli of the ghrelin hormone on the jejunal muscles are reduced by obestatin.[43] It is stated that obestatin prevents thirst, strengthens memory and affects sleep. In addition, it is stated that it positively affects cell proliferation, release of pancreatic enzymes, survival, and inhibits the stimulation of insulin release by glucose.[44]

In a study conducted on rats that underwent gastrectomy, it was found that obestatin and ghrelin levels decreased by 50-80%.[45] Anorexigenic effects have been found to occur in rats after the first peripheral or intracerebroventricular injection of obestatin.[43,46] In some recent studies, it is stated that Obestatin has no inhibitory effect on food intake and weight gain.[47] Lagaud et al.[46] demonstrated the effects of obestatin on the diet of rats at different dose ranges. Treatment with obestatin for a period of 7 days was found to suppress food intake and weight gain in rodents.[46]

PREPTIN

Isolated from the beta cells of the rat Pancreas in 2001, the amount of preptin in circulation is halved in less than five minutes. An increase or decrease in its level is closely related to insulin levels in humans. Preptin-stimulated Insulin secretion has been found to be at a similar level to glibenclamide in mice.[49]

It is revealed in the above study that preptin and amylin are produced at the same time by the beta cells of the pancreas. Infusion of preptin into isolated and perfused rat pancreas increases glucose-mediated insulin secretion by 30% in the second phase. It is reported that antipreptin immunoglobulin infusion reduces first phase secretion by 29% and second phase secretion by 26%.[50] Preptin levels were found to be higher in patients with diabetes mellitus than in healthy individuals. In addition, a positive correlation was observed between diastolic blood pressure, triglyceride, total cholesterol, HbA1c and HOMA-IR index and plasma preptin concentrations.[48]

In a study, preptin levels in serum and fetal cord blood of 31 pregnant women of the same age with and without gestational diabetes were investigated. Preptin levels were found to be higher in the maternal serum and fetal cord blood of the diabetic group. A positive correlation was found between preptin levels and maternal age, fasting insulin level, blood glucose level in the first hour after sugar loading, and fetal cord preptin.[50]

Conclusion

As a result of a study conducted on obese individuals who received nutrition and exercise training, it was found that irisin levels did not change, but there was a moderate correlation between plasma irisin levels and HOMA-IR levels. In this way, it was determined that adiponectin showed anti-obesity property.

Hormones that inform the hypothalamus about the body's energy stores prevent eating and ensure that body weight remains within certain physiological limits. It is very crucial to clarify obesity, which has emerged as an increasing health problem in recent years, and hormones related to obesity. In this context, we conclude that the functions of obesity-related hormones mentioned above will guide further studies.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Ethics Committee Permission

Since the study is a compilation, ethics committee permission is not required.

Authors' Contributions

Concept/Design: SK, EM. Literature Search: SK, LS. Drafting manuscript: SK, LS, EM. Critical revision of manuscript: EM, LS. Supervisor: EM.

REFERENCES

1. Aktaş D, Öztürk FN, Kapan Y. Adölesanlarda obezite sıklığı ve etkileyen risk faktörleri, beslenme alışkanlıklarının belirlenmesi. TAF Prev. Med. Bull. 2015;14(5):406-412.
2. Aysoydan E, Çakır N. Adölesanların beslenme alışkanlıkları, fiziksel aktivite düzeyleri ve vücut kitle indekslerinin değerlendirilmesi. Gulhane Med J. 2011; 53(4):264-270.
3. Ergül Ş, Kalkım A. Önemli bir kronik hastalık: çocukluk ve ergenlik döneminde obezite. TAF Prev. Med. Bull. 2011;10(2):223-230.
4. Uskun E, Öztürk M, Kişioğlu A, Kirbiyik S, Demirel R. İlköğretim öğrencilerinde obezite gelişimini etkileyen. SDÜ Tıp Fak Derg. 2005;12(2):19-25.
5. Hızlı H, Büyükuslu N. Yüksek yağlı diyetin açlıktokluk metabolizmasında görevli hormonlar ve nöropeptidler üzerine etkileri. Saglik Bilim. Derg. 2018; 27(3):239-344.
6. Zhang F, Chen Y, Heiman M, DiMarchi R. Leptin: structure, function, and biology. Vitam. Horm. 2005;71:345-372.
7. Öztürk AS, Arpacı A. Obezite ve Ghrelin/Leptin ilişkisi. Mustafa Kemal univ. tıp derg. 2018;9(35): 136-151.
8. Yura S, Itoh H, Sagawa N. et al. Role of premature leptin surge in obesity resulting from intrauterine undernutrition. Cell metabolism. 2005;1(6):371-378.
9. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999; 402(6762):656-660.
10. McKee KK, Palyha OC, Feighner SD, et al. Molecular analysis of rat pituitary and hypothalamic growth hormone secretagogue receptors. Mol. Endocrinol. 1997; 11(4):415-423.
11. Schmid SM, Hallschmid M, Jauch-chara K, Born J, Schultes B. A single night of sleep deprivation increases ghrelin levels and feelings of hunger in normal-weight healthy men. J. Sleep Res. 2008;17(3): 331-334.
12. Wyss P, Stricker-Krongrad A, Brunner L, et al. The pharmacology of neuropeptide Y (NPY) receptor-mediated feeding in rats characterizes better Y5 than Y1, but not Y2 or Y4 subtypes. Regul. Pept. 1998;75:363-371.
13. Holzer P, Reichmann F, Farzi A. Neuropeptide Y, peptide YY and pancreatic polypeptide in the gut–brain axis. Neuropeptides. 2012;46(6):261-274.
14. Ueno H, Yamaguchi H, Mizuta M, Nakazato M. The role of PYY in feeding regulation. Regul. Pept. 2008;145(1-3):12-16.
15. Cox HM. Neuropeptide Y receptors; antisecretory control of intestinal epithelial function. Auton. Neurosci. 2007;133(1):76-85.
16. Rozengurt N, Wu SV, Chen MC, Huang C, Sternini C, Rozengurt E. Colocalisation of the a subunit of gustducin with PYY and GLP-1 in L-cells of human colon. Am. J. Physiol. 2006;291(5):792-802.
17. Murphy KG, Bloom SR. Gut hormones and the regulation of energy homeostasis. Nature. 2006;444(7121): 854-859.
18. Shimizu H, Oh IS, Satoh T, et al. Identification of nesfatin-1 as a satiety molecule in the hypothalamus. Nature. 2006;443(7112):709-712.
19. İşgüzar Y, Akbulut G. Obezite ile ilgili güncel iki hormon: Nesfatin-I ve Omentin-I. Türkiye Klinikleri J Health Sci. 2019;4(1):57-61.
20. Gülmez C, Atakişi O. Yeni hormonlar: R-Spondin-1, Nesfatin-1 ve İrisin. Caucasian Med J. 2019;6(1):37-50.
21. Daisuke K, Mascroni N, Yuko M, Hiroyuki S, Udual S, Natsu Y. Nesfatin 1 neurons in paraventricular and supraoptic nuclei of the rat hypothalamus coexpress oxytocin and vasopressin anda re activated by. Endocrinology. 2008;149(3):1295-1301.
22. Abaci A, Catli G, Anik A, Kume T, Bober E. The relation of serum nesfatin-1 level with metabolic and clinical parameters in obese and healthy children. Pediatr. Diabetes. 2013;14(3):189-195.

23. Lees G, Coyne L. The orexins: a novel family of sleep regulating neuropeptides. CACC 2004;15(1):75-77.
24. Mondal MS, Nakazato M, Matsukura S. Orexins (hypocretins): novel hypothalamic peptides with divergent functions. Biochem. Cell Biol. 2000;78(3): 299-305.
25. Nakabayashi M, Suzuki T, Takahashi K, et al. Orexin-A expression in human peripheral tissues. Mol. Cell. Endocrinol. 2003;205(1-2):43-50.
26. Bülbül A, Tülüceoğlu EE, Öztürk Ö, Calapoğlu NŞ, Gonca T, Calapoğlu M. Serum oreksin seviyelerinin obezite ile ilişkisi: kesitsel ilişkilendirme çalışması. SDÜ Tıp Fak Derg. 2018;9(4):37-43.
27. Yurtseven DG, Minbay Z, Eyigör Ö. Nesfatin-1 ve Oeksin A nöronları arasındaki etkileşimin immünohistokimyasal olarak araştırılması. UÜTFD. 2019; 45(3):243-249.
28. Karadağ MG, Aksoy M. Yeni keşif nöropeptitlerden: Oreksin.GTD.2009;24(2):79-87.
29. Beck B, Richy S, Hypothalamic hypocretin/orexin, and neuropeptide Y: divergent interaction with energy depletion and leptin. Biochem. Biophys. Res. Commun. 1999;258(1):119-122.
30. Pontus B, Jun W, Mark PJ at all. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012:481(7382): 463-810.
31. Sarioğlu B. İrisin hormonu. Sağlık ve Toplum. 2021; 31(3):59-66.
32. Aydın SF. Three new players in energy regulation: preptin, adropin and irisin. Peptides. 2014;56:94-110.
33. Crujeiras AB, Zulet MA, Lopez LP, et al. Association between circulating irisin levels and the promotion of insulin resistance during the weight maintenance period after a dietary weight-lowering program in obese patients. Metabolism. 2014;63(4):520-531.
34. Martinez Munoz IY, Camarillo Romero EdS, Garduno Garcia JdJ. Irisin a novel metabolic biomarker: present knowledge and future directions. Int. J. Endocrinol. 2018:7816806.
35. Huh JY, Mougios V, Skraparlis A, Kabasakalis A, Mantzoros CS. Irisin in response to acute and chronic whole-body vibration exercise in humans. Metabolism. 2014;63(7):918-921.
36. Boström P, Wu J, Jedrychowski MP, et al. A PGC1- -dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012; 481(7382):463-468.
37. Montez JM, Soukas A, Asilmaz E, Fayzikhodjaeva G, Fantuzzi G, Friedman JM. Acute leptin deficiency, leptin resistance, and the physiologic response to leptin withdrawal. Proc Natl Acad Sci. 2005;102(7): 2537-2542.
38. Sanchis-Gomar F, Lippi G, Mayero S, Perez-Quilis C, García-Giménez JL. Irisin: a new potential hormonal target for the treatment of obesity and type 2 diabetes. J Diabetes. 2012;4(3):196-196.
39. Ogawa A, Harris V, McCorkle SK, Unger RH, Luskey KL. Amylin secretion from the rat pancreas and its selective loss after streptozotocin treatment. J Clin Invest. 1990;85(3):973-976.
40. Boccia L, Gamakharia S, Coester B, Whiting L, Lutz TA, Le Foll C. Amylin brain circuitry. Peptides 2020; 132:170366.
41. Qiu WQ, Zhu H. Amylin and its analogs: a friend or foe for the treatment of Alzheimer's disease? Front Aging Neurosci. 2014;6:186.
42. Babak D, Nicholas RSS, Carel WR. Amylin as a future obesity treatment. J Obes Metab Syndr. 2021;30(4): 320-325.
43. Zhang JV, Ren PG, Avsian-Kretchmer O, et al. Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. Science. 2005; 310(5750):996-999.
44. Ren AJ, Guo ZF, Wang YK, et al. Inhibitory effect of obestatin on glucose-induced insulin secretion in rats. Biochem Biophys Res Commun. 2008;369(3):969-972.
45. Furnes WM, Stenstro¨m B, Tømmera˚ s K, et al. Feeding behaviour in rats subjected to gastrectomy or gastric bypass surgery. Eur Surg Res. 2008;40(3):279-288.
46. Lagaud GJ, Young A, Acena A, Morton MF, Barrett TD, Shankley NP. Obestatin reduces food intake and suppresses body weight gain in rodents. Biochem Biophys Res Commun. 2007;357(1):264-269.
47. Sibilia V, Bresciani E, Lattuada N, et al. Intracerebroventricular acute and chronic administration of obestatin minimally affect food intake but not weight gain in the rat. J Endocrinol Invest. 2006;29:31-34.
48. Yang GY, Li L, Chen WW, Liu H, Boden G, Li K. Circulating preptin levels in normal, impaired glucose tolerance, and type 2 diabetic subjects. Ann Med. 2009;41(1):52-56.
49. Cheng KC, Li YX, Asakawa A, et al. Characterization of preptin-induced insulin secretion in pancreatic-cells. J Endocrinol. 2012;215(1):43-49.
50. Aslan M, Celik O, Karsavuran N, et al. Maternal serum, and cord blood preptin levels in gestational diabetes mellitus. J Perinatol. 2011;31(5):350-355.

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Hipofiz Adenomu Olan Bir Hastada Sertralin Kullanımına Bağlı Prolaktin Yüksekliği: Bir Olgu Sunumu

Prolactin Elevation Due to Sertraline Use in a Patient with Pituitary Adenoma: A Case Report

Meltem PUŞUROĞLU[1] ***Sefanur KÖSE[1]*** ***Çiçek HOCAOĞLU[1]***

ÖZ

Antipsikotikler psikiyatri ilaç grupları arasında en sık prolaktinemiye yol açan ilaç grubudur. Prolaktin yüksekliği genellikle antipsikotiklere bağlı bir yan etki olarak düşünülmektedir. Ancak klinikte antidepresan kullanımına bağlı prolaktin yüksekliği de gözlenmektedir. İlaçların sebep olduğu prolaktin yüksekliğini belirlemek ve tedavi seçeneklerini gözden geçirmek önemlidir. Olgumuzda hipofiz adenomu olan bir hastada sertralin kullanımı sonrasında prolaktin yüksekliği bildirilmiştir. Hastanın adenomu olmasına rağmen prolaktin yüksekliğinin nedeni sertralin kullanımı olarak görülmüştür. Prolaktin yüksekliği ile başvuran bir hastada kullandığı ilaçlar ve prolaktin düzeyine olan etkisi ilk değerlendirilmesi gereken konulardan biridir.

Anahtar Kelimeler: galaktore; prolaktinemi; yan etki

ABSTRACT

Antipsychotics are the drugs that most frequently cause prolactinemia among the psychiatric drug groups. When prolactin eleva tion is mentioned, it is generally considered as a side effect related to antipsychotics. However, prolactin elevation is also obs erved in the clinic due to the use of antidepressants. It is important to identify prolactinoma via drugs and to review treatment options. In our case, prolactin elevation of patient with pituitary adenoma was reported after the use of sertraline. Although the patient had aden oma, sertraline was found to be the cause of elevated prolactin. In a patient presenting with elevated prolactin, medications and their effect on prolactin levels are among the first issues to be evaluated.

Keywords: galactorrhea; prolactinemia; side effects

Gönderilme tarihi: 11.12.2022; Kabul edilme tarihi: 03.04.2023

[1]Recep Tayyip Erdoğan Üniversitesi, Tıp Fakültesi, Ruh Sağlığı ve Hastalıkları Ana Bilim Dalı, Rize, Türkiye.

Sorumlu Yazar: Meltem Puşuroğlu, Recep Tayyip Erdoğan Üniversitesi, Tıp Fakültesi, Ruh Sağlığı ve Hastalıkları Ana Bilim Dalı, Rize, Türkiye.
e-posta: meltempusuroglu@gmail.com

Makaleye atıf için: Puşuroğlu M, Köse S, Hocaoğlu Ç. Hipofiz adenomu olan bir hastada sertralin kullanımına bağlı prolaktin yüksekliği: Bir olgu sunumu. Ahi Evran Med J. 2024;8(1):121-125. DOI: 10.46332/aemj.1217431

GİRİŞ

Prolaktin ön hipofiz laktotroflarından salgılanan bir hormondur. Yarılanma ömrü 25–50 dakikadır ve çoğunluğu karaciğerden bir kısmı ise böbreklerden metabolize edilmektedir. Kanda prolaktin düzeyinin artışı hiperprolaktinemi olarak adlandırılır ve kronik hastalıklar, ilaç kullanımı, fizyolojik nedenler gibi birçok sebebi olabilir. Bazen asemptomatik seyredebileceği gibi bazen de cinsel isteksizlik, galaktore, amenore gibi semptomlar gösterebilir.[1] Prolaktin yüksekliği orta yaş kadınlarda daha sıklıkta gözlenmekte olup erkeklerde de görülebilir. Kadınlarda daha sık semptom görülmekteyken erkeklerde uzunca süreler semptomsuz seyredebilir. Ancak erkeklerde de kliniğe yansıyarak semptomatik olabilir.[2] Gebelik sürecinde, egzersiz yapıldığında, meme ucuna uyarı verildiğinde, stres durumlarında, uykuda, cinsel ilişki sonrasında ve epileptik nöbet sonrasında fizyolojik olarak prolaktin yüksekliği görülebilir.[1] Hipofiz bezi, beyin sapı hastalıkları, tümörler, genetik birçok hastalık prolaktin yüksekliğine yol açabilir. Bir diğer önemli neden de ilaç kullanımıdır. Antipsikotikler, antihipertansifler, antiemetikler, antikonvülsanlar, antihistaminikler gibi birçok ilaç grubu prolaktin yüksekliğine yol açabilir.[3]

Antipsikotikler psikiyatride kullanılan ilaçlar arasında en sık hiperprolaktinemiye yol açan ilaç grubudur. Dopamin prolaktin salınmasını inhibe eden ana faktördür. Psikotrop ilaçlarla dopamin salınımının baskılanması dolaylı yoldan prolaktin yüksekliğine yol açabilir.[4] Prolaktin yüksekliği denildiğinde genellikle antipsikotiklere bağlı bir yan etki olarak düşünülmektedir. Antipsikotiklerin etki mekanizmasının direk etkisi bu sonucun sebebidir. Ancak klinikte sıklıkla kullanmakta olduğumuz serotonin geri alım inhibitörleri (SSRI) de tubuloinfindubular yolakta Dopamin salınımını baskılayarak prolaktin yüksekliğine yol açabilir. Bu durumda klinikte, antipsikotikler kadar sıklıkla görülmese de, SSRI kullanımına bağlı prolaktin yüksekliği olan olgular görülmektedir.[5] Literatüre bakıldığında essitalopram, sertralin, fluoksetin gibi SSRI kullanımına bağlı hipreprolaktinemi olguları mevcuttur. Antipsikotiklerin hiperprolaktinemiye yol açma mekanizması daha fazla bilinmektedir. Ancak SSRI kullanımına ait bilgiler daha kısıtlıdır.[6-8]

İlaçların sebep olduğu prolaktin yüksekliğini belirlemek ve tedavi seçeneklerini gözden geçirmek önemlidir. Prolaktin yüksekliği ile başvuran bir hastada kullandığı ilaçlar ve prolaktin düzeyine olan etkisi ilk değerlendirilmesi gereken konulardan biridir.[3] Çalışmamızda kadın doğum polikliniğine adet olamama şikâyeti ile başvuran bir hastada sertralin kullanımına bağlı prolaktin yüksekliği vurgulanacaktır. Olgumuzda aynı zamanda hipofiz adenomu da bulunmaktadır. Ancak klinik izlemde bu yüksekliğin sebebinin sertralin kullanımının olabileceği görülmüştür. Prolaktin yüksekliği açısından farkındalık kazanılması ve klinisyenlere ışık tutması adına olgumuz literatüre sunulmuştur.

OLGU SUNUMU

H.U, 48 yaşında, evli, 3 çocuğu olan, ilkokul mezunu, eşi ve çocukları ile kırsal alanda yaşayan kadın hasta. Hasta 4 aydır adet görememe nedeniyle Kadın Hastalıkları ve Doğum polikliniğine başvurmuş. Öncesinde adetleri düzenli olan hastanın son 4 aydır adet olmadığı, adetlerinin kesilmesi dışında herhangi bir yakınması olmadığı öğrenilmiştir. Kadın doğum polikliniğinde yapılan incelemesinde hastada prolaktin yüksekliği saptanmış ve prolaktin yüksekliği dışında herhangi bir bulgu saptanmayan hasta, son 5 aydır sertralin 50 mg/g kullanımı olması nedeniyle ilaca bağlı prolaktin yüksekliği açısından değerlendirilmesi amacıyla tarafımıza yönlendirilmiştir.

Hastanın öyküsünde ilk şikayetleri yaklaşık 20 yıl önce doğum sonrası dönemde moralsizlik, keyifsizlik, hayattan keyif alamama gibi yakınmalar ile başlamış. Hastaya bu dönemde essitalopram 10 mg/gün tedavisi başlanmış ve hasta bu bir yıllık süre içerisinde ilacını düzenli kullanmış ve fayda görmüş. Hastada iyilik hali olması üzerine bir yılın sonunda ilacı hekim kontrolünde azaltılarak kesilmiş. Hastanın bu dönemde essitalopram kullanımına bağlı herhangi bir yan etkisi olmamış. Bu yirmi yıllık süre içerisinde belirgin yakınması olmayan hastanın son dönemlerde ara ara hafif mutsuzluk yakınmaları olmuş ancak yaklaşık 5-6 ay önce belirgin mutsuzluğu ve keyifsizliği olması üzerine psikiyatri polikliniğine başvurmuş. Hastaya depresyon tanısı konularak Sertralin 50 mg/gün tedavisi başlanmış. Hasta ilacından belirgin fayda görmüş ve özellikle son bir aydır şikayetlerinde belirgin gerileme olmuş. Hasta bu süre içerisinde psikiyatri takiplerini sürdürmüş. İlaçla ilgili herhangi bir yan etki yaşamamış. İlaca

başladıktan sonraki ilk siklusta adeti azalmış ve sonrasında adet görmemeye başlamış. 4-5 aydır adet görememe şikâyeti olması üzerine kendisi kadın hastalıkları ve doğum polikliniğine başvurmuş. Kadın hastalıkları ve doğum polikliniğinde hastanın adet görememesi açısından ayrıntılı değerlendirilmesi yapılmış ve hastaya yapılan tetkikler sonrasında bu durumun kullandığı psikiyatri ilacından kaynaklanabileceği belirtilmiş ve psikiyatri polikliniğine yönlendirilmiş. Hastanın konsültasyon notunda adet görememesini açıklayacak başka bir bulgusunun olmadığını, yapılan tetkiklerinin menopoz süreci ile uyumlu olmadığı, mevcut durumu prolaktin yüksekliği ile ilişkilendirildiği bu yönden değerlendirilmesi gerektiği belirtilmiştir. Hastanın şu anki yapılan ruhsal durum muayenesi; yaşında gösteren, giyimi sosyokültürel seviyesi ile uyumlu olan bilinci açık, oryante-koopere hasta. Görüşmeye istekli, göz teması kuruyor. Konuşma miktarı, hızı ve ses tonu olağan. Dikkat ve konsantrasyon olağan. Yakın ve uzak bellek korunmuş, duygudurum ötimik, duygulanım stabil. Düşünce süreci olağan, düşünce içeriğinde ve algıda aktif psikotik bulgu saptanmadı. Yargılama, soyutlama yetileri korunmuş, zekâ normal aralıkta. Psikomotor davranış olağan olup mevcut haliyle ruhsal durum muayenesinde belirgin psikopatoloji saptanmamıştır. Hastanın genel tıbbi öyküsünde 8 yıldır hipertansiyon tanısı ile takipli olduğu perindopril+amlodipin 5/10 mg/gün kullandığı ve miyoma uteri tanısı ile levonorgestrel 20 mcg/24 saatte salıverilen rahim içi araç kullanımı olduğu öğrenilmiştir. Hastanın genel fizik muayenesinde belirgin bir bulgu saptanmamış olup adet görememe dışında da bir semptomu yoktur. Alkol, madde kullanımı olmayan hastanın 33 yıldır 1 pk/gün sigara kullanımı mevcut. Hastanın tansiyon ilacı ve antidepresan tedavisi dışında herhangi bir ilaç kullanımı olmadığı, herhangi bir bitkisel takviye kullanmadığı ya da son dönemlerde farklı bir ajana maruz kalmadığı öğrenilmiştir. Hastanın özgeçmişinde özellik yoktur ve ailesinde psikiyatrik hastalık öyküsü bulunmamaktadır. Olgu yazımı öncesi hastanın kendisine yazı hakkında bilgilendirilme yapılarak yazılı ve sözlü onamı alınmıştır.

Yapılan Rutin kan tetkiklerinde tam kan sayımı, kan biyokimyası, tiroit fonksiyon testleri normal aralıkta saptanmış ve prolaktin yüksekliği (72.9 ng/ml) dışında patolojik bulgu saptanmamıştır. Hastanın herhangi bir kronik hastalık öyküsü de yoktur. Prolaktin yüksekliğine yol açacak diğer patolojilerin dışlanması amacıyla istenen Beyin manyetik rezonans (MR) görüntülemesinde hipofiz bezi sağ lateral kesiminde dinamik incelemede beze göre daha düşük oranda kontrast etkileşimi gösteren 5 mm çapında nodüler odak izlenmiştir. Hipofizer infindubulum hafif sola deviye olduğu gözlenmiştir. Hipofiz MR görünümü adenom lehine değerlendirilmiştir. Hastanın prolaktin yüksekliğinin adenom nedeniyle olabileceği düşünülüp sertralin tedavisi kesilmeden tarafımızca endokrinoloji ve beyin cerrahi bölümlerine konsülte edilmiştir. Konsültasyonu sonrasında hasta tarafımıza tekrar yönlendirilmiştir. Hastanın endokrinoloji ve beyin cerrahi konsültasyon notunda hastada hipofiz adenomuna bağlı herhangi bir bulgu gözlenmediği, adenomun asemptomatik olma ihtimalinin daha yüksek olduğu, hastanın prolaktin yüksekliğinin en olası nedeninin sertralin kullanımı olabileceği, bu nedenle ilaca bağlı prolaktin yüksekliği açısından tarafımızca tekrar değerlendirilmesi gerektiği belirtilmiştir. Bunun üzerine tüm konsültasyon bulguları ile hasta ilaç yan etkisi açısından yeniden değerlendirilmiştir. Hastanın ilaç yan etki profili açısından yapılan değerlendirilmesi neticesinde Naranjo ilaç yan etki olasılık ölçeğinden 7 puan almıştır ve ilaç yan etkisi Dünya Sağlık Örgütünün Nedensellik Değerlendirme Sistemine göre "Olası Muhtemel Yan Etki" kategorisinde değerlendirilip hastanın Sertralin ilaç dozu tedricen azaltılarak kesilmiştir. Hastanın sertralin kullanımı kesildikten sonra kan prolaktin değeri (3.26 ng/ml) dramatik olarak gerilemiştir. Hastanın adenomunun asemptomatik olduğu prolaktin yüksekliğinin adenom nedeni ile değil sertralin kullanımı nedeni ile olduğu düşünülmüştür. Hastanın asemptomatik adenomu nedeniyle hastaya beyin cerrahi polikliniği tarafından düzenli aralıklarla kontrol önerilmiştir. Sertralin tedavisi sonlandırılan hasta bir süre ilaç kullanımı olmadan takip edilmiştir ancak hastanın depresyon semptomlarının tekrar başlaması üzerine tarafımızca tekrar Sertralin tedavisi başlanmamış onun yerine geçmiş dönemde kullandığı ve faydalandığı essitalopram 10 mg/gün tedavisine başlanmıştır. Halen poliklinik takipleri süren hasta mevcut haliyle ilaçtan fayda görmüştür ve hastanın adet görememe şikâyeti düzelmiş ve tekrar adet görmeye başlamıştır. Yapılan laboratuvar incelemesi takiplerinde ise hastada prolaktin yükselmesi gözlenmemiştir.

TARTIŞMA

Yukarıda sunduğumuz olgumuzda prolaktin yüksekliğine bağlı amenore gelişmiştir. Literatüre bakıldığında benzer şekilde sertralin kullanımı sonrasında prolaktin yüksekliğine bağlı amenore yakınması ile kliniğe başvuran olgular bildirilmiştir.[5] Olgumuzun ilk değerlendirmesinde prolaktin yüksekliğinin öncelikli olarak hipofiz adenomundan kaynaklanabileceği düşünülmüş ve sertralin tedavisinin kesilmesi planlanmamıştır. Bu noktada hastanın ilk olarak adenomuna bağlı incelenmesi açısından endokrinoloji ve beyin cerrahisine yönlendirilmiştir. Ancak hastanın tüm kliniklerce değerlendirilmesi neticesinde hastanın hiperprolaktinemisinin en olası nedeninin sertralin kullanımı olduğu düşünülmüş ve sonraki süreçte sertralin tedavisinin kesilmesi planlanmıştır. Prolaktin yüksekliği yan etkisi denildiğinde akla ilk olarak antipsikotik kullanımı gelmektedir. Antidepresanlara bağlı daha az prolaktin yüksekliği bildirilmesi nedeniyle hastada hiperprolaktineminin ilaç kullanımına bağlı olacağı düşünülmemiştir. Ancak görüldüğü üzere hiperprolaktinemi varlığında tüm psikiyatri ilaçlarının gözden geçirilmesi bu hastalarda hiperprolaktinemiye müdahalede gecikmenin önüne geçmektedir.

Prolaktin hipofiz bezinden salgılanan bir hormondur. Hipofizden salgılanan diğer hormonların aksine prolaktin salınımı hipotalamus tarafından inhibe edilerek kontrol edilmektedir. Bu inhibisyondaki asıl görevli dopamindir. Dopamin prolaktinin salınımını inhibe etmektedir. Dopaminin inhibe edilmesi prolaktin salınımının artışı ile sonuçlanmaktadır. Klinikte dopamini inhibe eden ilaçların kullanımı ile prolaktin yükselmesi gözlenmektedir.[3] Antipsikotiklerin özellikle tipik antipsikotiklerin tubuloinfindubuler yolakta belirgin Dopamin inhibisyonu ile birlikte prolaktin yüksekliğine yol açması sıklıkla gözlenen bir yan etkidir. Atipik antipsikotiklerin hayatımıza girmesi ile birlikte klinikte prolaktin yüksekliği daha az görülmeye başlanmıştır. Ancak klinik gözlemlerde sadece antipsikotiklere bağlı değil antidepresan kullanımına bağlı da prolaktin yüksekliği gözlendiği bildirilmektedir.[9] Antidepresanlara bağlı prolaktin yüksekliği bildirilse de en sık görüldüğü ilaç grubu SSRI grubu ilaçlardır. SSRI ların prolaktini yükseltme mekanizması tam olarak net anlaşılamamıştır. Ancak altta yatan mekanizmanın serotonin-dopamin-Gamaaminobutirik asit ilişkisi ile olabileceği düşünülmektedir. Ayrıca SSRI ların dopaminerjik nörotransmisyon üzerine olan etkileri üzerinden de hiperprolaktinemiye yol açabileceğine dair araştırmalar mevcuttur.[10] Altta yatan mekanizma tam olarak netleştirilememişse de literatürde prolaktin yüksekliği olan olgular bildirilmiştir.[11]

SSRI ların hiperprolaktinemiye neden olması nadir görülmektedir ve literatürde genelde olgu bildirimleri şeklinde yer almaktadır.[12] Bizim olgumuzda da aynı şekilde SSRI grubunda yer alan sertralin kullanımı mevcuttur. Hastaların klinikte ilk değerlendirilmelerinde prolaktin ölçümü önemlidir. Ayrıca prolaktin yüksekliğini tetikleyebilecek diğer klinik faktörlerin de belirlenmesi önemlidir. Hastalarda primer hipotiroidizm, prolaktinoma, kafa travması, hipofiz tümörleri gibi nedenler hiperprolaktinemiye yol açabileceği gibi tümörler dışında hiperprolaktineminin en önemli nedenleri ilaç kullanımıdır. Opiyatlar, antihipertansifler, östrojen, H2 reseptör blokörleri, antikonvülzanlar gibi birçok ilaç prolaktin yükselmesine neden olabilir. Ancak tüm bu uzun ilaç listesinin içerisinde en sık neden antipsikotik ilaçlardır.[12] Bizim olgumuzda hipofizde adenom varlığı aslında prolaktin yüksekliği için bir yatkınlık oluştursa da bir yandan sertralinin kesilmesi ile birlikte prolaktin düzeyinde belirgin bir düşüşte gözlenmiştir. Prolaktin yüksekliğinde hipofiz adenomunun varlığı sıklıkla gözlenen sebeplerden biri olması nedeniyle ilk olarak bu sebepten şüphelenilmiştir. Ancak bu durumda Prolaktin yüksekliğinde yapılan ilk değerlendirme yöntemlerinden biri hipofiz MR görüntülemesi olmakla birlikte diğer risk faktörleri de belirlenmelidir ve bunlara yönelik tetkikler de planlanmalıdır.[13] Klinikte prolaktin yüksekliğinin araştırılmasına yönelik yapılacak ilk tetik hipofiz MR görüntülemesi olmakla birlikte tam kan sayımı, böbrek fonksiyon testleri, hormonal incelemeler, tiroit fonksiyon testleri de yapılmalıdır. Ayrıca hastanın özellikle kullandığı ilaçlar, aldığı takviye gıdalar ayrıntılı şekilde değerlendirilmelidir.[14]

Hastalar kliniğe birçok semptomla gelebilmektedir. Prolaktin yüksekliği klinikte özellikle erkekler de sessiz de seyredebilmektedir.[2] Hastalarda görülen semptomlar yaşa ve cinsiyete göre değişkenlik gösterebilmektedir. Prolaktinin esas fizyolojik rolü laktasyon üzerinedir. Serum prolaktin seviyesinin yüksekliğinin belirtilerinden biri bu sebeple galaktoredir.[15] Diğer semptomlar cinsel istekte

azalma, amenore, jinekomasti, kısırlık gibi semptomlardır.[16] Kliniğe sıklıkla amenore ile başvurular olmaktadır.[17] Olgumuzda amenore sonrasında hipofiz adenomundan şüphelenilmesi ve MR da görülmesi üzerine ilk olarak adenomdan şüphelenilse de esas nedenin sertralin kullanımının olma ihtimalinin daha fazla olduğu görülmüştür. Hastalarda aynı grup ilaç olan farklı SSRI ilaçlarının kullanımına bağlı prolaktin yüksekliği her zaman görülmemektedir. Olgumuzda da öncesinde essitalopram kullanımı olmasına rağmen prolaktinemi gözlenmemiştir. Altta yatan mekanizma belli olmamakla birlikte bu hasta grubunda kullanılan antidepresanın değişimi tedavi seçeneklerinden biridir.[10,18,19] ilaca bağlı hiperprolaktinemi tedavisinde düşünülecek ilk seçenek ilacın azaltılarak kesilmesidir. Bu durumda tekrarlayan semptomlar için farklı gruptan ilaçlar seçilebilir. Tedavide Kabergolin, bromokriptin gibi dopamin agonistleri kullanılabileceği gibi antipsikotik kullanımlarında aripiprazol gibi antipsikotiklerin tedaviye eklenmesi de bir diğer seçenektir.[20,21] Prolaktin yüksekliği açısından sadece tek bir etyolojik faktöre odaklanılmaması, hastanın her açıdan ayrıntılı değerlendirilmesi ve tüm risk faktörlerinin en aza indirgenmesi önemlidir. Prolaktinemiye yol açabilen birçok neden mevcuttur. Klinisyenlerin tüm olası nedenleri bilmesi ve her nedeni ayrıntılı incelemesi ve erken müdahalede bulunulması önemlidir. Bu yazımızda özellikle olgumuzun klinik yönetiminde hipofiz adenomuna odaklanılmış ve antidepresan tedavinin kesilmesi ikinci planda düşünülmüştür. Bu durumda bize hastanın değerlendirilmesinde tüm olası nedenlerin aynı anda değerlendirilmesinin önemliliğini vurgulamaktadır.

Çıkar Beyannamesi

Herhangi bir çıkar çatışmasının olmadığını yazarlar beyan etmektedirler.

Etik Kurul İzni

Hastadan yazılı ve sözlü onamı alınmıştır.

Araştırmacıların Katkı Oranı Beyanı

Ana fikir/Planlama: MP, SK. Veri toplama/İşleme: MP, SK. Veri analizi ve yorumlama: MP, SK. Literatür taraması: MP, SK, ÇH. Yazım: MP, SK. Gözden geçirme ve düzeltme: ÇH. Danışmanlık: ÇH.

KAYNAKÇA

1. Thapa S, Bhusal K. Hyperprolactinemia. USA: StatPearls Publishing;2019.
2. Ciccarelli A, Guerra E, De Rosa M, et al. PRL secreting adenomas in male patients. Pituitary. 2005;8(1):39-42.
3. Molitch ME. Drugs and prolactin. Pituitary. 2008;11(2):209-218.
4. Chen JX, Su YA, Bian QT, et al. Adjunctive aripiprazole in the treatment of risperidone-induced hyperprolactinemia: A randomized, double-blind, placebo-controlled, dose-response study. Psychoneuroendocrinology. 2015;58:130-140.
5. Ekinci N, Günes S, Kalinli M, Ekinci Ö. Sertraline-Related Amenorrhea in an Adolescent. Clin. Neuropharmacol. 2019;42(3):99-100.
6. Wessels-van Middendorp AM, Timmerman L. Galactorrhoea and the use of selective serotonin reuptake inhibitors. Tijdschr. Psychiatr. 2006;48(3):229-234.
7. Bronzo MR, Stahl SM. Galactorrhea induced by sertraline. Am J Psychiatry. 1993;150(8):1269-1270.
8. Bulut SD, Tüzer V, Bulut S, Göka E. Essitalopram ile Gelişen Hiperprolaktinemi Olgusu: Ketiapin Kullanımı Bir Seçenek Olabilir mi? Klın Psıkofarmakol B. 2009;19:272-274.
9. Petty RG. Prolactin and antipsychotic medications: mechanism of action. Schizophr. Res. 1999;35:67-73.
10. Damsa C, Bumb A, Bianchi-Demicheli F, et al. "Dopamine-dependent" side effects of selective serotonin reuptake inhibitors: a clinical review. J Clin Psychiatry. 2004;65(8):1064-1068.
11. Park Y-M. Serum prolactin levels in patients with major depressive disorder receiving selective serotonin-reuptake inhibitor monotherapy for 3 months: a prospective study. Psychiatry Investig. 2017;14(3):368.
12. Torre DL, Falorni A. Pharmacological causes of hyperprolactinemia. Ther Clin Risk Manag. 2007;3(5): 929-951.
13. Cortet-Rudelli C, Sapin R, Bonneville JF, Brue T. Etiological diagnosis of hyperprolactinemia. Ann. Endocrinol. 2007;68(2-3):98-105.
14. Melgar V, Espinosa E, Sosa E, et al. Current diagnosis and treatment of hyperprolactinemia. Rev Med Inst Mex Seguro Soc. 2016;54(1):111-121.
15. Güzel Ö, Atan A, Aslan Y. Hiperprolaktinemi ve erektil disfonksiyon. Androl Bul. 2018;20(3):90-94.
16. Luciano AA. Clinical presentation of hyperprolactinemia. J Reprod Med. 1999;44(12): 1085-1090.
17. Capozzi A, Scambia G, Pontecorvi A, Lello S. Hyperprolactinemia: pathophysiology and therapeutic approach. Gynecol. Endocrinol. 2015;31(7):506-510.
18. Spigset O. Adverse reactions of selective serotonin reuptake inhibitors: reports from a spontaneous reporting system. Drug safety. 1999;20(3):277-287.
19. Edwards JG, Anderson I. Systematic review and guide to selection of selective serotonin reuptake inhibitors. Drugs. 1999;57(4):507-533.
20. Ajmal A, Joffe H, Nachtigall LB. Psychotropic-induced hyperprolactinemia: a clinical review. Psychosomatics. 2014;55(1):29-36.
21. Verhelst J, Abs R. Hyperprolactinemia: pathophysiology and management. Treatments in endocrinology. 2003;2(1):23-32.

CASE REPORT

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Secondary Antiphospholipid Antibody Syndrome Due to Systemic Lupus Erythematosus: A Case Report with Superior Mesenteric Artery Involvement

Sistemik Lupus Eritematozusa Bağlı Sekonder Antifosfolipid Antikor Sendromu: Superior Mezenterik Arter Tutulumuyla Seyreden Olgu Sunumu

***Beliz KARATAŞ*[1] *İlker YALÇIN*[1] *Neşe ÇABUK ÇELİK*[1] *Gizem PİRE*[1]**

***Hatice Şeyma EREN*[1] *Ali ŞAHİN*[1]**

ÖZ

Antifosfolipid antikor sendromu (AFAS); antifosfolipid protein antikor pozitifliği yanı sıra rekurren vasküler tromboz ve/veya gebelik kayıpları ile karakterize bir hastalıktır. Altta yatan bir hastalık saptanmadığında primer tip; altta yatan başka bir romatolojik hastalık varlığında sekonder tip olarak sınıflandırılır. Sekonder AFAS, en sık sistemik lupus eritematozusa (SLE) bağlı gelişir. Burada, AFAS'ta superior mezenterik arter tutulumuna bağlı iskemik kolit vakasını sunduk. 59 yaşında SLE tanısı bulunan kadın hastaya, ani gelişen hematokezya ve akut batın kliniği olması üzerine çekilen kontrastlı bilgisayarlı tomografi anjiografide (BT-anjiografi) superior mezenterik arterde tromboz saptandı. Bu olgu AFAS'a bağlı gastrointestinal sistemdeki farklı damar tutulumu ve tedavi stratejisi açısından ilginçti.

Anahtar Kelimeler: antifosfolipid antikor sendromu; iskemik kolit; sistemik lupus eritematozus

ABSTRACT

Antiphospholipid antibody syndrome (APS); is a disease characterized by anti-phospholipid protein antibody positivity as well as recurrent vascular thrombosis and/or pregnancy loss. When no underlying disease is detected, it is classified as primary type; when there is another underlying rheumatologic disease, it is classified as secondary type. Secondary APS, most commonly develops due to systemic lupus erythematosus (SLE). We present a case of ischemic colitis due to superior mesenteric artery involvement in APS. 59-year-old female patient diagnosed with SLE had sudden-onset hematochezia and acute abdomen. Therefore, the patient underwent contrast-enhanced computed tomography angiography (CT angiography). Thrombosis was detected in the superior mesenteric artery. This case was interesting in terms of different vascular involvement and treatment strategy in the gastrointestinal tract due to APS.

Keywords: anti-phospholipid antibody syndrome; ischemic colitis; systemic lupus erythematosus

Received: 09.05.2022; Accepted: 04.06.2023

[1]Cumhuriyet University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Sivas, Türkiye.
Corresponding Author: Beliz Karataş, Cumhuriyet University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Sivas, Türkiye.
e-mail: dr_lizim@hotmail.com

How to cite: Karataş B, Yalçın İ, Çabuk Çelik N, Pire G, Eren HŞ, Şahin A. Secondary antiphospholipid antibody syndrome due to systemic lupus erythematosus: a case report with superior mesenteric artery involvement. Ahi Evran Med J. 2021;8(1):126-129. DOI: 10.46332/aemj.1114233

INTRODUCTION

APS is an autoimmune disease that develops due to pathogenic antiphospholipid antibody positivity, mostly accompanied by venous and less commonly arterial thrombosis and recurrent pregnancy loss.[1,2,3] It is classified as secondary type in the presence of another underlying rheumatological disease. Secondary APS, most commonly develops due to systemic lupus erythematosus (SLE). APS was first described by Graham RV Hughes in 1983.[1] For this reason, it is also known as "Hughes Syndrome". The approximate incidence of APS is 5 cases per 100.000 people, and the estimated prevalence is 40-50 cases per 100.000 people.[2,3] The clinical spectrum of APS includes hematologic, obstetric, neurological, cardiovascular, dermatological, renal and orthopedic findings.[3] The clinical findings it contains are shown in the Table 1 below.

Table 1. The clinical findings in APS.

Hematological	Thrombocytopenia, thrombosis, microangiopathic hemolysis
Obstetrics	Recurrent abortions
Neurological	İschemic attack, epileptic seizures, cognitive disorders, chorea, transverse myelitis, multiple sclerosis
Cardiovascular	Endocarditis, myocardial infarction
Dermatological	Livedo reticularis, skin necroses
Renal	Glomerulonefrit, renal thrombotic microangiopathy
Orthopedic	Avascular necrosis of bones, non-traumatic fractures

Serious thrombotic events are more common in patients with SLE-related APS.[2] Liver-related vascular pathologies are most common in gastrointestinal system involvement of APS. Budd-Chiari syndrome, hepatic-veno-occlusive disease, small hepatic vasculitides, hepatic infarction, portal hypertension-associated cirrhosis have been reported among hepatic manifestations. Spleen infarction, acute pancreatitis, acute intestinal infarction are seen less frequently.[4]

CASE REPORT

A 59-year-old female patient with a diagnosis of hypertension (HT) was admitted to our outpatient clinic with complaints of widespread body pain for 6 months, a butterfly-shaped rash on the face, alopecia without scarring, and aphthae in the mouth. The patient had previously abortions 3 times earlier than 10 weeks. Therefore, the Anti-nuclear antibody (ANA) and double-stranded DNA antibody (Anti-dsDNA) that we examined with the immunofluorescent essay (IFA) method were positive, the ANA titer was 1:320 in the nuclear pattern The patient was diagnosed with SLE with a total score of 10 according to the 2019 European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) classification criteria. Organ involvement due to SLE was investigated and there was no evidence of involvement. Anti-cardiolipin immunoglobulin M and G and Beta2-glycoprotein values, which we did due to recurrent abortions and repeated at 12-week intervals, were negative. Lupus anticoagulant was repeated at 12-week and was positive. The patient's C reactive level was 12 mg/l and her erythrocyte sedimentation rate was normal. (Table 2) We prescribed hydroxychloroquine, acemethazine, pantoprazole, and acetylsalicylic acid treatments for the patient who had no history of thrombosis and was diagnosed with SLE and secondary APS. In the follow-up of the patient, sudden abdominal pain and hematochezia developed 4 months later. Since we detected rebound and defense in the abdominal examination, we decided to perform contrast-enhanced computed tomography angiography (CT angiography) for the acute abdomen. Since we detected an image compatible with ischemic colitis secondary to superior mesenteric artery (SMA) thrombosis in CT angiography, we decided to perform rectosigmoidoscopy and we detected ischemic colitis.(Figure 1) In our examination for the etiology, we did not detect cardiac arrhythmia of patient. No intracardiac thrombus was detected in echocardiography. We did not detect factor V Leiden mutation, prothrombin mutation, antithrombin and protein C and S deficiency, which are hematological causes that may predispose to thrombosis. Our patient was diagnosed with HT 1 year ago and was under control with antihypertensive medication. No hypertensive retinopathy was detected in retinal examination. We terminated the oral treatment and prescribed intravenous pantoprazole, high-dose methylprednisolone and cyclophosphamide for the patient with a diagnosis of SLE-related APS. In addition, metronidazole and ceftriaxone were given with the possible risk of perforation. The dose of methylprednisolone was gradually reduced to 1 mg/kg. After the bleeding stopped, subcutaneous enoxaparin every 12 hours and oral warfarin were given until the target INR was between 2-3. Since the patient responded to the treatment, it was planned to continue with

oral warfarin, oral methylprednisolone (MP) and 150 mg azathioprine (AZA) as maintenance after 6 cycles of cyclophosphamide-mesna treatment was completed. Written informed consent was obtained from the patient.

Table 2. Laboratory tests of the patient.

IFA-ANA *	1:320 (nuclear pattern) Positive
IFA Anti-dsDNA**	Positive
CRP †	12 mg/l
ESR‡	9 mm/h
Beta2-glycoprotein ††	Negative
Anti-cardiolipin immunoglobulin M and G ††	Negative
Lupus anticoagulant ††	Medium Titer Positive

*: Anti nuclear antibody
**: Double-stranded DNA antibody
†: C reactive protein
‡: Eryrocyte sedimentation rate
††: Tested twice, 12 weeks apart

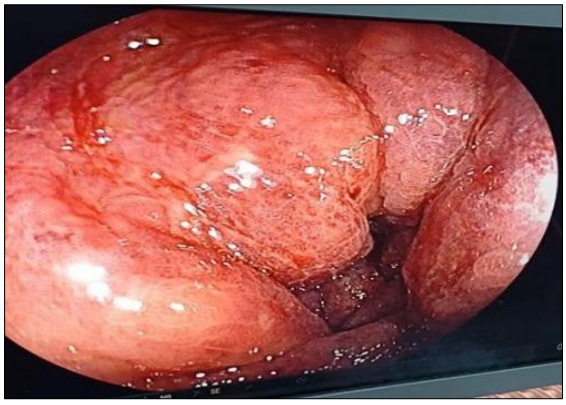


Figure 1. Colonoscopy images of the patient compatible with Ischemic colitis.

DISCUSSION

The patient's age, APS auto-antibodies and vascular involvement are among the features that make our case different.In the study conducted by Yayla et al. reported that 76% of 43 APS patients were women and the median age was 46 years.[5] Our case was a 59-year-old female and was compatible with the literature in terms of gender. However, she was older in terms of age. When this situation was analyzed, it was emphasized that the patient did not go to the doctor's control in terms of recurrent abortions, so the diagnosis might have been determined at an older age. However, the patient had rash, alopecia, oral aphthae and widespread body pain for 6 months. There was also no previous history of thrombosis. Bagger et al. reported that of 158 female patients with recurrent abortions showing moderately positive anticardiolipin antibodies have an increased risk of developing SLE in the future and that these patients should be followed up.[6] In line with this information, it is useful to monitor anticardiolipin antibodies of patients with recurrent abortions and to be careful in terms of the possibility of developing SLE and APS, even if there is no previous thrombotic event. Our case is significant in this respect.

Although the classical auto-antibodies involved in the pathogenesis of APS are anti-cardiolipin antibodies which are lupus anticoagulant, and β2-glycoproteins, it is accepted that new auto-antibodies and different subtypes also play a role in the pathogenesis.[3] Although anti-cardiolipin and β2-glycoprotein were negative in our patient, the lupus anticoagulant during 12 weeks, at least twice a week, was positive. This may be due to different subtype antibody positivity that has not yet been detected.

Superior mesenteric artery thrombosis is rare in APS. In one case report of England et al. expalined that mesenteric artery involvement is rare in APS because relatively more prostacyclin is secreted in this region.[7] The study of Kaushik et al. about intra-abdominal involvement in APS showed that abdominal thrombosis or ischemic event was reported in 42 (19.5%) of 215 patients. Major vascular thrombosis including inferior vena cava, portal and superior mesenteric veins, splenic vein and aorta was analyzed in 52% of 42 patients, and abdominal visceral ischemia resulting in renal infarction, intestinal ischemia, spleen infarction, pancreatitis, liver infarction was reported in 36 patients.[8] Our case progressed with superior mesenteric artery thrombosis.

Treatment of acute mesenteric ischemia includes open surgery or revascularization with endovascular approach. Bowel resection may be required in delayed and necrotic cases.[9] In our patient, general surgery consultation was performed after SMA thrombosis was seen in contrast-enhanced CT angiography. We predicted that this condition was not caused by atherosclerosis or embolism, but was due to immunity, so surgery or endovascular intervention may lead to re-thrombosis with endothelial damage. Therefore, immunosuppressive therapy was planned for the patient. In addition, antibiotherapy was started for the risk of bowel perforation.

According to the APS guideline published by EULAR (European Alliance of Associations for Rheumatology), it

is recommended to keep the INR target between 2-3 in patients with arterial thrombosis for the first time. Rituximab treatment comes to the fore in resistant cases where recurrent arterial thrombosis is observed despite an INR between 3-4.[10] Since SLE was accompanying in our case, pulse methylprednisolone treatment with cyclophosphamide was applied. When the bleeding caused by hematochezia was under control, subcutaneous enoxaparin was administered every 12 hours and oral warfarin treatment was given until the INR was between 2-3, in line with the recommendations of the cardiovascular surgeons. Since the patient responded to the treatment, it was planned to continue with oral warfarin, oral methylprednisolone (MP) and 150 mg azathioprine (AZA) as maintenance after 6 cycles of cyclophosphamide-mesna treatment was completed.

In conclusion, APS should be considered in cases with recurrent pregnancy loss, unexplained thrombosis in atypical regions, and underlying rheumatological disease. In this way, early diagnosis helps prevent serious complications. It should not be forgotten that immunosuppressive agents are also included in the treatment as well as anticoagulants.

Conflict of Interests

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

Written informed consent was obtained from the patient.

Authors' Contributions

Concept/Design: BK. Data Collection and Processing: BK. Data analysis and interpretation: BK, İY, NCÇ, GP, HŞE, AŞ. Literature Search: BK, İY, NCÇ, GP, HŞE, AŞ. Drafting manuscript: BK, İY, NCÇ, GP, HŞE, AŞ. Critical revision of the manuscript: AŞ. Supervision: AŞ.

REFERENCES

1. Negrini S, Pappalardo F, Murdaca G, Indiveri F, Puppo F. The anti phospholipid syndrome: from pathophysiology to treatment. Clin Exp Med. 2017;17(3):257-267.
2. Pons-Estel GJ, Andreoli L, Scanzi F, Cervera R, Tincani A. The anti phospholipid syndrome in patients with systemic lupuserythematosus. J Autoimmün. 2017;76(1):10-20.
3. Uthman I, Noureldine MHA, Ruiz-Irastorza G, Khamashta M. Management of anti phospholipid syndrome. Ann Rheum Dis. 2019;78(2):155-161.
4. Uthman I, Khamashta M. The abdominal manifestations of the antiphospholipid syndrome. Rheumatology (Oxford). 2007;46(11):1641-1647.
5. Yayla ME, Yüksel M, Şahin D, et. al. Clinical Features of Patients with Anti phospholipid Syndrome and Differences of Patients with Recurrent Thrombosis, A Single Center Retrospective Study. J Ankara Univ Fac Med. 2021;74(1):52-59.
6. Bagger PV, Andersen V, Baslund B, et. al. Anti-cardiolipin Antibodies (IgG and IgA) in Women with Recurrent Fetal Loss Correlate to Clinical and Serological Characteristics of SLE. Acta Obstet Gynecol Scand. 1993;72(6):465-469.
7. England RJA, Woodcock B, Zeiderman MR. Superior Mesenteric Artery Thrombosis in a Patient with the Anti phospholipid Syndrome. Eur J Vasc Endovasc Surg. 1995;10(3):372-373.
8. Kaushik S, Federle MP, Schur PH, Krishnan M, Silverman SG, Ros PR. Abdominal Thrombotic and Ischemic Manifestations of the Anti phospholipid Antibody Syndrome: CT Findings in 42 Patients. Radiology. 2001;218(3):768-771.
9. Kerzmann A , Haumann A , Boesmans E , Detry O, Defraigne JO. Acute mesenteric ischemia. Rev Med Liege. 2018;73(5-6):300-303.
10. Tektonidou MG, Andreoli L, Limper M, et. al. EULAR recommendations for the management of anti phospholipid syndrome in adults. Ann Rheum Dis. 2019;78(10):1296-1304.