KAFKAS TIP BİLİMLERİ DERGİSİ

Kafkas Journal of Medical Sciences

ISSN: 2146-2631
eISSN: 2587-053X

Cilt / Volume 13
Sayı / Issue 1
Nisan / April 2023

ISSN: 2146-2631
eISSN: 2587-053X

KAFKAS
TIP BİLİMLERİ DERGİSİ

Kafkas Journal of Medical Sciences

Kafkas J Med Sci

Bu dergi Kafkas Üniversitesi Tıp Fakültesi'nin akademik yayın organıdır.
This journal is an official academic publication of Kafkas University Faculty of Medicine.

Endekslenme *(Indexed in)*

TÜBİTAK-ULAKBİM
Türkiye Atıf Dizini
Türk Medline
EBSCO
Google Scholar
DergiPark Akademik

Yönetim *(Administration)*

Prof. Dr. Hüsnü KAPU, İmtiyaz Sahibi / Rektör *(Owner / President)*

İletişim *(Correspondence)*

Kafkas Tıp Bilimleri Dergisi
Kafkas Üniversitesi, Tıp Fakültesi
36300 KARS - TÜRKİYE
Tel: 474 225 11 96
Fax: 474 225 11 93
E-mail: meddergi@kafkas.edu.tr
Web: http://meddergi.kafkas.edu.tr

Yayın Hizmetleri *(Publication Service)*

Tasarım ve Uygulama *(Graphic Design)*
BAYT Bilimsel Araştırmalar Basın Yayın ve Tanıtım Ltd. Şti.
Ziya Gökalp Cad. 30/31, Kızılay - Ankara
Tel: (312) 431 30 62
www.bayt.com.tr

Baskı *(Printing)*
Miki Matbaacılık Ltd. Şti.
Matbaacılar Sitesi, 560 Sk. No:27, İvedik - Ankara
Tel: (312) 395 21 28

Baskı Tarihi *(Printing Date)*: 26 Nisan 2023

Danışma Kurulu *(Advisory Board)*

Hakem Listesi *(Referees List)*

İçindekiler / *Contents*

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

OLGU SUNUMU / *CASE REPORT*

DERLEME / *REVIEW*

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Ultrasound Examination of the Optic Nerve Sheath Diameter in the Patients Presenting with Carbon Monoxide Poisoning: A pilot study

Karbonmonoksit Zehirlenmesi ile Başvuran Hastalarda Optik Sinir Kılıf Çapının Ultrasonografi ile İncelenmesi: Pilot Çalışma

Emel Altintas[1], Sertac Guler[1], Hayri Ramadan[1]

[1]*Ankara Training and Research Hospital, Department of Emergency Medicine, Ankara, Turkiye*

ABSTRACT

Aim: *In carbon monoxide poisoning, hypoxia results in neuronal damage and death of brain cells. It is considered that cerebral edema occurs consequently, with an associated increase in intracranial pressure. The present study evaluates the presence of increased intracranial pressure using the measurement of optic nerve sheath diameter by ultrasonography in patients presenting with carbon monoxide poisoning.*

Material and Method: *Twenty-eight patients diagnosed with carbon monoxide poisoning after presenting to the emergency department underwent the bilateral measurement of optic nerve sheath diameter by ultrasonography. In addition, the patient's demographic data, laboratory results, stage of the poisoning, and optic nerve sheath diameters were recorded.*

Results: *The median optic nerve sheath diameter on the right and left sides was greater than 5 mm. The optic nerve sheath diameter of the right and the left eye was significantly higher in patients with severe carbon monoxide poisoning than in those with moderate and mild poisoning.*

Conclusion: *The optic nerve sheath diameter measurement can be used to evaluate increased intracranial pressure in patients with carbon monoxide poisoning.*

Keywords: carbon *monoxide poisoning; elevated intracranial pressure; ultrasonography; optic nerve sheath diameter*

ÖZET

Amaç: *Karbon monoksit zehirlenmesinde hipoksi nöronal hasara ve beyin hücrelerinin ölümüne neden olur. Sonuç olarak, kafa içi basıncında ilişkili bir artışla birlikte beyin ödeminin meydana geldiği düşünülmektedir. Bu çalışmada karbonmonoksit zehirlenmesi ile başvuran hastalarda ultrasonografi ile optik sinir kılıf çapı ölçümü kullanılarak kafa içi basınç artışının varlığı değerlendirilmiştir.*

Materyal ve Metot: *Acil servise başvurduktan sonra karbon monoksit zehirlenmesi tanısı alan 28 hastaya ultrasonografi ile bilateral optik sinir kılıf çapı ölçümü yapıldı. Hastaların demografik verileri, laboratuvar sonuçları, zehirlenme evresi ve optik sinir kılıf çapları kaydedildi.*

Bulgular: *Sağda ve solda median optik sinir kılıf çapı 5 mm'den büyüktü. Sağ ve sol gözde optik sinir kılıf çapları şiddetli karbon monoksit zehirlenmesi olan hastalarda orta ve hafif zehirlenmesi olanlara göre anlamlı olarak daha yüksekti.*

Sonuç: *Karbonmonoksit zehirlenmesi olan hastalarda optik sinir kılıf çapı ölçümü kafa içi basınç artışının varlığını değerlendirmede kullanılabilir.*

Anahtar Kelimeler: *karbon monoksit zehirlenmesi; kafa içi basınç artışı; ultrasonografi; optik sinir kılıf çapı*

Introduction

Carbon Monoxide is an odorless and colorless gas. Carbon Monoxide poisoning results in hypoxia, cellular death, and death[1]. The symptoms are associated with the brain and heart, which are most sensitive to hypoxia. The patients may present to the emergency department with headache, weakness, chest pain, shortness of breath, seizures, and consciousness impairment[2].

The increase in intracranial pressure can be caused by various mechanisms such as venous obstruction, increased blood and brain volumes, mass effect, and

İletişim/Contact: *Emel Altıntaş, Ankara Training and Research Hospital, Department of Emergency Medicine, Ankara, Türkiye* • ***Tel:*** *0554 598 2714* • ***E-mail:*** *emelaltintas61@gmail.com* • ***Geliş/Received:*** *17.11.2021* • ***Kabul/Accepted:*** *18.01.2023*

ORCID: *Emel Altıntaş, 0000-0003-4487-5661* • *Sertaç Güler, 0000-0002-6266-6145* • *Hayri Ramadan, 0000-0002-5018-152X*

cerebral edema. Intracranial pressure increases in many conditions, such as hydrocephalus, traumatic brain injury, intracerebral and subarachnoid hemorrhage, and ischemic stroke. The symptoms include headache, nausea, vomiting, consciousness impairment, and Cushing reflex[3].

In carbon monoxide poisoning, hypoxia has been reported to be the most critical mechanism for brain damage. In addition, animal studies have reported that increased cerebral blood flow leads to the loss of consciousness[4]. The brain areas often involved in carbon monoxide poisoning are basal ganglia (globus pallidus), hippocampus, white matter, cortex, cerebellum, corpus callosum, and hypoxia resulting in neuronal damage and death[5]. The authors consider that cerebral edema occurs consequently, with an associated increase in intracranial pressure. The increase in intracranial pressure can be measured by various interventional methods. However, in recent years, ultrasonography's optic nerve sheath diameter measurement has become a non-invasive method to determine increased intracranial pressure[6–8]. The present study aims to evaluate the presence of increased intracranial pressure using the measurement of optic nerve sheath diameter by ultrasonography in patients presenting with carbon monoxide poisoning.

Material and Method

The present study was carried out in a tertiary emergency department with an average annual visit number of 360.000. The study was conducted after ethics committee approval had been granted. Patients started after the ethics committee's approval and the study ended when the number of patients in the sample size is completed. After receiving 1-hour theoretical and applied training with a certificate on ultrasonographic measurement of optic nerve sheath diameter, pilot measurements were made on both eyes of 10 patients, including five positive patients (with increased optic nerve sheath diameter due to pathologies such as intracranial hemorrhage, ischemic cerebrovascular accident) and five negative patients. The measurements were only made by the emergency medicine specialist involved in the study. The study included the patients aged 18 years and older with a blood carbon monoxide level of higher than 10% and a time interval of no more than one hour after being diagnosed with carbon monoxide poisoning.

The stage of carbon monoxide poisoning was determined as follows[1].

1- Mild poisoning: COHb >10% without clinical signs and symptoms

2- Moderate poisoning: COHb >10% with mild signs and symptoms [headache, lethargy, fatigue]

3- Severe poisoning: COHb >20–25% with a loss of consciousness, confusion, or findings of cardiac ischemia

The measurement of optic nerve sheath diameter was made as follows. The patients were placed in a supine position with 20 degrees horizontal angle. Tegaderm medical dressing was placed on the eye to avoid contact of the eyelid with ultrasound gel. The Tegaderm dressing was covered with an ultrasound gel with an insonation depth of 5–8 cm. The ultrasound probe was placed on the temporal region of the eyelid. The angle of the probe was adjusted to visualize the entrance of the optic nerve. A two-dimensional image was used, and the diameter of the optic nerve sheath was measured electronically in 3 mm behind the globe with a perpendicular axis to the optic nerve. Fujifilm-Sonosite FC-1 brand ultrasound device and a high-frequency (10 mHz) linear probe were used in the measurement. Two measurements were made for each eye, and the average of the two measurements was recorded.

Exclusion criteria:

1. Conditions resulting in an increased optic nerve sheath diameter a-Not accompanied by increased intracranial pressure: Optic neuritis, optic nerve trauma, arachnoid cyst of the optic nerve, anterior orbital or cavernous sinus mass b-Accompanied by increased intracranial pressure: A mass or a space-occupying lesion in the central nervous system, pseudotumor cerebri, decreased cerebrospinal fluid (CSF) resorption (cerebral venous sinus thrombosis, subarachnoid hemorrhage, meningitis, inflammatory conditions), increased CSF production (tumors), ventricular system obstruction, cerebral edema, encephalitis, craniostenosis)
2. Unstable patients for ocular ultrasonography
3. The patients with eyelids ineligible for ultrasonography
4. Conditions where ultrasound operator is not available

5. Pregnant patients
6. The patients who did not give consent to participate in the study.
7. Patients who are not in the first hour of admission to the emergency department

Sample size: H1 hypothesis of the study; The optic nerve sheath diameter measurement of carbonmonoxide poisoning is >5 mm. Our hypothesis is one-sided. When this alpha error was calculated as 0.05 and the power 80% standardized effect size was calculated as 0.5, the number of samples was calculated as 25. Since there may be 10% data loss, it is planned to take a total of 28 patients.

Demographic data of patients suffering from carbon monoxide poisoning, laboratory results, exposure to carbon monoxide gas, stage of poisoning and optic nerve sheath diameters were recorded.

IBM Statistical Package for Social Sciences (SPSS) program version 22.0 (IBM, *Chicago*, USA) statistical software package was used in the statistical analysis. A Shapiro-Wilk test was used to test whether the variables were normally distributed. In order to determine whether the optic nerve sheath diameter measurement of the patients with carbon monoxide poisoning was larger than the population median, the non-parametric single-sample test, the sign test, was used. The median value of 5 mm was taken to evaluate the optic nerve sheath diameter in patients with carbon monoxide poisoning[9]. A Kruskal-Wallis test was used to compare numeric variables between more than two independent groups without normal distribution. A p-value of less than 0.05 was considered statistically significant.

Results

The study included 28 participants. A total of 33 patients were diagnosed with carbon monoxide poisoning during the study period. One patient was unstable (cardiac arrest) to undergo the measurement of optic nerve sheath diameter by ultrasonography, one patient was pregnant, and three other patients were excluded due to the unavailability of an ultrasound operator. Demographic data of the patients are presented in Table 1.

A median optic nerve sheath diameter of the right and left eyes greater than 5 mm was found to be significant (the sign test, p <0.001) (Table 2).

Table 1. *The characteristics of patients with carbon monoxide poisoning*

Age	48.07±18.75	
	Number	%
Gender		
Female, n, %	15	53.6
Duration of exposure		
<6 hours, n, %	19	67.9
6–12 hours, n, %	7	25
12–24 hours, n, %	2	7.1
Stage		
Mild, n, %	1	3.6
Moderate, n, %	16	57.3
Severe, n, %	11	39.1
Symptom		
Nausea-vomiting, n, %	13	32.5
Headache, n, %	11	27.5
Dizziness n, %	7	17.5
Syncope, n, %	5	12.5
Chest pain, n, %	2	5
Loss of consciousness, n, %	2	5
Treatment		
100% oxygen n, %	18	64.3
100% oxygen+Hyperbaric Oxygen n, %	8	28.6
100% oxygen+Hyperbaric Oxygen with Intubation n, %	2	7.1
Laboratory parameters		Median (IQR)
WBC uL	28	9.96 (8.31–12.85)
Creatinine mg/dl	28	0.82 (0.68–1.07)
Lactate mmol/L	25	2.7 (1.55–3.55)
CK-MB uq/L	28	1.74 (1.14–4.18)
Troponin uq/L	28	10.05 (4.43–14.46)
CO Hb %	28	18.5 (14.05–28.85)

Table 2. *Optic nerve sheath diameter measurements of patients with carbon monoxide poisoning*

	Median (IQR), mm	p value
Right eye optic nerve sheath diameter	5.8 (5.5–6.3)	<0.001*
Left eye optic nerve sheath diameter	6.0 (5.2–6.3)	<0.001*

*The sign test was used with a median value of 5 mm.

A statistically significant difference was found in median optic nerve sheath diameters of the left and right eye between carbon monoxide poisoning stages (Kruskal-Wallis, p=0.027, and p=0.043, respectively) (Table 3). In paired comparisons of the groups, optic nerve sheath diameters of the left and right eyes were significantly higher in patients with severe carbon monoxide poisoning than the patients with mild and moderate poisoning.

Table 3. *Optic nerve sheath diameter measurements of the right and left eye according to the stage of carbon monoxide poisoning*

	Right eye optic nerve sheath diameter, mm	p value	Left eye optic nerve sheath diameter, mm	p value
Mild n=1	4.4	0.317	5.2	0.317
Moderate n=16	5.5 (5.4–5.9)	0.003**	5.7 (5.1–6.2)	0.001**
Severe n=11	6.2 (5.8–6.5)	0.003**	6.3 (5.9–7.0)	0.003**
p value	0.027*		0.043*	

*A Kruskal-Wallis test was used.
** The sign test was used with median value of 5 mm.

Discussion

In this study, it was determined that the optic nerve sheath diameter measurement in patients with carbon monoxide poisoning was larger than the population median. It was determined that the median of optic nerve sheath diameter measurement in the patients with the severe stage was larger than those in the moderate stage. We concluded that there is an increase in optic nerve sheath diameter in carbon monoxide poisoning.

The mortality rate is higher among the patients with acute brain injury after sustaining carbon monoxide poisoning, and the development of acute brain injury is associated with blood carbon monoxide levels, but no association exists with the symptoms[5]. Late neuropsychiatric symptoms are associated with secondary brain damage occurring 2–40 days after carbon monoxide poisoning and are encountered in approximately 15–30% of successfully treated patients[10,11]. Carbon monoxide poisoning remains a significant health problem as it results in death in the short term and various neurological sequels in the long term due to brain damage.

The optic nerve sheath diameter measurement by ultrasonography has come into use as a non-invasive method in recent years to determine an increase in intracranial pressure[6–8]. It was reported emergency medicine physicians without previous ultrasound education could accurately detect pathological conditions on ocular ultrasound after gain an experience of 15–75 attempts[12]. The optic nerve sheath diameter has also been evaluated according to the types of ischemic stroke and increased values have been reported in all types of ischemic stroke, the values being higher in the patients with more extensive ischemic area[13]. The increase in intracranial pressure has always been attributed to widespread cerebral edema[14–16].

In the present study, the optic nerve sheath diameter was significantly higher when tested against a median value of 5 mm. The authors consider that an increase in intracranial pressure is associated with increased blood volume caused by anoxia and the development of cytotoxic cerebral edema due to ischemia[3].

It was reported that the extent of brain damage on computed tomography (CT) and magnetic resonance imaging (MRI) scans are associated with prognosis in the patients with carbon monoxide poisoning[17,18]. In the present study, optic nerve sheath diameters were significantly higher in the patients with severe carbon monoxide poisoning than the patients with mild and moderate poisoning. The presence of three or more lesions in the white matter on MRI scans or a lesion in the initial diffusion MRI scans has been identified as the independent predictor of delayed neuropsychiatric symptoms[19–21].

The authors suggest that an increase in intracranial pressure can be estimated and monitored by the measurement of optic nerve sheath diameter, as the detection of increased intracranial pressure is essential to determine the severity of the condition and to prevent secondary brain damage[3]. Also, the patients with intracranial lesions on initial MRI studies have a poorer prognosis. However, the use of MRI scans in all patients is not cost-effective, and not all patients (with implanted cardioverter/defibrillator, platinum implantation) are eligible to undergo MRI.

The increase in intracranial pressure estimated by optic nerve sheath diameter measurement in carbon monoxide poisoning is considered to cause symptoms. Based on the relationship between optic nerve sheath diameter and the severity of carbon monoxide poisoning, the authors of the present manuscript suggest that further studies must be conducted to evaluate whether optic nerve sheath diameter could be used as a parameter to monitor the outcomes of the treatment and whether the measurement of optic nerve sheath diameter could predict delayed neurological sequels.

Limitations

The sources of carbon monoxide gas responsible for the poisoning in the present study, the patients were not specified. No comparison was made between the optic nerve sheath diameter and CT/MRI findings.

No other measurement was made for intracranial pressure increase except ONSD measurement. The link between the increase in intracranial pressure and the measurement of ONSD has been accepted in principle. We do not have a control group to compare and no control measurement after treatment. Due to these limitations, this study is a pilot study.

Also, no comparison was made between the optic nerve sheath diameter and mortality/late neurological sequels.

Conclusion

Increased intracranial pressure can be estimated by measuring optic nerve sheath diameter in patients presenting with carbon monoxide poisoning. The optic nerve sheath diameter is greater in patients with severe poisoning.

References

1. Smollin C, Olson K. Carbon monoxide poisoning (acute). BMJ Clin Evid. 2010;2010.
2. Eichhorn L, Thudium M, Jüttner B. The Diagnosis and Treatment of Carbon Monoxide Poisoning. Dtsch Arztebl Int. 2018;115(51-52):863–870.
3. Saria MG, Kesari S. Increased Intracranial Pressure: The Use of an Individualized Ladder Approach. Seminars in oncology nursing. 2021:151133.
4. Chung-Ping Lo, Shao-Yuan Chen, Kwo-Whei Lee, Wei-Liang Chen, Cheng-Yu Chen et al. Brain injury after acute carbon monoxide poisoning: early and late complications. AJR Am J Roentgenol 189(4):W205-211.
5. Kavak N, Doğan B, Sultanoğlu H, Kavak RP, Özdemir MJKD. Clinical and Magnetic Resonance Imaging Findings of Patients with Acute Carbon Monoxide Poisoning.12(3):443-50.
6. Girisgin AS, Kalkan E, Kocak S, Cander B, Gul M, et al. The role of optic nerve ultrasonography in the diagnosis of elevated intracranial pressure. Emerg Med J. 2007;24(4):251–4.
7. Robba C, Santori G, Czosnyka M, Corradi F, Bragazzi N, et al.Optic nerve sheath diameter measured sonographically as non-invasive estimator of intracranial pressure: a systematic review and meta-analysis. Intensive Care Med. 2018;44(8):1284–1294.
8. Miller MT, Pasquale M, Kurek S, White J, Martin P, et al. Initial head computed tomographic scan characteristics have a linear relationship with initial intracranial pressure after trauma. J Trauma. 2004;56(5):967–72.
9. Major R, Girling S, Boyle A. Ultrasound measurement of optic nerve sheath diameter in patients with a clinical suspicion of raised intracranial pressure. Emerg Med J. 2011;28(8):679–81. doi:10.1136/emj.2009.087353.
10. Nah S, Choi S, Kim HB, Lee J, Lee SU, et al. Cerebral White Matter Lesions on Diffusion-Weighted Images and Delayed Neurological Sequelae after Carbon Monoxide Poisoning: A Prospective Observational Study. Diagnostics (Basel, Switzerland). 2020;10(9).
11. Han S-T, Bhopale VM, Thom SR. 2007. Xanthine oxidoreductase and neurological sequelae of carbon monoxide poisoning. Toxicol Lett. 170(2):111–115.
12. Blaivas M, Theodoro D, Sierzenski PR. A study of bedside ocular ultrasonography in the emergency department. Academic emergency medicine: official journal of the Society for Academic Emergency Medicine. 2002;9(8):791–9.
13. Gökcen E, Caltekin İ, Savrun A, Korkmaz H, Savrun Ş T, et al. Alterations in optic nerve sheath diameter according to cerebrovascular disease sub-groups. The American journal of emergency medicine. 2017;35(11):1607–11.
14. Ropper AH, Shafran B. Brain edema after stroke. Clinical syndrome and intracranial pressure. Arch Neurol. 1984;41:26–9.
15. Schwab S, Schwarz S, Spranger M, Keller E, Bertram et al. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. Stroke. 1998;29:2461–6.
16. Morley NC, Berge E, Cruz-Flores S, Whittle IR. Surgical decompression for cerebral oedema in acute ischaemic stroke. Cochrane Database Syst Rev. 2002;3: CD003435.
17. O'Donnell P, Buxton PJ, Pitkin A. The magnetic resonance imaging appearances of the brain in acute carbon monoxide poisoning. Clin Radiol. 2000; 55(4):273–280.
18. T Miura, M Mitomo, R Kawai, K Harada. CT of the brain in acute carbon monoxide intoxication: characteristic features and prognosis. Am J Neuroradiol. 1985; 6(5):739–742.
19. Jeon S-B, Sohn CH, Seo D-W, Oh BJ, Lim KS, et al.2018. Acute brain lesions on magnetic resonance imaging and delayed neurological sequelae in carbon monoxide poisoning. JAMA Neurol. 75(4):436–443.
20. Kim YS, Cha YS, Kim MS, Kim HJ, Lee YS, et al. The usefulness of diffusion-weighted magnetic resonance imaging performed in the acute phase as an early predictor of delayed neuropsychiatric sequelae in acute carbon monoxide poisoning. Human & experimental toxicology. 2018;37(6):587–95.
21. Kokulu K, Mutlu H, Sert ET. 2020. Serum netrin-1 levels at presentation and delayed neurological sequelae in unintentional carbon monoxide poisoning. Clin Toxicol (Philadelphia, Pa). 58(12):1313–1317.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Lower Gastrointestinal System Endoscopy Findings in Şırnak: A Retrospective Study

Şırnak İlinde Alt Gastrointestinal Sistem Endoskopi Bulguları: Retrospektif Çalışma

Selma Demirbas Yuceldi[1]

[1]*Sakarya Training and Research Hospital, Department of Internal Medicine, Department of Gastroenterology, Sakarya, Turkiye*

ABSTRACT

Aim: *It was aimed to evaluate endoscopy reports in patients who had lower gastrointestinal system complaints and underwent endoscopy in Şırnak to determine up-to-date findings and their frequency and to compare them with the literature data.*

Materials and Methods: *Demographic characteristics, endoscopy, and pathology results of patients who underwent lower gastrointestinal system endoscopy in the gastroenterology clinic endoscopy unit of Şırnak State Hospital between November 2019 and August 2021 were evaluated retrospectively. The findings were described with the help of the SPPS 25 statistical program.*

Results: *Of the 728 patients in the study, colonoscopy was performed in 632, and rectosigmoidoscopy was performed in 96 patients. 57.8% (n: 421) were male. The mean age was 46±18.46 (range 18–120 years). The most common indication was rectal bleeding, hematochezia, or, rarely, unexplained melena in 139 (19.1%) patients. Unexplained anemia was the second most common indication in 120 (16.5%) patients. Four hundred and fifty (61.8%) patients had pathological findings. The most common results were 44% (n: 317) hemorrhoids and 19.1% (n: 139) colorectal polyps. The frequency of colorectal cancer, inflammatory bowel disease, solitary rectal ulcer, and diverticulum was 3.4% (n: 25), 9.2% (n: 67), 4.4% (n: 32), and 3.6% (n: 26), respectively.*

Conclusion: *In this study, epidemiological data of lower gastrointestinal system endoscopy in Şırnak were obtained for the first time and compared with literature data. This study, with its up-to-date data, will contribute to regional epidemiological studies.*

Keywords: lower *gastrointestinal system; endoscopy; diagnosis; epidemiology*

ÖZET

Amaç: *Şırnak ilinde, alt gastrointestinal sistem şikâyetleri ile gelen ve endoskopi yapılan hastalarda endoskopi raporlarının değerlendirilmesi; güncel bulgular ve sıklıklarının belirlenmesi ve literatür ile karşılaştırılması amaçlandı.*

Materyal ve Metot: *Kasım 2019 ve Ağustos 2021 tarihleri arasında, Şırnak Devlet Hastanesi gastroenteroloji kliniği endoskopi ünitesinde, alt gastrointestinal sistem endoskopi işlemi yapılan hastaların demografik özelikleri, endoskopi ve patoloji sonuçları retrospektif olarak tarandı; bulgular SPPS 25 istatistik programı yardımı ile tanımlandı.*

Bulgular: *Çalışmaya dahil edilen 728 hastanın 632'sinde kolonoskopi, 96'sında rektosigmoidoskopi işlemi yapıldı. %57,8 (n: 421)'i erkek; %42,2 (n: 307)'si kadın idi. Yaş ortalamaları 46±18,46 (dağılım 18–120) yıl idi. Ensık endikasyon 139 (%19,1) hastada rektal kanama, hematokezya veya nadiren açıklanamayan melena; ikinci sıklıkta 120 (%16,5) hastada açıklanamayan anemi idi. Dört yüz elli (%61,8) hastada patolojik bulgu saptandı. En sık saptanan bulgular 317 (%44) hemoroid, 139 (%19,1) kolorektal polip idi. Kolorektal kanser, enflamatuvar bağırsak hastalığı, soliter rektal ülser, divertikül sıklıkları, sırasıyla, %3,4 (n: 25), %9,2 (n: 67), %4,4 (n: 32), %3,6 (n: 26) saptandı.*

Sonuç: *Bu çalışma ile Şırnak ilinde, alt gastrointestinal sistem endoskopi epidemiyolojik verileri, ilk kez elde edildi ve literatür bilgileri ile karşılaştırması yapıldı. Güncel olan verileri ile bu çalışmanın bölgesel epidemiyolojik çalışmalara katkı saylayacağı düşünülmektedir.*

Anahtar kelime: *alt gastrointestinal sistem; endoskopi; tanı; epidemiyoloji*

Introduction

Today, lower gastrointestinal system (GIS) endoscopies, colonoscopy, and flexible rectosigmoidoscopy, are widely used in diagnosing and treating patients with lower GIS symptoms and in the screening and surveillance of lower GIS diseases[1–3].

The incidence of GIS pathologies varies according to countries and regions and sometimes over time. This may require differences in disease prevention, diagnosis, and follow-up approaches. When we look at the literature, there are studies conducted in other eastern/southeastern provinces and in the past years in our country[2,6], however, there is no recent epidemiological study on lower GIS endoscopy and pathology in Şırnak province.

İletişim/Contact: *Selma Demirbaş Yüceldi, Sakarya Training and Research Hospital, Department of Internal Medicine, Department of Gastroenterology, Sakarya, Türkiye* • ***Tel:*** *0505 873 9603* • ***E-mail:*** *selmademirbas@yahoo.com* • ***Geliş/Received:*** *28.11.2021* • ***Kabul/Accepted:*** *21.12.2022*

ORCID: *Selma Demirbaş Yüceldi, 0000-0002-2533-0845*

Kafkas J Med Sci 2023; 13(1):6–10
doi: 10.5505/kjms.2023.78553

This study aimed to detect up-to-date lower GIS endoscopy indications, findings, and frequencies, in the Şırnak State Hospital Gastroenterology clinic endoscopy unit and compared the results with the literature.

Material and Methods

This study was designed as cross-sectional, single-center, and retrospective. The data of 763 patients who underwent lower GIS endoscopy between November 2019 – August 2021 in Şırnak State Hospital Gastroenterology clinic endoscopy unit were scanned. Thirty-five of them, those under the age of 18, pregnant, and those who did not have sufficient data, were excluded from the study. Seven hundred and twenty eight patients were included in the study.

The endoscopy and pathology reports of the patients included in the study were scanned retrospectively from online hospital data and patient files. Age, gender, endoscopy indications and findings, and pathology results were recorded.

Watery, low-fiber diet two days before and an oral laxative the day before the procedure was applied for colonoscopy bowel preparation. Rectosigmoidoscopy was performed after preparation with a rectal enema, applied on the procedure day. For all of the rectosigmoidoscopy procedures, most of the colonoscopy procedures were performed without sedation due to an insufficient number of assistant health personnel. However, in a small number of patients who could not tolerate it, the procedure was performed after sedation with midazolam, meperidine, and propofol. Before the procedure, patients were informed, and their consent was obtained.

Statistical Analysis

The obtained data were defined using the IBM Statistical Package for Social Sciences (SPSS) version 25 statistical program. Descriptive statistics were expressed as numbers and percentages for categorical variables, as means, standard deviations, and ranges for numerical variables.

Ethical Issues of The Study

The study was conducted by the Principles of the Helsinki Declaration. Before the study, the ethics committee approval dated 25.10.2021 and numbered 74646–471 was obtained from the Sakarya University Faculty of Medicine Ethics Committee.

Results

Of the 728 procedures, 632 were colonoscopy, and 96 were rectosigmoidoscopy. Of the patients, 421 (57.8%) were male, and 307 (42.2%) were female; The mean age was 46±18.46 (range 18–120) years. Indications, rectal bleeding, hematochezia, or rarely unexplained melena in 139 (19.1%) patients, unexplained anemia in 120 (16.5%) patients, chronic diarrhea in 117 (16.1%) patients, chronic constipation in 50 (6.9%) patients, bowel habit changes in the form of constipation-diarrhea attacks lasting longer than 2 weeks in 8 (1.1%) patients, chronic bloody mucus diarrhea in 43 patients (5.9%), abdominal pain in 112 (15.4%) patients, stool occult blood positivity in 39 (5.4%) patients, premalignant and malignant lesions screening and follow-up in 88 (12.1%) patients, tenesmus in 5 (0.7%) patients, and rectal pain in 7 (1%) patients. No complications developed during or after any procedure.

Endoscopic pathological findings were detected in 450 (61.8%) patients. The results are given in Table 1.

As a result of the evaluation of the clinical, laboratory, imaging, and histological data of 69 (9.5%) patients with endoscopically suspected inflammatory bowel disease, ulcerative colitis (UC) was diagnosed in 43 (62.3%), and Crohn's disease (CH) was diagnosed in 24 (34.8%); intestinal tuberculosis was diagnosed in 2 (2.9%) patients. The mean age of UC patients was 31.23±10.09; 28 (65.1%) were male. The mean age of CD patients was 32.16±13.8; 16 (66.7%) were male. Both patients with intestinal tuberculosis were women aged 25 and 46 years.

9 (6.5%) of 139 (19.1%) patients with colorectal polyps had more than three polyps. Familial adenomatous polyposis was detected in 1 (0.1%). Of the patients, 55 (35.7%) had polyps in the rectum, 28 (18.2%) had in the sigmoid colon, 21 (13.6%) had in the descending colon, 9 (5.8%) had in the transverse colon, 11 (7.1%) had in the ascending colon, 7 (4.5%) had in the cecum, and polyps were scattered in 23 (14.9%). Pathology reports of 145 out of 154 removed polyps could be accessed. Their histopathological examination findings are given in Table 2. Low-grade dysplasia was found in 6 (7.2%) of the adenomas, and high-grade dysplasia was found in 1 (1.2%). 64.5% of the patients detected hyperplastic, inflammatory polyp, and pseudopolyp were male, mean age of 49.8±16.4 (range 19–83 years); 60.8% of the patients detected adenoma were male, the mean age was 59.07±15.08 (range 33–94 years).

Table 1. *Lower gastrointestinal system endoscopy findings, in Şırnak*

Endoscopic findings	Number (N; %)
Normal	278 (38.2)
Hemorrhoids	317 (43.5)
Anal fissure	33 (4.5)
Anal fistula	3 (0.4)
Rectal prolapse	3 (0.4)
Perianal abscess	1 (0.1)
Solitary rectal ulcer	32 (4.4)
Diverticulum	26 (3.6)
Angiodysplasia	22 (3)
Melanosis coli	2 (0.3)
Subepithelial lesion	13 (1.8)
Enterobiasis	5 (0.7)
Nodular lymphoid hyperplasia	4 (0.5)
Sigmoid colon volvulus	3 (0.4)
Operated colon	8 (1.1)
Nonspecific ileitis/colitis	17 (2.3)
Inflammatory bowel disease	67 (9.2)
Intestinal tuberculosis	2 (0.3)
Colorectal polyp	139 (19.1)
Malignancy	25 (3.4)

Table 2. *Histopathological findings of colorectal polyps, detected on lower gastrointestinal system endoscopy, in Şırnak*

Histopathological diagnosis	Number (N; %)
Hyperplastic polyp	44 (30.3)
Adenoma	83 (57.2)
Pseudopolyp	4 (2.8)
Inflammatory polyp	14 (9.7)
Total	145 (100)

Table 3. *Cancer distribution by colon segments, in lower gastrointestinal system endoscopy, in Şırnak*

Colon segment where cancer is detected	Number (N; %)
Anal canal	1 (4)
Rectum	6 (24)
Sigmoid colon	8 (32)
Descending colon	1 (4)
Transverse colon	1 (4)
Ascending colon	6 (24)
Cecum	2 (8)
Total malignancy	25 (100)

Seventeen (68%) of 25 patients detected colorectal cancer were male; 2 (8%) were under the age of 40, 7 (28%) were in the 40–50 age range, 16 (64%) were 50 years and over. The mean age was 58.59±14.68 (range 31–81 years). Cancer distribution by colon segments is shown in Table 3.

Discussion

Endoscopy is a very effective procedure in diagnosing, treating, and following lower GIS diseases; However, the disadvantages are that it is invasive, painful, and can cause serious complications. Complications are 0.08–0.19% in diagnostic colonoscopy; 0.15–3% in colonoscopies performed for therapeutic purposes[1]. In this study, most procedures were for diagnostic purposes. Therapeutic procedures performed in this study included removing polyps with forceps or snare in 135 (18.5%) patients; thermal coagulation of bleeding angiodysplasias in 20 (2.7%) patients. All of the removed polyps were under 2 cm. No complications developed.

The most common indication in this study was an investigation of rectal bleeding, hematochezia, and unexplained melena bleeding for lower GIS endoscopy (19.1%), while in previous studies, it was an investigation of constipation, diarrhea, and bowel habit changes[5,6]. This may be because of the Coronavirus disease 2019 (Covid-19) and insufficient staff and equipment. Most of the procedures in this study were performed during the Coronavirus disease 2019 (Covid-19) pandemic. The worldwide pandemic, Covid-19, emerged in Türkiye in early 2020. In the Covid-19 pandemic, like in the world and Türkiye, in the city, with national population lockdown, elective endoscopy procedures, like other interventional procedures, were postponed due to the risk of virus transmission[4]. As new cases decreased, elective endoscopic procedures were gradually resumed with protective measures. Moreover, the unit was the only gastroenterology endoscopy center in the city of over 500,000 population. There was only one gastroenterologist and one active endoscopy equipment. So emergent procedures such as GIS bleeding were given priority; elective procedures had to be postponed.

However, it was observed that this situation did not make any difference in this study's most common endoscopic findings. Normal colonoscopic findings were found in 29–54% of patients who underwent colonoscopy in previous studies throughout our country. The most common result was hemorrhoids[1]. The frequency of hemorrhoids was 39%–50% in America[1,3], 8–58% in studies conducted in different regions of

our country[1,3,5–7]. Similarly, this study found normal findings in 38.2% of the procedures. The most common result was hemorrhoids, detected in 317 (43.5%) patients.

Colorectal polyps were the second most common finding. In previous studies throughout our country, the frequency of colorectal polyps is between 7–20%[1–3,5–7]. A similar rate was found in this study, 19.1%. In previous studies, the frequency of colorectal polyps has been reported as 53–59% in men and 40–46% in women[2]. Adenomas are the most commonly detected neoplastic polyps; The incidence increases with age and is more common in men[1,2]. Similarly, in this study, all polyps were more common in men; 64.5% of the patients with a nonneoplastic hyperplastic, inflammatory polyp, and pseudopolyp were male, and the mean age was 49.8±16.4 (range 19–83 years), 60.8% of the patients with neoplastic adenoma were male, the mean age was 59.07±15.08 (range 33–94 years).

Although it varies according to region, colorectal cancer ranks 3rd among all cancers with 13% and 4th in cancer deaths[1–3]. Colorectal cancer mortality decreases with early diagnosis. In other studies in endoscopy units throughout our country, colorectal cancer frequency varies between 1.4–14% according to regions[1–3,5]. The rate found in this study was 3.4%.

Although it has been determined in recent studies that the location of colorectal cancers tends to shift from the left colon to the right colon[1], many studies have shown that 55–60% of colorectal cancers are located in the left colon, especially in the rectum and rectosigmoid region[1,2,5]. Similarly, this study detected it most frequently in the left colon; in the sigmoid colon 32%, rectum 24%, and ascending colon 24%, in order of frequency. Similar to the literature, the frequency of colorectal cancer was found to be higher in men in this study; 68% of cancer patients were male[1,2,5]. The risk of colorectal cancer increases with age. With a significant increase between the ages of 40–50, these rates continue to increase every decade after the age of 50 [1,2,3,5]. It is reported that 2–6% of all colorectal cancer cases are under 40 [2]. In this study, 8% of cancer patients were under 40, 28% were between 40–50, and 64% were over 50. These findings support the necessity of colon cancer screening with colonoscopy over 45–50; they suggest that colonoscopic examination should also be performed in younger individuals, those with alarm symptoms, and those with treatment-resistant lower GIS symptoms.

The frequency of inflammatory bowel disease (IBD) varies considerably geographically around the world. Inflammatory bowel disease is more common in western societies with better hygienic conditions and higher socioeconomic status[8–14]. It is most frequently observed in Western Europe and North America; the prevalence was 505 and 286 per 100,000 subjects, respectively, for ulcerative colitis (UC); 319–322 per 100,000 subjects for Crohn's disease (CD)[14]. As a developing country, Türkiye is transitional between east and west. Although the incidence of the disease is not as high as in western societies, it is not as low as in the east. In previous studies in our country, the prevalence rates were reported to be between 3.27–4.9/10^5 for UC and 1.2–2.2/10^5 for CD[10–13]. Most recently, in the study conducted between 2004–2013 in the Western Black Sea region located in the Northern region of Türkiye, a higher overall prevalence of IBD was detected; 31.83/10^5 for UC and 12.53/10^5 for CD[9]. Recently, the incidence of IBD has been increasing in Türkiye and developing countries. This increase is attributed to environmental factors such as industrialization and the spread of western lifestyle, dietary changes, improved hygiene, microbial exposure, increased use of antibiotics and other drugs, and exposure to air pollution[8–13]. Although there are studies on the epidemiological data of IBD in Türkiye[8–13], no studies have been conducted in recent years, especially in the east-southeast region. In our country, which has a very heterogeneous structure in terms of ethnic origin, the disease frequency may differ according to the region. While the frequency of inflammatory bowel disease was 1.7–4.9% in studies conducted in endoscopy centers in Türkiye in previous years[1–3,5–7], the rate was found to be 9.2% in this recent study. This detected high frequency can be explained by the increase in urbanization and exposure to changing environmental factors in the east and southeast regions in Türkiye, as well as worldwide. Additionally, the increase in awareness of the disease, significant progress in diagnostic methods, more opportunities to benefit from health services, and easier access to colonoscopy, compared to previous periods, may be effective factors in the increase in frequency.

Ulcerative colitis is more common than CD[6–11]. In this study, 43 (64.2%) of IBD patients were UC and 24 (35.8%) CD. The female/male ratio ranges from 0.51–1.58 for UC and 0.34 to 1.65 for CD, and when evaluated in general, there is no difference in frequency between males and females in IBD[8]. However, there was mild male predominance in a few studies for UC and CD

in Türkiye[11,12]. Similarly, this study had a male predominance; 65.9% of IBD patients were male. Age at onset of IBD usually peaks in the 2nd and 3rd decades, followed by the 6th decade[8–11]. In this study, the mean age of IBD patients was 31.57±11.46 (range 18–66 years).

Colon diverticulum frequency was 0.6–5.3% in studies conducted in endoscopy centers in Türkiye[1,3,5–7]. Similarly, its frequency was 3.6% in this study.

Enterobius vermicularis was found at a rate of 0.1–3.3% in studies throughout Türkiye[5,7], and similarly at 0.7% in this study.

Solitary rectal ulcer syndrome (SRUS) is a rare condition of unknown exact cause and prevalence. It usually occurs after chronic constipation, pelvic floor dysfunction, or rectal mucosal prolapse[15]. The frequency of SRUS was 0.6–1.3% in studies in Türkiye[1–3,5–7]. In this study, a higher rate of 4.4% was found. In the eastern and southeastern regions, consumption of fatty, spicy, and low-fiber foods, such as meat products, more frequently; of high-fiber foods, such as fruits and vegetables, less frequently and especially in the Covid-19 pandemic, due to social isolation rules, more sedentary life may trigger chronic constipation. The high incidence of SRUS may be related to this.

Conclusion

The frequency of GIS pathologies differs between countries and regions and over time. In addition, the frequency can change as awareness, living conditions, and diagnostic possibilities change. In this study, the frequency of lower GIS pathologies in patients who underwent lower GIS endoscopy in Şırnak State Hospital Gastroenterology clinic endoscopy for approximately two years was determined for the first time. These up-to-date results support the variation of the frequency of especially IBD and SRUS, between regions and over time in Türkiye. With its up-to-date data, the study is thought to contribute to epidemiological research.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject nor from a company that provides or produces medical instruments and materials, which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding, and similar situations in any firm.

References

1. Yücel Y, Aktümen A, Aydoğan T, Uyanıkoğlu A, Şeker A, Gözeneli O, et al. Lower gastrointestinal system endoscopy: Retrospectively analysis of 1800 cases and determination of the frequency of colorectal cancer. Endoscopy. 2015;23:6–8.
2. Güvendi Fındık G, Eroğlu HA, Adalı Y. Lower Gastrointestinal Endoscopic Biopsy Results of Kars Region. Kafkas J Med Sci. 2018;8(1):70–9.
3. Kosus A, Ates M, Kosus N. Endoscopic Findings In Women With Lower Gastrointestinal System Symptoms. Turkiye Klinikleri J Med Sci. 2008;28:635–9.
4. Lantinga MA, Theunissen F, Ter Borg PCJ, Bruno MJ, Ouwendijk RJT, Siersema PD. Impact of the COVID-19 pandemic on gastrointestinal endoscopy in the Netherlands: analysis of a prospective endoscopy database. Endoscopy. 2021; 53:166–170.
5. Korkmaz H, Kendir İC, Kerpiç O. Evaluation of colonoscopy outcomes with the indications, complications, and success of the procedure in our gastroenterology unit. Endoscopy. 2015; 23(1):9–13.
6. Şit M, Aktaş G, Yılmaz EE. Lower Gastrointestinal Endoscopy Results: Region of Ağrı Doğubayazıt. Medical Journal of Kocaeli. 2012;3:1–4.
7. Tamer A, Korkut E, Korkmaz U, Akcan Y. Low Gastrointestınal Endoscopy, An Institutional Results: Region of Düzce. The Medical Journal of Kocatepe. 2005;6:29–31.
8. Özgürsoy Uran BN, Yüksel Sarıtaş E, Avdal Ünsal E, Arkan B. Epidemiological characteristics and awareness of inflammatory bowel diseases: a cross-sectional study in Izmir. The Turkish Journal of Academic Gastroenterology. 2019;18:112–9.
9. Can G, Poşul E, Yılmaz B, Can H, Korkmaz U, Ermiş F, et al. The rates of incidence and prevalence of inflammatory bowel diseases in Bolu/Düzce Region: Retrospective cohort study between 2004-2013. Abant Med J. 2015;4:210–20.
10. Özin Y, Kılıç MZ, Nadir I, Cakal B, Disibeyaz S, Arhan M, et al. Clinical features of ulcerative colitis and Crohn's disease in Turkey. J Gastrointestin Liver Dis. 2009;18:157–62.
11. Tözün N, Atug O, Imeryuz N, Hamzaoglu HO, Tiftikci A, Parlak E, et al. Members of The Turkish IBD Study Group. Clinical characteristics of inflammatory bowel disease in Turkey: A multicenter epidemiologic survey. J Clin Gastroenterol. 2009;43:51–7.
12. Tezel A, Dökmeci G, Eskiocak M, Umit H, Soylu AR. Epidemiological features of ulcerative colitis in Trakya, Turkey. J Int Med Res. 2003;31:141–8.
13. Özden A. İnflamatuvar bağırsak hastalığının tarihine kısa bir bakış. Güncel Gastroenteroloji. 2013;17:294–301.
14. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390(10114):2769–78.
15. Aygün C, Bahçecioğlu İH. Soliter Rektal Ülser Sendromu. Güncel Gastroenteroloji. 2010;14:35–8.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Investigation of *Bartonella hanselae* Seroprevalence in the Northern Countryside of Denizli Province

Denizli Kuzey Kırsalında Bartonella hanselae Seroprevalansının Araştırılması

Yuksel Akkaya[1], Cagri Ergin[2]

[1]Health Sciences University, Hamidiye Faculty of Medicine, Department of Medical Microbiology, Istanbul;
[2]Pamukkale University, Faculty of Crochet, Department of Medical Microbiology, Denizli, Turkiye

ABSTRACT

Aim: *Bartonella species are zoonotic bacteria that are transmitted through gram negative coccobacillus/bacillus. The importance of the Bartonella species has increased with there cent epidemiological studies on human sand animals. The proportions differ according to the epidemiological studies conducted in different risk groups. The B.henselae ranges between 5.5% and 57.3% in seroprevalence studies conducted in differen tparts of the world. It is important to expand the seroprevalence studies of bartonellosis at Türkiye. The aim of this study was to determine the seroprevalence of in working adults at risk by occupational groups in northern rural area of Denizli.*

Material and Method: *Antibodies against B.henselae ATCC 49882 (Houston-1) strain were detected using immunofluorescent antibody technique in serum samples collected from 477 healthy adult volunteers working in risky occupational groups in then norther countryside of Denizli. Serum samples were studied in laboratory of Medical Microbiology Department, Faculty of Medicine, Pamukkale University.*

Results: *The prevalence of B.henselae seropositive was found to be 44.0%. Antibodiesof B.henselae were found in 26.8% volunteers at 1/64, in 13.8% at 1/128, in 2.7% at 1/256, in 0.6% at 1/512 dilutions. The analysis of the data revealed that statistical difference sexist for B.henselae according to tick, exposure to sandfly, live in wetlands, agriculture, and age groups (p<0.005).*

Conclusion: *This study makes an important contribution in determining the seroprevalence of bartonellosis relevant to Türkiye. According to the screening of seroprevalence by risk occupational groups in this study, it is concluded that risk groups with different regional and geographical features should be preferred for bartonellosis seroprevalence examinations.*

Keyword: *Bartonella henselae; seroprevalence; zoonosis; risk occupational groups*

ÖZET

Amaç: *Bartonella türleri Gram negatif kokobasil/basil şeklinde, vektörlerle geçiş yapan, zoonotik bakterilerdir. Son yıllarda insanlarda ve hayvanlarda yapılan epidemiyolojik çalışmalar ile Bartonella türleri önem kazanmıştır. Risk gruplarında yapılan epidemiyolojik çalışmalarda oranlar değişkenlik göstermektedir. Dünyanın farklı bölgelerinde yapılan seroprevalans çalışmalarında B.henselae %5,5 ile %57,3, oranında saptanmıştır. B.henselae ülkemizde de görülmekte olan vektörel yayılımlı bir enfeksiyon etkenidir. Ülkemizin coğrafik ve iklimsel özellikleri gözönüne alındığında bartonellozun seroprevalans çalışmalarının yaygınlaştırılması önem arzetmektedir. Sunulan çalışmada Denizli'nin kuzey kırsalında risk oluşturan meslek gruplarında çalışan yetişkinlerde B.henselae seroprevalansının saptanması amaçlandı.*

Materyal ve Metot: *Denizli'nin kuzey kırsalında risk oluşturan meslek gruplarında çalışan Sağlıklı 477 yetişkin gönüllüden toplanan serum örneklerinde immünfloresan antikor tekniği kullanılarak B.henselae ATCC 49882 (Houston-1) kökenine karşı oluşan antikorlar saptandı. Toplanan serum örnekleri Pamukkale Üniversitesi Tıp Fakültesi Mikrobiyoloji Anabilim Dalı laboratuvarında çalışıldı.*

Sonuçlar: *B.henselae seropozitiflik oranı %44,0 olarak bulundu. Gönüllülerin %26,8'inde 1/64, %13,8'inde 1/128, %2,7'sinde 1/256, %0,6'sında 1/512 dilüsyonda B.henselae antikorları pozitif saptandı. B.henselae için kene teması, tatarcık maruziyeti, sulak alanda yaşama, tarım yapma ve yaş gruplarında istatistiksel farklılık saptandı (p<0,005).*

Tartışma: *Türkiye'de seroprevalans çalışmaları sınırlı sayıdadır. Sunulan çalışma Türkiye'de bartonellozseroprevalansının saptanması açısından önemlidir. Risk oluşturan meslek gruplarında yaptığımız seroprevalans taraması ile bölgesel ve farklı coğrafik özellik gösteren risk gruplarında bartonellozseroprevalans çalışmalarının yapılması gerektiği sonucuna varıldı.*

Anahtar Kelimeler: *Bartonella henselae; seroprevalans; zoonoz; risk oluşturan meslek grupları*

İletişim/Contact: *Yüksel Akkaya, Health Sciences University, Hamidiye Faculty of Medicine, Department of Medical Microbiology, 34668, Üsküdar/İstanbul - Türkiye* • ***Tel:*** *+90 505 745 49 80* • ***E-mail:*** *yuksel.akkaya@sbu.edu.tr* • ***Geliş/Received:*** *24.02.2022* • ***Kabul/Accepted:*** *10.01.2023*

ORCID: *Yüksel Akkaya, 0000-0003-1297-944X* • *Cağrı Ergin, 0000-0001-7783-8723*

Introduction

Bartonella are important vector transmitted inflammatory conditions in both animals and humans[1]. *Bartonella* are members of a small genus, pleomorphic, Gram-negative, weakly staining bacilli and coccobacilli, oxidase, and catalase negative microorganisms. There are more than 30 known types of these bacteria, which are members of the phylum *α-Protobacteria*[2,3]. Bartonellosis could often be overlooked while it progresses as a silent infection. Hence, seroprevalence methods have been favored when it comes to investigating the existence of regional illness. Seroprevalence values ranging from 5.5% to 60.5% have been detected in different risk groups in studies carried out in rural areas and different regions of the world[4–8]. In Türkiye, although there are case reports, a limited number of studies have reported seroprevalence in different risk groups[1,9,10].

Material and Methods

This study presents the risk factors and seroprevalence of *Bartonella henselae* in a well-defined and confined geographical area.

Study Design and Area

The study was carried out in Denizli province, Menderes Valley, North region. The region's main source of livelihood is agriculture (crops production and raising livestock). The area of study was divided into four main regions corresponding to the differences of altitude and settlement characteristics of the regions (Fig. 1). Population density is 25 person/km^2 in mountainous areas and valleys (I, II, III; 600–2000 m) and >200 person/km^2 in the central rural area (IV; <600 m). According to Köpplen-Geiger climate classification, the region is "CSA" (mild winter, very hot summers, and arid climate (Mediterranean climate) with temperatures ≥22°C)[11].

Study Groups

A total of 477 adult volunteers from the northern rural area of Denizli province were included in the study. Detailed questionnaires were filled during the meetings with the adult volunteers. Demographic data of the adults included in the study were recorded. Collected serum samples were centrifuged the same day and were preserved in sterile eppendorf tubes at -20^{0}C until the experimental study.

Laboratory testing

The lyophilized *B.henselae* ATCC 49882 (Houston-1) was plated in 5% defibrinated brain heart infusion agar media with horse blood by suspending it with sterile saline and was bred in a humid incubator at 37°C which has 10% CO_2. Control breeding was carried out using auramine–rhodamine fluorescence and Gram staining. Reproducing bacteria were co-cultured with Vero cell lines growing in 25 cm^2 flasks. Briefly, 2 ml trypsin was added to Vero cell lines which were attached to the flask surface through reproducing. After 3 minutes, 7 ml cell growth solution (100 ml Eagle's Medium, 10 ml Fetal Calf Serum, 2 ml L-glutamine, 1 ml HEPES solution and 0.4 ml amphotericin-B) was added to the medium. The suspension liquid with the cells were centrifuged for 5 minutes at 25°C 1000 g. The supernatant fluid floating after the centrifugation was added to the 2 ml growth solution pre-prepared on outer cell pellet. The cells added to flasks continued to incubate in incubators providing a humid atmosphere at 37°C which has 5–10% CO_2 until a monolayer cell line was formed with an inverted microscope. 100 µl of the *B.henselae* ATCC 49882 (Houston-1) cell species which has formed monolayer was added and taken to co-cultivation. Those cells were incubated in an incubator at 37°C, which was providing humidity and had 5–10% CO_2. After the incubation, co-culture cells were deactivated by making them sit in a water bath at 56°C for 30 minutes. After transferring 10 µl to commercially bought teflon coated microscope slides, they were dried using room temperature laminar air flow. Dried slides were immobilized in acetone at -20°C for 15 minutes. After the immobilization of slides using acetone, the slides were preserved in a container at -70°C until the time of study. The test for antibodies in the collected serum samples was carried out using the immunofluorescence antibody detection method described by Regnery et al.[12] During the study, the serum of a patient who was diagnosed with bacillary angiomatosis both pathologically and clinically was used as positive control. Specific immunofluorescence scoring of the serum sample examinations from 0 to +3 was done considering the pre-defined fluorescence reflection intensity subjectively[13]. For *B.henselae*, a positivity of +2 in ≥1/64 dilution was accepted as seropositive[3,13,14].

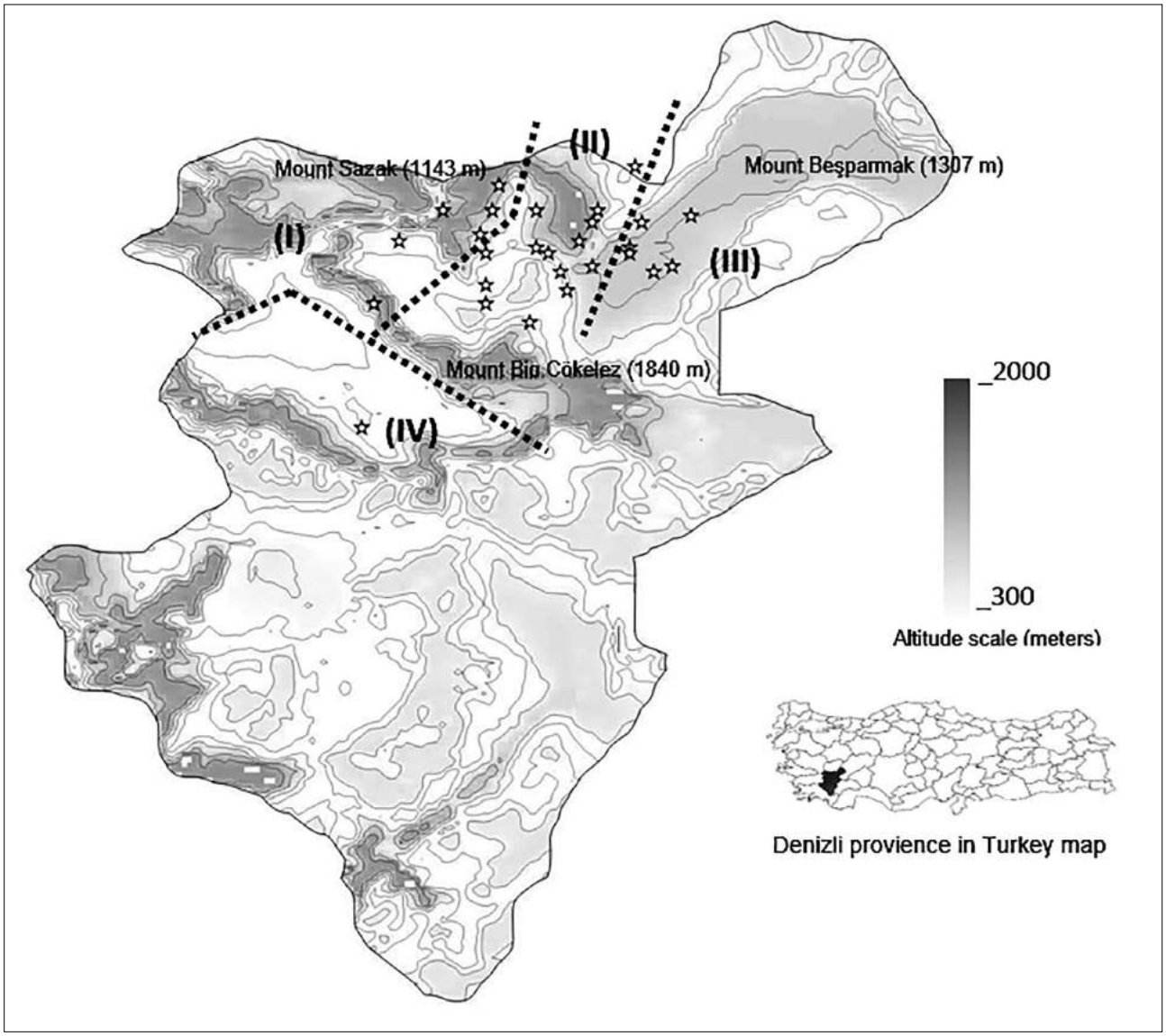

Figure 1. *Geographical study parts of Denizli province, sampling points as (I) Bekilli villages area; (II) Çal villages area; (III) Baklan villages area; (IV) Denizli city center.*

Data Analysis

IBM Statistical Package for Social Sciences (SPSS) program version 18.0 (IBM Corp, Armonk, NY, USA) was used for the statistical analyses with 95% confidence.

Ethical Consideration

This research has been approved by Pamukkale University Medical Ethics Council with the number 2008/7-1.

Results

The screening of 477 people included in the study demonstrated the existence of antibodies in ≥1/64 dilutions of 210 volunteers (44.0%) (Table 1).

Seropositivity-wise, there were no differences between male volunteers (111/242; 23.3%) and female volunteers (99/235; 20.7%) participating in the study. Among the regions included in the study, the highest amount of seropositivity was found in (Fig. 1-II) Çal region (Table 2; $p<0.05$).

The differences of antibody seroprevalence among people living in different altitudes (Fig. 1) are given in the Table 3. Antibody prevalence is higher in people living at altitudes ≥600 m but the estimated relative risk ratio drops as the altitude rises ($p<0.001$; Table 3). Further, the statistical analysis demonstrated the following:

Table 1. *The distribution of Bartonella henselae antibodies in the study groups (N=477)*

Percentage	Number of samples	Positive sample (%)	Cumulative positivity (%)
<1:64	267	56.0	0.0
1:64	128	26.9	26.9
1:128	66	13.8	40.7
1:256	13	2.7	43.4
1:512	3	0.6	44.0

Table 2. *The distribution of Bartonella henselae antibodies in the study group in accordance with the sample collection region*

Region	Sample number (N)	Seropositive sample n (%)
(I) Bekilli	31	9 (1.8)
(II) Çal	313	141 (29.5)
(III) Baklan	78	43 (9.0)
(IV) Central rural area	55	18 (3.8)

Table 3. *The distribution of Bartonella henselae antibodies in the study group according to the residency in altitudes*

Altitude (m)	Sample number (N)	Seropositive sample n (%)	Odds percentage	p value
300–600	22	9 (40.9)	0.90	0.82
600–1600	214	113 (54.6)	2.04	<0.001
1600+	241	84 (34.9)	0.49	<0.001

Table 4. *The distribution of Bartonella henselae antibodies in the study group in accordance with the age groups*

Age group	Sample Number (N)	Seropositive sample n (%)
10–19	16	7 (1.5)
20–29	56	25 (5.2)
30–39	116	45 (9.4)
40–49	56	56 (11.7)
50–59	83	44 (9.2)
60–69	40	25 (5.2)
70–79	15	7 (1.4)
80+	5	1 (0.2)

- Difference in *B.henselae* seropositivity based on age groups of the volunteers participating in the study was not significant (p>0.05; Table 4).
- Difference in *B.henselae* seropositivity and the job groups of the volunteers participating in the study was not found (p>0.05; Table 5).
- People with history of working or doing agriculture in wetlands and contact with ticks had higher *B.henselae* seroprevalence.

Discussion

The aim of this study was to detect and examine the seroprevalence of *B.henselae* in occupational groups susceptible to bartonellosis among the locals living in the northern rural area of Denizli. Risk groups were formed using factors such as occupation, area of residence, characteristics of life, exposure to vector. In variations of the study, the *B.henselae* seropositivity was found as 44.0% in northern rural area of Denizli.

The studies carried out to determine *B.henselae* antibodies in healthy humans vary greatly in different regions of the world. These differences are attributed to the characteristics of life of societies and the ecological variabilities of the regions they live in. During the scanning of people living in rural areas, *B.henselae* seroprevalence has been detected as 5.5% in Thailand[6], 9.6% in China[15] in Tianjin region, 13.3% in Brazil[16], 15% in Korea[17], 15.9% in Crete[18], 19.6% in East China[19], 19.8% in Greece[20], 36.8% in Canada British Columbia[21], 0.8–9.3% in the United States of America[13], 57.3% in Croatia[6], 65% in Austria[22], 11.9–60.5% in Spain[23] and 30.4–48. % in Poland[2,24]. The amount of *B.henselae* seroprevalence of the healthy blood donors consulting in hospitals within the region of this study has been found to be 6.0% [14]. This percentage is relatively 96/9 low considering the result of the study (44%.0) conducted in rural areas.

In the study conducted in four regions according to their characteristics of life and geography, high seropositivity was detected in (II) Çal region (Fig. 1; Table 2; p<0.05). Similar results have also been achieved by the epidemiologic studies conducted in the world. Sun et al.[19] reported different percentages of seropositivity in the eastern regions of China. Studies conducted in the rural areas of Brodsko and Posavka of Crotia on *B.henselae* seroprevalence among the healthy population detected seropositivity to be 42.9% and 62.2% respectively[6].

The rural as well as the mild climatic nature of the region located in Northern part of Croatia serves as the primary reasons for the high *B.henselae* seropositivity

Table 5. *The distribution of anti-Bartonella henselae antibodies in the study group in accordance with the occupational groups*

Occupational group	Sample number (N)	Seropositive sample n (%)
Farmer	401	174 (36.5)
Veterinary	22	12 (2.5)
Shepherd	18	6 (1.3)
Livestock breeder	9	3 (1.3)
Retiree	8	6 (1.3)
Veterinary technician	6	2 (0.4)
Butcher	4	3 (0.6)
Forester	3	3 (0.6)
Other	6*	1 (0.2)

* Student, janitor, worker.

Table 6. *The distribution of Bartonella henselae seropositivity in accordance with the risk factors*

Risk factor	Odds percentage	95% Confidence interval	p value
Barn livestock raising	1.277	0.67–2.41	0.450
Domestic animal bite/scratch	0.705	0.46–1.06	0.095
Wild animal bite/scratch	1.449	0.54–3.82	0.453
Working at wetlands	1.857	1.19–2.88	0.005*
Working at a farm	0.633	0.41–0.96	0.032*
Hunting	0.809	0.49–1.32	0.389
Exposure to gnats	0.635	0.34–1.15	0.138
Exposure to fleas	0.836	0.56–1.24	0.374
Exposure to ticks	0.670	0.45–0.99	0.046*
Exposure to (body/hair) lice	1.324	0.90–1.93	0.143
Exposure to mang	0.962	0.32–2.81	0.944
Travelling abroad (>1 month)	1.078	0.62–1.86	0.785

* $p<0.05$

percentages. This data is in compliance with our findings. (II) Çal region, where high seropositivity was detected, is a low-altitude land compared to (I) Bekilli and (III) Baklan regions and it is located at a higher altitude than (IV) rural area of Denizli (Table 3). This finding shows that the role of fauna and vector transmissions are affected by the altitude.

Studies conducted in People's Republic of China, Thailand[5], Croatia [6], Greece [20] and Korea [17] report no difference of *B.henselae* seroprevalence between genders. This study confirms that finding by determining no difference in percentages of seropositive cases between genders.

When the occupational groups were evaluated, no statistical difference of *B.henselae* seropositivity was found ($p>0.05$). The highest percentage of seropositivity was found among farmers (36.5%; Table 5). *B.henselae* positivity was found in 65% of the healthy workers working in a zoo in Austria in Tianjin China among 365 agriculture workers, *B.henselae* was found in 79.8% of those who herd cattles, 14.5% of milkers, 14.5% of those who work at packaging and 1.7% of the vets [15,22]. Long durations of animal contact have been put forward as the reason for these increasing percentages. In Poland, it was found in 27.7% and 31.5% of farmers and foresters respectively, in 2015[24]. In a screening made using San Antonio 2 isolate in Spain's La Rioja region, it was found in 53.6% of health workers who frequently encountered cat scratch disease as well as in other bartonellosis patients[3].

While 2.5% seroprevalence was detected in vets, this percentage was reported as 12.5% among the vets who live in Denizli province center but work at a neighboring rural area[10]. The percentage found as 30% in Aydin, a neighboring province, is higher[10]. In different parts of the world, vets have been studied as risk group and seroprevalence was reported to range between 2.3 and 51.1%[10]. Chmielewski et al.[2]have researched the existence of *Bartonella spp.* in different occupational groups and while seropositivity was detected in 48.3% of homeless alcoholics, 45% of vets and 53.3% of cat breeders, no antibodies were found in people who take intravenous medicines. In this study, participants are farmers engaged in both crop and animal husbandry, therefore, similar to studies done in Austria[22] and China[15], this study considered long durations of contact with animals, as the primary reason for the high prevalence of seroprevalence among the farmers.

Among the people living in rural areas, no statistical difference of *B.henselae* antibodies between age groups were detected. Similar data were acquired in studies conducted in different parts of the world. Despite high percentages in this metric in various parts of the world such as 26.9% in the age group of 45–59 in China[19], 57.8% in the age group of 19–65 in Croatia[6] and 21.6% in the age group of 60 and over in Korea[17]. The analysis in this study did not find a statistical difference between age groups. On the other hand, Pons et al.[23] found a statistical difference in the age group of 30–64 compared to other groups in Northern Spain using IFA. These differenced could be explained by regional differences.

According to this study, *B.henselae* antibodies are higher in people who work on farms and wetlands than those who do not work in wetlands (Table 6; $p<0.05$). One of the big branches of Büyük Menderes lies in the (IV) north rural area of Denizli and this is where the sample is collected. This region also has large irrigation areas, which have branches of Büyük Menderes in them. The fact that there is a dam on this river and canals to use the river water for irrigation throughout the region is important because conducive environment for thriving is provided for vectors such as gnats. However, the *B.henselae* seroprevalence is not high among those who reported exposure to gnats ($p>0.05$; Table 6). In higher altitudes, the risk factor dropping and making an ecological restriction supports the vectoral transmission (Table 3). One finding of the current study is that people with exposure to ticks have high antibody levels ($p<0.05$; Table 6) and this is in line with the ecological restriction explanation.

Arthropod contact is reported to play a big role in *B.henselae* infections[24–28]. Different studies proposed that ticks are important vectors when it comes to *Bartonella* species' infecting humans and animals[24,25,27,28]. In this study, the amount of *B.henselae* antibodies was found to be statistically higher in people in contact with ticks (Estimated relative risk: 0.67; $p<0.02$). Studies conducted in Poland[24], Austria[26] and the US[28] proposed the infection via ticks as only one of the factors. In this study, statistical difference of contact with ticks was significant and this leads one to consider that it is necessary to assess the tick population in the rural areas of Denizli for *Bartonella spp*. isolation. Contact with ticks should be evaluated during bartonellosisprediagnosis.

There were no statistical differences in seropositivities of *B.henselae* between contact and bites of domesticated and wild animals ($p>0.05$; Table 6). Sun et al.[19] and Breitscwerdit et al.[26] have proposed that regular contact with domesticated and wild animals increase the *B.henselae* positivity percentages. In this study, there were no long periods of cat and dog contacts. Only short periods of contact outside of house have been indicated. In the rural areas of Denizli, dogs are raised as shepherd dogs and their contact with humans is limited to when their owners feed them. Cats are mostly raised outside in farms to catch mice in barns. Therefore, it was concluded that there were no long periods of contact in this study. Regional customs can be thought to have played a role in these contacts and affected the seropositivity.

As a result, the rural nature of the regions included in the study, the characteristics of common occupations, vector contacts, and region's geographical features indicate that encountering *B.henselae* is related to regional distribution. Acquiring epidemiological data from similar geographical areas of Türkiye will provide information about the up-to-date status of bartonellosis.

Conflict of Interest Statement

We declare that we have no conflict of interest.

Funding

This research was supported by Pamukkale University Scientific Research Projects with the number 2008TPF027.

References

1. Celebi B. Bartonella henselae and its infections. Mikrobiyol Bul. 2008;42:163–75.
2. Chmielewski T, Podsiadly E, Tylewska-Wierzbanowska S. Presence of Bartonella spp. in various human populations. Pol J Microbiol. 2007;56:33–8.
3. Portillo A, Maggi R, Oteo JA, Bradley J, Garcia-Alvarez L, San-Martin M, et al. Bartonella spp. prevalence (Serology, culture, and PCR) in sanitary workers in La Rioja Spain. Pathogens. 2020;9. DOI:10.3390/pathogens9030189.
4. Leibler JH, Zakhour CM, Gadhoke P, Gaeta JM. Zoonotic and vector-borne infections among urban homeless and marginalized people in the United States and Europe, 1990-2014. Vector Borne Zoonotic Dis. 2016;16:435–44. DOI:10.1089/vbz.2015.1863.
5. Maruyama S, Boonmar S, Morita Y, Sakai T, Tanaka S, Yamaguchi F, et al. Seroprevalence of Bartonella henselae and Toxoplasma gondii among healthy individuals in Thailand. J Vet Med Sci. 2000;62:635–7. DOI:10.1292/jvms.62.635.
6. Pandak N, Dakovic-Rode O, Cabraja I, Kristof Z, Kotarac S. Prevalence of Bartonella henselae antibodies in children and blood donors in Croatia. Infection. 2009;37:166–7. DOI:10.1007/s15010-008-8113-0.
7. Troncoso I, Fischer C, Arteaga F, Espinoza C, Azocar T, Abarca K. Seroprevalence of Bartonella henselae in occupational risk persons. Rev Chilena Infectol. 2016;33:355–7. DOI:10.4067/S0716-10182016000300019.

8. Zhang Y, Zhang ZL, Yin JY, Lv J, Yu HL, Liang CW, et al. Sero-epidemiological investigation on Rickettsia typhi, Bartonella henselae and Orientia tsutsugamushi in farmers from rural areas of Tianjin, 2007 - 2009. Zhonghua Liu Xing Bing Xue Za Zhi. 2011;32:2569.
9. Aydin N, Bulbul R, Telli M, Gultekin B. Seroprevalence of Bartonella henselae and Bartonella quintana in blood donors in Aydin province, Turkey. Mikrobiyol Bul. 2014;48:477–83.
10. Sayin-Kutlu S, Ergin C, Kutlu M, Akkaya Y, Akalin S. Bartonella henselae seroprevalence in cattle breeders and veterinarians in the rural areas of Aydin and Denizli, Turkey. Zoonoses Public Health. 2012;59:445–9. DOI:10.1111/j.1863-2378.2012.01486.x.
11. Ozturk MZ, Cetinkaya G, Aydin S. Climate types of Turkey according to Köppen-Geiger climate classification. J Geography. 2017;35:17–27. DOI:10.26650/JGEOG330955.
12. Regnery RL, Olson JG, Perkins BA, Bibb W. Serological response to "Rochalimaea henselae" antigen in suspected cat-scratch disease. Lancet. 1992;339:1443–5. DOI:10.1016/0140-6736(92)92032-b.
13. Jackson LA, Perkins BA, Wenger JD. Cat scratch disease in the United States: an analysis of three national databases. Am J Public Health. 1993;83:1707–11. DOI:10.2105/ajph.83.12.1707.
14. Yilmaz C, Ergin C, Kaleli I. Investigation of Bartonella henselae seroprevalence and related risk factors in blood donors admitted to Pamukkale University Blood Center. Mikrobiyol Bul. 2009;43:391–401.
15. Zhang L, Shan A, Mathew B, Yin J, Fu X, Zhang J, et al. Rickettsial seroepidemiology among farm workers, Tianjin, People's Republic of China. Emerg Infect Dis. 2008;14:938–40. DOI:10.3201/eid1406.071502.
16. Costa PS, Brigatte ME, Greco DB. Antibodies to Rickettsia rickettsii, Rickettsia typhi, Coxiella burnetii, Bartonella henselae, Bartonella quintana, and Ehrlichia chaffeensis among healthy population in Minas Gerais, Brazil. Mem Inst Oswaldo Cruz. 2005;100:853–59. DOI:10.1590/s0074-02762005000800006.
17. Kwon HY, Im JH, Lee SM, Baek JH, Durey A, Park SG, et al. The seroprevalence of Bartonella henselae in healthy adults in Korea. Korean J Intern Med. 2017;32:530–5. DOI:10.3904/kjim.2016.010.
18. Antoniou M, Economou I, Wang X, Psaroulaki A, Spyridaki I, Papadopoulos B, et al. Fourteen-year seroepidemiological study of zoonoses in a Greek village. Am J Trop Med Hyg. 2002;66:80–5. DOI:10.4269/ajtmh.2002.66.80.
19. Sun J, Fu G, Lin J, Song X, Lu L, Liu Q, et al. Seroprevalence of Bartonella in Eastern China and analysis of risk factors. BMC Infect Dis. 2010;10:121. DOI:10.1186/1471-2334-10-121.
20. Tea A, Alexiou-Daniel S, Arvanitidou M, Diza E, Antoniadis A. Occurrence of Bartonella henselae and Bartonella quintana in a healthy Greek population. Am J Trop Med Hyg. 2003;68:554–6. DOI:10.4269/ajtmh.2003.68.554.
21. Cimolai N, Benoit L, Hill A, Lyons C. Bartonella henselae infection in British Columbia: evidence for an endemic disease among humans. Can J Microbiol. 2000;46:908–12.
22. Juncker-Voss M, Prosl H, Lussy H, Enzenberg U, Auer H, Lassnig H, et al. Screening for antibodies against zoonotic agents among employees of the Zoological Garden of Vienna, Schonbrunn, Austria]. Berl Munch Tierarztl Wochenschr. 2004;117:404–9.
23. Pons I, Sanfeliu I, Cardenosa N, Nogueras MM, Font B, Segura F. Serological evidence of [[Bartonella henselae infection in healthy people in Catalonia, Spain. Epidemiol Infect. 2008;136:1712–6. DOI:10.1017/S0950268808000368.
24. Zajac V, Wojcik-Fatla A, Dutkiewicz J, Szymanska J. Bartonella henselae in eastern Poland: the relationship between tick infection rates and the serological response of individuals occupationally exposed to tick bites. J Vector Ecol. 2015;40:75–82. DOI:10.1111/jvec.12135.
25. Angelakis E, Billeter SA, Breitschwerdt EB, Chomel BB, Raoult D. Potential for tick-borne bartonelloses. Emerg Infect Dis. 2010;16:385–91. DOI:10.3201/eid1603.081685.
26. Breitschwerdt EB, Maggi RG, Duncan AW, Nicholson WL, Hegarty BC, Woods CWet all: Bartonella species in blood of immunocompetent persons with animal and arthropod contact. Emerg Infect Dis. 2007;13:938–41. DOI:10.3201/eid1306.061337.
27. Chang CC, Chomel BB, Kasten RW, Romano V, Tietze N. Molecular evidence of Bartonella spp. in questing adult Ixodes pacificus ticks in California. J Clin Microbiol. 2001;39:1221–6. DOI:10.1128/JCM.39.4.1221-1226.2001.
28. Muller A, Reiter M, Schotta AM, Stockinger H, Stanek G. Detection of Bartonella spp. in Ixodes ricinus ticks and Bartonella seroprevalence in human populations. Ticks Tick Borne Dis 2016;7:763-7. DOI:10.1016/j.ttbdis.2016.03.009.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Comparison of Serum Malondialdehyde and Paraoxonase-1 Levels in Patients with Epilepsy with and without Status Epilepticus

Status Epileptikusta Olan ve Olmayan Epilepsi Tanılı Hastalarda Serum Malondialdehit ve Paraoksonaz-1 Düzeylerinin Karşılaştırılması

Ahmet Dundar[1], Demet Arslan[2], Gulsume Celik Uysal[3], Ahmet Yilmaz[4]

[1]Mardin Artuklu University, Vocational School of Health Services, Department of Medical Services and Techniques, Mardin; [2]Department of Neurology, Private Memorial Hospital, Diyarbakir; [3]Department of Neurology, Gazi Yasargil Training and Research Hospital; [4]Dicle University Medical Faculty, Department of Family Medicine, Diyarbakir, Turkiye

ABSTRACT

Aim: *The underlying pathophysiological mechanisms in epilepsy are still not fully known. Paraoxonase (PON)-1 activity and malondialdehyde (MDA) levels are biomarkers used in the measurement of oxidative stress. Studies show that oxidative stress has a role in the pathophysiology of epilepsy. The aim of our study is to evaluate serum PON-1 activity and MDA levels in epilepsy patients with and without status epilepticus (SE).*

Materials and Method: *The subjects included in the study were established in two groups. Group I: The patient diagnosed with status epilepticus (n=30), group II: 30 adult patients with epilepsy who were in the outpatient policlinic follow-up and were not in status were included in the study. Serum MDA levels and PON-1 activity were measured by spectrophotometric method in the biochemistry laboratory.*

Results: *Serum MDA levels were found to be 86.8±32.4 nmol/mL in patients with SE and 65.8±15.7 nmol/mL in patients without SE. Serum PON-1 activity was 180.8±28.3 U/L in patients with SE and 170.2±25.0 U/L in patients without SE. When patients with SE and patients without SE were compared, serum MDA levels were found to be higher than patients without SE and statistically significant (p<0.001). There was no significant difference between the two patient groups in terms of PON-1 activity (p>0.05).*

Conclusion: *The results of our study indicate that the oxidant/antioxidant balance in the pathogenesis of status epilepticus has deteriorated in favor of oxidative stress and the antioxidant system cannot give an adequate response. Larger research should be conducted to evaluate the use of serum MDA levels as a biomarker*

Keywords: *status epilepticus; MDA; PON-1; antioxidant/oxidant status*

ÖZET

Amaç: *Epilepside altta yatan patofizyolojik mekanizmalar halen tam olarak bilinmemektedir. Paraoksonaz (PON)-1 aktivitesi ve malondialdehit (MDA) seviyeleri oksidatif stresin ölçümünde kullanılan biyomarkerlardır. Yapılan çalışmalar oksidatif stresin epilepsi fizyopatolojisinde rolü olduğunu göstermektedir. Çalışmamızın amacı, status epileptikusta (SE) olan ve olmayan epilepsi hastalarında serum PON-1 aktivitesi ve MDA düzeylerini araştırmaktır.*

Materyal ve Metot: *Çalışmaya alınan denekler iki gruba ayrıldı. Grup I: Status epileptikus tanısı alan hasta (n=30), grup II: Poliklinik takiplerine gelen erişkin yaş grubundaki statusta olmayan 30 epilepsi hastası çalışmaya dahil edildi. Serum MDA seviyeleri ve PON-1 aktivitesi biyokimya laboratuvarında spektrofotometrik yöntemle ölçüldü.*

Bulgular: *SE'ta olan hastalarda serum MDA seviyesi 86,8±32,4 nmol/mL SE'ta olmayan hastalarda ise serum MDA düzeyleri 65,8±15,7 nmol/mL olarak bulundu. Serum PON-1 aktivitesi SE'ta olan hastalarda 180,8±28,3 U/L SE'ta olmayan hastalarda ise 170,2±25,0 U/L olarak tespit edildi. SE'ta olan hastalar ile SE'ta olmayan hastalar karşılaştırıldığında serum MDA düzeylerinin SE'ta olmayan hastalara göre daha yükseldiği ve istatistiksel olarak anlamlı olduğu bulundu (p<0,001). PON-1 aktivitesi açısından iki hasta grubu arasında anlamlı fark bulunmadı (p>0,05).*

Sonuç: *Çalışmamızın sonuçları status epileptikus patogenezinde oksidan/antioksidan dengenin oksidatif stres lehine bozulduğunu ve antioksidan sistemin yeterli cevabı veremediğini işaret etmektedir. Bir biyomarker olarak serum MDA düzeylerinin kullanımını değerlendirmek için daha geniş çaplı araştırmalar yapılmalıdır*

Anahtar Kelimeler: *status epileptikus; MDA; PON-1; antioksidan/oksidan statü*

İletişim/Contact: *Ahmet Dündar, Mardin Artuklu University, Vocational School of Health Services, Department of Medical Services and Techniques, 47060, Mardin, Türkiye* • ***Tel:*** *0544 860 54 08* • ***E-mail:*** *ahmetdundar83@hotmail.com* •
Geliş/Received: *11.03.2022* • ***Kabul/Accepted:*** *09.01.2023*

ORCID: *Ahmet Dündar, 0000-0003-0527-189X* • *Demet Arslan, 0000-0001-6934-1397* • *Gülsüme Çelik Uysal, 0000-0001-7103-6770* • *Ahmet Yılmaz, 0000-0002-2648-2824*

Introduction

Epilepsy is a common neurological disease that affects more than 50 million people worldwide[1]. Status epilepticus (SE), which we can define as a prolonged epileptic seizure state, is one of the neurological emergencies with high morbidity and mortality[2]. It may result in permanent changes in normal brain functions and cognitive functions[3]. Studies have shown that excessive oxidative stress is involved in the physiopathology of SE[1]. Oxidative stress occurring during SE leads to lipid peroxidation, DNA damage, and cell death[4]. The role of oxidative stress in SE is examined through lipid peroxidation levels[5].

Malondialdehyde (MDA) is the end product of nonenzymatic oxidation of lipid peroxides and is used as a biomarker of oxidative stress in many diseases[6,7]. In addition, it is a by-product of prostaglandin and thromboxane biosynthesis[8]. The increase in free radicals also increases MDA production[7]. In addition to being a biomarker, this toxic molecule is potentially mutagenic and atherogenic[9]. Highly reactive MDA reacts with proteins and DNA and causes mutations by forming crosslinks[10].

Paraoxonase (PON)-1 is an enzyme mostly produced in the liver and found in the structure of high-density lipoprotein molecules in human serum[11]. This enzyme, called paraoxonase, also hydrolyzes homocysteine, as it provides the detoxification of toxic organophosphates such as paraoxone and diazinon[12]. It is a protective enzyme against lipid peroxidation[13]. Although there are three types of paraoxonase genes, PON-1, PON-2, and PON-3, the most studied of this family is PON-1. It shows its antioxidant properties mainly in blood circulation. It is known that PON-1 is both synthesized in the brain tissue and can cross the blood-brain barrier[14,15]. It is known that it loses its activity in the oxidative phase[16].

It has been shown that antiepileptic drugs partially disrupt the antioxidant system and therefore may initiate oxygen-related tissue injury by free radicals, especially in patients treated with valproic acid and carbamazepine[17]. In addition, it has been shown that long-term use of antiepileptic drugs may increase the formation of free radicals and cause oxidative damage in neurons[18,19]. Our aim is to evaluate serum MDA level and PON-1 activity in the physiopathology of epilepsy patients with and without SE.

Material and Methods

This study was confirmed by the Ethics Committee of Dicle University (Ethics committee approval no; 22.05.2017/126). The patients with epilepsy were assessed by two expert neurologists. The seizure typing of the patients included in the study was classified according to the criteria of International League Against Epilepsy (ILAE) 2017 seizure classifications[20]. Electroencephalography (EEG) and magnetic resonance imaging (MRI) the patients were taken.

Patients with pathological EEG findings were not included in the study. Patients with psychogenic seizures were not included in the study. This study was established two groups. Group I: The patient diagnosed with status epilepticus (n=30), group II: The epilepsy patient in the adult age group who was followed up in the outpatient clinic and not in status were included in the study (n=30). Acute and chronic infection, fever, diabetes mellitus, rheumatological diseases, anemia, kidney and thyroid dysfunction, mental retardation, hypertension, use of antioxidant agents, trauma, autoimmune disease, local and systemic inflammation were determined as the exclusion criteria of the study.

All participants in the study were informed about the study. It was conducted in line with the Declaration of Helsinki. Venous blood was drawn in the first 24 hours from the onset of status for biochemical analysis. In patients who were not in status, blood samples were taken into biochemistry tubes at any time and then kept in the laboratory for 15 minutes to facilitate coagulation. The blood samples were centrifuged at 5000 rpm for 10 minutes according to the study protocol and kept in a deep freezer at -80°C until analysis.

PON-1 and MDA Measurement Method

Serum PON-1 enzyme activity was analyzed by the Eckerson method using the commercial (Rel Assay Diagnostic, Gaziantep, Türkiye) kit according to the manufacturer's instructions with the Architect C16000 brand auto analyzer and the enzyme activity was expressed as U/L[21].

Serum MDA level was read by the Ohkawa method according to the manufacturer's instructions (Northwest MDA, Abcam, USA) using a commercial kit at 532 nm and absorbance was measured by spectrophotometric method[22].

Statistical Analysis

IBM Statistical Package for Social Sciences (SPSS) program version v. 17 statistical package program was conducted for calculations. The descriptive statistics were submitted as standard deviation, means, minimum and maximum values, while presented as numbers and percentages for categorical variables. The conformity of the data to the normal distribution was checked with Kolmogrov-Smirnov and Shapiro-Wilk tests. The categorical data using the Chi-Square test were compared. The 2-group Student-T test was used for parameters that were normally distributed, and the Mann-Whitney-U test was used to compare pairwise groups for parameters that were not normally distributed. The statistical significance level was taken as p-values less than 0.05.

The sample size was calculated by using the mean and standard deviation values of the pilot study with 10 patients (G*Power v3.1.9.4). For the MDA variable, 1.33 effect size was obtained, yielding 80% power, and it was seen that the minimum number of patients to be included in each group was 10. However, since PON-1 variable values have very high standard deviation, it was seen that it had a very small effect size value (0.01) and required a very high sample size. According to the central limit theorem[23], it is appropriate to include 30 patients in samples with non-parametric distribution (especially considering the budget). Therefore, it was decided to include 30 patients in each group.

Results

Sixty patients were enrolled in our study. The mean age of the patients who were not in SE was 24.5±6.7 (14 males and 16 females). It was observed that the mean age of patients with SE (17 females and 13 males) was 26.4±7.2. No statistically significant difference was found in the comparison of age and gender of patients with and without SE (p>0.05) Table 1.

The mean serum MDA levels of the patients without SE were 65.8±15.7 nmol/mL, and the serum MDA levels of the patients with SE were 86.8±32.4 nmol/mL. It was observed that the serum MDA level of the patients with SE was higher than the patients without SE and it was statistically significant (p<0.001). The mean serum PON-1 activity of patients without SE was found to be 180.8±28.3 U/L nmol/mL in patients with a mean serum PON-1 activity of 170.2±25.0 U/L. It was observed that serum PON-1 activity was increased in patients with SE compared to patients without SE, but it was not statistically significant (p>0.05) Table 2.

Discussion

Brain tissue is more sensitive to oxidation than other tissues due to its high content of oxidation-sensitive unsaturated fats and metals, high oxygen consumption, high metabolic rate, and fewer antioxidant mechanisms[24]. While the balance between the oxidant and antioxidant system was investigated in various

Table 1. *Demographic data of patient groups*

		Patients without status epilepticus (n=30)	Patients with status epilepticus (n=30)	p value
Gender [a]	Female	16 (53%)	17 (57%)	0.795
	Male	14 (47%)	13 (43%)	
Age (Years) [b]		24.5±6.7	26.4±7.2	0.095
High (cm) [c]		171.0 (160–181)	173.0 (164–184)	0.084
Weight (kg) [c]		66 (63–71)	67 (64–72)	0.940
BMI (Kg/m^2) [c]		26.0 (24,8–27,8)	26.5 (24,0–28,1)	0.210

Data are median (min-max) or mean ± SD (standard deviation). Statistical method: [a] Chi-Square Tests; [b] Student-T test; [c] Mann Whitney-U test. Gender: patients without status epilepticus female: 16(53%); male 14(47%); patients with status epilepticus female: 17(57%); male: 13(43%).

Table 2. *Serum MDA levels and PON-1 activities of patients with and without status epilepticus*

Parameters	Patients without status epilepticus	Patients with status epilepticus	p value
MDA (nmol/mL) [b]	65.8±15.7	86.8±32.4**	0.0002
PON-1 (U/L) [b]	180.8±28.3	170.2±25.0	0.779

Statistical method: [b] Student-T test. MDA data are shown as mean ± SD (standard deviation) and PON-1 data as mean ± SE (standard error). ** p<0.001. Significance between serum MDA levels of patients with and without status epilepticus. MDA: Malondialdehyde; PON-1: Paraoxonase-1.

neurological diseases in the 1990 s, these studies have also been carried out in epilepsy since the 2000 s[25].

In experimental epilepsy models, it has been shown that excessive free oxygen radical formation, an increase in lipid peroxidation and reduced glutathione levels during SE[24]. Free oxygen radicals, which are formed in small amounts during normal cell metabolism, are produced in large quantities during prolonged seizure activity and oxidative stress occurs when these formed free oxygen radicals exceed the antioxidant capacity. These formed free oxygen radicals interact with biological materials such as proteins, lipids, carbohydrates and nucleic acids in the cell. By interacting with lipids, it disrupts the physical properties of the cell membrane and indirectly the structural connection between cells, and causes damage and even neuron death by interacting with DNA[10,26]. Experimental epilepsy studies and some clinical studies have shown that the presence of neuronal damage and excessive oxidative stress plays a vital role in the pathophysiology of SE[2,27]. In different studies, it has been found that the oxidant-antioxidant system balance is impaired and PON-1 activity levels decrease in case of increased oxidative stress[28]. Serum PON-1 levels were evaluated in some neuropsychiatric diseases. In particular, PON-1 activity decreases in the pathophysiology of of dementia, stroke, Alzheimer's and Parkinson's[13,29]. Studies have shown that there is a decrease in the functions of antioxidant systems during SE. This decrease results in an increase in lipid peroxidation and the level of free oxygen radicals[19]. In the study conducted by Dönmezdil et al.[30] no significant difference was found between PON-1 levels between newly diagnosed epilepsy patients and the control group. PON-1 level was found to be lower in epilepsy patients, but it was not statistically significant. In another study, serum PON-1 level measured in the interictal period in epilepsy patients was found to be low[31]. In our study, it was found that PON-1 activity in patients with SE was lower than in patients without SE, but it was not found statistically significant.

It has been reported that MDA, the end product of lipid peroxidation, which is a biomarker of oxidative stress, may be an indicator of the production of free oxygen radicals[32]. Related studies have been conducted on MDA levels in many different neurological diseases. It has been shown that MDA plays an important role in the pathophysiology of diseases such as migraine, multiple sclerosis, and stroke[33–35]. Different results were obtained in different studies on epilepsy patients and serum MDA levels[30,31]. Verotti et al.[36] showed that MDA level was high in pediatric epilepsy patients who received valproic acid treatment for one year. Tong et al.[37] reported that the MDA concentration was significantly higher on the 14th day of rats given valproic acid. Hamed et al.[38] reported that serum MDA concentration was higher in epilepsy patients treated with phenytoin. Das et al.[39] demonstrated that MDA level was higher in epilepsy patients compared to the control group.

Menon et al.[40] demonstrated that oxidative stress was not different in treated and untreated epilepsy patients. Pandey et al.[41] reported that MDA concentration was higher in epilepsy patients receiving carbamazepine treatment. However, they reported a decrease in oxidative stress in those receiving antiepileptic therapy for one year. They have shown that this situation can be achieved with adequate antiepileptic therapy. It has been reported that oxidative stress is reduced due to the fact that antiepileptic drugs such as carbamazepine can have antioxidant effects[42].

This study has several limitations. One of the limitations of our study is that the control group was not included in the study. Another limitation of our study is that epilepsy type, duration of disease, medications used and seizure frequency were not followed up in epilepsy patients.

In our study, although there was a significant increase in MDA level, which is a biomarker of oxidative stress, between epilepsy patients with and without SE, no significant increase was found in PON-1 activity, which is a part of the antioxidant system responsible for preventing lipid peroxidation. This result makes us think that the oxidant/antioxidant balance has deteriorated in favor of oxidative stress in the pathogenesis of SE and the antioxidant system cannot give an adequate response.

Conclusion

It was observed that serum MDA level was increased and statistically significant in SE patients receiving antiepileptic therapy, and there was no significant difference in PON-1 activity. The results of our study indicate that while conventional treatments used in the treatment of SE are effective in stopping seizure activity, they may cause neuronal damage by increasing oxidative damage.

It shows that neuronal loss can be minimized by adding antioxidant treatments to these treatments. Therefore, studies on oxidant damage and antioxidant activity in SE will contribute to the development of new drugs that will have a positive effect on morbidity and mortality by minimizing oxidant damage.

Conflict of Interest

The authors report no declarations of interest.

This study was presented as an oral presentation at the INESEC IHSC 2020 congress on 15/10/2020.

References

1. Abdel-Salam OME, Sleem AA, Sayed MAEBM, Youness ER, Shaffie N. Capsaicin exerts anti-convulsant and neuroprotective effects in pentylene tetrazole-induced seizures. Neurochem Res. 2020; 45(5):1045–1061.
2. Lin TK, Chen SD, Lin KJ, Chuang YC. Seizure-induced oxidative stress in status epilepticus: is antioxidant beneficial? Antioxidants (Basel). 2020; 9(11):1029.
3. Santos LF, Freitas RL, Xavier SM, Saldanha GB, Freitas RM. Neuroprotective actions of vitamin C related to decreased lipid peroxidation and increased catalase activity in adult rats after pilocarpine-induced seizures. Pharmacol Biochem Behav. 2008; 89(1):1–5.
4. Shekh-Ahmad T, Kovac S, Abramov AY, Walker MC. Reactive oxygen species in status epilepticus. Epilepsy Behav. 2019; 101(Pt B):106410.
5. Freitas RM, Vasconcelos SM, Souza FC, Viana GS, Fonteles MM. Oxidative stress in the hippocampus after pilocarpine-induced status epilepticus in Wistar rats. FEBS J. 2005; 272(6):1307–12.
6. Abuja PM, Albertini R. Methods for monitoring oxidative stress, lipid peroxidation and oxidation resistance of lipoproteins. Clin Chim Acta. 2001; 306(1-2):1–17.
7. Gawel SH, Davis GJ, Luo M, Deutz NEP, Wolfe RR, Pereira SL. Serum biomarkers that predict lean mass loss over bed rest in older adults: An exploratory study. Clin Chim Acta. 2020; 509:72–78.
8. Lyon FR. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide international agency for research on cancer. IARC Monogr Eval Carcinog Risks Hum. 1999; 71 Pt 1(PT 1):1–315.
9. Del Rio D, Stewart AJ, Pellegrini N. A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. Nutr Metab Cardiovasc Dis. 2005; 15(4):316–28.
10. Gaschler MM, Stockwell BR. Lipid peroxidation in cell death. Biochem Biophys Res Commun. 2017; 482(3):419–425.
11. Altınkaynak Y, Örem A, Altınkaynak BA, Kural B, Balaban Yücesan F, Örem C. Investigation of serum paraoxonase 1 (PON1) activity in postprandial lipemia. Acta Med Alanya. 2018; 3(1):3–11.
12. Nguyen SD, Sok DE. Preferential inhibition of paraoxonase activity of human paraoxonase 1 by negatively charged lipids. J Lipid Res. 2004; 45(12):2211–20.
13. Bednarz-Misa I, Berdowska I, Zboch M, Misiak B, Zieliński B, Płaczkowska S, et al. Paraoxonase 1 decline and lipid peroxidation rise reflect a degree of brain atrophy and vascular impairment in dementia. Adv Clin Exp Med. 2020; 29(1):71–78.
14. Saeidi M, Shakeri R, Marjani A, Khajeniazi S. Alzheimer's disease and paraoxonase 1 (pon1) gene polymorphisms. Open Biochem J. 2017; 11:47–55.
15. Boado RJ, Zhang Y, Zhang Y, Wang Y, Pardridge WM. IgG-paraoxonase-1 fusion protein for targeted drug delivery across the human blood-brain barrier. Mol Pharm. 2008; 5(6):1037–43.
16. Nguyen SD, Sok DE. Oxidative inactivation of paraoxonase 1, an antioxidant protein and its effect on antioxidant action. Free Radic Res. 2003; 37(12):1319–30.
17. Karikas GA, Schulpis KH, Bartzeliotou A, Regoutas S, Thanopoulou C, Papaevangelou V, et al. Early effects of sodium valproate monotherapy on serum paraoxonase/arylesterase activities. Scand J Clin Lab Invest. 2009; 69(1):31–5.
18. Yüksel A, Cengiz M, Seven M, Ulutin T. Erythrocyte glutathione, glutathione peroxidase, superoxide dismutase and serum lipid peroxidation in epileptic children with valproate and carbamazepine monotherapy. J Basic Clin Physiol Pharmacol. 2000; 11(1):73–81.
19. Yüksel A, Cengiz M, Seven M, Ulutin T. Changes in the antioxidant system in epileptic children receiving antiepileptic drugs: two-year prospective studies. J Child Neurol. 2001; 16(8):603–6.
20. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international league against epilepsy: Position paper of the ILAE commission for classification and terminology. Epilepsia. 2017; 58(4):522–530.
21. Eckerson HW, Wyte CM, La Du BN. The human serum paraoxonase/arylesterase polymorphism. Am J Hum Genet. 1983; 35(6):1126–38.
22. Eckerson HW, Romson J, Wyte C, La Du BN. The human paraoxonase polymorphism: identification of phenotypes by their response to salts. Am J Hum Genet. 1983; 35(2):214–27.
23. Islam MR. Sample size and its role in central limit theorem (CLT). Computational and Applied Mathematics Journal. 2018; 4(1):1–7.
24. Freitas RM. Investigation of oxidative stress involvement in hippocampus in epilepsy model induced by pilocarpine. Neurosci Lett. 2009; 462(3):225–9.
25. Carmona-Aparicio L, Zavala-Tecuapetla C, González-Trujano ME, Sampieri AI, Montesinos-Correa H, Granados-Rojas L, et al. Status epilepticus: Using antioxidant agents as alternative therapies. Exp Ther Med. 2016; 12(4):1957–1962.
26. Ramaekers VT, Bosman B, Jansen GA, Wanders RJ. Increased plasma malondialdehyde associated with cerebellar structural defects. Arch Dis Child. 1997; 77(3):231–4.
27. Alachkar A, Azimullah S, Ojha SK, Beiram R, Łażewska D, Kieć-Kononowicz K, et al. The neuroprotective effects of histamine h3 receptor antagonist e177 on pilocarpine-induced status epilepticus in rats. Molecules. 2019; 24(22):4106.

28. Garin MC, Kalix B, Morabia A, James RW. Small, dense lipoprotein particles and reduced paraoxonase-1 in patients with the metabolic syndrome. J Clin Endocrinol Metab. 2005; 90(4):2264–9.
29. Shunmoogam N, Naidoo P, Chilton R. Paraoxonase (PON)-1: A brief overview on genetics, structure, polymorphisms and clinical relevance. Vasc Health Risk Manag. 2018; 14:137–143.
30. Dönmezdil N, Çevik MU, Özdemir HH, Taşin M. Investigation of PON-1 activity and MDA levels in patients with epilepsy not receiving antiepileptic treatment. Neuropsychiatr Dis Treat. 2016; 12:1013–7.
31. Çevik MU, Varol S, Yücel Y, Akıl E, Çelepkolu T, Arıkanoğlu A, et al. Epilepsili hastalarda serum paraoksonaz-1 aktivitesi ve malondialdehit düzeyleri. Dicle Tıp Dergisi. 2012; 39 (4):557–560.
32. Marrocco I, Altieri F, Peluso I. Measurement and clinical significance of biomarkers of oxidative stress in humans.Oxid Med Cell Longev. 2017; 2017:6501046.
33. Togha M, Razeghi Jahromi S, Ghorbani Z, Ghaemi A, Rafiee P. An investigation of oxidant/antioxidant balance in patients with migraine: a case-control study. BMC Neurol. 2019; 19(1):323.
34. Schreibelt G, van Horssen J, van Rossum S, Dijkstra CD, Drukarch B, de Vries HE. Therapeutic potential and biological role of endogenous antioxidant enzymes in multiple sclerosis pathology. Brain Res Rev. 2007; (2):322–30.
35. Menon B, Ramalingam K, Kumar R. Evaluating the role of oxidative stress in acute ischemic stroke. J Neurosci Rural Pract. 2020; 11(1):156–159.
36. Verrotti A, Scardapane A, Franzoni E, Manco R, Chiarelli F. Increased oxidative stress in epileptic children treated with valproic acid. Epilepsy Res. 2008; 78(2-3):171–7.
37. Tong V, Teng XW, Chang TK, Abbott FS. Valproic acid I. time course of lipid peroxidation biomarkers, liver toxicity, and valproic acid metabolite levels in rats. Toxicol Sci. 2005; 86(2):427–435.
38. Hamed SA, Abdellah MM. Trace elements and electrolytes homeostasis and their relation to antioxidant enzyme activity in brain hyperexcitability of epileptic patients. Journal of Pharmacological Sciences. 2004; 96(4):349–59.
39. Das A, Sarwar MS, Hossain MS, Karmakar P, Islam MS, Hussain ME, et al. Elevated serum lipid peroxidation and reduced vitamin C and trace element concentrations are correlated with epilepsy. Clin EEG Neurosci. 2019; 50(1):63–72.
40. Menon B, Ramalingam K, Kumar RV. Oxidative stress in patients with epilepsy is independent of antiepileptic drugs. Seizure. 2012; 21(10):780–4.
41. Pandey MK, Mittra P, Maheshwari PK. The lipid peroxidation product as a marker of oxidative stress in epilepsy. J Clin Diagn Res. 2012; 6(4):590–92.
42. Wojciech S, Elzbieta S, Wojciech K. Evaluation of the influence of the antiepileptic therapy on the antioxidant enzyme activity and the lipid peroxidation in the erythrocytes of children with epilepsy. J Child Neurol. 2006; 21(7):558–62.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Analysis of Diagnosis Changes in Patients Followed Up by the Child and Adolescent Psychiatry Clinic in a State Hospital

Bir Devlet Hastanesinin Çocuk ve Genç Psikiyatri Kliniğinde Takipli Hastalarda Tanı Değişimlerinin İncelenmesi

Mutlu Muhammed Ozbek[1], Remzi Ogulcan Ciray[2], Ugur Eray[3], Cagatay Ermis[4], Doga Sevincok[5]

[1]Kars Harakani State Hospital, Department of Child and Adolescent Psychiatry, Kars; [2]Mardin State Hospital, Department of Child and Adolescent Psychiatry, Mardin; [3]Kars Harakani State Hospital Department of Psychiatry, Kars; [4]Diyarbakir Children's Hospital, Department of Child and Adolescent Psychiatry, Diyarbakir; [5]Istanbul Traning and Research Hospital, Department of Child and Adolescent Psychiatry, Istanbul Turkiye

ABSTRACT

Aim: *It has been reported that many psychiatric disorders seen in childhood persist into adulthood as well. It is known that accurate diagnosis and early intervention can allow children to catch up with their normal development process and prevent other medical or psychiatric diseases in later developmental stages. Our study, through hospital records, aimed to explore the diagnostic changes in the young population during the initial diagnosis and follow-up processes. Considering the limited data about this subject, we aimed to contribute to the literature by exploring children with neurodevelopmental disorders.*

Material and Method: *The diagnosis and diagnosis change rates of the cases included in the study at the first examination and during the follow-up were analyzed using descriptive statistical analysis. Afterward, the cases were divided into two groups with and without neurodevelopmental disorders according to their diagnoses at the first admission. Later on, the chi-square test was used to compare diagnostic change rates. In this study, changes in the primary diagnoses of the patients were taken into account, and the changes in the secondary diagnoses were not considered diagnostic changes.*

Results: *The group of neurodevelopmental disorders was compared with Chi-Square Test in terms of the rates of diagnostic changes. It was found that other disorders' diagnosis change rates were significantly higher than neurodevelopmental disorders.*

Conclusion: *It was suggested that estimating the diagnostic stability and diagnosis change in the child and young population is crucial to determine the course of psychiatric disorders and the appropriate treatment options. In light of our results, neurodevelopmental disorders may be more stable in the follow-up process. Studies are needed to examine diagnostic changes to prevent inappropriate treatment approaches and harmful interventions in children and young people.*

Keywords: *neurodevelopmental disorders; autism; attention deficit disorder with hyperactivity*

ÖZET

Amaç: *Çocukluk döneminde görülen birçok psikiyatrik bozukluğun erişkinlik döneminde de devam ettiği bildirilmiştir1. Erken müdahaleler ve doğru tanının çocuğun normal gelişimini tamamlamasını ve ileride eşlik edebilecek tıbbi ve psikiyatrik hastalıkların önlenmesini sağlayabileceği bilinmektedir2. Çalışmamızda çocuk ve genç popülasyonda, ilk tanı ve takip sürecinde değişimlerin, hasta kayıtları üzerinden araştırılması ve bu konuda kısıtlı çalışma olan alan yazına katkıda bulunulması amaçlanmıştır.*

Materyal ve Metot: *Çalışmaya dahil edilen olguların, ilk başvuruda ve takip sürecinde aldığı tanı ve tanı değişim oranları tanımlayıcı istatistiksel yöntemler kullanılarak incelenmiştir. Sonrasında olgular, ilk başvuruda aldıkları tanılara göre, nörogelişimsel bozukluk tanısı alanlar ve almayanlar olmak üzere iki gruba ayrılarak, tanı değişim oranlarını karşılaştırabilmek için ki-kare testi kullanılarak karşılaştırılmıştır. Çalışmada hastaların birincil tanılarının değişimleri dikkate alınmış, ikincil tanıların değişimleri tanı değişimi olarak değerlendirilmemiştir.*

Bulgular: *Nörogelişimsel Bozukluklar (NGB); diğer bozuklukların ile tanı değişim oranları açısından Ki Kare Testi ile karşılaştırılmış, diğer bozuklukların nörogelişimsel bozukluklara göre tanı değişim oranlarının anlamlı olarak daha fazla olduğu saptanmıştır.*

Sonuç: *Çocuk ve genç popülasyonunda tanısal stabilite ve değişimin bilinmesinin, bozuklukların seyri ve bu seyre uygun tedavinin belirlenmesinde önemli olduğu düşünülmektedir. Çocuk ve gençlerde NGB tanılarının ortak özelliği olarak yaşam boyu devam edebilmesi nedeniyle diğer psikiyatrik tanılara göre, daha stabil seyirli olduğu, uzun süre takip gerektiği görülmektedir3. Çocuk ve gençlerde uygun olmayan tedavilerin ve zarar verebilecek müdahalelerin önüne geçmek için, tanısal değişimlerin incelenmesine yönelik çalışmalara ihtiyaç bulunmaktadır.*

Anahtar Kelimeler: *nörogelişimsel bozukluklar; otizm; dikkat eksikliği hiperaktivite bozukluğu*

İletişim/Contact: *Mutlu Muhammed Özbek, Department of Child and Adolescent Psychiatry, Kars State Hospital, Postcode: 36000, Kars, Turkiye* • ***Tel:*** *0553 389 9413* • ***E-mail:*** *mutluozbekk@hotmail.com* • ***Geliş/Received:*** *17.03.2022* • ***Kabul/Accepted:*** *10.01.2023*

ORCID: *Mutlu Muhammed Özbek, 0000-0002-0928-2820* • *Remzi Oğulcan Çıray, 0000-0003-2864-613X* • *Uğur Eray, 0000-0001-5417-3394* • *Çağatay Ermiş, 0000-0002-8412-8049* • *Doğa Sevinçok, 0000-0003-3138-6922*

Kafkas J Med Sci 2023; 13(1):24–31
doi: 10.5505/kjms.2023.68889

Introduction

Psychiatric disorders observed in children and adolescents may cause difficulties in the individual's life and their immediate surroundings in social, emotional, academic, and financial areas[1]. In a meta-analysis to identify the prevalence of psychiatric disorders in children and adolescents, covering data from more than 20 countries, the rate of psychiatric disorders in children and adolescents was 15.8%[2]. It has been reported that many psychiatric disorders in childhood persist in adolescence as well[3]. Another study said that the severity of psychiatric symptoms in early childhood predicts the severity of psychiatric symptoms in later periods[3]. Therefore, the early diagnosis and treatment of child and adolescent psychiatric disorders are particularly important. It has been reported that early interventions and accurate diagnoses can be helpful for the typical development of children and prevent medical and psychiatric conditions which may accompany other symptoms in the future[4].

In general, Neurodevelopmental Disorders (NDD) are a group of developmental problems that emerge with neurological and psychiatric symptoms that result from various factors during the development of the brain[5]. It is stated that the most common characteristic of these disorders may appear in a wide range, and the diagnosis covers neurological problems, birth anomalies, and behavior problems whose initial symptoms are seen in the early childhood period[6]. In addition, it is reported that psychiatric and other medical problems associated with NDD can cause problems in specific areas, such as learning and communication and affective-cognitive functions or social communication[7]. The most common neurodevelopmental disorders we come across in clinical practice are Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and Intellectual Disability (ID)[5].

Attention Deficit Hyperactivity Disorder is a neurodevelopmental disorder with symptoms of carelessness, impulsivity, and hyperactivity that are inconsistent with the developmental level and begin in the early childhood period[5]. Impulsivity, hyperactivity, behavioral and emotional domains are clinical symptoms that may appear commonly with ADHD and many other psychiatric disorders and have clinical similarities, especially with conduct disorder, oppositional defiant disorder, and elimination disorders that should be analyzed carefully[8]. When the literature was reviewed, it was seen that a study determined that at least one mental disorder at the rate of 73.7% and two or more mental disorders at the rate of 55.6% accompanied children and adolescents diagnosed with ADHD[9]. In the same research, it was reported that the most frequently seen diagnoses are, respectively, oppositional defiant disorder (43.6%), enuresis (21.1%), specific phobia (17.3%), social anxiety disorder (14.3%), and major depression (7.5%)[9]. In addition, it is reported that in the childhood period, MDD can progress differently compared to adults in the form of unrest, temper tantrums, hyperactivity, and attention problems and that anxiety disorders should be considered in the differential diagnosis of ADHD due to their symptoms such as fidgeting and not being able to gather attention[10]. In a study about the clinical course of ADHD, it was reported that in 60% of children and adolescents diagnosed with ADHD, symptoms persist in their adulthood, and 10% of their symptoms get worse[11]. In another study in which subjects diagnosed with ADHD were followed up for four years, it was concluded that 40% of the patients were still diagnosed[12].

Autism Spectrum Disorder is a neurodevelopmental disorder whose symptoms include inadequate verbal and non-verbal communication, repetitive behaviors, and interests. It is known that most children diagnosed with ASD are followed up with the same diagnosis in the forthcoming years. In a longitudinal study of children diagnosed with ASD, it was reported that only 1.5% of children with ASD had sufficient functionality in their later years[13]. Recent studies have reported that positive results are achieved through early diagnosis and new intervention programs in adaptive functions and the core symptoms of ASD[14–15]. Clinicians should consider cases that may be misdiagnosed as ASD and that in the differential diagnosis are reported as language impairments, ID, reactive attachment disorder, very early-onset schizophrenia, disorders accompanied by sight-hearing impairments, and selective mutism[16]. Thus, it is possible to change the diagnosis due to inadequate initial assessment.

Enuresis is defined as involuntary urinary incontinence, which can emerge due to numerous factors, repeats at least twice a week, and continues for at least three months[5]. In a study done in Türkiye, its frequency was found as 12.4%, decreasing with age[17]. In another study by Biederman et al., it was reported that enuresis and ADHD could be seen together at the rate of 30–45%[18]. Another study done with children diagnosed with enuresis found that they experienced

more attention and behavior problems after age ten compared to their peers and that their anxiety level was much higher[19].

It is reported in children and adolescent psychiatry clinics that one of the most frequent diagnoses is major depressive disorder (MDD), particularly in adolescents[20]. The prevalence of MDD has increased in recent years, and it can vary between 5 to 15.8% in the adolescence period[21–22].

Another clinical picture whose prevalence increases in adolescence, like MDD, is early-onset schizophrenia (EOS). It is reported that it can be seen much more in subjects with negative psychotic symptoms and affective blunting[23]. Additionally, many subjects diagnosed with EOS apply to clinics with non-specific prodromal symptoms[24]. It is stated that making an EOS diagnosis is difficult since its symptoms, such as behavior problems, social withdrawal, or unreasonable decrease in school performance, can be misdiagnosed as MDD[25].

Anxiety disorders (AD) are one of the most commonly seen psychiatric disorders, which generally begin in childhood and adolescence with a prevalence of 8–30%[25]. It has been reported that it can be seen more frequently in children diagnosed with NDD. Furthermore, given that some symptoms seen in ADHD, such as irritability or anger tantrums, can be mistaken for AD in the early period, ADHD should be considered in the differential diagnosis. In studies on AD and MDD, it has been stated that because of the underlying common genetic and psychosocial predisposition, these two psychiatric disorders can persist over time with frequent transformation into each other and that both disorders can be antecedents of each other in adolescence and early adulthood[26–27].

Child and adolescent psychiatry is very important in finding solutions for public health problems like mental disorders that emerge early in life. However, psychiatric conditions displaying many similar symptoms within the developmental process and emerging other comorbid psychiatric disorders, especially between NDDs, make the diagnostic process challenging. Thus, diagnostic changes and the development of additional comorbid conditions may take place during the follow-up periods. To avoid treatments that are not suitable and interventions that may be damaging for children and adolescents, there is a need for studies that analyze diagnostic changes. When the literature was reviewed, it was seen that there is limited data on changes in diagnosis in the follow-up periods in the area of child and adolescent psychiatry. Therefore, our study was planned to analyze the initial diagnoses and changes made in the follow-up period in the child and adolescent population through patient records.

Material and Methods

After the approval of the Ethics Committee of Kars Kafkas University, our study received approval from Kars Harakani State Hospital Chief Physician's Department. The study was conducted by retrospective scanning of electronic patient files containing the records of child and adolescent subjects whose follow-up has been done regularly for at least three years between January 2011 and December 2019.

Through the subjects' files, the subjects' age, gender, average follow-up time, initial diagnosis, comorbid diagnosis, diagnosis, and comorbid diagnosis changes throughout the follow-up period were analyzed. Subjects with insufficient data in the electronic patient files and subjects who have not come regularly for follow-up were excluded from the study. Subjects who had not been diagnosed or for whom follow-up was suggested with pre-diagnosis were also excluded from the study. Only subjects whose diagnosis has been finalized through clinical examination or semi-structured tests have been included in the study. Two evaluators evaluated and recorded the files as a blind review to analyze the data. Subjects whose treatments had been completed and files had been closed with full recovery were excluded from the study.

In the study, the changes in the patients' initial diagnosis were considered, and changes in their secondary diagnosis were not evaluated as diagnosis changes. If the initial diagnoses were not changed, the new diagnoses made were evaluated as comorbidity. The patient's follow-up duration was determined through literature reviews and in line with the average data in the literature.

Statistical Analysis

The study analyzed the rate of the subjects' diagnoses and diagnoses changes during their first evaluation and the follow-up period using descriptive statistics methods. Afterward, the subjects were separated into two groups, those diagnosed with and without neurodevelopmental disorders, and were compared with the Chi-Square Test to compare their rates of diagnosis change.

The IBM Statistical Package for Social Sciences (SPSS) program version 24 was used for the analysis.

Results

In this study, the age, initial diagnosis, and changes in diagnosis within the process and comorbid diagnosis of 48 subjects who fulfilled all of the inclusion-exclusion criteria out of 92 subjects and whose follow-up has been done regularly for at least three years in the child psychiatry outpatient clinic were analyzed retrospectively using their recorded files and the age, gender, initial diagnosis, new diagnoses, follow-up duration and diagnosis change duration of the patients were recorded. In our study, it was determined that the average age of the subjects was 14.37 (±2.73), the average follow-up duration was 5.83 years (±2.20), and 64.6% of the subjects were male (Table 1). When the subjects were analyzed according to their initial diagnosis, it was seen that the highest rate of diagnosis was ADHD (52.1%) and this was followed by Intellectual Disability (10.4%), Specific Learning Disorder (8%.4), and Anxiety Disorders (8.4%) (Table 2). When the subjects were analyzed in terms of diagnosis change during follow-up, it was seen that the initial diagnosis of 22.9% of the subjects changed, changes have been made during follow-up in 12% of the ADHD patients

Table 1. *Average age and sex rates of the sample*

Variable	Average	Standard deviation
Age	14.37	2.73
Average follow-up duration	5.83	2.20
Sex	N	%
Male	31	64.6
Female	17	35.4

Table 2. *Rates of the initial diagnoses of the subjects in their first examination and follow-up period*

	First consultation	
Diagnoses	N	%
ADHD	25	52.1
Growth retardation/mental incompetence	5	10.4
Specific learning disability	4	8.4
Anxiety disorder	4	8.4
Enuresis/encopresis	3	6.3
Autism spectrum disorder	2	4.2
Major depression	2	4.2
Conduct disorder	1	2.1
Schizophrenia	1	2.1
Bipolar disorder	1	2.1
Obsessive compulsive disorder	0	0

* Diagnosis change or comorbidity did not take place in 52.1% of the subjects.

Table 3. *Diagnosis change rates according to the initial diagnoses and new diagnoses of the subjects*

	Change rate*				
Initial diagnoses	N	%**	New diagnoses	N	%***
ADHD (n=25)	3	12.0	Major depression	2	66.6
			Anxiety disorder	1	33.3
Growth retardation/Mental incapacity (n=5)	0	0	-	-	-
Specific learning disability (n=4)	0	0	-	-	-
Anxiety disorder (n=4)	2	50.0	ADHD	1	50
			Major depression	1	50
Enuresis/Encopresis (n=3)	3	100	ADHD	3	100
Autism spectrum disorder (n=2)	0	0	-	-	-
Major depression (n=2)	2	100	Schizophrenia	2	100
Conduct disorder (n=1)	1	100	ADHD	1	100
Schizophrenia (n=1)	0	0	-	-	-
Bipolar disorder (n=1)	0	0	-	-	-
Obsessive compulsive disorder (n=0)	0	0	-	-	-
Whole sample	11	22.9			

* Average diagnosis change time: 1.18 years (±1.81).
** Shows the rate of change in the subjects' initial diagnoses.
*** Shows the rate of new diagnoses in subjects whose initial diagnoses were changed.

Table 4. *Comparison of neurodevelopmental disorders and other disorders in terms of diagnosis change*

	Diagnosis change			
Initial diagnoses	Yes	No	X^2	p
Neurodevelopmental disorders	3	33	17.337	0.000
Other disorders	8	4		
Total	11	37		

* Chi-Square Test.

(n=3), and that these subjects were diagnosed with MDD (n=2) and AD (n=1) (Table 3). It was found that the patients whose initial diagnoses have been ID, SLD, or ASD have not changed during the follow-up period (Table 3). In addition, Neurodevelopmental Disorders, which include ADHD, ASD, ID, and SLD groups, were compared with the Chi-Square Test in terms of the rates of other disorders and diagnosis change. It was found that other disorders' diagnosis change rates were significantly higher compared to neurodevelopmental disorders ($p<0.001$) (Table 4).

Discussion

The diagnostic stability of psychiatric disorders during the follow-up period presents important information in estimating the course and prognosis of a particular disorder. It also provides treatment-based evidence[28].

Our study aimed to analyze the initial diagnoses and diagnostic changes in the follow-up period of the child and adolescent population over patient records and contribute to the literature in which there is a limited amount of studies in this area.

Attention deficit hyperactivity disorder is one of the most frequent psychiatric disorders seen in the childhood period[29]. When the initial diagnoses of children and adolescents included in our study were analyzed, ADHD was the most frequent clinical diagnosis (52.1%), in line with the literature. It was seen that while 22 (88%) of the 25 patients diagnosed with ADHD continued to be diagnosed with ADHD in their follow-up period, 3 (12%) patients' diagnoses changed. This finding was in line with the fact that ADHD symptoms begin during childhood and that it is a disorder that persists into adolescence (60–80%) and adulthood (40–60%)[30]. In studies that children diagnosed with ADHD were followed long-term, it is reported that the rate of comorbid psychiatric diagnoses increases over time, and there is a risk of experiencing more problems in social, academic, and work areas[31–32]. In another study in which ADHD patients were followed, it was shown that the group which was regularly followed up and treated experienced fewer social, academic, and work problems in their adulthood[33]. Although ADHD is a disorder that can last throughout life and follow a chronic course, it is considered that long-term follow-up and treatment of the patients are important since one of the most important factors determining the prognosis is an accurate diagnosis, efficient treatment, and follow-up.

It has been stated that although hyperactivity symptoms decrease with age in some patients diagnosed with ADHD, difficulties such as organization problems and difficulty in focusing may be more permanent in future periods, and for this reason, even if the subjects are partially in remission between the ages of 12–20, substance abuse and mood disorders may accompany the clinical picture[34]. Our study found that 2 (8%) subjects diagnosed with ADHD were followed up with MDD diagnosis later on. Although clinical remission can be seen in ADHD symptoms, this finding is important considering the psychosocial burden in ADHD diagnosis may cause MDD in follow-up. In addition, some publications show that depressive symptoms can cause attention problems in children and thus may cause misdiagnosis as ADHD and SLD[35–36]. In light of these findings, it would be crucial to consider that MDD's phenomenology in children may be mistaken for symptoms of attention deficit.

In our study, we found that no diagnosis change in children and adolescents have been initially diagnosed with intellectual disability (n=5), autism spectrum disorder (n=2), and specific learning disorder (n=4) in the follow-up period, which covers a period of an average 5.83 years. In a study on the analysis of children who received ASD in the early period and research on ASD prognosis, it was reported that one of the most important prognostic factors is early diagnosis and intervention[37]. In another study that involved subjects aged 15–25 years with ASD diagnosis, one of the reasons for the late diagnosis of these subjects was that their language and cognitive development were close to the normal level[38]. It was also reported that ASD cases with verbal deficiency are diagnosed at earlier ages[39]. In our study, since verbal and non-verbal communication skills of children diagnosed with ASD were assessed only in clinical evaluations, it was considered that their rate of misdiagnosis might be lower compared to the

literature. A review that involved studies analyzing the reliability of diagnostic criteria concluded that early diagnosis of ASD was reliable, and the diagnostic criteria were useable[40]. In line with the literature, we found that ASD subjects (n=2) diagnosed at an early age continued to be diagnosed with ASD in their follow-up period. There is a need for longitudinal studies with wider samples on the reliability of ASD diagnosis.

Besides being one of the most frequently seen psychiatric disorders in the adolescent period, it is important to know that MDD's symptoms can be mistaken for EOS's symptoms. In EOS, there may be prodromal symptoms such as behavior problems, social withdrawal, decrease in academic performance, which begin insidiously weeks and months before the beginning of positive symptoms[41]. In our study, two subjects were diagnosed with MDD, and it was seen that both were diagnosed as EOS in their follow-up period. Besides the difficulty in making an accurate diagnosis in childhood and adolescence, it is considered that having information about other disorders that may cause similar clinical appearance is important since EOS symptoms are quite heterogeneous. A meta-analysis by Daz et al. found that the length of time without treatment is the most important factor that predicts remission. Due to the importance of the period without any treatment in EOS patients, follow-up of the subjects and their families with repeating visits may play a key role in early diagnosis and treatment.

Epidemiological studies on the diagnostic stability of anxiety disorders present contradictory results. In a study conducted by Cohen et al., which worked with adolescents with anxiety disorder, it was reported that diagnosis stability during a two-year observation period was at the medium level[42]. In another study by Biedel et al., which involved a shorter observation period and a smaller sample group, a similar result was achieved[43]. Four subjects in our study were initially diagnosed with AD; diagnosis change was observed in two in the follow-up period. This finding aligns with previous studies that report that anxiety disorders and depressive symptoms can follow a heterotypical course[44–45].

Thus, we suppose that anxiety disorders and depressive symptoms may be a precursor to each other. However, it is considered that further studies with wider samples are needed to understand the heterotypical course of AD and MDD.

In epidemiological studies on enuresis, it has been reported that while enuresis is seen in 15% of children aged 5, 5% of children aged 10, and 1% of children aged 15, spontaneous remission is seen in 15% of children diagnosed with enuresis within one year period[46]. Three of the subjects included in our study were diagnosed with enuresis, and it was seen that they were no longer diagnosed in their follow-up period. This finding is in line with the literature. In addition, it can be seen that all children followed up with enuresis diagnosis are later diagnosed with ADHD. In a study involving children diagnosed with enuresis, it was seen that these children were accompanied by ADHD diagnosis at a rate of 30–45%. Therefore, it is considered that the ADHD diagnosis of children included in our study, who were diagnosed with enuresis, during the follow-up period and after treatment/spontaneous remission, is caused by the high comorbidity rates between these two disorders. In addition, it was seen that it is necessary to analyze children diagnosed with enuresis in detail regarding ADHD comorbidity at the time of initial diagnosis and during their follow-up period.

There are various limitations in our study. Firstly, the sociodemographic and diagnostic information of the patients were obtained retrospectively by scanning their files. Since the data were analyzed retrospectively, the data of all patients could not be reached. Secondly, the cases whose data were obtained were evaluated cross-sectionally, and the average follow-up period was 5.83 years. Therefore, studies need to be conducted in which the diagnosis change rate is observed for a more extended period. Thirdly, the sub-groups of the patients' psychiatric illnesses could not be evaluated since the small sample size and the data were analyzed retrospectively. Fourthly, the sample size was small. Although this is due to applying strict inclusion-exclusion criteria, it may decrease reliability and statistical power. Despite the small sample size, the percentage distribution of the illnesses is close to that of the general population. Additionally, changes in diagnostic criteria between the years the study was carried out, the experience level of the physician who made the evaluation, a medication used during the follow-up period or before the follow-up period, and their effects on the symptoms and not including whether the subjects other psychiatric illnesses or not in the evaluation may be listed as the other limitations. As a result, it is considered that information about diagnostic stability and change in the child and adolescent population is important in identifying the course of the disorders and the treatment suitable for their course. Since NDD diagnoses in children and adolescents follow a more stable course compared to other psychiatric diagnoses, they

can continue throughout life as a common characteristic; it is considered that they need to be followed up for longer periods. It is also believed that in addition to the heterotypical course of AD and MDD, clinicians should keep EOS and MDD's common clinical symptoms in mind during the follow-up period. To prevent unsuitable treatments for children and adolescents and interventions that may cause damage, studies need to analyze diagnostic changes[47]. Advanced follow-up studies with large sample sizes will be important in predicting the transition between illnesses and differentiating diseases with common symptomology in the young population.

References

1. Compas BE, Connor-Smith J, Jaser SS. Temperament, stress reactivity, and coping: Implications for depression in childhood and adolescence. Journal of Clinical Child & Adolescent Psychology,. 2004;21–31.
2. Roberts RE, Attkisson CC, Rosenblatt A. Prevalence of psychopathology among children and adolescents. Am J Psychiatry. 1998; 155:715-25.
3. Kumpulainen K, Rasanen E, Henttonen I. The persistence of psychiatric deviance from the age of 8 to the age of 15 years. Soc Psychiatry Psychiatr Epidemiol. 2000; 35:5-11.
4. World Health Organization. Child and Adolescent Mental Health Policies and Plans. WHO Library Cataloguing-in-publication Data. Mental Health Policy and Services Guidance Package, 2005.
5. APA. Diagnostic and Statistical Manual of mental disorders, 5th edition. Washington: American Psychiatric Association, 2013.
6. Thapar A, Cooper M, Rutter M. Neurodevelopmental disorders., The Lancet Psychiatry. 2017;4(4):339–46.
7. Aksoy UM. Nörogelişimsel Bozukluklar: Bir Ağacın Farklı Dalları, İstanbul Kanuni sultan Süleyman Tıp Dergisi,. 2019;11(Ek sayı):1-4.
8. Pliszka SR, Carlson CL, Swanson JM. ADHD with comorbid disorders: Clinical assessment and management. ADHD with comorbid disorders: Clinical evaluation and management. 1999. 325-NaN, 325 p.
9. Hergüner S, Hergüner A. Dikkat eksikliği hiperaktivite bozukluğu olan çocuk ve ergenlerde eşlik eden psikiyatrik BOZUKLUKLAR. Noropsikiyatri Ars. 2012;49(2):114–8.
10. Öner P, Öner Ö, Aysev A. Dikkat Eksikliği Hiperaktive Bozukluğu, Ankara Üniversitesi Yayınları,. 2003;cilt 12: sayı 3-9.
11. Biederman J, Monuteaux MC, Mick E, Spencer T, Wilens TE, Silva JM, Snyder LE, et al. Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. Psychol Med, 2006, 36:167- 179.
12. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. Am J Psychiatry. 2000; 157:816-818.
13. Rutter M. Autistic children: infancy to adulthood, Seminars in Psychiatry, 1970, vol. 2, no. 4, pp. 435–450.
14. Lovaas O. Behavioral treatment and normal educational and intellectual functioning in young autistic children, Journal of Consulting and Clinical Psychology, 1987, vol. 55, no. 1, pp. 3–9,
15. Rogers S, Vismara A. Evidence-based comprehensive treatments for early autism. Journal of Clinical Child and Adolescent Psychology, 2008, vol. 37, no. 1, pp. 8–38,
16. Mukaddes NM, Tutkunkardas MD, Sari O, Aydin A, Kozanoglu P. Characteristics of Children Who Lost the Diagnosis of Autism: A Sample from Istanbul, Turkey. Hindawi Publishing Corporation Autism Research and Treatment, 2014, Article ID 472120, 1-10.
17. Gür E, Turhan P, Can G, Akkufl S, Sever L, Güzelöz S, et al. Enuresis: prevalence, risk factors and urinary pathology among school children in Istanbul. Turkey.Pediatr Int;. 2006; 46:58-63.
18. Biederman J, Santangelo SL, Faraone SV, Kiely K, Guite J, Mick E. Clinical correlates of enuresis in ADHD and non-ADHD children. J Child Psychol Psychiatry. 1995; 36(5):865- 877.
19. Fergusson DM, Horwood LJ. Nocturnal enuresis and behavioral problems in adolescence: a 15-year longitudinal study. Pediatrics. 1994; 94:662-668.
20. Eskin M, Ertekin K, Harlak H. Lise öğrencilerde ergenlerde depresyonun yaygınlığı ve ilişkili olduğu etmenler. DEUHYO ED 2013, 6 (2), 67-74.
21. Rey JM, Bella-Awusah TT, Liu J. Depression ın children and adolescents IACAPAP textbook of Child and Ad. Mental Health, 2012.
22. Lewandowski RE, Acri MC, Hoagwood KE. Evidence for the management of adolescent depression. Pediatrics. 2013;132(4):e996–e1009.
23. Green WH, Padron-Gayol M, Hardesty A. Schizophrenia with Childhood Onset A Phenomenological Study of 38 Cases. Journal of the American Academy of Child & Adolescent Psychiatry. 1992;31–5, 968-976.
24. Maria P, Lecce P, Toderello O, et al. Familial liability, obstetric complications and childhood development abnormalities in early onset schizophrenia: a case control study, BMC Psychiatry,. 2011;11–60, 67-84.
25. McClellan J, Saundra S. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Schizophrenia, Journal of the American Academy of Child & Adolescent Psychiatry, 2013, Volume 52, Issue 9, September 2013, Pages 976-990.
26. H U Wittchen, R C Kessler, H Pfister, M Lieb. Why do people with anxiety disorders become depressed? A prospective-longitudinal community study, Acta Psychiatr Scand Suppl. 2000;(406):14–23.

27. Maughan B, Collishaw S. Depression in childhood and adolescence, J Can Acad Child Adolesc Psychiatry 2013;22(1):35–40.
28. Mattanah JJ, Becker DF, Levy KN, Edell WS, McGlashan TH Diagnostic stability in adolescents followed up 2 years after hospitalization. Am J Psychiatry, 1995, 152:889–894.
29. Castellanos FX. Toward a pathophysiology of attention deficit hyperactivity disorder. Clin. Pediatrics. 1997; 381-393.
30. Plizska S, Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry, 2007;46(7):894–921.
31. Barkley RA, Murphy KR ve Fischer M. ADHD in Adults: What the Science Says. New York: Guilford Publications, 2008,
32. Rasmussen P, Gillberg C. Natural outcome of ADHD with developmental coordination disorder at age 22 years: A controlled, longitudinal, community-based study. Journal of the American Academy of Child and Adolescent Psychiatry,. 2001; 39, 1424-1431.
33. Wilens TE, Martelon M, Joshi G. Does ADHD predict substance-use disorders? A 10-year follow up study of young adults with ADHD. J Am Acad Child Adolesc Psychiatry;. 2011; 50(6):543-53.
34. Stringaris A, Baroni A, Haimm C, et al. Pediatric Bipolar Disorder Versus Severe Mood Dysregulation: Risk for Manic Episodes on Follow-Up. Journal of the American Academy of Child & Adolescent Psychiatry. 2010; 49(4):397–405.
35. Sciutto MJ, Eisenberg M. Evaluating the evidence for and against the overdiagnosis of ADHD. J Atten Disord. 2007;11:106–13.
36. Colbert P, Newman B, Ney P, Young J. Learning disabilities as a symptom of depression in children. J Learn Disabil. 1982;15(6):333–6.
37. Dawson G. Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. Dev Psychopathol. 2008; 20:775–803.
38. Aggareal S, Angus B, Misdiagnosis versus missed diagnosis: diagnosing autism spectrum disorder in adolescent, Australas Psychiatry 2015;23(2):120–3.
39. Fusar-Poli L, Brondino N, Politi Pierluigi, Aguglia E. Missed diagnosis and misdiagnosis of adults autism spectrum disorder. European Archives of Psychiatry and Clinical Neuroscience. 2020; 272, 187–198.
40. Young H, Saprenza M. Clinical characteristics and problems diagnosing autism spectrum disorder in girls. Archives de Pédiatrie August. 2018; 25-6, 399-403.
41. McClellan J, Stock S. Practice parameter for the assessment and treatment of children and adolescent with schizophrenia. J Am Acad Child Adolesc Psychiatry,. 2013;52:976–990.
42. Bögels SM, Alden L, Biedel DC. Social anxiety disorder: questions and answers for the DSM-V. Depress Anxiety,. 2010;27(2):168–189.
43. Biedel DC, Turner SM, Shy Children, Phobic Adults: Nature and Treatment of Social Phobia (2nd ed.). American Psychological Association. 2007; 978-1-59147-452-4, 1-398.
44. Caraballo JJ, Baca-Garcia E, Blanco C. Stability of childhood anxiety disorder diagnoses: a follow up naturalistic study in psychiatric care. Eur Chid Adolesc Psychiatyr,. 2010;19:395–403.
45. Moffit TE, Harrington H, Caspi. Depression and generalized anxiety disorder - cumulative and sequential comorbidity in birth cohort follow Ed prospectively to age 32. Archives of General Psychiatry,. 2007;64:651–666.
46. Ozden C, Ozdal OL, Altinova S. Prevalence and associated factors of enuresis in Turkish children. Int Braz J Urol. 2007;33:216–222.
47. Baca-Garcia E, Perez-Rodriguez MM, Basurte-Villamor I, Lopez-Castroman J, Fernandez Del Moral AL, Jimenez-Arriero MA, et al. Diagnostic stability and evolution of bipolar disorder in clinical practice:a prospective cohort study. Acta Psychiatr Scand, 2007;115:473–480.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of the Attitudes of Married Women Aged 15-49 Living in Kars/Digor District About Family Planning Before and After the Training

Kars/Digor İlçesinde Yaşayan 15–49 Yaş Evli Kadınların Aile Planlaması Hakkında Eğitim Öncesi ve Sonrası Tutumlarının Değerlendirilmesi

Nazli Akar[1], Sevda Elis Yildiz[1]

[1]Department of Midwifery, Faculty of Health Sciences, Kafkas University, Kars, Turkiye

ABSTRACT

Aim: *This study was conducted to determine the effect of the interactive training about family planning given to married women on family planning attitudes.*

Material and Method: *The study was quasi-experimental; the sample consisted of 60 women who met the sampling criteria. The Family Planning Attitude Scale was applied to the married women who agreed to participate in the study, with a questionnaire created by the researcher. After the pretest was applied to the women, educational material was created, interactive training was given, and posttest was applied. The IBM Statistical Package for Social Sciences (SPSS) program version package program was used to evaluate the data of the study.*

Results: *The scores of the women before the training are 47.40±11.98 as the sub-dimension regarding society, 40.57±8.80 as the sub-dimension regarding the method, 27.30±6.93 as the sub-dimension regarding pregnancy, and 115.27±24.46 as sub-dimension regarding total family planning attitude scale. The scores of the women in the posttest applied after the training; sub-dimension for society was 47.88±9.40, the sub-dimension 48.75±5.71 for method, 31.08±5.38 for pregnancy, and the total score for the family planning attitude scale was 127.72±17.07. The difference between the pretest and posttest mean scores of the women's total family planning attitude scale, contraceptive methods, and subscales related to pregnancy is statistically significant (p<0.05).*

Conclusion: *It was determined that the difference between the attitude towards pregnancy subscale according to the contraceptive use status of the women was significant. Women who use family planning methods have a higher attitude towards pregnancy. Women are thought to develop a positive attitude towards contraceptive use as their knowledge about contraceptive methods increases.*

Key words: *contraceptive; woman; midwife; attitude; interactive training*

ÖZET

Amaç: *Bu çalışma evli kadınların aile planlaması hakkında verilen interaktif eğitimin aile planlaması tutumu üzerine etkisini belirlemek amacıyla yapılmıştır.*

Materyal ve Metot: *Çalışma yarı deneysel olarak yapılmıştır ve çalışmanın örneklemini örneklem kriterlerini sağlayan 60 kadın oluşturdu. Çalışmaya katılmayı kabul eden evli kadınlara araştırmacı tarafından oluşturulan anket ile Aile Planlaması Tutum Ölçeği uygulandı. Kadınlara ön test uygulandıktan sonra eğitim materyali oluşturularak interaktif eğitim verilip daha sonra son test uygulanmıştır. Çalışmanın verilerinin değerlendirilmesinde IBM Sosyal Bilimlerde İstatistik Paket Programı (SPSS) paket programı kullanılmıştır.*

Bulgular: *Kadınların eğitim öncesi puanları topluma ilişkin alt boyut 47,40±11,98, yönteme ilişkin alt boyut 40,57±8,80, gebeliğe ilişkin alt boyut 27,30±6,93 ve toplam aile planlaması tutum ölçeğine ilişkin aldığı puan 115,27±24,46'dır. Eğitimden sonra uygulanan son teste kadınların aldıkları puanları; topluma yönelik alt boyut 47,88±9,40, yönteme ilişkin alt 48,75±5,71, gebeliğe ilişkin 31,08±5,38, aile planlaması tutum ölçeğine ilişkin aldığı toplam puan ise 127,72±17,07'dir. Kadınların toplam aile planlaması tutum ölçeği, kontraseptif yöntemlere ve gebeliğe ilişkin alt ölçeklerin ön test ve son test puan ortalamaları arasındaki fark istatistiksel bakımından anlamlıdır (p<0,05).*

Sonuç: *Kadınların kontraseptif kullanım durumuna göre gebeliğe ilişkin tutum alt ölçeği arasındaki farkın anlamlı olduğu tespit edilmiştir. Aile planlaması yöntemi kullanan kadınların gebeliğe yönelik tutumu daha yüksektir. Kadınların kontraseptif yöntemlerine yönelik bilgi seviyeleri arttıkça kontraseptif kullanımına yönünde pozitif tutum geliştirdikleri düşünülmektedir.*

Anahtar Kelimeler: *kontraseptif; kadın; ebe; tutum; interaktif eğitim*

İletişim/Contact: *Nazlı Akar, Kafkas University Faculty of Health Sciences Department of Midwifery, Kars 36000, Türkiye* • ***Tel:*** *0474 225 15 67* • ***E-mail:*** *nazakr80@gmail.com* • ***Geliş/Received:*** *15.04.2022* • ***Kabul/Accepted:*** *10.01.2023*

ORCID: *Nazlı Akar, 0000-0001-8310-1234 • Sevda Eliş Yıldız, 0000-0002-3585-6648*

Kafkas J Med Sci 2023; 13(1):32–38
doi: 10.5505/kjms.2023.39112

Introduction

Family planning (FP) is a phenomenon that allows spouses to have as many children as and when they want, or which aims to determine the number of children according to their personal wishes and economic possibilities and to enable them to realize the birth intervals as they wish[1,2]. Family planning and contraception, should not only be perceived as limiting the number of children[3,4]. From the moment that human beings learned that pregnancy is the result of sexuality, they have sought ways to prevent pregnancy, and therefore, family planning methods are as old as human history[3,5]. It is known that Arab people placed stones in the wombs of camels to prevent the camels from getting pregnant while crossing the desert. Muslim women used palm leaves, and Japanese women used bamboo paper as a method to prevent pregnancy[3,6,7].

One of the facts showing the health level of women is family planning[8,9]. The main purpose of Family Planning services is to protect mother and child health at the highest level, to give birth to healthy individuals, to ensure a planned pregnancy when the family/individual wants to have a child[10–12]. Methods to prevent pregnancy has an important place in preventive health services and when it is not used adequately, it creates problems related to society and health[13,14]. Thousands of children and women die every year due to lack of family planning[7,15]. This is to prevent unhealthy abortions, especially by preventing unwanted pregnancies and related complications. In order to prevent these problems, it is necessary to increase the appropriate use of family planning methods[13,16].

This attitude is a system that includes a behavioral tendency with cognitive and affective elements towards any particular object, mind or individual[17,25].

In order to learn the attitudes of individuals about contraceptive methods, it is necessary to look at their behavior, but individuals do not always transform these attitudes into behavior and although they do, they can hide their true attitudes[17]. As people's experiences and knowledge change, their attitudes change as well[18]. People learn attitudes through experience. Age factor is also effective in the formation of attitudes. As you get older, it becomes harder to change attitudes[19,20]. Once attitudes are gained, it is difficult to change[21].

Attitudes can be positive as well as negative. For example, not believing in, liking, or accepting an object or thought is a negative attitude. Or adopting, believing, accepting and loving any object or idea is a positive attitude[17,20].

According to Turkey Demographic and Health Survey (TNSA) 2018 data; the total fertility rate is 2.3. The age at first marriage for women is 21.4, the ideal number of children is 3.70% of the society uses family planning method and only 49% of those who use this method use modern methods. This rate is 34% in the Eastern Anatolia Region. While the use of traditional methods is 21% in Türkiye, it is 23% in the Eastern Anatolia Region, and the most used modern method is condom with 19%. The most used traditional method is retraction with 20%. 6 out of every hundred pregnant women have an induced abortion. Family planning is still considered an important health problem due to the lack of knowledge about family planning and its methods, insufficient positive attitude, low rate of using modern methods and undesired pregnancies due to these, and as a result, high maternal and infant morbidity and mortality rate[22].

Although there are studies on the reasons for not using contraceptive methods in our country, there are not enough studies examining FP attitudes of individuals before and after education on family planning. Therefore, there is a need for more studies on the attitudes of individuals in the selection of contraceptive methods.

The aim of this study is to determine the attitudes of married women between the ages of 15 and 49 towards family planning, to create educational material, and to reinforce their positive attitudes in the Digor district of Kars province in the Eastern Anatolia Region. It is to transform negative attitudes towards family planning into positive attitudes after education.

Material and Methods

Study Type and Location

This study was carried out semi-experimentally with women aged between 15 and 49 years of age, who were married in marital status, who were referred to the Community Health Center by the Kars Province Digor District Family Health Center.

Research Hypotheses

Hypothesis 0: The family planning education given does not change the attitude of women towards family planning.

Hypothesis 1: Family planning education given positively changes women's attitudes towards family planning.

Hypothesis 2: The training given, causes the family planning attitude to change in a negative way.

Population/Sample of the Study

The population of the research consists of 930 married women living in Digor district center between 2016–2017. The sample, on the other hand, consisted of 60 women living in this center who were randomly selected, married, between the ages of 15 and 49, who did not go through menopause and did not have communication problems.

Data Collection Tools

A personal information form consisting of 22 items, including socio-demographic characteristics and obstetric histories, developed in line with the literature review[14,19,23], and the Family Planning Attitude Scale (APTS), of which the validity and reliability was developed by Örsal, were used to determine attitudes towards family planning[24].

Personal Data Form

This part consists of a 22-item questionnaire, 14 of which are open-ended and 8 of which are closed-ended.

Family Planning Attitude Scale Form

The validity and reliability of this scale form was developed by Örsal and Kubilay (2006). Family Planning Attitute Scale consists of 34 items with 3 subscales. The first 15 items include the "Attitude towards Society" subscale, a total of 11 questions from the 16th to the 27th items include the "Attitude towards Methods" subscale, and a total of 8 items from the 28th to the last item include the "Attitude towards Pregnancy" subscale. Each item receives a minimum of 1 point and a maximum of 5 points.

The highest score in the total of the scale is 170 and the lowest score is 34.

The lowest score of the Attitude towards Society subdimension is 15, and the highest is 75.

The lowest score for the Attitude towards Methods Sub-Dimension is 11, and the highest is 55.

The lowest score of the Attitude Regarding Pregnancy Sub-Dimension is 8 and the highest is 40.

As the number of points increases, the reliability coefficient also increases. The Cronbach alpha reliability coefficient is 0.90.

Internal Validity of Scale

As seen in the table below, the Cronbach α coefficient of the attitude towards society subscale is 0.903, the Cronbach α coefficient of the attitude towards methods subscale is 0.851, the Cronbach α coefficient of the attitude towards pregnancy subscale is 0.840, and the Cronbach α coefficient of the total scale is 0.939.

Implementation of the Research

After obtaining the necessary permission from the Digor Community Health Center after obtaining the approval of the Ethics Committee of the Caucasus University Faculty of Medicine, Clinical Researches on Interventional Research for the study, after obtaining approval from married women between the ages of 15 and 49 who applied to the Digor Family Health Center and were referred to the Community Health Center, 13.01.2017-28.02. A questionnaire form was applied between 2017.

The questionnaire form applied to the women before the training and the family planning attitude scale and their performance levels were determined, and then a draft of the family planning education material was prepared.

In the evaluation of this application, an interactive training program was used and it was carried out with 2 groups of 30 people. A total of four hours of training was given to the first group on 02.03.2017, and the second group on 07.03.2017, two hours in the morning and in the afternoon. The information given within the scope of the training was reinforced by using demonstration, discussion, question-answer techniques. The content of the training includes the definition of health, female/male reproductive organs anatomy, the formation of pregnancy, contraceptive methods and the concept of attitude. Attitude levels towards family planning were evaluated with the Family Planning Attitude Scale, which was reapplied immediately after the training.

Research Ethics

Before the research was conducted, approval was obtained from the Non-Invasive Clinical Research Ethics Committee of the Faculty of Medicine of Kafkas University on 26/10/2016 with the decision number

20. Written permission was obtained from the institution and scale owner, where the study will be conducted, first via email and then on 21/10/2016. In addition, verbal consent was obtained from the women included in the study.

Data Assessment

The data were analyzed with the IBM Statistical Package for Social Sciences (SPSS) program. In analysis; Percentages, min-max values and mean, numbers, Will Coxon test, standard deviation, Paried t test, t test for independent groups, Kruskall Wallis, Analysis of Variance, Correlation and Mann Whitney-U were used to evaluate the data.

Results

As seen in Table 1, 93.3% of the participants are unemployed and 51.7% of their spouses are shopkeepers. 75% of the participants are not related to their spouse. 46.7% of women and 45% of their spouses are primary education graduates and 81.7% of them have health insurance.

The mean age of the participants was 36.08±8.64, the mean age at marriage was 16.57±9.92, and the mean age at marriage was 19.57±3.15 (Table 1).

The number of pregnancies of the participants was 3.87±2.78, the number of stillbirths was 0.35±0.63, the mean age at first pregnancy was 19.13±6.26, and the number of living children was 3.12±2.19. The mean number of Intentionally stillbirth was 0.23±0.67, the number of die stillbirths was 0.12±0.32, the ideal number of children was 3.48±1.24, and the interval between two pregnancies was 3.13±1.46 years. 2, 63.3% of the participants do not want pregnancy, 90% of them have normal birth as the last way of delivery and 70% of them use family planning method. The most used family planning method is the RIA with 28.3% (Table 2).

The pretest score of attitude towards society is 47.40±11.98, pretest score of attitude towards methods is 40.57±8.80, pretest score of attitude towards pregnancy is 27.30±6.93 and total scale pretest score is 115.27±24.46 (Table 3).

The attitude towards society posttest score is 47.88±9.40, the attitude towards methods posttest score is 48.75±5.71, the attitude towards pregnancy posttest score is 31.08±5.38, and the total scale posttest score is 127.72±17.07 (Table 4).

Table 1. *Distribution of demographic characteristics of the participants*

		n	%
Occupation	Not working	56	93.3
	Working	4	6.7
Spouse's occupation	Self employed	31	51.7
	Farmer	6	10.0
	Officer	19	31.7
	Driver	4	6.7
Kinship with spouse	Yes	15	25.0
	No	45	75.0
Income	Below 500 TL	5	8.3
	Between 501–1500 TL	23	38.3
	Between 1501 – 3000 TL	21	35.0
	Over 3000 TL	11	18.3
Education	Not literate	6	10.0
	Literate	5	8.3
	Primary school	28	46.7
	Middle school	7	11.7
	High school	8	13.3
	University	6	10.0
Spouse education	Literate	1	1.7
	Primary school	27	45.0
	Middle school	11	18.3
	High school	11	18.3
	University	10	16.7
Social security	Yes	49	81.7
	No	11	18.3
	N	Min-Max	Avr.	SS.
Age	60	19–49	36.08	8.64
Marriage age	60	14–30	19.57	3.15
Marriage duration	60	1–34	16.57	9.92

N/n: Number; SS: Standard Deviation; Avr: Average; Min: Minimum; Max: Maximum.

Pre-Test – Post-Test

The difference between the pre- and post-education mean scores of the attitude towards methods, attitude towards pregnancy subscales and total family planning attitude scale is statistically significant ($p<0.05$). After the training; Attitude towards contraceptive methods, sub-dimensions of attitude towards pregnancy and total score of family planning attitude scale were higher. In the attitude towards society sub-dimension, the difference between pre- and post-education measurement scores is statistically insignificant ($p>0.05$) (Table 5).

Table 2. *Distribution of family planning and obstetric characteristics of the participants*

		N	%
Desire for pregnancy	Yes	22	36.7
	No	38	63.3
Last pregnancy	Normal	54	90.0
	Abortion	4	6.7
	Natural stillbirth	2	3.3
Using family planning method	Using	42	70.0
	Not using	18	30.0
Used family planning method			
	Ria	17	28.3
	Pill	5	8.3
	Tubing	7	11.7
	Condom	8	13.3
	Retraction	5	8.3

	N	Min-Max	Avr.	SS.
Age of first pregnancy	60	0–33	19.13	6.26
Number of pregnancy	60	0–12	3.87	2.78
Number of living children	60	0–9	3.12	2.19
Natural stillbirth	60	0–2	0.35	0.63
Intentionally stillbirth	60	0–3	0.23	0.67
Number die births	60	0–1	0.12	0.32
Ideal number of children	60	1–8	3.48	1.24
Time between two pregnancy	60	1–7	3.13	1.46

N/n: Number; SS: Standard Deviation; Avr: Average; Min: Minimum; Max: Maximum; RIA: intrauterine vehicle.

Table 3. *Pre-test family planning attitude scale and distribution of scores they get from their sub-dimensions*

	N	Min-Max	Avr.	SS.
Attitude towards society	60	22–72	47.40	11.98
Attitude towards methods	60	16–55	40.57	8.80
Attitude towards pregnancy	60	14–40	27.30	6.93
Total scale	60	52–166	115.27	24.46

N: Number; SS: Standard Deviation; Avr: Average, Min: Minimum; Max: Maximum.

Table 4. *Post-test family planning attitude scale and distribution of scores from their sub-dimensions*

	N	Min-Max	Avr.	SS.
Attitude towards society	60	27–68	47.88	9.40
Attitude towards methods	60	36–55	48.75	5.71
Attitude towards pregnancy	60	18–40	31.08	5.38
Total scale	60	94–162	127.72	17.07

N: Number; SS: Standard Deviation; Avr: Average; Min: Minimum; Max: Maximum.

Table 5. *Comparison of participants' pre-test post-test family planning attitude scale and sub-dimension scores*

		n	Avr.	SS.	Significance
Attitude towards society	Pre-test score	60	47.40	11.98	t=-0.686* p=0.495
	Post test score	60	47.88	9.40	
Attitude towards methods	Pre-test score	60	40.57	8.80	t=-9.755** p=0.000
	Post test score	60	48.75	5.71	
Attitude towards pregnancy	Pre-test score	60	27.30	6.93	Z=-5.537** p=0.000
	Post test score	60	31.08	5.38	
Scale total	Pre-test score	60	115.27	24.46	t=-7.384* p=0.000
	Post test score	60	127.72	17.07	

* paired t test, ** Will coxon test; n: number; SS: Standard Deviation; Avr: average.

Discussion

The research was conducted to evaluate the attitudes of married women towards family planning before and after education.

The most commonly used contraceptive method by the participants is the intrauterine device with 28.3%. Akin et al. In 2006, in the study of women between the ages of 15 and 49 who were married in Konya province, 26.8% of the women stated that they were protected by an intrauterine device. Giliç et al. In their 2009 study in Niğde, they emphasized that 31.0% of women used intrauterine devices. According to the results of the study; It is thought that the reason why a significant portion of women prefer an intrauterine devices is that it does not require constant monitoring and reminders, and that it protects against long-term unwanted pregnancies[5,10].

Looking at Table 3, the total pre-test score of the scale was 115.27±24.46. Looking at Table 4, the total scale posttest score is 127.72±17.07. Apay et al.'s 2009 study found it to be 114.11±0.91. Looking at the results, it is seen that this is similar to the pre-test score of our study, but there is a significant difference with the post-test score. The reason for this is that it can be said that the training given has an effect on the family planning attitude of women[7].

As seen in Table 5, there was an important difference in the attitudes of women towards pregnancy and

methods of the Family Planning Attitude Scale before and after training, but no significant difference was observed in attitudes towards society. Based on results of this study, it is thought that training is beneficial and increases positive attitudes in women's attitudes about contraceptive methods and pregnancy, and turns negative attitudes into positive ones. It is thought that the reason why there is not much difference in the attitude towards society compared to the situation pre and post training may be due to the fact that it is not easy to give up the cultural differences and habitual social attitudes immediately.

Consequently of the study, when the sub-dimension of attitude towards methods is examined in Table 5, the average pre-test score is 40.57 and the post-test score is 48.75. In the 2009 study of Apay et al., the Attitude Towards Methods sub-dimension was 36.72[7]. It is expressed that the difference between them with the pre-test is due to the individual and cultural differences of the women, and the significant difference with the post-test is that the training given affects the attitudes of the women towards the method.

Conclusion and Suggestions

In the study, the total scores of married women's sub-dimensions regarding methods and pregnancy and family planning attitude scale after education were higher than before education.

It has been determined that the education given has a positive effect on their attitudes about family planning.

Individuals who apply to family planning services of midwives should be aware of their attitudes towards family planning and its methods and should organize training plans that can change their negative attitudes. Feedback is required, especially in individuals who apply for method-specific counseling.

Personnel providing Family Planning counseling should pay attention to the preparation of training programs by respecting and considering the socio-economic level, educational level, cultural differences and preferences of the individual.

Health services that can be lived in rural areas are inadequate and need to be designed appropriately, and these need to be repeated at certain intervals. It can be recommended to repeat the research in regions with different characteristics and to compare the obtained data with these results.

Acknowledgment

This study was produced in the master thesis of the 1st Author and presented as an oral presentation at the 1st International/5th National Sivas Midwifery Symposium held on 24-26 April 2018.

References

1. Çetişli NE, Top ED, Arkan G, Kaba F, Ertop F. Evli Kadınların Kullandıkları Aile Planlaması Yönteminin Cinsel Yaşam ve Benlik Saygısına Etkisi. Hemşirelikte Eğitim Ve Araştırma Dergisi. 2016;13 (2):101-06.
2. Öner C, Çatak B, Teletar B. Rahim içi araç (RİA) uygulaması için başvuranların bilgi düzeyleri. Türk Aile Hek Derg. 2014;18(1):31–34.
3. Taşkın L. (2016) Aile Planlaması/Gebeliğin Önlenmesi, Doğum ve Kadın Sağlığı Hemşireliği (genişletilmiş 13. bs.), Ankara Akademisyen Tıp Kitabevi, Ankara, Türkiye.
4. Coşkun AM (Ed). Kadın Sağlığı ve Hastalıkları Hemşireliği El Kitabı. Sf:356-395. İstanbul Mart 2012.
5. Akın B, Ege E, Erdem H. 15-49 yaş Evli Kadınlarda Vajinal Duş Uygulaması (VD) ve Olumsuz Etkileri. Uluslararası İnsan Bilimleri Dergisi. 2006; 3(2):1-16.
6. Altay B, Gönener D. Evli Erkeklerin Aile Planlaması Yöntemlerini Bilme ve Kullanma Durumları ve Etkileyen Faktörler. Fırat Tıp Dergisi. 2009; 14(1):56-64.
7. Apay SE, Nazik E, Özdemir F, Pasinlioğlu T. Kadınların Aile Planlamasına İlişkin Tutumların Değerlendirilmesi. Anadolu Hemşirelik ve Sağlık Bilimleri Dergisi,. 2010; 13(3):1-8.
8. Rehimli S, Ocakoğlu G, Sığırlı D, Büyükuysal MÇ. Türkiye ve OECD' ye Üye Ülkelerin Kadın Sağlığı Göstergeleri Bakımından Değerlendirilmesi. İnönü Üniversitesi Tıp Fakültesi Dergisi,. 2008; 15(4):261-266.
9. Kaya H, Tatlı H, Açık Y, Deveci SE. Bingöl İli Uydukent Sağlık Ocağı Bölgesindeki 15–49 Yaş Kadınların Aile Planlaması Yöntemi Kullanım Düzeyinin Belirlenmesi. Fırat Üniv. Sağlık Bilimleri Tıp Derg, 2008:22 (4):185–91.
10. Gılıç E, Ceyhan O, Özer A. Niğde Doğumevi'nde Doğum Yapan Kadınların Aile Planlaması Konusundaki Bilgi, Tutum ve Davranışları. Fırat Tıp Dergisi. 2009; 14(4):237-41.
11. Gür F, Sohbet R. Gaziantep İlinde El Beceri Kurslarına Gelen Kadınların Aile Planlamasına Yönelik, Bilgi Tutum ve Davranışları. Medical Sciences dergisi. 2017; 12(1):10-21.
12. Oltuluoğlu H, Başer M. Malatya İl Merkezinde Yaşayan Evli Kadınların Kullandıkları Aile Planlaması Yöntemleri ve Seçme Nedenlerinin İncelenmesi. İnönü Üniversitesi Tıp Fakültesi Dergisi,. 2012;19(3):167–74.
13. Çalışkan BG, Doğan B, Olçum GG. Kırsal Bölgede Yaşayan Kadınların Aile Planlaması Yöntemi Tercihlerine Yaş ve Eğitimin Etkisi. Türk Aile Hekimliği Dergisi. 2014; 18 (4):189-94.

14. Tanrıverdi G, Özkan A, Şenveli S. Çanakkale'deki Kadınların Aile Planlaması Yöntemlerini Tercih Nedenleri. Fırat Tıp Derg,. 2008; 13(3):251-254.
15. Kocaöz S, Peksoy S, Atabekoğlu CS. Kadınların Gebelikten Önce Kullandığı ve Doğum Sonrası Dönemde Kullanmayı Tercih Ettiği Kontraseptif Yöntemler. Balıkesir Sağlık Bil Dergisi,. 2013; 2 (1):2.
16. Giray H, Keskinoğlu P. Işıkkent Sağlık Ocağına Başvuran 15-49 Yaş Evli Kadınların Etkili Aile Planlaması Yöntemi Kullanımı ve Etkileyen Etmenler. Sted Derg.2006; 15(2):24.
17. Örsal Ö, Köşgeroğlu N. Aile Planlaması Tutumun Özellikleri, Oluşması ve Ölçülmesi. Aylık Aktüel Tıp Dergisi. 2007;19(10):86.
18. Diri FÜ. İstatistik Dersine Yönelik Tutumların Araştırılması Meslek Yüksek Okul Örneği. (Yüksek Lisans Tezi), Ankara: Gazi Üniversitesi, Fen Bilimleri Enstitüsü, İstatistik. 2007.
19. Çayan A. 15–49 Yaş Evli Kadınların Aile Planlaması Yöntemlerine İlişkin Tutumlarının Kullandıkları Kontraseptif Yöntemler İle İlişkisi. (Yüksek Lisans Tezi). Aydın: Adnan Menderes Üniversitesi, Sağlık Bilimleri Enstitüsü, Hemşirelik Bölümü, Türkiye. 2009.
20. Güllü M, Güçlü M. Ortaöğretim Öğrencileri İçin Beden Eğitimi Dersi Tutum Ölçeği Geliştirilmesi. Niğde Üniversitesi, Beden Eğitimi ve Spor Bilimleri Dergisi,. 2009; 3(2):139.
21. Örsal Ö. Ankara Belediye Sınırları İçinde Yaşayan Bireylerin Aile Planlamasına Yönelik Tutum Ölçeğinin Geliştirilmesi. (Doktora Tezi). Ankara: Hacettepe Üniversitesi, Sağlık Bilimleri Enstitüsü, Halk Sağlığı Hemşirelik Programı, Hemşirelik Bölümü. 2006.
22. Hacettepe Üniversitesi Nüfus Etütleri Enstitüsü. (2019). 2018 Türkiye Nüfus ve Sağlık Araştırması.
23. Eryılmaz E, Ege E. Doğum sonu dönemdeki kadınların aile planlaması konusundaki tutumları ve ilişkili faktörler. Journal of Human Sciences,. 2016;13(2):3389–3401.
24. Örsal Ö, Kubilay G. Aile Planlaması Tutum Ölçeğinin Geliştirilmesi. İstanbul Üniversitesi, Florence Nıghtıngale Hemşirelik Yüksekokulu Dergisi,. 2007;15(60):155–64.
25. Ayaz S, Efe ŞY. Family planning attitudes of women and affecting factors. J Turkish-German Gynecol Assoc. 2009; 10:137-41.
26. Hacettepe Üniversitesi Nüfus Etütleri Enstitüsü . "2018 Türkiye Nüfus ve Sağlık Araştırması". Hacettepe Üniversitesi Nüfus Etütleri Enstitüsü, T.C. Kalkınma Bakanlığı ve TÜBİTAK, Ankara, Türkiye 2019.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Cost-effectiveness of Clomiphene Citrate Against Gonadotropin Therapy in Women with Unexplained Infertility

Açıklanamayan İnfertilitesi Olan Kadınlarda Klomifen Sitratın Gonadotropin Tedavisine Karşı Maliyet Etkinliği

Meryem Kuru Pekcan[1], Nilufer Akgun[2], Hasan Ulubasoglu[1], Refik Ersin Eroglu[3], Yasemin Tasci[4]

[1]Department of Obstetrics and Gynecology, University of Health Sciences Ankara City Hospital, Ankara; [2]Department of Obstetrics and Gynecology, Ankara Training and Research Hospital, Ankara; [3]Department of Obstetrics and Gynecology, Kafkas University, Kars; [4]Department of Obstetrics and Gynecology, Kutahya University of Health Sciences, Kutahya, Turkiye

ABSTRACT

Aim: *Clomiphene citrate (CC) is the most frequently used agent for ovarian stimulation (OS). Gonadotropin (GND) treatment can be encouraged as a next step in women who are not able to become pregnant with CC. We aimed to determine the efficacy and cost-effectiveness of CC and GND in patients with unexplained infertility undergoing OS and intrauterine insemination.*

Material and Method: *The cost-effectiveness and success of CC and GND were retrospectively evaluated in 358 infertile women, of whom 247 received CC and 11 received GND treatment. The total CC/GND dose, endometrial thickness, semen parameters, duration of OS, follicle size, and pregnancy outcome were recorded. The medical costs of both strategies were analyzed, including the costs of medication and cycle monitoring. The cost of insemination was not evaluated since it was applied in both groups. The Shapiro-Wilk test, Student's t-test and Mann-Whitney U test were used for statistical analyses.*

Results: *There were no statistically significant differences between the groups in terms of cycle characteristics, semen analysis, total drug dose used, duration of OS, and dominant follicle size (p>0.05 for all). The pregnancy rate was 23.5% among the 264 (73.7%) patients with primary infertility and 17% among the 94 (26.3%) patients with secondary infertility. No significant difference was observed between the CC and GND groups with regard to the achieved pregnancy rate (21.1% vs. 23.4%, p=0.615). No side effect was observed. The cost of treatment for a couple with unexplained infertility was 1,716.42 TL for GND and 30.67 TL for CC.*

Conclusion: *The treatment success of OS with CC and GND seems to be similar in patients with unexplained infertility. Therefore, considering the cost-effectiveness and side effects of GND medication, the first choice should be CC in these patients.*

Keywords: *clinical pregnancy; clomiphene citrate; gonadotropin; ovulation induction; unexplained infertility*

ÖZET

Amaç: *Klomifen sitrat (CC), over stimülasyonu (OS) için en sık kullanılan ajandır. Klomifen sitrat ile gebe kalamayan kadınlarda gonadotropin (GND) tedavisi bir sonraki adım olarak teşvik edilebilir. Biz bu çalışmada açıklanamayan infertilitesi olan OS ve intrauterin inseminasyona giden hastalarda CC ve GND'nin etkisini ve maliyet etkinliğini belirlemeyi amaçladık.*

Materyal ve Metot: *CC ve GND'nin maliyet etkinliği ve başarısı, 247'si CC ve 11'i GND tedavisi alan 358 infertil kadında geriye dönük olarak değerlendirildi. Toplam CC/GND dozu, endometriyal kalınlık, semen parametreleri, OS süresi, folikül boyutu ve gebelik sonucu kaydedildi. İlaç maliyetleri ve döngü izleme dahil olmak üzere her iki stratejinin tıbbi maliyetleri analiz edildi. Her iki grupta da inseminasyon uygulandığı için onun maliyeti değerlendirilmemiştir. İstatistiksel analizler için Shapiro-Wilk testi, Student's t-testi ve Mann-Whitney U testi kullanıldı.*

Bulgular: *Siklus özellikleri, semen analizi, kullanılan toplam ilaç dozu, OS süresi ve dominant folikül boyutu açısından gruplar arasında istatistiksel olarak anlamlı fark yoktu (tümü için p>0,05). Primer infertilitesi olan 264 (%73,7) hastada gebelik oranı %23,5, sekonder infertilitesi olan 94 (%26,3) hastada ise %17 idi. Elde edilen gebelik oranı açısından CC ve GND grupları arasında anlamlı bir fark gözlenmedi (%21,1'e %23,4, p=0,615). Herhangi bir yan etki gözlenmedi. Açıklanamayan infertilitesi olan bir çiftin tedavi maliyeti GND için 1.716,42 TL ve CC için 30,67 TL idi.*

Sonuç: *Açıklanamayan infertilitesi olan hastalarda OS'nin CC ve GND ile tedavi başarısı benzer görünmektedir. Bu nedenle GND tedavisinin maliyet etkinliği ve yan etkileri göz önüne alındığında bu hastalarda ilk tercih CC olmalıdır.*

Anahtar Kelimeler: *klinik gebelik; klomifen sitrat; gonadotropin; ovulasyon endüksiyonu; açıklanamayan infertilite*

İletişim/Contact: *Meryem Kuru Pekcan, Department of Obstetrics and Gynecology, University of Health Sciences Ankara City Hospital, Bilkent-Ankara, Türkiye* • ***Tel:*** *0312 306 50 00 / 5797* • ***E-mail:*** *meryemkuru@gmail.com* • ***Geliş/Received:*** *16.06.2022* • ***Kabul/Accepted:*** *20.12.2022*

ORCID: *Meryem Kuru Pekcan, 0000-0002-4144-2900 • Nilüfer Akgün, 0000-0003-0414-9470 • Hasan Ulubaşoğlu, 0000-0001-9157-0612 • Refik Ersin Eroğlu, 0000-0002-9865-1180 • Yasemin Taşcı, 0000-0002-6612-7042*

Introduction

Infertility is defined as the inability of couples to obtain pregnancy despite at least one year of unprotected sexual intercourse[1]. Ovulation stimulation (OS) with intrauterine insemination (IUI) is recommended as a primary treatment option for infertility due to mild male factor, unexplained infertility[2]. Clomiphene citrate (CC) is the most frequently used agent in clinical practice for OS[3]. Pregnancy rates per cycle range from 10 to 20% in CC treatment[4].

Women who have not been able to become pregnant with CC may be encouraged to try gonadotropin (GND) as a next step. The advantage of the latter is that the dosage can be adjusted in the same cycle. The cost of GND therapy is significantly higher than in CC. However, it also has the disadvantages of requiring monitoring during treatment, involving the risk of ovarian hyperstimulation, and having a high rate of multiple pregnancies. Clomiphene citrate also has an anti-estrogenic effect on the endometrium and cervical mucus[5]. Recently, there has been a debate concerning whether GND treatment is unnecessary and extends the time to reach pregnancy, especially in couples with unexplained infertility following CC treatment.

The real cost of IUI treatment differs from one country to another, mainly due to the different costs of healthcare services and medicine. The Turkish Social Security Institution (SGK), the main governor of healthcare insurance in Türkiye, reimburses patients for the costs of cycle monitoring, IUI, and medication to a certain extent according to Supplement-2C of the Health Application Statement (SUT-Ek-2C) (http://www.sgk.gov.tr).

In our study, we aimed to investigate whether there was any difference between the treatment efficacy and pregnancy outcome of patients treated with CC and GND and determine the cost-effectiveness of the two methods for patients with unexplained infertility.

Material and Methods

This retrospective study included 358 women diagnosed with unexplained infertility who presented to the reproductive endocrinology and infertility clinic of Zekai Tahir Burak Women's Health Research and Education Hospital between June 2013 and April 2015. The study was approved by the ethics committee and institutional review board of the hospital (date and decision number: 04.27.2016-21). All the consecutive patients who met the study criteria were included in the sample. The sample comprised 358 patients aged 22–45 years who had an unexplained infertility diagnosis and underwent IUI after CC/GND and Ovulation Induction. On the third day of menstrual cycle, an ultrasonographic examination was performed and serum baseline hormones, such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), thyroid-stimulating hormone (TSH), prolactin (PRL), free testosterone, and dehydroepiandrosterone-sulfate were evaluated. All the patients underwent hysterosalpingography (HSG), and at least one tube showed patency with normal uterine cavity. Semen specimens were collected after at least two to five days of sexual abstinence, and the results were recorded in order to exclude the male factor. Semen parameters were analyzed according to the WHO 2010 criteria[6]. One IUI procedure was performed in each patient. Patients with severe male infertility, stage 3–4 endometriosis, polycystic ovarian syndrome , bilateral tubal occlusion according to HSG, ovarian hyperstimulation during treatment, additional drug use, thyroid dysfunction, or hyperprolactinemia were excluded from the study.

Clinical and demographic features, such as basal hormone (FSH, LH, and E2) levels, sperm count, morphology and volume, duration of OS, total CC/GND dose for induction, endometrium thickness on the day of human chorionic gonadotropin (hCG), and follicle size were recorded from the patients' files. Clomiphene citrate was used as the first step treatment in patients with unexplained infertility. Women who were not able to conceive with CC were treated with GND as the next step. However, patients who did not want to use CC treatment, those aged over 35 years, and those with a long duration of infertility underwent direct GND treatment. Multiple clinicians were involved in the treatment of patients evaluated in the study. In the group receiving CC treatment, 50–100 mg/day CC was initiated on the third to fifth day of menstrual cycle, while the GND group received 37.5–75 IU/day follicle-stimulating hormone/human menopausal gonadotropin (FSH/HMG) therapy starting from the second or third day of menstrual cycle. Serial transvaginal ultrasonography examinations were performed during OS. When at least one follicle reached a maximum diameter of 18–20 mm, 10.000 IU hCG was administered intramuscularly. Intrauterine insemination was performed 24/36 hours after administering hCG. The dosage of the drug was individualized according to the response of each patient and/or the data from their previous cycles. Luteal phase

support was provided with vaginal progesterone 200 mg/day for the patients in the GND group.

The cost-effectiveness analysis was performed from a health care perspective by taking into account the current direct medical costs of IUI. The fees for the gynecologist's cyclic monitoring or IUI treatment were not included in the calculation due to the absence of any difference in the fees of gynecologists working in state hospitals. The medication costs were calculated based on the total number units of GND or milligram of CC and the ovulation trigger used. In this process, the costs and reimbursement amounts for cycle monitoring and IUI and other costs of medication were obtained from Supplement 2C of the Health Application Statement presented on the SGK website (http://www.sgk.gov.tr).

The serum β-hCG test was performed at nearly two weeks after IUI. The diagnosis of clinical pregnancy was made six weeks after IUI based on the fetal heartbeat. The patients were divided into two groups according to pregnancy success (n=280) or failure (n=78). The groups were statistically compared in terms of the variables mentioned. There was one twin pregnancy but there no ectopic pregnancy. It was calculated that a total sample size of 357 infertile women would be needed for the expected pregnancy rate of 10% estimated from the existing literature data, with a power of 0.95 and a significance level of 5%.

Statistical Analysis

All statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) program version 17 for Windows. The Kolmogorov-Smirnov test was used to test the normality of data distribution. Normally distributed continuous variables were expressed as mean standard deviation, and those that were not normally distributed were shown as median (minimum–maximum) values. Categorical variables were presented with number and percentages. The independent-samples t-test was used for the comparison of the groups when the parametric test conditions were met, and the Mann-Whitney U test otherwise. In order to compare categorical variables between the groups, the chi-square test was used. A p value of less than 0.05 was considered statistically significant.

Results

Of the 358 patients included in the study, 78 achieved pregnancies with the treatment applied, and their mean age was 27.3 (5.04) years. In the pregnant group, the mean age of the partners was 30.4 (5.15) years. Among the 280 patients without pregnancy, the mean age was 27.6 (5.06) years and that of their partners was 30.48 (5.22) years. There was no statistically significant difference between the groups in terms of age, body mass index, number of treatment cycles, sperm count, morphology, total CC dose, total GND dose, duration of treatment, dominant follicle diameter, and pregnancy outcomes (p>0.05)

Table 1. *Demographic and clinical characteristics of the patients*

	Pregnancy Outcome				
	Not Pregnant (n=280)		Pregnant (n=78)		
Variables	Mean (SD)	Median (Min-Max)	Mean (SD)	Median (Min-Max)	p-value
Age, woman (years)	27.60 (5.06)	28.00 (19.00–44.00)	27.38 (5.04)	26.50 (19.00–40.00)	0.665
Age, man (years)	30.48 (5.22)	30.00 (20.00–54.00)	30.40 (5.15)	29.50 (20.00–54.00)	0.798
BMI (kg/m^2)*	27.92(5.33)	27.54 (17.80–44.73)	28.92 (4.94)	28.06 (20.70–40.00)	0.101
Number of cycles	2.46 (1.37)	2.00 (1.00–6.00)	2.10 (1.06)	2.00 (1.00–6.00)	0.072
Sperm count (mil)	52.33 (24.51)	44.50 (7.00–152.00)	49.23 (20.17)	44.50 (15.00–152.60)	0.601
TMSC (mil)**	37.73 (11.48)	35.00 (18.00–81.00)	34.91 (10.17)	33.00 (12.50–63.00)	0.086
Morphology (%)	8.50 (5.39)	7.00 (3.00–50.00)	7.64 (3.06)	6.50 (5–17.40)	0.174
Sperm volume (ml)	2.59 (1.06)	2.00 (0.70–6.50)	2.52 (0.88)	2.00 (1.5–7.00)	0.798
Dominant follicle diameter (cm)	18.82 (2.04)	19.00 (10.00–26.00)	18.76 (1.72)	19.00 (14.00–24.00)	0.980
Endometrial thickness (mm)	8.90 (2.27)	9.00 (4.00–19.00)	9.05 (2.09)	9.00 (5.00–14.00)	0.509
Infertility duration (years)	3.73 (2.34)	3 (1–16)	3.41 (1.72)	3 (1–9)	0.624
	n (%)		n (%)		
Multifollicular development	109 (38.9%)		26 (33.3%)		0.367

*BMI: Body Mass Index; SD: Standart Deviation **TMSS: Total Motile Sperm Count

Table 2. *Pregnancy outcome according to the infertility type and treatment groups*

Variables		Pregnancy Outcome		p value
		Not Pregnant (n=280)	Pregnant (n=7 8)	
Infertility type, n (%)	Primary	202 (76.5)	62 (23.5)	0.192
	Secondary	78 (83.0)	16 (17.0)	
Treatment, n (%)	CC	195 (78.9)	52 (21.1)	0.615
	GND	85 (76.6)	26 (23.4)	

CC: Clomiphene sitrate; GND: Gonadotropin.

Table 3. *Resource use per woman*

	Gonadotropin (n=111)			Clomiphene Citrate (n=247)			
Pregnancy Outcome	(n)	Total dose (IU) Mean (SD)	Median (Min-Max)	(n)	Total dose (mg)	Median (Min-Max)	p-value
Pregnant	26	926.64(498.22)	825 (375–2.550)	52	407.87(149.98)	500(125–750)	0.824
Non Pregnant	85	951.81(645.07)	750.00 (300–4.450)	195	411.57(144.43)	500(125–750)	0.743
Cost (TL)							
Pregnant	26	1.716.42			30.67		
Non-Pregnant	85	1.763.03			30.95		<0.001

(Table 1). Ovarian hyperstimulation syndrome (OHSS) did not develop in any of the patients. A total of 264 (73.7%) patients had primary infertility, and their pregnancy rate was 23.5%, while the remaining 94 (26.3%) had secondary infertility and had a pregnancy rate of 17%. According to the treatment applied, the rate of pregnancy was determined as 21.1% for the CC group and 23.4% for the GND group. Twin pregnancy occurred in one (1.3%) patient who had been treated with GND. No statistically significant difference was observed between the treatment groups in terms of pregnancy outcome. There was also no statistically significant difference in relation to the infertility type, total CC/GND dose, and follicle count and size (p>0.05) (Table 2). However, a statistically significant difference was detected in the costs of GND and CC in the treatment of patients with unexplained infertility (p<0.001) (Table 4).

Table 4. *Unit and total costs of the treatments*

Cost Item	Unit	Unit Costs (€) *	TL **
Medication			
Gonadotropin	75 IU	24.75	1.852 TL
Clomiphene citrate	50 mg	0.53	1.8/25 mg
HCG for ovulation induction	5.000 IU	5.83	132.4

* Costs were derived from the expert panel of the Dutch Consortium for Research in Women's Health.
** Prices of pharmaceuticals were obtained from the Turkish Social Security Institution website (htpp://www.sgk.gov.tr)

Discussion

Clomiphene citrate is the first-line agent in the treatment of women with anovulatory infertility. Many factors play a role in the selection of the induction protocol to be administered, including patient age, result of ovarian reserve tests, and semen parameters. Clomiphene citrate is especially preferred in young, non-obese women, and in those that will receive treatment for the first time, whereas GND is preferred in patients who have not responded to CC and have additional risk factors, such as advanced age and moderate male factor. However, careful attention should be paid to possible complications, such as multifollicular development, OHSS, and multiple gestation during GND therapy.

In our study, when we compared the GND and CC groups, we found no difference in terms of pregnancy achievement rates. Based on our findings, CC presents as a more cost effective treatment in eligible patients. In addition, GND has certain disadvantages, including requirement of daily injections and a close follow-up, as well as side effects, such as pain and redness. In addition, the risk of multifollicular development is lower with the use of low-dose drugs, which reduces the possibility of OHSS. Observational studies conducted with large populations showed a pregnancy rate of 10% per cycle and a multiple pregnancy rate of 30% after GND and IUI[7,8]. In another prospective, randomized, controlled trial comparing letrozole + HMG stimulation with CC + HMG, the incidence of OHSS was determined 3% in

the CC + HMG group, while no OHSS was observed in the letrozole + HMG stimulation group[9]. The cost of treatment is another important factor to be considered. Karen et al.[10] showed that although HMG treatment was more expensive than CC treatment, it had better clinical pregnancy outcomes per cycle.

Dankert et al.[11] found that the live birth rates per cycle in the CC and r-FSH treatment groups were 10% and 8.7%, respectively in women treated with IUI. In another prospective study, patients who received CC and FSH therapy were compared, and the pregnancy rate per cycle was reported to be lower in the CC group (4%) than in the FSH group (13%). In our study, the success rate of IUI was 21% (78/358), which is higher than presented in the literature. This may be due to our strict inclusion criteria.

Intrauterine insemination studies reported different results on the endometrial thickness on the day of HCG and pregnancy rates. In one study on CC, the endometrial thickness and pregnancy rate were evaluated and found to have no association with pregnancy[12]. In another study using CC and HMG, a triple-line appearance of the endometrium on the day of IUI had a positive effect on pregnancy[13]. In our study, there was no significant difference between the endometrial thickness and pregnancy rate of the two groups, which is consistent with the literature.

Early stage endometriosis, minimal pelvic adhesions, cervical factor, and subclinical male factor are often assessed in unexplained infertile groups. Badaway et al. concluded that laparoscopy (L/S) could be postponed when proceeding in the management of unexplained infertility until the timed sexual intercourse with OS fails to achieve pregnancy[14]. However, there is still no consensus among researchers in the management of patients after CC therapy failure. Some authors perform L/S on women with pelvic symptoms, such as endometriosis and proceed with GND in women without pelvic symptoms. For symptomatic women, the treatment decision following L/S is taken based on intraoperative findings (e.g., endometriosis and adhesions). For asymptomatic women, OS with GND and IUI is offered as a well-established approach in the treatment of unexplained infertility with a higher rate of conception compared with CC/IUI or aromatase inhibitors[15]. However, patients should be informed that GND/IUI also increases the possibility of multiple gestation, compared with either CC or the aromatase inhibitor letrozole. Some authors perform L/S, rather than offering GND/IUI, as the next treatment step for women unable to pursue in vitro fertilization (IVF). According to these authors, a number of these women will have findings of endometriosis and/or adhesive disease at the time of L/S, regardless of symptomatology, and the surgical treatment of endometriosis will be associated with improved fertility[16]. After L/S, another course of CC/IUI is initiated since GND/IUI is associated with a high rate of multiple gestation and increases the cost out of proportion to the modest improvement in outcome (live birth rate reported as 32% for GND/IUI compared with 23% for CC/IUI)[15] On the other hand, some women who initially decline IVF and do not respond to other treatments may change their decision and pursue IVF rather than GND treatment because the live birth rate is higher with IVF compared with GND (45 versus 32%)[15.17], and their costs are similar.

In general, due to the increased risk of multiple gestation associated with OS with GND and IUI and the increased efficacy of IVF compared with OS, the American Society for Reproductive Medicine practice committee favors IVF rather than GND/IUI in cases where CC/IUI has failed[18] . This approach is supported by a randomized trial that compared the treatment outcomes of couples assigned to receive three cycles of CC/(IUI), three cycles of FSH/IUI, and up to six cycles of IVF (conventional approach)[19]. For the couples who did not conceive with CC/IUI, omitting the FSH/IUI cycles resulted in less time to achieve pregnancy (median time to pregnancy for accelerated or conventional approach: 8 versus 11 months), fewer treatment cycles, and significantly lower total costs. The cumulative pregnancy rate was slightly higher in the accelerated approach group initially but similar to the conventional treatment group after 11 months. The incidence of multiple gestation was also similar in both groups. Although our study was not randomized or prospective, we obtained similar results. In another randomized controlled trial, CC and GND treatments were compared in patients with unexplained subfertility undergoing IUI. The ongoing pregnancy rates were 31% in the GND group and 26% in the CC treatment group[20] . Bordewijk et al. compared the cost-effectiveness of GND versus CC in women with normogonadotropic anovulatory women. The authors found no significant difference in the rate of live births between the CC and GND groups[21] .

Limitations

The limitations of our study include the short follow-up period after pregnancy, resulting in the inability to detect pregnancy outcome in all patients, and serial ultrasonography being performed by more than one sonologist for the evaluation of follicular growth and endometrial thickness. However, we observed no adverse outcomes after either treatment.

Conclusion

In infertile patients, CC seems to be the first-choice treatment due to its ease of use and cost-effectiveness, as well as similar treatment success to GND in OI with IUI cycles. Similar pregnancy rates in both treatment groups suggest that in patients with unexplained infertility, the GND step can be omitted after CC treatment. This can may shorten the time for the patients to achieve pregnancy and reduce the cost of treatment.

References

1. Tomlinson MJ, Amissah-Arthur JB, Thompson KA, Kasraie JL, Bentick B. Prognostic indicators for intrauterine insemination (IUI): statistical model for IUI success. Hum Reprod. 1996;11:1892–6.
2. Dankert T, Kremer JA, Cohlen BJ, Hamilton CJ, Pasker-de Jong PC, Straatman H, et al. A randomized clinical trial of Clomiphene citrate versus low dose recombinant FSH for ovarian hyperstimulation in intrauterine insemination cycles for unexplained and male subfertility. Hum Reprod. 2007;22:792–7.
3. Barroso G, Menocal G, Felix H, Rojas-Ruiz JC, Arslan M, Oehninger S. Comparison of the efficacy of the aromatase inhibitor letrozole and Clomiphenee citrate as adjuvants to recombinant folliclestimulating hormone in controlled ovarian hyperstimulation: a prospective, randomized, blinded clinical trial. Fertil Steril. 2006;86:1428–31.
4. Fisher SA, Reid RL, Van Vugt DA, Casper RF. A randomized double-blind comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on ovulatory function in normal women. Fertil Steril. 2002;78:280–5.
5. Kaplan PF, Patel M, Austin DJ, Freund R. Assessing the risk of multiple gestation in gonadotropin intrauterine insemination cycles. Am J Obstet Gynecol. 2002;186:1244–7.
6. World Health Organization. Laboratory manual for the examination of human semen and semen- cervical mucus interaction, 4th ed. Cambridge: Cambridge University Press; 1999.
7. Gleicher N, Oleske DM, Tur-Kaspa I, Vidali A, Karande V. Reducing the risk of high-order multiple pregnancy after ovarian stimulation with gonadotropins. N Engl J Med. 2000;343:2–7.
8. Tur R, Barri PN, Coroleu B, Buxaderas R, Martínez F, Balasch J. Risk factors for high-order multiple implantation after ovarian stimulation with gonadotrophins: evidence from a large series of 1878 consecutive pregnancies in a single centre. Hum Reprod. 2001;16:2124–9.
9. Dhaliwal LK, Sialy RK, Gopalan S, Majumdar S. Minimal stimulation protocol for use with intrauterine insemination in the treatment of infertility. J Obstet Gynaecol Res. 2002;28:295–9.
10. Karen Peeraer, J. Luyten, C. Tomassetti, S. Verschueren, C. Spiessens, A. Tanghe, et al. Cost-effectiveness of ovarian stimulation with gonadotrophin and clomiphene citrate in an intrauterine insemination programme for subfertile couples. Reproductive BioMedicine Online. 2018; 36(3):302–10.
11. Balasch J, Ballescá JL, Pimentel C, Creus M, Fábregues F, Vanrell JA. Late low-dose pure follicle stimulating hormone for ovarian stimulation in intra-uterine insemination cycles. Hum Reprod. 1994;9(10):1863–6.
12. Kolibianakis EM, Zikopoulos KA, Fatemi HM, Osmanagaoglu K, Evenpoel J, Van Steirteghem A, et al. Endometrial thickness cannot predict ongoing pregnancy achievement in cycles stimulated with clomiphene citrate for intrauterine insemination. Reprod Biomed Online. 2004;8(1):115–8.
13. Tsai HD, Chang CC, Hesieh YY, Lee CC, Lo HY. Artificial insemination. Role of endometrial thickness and pattern, of vascular impedence of the spiral and uterine arteries, and of the dominant follicle. J Reprod Med. 2000; 45(3):195–200.
14. Badawy A, Khiary M, Ragab A, Hassan M, Sherif L. Laparoscopy-or not-for management of unexplained infertility. J Obstet Gynaecol. 2010;30(7):712–5.
15. Diamond MP, Legro RS, Coutifaris C, Alvero R, Robinson RD, Casson P, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. N Engl J Med. 2015;373:1230.
16. Marcoux S, Maheux R, Bérubé S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. N Engl J Med. 1997; 337:217.
17. Sunderam S, Kissin DM, Crawford SB, Suzanne G Folger, Denise J Jamieson, Lee Warner, et al. Assisted Reproductive Technology Surveillance-United States, 2012. MMWR Surveill Summ. 2015;64:1.
18. Practice Committee of American Society for Reproductive Medicine. Multiple gestation associated with infertility therapy: an American Society for Reproductive Medicine Practice Committee opinion. Fertil Steril. 2012;97:825.
19. Reindollar RH, Regan MM, Neumann PJ, Levine BS, Thornton KL, Alper MM, et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertil Steril. 2010;94:888.
20. Danhof NA, van Wely M, Repping S, Koks C, Verhoeve HR, de Bruin JP, et al. Follicle stimulating hormone (FSH) versus Clomiphene Citrate (CC) in intrauterine insemination for unexplained subfertility: A randomized controlled trial. Hum Reprod. 2018;33:1866–74.
21. Bordewijk EM, Weiss NS, Nahuis MJ, Bayram N, van Hooff MHA, Boks DES, et al; M-ovin study group. Gonadotrophins versus clomiphene citrate with or without IUI in women with normogonadotropic anovulation and clomiphene failure:a cost-effectiveness analysis. Hum Reprod. 2019;34(2):276–84.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Chest Pain in the Pediatric Emergency Department: Evaluation of Clinical and Laboratory Findings of Patients

Çocuk Acil Serviste Göğüs Ağrılı Çocuk Hastaların Klinik ve Laboratuvar Bulgularının Değerlendirilmesi

Hale Citlenbik[1], Asli Sener[2]

[1]*Izmir Bakircay University Cigli Training and Research Hospital, Department of Pediatric Emergency, Izmir, Turkiye*
[2]*Izmir Bakircay University Cigli Training and Research Hospital, Department of Emergency, Izmir, Turkiye*

ABSTRACT

Aim: *Chest pain is a very common complaint in children and adolescents, and it is one of the common reasons for applying to the pediatric emergency department. Determining the etiological causes of chest pain in childhood is necessary to apply the right treatment and relieve the family and child's concerns. This study was planned to retrospectively examine the clinical and laboratory findings of children admitted to the pediatric emergency department with chest pain, evaluate the etiological causes, and investigate the pathological findings detected in cases with a cardiac cause.*

Material and Method: *The study included pediatric patients aged <18 who presented to the pediatric emergency department with chest pain between January 2019 and January 2022. Patient files were reviewed retrospectively, and age, gender, time of admission and season, symptoms at presentation, physical examination findings, chest X-ray findings, electrocardiography and echocardiography findings, laboratory findings, final diagnosis, hospitalization, and duration were recorded.*

Results: *Two hundred and forty-eight patients were included in the study, 119 (48%) of whom were male, while 129 (52%) were female. The median age was 14 years (IQR: 10–16). Mostly musculoskeletal, respiratory, and idiopathic causes were identified in the etiology of chest pain. In the cases with a cardiac cause, it was observed that chest pain was accompanied by symptoms such as palpitation and syncope, and pathological physical examination and ECG findings were more common.*

Conclusion: *Chest pain is one of the most common reasons for referral to the pediatric emergency department. In contrast to adults, chest pain of cardiac origin is extremely rare in childhood, and the cause of chest pain is usually benign. While evaluating patients who present to the pediatric emergency department with chest pain, a detailed anamnesis, and comprehensive physical examination should provide guidance, and detailed tests should be performed in necessary cases.*

Keywords: *children; chest pain; pediatric emergency department*

ÖZET

Amaç: *Göğüs ağrısı çocuk ve adolesanlarda oldukça çok görülen bir şikâyet olup, çocuk acil servise sık başvuru nedenlerinden biridir. Çocukluk çağında görülen göğüs ağrılarının etiyolojik nedenlerinin belirlenmesi hem doğru tedavinin uygulanması için hem de ailenin ve çocuğun endişelerini gidermek için gereklidir. Çalışmamızda çocuk acil servise göğüs ağrısı nedeniyle başvuran çocukların klinik ve laboratuvar bulguları geriye dönük olarak incelenerek etiyolojik nedenlerin değerlendirilmesi ve kardiyak neden düşünülen olgularda tespit edilen patolojik bulguların araştırılması planlanmıştır.*

Materyal ve Metot: *Çalışmaya Ocak 2019 – Ocak 2022 tarihleri arasında, yaşları <18 yaş olan, çocuk acil servise göğüs ağrısı nedeni ile başvuran çocuk hastalar dahil edildi. Hasta dosyaları geriye dönük olarak incelenerek; yaş, cinsiyet, başvuru saati ve mevsim, başvuru semptomları, fizik muayene bulguları, akciğer grafisi bulgusu, elektrokardiyografi bulgusu, ekokardiyografi bulgusu, laboratuvar bulguları, son tanı, hastaneye yatış ve süresi kayıt edildi.*

Bulgular: *Çalışmaya dahil edilen 248 hastanın, 119 (%48)'u erkek, 129 (%52)'u kız cinsiyette ve yaş ortancası 14 (IQR: 10–16) saptandı. Göğüs ağrısının etiyolojisinde sırasıyla en çok kas-iskelet sistemi kaynaklı, solunum sistemi kaynaklı ve idiyopatik nedenler bulundu. Kardiyak neden saptanan olgularda ise; göğüs ağrısına çarpıntı, senkop gibi semptomların eşlik ettiği ve patolojik fizik muayene ve ekg bulgularının daha çok saptandığı görüldü.*

Sonuç: *Göğüs ağrıları çocuk acil servise sık başvuru nedenlerinden biridir. Erişkinlerin aksine, çocukluk çağında kardiyak kökenli göğüs ağrıları oldukça nadirdir ve göğüs ağrısının nedeni çoğunlukla iyi huyludur. Çocuk acil servise göğüs ağrısı ile başvuran hastaları değerlendirirken; ayrıntılı anamnez ve kapsamlı fizik muayene yol gösterici olmalı ve gereken olgulara ayrıntılı tetkikler yapılmalıdır.*

Anahtar Kelimeler: *çocuk; göğüs ağrısı; çocuk acil*

İletişim/Contact: *Hale Çitlenbik, İzmir Bakırçay University, Çiğli Training and Research Hospital, Department of Pediatric Emergency, İzmir, Turkiye* • ***Tel:*** *0232 398 37 00* • ***E-mail:*** *drcitlenbik@hotmail.com* • ***Geliş/Received:*** *07.07.2022* • ***Kabul/Accepted:*** *10.01.2023*

ORCID: *Hale Çitlenbik, 0000-0001-7819-0412* • *Aslı Şener, 0000-0002-2107-9438*

Introduction

Chest pain is a very common complaint in children and adolescents, and it is one of the common reasons for applying to the pediatric emergency department. Although the etiological cause is not cardiac in most cases, the pain is important because it may cause absenteeism from school, limitations in sports activities, and high anxiety for the family and the child[1–3]. Studies have shown that chest pain in children is mostly due to idiopathic, musculoskeletal, gastrointestinal, respiratory, or psychogenic causes[3,4]. Chest pain is usually associated with angina pectoris and myocardial infarction in adult patients. In childhood, cardiac chest pain is extremely rare, reported at rates ranging from 0% to 10% among all causes of chest pain[5,6]. Therefore, detailed history and physical examination usually identify the cause of the chest pain and patients requiring acute intervention, and diagnostic testing is needed in very few cases. On the other hand, heart diseases, which can cause chest pain in children, can also cause sudden death[2,7,8]. Therefore, chest pain in children should be taken seriously, and its differential diagnosis should be performed accurately. Especially in recent years, sudden cardiac death in athletes and adolescents has increased the interest in this subject[9].

Determining the etiological causes of chest pain in childhood is necessary to apply the right treatment and relieve the family and child's concerns. Therefore, this study was planned to retrospectively examine the clinical and laboratory findings of children who presented to the pediatric emergency department with chest pain, evaluate the etiological causes, and explore the pathological findings detected in cases with a cardiac cause.

Materials and Methods

The study included pediatric patients <18 years who presented to the pediatric emergency department with chest pain between January 2019 and January 2022. Patients with known cardiac pathology taking medication or with a recent history of cardiac surgery were excluded from the study. Patient files were reviewed retrospectively, and age, gender, time of admission and season, symptoms at presentation, physical examination findings, chest X-ray findings, electrocardiography (ECG) and echocardiography (ECHO) findings, laboratory findings, final diagnosis, hospitalization, and duration were recorded. The patients' final diagnoses were divided into groups idiopathic, musculoskeletal, respiratory, gastrointestinal, cardiac, and psychogenic. Before the study, approval was obtained from the ethics committee of Bakirçay University (Decision no. 569, Research no: 549, Date: 20/04/2022).

IBM Statistical Package for Social Sciences (SPSS) program version 24.0 was used to evaluate the data. All data were calculated as mean or median and percentage (%). The differences between categorical variables were assessed using the chi-square test. Values of $p<0.05$ were considered statistically significant.

Results

Two hundred and forty-eight patients were included in the study, 119 (48%) of whom were male, while 129 (52%) were female. The median age was 14 years (IQR: 10–16), and 68.1% (n: 169) of the patients were over 12 years of age. Considering the hours of admission to the pediatric emergency service, it was seen that 71.8% (n: 178) of the patients presented during daytime hours. When the seasonal distribution was examined, it was observed that 48% (n: 119) was shown in autumn, with the order of seasonal frequency being autumn, winter, summer, and spring. Of these patients, 69% presented with chest pain only, and chest pain was accompanied mainly by palpitation (n: 70, 28.2%). Pathological physical examination findings were present in 27.8% (n: 69) cases. The most common findings were upper respiratory tract infection (nasal congestion, watery eyes, postnasal discharge, etc.), tachycardia, and lower respiratory tract infection (tachypnea, rales, rhonchi, etc.) at 10.5%, 6%, and 5.6%, respectively. Only one patient showed signs of cardiopulmonary failure. Chest X-rays were taken for 236 patients, and ECG was performed for all of them. As a result, 76.2% (n: 189) of the chest X-rays were normal, consolidation was found in 16.9% (n: 42) of cases, and pneumothorax was found in 2% (n: 5). When the ECG findings were examined, normal sinus rhythm was observed in 94.4% (n: 234) of cases. Supraventricular tachycardia was found in 6 patients (2.4%), sinus tachycardia in 5 patients (2%), ventricular tachycardia in 2 patients (0.8%), and right bundle branch block in 1 patient (0.4%). Thirty-eight patients consulted with pediatric cardiology and, in the echocardiographic evaluations, abnormal findings were identified in 11 cases, with mitral valve prolapse (MVP), patent foramen ovale (PFO), tricuspid regurgitation (TR), and mitral regurgitation (MR) being most common. The patients' laboratory findings and final diagnoses are shown in Tables 1 and 2. Sixteen patients (6.5%) were hospitalized in the pediatric service and 1 (0.4%) in the intensive care unit. The median length of hospital stay was five days (IQR: 2.25–6).

Table 1. *Laboratory and imaging findings of patients with chest pain*

Diagnostic test	Results
Leukocyte count (white blood cells) (10^3/μL)	Normal (n: 128, 51.6%) Leukocytosis (n: 44, 17.7%) Not measured (n: 76, 30.6%)
Neutrophil count (10^3/μL)	Mean: 5158±2360 Min: 1500 Max: 15300
Lymphocyte count (10^3/μL)	Mean: 2651±996 Min: 400 Max: 6100
C-reactive protein (CRP) (mg/dL)	Normal (n: 145, 58.5%) High (n: 15, 6%) Not measured (n: 88, 35.5%)
Troponin T (ng/mL)	Normal (n: 187, 75.4%) High (n: 9, 3.6%) Not measured (n: 52, 21%)
Chest X-ray	Normal (n: 189, 76.2%) Consolidation (n: 42, 16.9%) Pneumothorax (n: 5, 2%) Not performed (n: 12, 4.8%)
Electrocardiography (ECG)	Normal sinus rhythm (n: 234, 94.4%) Sinus tachycardia (n: 5, 2%) Supraventricular tachycardia (n: 6, 2.4%) Ventricular tachycardia (n: 2, 0.8%) Bundle branch block (n: 1, 0.4%)
Echocardiography (ECHO)	Normal (n: 27, 10.9%) Abnormal (n: 11, 4.4%) Not performed (n: 210, 84.7%)

The clinical and laboratory findings of the cases with cardiac causes (n: 19) and those with noncardiac causes (n: 229) were compared. No statistically significant difference was found between the two groups in age, gender, time of admission to the pediatric emergency department, or seasonal distribution ($p>0.05$). When presenting symptoms were considered, chest pain was mostly accompanied by palpitations or syncope in patients with a cardiac cause (73.6%, n: 14), and this finding was statistically significant ($p<0.001$). When the physical examination findings were reviewed, in 13 (68.4%) cardiac cases, positive findings such as tachycardia, high blood pressure, and circulatory disorder were seen, and these were statistically significant ($p<0.001$). Troponin elevation was present in 8 (42%) of the cases with a cardiac cause, which was statistically significant ($p<0.001$). Considering the ECG and ECHO findings, a statistically significant difference was found between cases with cardiac and noncardiac causes (63.1% positive ECG findings, 26.3% positive ECHO findings; $p<0.001$).

Table 2. *Etiological classification of patients with chest pain*

Diagnosis	n	Percent (%)
Musculoskeletal system	74	29.8
Respiratory system	71	28.6
Idiopathic	53	21.4
Psychogenic	23	9.3
Cardiac	19	7.7
Gastrointestinal system	8	3.2

Discussion

In our study, patients who presented to the pediatric emergency department with chest pain were examined, and two main results were obtained. First, mostly musculoskeletal, respiratory, and idiopathic causes were identified in the etiology of chest pain. Second, in cardiac causes, chest pain was accompanied by symptoms such as palpitation and syncope, and pathological physical examination and ECG findings were more common.

Pediatric chest pain is more common in girls and children over 12 during puberty[10,11]. In our study, there was no difference in terms of gender, but by the literature, the majority of our patients were found to be above 12 years of age. Studies have shown that chest pain is more common in pubertal children[10]. In our study, the included patients were mostly in the pubertal period among boys and girls. This finding may also indicate why chest pain of psychogenic origin is common in children. The absence of gender differences is thought to be due to sociocultural differences in the patient population. Considering the seasonal distribution in our study, it was seen that patients presented to the pediatric emergency department most often in autumn, winter, summer, and spring in order of frequency. Aygun[12] et al., in their study of patients who presented to a pediatric cardiology outpatient clinic with chest pain, found that the adolescent age group presented significantly more often in winter and autumn months. Doğan[13] et al., in their study of children with chest pain in a pediatric emergency department, found that the most frequent admissions were in the winter and spring months. The data of our study were found to be compatible with the literature. The fact that admission is widespread in autumn and winter suggests that it may be related to increased stress and anxiety with the school.

A good anamnesis and detailed physical examination are basic steps in managing children and adolescents presenting with chest pain in determining the etiology[14]. The character and duration of the pain, its relationship with effort and food, other accompanying symptoms, and trauma history should all be considered. In physical examination, vital signs should be evaluated, the chest skin tissue and presence of tenderness should be carefully examined, the lungs and heart should be carefully auscultated, and a detailed circulatory examination should be performed[15.16]. Auxiliary examinations such as chest X-rays, ECG, and ECHO should be performed to exclude other possible causes. The physical examination is expected to yield abnormal results if a serious organic cause may lead to underlying chest pain[17.18]. In our study, it was observed that chest pain of cardiac origin was accompanied by palpitations or syncope in 73.6% of the cases, and pathological physical examination findings were found in 68.4% of the cases. However, when the literature is reviewed, it is seen that physical examinations generally yielded normal results in approximately 2/3 of the patients with coronary artery anomalies. Various algorithms have been developed to evaluate children presenting with chest pain and limit the use of invasive tests. If the history, physical examination, and ECG results suggest a possible cardiac etiology, ECHO evaluation is recommended[19.20]. In our study, ECHO was performed for 15.3% of the patients who presented with chest pain, and pathological findings was found in 28.9% of those ECHO results. For chest pain of cardiac origin, 63% positive ECG and 26.3% positive ECHO findings were detected. These findings show that invasive examinations should be performed in necessary cases after a detailed anamnesis and physical examination.

The most common etiological causes of chest pain in children are idiopathic, musculoskeletal system diseases, psychological causes, respiratory pathologies, and cardiac and gastrointestinal system-related causes[6.7.10]. Studies have shown that the incidence of cardiac causes in pediatric patients with chest pain is 0–10%[5.6]. In our study, musculoskeletal system diseases, respiratory system pathologies, and idiopathic causes were seen most frequently, respectively. Cardiac causes were seen at a rate of 7.7%, consistent with the literature. Chest pain caused by the musculoskeletal system is the most common type of chest pain, with an identifiable cause among children. It is detected in 31% of patients complaining of chest pain and is, therefore, the most common specific diagnosis for chest pain in children[1.2.21]. A history of strenuous exercise, chest wall tenderness on physical examination, and changes in pain intensity with breathing are helpful in most cases. When we look at the literature, contrary to the studies of Khairandish[22] et al. and Lin[23] et al. (musculoskeletal causes at rates of 7.7% and 6.7%, respectively), chest pain caused by the musculoskeletal system generally constitutes nearly half of all cases[20]. Aygun[12] et al. found that 33% of cases of chest pain originated from the musculoskeletal system. In our study, the most common cause of chest pain was musculoskeletal, identified for 29.8% of the patients who presented with chest pain, and this is consistent with the literature. This finding reflects the necessity of a good anamnesis and a careful physical examination for a correct diagnosis.

Respiratory diseases, including pneumonia and asthma, are common causes of acute pediatric chest pain. These patients usually have a fever, cough, and tachypnea. In addition, there may be crackles and tubular breath sounds on lung examination. Less commonly, chest pain may result from pleuritis, pleural effusion, and pneumothorax. If abnormal respiratory sounds are detected in the physical examination, chest X-rays should be taken, necessary interventions should be performed, and treatment should be started[24.25]. The incidence of chest pain originating from the respiratory system ranges from 3% to 12%[2]. Lin[23] et al., in their study of 103 patients in an emergency department, found chest pain originating from the respiratory system at a rate of 24.3%, while Doğan[13] et al. found a rate of 9.1%. In our study, pathologies of the respiratory system were detected at a rate of 28.6%, and the most common observations were pneumonia, asthma, and pneumothorax, respectively. In 21–45% of pediatric and adolescent patients, no cause can be found to explain the chest pain, and these cases are considered idiopathic chest pain. Before diagnosing idiopathic chest pain, a detailed anamnesis should be taken, a physical examination should be performed, and possible organic causes should be excluded by performing the necessary tests[2.6.9]. Idiopathic chest pains are chronic, recur frequently, and resolve spontaneously. These chest pains are not affected by breathing or position. In a study of 31 children with idiopathic chest pain followed for an average of 4 years, it was observed that chest pain recurred in 45% of cases and wholly regressed in 81% of cases[26]. Aygun[12] et al. found idiopathic chest pain at a rate of 11.6% among their cases, while Lin[23] et al. reported 59.2% and Doğan[13] et al. reported 57.9%. In our study, idiopathic chest pain was

found at a rate of 21.4%, consistent with the literature. The variable data in the literature may be due to the different patient populations presenting to pediatric emergency departments.

Chest pain of cardiac origin is extremely rare in children, unlike adults. While myocardial infarction is most common in adults, many factors can cause cardiac chest pain in children. The most common causes are coronary artery of abnormal origin, Kawasaki disease, left ventricular outflow tract obstruction, tachyarrhythmias, myocarditis, pericarditis, and MVP[27]. Studies show that rates of chest pain of cardiac origin vary in the range of 0–10%[5,6]. Saleeb[9] et al., in a cohort study with 3700 patients, found cardiac chest pain at a rate of 1%. Chon[20] et al., in their study with 203 patients in a pediatric cardiology clinic, found the rate of chest pain of cardiac origin to be 2.5%, and they reported that the main cardiac causes were pericarditis, myocarditis, and MVP. Friedman[14] et al. identified pericarditis and arrhythmia as the main cardiac causes, while Drossner[18] et al. identified arrhythmia, myocarditis, and pericarditis. Viral myocarditis is associated with chest pain in children, but other symptoms are also often present, such as fever, respiratory distress, malaise, tachycardia, and poor circulation. Arrhythmias may present as chest pain. Chest pain can result from changes in cardiac output. In children with arrhythmias, palpitations are often seen together with chest pain[27,28]. In our study, 19 (7.7%) cases of chest pain of cardiac origin were detected, and 11 of the cases were evaluated as myocarditis, while 8 were arrhythmia. These findings are compatible with the literature. In childhood chest pain, the frequency and type of cardiac disease vary according to the center and methodology of the study.

There are some limitations of our study. First of all, it was a retrospective, single-center study. It was thus not possible to obtain detailed patient history, family history, or multidisciplinary evaluations. In addition, the majority of patients were excluded from follow-up after discharge. Therefore, prospective and multicenter studies are needed to provide more detailed results.

Conclusion

In conclusion, chest pain is one of the most common reasons for referral to the pediatric emergency department. In contrast to adults, chest pain of cardiac origin is extremely rare in childhood, and the causes of chest pain are mostly benign. While evaluating patients who present to the pediatric emergency department with chest pain, a detailed anamnesis, and comprehensive physical examination should provide guidance, and detailed tests should be performed in necessary cases.

References

1. Selbst SM, Ruddy RM, Clark BJ, Henreting FM, Santulli Jr T. Pediatric chest pain: a prospective study. Pediatrics. 1988; 82:319–23.
2. Friedman KG, Alexander ME. Chest pain and syncope in children: a practical approach to the diagnosis of cardiac disease. J Pediatr. 2013; 163:896–901.
3. Danduran MJ, Earing MG, Sheridan DC, Ewalt LA, Frommelt PC. Chest pain: characteristics of children/adolescents. Pediatr Cardiol. 2008; 29:775–81.
4. Rowe BH, Dulberg CS, Peterson RG, Vlad P, Li MM. Characteristics of children presenting with chest pain to a pediatric emergency department. CMAJ. 1990; 143:388–94.
5. Saleeb SF, McLaughlin SR, Graham DA, Friedman KG, Fulton DR. Resource reduction in pediatric chest pain: standardized clinical assessment and management plan. Congenit Heart Dis. 2018; 13:46–51.
6. Chun JH, Kim TH, Han MY, Kim NY, Yoon KL. Analysis of clinical characteristics and causes of chest pain in children and adolescents. Korean J Pediatr. 2015; 58:440–5.
7. Sert A, Aypar E, Odabas D, Gokcen C. Clinical characteristics and causes of chest pain in 380 children referred to a pediatric cardiology unit. Cardiol Young. 2013; 23:361–7.
8. Gesuete V, Fregolent D, Contorno S, Tamaro G, Barbi E, Cozzi G. Followup study of patients admitted to the pediatric emergency department for chest pain. Eur J Pediatr. 2019; 179:303–8.
9. Saleeb SF, Li WY, Warren SZ, Lock JE. Effectiveness of screening for life-threatening chest pain in children. Pediatrics. 2011; 128:1062–8.
10. Hanson CL, Hokanson JS. Etiology of chest pain in children and adolescents referred to cardiology clinic. WMJ. 2011; 110:58–62.
11. Geggel RL. Conditions leading to pediatric cardiology consultation in a tertiary academic hospital. Pediatrics. 2004; 114:409–17.
12. Aygun E, Aygun ST, Uysal T, Aygun F, Dursun H, Irdem A. Aetiological evaluation of chest pain in childhood and adolescence. Cardiol Young. 2020; 30:617–23.
13. Doğan M, Kalın T, Özer U, Öztürk MA. Çocuk acil servisine göğüs ağrısı nedeniyle başvuran hastaların değerlendirilmesi. MKÜ Tıp Dergisi. 2020; 11:9–13.
14. Friedman KG, Kane DA, Rathod RH, Renaud A, Farias M, Geggel R, et al. Management of pediatric chest pain using a standardized assessment and management plan. Pediatrics. 2011; 128:239–45.
15. Akalın F. Adölesanda göğüs ağrısına yaklaşım. Türk Pediatri Arşivi. 2010; 3:164–6.

16. Driscoll DJ. Chest pain in children and adolescents. In: Allen HD, Driscoll DJ, Shaddy RE, Feltes TF (eds). Moss and Adams' Heart Disease in infants, children, and Adolescents: Including the Fetus and Young Adult. 7th ed. Philadelphia, Lippincott Williams & Wilkins,. 2008; pp. 1444–6.
17. Mohan S, Nandi D, Stephens P, M'Farrej M, Vogel RL, Bonafide CP. Implementation of a clinical pathway for chest pain in a pediatric emergency department. Pediatr Emerg Care. 2018; 34:778–82.
18. Drossner DM, Hirsh DA, Sturm JJ, Mahle WT, Goo DJ, Massey R, et al. Cardiac disease in pediatric patients presenting to a pediatric ED with chest pain. Am J Emerg Med. 2011; 29:632–8.
19. Kane DA, Friedman KG, Fulton DR, Geggel RL, Saleeb SF. Needles in hay II. detecting cardiac pathology by the pediatric chest pain standardized clinical assessment and management plan. Congenit Heart Dis. 2016; 11:396–402.
20. Cohn HE, Arnold LW. Chest pain in young patients in an office setting: cardiac diagnoses, outcomes, and test burden. Clin Pediatr (Phila). 2012; 51:877–83.
21. Pantell RH, Goodman BW Jr. Adolescent chest pain: a prospective study. Pediatrics. 1983; 71:881–7.
22. Khairandish Z, Jamali L, Haghbin S. Role of anxiety and depression in adolescents with chest pain referred to a cardiology clinic. Cardiol Young. 2017; 27:125–30.
23. Lin CH, Lin WC, Ho YJ, Chang JS. Children with chest pain visiting the emergency department. Pediatr Neonatol. 2008; 49:26–9.
24. Geggel R, Endom E. Nontraumatic chest pain in children and adolescents: approach and initial management. Available at: https://www.uptodate.com/contents/nontraumatic-chest-pain-in-children-and-adolescents-approach-and-initial-management.
25. Veeram SR, Reddy MD, Harinder R, Singh MD, Reddy V. Chest pain in children and adolescents. Pediatr Rev. 2010; 31:1–9.
26. Rowland TW, Richards MM. The natural history of idiopathic chest pain in children. A follow-up study. Clin Pediatr (Phila). 1986; 25:612–4.
27. Cava JR, Sayger PL. Chest pain in children and adolescents. Pediatr Clin N Am. 2004; 51:1553–68.
28. Evangelista JK, Parsons M, Renneburg AK. Chest pain in children: diagnosis through history and physical examination. J Pediatr Health Care 2000; 14:3–8.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Diagnostic Parameters for Body Packers

Vücut Paketçileri İçin Tanısal Parametreler

Kemal Sener[1], Ertugrul Altug[1], Nazife Didem Hanoglu[1], Gokhan Eyupoglu[1], Ramazan Guven[1]

[1]Department of Emergence Medicine, Republic of Turkiye, Ministry of Healthy Basaksehir Cam and Sakura State Hospital, Istanbul, Turkiye

ABSTRACT

Aim: *We aimed to present our experience about the cases brought with the suspicion of body packing and our algorithm to diagnose those cases.*

Material and Method: *Our study was conducted with 47 of 55 patients brought to the emergency department of our tertiary care hospital by the narcotic police from a major airport in our city with the suspicion of carrying a substance in their bodies.*

Results: Computed tomography showed the presence and absence of capsules with 100% accuracy. No false positive or false negative results were obtained from any admitted patients. The power of computed tomography to detect both the presence and absence of a capsule is determined as p<0.001 according to the statistical analysis

Conclusion: *In our study, it is seen that the most appropriate imaging method for diagnosing patients brought to the emergency room due to substance carrying in the body is abdominal non-contrast tomography. Blood tests do not give an absolute result about whether the patient carries substances. Considering all these results, non-contrast abdominal computed tomography is recommended for patients that are brought in with the suspicion of substance carrying in their bodies.*

Keywords: *body packer; computed tomography; diagnosis*

ÖZET

Amaç: *Çalışmamızda madde taşıyıcılığı şüphesi ile getirilen olgularda elde etttiğimiz tecrübeyi ve uyguladığımız algoritmayı sunmayı amaçladık.*

Materyal ve Metot: *Çalışmamız, narkotik polisleri tarafından ilimizde önemli bir havalimanından üçüncü basamak hastanemizin acil servisine vücudunda madde taşıma şüphesiyle getirilen 55 hastadan 47'si ile gerçekleştirildi.*

Bulgular: *Bilgisayarlı tomografi kapsülün varlığını ve yokluğunu %100 doğruluk ile göstermiştir. Başvuran hastaların hiçbirisinde yanlış pozitif ya da yanlış negatif bir sonuç elde edilmemiştir. Bilgisayarlı tomografinin kapsül varlığını tespit etme gücünün istatistiksel analizinde p<0,001 olarak tespit edilmiştir. Aynı şekilde kapsül yokluğunun tespitinin istatistiksel analizinde p<0,001 olduğu görülmektedir*

Sonuç: *Çalışmamızda acil servise vücutta madde taşıyıcılığı nedeni ile getirilen hastaların tanısının konması için en uygun görüntüleme yönteminin abdomen kontrastsız tomografi olduğu görülmektedir. Kan testleri bize hastanın madde taşıyıp taşımadığı konusunda mutlak bir sonuç vermemektedir. Tüm bu sonuçlar göz önünde alındığında; vücutta madde taşıyıcılığı şüphesiyle getirilen hastalara başvuru anından itibaren kontrastsız abdominal bilgisayarlı tomografi çekilmesini önermekteyiz.*

Anahtar Kelimeler: *vücut paketçisi; bilgisayarlı tomografi; tanı*

Introduction

The use of substances and illegal drugs is increasing all over the world and causes bigger problems day by day. Those who carry and smuggle drugs in their body cavities are called body packers. The first body packer case was published in 1973 and their numbers are still increasing worldwide[1]. The most commonly used body cavities for this purpose are the gastrointestinal tract (GIS) from the mouth to the anus, vagina, and ears, and latex gloves, plastic bags, condoms, aluminum foil, finger parts of surgical gloves, and balloon-like materials are used to pack and store the chemicals inside the body[2,3]. In this way, many illegal substances such as cocaine, heroin, cannabis, amphetamines and ecstasy could be transported[1].

İletişim/Contact: *Kemal Şener, Department of Emergence Medicine, Republic of Türkiye, Ministry of Healthy Başaksehir Çam and Sakura State Hospital, Istanbul, Türkiye* • ***Tel:*** *0506 915 62 12* • ***E-mail:*** *drkemalsener@hotmail.com* • ***Geliş/Received:*** *24.07.2022* • ***Kabul/Accepted:*** *13.02.2023*

ORCID: *Kemal Şener, 0000-0002-8579-6663 • Ertuğrul Altuğ, 0000-0001-6807-643X • Nazife Didem Hanoğlu, 0000-0002-6150-3029 • Gökhan Eyüpoğlu, 0000-0001-8583-3690 • Ramazan Güven, 0000-0003-4129-8985*

Back in time, careless packing of packages caused puncture and exposure, causing mortality and morbidity for the carrier. Today, drug packs are machine-produced and therefore appear in uniform sizes and weights. These new packs contain high volumes of medication compressed in several latex layers. In the past, mortality rates of up to 56% have been reported, and the introduction of these latest manufactured packs has reduced the likelihood of rupture, thus reducing morbidity and mortality rates[4–7].

Although there is an increase in substance types transported in body packing and improvements in the way of transportation, it still could hardly be detected in customs and airports. And also; with the lack of technology to detect body packing and the ability to smuggle large volumes of drugs at the same time, body packing has become a huge phenomenon[8]. This new packing technique is not always visible (radio-opaque) on abdominal radiographs and that is creating difficulties in terms of diagnosis for healthcare professionals. Delays in diagnosis or misdiagnosis lead to retardation in the treatment processes of patients; in addition, in case of misdiagnosis, emergency clinicians face legal problems because both the undetected transported substance reaches the market and the misdiagnosed case is innocently exposed to forensic processes[9].

It has been shown that approximately 1 kg of substance can be transported by body packing. In these cases, it has been observed that cocaine is divided in 1–3 g containing packages placed in the carrier and transported in this way. Toxidrome could be fatal, when even 1–3 gr packages are punctured or exploded. Therefore, early detection of the carrier is important in terms of reducing mortality and morbidity[10].

The number of cases brought to the emergency services with the suspicion of carrying packages in their bodies is increasing. A definitive universal diagnostic algorithm is still not available today neither to detect the presence of any package in the body nor the treatment needs. Each clinic in this field has arranged an algorithm according to its own functioning and is trying to implement this algorithm. In addition to many laboratory tests and imaging tests, substance analyses are also used in clinics to determine the substance carrier[11–14]. In our study, we aimed to present our experience and the algorithm we applied in cases brought with the suspicion of substance carrying.

Material and Method

Ethical Considerations

Ethics committee approval was obtained from Basaksehir Cam and Sakura City Hospital Ethics Committee (Ethics committee no: 2021.09.184). The entire study was performed in accordance with the Declaration of Helsinki.

Study Setting

The study was conducted retrospectively between 15 July 2020 and 15 July 2021. This study was carried out with 47 patients who met the study criteria from 55 patients who were brought to the emergency department of our tertiary level hospital by the narcotic police from a big airport in our city on suspicion of carrying substances in their bodies.

Study Population

The study was conducted in the emergency medicine clinic of a tertiary-level hospital. Our hospital provides health services to all patients brought from the airport on the European side of our city and to patients brought to our hospital by the security forces with the suspicion of carrying substances in their bodies.

Among all the patients brought by the security forces on suspicion of carrying substances in their bodies, those with missing data in the hospital automation system were excluded from the study.

Data Collection

The study was started after obtaining approval from the ethics committee. In the study, patients brought to the emergency room with the suspicion of substance transport in the body were scanned from the hospital automation system (Hospital Information Management Systems-HIMS). All forensic cases admitted to the hospital were screened, and all the patients admitted to the hospital because of body packing were included in the study. Of the 55 patients, 8 patients with missing data were excluded from the study and overall 47 patients were included in the study.

Demographic characteristics of the patients (age, gender, comorbid disease), presence of packages in their bodies, laboratory parameters, outcomes (discharge, hospitalization and death status), detection of packages in non-contrast abdominal computed tomography

(CT) and plain abdominal X-ray, hours of admission were obtained from patient files and hospital automation system and recorded in the previously created study form. The forms were numbered and archived. After the study was completed, data was transferred to the digital environment and statistical analysis was performed.

Statistical Analysis

Statistics were performed using the IBM Statistical Package for Social Sciences (SPSS) program version 23.0 for Windows® statistical program (IBM Inc. Chicago, IL, USA). Number, percentage, mean, standard deviation, median, minimum, and maximum values were used in the presentation of descriptive data. The conformity of the data to the normal distribution was evaluated with the Kolmogorov-Smirnov Test. Pearson chi-square test and Fisher's Exact test were used to compare categorical data. T-Test was used to compare two independent numerical data and Kruskal Wallis Test was used to compare triple numerical data. $p<0.05$ was accepted as statistically significant.

Results

Forty-seven cases were included in the study. 87.2% of these cases were male and the mean age was 34.93±8.89 years. All but 2 of the cases were discharged after follow-up. According to the clinical evaluation, 70.2% of the cases were found to have substance capsules, whereas no capsules have been found in 29.8% of the cases. Computed tomography imaging was performed for all cases, and as a result of the imaging, a foreign body image suggesting the presence of a capsule was observed in 74.5% of the cases (Table 1).

Table 1. *Frequency values of demographics and disease data of cases*

Parameter		n (%)
Number of cases		47 (100,0)
Sex	Female	6 (12,8)
	Male	41 (87,2)
Outcome	Discharge	45 (95,7)
	Admission	1 (2,1)
	Mortality	1 (2,1)
Capsule seen on CT	No	12 (25,5)
	Yes	35 (74,5)

Table 2. *Evaluation of the changes in the laboratory levels of the cases according to the presence of capsules*

Parameter	All cases Mean ± SD	No capsules Mean ± SD	Capsule seen Mean ± SD	p
WBC ($x10^3/mm^3$)	10.80±2.72	10.50±2.58	10.83±2.80	0.710
PLT ($x10^3/mm^3$)	265.62±73.63	271.07±47.64	260.30±83.94	0.656
HGB (mg/dL)	15.46±1.57	14.97±1.30	15.68±1.60	0.151
MPV	10.11±0.99	9.89±0.90	10.19±1.01	0.355
Percentage of Neutrophil	75.64±6.81	73.57±7.46	76.06±6.90	0.276
Percentage of Lymphocyte	17.83±5.82	20.27±6.18	17.13±5.88	0.106
Neutrophil/Lymphocyte Ratio	5.40±5.41	3.96±1.30	5.90±6.23	0.259
CPR (mg/dL)	6.52±11.30	3.47±2.90	7.70±13.15	0.243
Glucose (mg/dL)	108.87±24.44	98.21±26.85	116.70±28.83	0.046
Urea (mg/dL)	31.78±8.42	29.86±7.16	31.99±9.13	0.442
Creatinine (mg/dL)	0.96±0.55	0.72±0.16	1.07±0.60	0.037
Sodium (mEq/L)	138.36±2.75	138.57±2.24	138.21±2.92	0.683
Potassium (mEq/L)	4.28±0.37	4.22±0.26	4.36±0.49	0.320
ALT (IU/mm^3)	109±555.51	23.50±7.11	139±648.61	0.509
AST (IU/mm^3)	149.89±835.55	22.86±7.09	196.64±975.44	0.511
Lactate (mg/dL)	1.51±0.85	1.30±0.40	1.63±0.96	0.231
pH	7.36±0.03	7.37±0.01	7.36±0.03	0.703
HCO_3	26.38±3.33	25.38±2.33	26.86±3.55	0.161
PCO_2	45.71±5.53	43.51±4.68	46.80±5.53	0.058

Independet T test is used.

The results of laboratory tests were compared between cases with and without capsules. According to the statistical analysis of complete blood count, biochemistry and blood gas tests, except for the glucose and creatinine results of the patients, the significance level was determined as $p>0.05$ which refers to no statistical significance. Comparison results of glucose and creatinine values of patients with and without packages revealed the significance level as $p<0.05$. The creatinine and glucose values of the cases carrying packages were found to be higher (Table 2).

Computed tomography results demonstrated the presence or absence of the capsule with 100% accuracy. No false positive or false negative result was obtained in any of the patients according to the statistical analysis regarding the power of CT to detect the presence of capsule, significance level determined as $p<0.001$. Likewise, the detection of the absence of a capsule was found to be $p<0.001$ according to the statistical analysis (Table 3).

It has been observed that substance carriers were mostly male patients. Except for 2 cases, all of the other cases were discharged after completing their follow-up period in the emergency department. The cases in which no package was detected were discharged after being followed up in the emergency department for an average of 1–2 hours. The cases with packages were followed up in the emergency room for approximately 24–36 hours and were discharged after all packages were released. While one of the 2 patients is discharged after hospitalization; mortality was observed in 1 patient (Table 3). Detection of capsules with CT was found to be significant.

Considering the duration of stay in the emergency room, patients with capsules in their bodies stayed longer than patients without capsules. The duration of stay in the emergency department of the patients without was 3±1 hours, while the duration of stay in the emergency department was 56±10 hours for the patients with capsules.

Discussion

Those who carry substances and contraband drugs in their body cavities are called body packers. Substance transport in the body is an increasing problem all over the world. The first case was described in 1973. Since 1973, the substances carried in the body are being packed better and better. Capsule covers are produced from special materials so that they could not be opened mechanically and could not be detected while passing through the x-ray device. As the transported capsules are not radiopaque, detection is difficult. This situation leads to medical and medicolegal problems related to patients. In this study, we aim to share our experiences from our clinic.

Generally, young men are chosen for the transportation of substances. The reason for this is thought to be the absence of comorbid diseases and better physical capacity of carriers. In the literature, it was seen that young male cases were selected as well according to several publications[15,16]. In addition to this situation, there are also studies in the literature reporting the use of pregnant and pediatric cases[17,18]. In our study, 87.2% of the cases brought to the emergency department were male. In this context, the data of our study were similar to the publications in the literature. Among the cases brought with this suspicion, we thought that professionals should be more careful about young male cases.

Complications have decreased over the years due to the development of packing techniques for materials. In the study of Schaper et al., they reported that the mortality was very low which has been shown to be at 1.4%. Again, in that study, it was observed that

Table 3. *Examination of the demographic data and disease data of the cases according to the presence of capsules*

Parameter		No capsules n (%)	Capsules seen n (%)	p
Sex	Female	5 (83.3)	1 (16.7)	0.006 **
	Male	9 (22.0)	32 (78.0)	
Capsule on CT	None	12 (100.0)	0 (0.0)	<0.001*
	Present	0 (0.0)	35 (100.0)	
Outcome	Discharge	14 (31.1)	31 (68.9)	0.484
	Admission	0 (0.0)	1 (100.0)	
	Exitus	0 (0.0)	1 (100.0)	

* Pearson Ki Kare Test.
** Fisher's Exact Test.

less than 1% of the cases required laparotomy[19]. In our study, mortality was observed in 1 case due to rupture of the capsule; and due to the ileus clinic, that appeared in another case, the necessity of operation arose and surgery was performed. In our study, the incidence of complications was found to be very low, and the data of our study are similar to the literature.

When the laboratory tests of patients carrying substances in their bodies are examined, it was investigated whether a diagnostic evaluation can be made with blood parameters in patients with and without capsules, and it has been found that there were higher creatinine levels in patients with capsules, which we think is the cause of low oral intake. In addition, when the patients with and without capsules were compared, blood glucose levels were statistically higher in those carrying capsules. We think that high blood sugar may be related to stress hyperglycemia. Apart from these laboratory levels, no finding that could indicate the presence of capsule was found in other laboratory parameters. Examination of laboratory results was not found to be significantly diagnostic for cases without toxidrome clinic. For this reason, we think that performing laboratory tests on these patients will cause both time and financial loss. When the literature was scanned, no study was found on the blood tests of the cases carrying packages in the body. Regarding the analysis of substances in urine in the literature; it is stated that although it was used at first, it is no longer useful due to weak sensitivity[20].

Detection of substance packages carried in the body is important for emergency clinicians to prepare treatment and forensic reports, as well as to assist investigations for security forces. In these patients, skipping existing drug packages or reporting non-existing drug capsules as false positives will lead to very serious medico-legal problems. In our clinic, non-contrast abdominal CT is used to evaluate the patients admitted with this suspicion. Abdominal CT without contrast is taken at the time of admission of the patients and the presence/absence of the package is determined according to the CT result. It is seen that non-contrast abdominal CT shows the package status with 100% success. When the literature is reviewed, publications are showing the use of plain abdominal radiography, abdominal CT, ultrasonography, magnetic resonance imaging for the detection of packages[21–25]. According to the study published by Maier et al. in 2017; they used abdominal CT because of its high diagnostic rate and ability to show even small amounts of substance packages[20]. Again, in a study by Shahnazi et al.; they stated that non-contrast abdominal CT should be preferred to direct radiography due to its higher sensitivity[3]. While in another study published by Hahn et al., they stated that 1 case was missed in abdominal CT with oral contrast[26], Karhunen et al. reported that plain radiography had false negative and false positive results in their study[23]. Again, in a similar study, they stated that there may be more false negatives due to the gradually developing packing techniques[27].

Patients brought in with the suspicion of carrying substances in their bodies are followed up in our emergency department and discharged in case of no complications. If these patients have capsules, they lead to long waiting times in emergency departments. In their study, Maier et al. reported that the average emergency department stay duration was 51.2 hours[20]. In our study, the duration of stay in the emergency room was 3±1 hours for the patients with no packages, and 56±10 hours for the patients with packages.

Study Limitations

This study has several limitations. One of them is that the data used was obtained from retrospective scanning due to the retrospective conduction of the study. A second limitation is the small number of patients included in the study, and larger prospective, multicenter studies are needed.

Conclusion

In our study, it is seen that the most appropriate imaging method for the diagnosis of patients brought to the emergency department due to substance carrying in their bodies is abdominal non-contrast tomography. The blood results do not give us an absolute result about whether the patient has substance or not. Considering all these results, we recommend non-contrast abdominal CT scan at the time of admission to patients brought in with the suspicion of carrying substances in their bodies.

Conflict of Interest

No conflict of interest was declared by the authors.

Financial Disclosure

The authors declared that this study received no financial support.

References

1. Ngatchou W, Lemogoum D, Essola B, Ramadan A, Ngassa M, Guimfacq V, et al. Cannabis body packing: a case report. Pan Afr Med J. 2016;24:327.
2. Özer E, Şam B, Özdeş T, Dokgöz H. Paket vücut sendromuna bağlı kokain intoksikasyonu sonucu ölüm: Olgu sunumu. Adli Tıp Bülteni. 2005 ;10(2):62–5.
3. Shahnazi M, Sanei Taheri M, Pourghorban R. Body packing and ıts radiologic manifestations: A review article. Iran J Radiol. 2011;8(4):205–10.
4. McCarron MM, Wood JD. The cocaine 'body packer' syndrome. Diagnosis and treatment. JAMA. 1983;250:1417–20.
5. Sinner WN. The gastrointestinal tract as a vehicle for drug smuggling. Gastrointest Radiol. 1981;6:319–23.
6. Suarez CA, Arango A, Lester JL., III Cocaine-codom ingestion. Surgical treatment. JAMA. 1977;238:1391–92.
7. Wetli CV, Mittlemann RE. The "body packer syndrome"-toxicity following ingestion of illicit drugs packaged for transportation. J Forensic Sci.1981;26:492–500.
8. Adem Ç, Ramazan G, Kemal Ş. High-Dose Poisoning, "Body Packers" Case That Ended in An Emergency: A Case Report. Open Acc J of Toxicol. 2021; 5(2):555659.
9. Cappelletti S, Aromatario M, Bottoni E, Fiore PA, Straccamore M, Umani Ronchi F, et al. (2016) Drug-related deaths with evidences of body packing: two case reports and medico-legal issues. Leg Med 20:23-6.
10. de Bakker JK, Nanayakkara PW, Geeraedts LM Jr, de Lange ES, Mackintosh MO, Bonjer HJ. Body packers: a plea for conservative treatment. Langenbecks Arch Surg. 2012;397(1):125–30.
11. Sengupta A, Page P. Window manipulation in diagnosis of body packing using computed tomography. Emerg Radiol. 2008;15(3):203–5.
12. Flach PM, Ross SG, Ampanozi G, Ebert L, Germerott T, Hatch GM, et al. "Drug mules" as a radiological challenge: sensitivity and specificity in identifying internal cocaine in body packers, body pushers and body stuffers by computed tomography, plain radiography and Lodox. Eur J Radiol. 2012;81(10):2518–26.
13. Horrocks AW. Abdominal radiography in suspected 'body packers'. Clin Radiol. 1992;45(5):322–5.
14. Makoto Nihira, Makiko Hayashida, Youkichi Ohno, Sho Inuzuka, Hiroyuki Yokota, Yasuhiro Yamamoto, Urinalysis of Body Packers in Japan, Journal of Analytical Toxicology, Volume 22, Issue 1, January-February 1998, Pages 61–5.
15. Heymann-Maier L, Trueb L, Schmidt S, Carron PN, Hugli O, Heymann E, et al. (2017) Emergency department management of body packers and body stuffers. Swiss Med Wkly 147:w14499.
16. Booker RJ, Smith JE, Rodger MP. Packers, pushers and stuffers—managing patients with concealed drugs in UK emergency departments: a clinical and medicolegal review Emergency Medicine Journal. 2009;26:316–20.
17. Cordero DR, Medina C, Helfgott A. Cocaine body packing in pregnancy. Ann Emerg Med. 2006;48(3):323–5.
18. Chakrabarty A, Hydros S, Puliyel JM. Images in paediatrics: smuggling contraband drugs using paediatric "body packers". Arch Dis Child. 2006;91:51.
19. Schaper A, Hofmann R, Bargain P, Desel H, Ebbecke M, Langer C. Surgical treatment in cocaine body packers and body pushers. Int J Colorectal Dis. 2007;22(12):1531–5.
20. Maier Liv, Trueb Lionel, Schmidt Sabine, Carron Pierre-Nicolas, Hugli Olivier, Heymann Eric, et al. Emergency department management of body packers and body stuffers. Swiss Med Wkly. 2017;147:w14499.
21. Bulakci M, Ozbakir B, Kiris A (2013b) Detection of body packing by magnetic resonance imaging: a new diagnostic tool? Abdom Imaging 38(3):436–41.
22. Hergan K, Kofler K, Oser W (2004) Drug smuggling by body packing: what radiologists should know about it. Eur Radiol 14:736–42.
23. Karhunen PJ, Suoranta H, Penttila A, Pitkaranta P (1991) Pitfalls in the diagnosis of drug smuggler's abdomen. J Forensic Sci 36:397–402.
24. Hierholzer J, Cordes M, Tantow H, Keske U, Mäurer J, Felix R. Drug smuggling by ingested cocaine-filled packages: conventional x-ray and ultrasound. Abdom Imaging 1995;20(4):333–8.
25. Cappelletti S, Piacentino D, Sani G, Bottoni E, Fiore PA, Aromatario M, et al. Systematic review of the toxicological and radiological features of body packing. Int J Legal Med. 2016;130(3):693–709.
26. Hahn IH, Hoffman RS, Nelson LS. Contrast CT scan fails to detect the last heroin packet. J Emerg Med. 2004;27(3):279–83.
27. Aldrighetti L, Paganelli M, Giacomelli M, Villa G, Ferla G. Conservative management of cocaine-packet ingestion: experience in Milan, the main Italian smuggling center of South American cocaine. Panminerva Med. 1996;38(2):111–6.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Diagnostic Importance of Lung Ultrasonography in the Follow-up of Patients with Blunt Chest Trauma

Künt Toraks Travmalı Hastaların Takibinde Toraks Ultrasonografisinin Tanısal Önemi

Guntug Batihan[1]

[1]*Harakani State Hospital, Department of Thoracic Surgery, Kars*

ABSTRACT

Aim: *Radiological follow-up of patients with blunt thoracic trauma is essential in providing a chance for early intervention for complications that may develop. The study aims to investigate lung ultrasound's diagnostic value in patients with blunt thoracic trauma.*

Material and Method: *Patients of adult age who were treated for blunt chest trauma in the thoracic surgery clinic of our center between February 2022 and June 2022 were evaluated retrospectively. Among these patients, those who radiologically followed up with a combination of lung US and chest radiography were included in the study. Radiological data that indicates pneumothorax, hemothorax, and atelectasis were recorded.*

Results: *A total of 60 patients with blunt thoracic trauma were included in the study. Forty-nine of the patients were male, and 11 were female. The mean age was 45.7±17.8, and the median was 49 (range 18–74). While the perfect agreement was observed in the detection of hemothorax between the lung US and chest radiogram, substantial agreement was observed in the detection of pneumothorax and atelectasis.*

Conclusion: *In the follow-up of patients with blunt chest trauma, lung ultrasound is a good alternative to standard posterolateral chest X-ray with its similar diagnostic success, easy reproducibility, and the possibility to be applied at the bedside.*

Keywords: *atelectasis; chest trauma; hemothorax; lung ultrasound; pneumothorax*

ÖZET

Amaç: *Künt toraks travmalarında radyolojik takip gelişebilecek komplikasyonlara erken müdahale şansı sunması açısından büyük öneme sahiptir. Bu çalışmada toraks ultrasonunun künt toraks travmalı hastaların takibindeki tanısal değerinin araştırılması amaçlandı.*

Materyal ve Metot: *Şubat 2022 ile Haziran 2022 tarihleri arasında erişkin yaştaki künt toraks travmalı hastaların verileri analiz edildi. Radyolojik takiplerinde toraks ultrason ve akciğer grafisinin kombine olarak kullanıldığı hastalar çalışmaya dahil edildi. Pnömotoraks, hemotoraks ve atelektaziye ait radyolojik bulgular kaydedildi.*

Bulgular: *Çalışmaya toplamda 60 hasta dahil edildi. Hastaların 49'u erkek 11'i kadındı. Ortalama yaş 45,7±17,8, ortanca yaş 49 (aralık: 18–74) yıl olarak bulundu. Hemotoraks tanısında toraks ultrasonu ve akciğer grafisi arasında mükemmel uyumluluk tespit edildi. Pnömotoraks ve atelektazi tanısında ise iyi derecede uyum tespit edildi.*

Sonuç: *Künt toraks travmalı hastaların takibinde toraks ultrasonu benzer tanısal değeri, kolay tekrarlanabilirliği ve hasta başında uygulanabilme imkânı tanıması ile standard posterolateral akciğer grafilerine iyi bir alternatiftir.*

Anahtar Kelimeler: *atelektazi; hemotoraks; pnömotoraks; toraks travması; toraks ultrasonu*

Introduction

Chest traumas are responsible for 20–25% of trauma-related mortality, and blunt injuries constitute the majority[1–3]. Mortality and morbidity may develop in the acute period due to complications that may develop during follow-up. Therefore, clinical and radiological follow-up is essential in chest traumas, even if the general condition of the patients is stable. Today, tomography is frequently preferred in the first evaluation of patients with chest trauma because of its easy accessibility and high performance in providing detailed data.

Following the initial evaluation in a significant proportion of patients with chest trauma, follow-up is required regarding hemothorax, pneumothorax, and atelectasis that may develop or progress. In the radiological follow-up of these patients, chest radiography is generally preferred if there is no indication for further examination[4,5]. However, lung ultrasound (US) is used to diagnose

İletişim/Contact: *Harakani State Hospital, Department of Thoracic Surgery, Kars* • ***Tel:*** *0532 576 45 46* • ***E-mail:*** *gbatihan@hotmail.com*
Geliş/Received: *01.08.2022* • ***Kabul/Accepted:*** *26.01.2023*

ORCID: *Güntuğ Batıhan, 0000-0001-5258-2856*

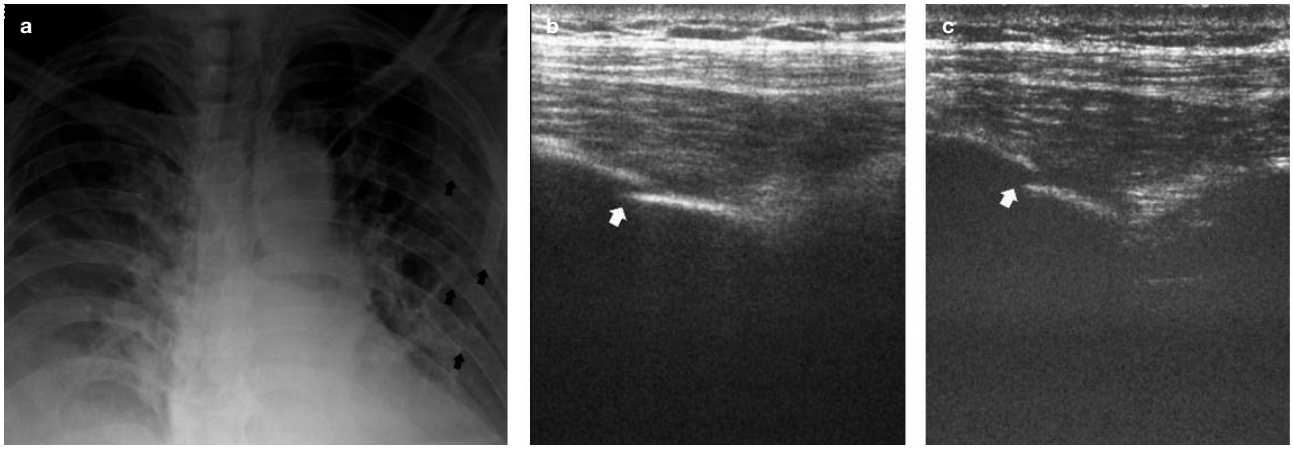

Figure 1. *Chest X-ray and US image of a patient with serial rib fractures on the left side. Arrows indicate fracture areas where cortical continuity is lost*

follow-up patients with chest trauma and has some potential advantages over the chest radiogram and CT scanning, including real-time imaging, being radiation-free, easy reproducibility, and point-of-care use[6].

This study explored lung US functionality in diagnosing hemothorax, pneumothorax, and atelectasis in the radiological follow-up of patients with chest trauma by comparing it with chest radiography.

Material and Method

The Institutional Ethics Committee approved this study, and informed consent was obtained from all participants. Patients of adult age who were treated for blunt chest trauma in the thoracic surgery clinic of our center between February 2022 and June 2022 were evaluated retrospectively. Among these patients, those who radiologically followed up with a combination of lung US and chest radiography were included in the study. Patients with multiple traumas open thoracic injuries, and needing surgical intervention were excluded from the study.

Lung ultrasound was performed by a thoracic surgeon with five years of ultrasound experience, using a Toshiba Aplio 500 machine with a high-resolution linear transducer of 7.5 MHz and a sector transducer of 3.5 MHz. Ultrasound examination was performed on the anterior, lateral, and posterior thorax in the sitting or supine position.

The diagnosis of pneumothorax was made by the disappearance of the normal sliding movement of the lung parenchyma and the presence of the "barcode/stratosphere" sign in M mode.

Fluid collection compatible with the trauma area on ultrasound was evaluated as hemothorax, and a "tissue-like" or "hepatized" appearance in which air bronchograms could be observed was evaluated as atelectasis.

Standard posteroanterior chest radiogram was obtained 1 hour before lung US in all patients. Radiological examinations were performed on the 1st and 3rd days of the follow-up. Data on pneumothorax, hemothorax, and atelectasis were recorded.

Statistical Analysis

Statistics analysis was performed with IBM Statistical Package for Social Sciences (SPSS) program version 25.0 (IBM Inc., Chicago, IL, USA). Continuous variables were expressed as mean value ± standard deviation (SD). Categorical variables were expressed with their ratios. The performance of ultrasound for detecting lung pneumothorax, hemothorax, and atelectasis was compared with that of CT using the Kappa agreement test. A p value less than 0.05 was considered statistically significant.

Results

A total of 60 patients with blunt thoracic trauma were included in the study. Forty-nine of the patients were male, and 11 were female. The mean age was 45.7±17.8, and the median was 49 (range 18–74). The data on the characteristic features of the patients are summarized in Table 1. On the 1st day of the follow-up, positive findings were detected in 29 (48.3 %) lung US patients; on the 3rd day, positive findings were detected in 36 (60.0 %) patients. At least one rib fracture was detected in 34 (56.7%) patients (Fig. 1). While the perfect agreement was observed in the detection of hemothorax between the lung US and chest radiogram, substantial agreement was observed in the detection of pneumothorax and atelectasis (Table 2).

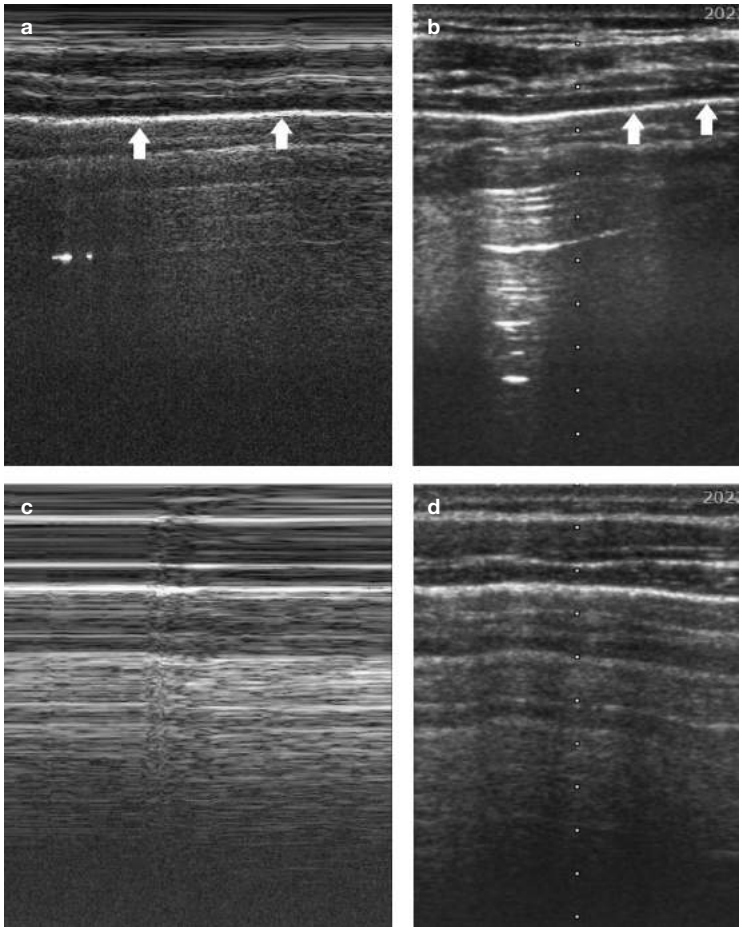

Figure 2. *The presence of an image resembling sea waves caused by pleural sliding in "a" indicates the absence of pneumothorax. The arrows in "a" and "b" indicate the pleural line. "c" and "d" are images of the thorax US of a patient with pneumothorax. In "c" it is seen that the "seaside" finding has disappeared. This view in the M mode of ultrasound is also called the "barcode/stratosphere" sign which is highly sensitive for the diagnosis of pneumothorax.*

Table 1. *Patient characteristics*

Variables	N=60 (%)
Age (mean ± SD)	45.7±17.8
Sex (male)	49 (81.7)
Trauma side	
Right	24 (40)
Left	27 (45)
Bilateral	9 (15)
Chest tube (yes)	14 (23.3)
Hospital stays (mean ± SD)	5.6±1.4

SD: Standard deviation.

Pneumothorax

On the 1st day of the follow-up, pneumothorax was detected in 8 patients on chest X-ray. Lung US detected pneumothorax in 6 patients (Fig. 2). The cases in which ultrasound could not detect pneumothorax were those with minimal pneumothorax observed in the apical region. On the 3rd day of the follow-up, the US detected pneumothorax in these cases because of the progression.

Hemothorax

On the first day of the follow-up, hemothorax that could not be detected in the chest X-ray was detected

Table 2. *Evaluation of the strength of agreement with Cohen's kappa*

	Day-1				Day-3			
	Thorax-US	Chest X-ray	Kappa	p-value	Thorax-US	Chest X-ray	Kappa	p-value
Pneumothorax	6 (10.0)	8 (13.3)	0.68±0.15	0.00	8 (13.3)	8 (13.3)	0.52±0.17	0.00
Hemothorax	18 (30.0)	14 (23.3)	0.83±0.08	0.00	20 (33.3)	15 (25.0)	0.88±0.07	0.00
Atelectasis	5 (8.3)	7 (11.7)	0.63±0.17	0.00	8 (13.3)	10 (16.7)	0.83±0.09	0.00

US: Ultrasound.

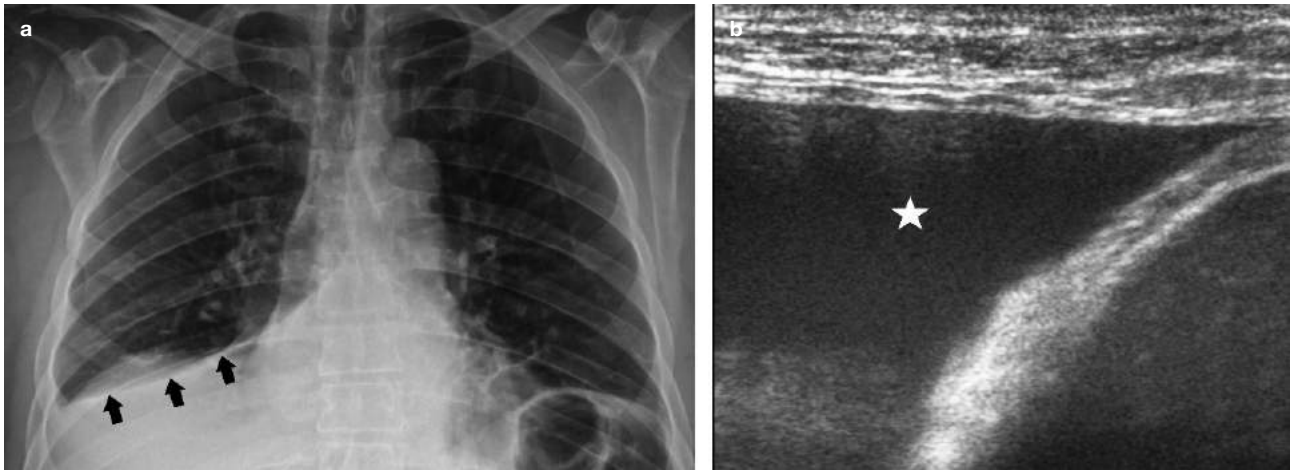

Figure 3. *In patients with suspected hemothorax, US is helpful in determining the characteristics (free flowing or loculated) and localization of pleural fluid. Chest X-ray of subpulmonary hemothorax (arrows) is shown in "a". In the lung US of the same patient, pleural fluid (asterisk) located in the costophrenic sinus is seen.*

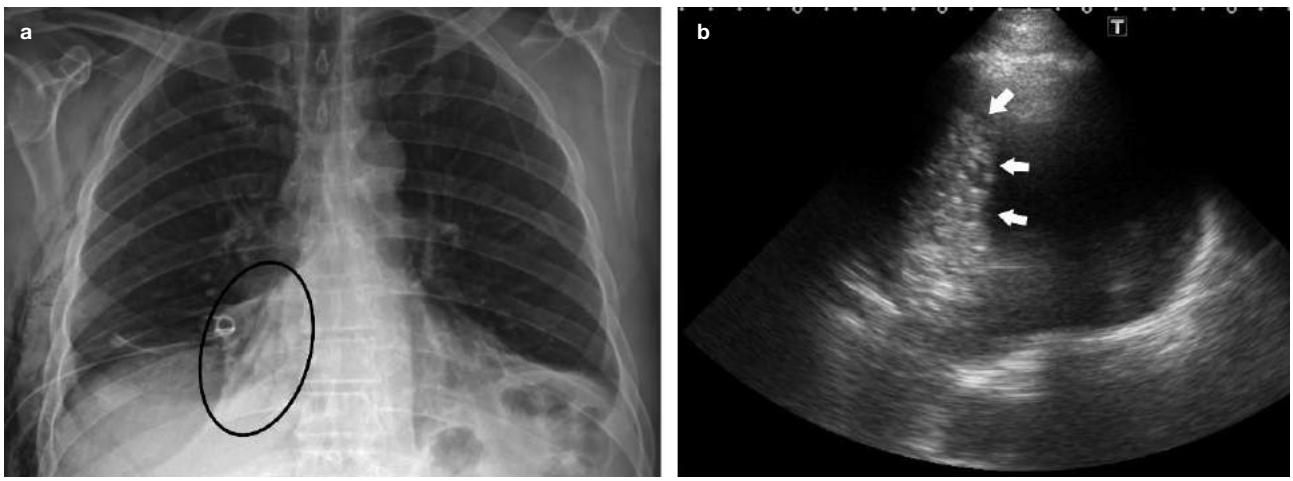

Figure 4. *The circled area in "a" is the entire right lower lobe in the atelectatic state. In "b", liver-like tissue in which air bronchograms are observed is the specific appearance of atelectasis.*

in 4 cases by the US (Fig. 3). On the 3rd day of the follow-up, this number increased to 5 patients. These cases were those with fluid accumulation in the posterior costodiaphragmatic recess.

Atelectasis

The rate of detecting atelectasis by ultrasound was lower than by chest radiography. The most easily detectable atelectasis localization by the US was the lower lobes (Fig. 4). Particularly, segmental/subsegmental atelectasis that did not cover the entire lobe could not be detected by ultrasound.

Discussion

Lung US has potential advantages over other radiological techniques in the follow-up of patients with blunt chest trauma. Lung US is a non-invasive method that provides real-time data, can be applied at the bedside, can be repeated, and does not carry the risk of radiation exposure[6–8].

It provides detailed information about the chest wall, diaphragm movements, pleural cavity, and lung parenchyma.

In this study, no significant difference was found between lung US and chest X-ray in the follow-up of patients with blunt thoracic trauma for the detection of pneumothorax, hemothorax, and atelectasis.

In studies in the literature, the sensitivity of lung US in the diagnosis of pneumothorax varies between 48% and 100%, and the specificity varies between 89.5% and 100%[7–10].

In the meta-analysis of Ebrahimi et al.[7], in which they included the data from 28 studies, lung US was superior to chest radiography in detecting pneumothorax.

In our study, 2 cases were detected by radiography but not by lung US. In these cases, the pneumothorax was partially located at the thoracic cavity's apex.

The feasibility of lung US in detecting hemothorax and rib fractures has been demonstrated in several studies[11–13]. Studies have shown that the sensitivity of the US in detecting hemothorax is between 81% and 97.5%; in particular, its superiority and reproducibility over chest X-rays were emphasized.

In the study of Sabri et al.[12], in which they included 107 patients with chest trauma, the success of lung US and tomography in detecting complications were compared, and the US was found to be particularly effective in detecting pleural lesions and rib fractures.

By the literature, hemothorax was detected by the US in 5 patients whose chest X-ray was interpreted as normal in our study.

Lung US is also functional in detecting changes in the lung parenchyma due to trauma, chest wall, and pleural complications. In a retrospective study by Helmy et al.[14], in which they analyzed the data of 50 patients with blunt chest trauma, the sensitivity of lung ultrasonography in the detection of lung contusion was 97.50%, and the specificity was 90.0%.

In the study of Yang et al.[15] in which they aimed to demonstrate the success of lung US in detecting atelectasis/consolidation in 81 patients with multi-trauma and under mechanical ventilator support, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were found to be 81.8, 100, 100, 85.9, and 91.4%, respectively.

We did not include data on pulmonary edema, consolidation, or contusion findings in our study. While there was 100% agreement with the chest X-ray in detecting lobar atelectasis, the same success was not observed in the US in sub-lobar atelectasis.

There are some limitations in this study. First, this is a retrospective study, and bias in patient selection cannot be excluded. Second, the number of patients is limited. Therefore, some subgroup analyses could not be performed. Finally, the etiology of trauma is not homogeneous due to the characteristics of the region where the study was conducted. Different results can be observed in blunt thoracic traumas due to different etiologies. For this reason, it is recommended that different comprehensive studies confirm these data.

In conclusion, lung US is a good alternative to traditional chest radiographs in the follow-up of patients with blunt chest trauma regarding pneumothorax, hemothorax, and atelectasis. Reproducibility, real-time imaging, and point-of-care application are the main parameters that make lung US attractive.

References

1. Dogrul BN, Kiliccalan I, Asci ES, Peker SC. Blunt trauma related chest wall and pulmonary injuries: An overview. Chin J Traumatol. 2020;23(3):125–138.
2. Milisavljevic S, Spasic M, Arsenijevic M. Thoracic trauma. In: Cagini L., editor. Current Concepts in General Thoracic Surgery. InTech; 2012.
3. Demirhan R, Onan B, Oz K. Comprehensive analysis of 4205 patients with chest trauma: a 10-year experience. Interact Cardiovasc Thorac Surg. 2009;9:450–453.
4. Berg RJ, Inaba K, Recinos G, Barmparas G, Teixeira PG, Georgiou C, et al. Prospective evaluation of early follow-up chest radiography after penetrating thoracic injury. World J Surg. 2013;37(6):1286–90.
5. Oikonomou A, Prassopoulos P. CT imaging of blunt chest trauma. Insights Imaging. 2011;2(3):281–295. doi:10.1007/s13244-011-0072-9. Epub 2011 Feb 11.
6. Larson MM. Ultrasound of the thorax (noncardiac). Vet Clin North Am Small Anim Pract. 2009;39(4):733–45. doi:10.1016/j.cvsm.2009.04.006.
7. A. Ebrahimi, M. Yousefifard, H. Mohammad Kazemi, Rasouli HR, Asady H, Jafari AM, et al. Diagnostic accuracy of chest ultrasonography versus chest radiography for identification of pneumothorax: a systematic review and meta-analysis Tanaffos,. 2014;13:29–40.
8. Wilkerson RG, Stone MB. Sensitivity of bedside ultrasound and supine anteroposterior chest radiographs for the identification of pneumothorax after blunt trauma. Acad Emerg Med. 2010;17(1):11–7.
9. Heydari F, Esmailian M, Dehghanniri M. Diagnostic Accuracy of Ultrasonography in the Initial Evaluation of Patients with Penetrating Chest Trauma. Emergency. 2014;2(2):81–4.
10. Ding W, Shen Y, Yang J, He X, Zhang M. Diagnosis of pneumothorax by radiography and ultrasonography: a meta-analysis. Chest. 2011;140(4):859–66.
11. McEwan K, Thompson P. Ultrasound to detect haemothorax after chest injury. Emerg Med J. 2007;24(8):581–2.
12. Sabri YY, Hafez MAF, Kamel KM, Abbas DA. Evaluating the role of ultrasound in chest trauma: Common complications and computed tomography comparative evaluation. The Egyptian Journal of Radiology and Nuclear Medicine. 2018;49(4):986–92.
13. M. Hurley, G. Keye, S. Hamilton Is ultrasound really helpful in the detection of rib fractures? Injury. 2004;35(6):562–566.
14. S. Helmy, B. Beshay, M. Abdel Hady, A. Mansour Role of chest ultrasonography in the diagnosis of lung contusion Egypt J Chest Dis Tuberculosis. 2015;64(2):469–475.
15. Yang Jx, Zhang M, Liu Zh, Ba L, Gan J, Xu S. Detection of lung atelectasis/consolidation by ultrasound in multiple trauma patients with mechanical ventilation. Crit Ultrasound J. 2009;1:13–16.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Diffusion MR Imaging in Evaluation of Treatment Response in Patients with Lung Cancer

Akciğer Kanserli Hastalarda Tedavi Yanıtının Değerlendirilmesinde Difüzyon MR Görüntüleme

Melike Sener Sorgun[1], Feray Aras[2], Cihan Goktan[3], Deniz Ozel[1]

[1]Department of Radiology, Cigli Training and Research Hospital, Bakırcay University, Izmir; [2]Department of Nuclear Medicine, Celal Bayar University, Manisa; [3]Department of Radiology, Celal Bayar University, Manisa, Türkiye

ABSTRACT

Aim: *To observe the change in apparent diffusion coefficient (ADC) value after chemoradiotherapy in lung cancer and to investigate the ability of the change in ADC values to detect response to treatment earlier than computed tomography (CT).*

Material and Methods: *This prospective study was performed in patients with a confirmed diagnosis of stage III-IV lung cancer and included 25 patients who underwent T2-weighted MR, diffusion-weighted images (DWI), CT, and FDG PET/CT. Thoracic diffusion MRI and CT examinations were performed on patients who received chemoradiotherapy. Post-therapy; Thoracic diffusion MRI was repeated one week after the two cycles of chemotherapy and two weeks after the end of the radiotherapy, while post-therapy CT was performed four or five weeks after therapy. Before and after treatment, ADCmin, ADCmean, and SUVmax values were compared with each other.*

Results: *Data analysis revealed a statistically insignificant inverse correlation between the pre-therapy ADCmin and SUVmax (r=-0.36; p=0.077) with ADCmean and SUVmax (r=-0.283; p=0.170). Post-therapy repeated measures revealed that increased ADCmin values were significantly higher with the tumor size change (r=-0.872; p=0.000) and median size (r=-0.847; p=0.001) tumor on CT.*

Conclusion: *ADC measurements with DWI may be a new prognostic marker in lung cancers predicting early response to chemotherapy in lung cancer.*

Keywords: *diffusion; apparent diffusion coefficient; lung cancer; responce to treatment; magnetic resonance imaging*

ÖZET

Amaç: *Akciğer kanserinde kemoradyoterapi sonrası görünür difüzyon katsayısı (ADC) değerindeki değişimi gözlemlemek ve ADC değerlerindeki değişimin bilgisayarlı tomografi (BT)'den daha erken tedaviye yanıtı belirleme yeteneğini araştırmak.*

Materyal ve Metot: *Bu prospektif çalışma, evre III-IV akciğer kanseri tanısı doğrulanmış hastalarda yapıldı ve T2 ağırlıklı MR, difüzyon ağırlıklı görüntüler (DAG), BT ve FDG PET/BT yapılan 25 hastayı içeriyordu. Kemoradyoterapi alan hastalara torasik difüzyon MRG ve BT incelemeleri yapıldı. Tedavi sonrası; Torasik difüzyon MRG, iki kür kemoterapi bitiminden bir hafta sonra ve radyoterapi bitiminden iki hafta sonra tekrarlanırken, tedavi sonrası BT, tedaviden dört veya beş hafta sonra yapıldı. Tedavi öncesi ve sonrası ADCmin, ADCmean ve SUVmax değerleri birbirleri ile karşılaştırıldı.*

Bulgular: *Veri analizi, tedavi öncesi ADCmin ve SUVmax (r=-0,36; p=0,077) ile ADCmean ve SUVmax (r=-0,283; p=0,170) arasında istatistiksel olarak anlamsız bir ters korelasyon ortaya çıkardı. Tedavi sonrası tekrarlanan ölçümler, BT'de tümörün büyük boyutunun (r=-0,872; p=0,000) ve median boyutunun (r=-0,847; p=0,001) değişimiyle, artan ADCmin değerlerinin önemli ölçüde daha yüksek olduğunu ortaya koydu.*

Sonuç: *DAG ile ADC ölçümleri, akciğer kanserinde kemoterapiye erken yanıtı öngören yeni bir prognostik belirteç olabilir.*

Anahtar Kelimeler: *difüzyon; görünür difüzyon katsayısı; akciğer kanseri; tedaviye yanıt; manyetik rezonans görüntüleme*

Introduction

Lung cancer is the most common type of cancer in the world and in our country, as well as the most common cause of cancer-related deaths[1,2]. While it was a rare disease in the early 20th century, its frequency increased in parallel with the increase in smoking habits[3,4]. Lung cancer is responsible for 12.8% of cancer cases and 17.8% of cancer deaths worldwide[5].

İletişim/Contact: *Melike Şener Sorgun, Bakırçay University, Çigli Regional Eduation Hospital, Çiğli, İzmir, Türkiye* • ***Tel:*** *0530 873 76 73* • ***E-mail:*** *melike.sener@hotmail.com* • ***Geliş/Received:*** *06.08.2022* • ***Kabul/Accepted:*** *27.02.2023*

ORCID: *Melike Şener Sorgun, 0000-0002-5422-9404 • Feray Aras, 0000-0001-5867-5367 • Cihan Göktan, 0000-0002-0147-1109 • Deniz Özel, 0000-0002-4950-001X*

Kafkas J Med Sci 2023; 13(1):62–70
doi: 10.5505/kjms.2023.47640

Determination of the individual response to treatment in lung cancer is extremely important in order to avoid unnecessary doses as well as to prevent unnecessary expenditure. The change in the size of the tumor may be behind the biological and molecular changes, therefore there may not be an early and sensitive indicator in the evaluation of response to treatment[6].

Due to the problems arising from the physics of the lungs, the use of MR in the evaluation of lung pathologies has lagged. However, with the new MR sequences and functional MRI applications, studies on the use of lung MRI in the early diagnosis, staging and follow-up of lung cancer have gained momentum. However, when applied after radiotherapy, MRI provides excellent soft tissue contrast and real-time adaptive therapy opportunity for tumor and normal tissue identification[7]. Computed tomography (CT) and Positron Emission Tomography / Computed Tomography (PET-CT), which are used routinely to evaluate tumor size and tumor metabolism after treatment, have some limitations in the differentiation of residual tumor tissue from necrotic tumor and fibrotic scar tissue. Diffusion-weighted imaging (DWI), which provides functional evaluation, provides additional important information in staging of lung cancer, calculating the true diameter of the tumor, separating tumor tissue from atelectasis, collapse, post-obstructive change, distinguishing high cell tumors from necrotic or normal tissue and evaluating early response to chemotherapy[8,9]. In lung cancer, DWI has been shown to more effectively delineate gross tumor volumes within the atelectatic lung than CT or PET/CT[7]. The ADC (Apparent Diffusion Coefficient), which shows the water mobility in the tumor and replaces the marker of tissue cellularity, can distinguish high cell tumor tissue from normal tissue or necrotic areas[8,9]. Therefore, changes in ADC values may be used in monitoring of response to treatment, which manifests itself as a change in the cellularity of the tumor[9,10].

Since diffusion MRI does not have a radiation risk, multiple examinations can be performed on the same patient and maybe an alternative to CT in follow-up[10,11]. Shorter examination time, noninvasive, relatively inexpensive examination and no need for contrast media are other advantages of the method. It has been shown in previous studies that the change of ADC values can be used as an indicator for the evaluation of response to treatment in many organ tumors.

The aim of our study was to investigate the ability of the change in ADC values after chemoradiotherapy in lung cancer in early detection of response to treatment.

Materials and Methods

Study Population

The study performed between February 2015 and December 2015. The patients were informed about the adverse effects of diffusion MRI and written informed consent was obtained from the patients who accepted the procedure. Computed tomography and PET-CT were performed according to the pre-treatment routine diagnosis and staging protocol. In addition, a thoracic MRI scan including axial T2-weighted MRI and Diffusion MR sequences was performed at 1.5 T MRI. Diffusion MRI was performed 1 week after two cycles of chemotherapy and 2 weeks after the radiotherapy. Post-control thorax CT imaging was performed 1 month after the treatment.

Inclusion Criteria

* Over 18 years old,
* Histopathologically diagnosed as primary lung cancer,
* Patients not previously treated for lung cancer
* Stage III and stage IV small cell and non-small cell lung cancers

The Criteria for Exclusion

* Contraindications to MRI
* Interruption of chemo-radiotherapy
* Tumor less than 1 cm in size
* DWI artifacts that prevent optimal evaluation
* Indeterminate tumor borders

In the axial plane, a single-shot inversion recovery echo-planar sequence (SSIR EPI) was administered without breath. SSEP-SE T2 was obtained by applying diffusion sensitive gradients at two different values in every 3 directions (x, y, z). 0 and 1000 s / mm^2 values were used for the b value. The mean duration of the test was about 5 minutes.

In addition to CT, PET-CT was performed for routine diagnosis and staging in the pre-treatment period, diffusion MRI and T2-weighted images were obtained in our study. In Fig. 1 and Fig. 2, there are pre-treatment images of the 84 years old male patient with SCC diagnosis.

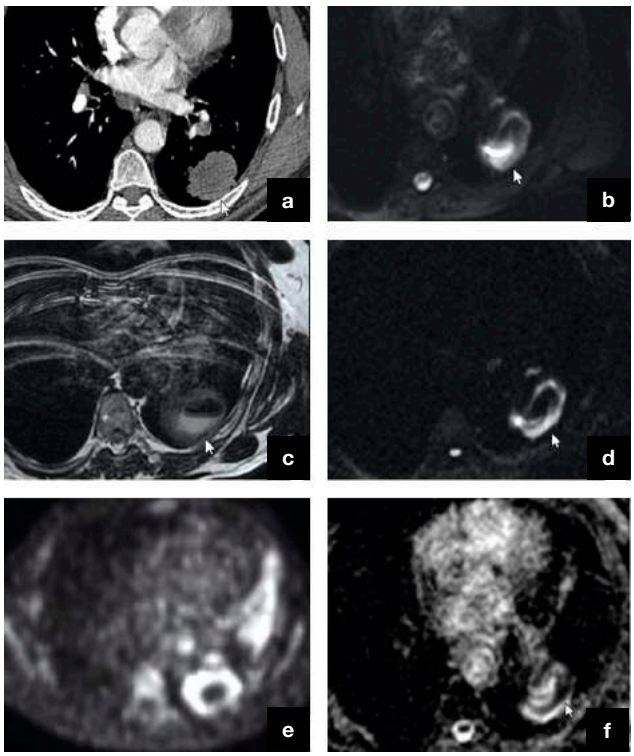

Figure 1. *Fifty-nine years old male patient with NSCLC. The central necrotic mass lesion is located in the left lung lower lobe superior segment, peripherally. Images are from the pre-treatment period.* ***a:*** *Enhanced CT;* ***b:*** *DWI 'b value 0 s/mm²';* ***c:*** *T2 weighted MRI;* ***d:*** *DWI 'b value 1000 s/mm²;* ***e:*** *PET* ***f:*** *ADC map.*

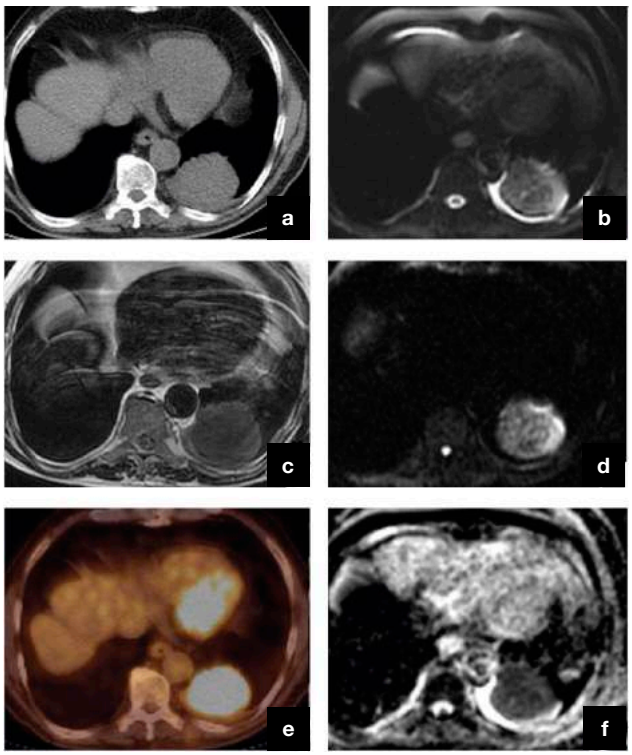

Figure 2. *Eighty-four years old male patient with SCC. A peripheral mass lesion is observed in the posterobasal segment of the lower lobe of the left lung. Images are from the pre-treatment period.* ***a:*** *Unenhanced CT;* ***b:*** *'b 0' value diffusion MR;* ***c:*** *T2 weighted MRI;* ***d:*** *'b 1000' weighted diffusion MR;* ***e:*** *PET-CT* ***f:*** *Apparent diffusion coefficient map. Minimal pleural effusion accompanying the mass lesion is observed in the images. The pleural fluid can be easily selected in b0 value diffusion MR images and on the ADC map, depending on the T2 shine effect.*

Table 1. *Recist guideline*[12]

Response assessment	RECIST guideline, version 1.1
Complete response (CR)	Disappearance of all target lesions and reduction in the short axis measurement of all pathologic lymph nodes to ≤10 mm.
Partial response (PR)	≥30% decrease in the sum of the longest diameter of the target lesions compared with baseline.
Progressive disease (PD)	≥20% increase of at least 5 mm in the sum of the longest diameter of the target lesions compared with the smallest sum of the longest diameter recorded. The appearance of new lesions, including those detected by FDG-PET.
Stable disease (SD)	Neither PR nor PD.

The images were evaluated by two radiologists and a nuclear medicine specialist. The anatomical information obtained from T2-weighted images was also used to evaluate the localization of the tumoral lesion while evaluating the diffusion-weighted images. Before ADC measurements were made, diffusion-weighted images obtained from b=0 sec / mm^2 and b=1000 sec / mm^2 were examined and localizations were determined. For each measurement, a circular shaped ROI (region of interest, interest) was placed on the ADC map of the hyperintense monitored view on b1000 images. The ADC measurements obtained from the imaging results were taken from the solid sections of the masses by considering the contour of the lesion on the ADC maps generated automatically by the device. When calculating ADCmean values, 2–5 times the mass lesion size and heterogeneity were taken into consideration, and these were averaged. Cystic and necrotic components were not included in ROI. The ROIs were circular and the surface area for each lesion was 0.3–0.7 cm^2.

In the pre-treatment period, the SUVmax value of each mass was calculated from the PET-CT images that were routinely performed for diagnosis and staging. The longest diameter of the tumor was determined from the axial sections according to RECIST 1.1 criteria[12] (Table 1) in CT examinations performed before and after treatment with or without contrast. Besides, mean diameters of short and long diameters were obtained. In addition, long dimensions of lesions were measured on axial T2-weighted images.

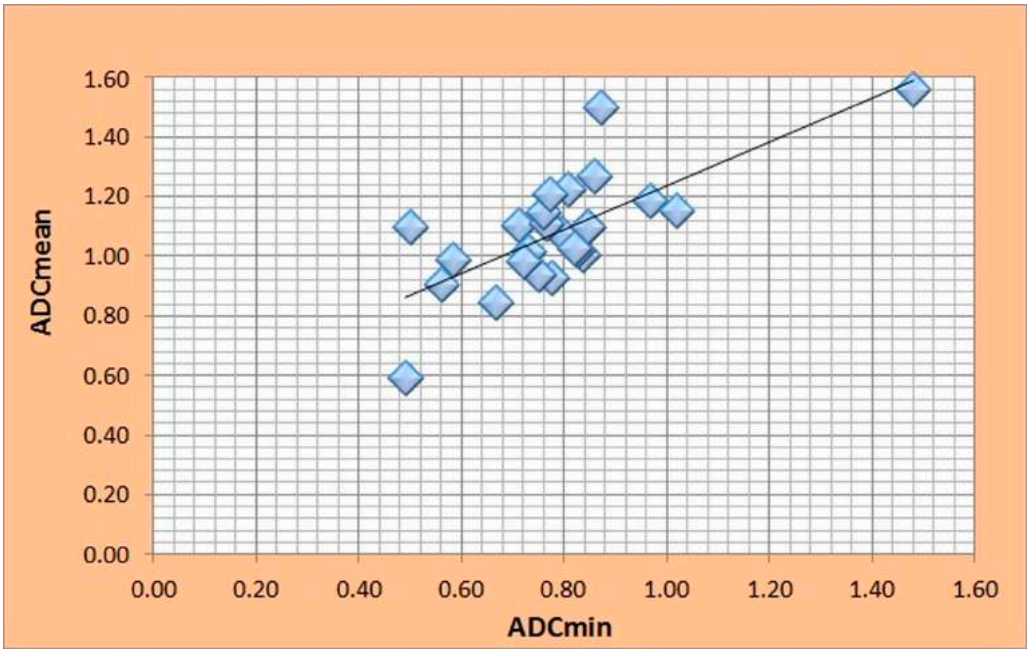

Figure 3. *The chart shows ADCmean and ADCmin values.*

Statistical Analysis

In cases without treatment, the correlation between SUVmax, ADCmin and ADCmean values obtained from the lesions before the treatment were investigated using Pearson's correlation coefficient (n=25). Figure 3 shows ADCmean and ADCmin values in this study.

In the cases treated; the percentage of ADC values and tumor diameters (long-short-mean dimensions in CT, long diameters in T2) were calculated. The rate of change between SUVmax, ADCmin, ADCmean values and the long, short and average diameters of the tumor before and after treatment was calculated as the percentage of four patients in whom the response to treatment with PET-CT in the post-treatment period was evaluated.

The correlation between tumor diameters, ADCmin and ADCmean values in the pre-treatment period, and the changes in the post-treatment period were investigated using the Wilcoxon signed ranks test (n=11). Spearman's statistical rho test was used to determine whether there was a statistically significant difference between ADCmin and ADCmean values and tumor diameters (n=11). $p<0.05$ was considered significant for statistical testing. Analyzes were done in the computer environment. IBM Statistical Package for Social Sciences program version 15.0 (USA) was used for statistical analysis.

Table 2. *Distribution of the data of the patient group according to histopathological typing (n=25)*

N=25	SCC	Adeno Ca	NSCLC	SCLC
Age range	44–86	65–69	58–80	56–70
Gender				
Male	16 –	2	4 –	2 –
Female		1		
Grade				
Stage 3	7	0	3	0
Stage 4	9	3	1	2
Placement				
Right lung	7	1	1	2 –
Left lung	9	2	3	
Intrapulmonary location				
Central	4	1	1	1
Peripheral	5	1	2	1 –
Central + peripheral	7	1	1	

SCC: Squamous Cell Cancer; NSCLC: Non-small cell cancer; SCLC: Small cell cancer.

Results

Twenty-five patients were included in the study. The mean age of the patients was 55.6 years (46–62) and 1 of the 25 patients (4%) was female and the others were male (96%). Pathological diagnosis of the patients was made by bronchoscopy in 17 (68%) and by transthoracic cutting needle biopsy in 8 (32%). Histopathological; 16 cases (64%) were diagnosed with squamous cell carcinoma, 3 (12%) adenocarcinoma, and 2 SCLC (8%). Subtyping was not performed in 4 cases (16%)

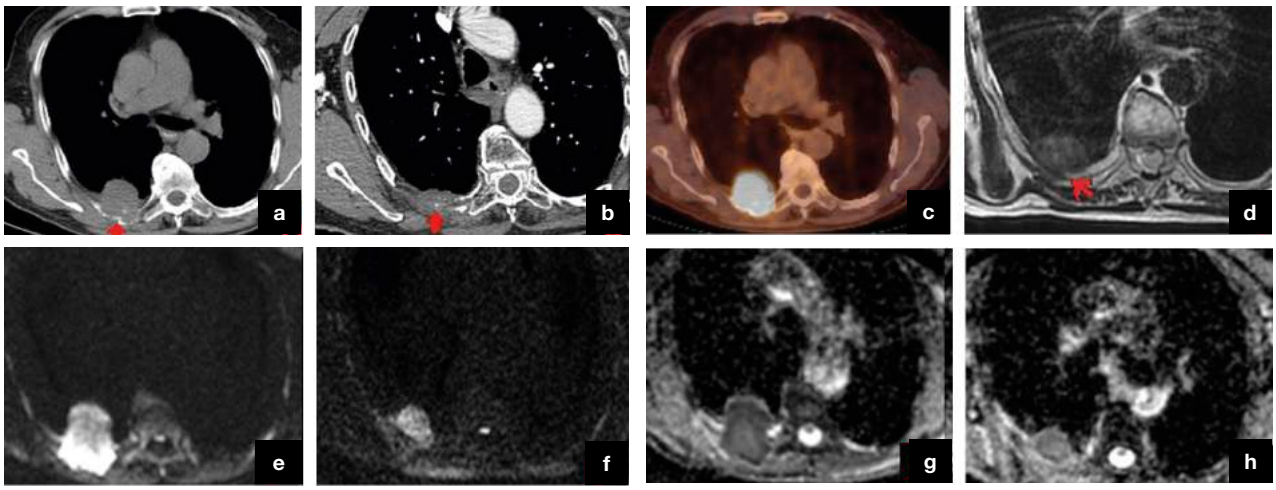

Figure 4. *Seventy-two years old male patient with SCC. The mass appears to have invaded the chest wall.* ***a:*** *Prettreatment non-enhanced CT imaging* ***b:*** *Posttreatment enhanced CT imaging* ***c:*** *pretreatment PET-CT* ***d:*** *Posttreatment T2 WI* ***e:*** *Pretreatment DWI* ***f:*** *Posttreatment DWI* ***g:*** *Pretreatment ADC* ***h:*** *Posttreatment ADC.*

diagnosed with NSCLC. There was no patient with a diagnosis of large cell lung cancer.

Tumoral lesions were located on the right lung in 11 patients (44%), and on the left in 14 patients (56%). Of these, 7 (28%) were central, 9 (36%) were peripheral, and 9 (36%) were both central and peripheral. In staging, 10 patients (40%) were classified as stage-III, and 15 patients (60%) as stage-IV. 9 patients (92%) were given cisplatin + gemcitabine, 1 patient (4%) gemcitabine + carboplatin treatment, and 1 patient (4%) radiotherapy (RT). In imaging modalities, the minimum and maximum diameters of the target lesions in the lungs were 94–16 mm according to RECIST 1.1 criteria. Table 2 shows the distribution of the data of the patient group participating in the study according to histopathological typing.

Thoracic CT, thorax diffusion MRI and PET-CT examinations of the patients were examined. ADC values were based on diffusion MR images obtained at our workstation before and 1 week after CRT; Mass sizes were also evaluated from thoracic CT images obtained before and 3–4 weeks after CRT. The correlation between SUVmax and ADCmin and ADCmean values in 25 cases in the pre-treatment period was evaluated using the Pearson correlation coefficient (r). The correlation coefficient is r=-0.36 between SUVmax-ADCmin values, and r=-0.283 between SUVmax-ADCmean values. According to these results, a negative but weak correlation was found between SUVmax and ADCmin-ADCmean. Table 3 shows the relationship between SUVmax and ADCmin and ADCmean values.

The correlation between ADCmin and ADCmean values is statistically significant (r=0.74, p=0.000).

Table 3. *Correlation of SUVmax with ADCmin and ADCmean values in the pre-treatment period*

Parameters	r	p
SUVmax-ADCmin	-0.360	0.077
SUVmax-ADCmean	-0.283	0.170

r: Pearson correlation coefficient.

Table 4. *Before and after treatment SUVmax, ADC values and tumor diameters change according to histopathological types*

Type	SUVmax (before)	ADCmin (before) (10^{-3} mm^2/s)	ADCmean (before) (10^{-3} mm^2/s)	Size (before) (mm)	SUVmax (after)	ADCmin (after) (10^{-3} mm^2/s)	ADCmean (after) (10^{-3} mm^2/s)	Size (after) (mm)
NSCLC	15.1	0.795	1.078	46	7.9	1.140	1.253	40
SCC	11.4	0.730	1.015	90	6	0.846	1.223	78
SCC	8.6	0.540	0.815	58	4.2	1.081	1.248	50
SCC	21.3	0.860	1.270	80	7.8	0.841	1.208	83

SCC: Squamous Cell Cancer; NSCLC: Non-small cell cancer.

Table 5. *Changes in ADC values and tumor diameters before and after treatment*

Parameters	Before treatment	After treatment	p	N
ADCmin (10^{-3} mm^2/s)	0.75±0.13	0.95±0.2	0.026	11
ADCmean (10^{-3} mm^2/s)	1.04±0.15	1.25±0.2	0.026	11
Longest diameter (cm)	6.7±2.2	6.3±2.8	0.248	11
Average diameter (cm)	5.5±2.2	4.8±2.3	0.130	11
Shortest diameter (cm)	4.7±1.8	3.8±2	0.083	11

Wilcoxon signed ranks test.

Table 6. *Correlation of the change in tumor size with ADCmin and ADCmean values in the post-treatment period (ρ=Spearman's rho coefficient)*

Parameters	r	p
ADCmin – long diameter	-0.870	0.000
ADCmin – average diameter	-0.774	0.005
ADCmin – short diameter	-0.450	0.165
ADCmin – T2 long diameter	-0.806	0.003
ADCmean – long diameter	-0.460	0.154
ADCmean – average diameter	-0.409	0.212
ADCmean – short diameter	-0.210	0.536
ADCmean – T2 long diameter	-0.473	0.142

PET-CT was performed on 4 patients for therapeutic evaluation after treatment. 3 of these were SCC and 1 of them was NSCLC with no subtype. In addition to ADC values and dimensions of the lesions in these patients, SUVmax values were noted, and percentage change values before and after treatment were calculated. Figure 4 shows the transformation of the tumoral lesion in the pre-treatment and post-treatment imaging. After therapy, a decrease in SUVmax values and in the longest diameter and an increase in ADC values were observed in tumoral lesions in all four patients. The change of tumor sizes in ADC, SUVmax and CT according to histopathological typing is shown in Table 4.

The change in ADC values and tumor diameters before and after the treatment is shown in Table 5. While the change of ADCmin and ADCmean values were found to be statistically significant (p <0.05), there was no statistically significant difference between the changes in lesion sizes (p >0.05).

In the post-treatment period, the relationship between ADCmin, ADCmean values and tumor size changes was evaluated with Spearman's rho test. (p=-0.870), long diameter of the tumor in ADCmin-T2AG (r=-0.806) and ADCmin-mean tumor diameter (p=– 0.774) after treatment (p <0.05). The correlation between ADCmean-tumor T2 long diameter (r=-0.473), ADCmean-tumor long diameter (p=– 0.460), ADCmin-short diameter (p=-0.450) and ADCmean-mean diameter (p=-0.409) and A statistically insignificant correlation was found (p >0.05). There was no correlation between ADCmean-tumor short diameter (Spearman's rho=-0.210, p=0.536) (Table 6).

Among the 11 patients who received treatment, post-treatment dimensional regression in 8 cases, whereas increase in ADCmin and ADCmean values; Dimensional progression and decrease in ADCmin and ADCmean values were observed in 3 cases. As a result, an inverse correlation was found between the post-treatment ADCmin and ADCmean values and the changes in lesion size.

When evaluated according to RECIST1.1; with a reduction of 47%, 32%, 33% and 30% in size, partial response was predicted in 4 patients, and progressive disease was predicted in 2 patients with a decrease of 10% and 13%.

Discussion

The most common histopathological type was squamous cell carcinoma with 16 cases (64%). Adenocarcinoma, the most common lung cancer besides SCC, was observed in only 3 of our cases. This may be because our working group is small-scale.

Approximately 30% of patients with NSCLC may have tumor progression after the onset of chemotherapy. It is important to recognize this situation as early as possible, to stop the treatment and apply an alternative treatment[13,14]. Thomas J. Vogl et al in their retrospective study, measured ADC values in 47 patients with 68 lung lesions, who underwent percutaneous microwave ablation with inoperable lung neoplasms. They found a statistically significant difference in ADC value measured 24 h after the ablation between the responding and non-responding groups[15]. In our study,

a decrease was observed in ADCmin and ADCmean values after treatment in 3 cases. Control CT examinations performed 1 month after the treatment showed an increase in tumor size. One of them was in the "stable disease" category according to RECIST 1.1, and the other two were in the "progressive disease" category. Changes in diameter and ADC values were found to be correlated with each other in all 11 cases.

Jagoda et al evaluated the tumor diameters and volumes in 20 patients with stage I-III NSCLC from CT i.v. contrast agent and non-enhanced MRI images before and 3, 6 and 12 months after radio-chemotherapy. They found no significant difference regarding longest longitudinal diameter and tumor volume between Diffusion MRI and CT in addition patients with a good tumor response have higher ADC values than non-responders[16]. In our study, we observed an inversely proportional change in the size of the tumor and ADCmin values after treatment, but we did not see a significant relationship between the categorization of treatment response according to the Recist's criteria and the percentages of changes in ADCmin values.

Apparent diffusion coefficient maps are generally not homogeneous on the normal and cancerous sides. Therefore, where the region of interest (ROI) is placed is very important. In our study, especially in ADC measurements performed several times from heterogeneous lesions, ADCmin values were obtained close to each other, while more variable values were obtained in repeated measurements in ADCmean values. For this reason, we think that ADCmin values give more stable and objective results than ADCmean. In our study, there was a significant correlation between ADCmin and the longest diameter and ADCmin and mean diameter changes in the post-treatment period, while there was no statistically significant correlation between ADCmean and tumor size changes (long-short-mean diameters). Significant values could not be obtained between ADCmin and the shortest diameter.

In one study, 45 FDG-PET / MRI scans were performed on 11 patients, and although the overall changes measured by ADC did not change significantly, a significant overall decrease in FDG uptake was found from pre-treatment scans to post-treatment scans[17]. In our study, the correlation between SUVmax-ADCmin and SUVmax-ADCmean values was investigated in 25 patients before treatment. Statistical significance was not detected between SUV and ADC values. Therefore, a negative correlation was found between SUVmax-ADCmin and SUVmax-ADCmean values. However, the correlation between SUVmax and ADCmin values was found to be more significant than the relationship between SUVmax and ADCmean values. In 4 of our patients who underwent PET after treatment, an inverse ratio was observed between the change in SUVmax values and the change in ADCmin values in all lesions. In three cases diagnosed with NSCLC, a strong relationship was observed in the change in ADCmin and SUVmax values compared to the case diagnosed with SCC. We have 3 cases with a dimensional progression and decrease in ADC values on CT and T2-weighted MR images. In these cases, pre-treatment SUVmax values were determined as 21.3, 15.5 and 10.5. SUVmax=21.3 also constitutes the highest SUV value in our patient group (n=25). In 2 of these 3 cases, SUVmax value was found to be above the average of 13.9 SUVmax values of 11 patients treated. ADCmin values are below the average value in all three cases and ADCmean values are above the average. Even though lesions showed an increase in size at CT, all 3 patients were stable according to the RECIST criteria. The change in SUVmax and ADCmin values were compatible and more pronounced than the change in tumor size.

In the case of SCC diagnosis, SUVmax value was 21.3 and ADCmin was 0.860×10^{-3} mm^2/s in central part of tumor. Posttreatment 1 week after chemotherapy ADCmin increased (51%) while 4 weeks after therapy SUVmax decreased (-63%). In the post-treatment period, SUVmax decreased by 178% and ADCmin value decreased by 53% in the peripheral part of the tumor. However long tumor diameter increased by 4 % were observed (Fig. 2). Brightening was detected in DWI compatible with PET-CT images. SUVmax and ADCmin values of the lesion, which was observed as a hilar localized mass in the post-treatment period it was interpreted as a significant regression. In the peripheral area, posttreatment SUVmax and ADCmin values were competent with progression. The increase in the size of the tumor also supported this. However, according to the RECIST criteria, it was categorized in the stable disease group.

In the study conducted by Komori et al on 16 patients with lung, colon, breast and parathyroid cancer, the examinations of the patients who underwent PET-CT and DWI were evaluated visually and more lesions were detected correctly in DWI than PET-CT[18]. As a result of the visual evaluations, we performed in our study, 2

tumoral lesions detected in PET-CT could not be observed in DWI, while all lesions detected in DAG were also observed in PET. These two lesions completely disappeared in post-treatment imaging. Considering the small number of patients, it is not possible to comment on the sensitivity of PET-CT and compare it with DWI for our study.

Thomas J. Vogl et al, performed ADC analysis on thirty-one patients with 13 primary and 29 secondary lung target lesions before and after the first session of trans arterial chemoperfusion or transpulmonary chemoembolization. They found that the ADC change showed a strong negative correlation with the change in diameter and volume in primary and secondary lung lesions, especially in primary lesions[19]. In our study, we obtained consistent directional changes in size measurements from ADC and post-treatment CT examinations in all patients who received treatment (n=11). However, in our study, there is a significant correlation between the changes in ADCmin values and the changes in the mean and long diameters of the tumor in the post-treatment period, and a negative correlation between the changes in the ADCmean and the tumor size (short-long-mean size). There was no correlation between the short dimension and ADCmin and ADCmean values.

There are some limitations of our study, the first of which is the small number of cases. Another limitation is the low histopathological diversity of our study group. Therefore, diffusion properties and ADC values of the lesions could not be compared according to histopathological types. Since PET-CT was performed on only 4 patients in the post-treatment period, the relationship between SUV and ADC values could not be investigated in the other 7 patients in the post-treatment period. Although there was a significant negative correlation between the post-treatment ADCmin values and the changes in the mean size and longest diameter of the tumor, statistically significant results could not be obtained due to the small number of patients who received treatment, and there is a need to study with larger patient groups.

In conclusion, Diffusion MR, which enables us to obtain information from tissues at a microscopic level; has very important advantages such as not using intravenous contrast material, no need for patient preparation, tolerable examination time (5 minutes), and obtaining PET-like images. In addition, the fact that it is relatively cheap and easily accessible, and most importantly, the absence of ionizing radiation exposure unlike CT, PET and PET-CT have accelerated the studies in this field.

Diffusion-weighted images can be used as an alternative method, especially in patients with a long life expectancy and PET-CT is contraindicated. Since it does not contain radiation, the radiation dose can be reduced with this method in patients who need to be followed up at short intervals.

The correlation of the change in ADC values after chemoradiotherapy (CRT) with the change in lesion sizes in patients with lung cancer can provide valuable information to the clinician in terms of evaluating the early response to CRT and establishing effective treatment protocols. In this way, patients can be protected from the toxicity of both ionizing radiation and contrast agents and chemo radiotherapeutics. We think that DWI and ADC measurements can be used as prognostic markers in evaluating the response to treatment in lung cancer.

Statement of Ethics

Our institutional human research ethics committee approved this prospective study (Approval no: 2015-20478486-66).

Conflict of Interest Statement

All the authors declare no conflict of interest.

References

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: Int J Cancer. 2010;127:2893–2917.
2. Yilmaz HH, Yazihan N, Tunca D, et al. Cancer trends and incidence and mortality patterns in Turkey Jpn J Clin Oncol. 2011;41:10–16.
3. Loeb LA, Ernster VL, Warner KE, et al. Smoking and lung cancer: an overview. Cancer Res. 1984;44(12 Pt 1):5940-5958.
4. Spiro SG, Porter JC. Lung cancer--where are we today? Current advances in staging and nonsurgical treatment. Am J Respir Crit Care Med. 2002;166:1166–1196.
5. Cai Z, Liu Q. Understanding the Global Cancer Statistics 2018: implications for cancer control. Sci China Life Sci. 2021;64:1017–1020.
6. Desar IM, van Herpen CM, van Laarhoven HW, et al. Beyond RECIST. molecular and functional imaging techniques for evaluation of response to targeted therapy. Cancer Treat Rev. 2009;35:309–321.

7. Austin J. Sim, Evangelia Kaza, Lisa Singer, et al. A review of the role of MRI in diagnosis and treatment of early stage lung cancer. Clin Transl Radiat Oncol. 2020; 24:16–22.
8. Zhang Y, Chen J, Shen J, et al. Apparent diffusion coefficient values of necrotic and solid portion of lymph nodes: differential diagnostic value in cervical lymphadenopathy. Clin Radiol.2013;68:224-231.
9. Barnes A, Alonzi R, Blackledge M, et al. UK quantitative WB-DWI technical workgroup: consensus meeting recommendations on optimisation, quality control, processing and analysis of quantitative whole-body diffusion-weighted imaging for cancer. Br J Radiol.2018;91:20170577.
10. Cui Y, Zhang XP, Sun YS, et al. Apparent diffusion coefficient: potential imaging biomarker for prediction and early detection of response to chemotherapy in hepatic metastases. Radiology. 2008;248:894–900.
11. Chen L, Zhang J, Chen Y, et al. Relationship between apparent diffusion coefficient and tumour cellularity in lung cancer. PLoS One. 2014;9:e99865.
12. Eisenhauer E, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228.
13. Lazzari C, Bulotta A, Ducceschi M, et al. Historical Evolution of Second-Line Therapy in Non-Small Cell Lung Cancer. Front Med (Lausanne). 2017;4:4.
14. Wei M, Ye Q, Wang X, et al. Early tumor shrinkage served as a prognostic factor for patients with stage III non-small cell lung cancer treated with concurrent chemoradiotherapy. Medicine (Baltimore)2018;97:e0632.
15. Vogl TJ, Emara EH, Elhawash E, et al. Feasibility of diffusion-weighted magnetic resonance imaging in evaluation of early therapeutic response after CT-guided microwave ablation of inoperable lung neoplasms. Eur Radiol. 2021;19.
16. Jagoda P, Fleckenstein J, Sonnhoff M, et al. Diffusion-weighted MRI improves response assessment after definitive radiotherapy in patients with NSCLC. Cancer Imaging. 2021;21:21.
17. Langer NH, Langer SW, Johannesen HH, et al. Very Early Response Evaluation by PET/MR in Patients with Lung Cancer-Timing and Feasibility. Diagnostics (Basel) 2019 26;9:35.
18. Komori T, Narabayashi I, Matsumura K, et al. 2-(Fluorine-18)-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography versus whole-body diffusion-weighted MRI for detection of malignant lesions: initial experience. Ann Nucl Med. 2007;21:209–215.
19. Vogl TJ, Hoppe AT, Gruber-Rouh T, et al. Diffusion-Weighted MR Imaging of Primary and Secondary Lung Cancer: Predictive Value for Response to Transpulmonary Chemoembolization and Transarterial Chemoperfusion. J Vasc Interv Radiol. 2020;31:301-310.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Factors Affecting Admission Frequency and Compliance with Antihypertensive Treatment of Patients Presenting to the Emergency Department with Hypertensive Attack

Acil Servise Hipertansif Atak Şikâyeti ile Başvuran Hastaların Antihipertansif Tedaviye Uyumu ve Başvuru Sıklığını Etkileyen Faktörler

Atakan Yilmaz[1], Uzeyir Cimen[2], Canan Uluoglu[3], Yesim Kinaci Cimen[4], Alten Oskay[5], Murat Seyit[1], Mert Ozen[1], Ibrahim Turkcuer[6], Gizem Oncel Yel[1], Mehmet Uluturk[1], Aykut Kemanci[1]

[1]Servergazi State Hospital, Emergency Service, Denizli; [2]Pamukkale University, Faculty of Medicine, Department of Emergency Medicine, Denizli; [3]Gazi University, Faculty of Medicine, Department of Medical Pharmacology, Ankara; [4]Pamukkale University, Faculty of Medicine, Department of Family Medicine, Denizli; [5]Burdur State Hospital, Emergency Service, Burdur; [6]Tavsanli State Hospital, Emergency Service, Kutahya, Türkiye

ABSTRACT

Aim: *Admission to the emergency department (ED) due to a hypertensive attack (HTA) is common. Our study explores patients' compliance with HTA to blood pressure (BP) treatment, the interrelationship of BP values, and their interaction with other factors.*

Material and Method: *Two hundred and sixty seven patients admitted to our ED with the complaint of HTA and previously diagnosed with hypertension were enrolled in this study. During the data collection phase of the study, the Hill-Bone Compliance to High Blood Pressure Therapy Scale (HBCS) and a questionnaire including the sociodemographic characteristics, hypertension-related status, and dietary habits were filled in through face-to-face interviews with the patients.*

Results: *The patients' mean systolic blood pressure (SBP) was 168.77±26.83, and their mean diastolic blood pressure (DBP) was 98.03±10.44 at the time of admission. Their mean HBCS score turned out to be 4.78±1.79. The mean HBCS total scores tended to decrease significantly as the level of education increased. The patients restricting their salt intake and going on a diet achieved lower HBCS scores, and the difference between the groups was significant. When the patients' mean SBP and DBP were compared with their HBCS scores, a moderately low correlation was noted between the mean HBCS scores and the mean SBP.*

Conclusion: *The patients with an educational status at the primary school level and below presented lower compliance with treatment. When the HBCS scores were compared in terms of whether the patients went on a diet or not, the mean scores of the dieters turned out to be lower. The patients with high compliance with treatment presented lower SBP and DBP.*

Key words: *compliance with treatment; hypertensive attack; lifestyle change*

ÖZET

Amaç: *Acil servise hipertansif atak nedeniyle başvuran hastalar sık görülmektedir. Çalışmamız hipertansif atak ile başvuran hastaların tansiyon tedavisine uyumunu ve tansiyon değerlerinin birbirleriyle ve diğer faktörlerle olan ilişkisini incelemeyi amaçlamaktadır.*

Materyal ve Metot: *Bu çalışmaya acil servisimize hipertansif atak şikâyeti ile başvuran ve daha önce hipertansiyon tanısı almış 267 hasta dâhil edildi. Araştırmanın veri toplama aşamasında, Hill-Bone Hipertansiyon Tedavisine Uyum Ölçeği (HBHTUÖ –HBCS) ile hastaların sosyodemografik özelliklerini, hipertansiyonla ilgili durumlarını ve beslenme alışkanlıklarını içeren bir anket hastalarla yüz yüze görüşülerek doldurduldu.*

Bulgular: *Hastaların acil servise başvurduklarında sistolik tansiyon ortalaması 168,77±26,83; diyastolik tansiyon ortalaması 98,03±10,44'dur. Katılımcıların ortalama HBHTUÖ puan ortalaması 4,78±1,79'dur. Hill-Bone hipertansiyon tedavisine uyum ölçeği total puan ortalamaları eğitim seviyesi arttıkça anlamlı olarak daha düşük bulunmuştur. Diyet haricinde tuz kısıtlaması yapan hastalarda HBHTUÖ puanları ortalaması daha düşük bulunmuştur ve gruplar arasındaki fark anlamlıdır. Hill-Bone hipertansiyon tedavisine uyum ölçeği ile hastaların ortalama sistolik ve diyastolik tansiyonları korelasyon açısından karşılaştırıldığında HBHTUÖ puanları ortalaması ile sistolik tansiyon ortalaması arasında orta düşük düzeyde korelasyon saptanmıştır.*

Sonuç: *Eğitim durumları ilköğretim ve altı düzeyinde hastaların tedaviye uyumu daha düşük bulunmuştur. Hastaların diyet yapıp/yapmama açısından HBHTUÖ puanları karşılaştırıldığında diyet yapan hastaların puan ortalamasının daha düşük olduğu görülmüştür. Tedaviye uyumu yüksek olan hastaların sistolik ve diyastolik tansiyonu daha düşük bulunmuştur.*

Anahtar Kelimeler: *hipertansif atak; tedavi uyumu; yaşam tarzı değişikliği*

İletişim/Contact: *Atakan Yilmaz, Department of Emergency Medicine, Pamukkale University Hospital, Pamukkale University, of Medical Sciences, Denizli, Türkiye* • ***Tel:*** *0258 296 48 74* • ***E-mail:*** *dr_atakanyilmaz@yahoo.com* • ***Geliş/Received:*** *15.09.2022* • ***Kabul/Accepted:*** *24.11.2022*

ORCID: *Atakan Yılmaz, 0000-0002-9773-5681 • Üzeyir Çimen, 0000-0002-0644-2630 • Canan Uluoğlu, 0000-0003-0682-5794 • Yeşim Kınacı Çimen, 0000-0002-7066-1299 • Alten Oskay, 0000-0003-4373-6280 • Murat Seyit, 0000-0002-8324-9471 • Mert Özen, 0000-0001-6653-3756 • İbrahim Türkçüer, 0000-0001-8342-4615 • Gizem Öncel Yel, 0000-0002-8306-5701 • Mehmet Ulutürk, 0000-0002-4066-3576 • Aykut Kemancı, 0000-0002-6308-3830*

Introduction

35% of the world population is afflicted with hypertension (HT), which is considered a major risk factor for cardiovascular diseases and causes the highest rate of death[1]. Hypertension is defined as 140/90 mmHg and above by the European Society of Cardiology guidelines and 130/80 mmHg and above by the guidelines of the American Heart Association[2,3].

Roughly 15 to 16 million inhabitants in Türkiye are estimated to suffer from HT. According to an updated systematic review in 2015, 22.1% of adults aged 18 years and older worldwide were diagnosed with HT. When it comes to Türkiye, its prevalence has been established as 20.3% in both genders[4].

Though the exact etiology of primary HT has not been fully elucidated, it is considered to be associated with risk factors, such as age, obesity, race, family history, high sodium diet, decreased nephron count, less physical exercise, and excessive alcohol consumption[5–13].

Hypertensive attack (HTA) is defined as hypertension with no risk of end-organ damage in individuals without severe blood pressure (BP) elevations who are aged under 60 years with BP above 140/90 and in those aged 60 years and older with BP above 150/90[14].

In order to achieve success in the treatment of HT, sufferers are supposed to strictly comply with medical treatment, implement lifestyle changes properly, have periodic examinations on time, and monitor their BP as prescribed[15,16]. However, a number of factors impair compliance with treatment in hypertensive patients. Lifestyle changes coupled with administration of medical treatment methods are of great importance in the treatment of HT.

Thus far, many different scales have been developed to evaluate compliance with treatment in patients. Among these scales is the Hill-Bone Compliance to High Blood Pressure Therapy Scale (HBCS), developed by Kim et al. in 2000[17]. This scale includes three important behavioral domains of HT treatment, such as reduced sodium intake, appointment keeping, and medication taking. It can be considered a preferable scale to evaluate the management of individuals with essential HT with respect to drug therapy and lifestyle changes. The validity and reliability of the scale in Turkish was assessed by Karademir et al.[18].

In the present study, we administered the HBCS, which enabled us to evaluate medical compliance, nutritional compliance, and total compliance separately. HBCS, which explores the potentiality of patients to comply with treatment through questions about the causes of non-compliance, was administered to the patients presenting to our emergency department (ED) with complaints of HTA. The importance of this study lies in the fact that it is a first step towards measuring hypertensive patients' compliance with HT treatment and their awareness level about HT.

Materials and Methods

Study Design

The HBCS and a questionnaire form including sociodemographic characteristics as well as the diagnosis, follow-up, and treatment of the participants' HT disease were administered to collect the data in our study. In addition, the BP of the patients was measured over the brachial artery with a digital device (Nihon Kohden® BSM-2301K) calibrated in accordance with the rules, and the measurements were recorded in the form. The questionnaire consisting of 37 questions in total was administered to the respondents through face-to-face interviews.

This descriptive study was conducted on the patients admitted to the ED of a tertiary hospital in Denizli, Türkiye due to HTA complaints between July and August 2022. The prior calculation of the sample size revealed that at least 215 subjects were required for the current study, assuming that the confidence interval was 90%, and that the prevalence was 27.3%. All the HTA patients who matched the research criteria and agreed to participate in the study between the specified dates were recruited for the study. Those over 18 who were diagnosed with HT and presented with HTA complaints were enrolled in the study, whereas those under 18 who suffered from cognitive impairment and the patients who did not agree to participate were excluded. Verbal consent was obtained from the recruited patients. Moreover, the study was initiated after granting the approval from the local ethics committee (approval number and date: 60116787-020/1958/2022). The sociodemographic data and scale scores of the enrolled patients were noted down in the questionnaire form through face-to-face interviews.

Data Collection

In order to collect the study data, we administered the HBCS along with a questionnaire including the

sociodemographic characteristics created as a result of the literature review and the questions about the diagnosis, follow-up, and treatment of the subjects' HT disease. The HBCS includes 14 items designed in a 4-point response pattern: (0) "None of the time", (1) "Some of the time", (2) "Most of the time", and (3) "All of the time". All of the items are constructed in the form of negative questions, except for the 6th question which was reverse coded. In the evaluation phase, the sum of all the questions is taken for the total score; that of 1, 2, 9, 10, 11, 12, 13 and 14th items is taken for the subscale of medication taking; that of 3, 4 and 5th items is taken for the subscale of reducing sodium intake; that of the 6, 7 and 8th items is taken for the subscale of appointment keeping. In addition, the patients' BP was measured over the brachial artery with a digital sphygmomanometer calibrated in accordance with the rules in the Hypertension Diagnosis and Treatment Guideline, and noted down in the questionnaire form. The questionnaire form consists of 37 questions in total (including the 14-item scale). The enrolled patients were interviewed face-to-face by the family medicine research assistant and the emergency medicine research assistants.

Data Analysis

All the collected data were subjected to statistical analysis with IBM Statistical Package for Social Sciences (SPSS) program version 22 package program. The conformity of the variables to the normal distribution was investigated using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk tests). The descriptive analyses were presented as mean and standard deviations for parametric variables, as median and interquartile differences for non-parametric variables, and as frequency tables for ordinal variables. A Chi-square test was used to compare categorical variables, while t-test and ANOVA analysis of variance were performed for normally distributed variables. Mann-Whitney U and Kruskal-Wallis tests were performed in the analysis of non-parametric variables. A Pearson Correlation test was used to calculate the correlation of numerical variables. The significance level was set at $p<0.05$ for all the statistical analyses.

Results

The demographic information of the study population reveals that 47.9% (n=128) of the subjects were women, and 52.1% (n=139) were men. The mean age of all the subjects turned out to be 62.60±10.21. Besides, 46.1% (n=123) resided in the city center, 78.3% (n=209) were married, 40.4% were primary school graduates, and 33% were entitled to social security.

Table 1. *Overall characteristics of the subjects*

	n (%)
	267(100)
Gender	
Female	128 (47.9)
Male	139 (52.1)
The longest residence	
Province	123 (46.1)
Town	83 (31.1)
Village	61 (22.8)
Marital status	
Single	10 (3.7)
Married	209 (78.3)
Divorced/Non-cohabiting	48 (18)
Educational status	
Illiterate	14 (5.2)
Literate	31 (11.6)
Primary school	108(40.4)
Secondary school	39 (14.6)
High school	46 (17.2)
College/University	29 (10.9)
Social security	
Social Insurance Institution (SII)	83 (31.1)
Insuranced Self-Employed Institution (ISEI)	88 (33)
Government Retirement Fund (GRF)	75 (28.1)
Private insurance	4 (1.5)
Green card	12 (4.5)
Not entitled to social security	5 (1.9)
Age (Mean ± S. D.)	62.60±10.26(41–88)
Systolic blood pressure (Mean ± S. D.)	168.77±26.83
Diastolic blood pressure (Mean ± S. D.)	98.36±10.59
Hill-Bone Compliance to High Blood Pressure Therapy Scale (HBCS) (Mean ± S. D.)	4.78±1.79

Their mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the time of admission were measured as 168.77±26.83 and 98.03±10.44, respectively. Their mean HBCS score was calculated as 4.78±1.79 (Table 1). Moreover, 59.2% were non-smokers, and 52.3% had never consumed alcohol before. In relation to chronic conditions, 47.9% had an underlying comorbid disease, and diabetes mellitus (n=56) was the most prevalent comorbid disease (Table 2).

Table 2. *Breakdown of subjects' habits and comorbidities*

	n (%)
	267(100)
Smoking	
Yes	36 (13.5)
Smoked but quit	73 (27.3)
No	158 (59.2)
Alcohol consumption	
Yes	46 (17)
Drank but quit	55 (20.7)
No	166 (62.3)
Comorbidity	
Yes	128 (47.9)
Comorbid disease	
Diabetes mellitus	56 (21)
Coronary artery disease	53 (19.9)
Hyperlipidemia	17 (6.4)
Asthma	10 (3.7)
Chronic renal failure	9 (3.4)
Lifestyle changes in Hypertension (HT)	
Dieting	
Yes	181 (67.8)
No	86 (32.2)
Reduced sodium intake	
Yes	225 (84.3)
No	42 (15.7)
Regular exercise	
Yes	161 (60.3)
No	106 (39.7)
Duration of HT disease	
1 year	16 (6)
1–10 years	159 (59.6)
10^{+} years	92 (39.5)
Regular blood pressure (BP) measurement	
1–3 times a month	74 (28.6)
1–6 times a week	104 (38.1)
Every day	70 (26.2)
Never	19 (7.1)
Medications taken	
Angiotensin converting enzyme (ACE) inhibitor	152 (56.9)
Angiotensin receptor blocker	89 (33.3)
Ca-channel blocker	62 (23.2)
Beta blocker	45 (16.9)
Diuretic	40 (15)

The findings suggest that 34.5% (n=92) had been suffering from HT for more than 10 years. In addition, 67.8% began to go on a diet after being diagnosed with HT, while 84.3% started to reduce their salt intake. The obtained findings also reveal that 60.3% reported to walk for at least 30 min a day once or twice a week, and that 39.5% had been afflicted with HT for more than 10 years. It should be also noted that 38.1% reported to measure their BP at home at least once a week. The most widely-used BP medication by patients was ACE inhibitors (56.9%), and 35.2% were taking more than one antihypertensive medicines (Table 2).

The socio-demographic information of the patients did not yield a significant difference with respect to gender, diet, and reduced sodium intake ($p>0.05$). However, the comparative analysis of these factors in terms of educational status and social security revealed a significant difference ($p<0.05$). As far as marital status is concerned, only reduced sodium intake was significant, with singles paying the least attention to salt restriction ($p<0.05$). Another point to highlight was that, as the education level increased, more attention was paid to diet and reduced sodium intake. It was observed that patients with Social Insurance Institution (SII) and Government Retirement Fund (GRF) as social security follow these recommendations more. When patients were categorized as those under 60 years of age and over 60 years of age, there was no significant difference in diet ($p>0.05$). Furthermore, a significant difference was observable in terms of reduced sodium intake, and those under 60 years of age seemed to attach more importance to this point ($p<0.05$).

When the HBCS scores were compared based on sociodemographic characteristics, no significant difference was evident, despite the gender-wise superiority in favor of women. Considering the total mean scores of HBCS by place of residence where the subjects had lived for the longest time, village had the highest score. As the population of the place of residence increased, the HBCS score decreased significantly. The HBCS scores did not differ significantly, based on the marital status of the subjects. However, the mean total HBCS scores differed significantly in terms of educational status. The mean total HBCS scores proved to be significantly lower as the level of education increased. When the HBCS scores were compared based on the duration of HT disease, the patients afflicted with HT for more than 10 years had higher scores than the other two groups, and a statistically significant difference was observed (Table 3). In addition, the subjects were asked to report whether they had made any lifestyle changes in terms of HT after being diagnosed with HT. When the HBCS scores of the dieters and non-dieters were compared, the mean score of the dieters turned out to be lower, which also yielded a significant difference. Moreover, the subjects who restricted their salt intake in addition to dieting were observed to have more reduced HBCS scores, and the difference between the groups was statistically significant.

Table 3. *Evaluation of HBCS total score averages based on sociodemographic data*

	n	HBCS Total Score (Mean ± SD)	p
Gender			
Female	128	4.96±1.97	0.110*
Male	139	4.61±1.59	
The longest residence			
Province	123	4.29±1.89	<0.001**
Town	83	4.87±1.60	
Village	61	5.63±1.45	
Marital status			
Single	10	4.60±2.41	0.191***
Married	209	4.69±1.63	
Divorced/Non-cohabiting	48	5.16±1.84	
Educational status			
Illiterate	14	7.93±1.21	<0.001***
Literate	31	6.26±1.26	
Primary school	108	5.44±1.19	
Secondary school	39	4.18±1.00	
High school	46	3.17±1.04	
College/University	29	2.59±1.05	
Duration of HT disease			
1 year	16	5.12±1.78	0.002**
1–10 years	159	4.48±1.74	
10^{+} years	92	5.22±1.77	
Comorbidity			
Yes	128	5.12±1.75	0.003*
No	139	4.47±1.77	

* Obtained from Independent Samples t-Test; ** Obtained from One-way Analysis of Variance (ANOVA); *** Obtained from Kruskal-Wallis test; HBCS: Hill-Bone Compliance to High Blood Pressure Therapy Scale; HT: Hypertension.

Table 4. *Evaluation of the subjects' habits and their HBCS total score averages*

Lifestyle changes in HT	n	HBCS Total Score Mean ± SD	p
Dieting			
Yes	181	4.43±1.82	<0.001*
No	86	5.51±1.47	
Reduced sodium intake			
Yes	225	4.48±1.74	<0.001*
No	42	6.40±0.99	
Regular exercise			
Yes	161	4.43±1.72	<0.001*
No	106	5.30±1.76	

* Obtained from Independent Samples t-Test; ** Obtained from Kruskal-Wallis test; HBCS: Hill-Bone Compliance to High Blood Pressure Therapy Scale; HT: Hypertension

Table 5. *Evaluation of the subjects' HBCS total scores*

	Mean	S. D.	1	2	3
1- HBCS [(1)]	4.78	1.79	¶	0.305*	0.239
2- SBP [(2)]	168.77	26.83	0.305*	¶	0.775*
3- DBP [(3)]	98.03	10.44	0.775*	0.239*	¶

[(1)] HSBC: Hill-Bone compliance to high blood pressure therapy scale; [(2)] SBP: systolic blood pressure; [(3)] DBP: diastolic blood pressure; * p<0.001

The subjects who had walked for 30 minutes or longer a day had lower HBCS scores than their counterparts who did not take any exercise, resulting in a significant difference (Table 4).

When the mean SBP and DBP values of the patients were compared with their HBCS scores, a moderately low correlation was noted between the mean HBCS scores and the mean SBP. In a similar vein, a low correlation was noted between the mean HBCS scores and the mean DBP. Furthermore, SBP were strongly correlated with DBP, which also indicated significant difference (Table 5).

Discussion

This study made use of HBCS, which provides researchers with the opportunity to assess compliance with HT treatment. In contradiction with earlier findings, the enrolled women in our study outnumbered the male subjects[18]. Our findings revealed that gender did not play a significant role in HBCS scores, which broadly supports the work of other studies addressing this issue. Furthermore, no significant relationship was observed between marital status and compliance with treatment. What is also revealed by our results is that, as the place of residence increased in population, compliance with treatment proved higher. This may have occurred because residing in a place with larger population facilitates both access to health institutions and follow-up of the disease.

Education-wise, the largest majority of our subjects were comprised of primary school graduates. Our further analyses indicated that compliance with treatment proved to be lower among those whose educational status was at primary school level and below. This leads us to conclude that, as the education level of the patients increases, so does compliance with treatment. Our findings are in accord with those of other recent studies revealing that illiterate patients tend to have lower compliance with treatment[15].

As identified by other clinical research, HT patients paying special attention to their diet and being careful to add less salt to their meals after being diagnosed with

HT are likely to have more increased compliance with HT treatment[19–21]. Our study likewise showed that the patients restricting their salt intake and going on a diet after the HT diagnosis manifested higher compliance with treatment.

Another point deserving attention in our study is that the patients with higher compliance with drug tended to have more reduced SBP and DBP. In accordance with the present results, several lines of evidence have demonstrated that patients with higher compliance have more reduced SBP and DBP[22,23]. We also observed lower compliance with treatment in the cases where the duration of HT diagnosis exceeded 10 years. Another study similar to ours reports conflicting results, suggesting that a higher compliance with treatment occurs when the treatment period is prolonged[24].

We found that those with underlying comorbid diseases had more reduced compliance with treatment. Contrary to our study, many clinical studies have shown that comorbidities accompanying HT increase compliance with treatment[24–27]. This finding in our study may be because patients who have to take too many drugs become tired of using this amount of medication continuously, thus not paying adequate attention to treatment.

Hypertension is a growing public health problem of both local and international concern due to its complications, increasing morbidity, and mortality. The presence of patients whose BP is not taken under control is multiplying in Türkiye, which also leads an increasing number of sufferers to present to the ED with HTA. In order to ensure BP compliance in HT, it is critical to comply with the recommended treatment and be mindful of lifestyle changes. Parameters, such as duration of HT diagnosis, salt restriction, and diet can be cited as some of the factors that could impact on compliance with treatment. In our study, compliance with treatment proved to be low, complicating BP control in general and causing the BP values to be high.

We propose that more comprehensive studies should be undertaken on compliance with treatment in HT. This pioneering research has given rise to many questions in need of further investigation. Informing patients about lifestyle changes, questioning the factors that affect their compliance with treatment, and making the required changes in this regard may yield more fruitful results in combating HTA.

Ethics Committee Approval

The study was initiated after granting the approval from the local ethics committee (approval number and date: 60116787–020/1958/2022).

Authorship Contributions

Concept: A. Y., U. C., C. U. Design: A. Y., U. C., C. U., Y. K. C. Data Collection or Processing: A. Y., U. C., C. U., Y. K. C., A. O., M. S., M. O, I. T., G. O. Y., M. U., A. K. Analysis or Interpretation: Y. K. C., A. K. Literature Search: A. Y., U. C., C. U., Y. K. C., A. O., M. S., M. O, I. T., G. O. Y., M. U., A. K. Writing: A. Y., U. C., C. U., Y. K. C.

Financial Disclosure

The author received no specific funding for this work.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

References

1. Torrellas C, Carril JC, Torrellas RC. Benefits of Pharmacogenetics in the Management of Hypertension. J Pharmacogenomics Pharmacoproteomics. 2014;5(2):1. doi:10.4172/2153-0645.1000126.
2. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, High Blood Pressure Clinical Practice Guideline. Hypertension. 2018;71(6):1269–1324. doi:10.1161/HYP.0000000000000066.
3. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al; List of authors/Task Force members:. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. J Hypertens. 2018;36(12):2284–2309. doi:10.1097/HJH.0000000000001961.
4. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2016; 387(10017), 435-443. doi:10.1016/S0140-6736(15)00805-3.
5. Kaplan NM, Lieberman E. Clinical Hypertension. 7th ed. Williams & Wilkins, Baltimore;1998:34-38.

6. Forman JP. Diet and Lifestyle Risk Factors Associated With Incident Hypertension in Women. JAMA. 2009;302(4):401–411. doi:10.1001/jama.2009.1060.
7. Sonne-Holm, S, Sørensen TI, Jensen, G, Schnohr P. Independent effects of weight change and attained body weight on prevalence of arterial hypertension in obese and non-obese men. BMJ (Clinical research ed.). 1989;299(6702):767–770. doi:10.1136/bmj.299.6702.767.
8. Staessen JA, Wang J, Bianchi G, Birkenhäger WH. Essential hypertension. Lancet. 2003;361(9369):1629–1641. doi:10.1016/S0140-6736(03)13302-8.
9. Wang, NY, Young JH, Meoni LA, Ford DE, Erlinger TP, Klag MJ. Blood pressure change and risk of hypertension associated with parental hypertension: the Johns Hopkins Precursors Study. Archives of internal medicine. 2008;168(6):643–648. doi:10.1001/archinte.168.6.643.
10. Carson AP, Howard G, Burke G, Shea S, Levitan EB, Muntner P. Ethnic differences in hypertension incidence among middle-aged and older adults: the multi-ethnic study of atherosclerosis. Hypertension. 2011;57(6):1101–1107. doi:10.1161/HYPERTENSION AHA.110.168005.
11. Ferreira I, Peeters LL, Stehouwer, CD. Preeclampsia and increased blood pressure in the offspring: meta-analysis and critical review of the evidence. Journal of hypertension. 2009;27(10) ;1955-1959. doi:10.1097/HJH.0b013e328331b8c6.
12. Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM. American Heart Association Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. Hypertension. 2006;47(2):296–308. doi:10.1161/01.HYP.0000202568.01167.B6.
13. Brook RD, Appel LJ, Rubenfire M, Ogedegbe G, Bisognano JD, Elliott WJ, et al. Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the american heart association. Hypertension. 2013;61(6):1360–1383. doi:10.1161/HYP.0b013e318293645f.
14. James PA, Oparil, S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014; 311(5):507–520. doi:10.1001/jama.2013.284427.
15. Gün Y, Korkmaz M. Hipertansif Hastaların Tedavi Uyumu ve Yaşam Kalitesi. Dergipark Dergisi. 2014;7(2):98–108.
16. Öngen Z. Çözümü Zor Bir Toplumsal Sorun: Hipertansiyon. Klinik Gelişim. 2005;18(2):4–7.
17. Kim MT, Hill MN, Bone LR, Levine DM. Development and Testing of The Hill-Bone Compliance to High Blood Pressure Therapy Scale. Progress in Cardiovascular Nursing. 2000;15(3):90–96. 36. doi:10.1111/j.1751-7117.2000.tb00211.x.
18. Karademir M, Köseoğlu IH, Vatansever K, Van Den Akker M. Validity and Reliability of The Turkish Version of The Hill-Bone Compliance to High Blood Pressure Therapy Scale for Use in Primary Health Care Settings. The European Journal of General Practice. 2009;15(4):207–211. doi:10.3109/13814780903452150.
18. Altun B, Arıcı M, Nergizoğlu G, Derici Ü, Karatan O, Turgan Ç, et al. Prevalence, Awareness, Treatment and Control of Hypertension in Turkey (The PatenT Study) in 2003. Journal of Hypertension. 2005;23(10):1817–1823. doi:10.1097/01.hjh.0000176789.89505.59.
19. İçyeroğlu G. Hipertansiyon Hastalarının Tedaviye Uyumu ve Yaşam Kalitesi. Elazığ: Fırat Üniversitesi. 2012; 24.
20. Şahin NŞ. Hipertansiyon Yönetiminde Hasta Uyumu ve Hastaların Sağlık Anlayışlarına Yönelik Bir Girişimin Uyum Üzerine Etkisi. Aile Hekimliği Uzmanlık Tezi. Adnan Menderes Üniversitesi Tıp Fakültesi, Aydın. 2014;25.
21. Vatansever Ö, Ünsar S. Esansiyel Hipertansiyonlu Hastaların İlaç Tedavisine Uyum/Öz Etkililik Düzeylerinin ve Etkileyen Faktörlerin Belirlenmesi. Turk Soc Cardiol Turkish Journal of Cardiovascular Nursing. 2014;5(8):66–74. doi:10.17049/ataunihem.527473.
22. Alhaddad IA, Hamoui O, Hammoudeh A, Mallat S. Treatment Adherence and Quality of Life in Patients on Antihypertensive Medications in a Middle Eastern Population: Adherence. Vasc Health Risk Manag. 2016;12:407–413. doi:10.2147/VHRM.S105921.
23. Oliveira-Filho AD, Barreto-Filho JA, Neves SJ, Lyra Junior DP. Association Between The 8-item Morisky Medication Adherence Scale (MMAS-8) and Blood Pressure Control. Arq Bras Cardiol. 2012;99(1):649–658. doi:10.1590/s0066-782x2012005000053.
24. Akgül C. Hipertansiyon Hastalarında Antihipertansif Uyumun Değerlendirilmesi. Yayınlanmamış Tıpta Uzmanlık Tezi, İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi, İstanbul, Türkiye. 2008.
25. Hashmi SK, Afridi MB, Abbas K, Sajwani RA, Saleheen D, Frossard PM, et al. Factors Associated With Adherence to Anti-hypertensive Treatment in Pakistan. PLoS One. 2007;2(3):280. doi:10.1371/journal.pone.0000280.
26. Özbayram A. Yeni Hipertansiyon Tanısı Almış Hastalarda Tedavi Uyumu ve Etkileyen Faktörler. Marmara Üniversitesi, Sağlık Bilimleri Enstitüsü; 2006.
27. Shaya FT, Du D, Gbarayor CM, Frech-Tamas F, Lau H, Weir MR. Predictors of Compliance With Antihypertensive Therapy in a High-Risk Medicaid Population. Journal of the National Medical Association. 2009;101(1):34-39. doi:10.1016/s0027-9684(15)30808-7.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Review of Clinical and Laboratory Findings of Patients with Primary Hyperparathyroidism by the Literature

Primer Hiperparatiroidi'li Hastaların Klinik ve Laboratuvar Bulgularının Literatür Eşliğinde Gözden Geçirilmesi

Suat Sen[1], Fettah Acibucu[2], Asim Tekin[3], Nese Bulbul[2], Ekin Yigit Koroglu[4]

[1]Adana Health Practice and Research Center, Department of Internal Medicine, University of Health Sciences; [2]Department of Endocrinology, Adana Health Application and Research Center, Department of Internal Medicine, University of Health Sciences, Adana; [3]Provincial Health Directorate, Suruc State Hospital, Internal Diseases Clinic, Sanliurfa; [4]Department of Internal Medicine, Department of Endocrinology and Metabolism, Ankara City Hospital, Ankara, Turkiye

ABSTRACT

Introduction: *Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by hypercalcemia and a high or normal parathyroid hormone (PTH) level inconsistent with calcium. Complications caused by hypercalcemia or excess PTH in patients affect many systems. Therefore, early diagnosis of PHPT can help prevent complications and determine the treatment.*

Method: *In our study, a total of 154 patients, 122 women and 32 men, who were diagnosed with PHPT in the Endocrinology outpatient clinic were retrospectively reviewed and evaluated in the light of the literature.*

Results: *The mean age of the patients was 53.83±13.80 years. Detected mean values for calcium were 11.83±1.28 mg/dl, for phosphorus 2.47±0.57 mg/dl, for PTH 357.32±424.08 pg/ml, for vitamin 25OH D_3 16.58±9.57 ng/ml, for estimated glomerular filtration rate (eGFR) was 99.03±23.84 ml/min/1.7 and for urinary calcium amount was 381.80±204.11 mg/24h. Bone mineral density (BMD) measurements were made in 64.3% (n: 99) of the patients, 38.4 % (n: 38) had osteopenia, and 42.4 % (n: 42) had osteoporosis. A history of urinary stones was found in 35.7% (n: 55) of the patients, and stone findings were found on ultrasonography in 36.1 % (n: 35). In total, 37% (n: 57) of the cases developed nephrolithiasis as a complication. In the localization study, adenoma was detected in 76.8% (n: 116) of the patients by ultrasonography, while 70.7% (n: 106) were found positive by Tc99 sestamibi scan. The lower right part was the most commonly detected adenoma localization in both imaging. In the pathology results of the operated patients, 91.5% (n: 118) were reported as adenomas. In the follow-up of the operated patients, recurrence was detected in 4.6% (n: 6).*

Conclusion: *Early diagnosis and treatment of PHPT are important to prevent serious complications. The absence of serious complications in the cases in our study shows the importance of early diagnosis.*

Keywords: *primary hyperparathyroidism; hypercalcemia; nephrolithiasis; osteoporosis*

ÖZET

Giriş: *Primer hiperparatiroidi (PHPT), hiperkalsemi ve paratiroid hormon (PTH) seviyesinin yüksek veya kalsiyum seviyesi ile uyumsuz olarak normal olması ile karakterize yaygın bir endokrin bozukluktur. Hastalarda hiperkalsemi ya da PTH fazlalığı ile oluşan komplikasyonlar birçok sistemi etkiler. PHPT'nin erken teşhis, oluşabilecek komplikasyonları önleyebilmek ve tedavi belirlemek açısından faydalı olabilir.*

Metot: *Çalışmamızda Endokrinoloji polikliniğinde PHPT tanısı alan 122 kadın 32 erkek toplamda 154 hasta retrospektif taranarak literatür eşliğinde değerlendirdik.*

Bulgular: *Hastaların yaş ortalaması 53,83±13,80 yıl saptandı. Ortalama kalsiyum 11,83±1,28 mg/dl, fosfor 2,47±0,57 mg/dl, PTH 357,32±424,08 pg/ml, 25OH D_3 vitamini 16,58±9,57 ng/ml, eGFR 99,03±23,84 ml/dk/1,7, hiperkalsiüri 381,80±204,11 mg/24s saptandı. Hastaların %64,3'ünde (n: 99) kemik mineral yoğunluğu (KMD) ölçümü yapılmış ve %38,4'ünde (n: 38) osteopeni, %42,4'ünde (n: 42) osteoporoz mevcuttu. Hastaların %35,7'sinde (n: 55) taş düşürme öyküsü ve %36,1'inde (n: 35) ultrasonografide taş bulgusu saptandı. Totalde vakaların %37'sinde (n: 57) nefrolithiazis komplikasyon olarak gelişmiştir. Lokalizasyon çalışmasında hastaların %76,8'inde (n: 116) ultrasonografide adenom bulgusu tespit edilirken Tc99M sestamibide %70,7'sinde (n: 106) pozitif bulundu. Her iki görüntülemede de adenom en sık sağ altta lokalizeydi. Opere olan hastaların patolojisinde %91,5'i (n: 118) adenom olarak raporlandı. Opere olan hastaların takiplerinde %4,6'sında (n: 6) nüks tespit edildi.*

Sonuç: *PHPT'nin erken teşhis ve tedavi ciddi komplikasyonları önlemek açısından önemlidir. Çalışmamızdaki vakalarda da ciddi komplikasyonların olmaması erken tanının önemini göstermektedir.*

Anahtar Kelimeler: *primer hiperparatiroidi; hiperkalsemi; nefrolitiazis; osteoporoz*

İletişim/Contact: *Suat Şen, Adana Şehir Eğitim ve Araştırma Hastanesi, Yüreğir, Adana, Türkiye* • ***Tel:*** *0505 504 29 09* • ***E-mail:*** *drsuatsen@gmail.com*
• ***Geliş/Received:*** *20.09.2022* • ***Kabul/Accepted:*** *12.02.2023*

ORCID: *Suat Şen, 0000-0003-1303-662X • Fettah Acıbucu, 0000-0002-2252-2112 • Asım Tekin, 0000-0001-5131-4884 • Neşe Bülbül, 0000-0002-6990-4337 • Ekin Yiğit Köroğlu: 0000-0003-3895-5817*

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by hypercalcemia and parathormone (PTH) levels being high or normal inconsistently with the calcium level[1]. The current prevalence of PHPT is approximately 0.25–0.66% of the population. The incidence increases with age and rises dramatically after 50 years of age. It is reported three times more in women[2]. The etiology of PHPT is solitary parathyroid adenoma in 80%, parathyroid hyperplasia in 10–15%, multiple adenomas in 5%, and parathyroid cancer in <1% of cases[1]. Most patients are sporadic, and approximately 5% are familial. Familial syndromes with PHPT components are; multiple endocrine neoplasias (MEN) I, MEN IIA, hyperparathyroidism-jaw tumor syndrome, and severe neonatal PHPT. Primary hyperparathyroidism clinical presentation can be in 3 different ways; symptomatic PHPT, asymptomatic PHPT, and normocalcemic PHPT[2]. Complications affecting many systems may develop due to hypercalcemia or excess PTH in patients. Clinically, it may present as asymptomatic or complicated by affecting especially kidney, bones, gastrointestinal, cardiovascular, or nervous systems. After the diagnosis of hyperparathyroidism is made biochemically, localization studies are performed. Ultrasonography and Tc99M sestamibi method are frequently used for localization. The genetic examination should only be requested occasionally but can be performed when genetic syndromes are considered[3].

Surgical treatment is recommended for all patients with laboratory-proven hyperparathyroidism and specific symptoms or signs of the disease. In asymptomatic patients, those who do not indicate surgery are followed up with medical treatment[3].

Patients diagnosed with primary hyperparathyroidism should be followed up after surgery and during medical treatment. In this study, we planned to evaluate the clinical presentations, biochemical findings, treatment, and post-treatment follow-ups of patients diagnosed with PHPT in our outpatient clinic.

Material and Methods

Patients who applied to Health Sciences University Adana City Training and Research Hospital Endocrinology and Metabolic Diseases Polyclinic between 2017–2020 and were diagnosed with PHPT were retrospectively screened. Demographic characteristics and clinical and laboratory findings of the cases diagnosed with PHPT included in the study were recorded. The study did not include those diagnosed with familial hypocalciuric hypercalcemia and those who used drugs that affect calcium metabolism. All were analyzed using the IBM Statistical Package for Social Sciences (SPSS) program version 24.0 (Chicago, IL, USA) statistical software package. Whether the distribution of continuous variables was normal or not was evaluated with the Kolmogorov-Smirnov test. Continuous variables in group data were expressed as mean ± standard deviation. Categorical variables were expressed as numbers and percentages. A ROC curve analysis was performed to reevaluate markers that were independent in detecting patients and to determine the breakpoint of these markers. The value of the area under the curve (AUC) was used to measure the test's accuracy. Univariate correlation analysis was performed using the Pearson-Spearman correlation method. Linear regression analysis was performed with statistically significant parameters in a multivariate model. The results were evaluated within the 95% confidence interval, and the statistical significance level was accepted as $p < 0.05$.

Results

In our study, 122 of 154 patients diagnosed with PHPT were female (79.2%), and 32 were male (20.8%). The mean age was 53.83±13.80 years. The demographic characteristics and biochemical results of the patients are summarized in Table 1.

Neck ultrasonography was performed in 151 patients, and Tc99M sestamibi imaging was performed in 150

Table 1. *Demographic characteristics and biochemical findings of the patients (n: 154)*

	Mean ± SD
Age (years)	53.83±13.80
PTH (pg/ml)	357.32±424.08
Vitamin 25OH D_3 (ng/ml)	16.58±9.57
Calcium (mg/dl)	11.83±1.28
Phosphorus (mg/dl)	2.47±0.57
Alkaline Phosphatase (U/L)	137.22±161.23
Albumin (g/L)	4.16±0.36
Creatinine (mg/dl)	0.71±0.26
eGFR (ml/dk/1.7)	99.03±23.84
Urinary Calcium (mg/24s)	381.80±204.11

Table 2. *Neck ultrasonography and Tc99M sestamibi imaging findings of the patients*

	Neck ultrasonography		Tc99M –sestamibi	
	n	%	n	%
Negative	35	23.2	44	29.3
Lower Right	55	36.4	56	37.4
Upper Right	2	1.3	3	2
Lower Left	53	35.1	42	28
Upper Left	3	2	3	2
Lower Right + Lower Left	3	2	2	1.3
Total	151	100.0	150	100.0

patients for localization. Neck ultrasonography was negative in 23.2% (n: 35) of the patients and positive in 76.8% (n: 116). Tc99M sestamibi imaging was negative in 29.3% (n: 44) and positive in 70.7% (n: 106). Localization sites are indicated in Table 2.

Bone mineral density (BMD) was measured in 64.3% (n: 99) of the patients; 19.2% (n: 19) were detected normal, 38.4% (n: 38) were detected as with osteopenia and 42.4% (n: 42) were detected with osteoporosis. In addition, a history of stone removal was found in 35.7% (n: 55) of the patients, and stone findings were found in 36.1% (n: 35) of 97 patients who underwent renal ultrasonography.

While 83.8% (n: 129) of the patients were operated on, 16.2% (n: 25) were followed up with medical treatment. In the follow-up of the operated patients, recurrence was detected in 4.6% (n: 6). The most common pathology results were adenoma with 91.5% (n: 118), and hyperplasia was the second most common with 5.4% (n: 7). Pathology results are summarized in Table 3.

Discussion

In the last 10–15 years, the prevalence of PHPT has increased, and new entities have been defined as a result of increased awareness and the development and widespread use of laboratory methods. Therefore, recognition and treatment of PHPT are significant for preventing complications. The most common complications are decreased BMD and subsequent development of osteoporosis and nephrolithiasis[4].

In primary hyperparathyroidism, increased demineralization in bone results in decreased bone mass and the development of osteoporosis in the chronic period[5]. For example, Cipriani et al.[6] found that 62.9% of 140 PHPT

Table 3. *Pathology results of patients who were operated on for PHPT*

Pathology	n	%
Adenoma	118	91.5
Hyperplasia	7	5.4
Right adenoma + Left hyperplasia	1	0.8
Adenoma + adenoma	3	2.3
Total	129	100.0

patients, and Lowe et al.[7] found that 57% of the PHPT patients had osteoporosis in their study. On the contrary, our research found that 38.4% (n: 38) of the patients had osteopenia, and 42.4% (n: 42) had osteoporosis. Our study's low rate of osteoporosis may be because our patients were easily diagnosed with PHPT due to easy access to the physician, advanced laboratory methods, and routine calcium value evaluation in the daily practice.

Although parathormone directly stimulates distal tubular reabsorption of calcium[8], urinary calcium excretion is increased in 35 to 40% of patients with PHPT due to the increased filtered calcium due to hypercalcemia, and kidney stones may develop due to hypercalciuria. Increased urinary calcium may result in nephrolithiasis and nephrocalcinosis[9]. Cipriani et al.[6] found kidney stones in 55% of the patients by ultrasound. Lowe et al.[7] stated a history of kidney stones in 14% of the patients. In their study, Anil Bhansali et al.[10] said that 21% of patients had recurrent kidney stones.

In our study, the mean PTH value of the patients was 357.32±424.08 pg/ml, the calcium value was 11.83±1.28 mg/dl, and the urinary calcium value was 381.80±204.11 mg/24h. In 38.1% (n: 35) of 92 patients whose 24-hour urine calcium was measured, hypercalciuria was present. In addition, 35.7% (n: 55) of the patients had a history of kidney stone reduction, and 36.1% (n: 35) had kidney stones on ultrasonography. In our study, it was the most common complication.

There are usually four parathyroid glands in humans, two above and two below, adjacent to the thyroid gland[11]. High-resolution ultrasonography and Tc99M-sestamibi imaging are the most important localization methods[3]. Tehseen Fatima et al.[12] found positive findings in the preoperative localization of PHPT in 84.1% of their patients in neck ultrasonography and 85.7% of their patients with Tc99M sestamibi. Our study found positive findings in 76.8% (n: 116) of the patients in neck ultrasonography performed for localization and

in 70.7% (n: 106) of Tc99M sestamibi. The resolution of the device used in ultrasonographic imaging and the physician's experience may affect the results if performed with a different physician and device. In Tc99M sestamibi, factors such as serum calcium, PTH, 25 hydroxy vitamin D_3 value, use of calcium channel blockers, average adenoma weight, and oxyphil cell content may affect the results[13]. These factors may be the reason why our imaging results are lower.

Berat Demir et al.[14] found a single parathyroid adenoma in 108 patients (78.8%) and found the most common adenoma localization in the left lower parathyroid gland (46.7%). In our study, the most frequent localization was the right lower quadrant, with 36.4% (n: 55) of the patients and 35.1% (n: 53) having adenoma in the lower left quadrant. In Tc99M sestamibi, the right lower quadrant was most frequently localized, with 37.4% (n: 56) and 28% (n: 42) of patients having adenoma in the lower left quadrant. In the pathology results of the patients, 91.5% (n: 118) adenoma and 5.4% (n: 7) hyperplasia were found.

Our study detected recurrence in 4.6% (n: 6) of the operated patients during their follow-up. CJ McIntyre et al.[15] found a 6.5% recurrence in their study. Surgical experience is the leading factor determining the recurrence rate. The limited number of physicians who perform parathyroid surgery in our hospital and their experience may explain the high success rate despite the low localization rate compared to other studies.

As a result, patients with PHPT may present with a high value of PTH and complications that affect many systems due to hypercalcemia. Therefore, early diagnosis and treatment of PHPT are important to prevent serious complications that affect many systems. The low complication rates in our patients also show the importance of early diagnosis.

References

1. Marcella D. Walker and Shonni J. Silverberg. Primary hyperparathyroidism. Nat Rev Endocrinol. 2018; 14(2):115–25.
2. Mehmet Uludağ, Nurcihan Aygün. Primer Hiperparatiroidi; Klinik ve Biyokimyasal Bulguların Güncel Durumu Şişli Etfal Hastanesi Tip Bülteni-2016; 50(3):171–80.
3. Aysen Akalın, Özlem Zeynep Akyay, Metin Alış, Betül Altun, Dilek Karakaya Arpacı, Ayşegül Atmaca ve ark. Türkiye Endokrinoloji ve Metabolizma Derneği Osteoporoz ve Metabolik Kemik Hastalıkları Tanı ve Tedavi Kılavuzu Primer Hiperparatiroidizm. 2020:145–53.
4. Karel Dandurand, Dalal S Ali, Aliya A Khan. Primary Hyperparathyroidism: A Narrative Review of Diagnosis and Medical Management. 2021;10(8):1604.
5. Liuping Chen, Yaling Pan, Fangyuan Zhong, Tian-Jiao Yuan, Hanqi Wang, Tongtong Chen, et al. Using QCT to evaluate bone mineral and abdominal adipose changes in patients with primary hyperparathyroidism and comparing it to DXA for bone status assessment: a retrospective case-control study. 2022; 10(10):606.
6. Cipriani C, Biamonte F, Costa AG, Zhang C, Biondi P, Diacinti D, et al. Prevalence of Kidney Stones And Vertebral Fractures in Primary Hyperparathyroidism Using Imaging Technology. J Clin Endocrinol Metab. 2015; 100:1309–15.
7. H Lowe, DJ McMahon, Bay Rubin, JP Bilezikian, SJ Silverberg. Normocalcemic primary hyperparathyroidism: Further characterization of a new clinical phenotype. J Clin Endocrinol Metab. 2007; 92:3001–5.
8. Maqsood Khan, Alvin Jose, Sandeep Sharma. Physiology, Parathyroid Hormone. 2022 Jan. 2022 Oct 29.
9. Yu-Kwang Donovan Tay, Minghao Liu, Leonardo Bandeira, Mariana Bucovsky, James A Lee, Shonni J Silverberg, et al. Occult urolithiasis in asymptomatic primary hyperparathyroidism. Endocr Res. 2018; 43:106–15.
10. Anil Bhansali, Shariq Rashid Masoodi, K S Somashekara Reddy, Arunanshu Behera, Bishan das Radotra, Bhagwant Rai Mittal, et al. Primary hyperparathyroidism in north India: a description of 52 cases. Ann Saudi Med. 2005 Jan-Feb; 25(1):29–35.
11. Ahmet Dağ. Paratiroid Bezi Embriyoloji, Histoloji ve Anatomisi. Türkiye Klinikleri; 2021. P.6-11.
12. Tehseen Fatima, Bhagwan Das, Saadia Sattar, Sumerah Jabeen, Abid Abbas Khan and Najmul Islam. The Utility of Ultrasound in the Preoperative Localization of Primary Hyperparathyroidism: Insights from Pakistan. Cureus. 2020; 12(8):e9835.
13. Subramanian Kannan, Mira Milas, Donald Neumann, Rikesh T Parikh, Alan Siperstein, Angelo Licata. Parathyroid nuclear scan. A focused review on the technical and biological factors affecting its outcome. Clin Cases Miner Bone Metab. 2014 Jan-Apr; 11(1):25–30.
14. Berat Demir, Adem Binnetoglu, Akın Sahin, and Dilek Gogas Yavuz. Single Center Experience in the Surgical Management of Primary Hyperparathyroidism. Clin Exp Otorhinolaryngol. 2020; 13(3):285–90.
15. CJ mcıntyre, JLY Allen, VA Constantinides, JE Jackson, NS Tolley, FF Palazzo. Patterns of disease in patients at a tertiary referral centre requiring reoperative parathyroidectomy. Ann R Coll Surg Engl. 2015 Nov 1; 97(8):598–602.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Does the Use of an Access Sheath in Flexible Ureteroscopic Stone Surgery Affect the Stone-Free Rate in the Late Postoperative Period?

Fleksible Üreteroskopik Taş Cerrahisinde Erişim Kılıfı Kullanımı Postoperatif Geç Dönemde Taşsızlık Oranını Etkiliyor mu?

Umit Yildirim[1], Mehmet Uslu[1], Mehmet Ezer[1], Bumin Ors[2]

[1]Kafkas Universitesi, Tip Fakultesi, Uroloji Anabilim Dali, Kars, Turkiye
[2]Ozel Saglik Hastanesi, Uroloji Klinigi, Izmir, Turkiye

ABSTRACT

Aim: *Studies indicate that a ureteric access sheath (UAS) is unnecessary for retrograde intrarenal surgery 5 (RIRS) if the surgeon enters the ureter directly. This research aims to look back on our case series in light of the existing literature and directly compare cases with and without a UAS in terms of efficacy, safety, and stone-free rates in the late postoperative period (3rd month).*

Materials and Methods: *From January 2019 to June 2022, a retrospective screening of kidney stone cases treated with RIRS in our clinic was carried out. The study included one hundred fifty-three participants who complied with all inclusion and exclusion criteria. Group UAS was created for individuals who received UAS applications, and Group N for those who did not. The demographics, preoperative and postoperative laboratory, and radiographic data have been compared between the two groups.*

Results: *A comparable distribution in terms of gender and age (50.85±13.20 vs. 52.84±14.27; p=0, 476) was seen between the groups. The Charlson Comorbidity Indexes were found to have a similar distribution [median (IQR): 1 (0.5–2.5) vs. 1 (0–3); p=0.986]. Serum creatinine levels (0.92±0.27 vs. 0.97±0.34; p=0, 560), fever or sepsis (0.0% vs. 1.0%; p=0, 686), and hospital stay (2.15±0.65 vs. 2.31±0.74; p=0, 691) were comparable between the groups during the surgical follow-up. Even though Group UAS was superior in the postoperative three-month stone-free assessment with computerized tomography, this difference was not statistically significant (72.9% vs. 73.3%; p=0, 552).*

Conclusion: *In the surgical management of kidney stones, RIRS can be used safely and effectively whether or not UAS is used. Complications and success rates in the late postoperative phase (3 months) are not significantly impacted by UAS use.*

Keywords: *access sheath; renal stones; retrograde intrarenal surgery*

ÖZET

Amaç: *Yapılan bazı çalışmalar, retrograd intrarenal cerrahi (RIRS) için cerrahın doğrudan üretere girmeyi seçmesi durumunda üreter erişim kılıfının (UAS) gerekli olmadığını göstermektedir. Bu araştırmanın amacı, vaka serilerimizi mevcut literatür ışığında geriye doğru incelemek ve UAS kullanılan ve kullanılmayan vakalar arasında etkinlik, güvenlik ve ameliyat sonrası geç dönemde (3. ay) taşsızlık oranları açısından doğrudan bir karşılaştırma yapmaktır.*

Gereç ve Yöntem: *Ocak 2019- Haziran 2022 tarihleri arasında kliniğimizde RIRS ile tedavi edilen böbrek taşı olgularının retrospektif taraması yapıldı. Dahil etme ve hariç tutma kriterlerinin tümüne uyan 153 katılımcı çalışmaya dahil edildi. Üreter erişim kılıfı kullanılan vakalar için Grup UAS, kullanılmayanlar için Grup N oluşturuldu. Demografik veriler, ameliyat öncesi ve sonrası laboratuvar sonuçları ve radyografik veriler iki grup arasında karşılaştırıldı.*

Bulgular: *Gruplar arasında cinsiyet ve yaş açısından karşılaştırılabilir bir dağılım (50,85±13,20 ve 52,84±14,27; p=0,476) görüldü. Charlson Komorbidite İndekslerinin benzer bir dağılıma sahip olduğu bulundu [medyan (IQR): 1 (0,5–2,5) vs. 1 (0–3); p=0,986]. Serum kreatinin düzeyleri (0,92±0,27 vs. 0,97±0,34; p=0,560), ateş veya sepsis (%0,0 vs. %1,0; p=0,686) ve hastanede kalış süresi (2,15±0,65'e karşı 2,31±0,74; p=0,691) cerrahi takipte gruplar arasında benzerdi. Bilgisayarlı tomografi ile postoperatif üç aylık taşsızlık değerlendirmesinde Grup UAS üstün olmasına rağmen bu fark istatistiksel olarak anlamlı değildi (%72,9'a karşı %73,3; p=0,552).*

Sonuç: *Böbrek taşlarının cerrahi tedavisinde UAS kullanılsın veya kullanılmasın RIRS güvenli ve etkili bir şekilde kullanılabilir. Postoperatif geç dönemdeki (üç ay) komplikasyonlar ve başarı oranları UAS kullanımından önemli ölçüde etkilenmez.*

Anahtar Kelimeler: *erişim kılıfı; böbrek taşları; retrograd intrarenal cerrahi*

İletişim/Contact: *Ümit Yıldırım, Kafkas Üniversitesi Tıp Fak. Dekanlığı Kars Merkez, Türkiye* • ***Tel:*** *0542 558 45 80* •
E-mail: *dr.umityildirim87@gmail.com* • ***Geliş/Received:*** *16.11.2022* • ***Kabul/Accepted:*** *19.01.2023*

ORCID: *Ümit Yıldırım, 0000-0003-3065-9001* • *Mehmet Uslu, 0000-0002-8370-3793* • *Mehmet Ezer, 0000-0003-4422-6768* • *Bumin Örs, 0000-0002-9471-7031*

Kafkas J Med Sci 2023; 13(1):82–86
doi: 10.5505/kjms.2023.81489

Introduction

Recent years have shown an increase in the incidence of urinary stone disease [1]. This improvement coincides with a general convergence in the technological sophistication of the instruments employed in the minimally invasive treatment of urinary stones [2]. Thanks to these remarkable technological developments, retrograde intrarenal surgery (RIRS) has emerged as a viable option for the minimally invasive therapy of stones between 10 and 20 millimeters in size[3]. According to the European Association of Urology's (EAU) Urolithiasis Guidelines, single-session external shock wave lithotripsy (ESWL) and RIRS are effective treatment modalities for kidney stones under 20 mm in diameter. In comparison, percutaneous nephrolithotomy (PCNL) is still used for stones over 20 mm due to its higher stone-free rates after a single session [4]. In addition, unlike ESWL or flexible ureterorenoscopy (URS), PCNL outcomes are less dependent on stone size. Nonetheless, PCNL is more invasive than RIRS and carries a higher risk of serious complications (bleeding, sepsis) [5].

Most endourologists routinely place a ureteral access sheath (UAS) during RIRS. Surgeons using UAS argue that the use of UAS provides repeated access to the ureter and kidney, reduces the internal pressure created by continuous irrigation in the kidney, and protects the ureter and ureteroscope from possible damage [6]. However, despite the number of pluses, UAS is not entirely innocent. In the literature, varying rates of minor and major complications related to the use of UAS have been reported [7]. And this has brought to mind the question of whether the use of UAS is an indispensable surgical necessity.

According to recent studies, depending on the surgeon's preference, retrograde intrarenal surgery can be successfully performed by directly entering the ureter without a UAS [8,9]. Therefore, this study's objective is to retrospectively review our case series in light of the literature and compare cases with and without a UAS regarding efficacy, safety, and stone-free rates in the late postoperative period (3rd month).

Material and Methods

Retrospective screening of kidney stone cases treated with RIRS in our clinic was done from January 2019 to June 2022. Our institute's ethics committee approved our study (80576354–050–99/96), and we abided by the Declaration of Helsinki's ethical principles. Patients undergoing uncomplicated RIRS to treat kidney stones met the inclusion criteria. Preoperatively implanted ureteral stents, ureteral stenosis, solitary kidneys, ectopic kidneys, and other anatomical anomalies were all excluded from the study. The study includes 153 individuals that met all inclusion and exclusion requirements.

In every instance, kidney-ureter-bladder graphy (KUB) and non-contrast computer tomography (NCCT) were used to assess the renal collecting system's kidney stone characteristics and morphological features. In addition, urinary USG examinations and radiographic evaluation procedures were carried out when needed during the pre-treatment. The biggest diameter was measured in the KUB for opaque stones, and for lucent stones, the NCCT. The parenchymal thickness was determined by measuring the thickest area on transverse sections on preoperative CT.

Before surgery, it was anticipated that all patients would have negative urine cultures. Those with confirmed urinary tract infections received the proper antibiotic treatment before the surgery. Throughout the surgery, prophylactic antibiotics were administered to all patients (single dose of 2nd generation cephalosporin). Non-contrast computer tomography was used to ascertain the patients' stone-free status three months after surgery. A satisfactory outcome was defined as the lack of any leftover fragments or the presence of tiny stone particles (<3 mm).

Under general anesthesia, all procedures were carried out while the patient was in the lithotomy position. Under the assistance of a fluoroscope, a 9.5 Fr semi-rigid ureteroscope was used to insert a 0.038 Fr guide wire into the renal pelvis. Retrograde pyelography was used to investigate the pelvicalyceal system. In the UAS group of patients, a UAS (9.5/11.5 Fr, Cook Medical, Bloomington, IN) was introduced under fluoroscopy before a flexible ureteroscope was used to access the collecting system (Storz FLEX-X2). Then, a 7.5 Fr fiberoptic flexible ureteroscope was used to directly access the remaining individuals' ureters (Storz FLEX-X2). Using a 273 fiber and a holmium laser, stones were disintegrated. In patients with a UAS, fragments bigger than 3 mm were removed using a nitinol basket (ZeroTipTM; Cook Urological Inc.). Smaller pieces were left open for natural passage. In patients for UAS was not used, it was impossible to extract fragments with a basket; instead, laser lithotripsy was used to ensure that no large fragments were left behind. Patients were split into two groups depending on whether UAS

was utilized during surgery according to the surgeon's preference. Those that submitted a UAS application were placed in Group UAS, while those who did not were placed in Group N. The two groups have compared certain preoperative and postoperative laboratory and radiological parameters.

Statistical Evaluation

IBM Statistical Package for Social Sciences (SPSS) program version 22.0 was used for the statistical evaluation (IBM Inc., Chicago, IL, USA). The presentation of continuous variables was as mean and standard deviation. When a normal distribution was not seen in these variables, the median and IQR were used to present the data. These variables were compared using either a Mann-Whitney U test or an independent T-test. Categorical variables were expressed using numbers and percentages (%). The Fisher's exact test or the Chi-square test was used to compare these variables. For all statistical studies, a p-value of <0.05 was used.

Results

When the received data are evaluated: A comparable distribution in terms of gender and age (50.85±13.20 vs. 52.84±14.27; p=0, 476) was seen between the groups. Body mass indices (27.38±4.21 vs. 28.39±4.54; p=0, 201), the frequency of diabetes (10.4% vs. 14.3%; p=0, 353), and the usage of anticoagulants (18.8% vs. 17.1%; p=0, 487) were comparable between the groups. The Charlson Comorbidity Indexes were found to have a similar distribution [median (IQR): 1 (0.5–2.5) vs. 1 (0–3); p=0.986]. There was no discernible difference between the two groups regarding stone lateralization, size (11.92±4.56 vs. 11.90±5.93; p=0, 998), opacity status, or location in the collecting system when the characteristic data of the stones were compared. In a similar vein, there was no statistically significant difference between the groups in terms of stone number (single, multiple) and density. There was no evident difference between the groups in terms of the frequency of hydronephrosis (45.8% vs. 40.0%; p=0, 307), infundibulopelvic angle (46.30±15.03 vs. 45.40±15.24; p=0, 648), or renal parenchymal thickness (26.19±7.31 vs. 26.46±7.81; p=0, 646) during the anatomical evaluation of the kidney and collecting system. The groups' creatinine and (0.92±0.25 vs. 0.98±0.35; p=0, 520) GFR (81.74±35.27 vs. 79.21±39.56; p=0, 563) values in the preoperative test results were comparable. Similar rates were found in terms of both past endoscopic stone therapy (62.5% vs. 55.2%; p=0, 253) and usage of alpha-blockers (4.2% vs. 5.7%; p=0, 515).

Last but more importantly, creatinine levels (0.92±0.27 vs. 0.97±0.34; p=0, 560), fever or sepsis (0.0% vs. 1.0%; p=0, 686), and hospital stay (2.15±0.65 vs. 2.31±0.74; p=0, 691) were comparable between the groups during the surgical follow-up. Even though Group UAS was superior in the postoperative three-month stone-free assessment with CT, this difference was not statistically significant (72.9% vs. 73.3%; p=0, 552). Patient demographics, pre-and post-operative clinical characteristics, and laboratory findings are given in Table 1.

Discussion

One of the primary objectives of current endourologic stone management is to achieve a completely stone-free status in a single session. To predict the ultimate success of this procedure in this aspect, some stone– and patient-related factors have been evaluated, including stone size, location, and hardness. The use of UAS is one of the issues that have already been looked into. Depending on the surgeon doing the surgery's clinical background and the institution's unwritten clinical protocols, different UAS may be used.

Ureteric access sheath use has consistently been promoted for RIRS [10]. Proponents of UAS point to the following advantages of the technology: they simplify various access to the ureter, which greatly facilitates flexible URS; they are expected to improve vision by optimizing irrigation flow; and they decrease pressure in the collecting system, which may lead to kidney injury and sepsis [11,12]. However, there are no formal suggestions for using UAS during RIRS. Additionally, there is very little data supporting the impact of UAS on perioperative outcomes and stone-free rates[13].

Various research looks into the impact of UAS in terms of stone-free rates following RIRS. Traxer et al.[14] stated that success rates were greater in patients where UAS was not utilized, contrary to Berquet et al.[15], who claimed that UAS use did not influence stone-free rates. The findings of our investigation supported Berquet et al. by demonstrating no distinction in stone-freeness between the two groups.

Huang et al. released a meta-analysis assessing the advantages and disadvantages of using UAS in 2018. This analysis identified 3127 surgeries after analyzing data from 8 studies with 3099 individuals. The length of the

Table 1. *Patient demographics, pre- and post-operative clinical characteristics, and laboratory findings*

		Group N		Group UAS		p
Gender	Male	25	52.1%	60	57.1%	0.341
	Female	23	47.9%	45	42.9%	
Age		50.85	±13.20	52.84	±14.27	0.476
Body Mass Index (kg/m²)		27.38	±4.21	28.39	±4.54	0.201
Diabetes		5	10.4%	15	14.3%	0.353
Anticoagulant Use		9	18.8%	18	17.1%	0.487
Charlson Comorbidity Index [median (IQR)]		1	(1–2.5)	1	(0–3)	0.986
Stone Lateralization	Right	22	45.8%	47	44.8%	0.520
	Left	26	54.2%	58	55.2%	
Stone Size (mm)		11.92	±4.56	11.90	±5.93	0.998
Opacity Status	Opaque	25	52.1%	52	49.5%	0.453
	Non-opaque	23	47.9%	53	50.5%	
Localization	Pelvis	20	41.7%	51	48.6%	0.689
	Lower	23	47.9%	40	38.1%	
	Midle	3	6.3%	7	6.7%	
	Upper	2	4.2%	7	6.7%	
Stone Number	Single	26	54.2%	56	53.3%	0.532
	Multiple	22	45.8%	49	46.7%	
Stone Density (Hounsfield Unit)		828.04	427.46	788.51	±394.43	0.750
Presence of Hydronephrosis		22	45.8%	42	40.0%	0.307
Infundibulopelvic Angle (°)		46.30	±15.03	45.40	±15.24	0.648
Renal Phrencymal Thickness (mm)		26.19	±7.31	26.46	±7.81	0.646
Preoperative Creatine (mg/dL)		0.92	±0.25	0.98	±0.35	0.520
Glomerular Filtration Rate (ml/min/1.73 m²)		81.74	±35.27	79.21	±39.56	0.563
Alpha-blocker Use		2	4.2%	6	5.7%	0.515
Previous Endoscopic Stone Treatment		30	62.5%	58	55.2%	0.253
Postperative Creatine (mg/dL)		0.92	±0.27	0.97	±0.34	0.560
Postoperative Fever/Sepsis		0	0.0%	1	1.0%	0.686
Hospitalization (days)		2.15	±0.65	2.31	±0.74	0.691
Postoperative 3rd Month Stone Free Rate		35	72.9%	77	73.3%	0.552

hospital stay, intraoperative problems, or stone-free results did not reveal appreciable variations. However, the UAS group had a greater rate of postoperative complications. The results of this meta-analysis largely support our conclusions that there are no appreciable benefits to using UAS during ureteroscopy. In our investigation, the incidence of postoperative complications was comparable among groups[16]. Similar to our study, some studies found each group to be similar regarding postoperative complications[17]. Also, about complications and success rates in RIRS, Yigit et al. discovered no noteworthy variations when comparing employing UAS or not[18].

A significant ureteral damage rate from UAS was found to be 13.3 % by Traxer et al. 7 In either group in our series; we did not document a significant ureteral injury. The practice of RIRS surgery at our clinic by surgeons nearing the end of their learning curve can be hypothesized as the cause.

Studies utilizing ultrasonography or KUB may overestimate the actual stone-free percentage because most of these investigations frequently need attention to very small fragments[19]. In our clinical protocol, we perform residual stone control with NCCT within three months postoperatively. Studies in the literature found stone-free rates above 90% after RIRS20. In our study, it is a fact that we could not achieve these rates within each group.

Limitations

The primary drawback of this study is that it was carried out retrospectively. Patients for whom UAS was not used may have been subject to selection bias in this retrospective analysis. In addition, we could not obtain other information, such as the operating durations. The findings may also have been impacted by the fact that the data originated from a single source and that many surgeons with varying degrees of experience performed the surgeries. Despite these drawbacks, this study will add to the literature because of the control of stones in the late postoperative period.

Conclusion

Whether or not UAS is utilized, RIRS can be employed safely and efficiently in the surgical management of kidney stones. In the late postoperative phase (3 months), complications and success rates are not significantly affected by UAS use. Undoubtedly, additional randomized controlled clinical studies on this topic are needed. Surgeon practice habits and unwritten regulations of the institution will continue to factor into UAS use until research with more exact and binding data on the subject is incorporated into the recommendations.

References

1. Romero V, Akpinar H, Assimos DG. Kidney Stones: A Global Picture of Prevalence, Incidence, and Associated Risk Factors. Rev Urol. 2010;12(2–3):e86. doi:10.3909/riu0459.
2. Chew BH, Lange D. The future of ureteroscopy. Minerva Urol Nefrol. 2016;68. (6):592–597. Accessed August 20, 2022. https://pubmed.ncbi.nlm.nih.gov/27759736/
3. Ghani KR, Wolf JS. What is the stone-free rate following flexible ureteroscopy for kidney stones? Nature Reviews Urology 2015 12:5. 2015;12(5):281–288. doi:10.1038/nrurol.2015.74.
4. Türk C, Petřík A, Sarica K, et al. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol. 2016;69(3):475–482. doi:10.1016/J.EURURO.2015.07.041.
5. Chung DY, Kang DH, Cho KS, et al. Comparison of stone-free rates following shock wave lithotripsy, percutaneous nephrolithotomy, and retrograde intrarenal surgery for treatment of renal stones: A systematic review and network meta-analysis. PLoS One. 2019;14(2). doi:10.1371/JOURNAL.PONE.0211316.
6. de Coninck V, Keller EX, Rodríguez-Monsalve M, Audouin M, Doizi S, Traxer O. Systematic review of ureteral access sheaths: facts and myths. BJU Int. 2018;122(6):959–969. doi:10.1111/BJU.14389.
7. Traxer O, Thomas A. Prospective evaluation and classification of ureteral wall injuries resulting from insertion of a ureteral access sheath during retrograde intrarenal surgery. J Urol. 2013;189(2):580–584. doi:10.1016/J.JURO.2012.08.197.
8. Torricelli FC, De S, Hinck B, Noble M, Monga M. Flexible ureteroscopy with a ureteral access sheath: when to stent? Urology. 2014;83(2):278–281. doi:10.1016/J.UROLOGY.2013.10.002.
9. Yitgin Y, Yitgin E, Verep S, Gasimov K, Tefik T, Karakose A. Is Access Sheath Essential for Safety and Effective Retrograde Intrarenal Stone Surgery? J Coll Physicians Surg Pak. 2021;31(10):1202–1206. doi:10.29271/JCPSP.2021.10.1202.
10. Takayasu H, Aso Y. Recent development for pyeloureteroscopy: guide tube method for its introduction into the ureter. J Urol. 1974;112(2):176–178. doi:10.1016/S0022-5347(17)59675-5.
11. Auge BK, Pietrow PK, Lallas CD, Raj G v., Santa-Cruz RW, Preminger GM. Ureteral access sheath provides protection against elevated renal pressures during routine flexible ureteroscopic stone manipulation. J Endourol. 2004;18(1):33–36. doi:10.1089/089277904322836631.
12. Noureldin YA, Kallidonis P, Ntasiotis P, Adamou C, Zazas E, Liatsikos EN. The Effect of Irrigation Power and Ureteral Access Sheath Diameter on the Maximal Intra-Pelvic Pressure During Ureteroscopy: In Vivo Experimental Study in a Live Anesthetized Pig. J Endourol. 2019;33(9):725–729. doi:10.1089/END.2019.0317.
13. Berquet G, Prunel P, Verhoest G, Mathieu R, Bensalah K. The use of a ureteral access sheath does not improve stone-free rate after ureteroscopy for upper urinary tract stones. World J Urol. 2014;32(1):229–232. doi:10.1007/S00345-013-1181-5.
14. Traxer O, Wendt-Nordahl G, Sodha H, et al. Differences in renal stone treatment and outcomes for patients treated either with or without the support of a ureteral access sheath: The Clinical Research Office of the Endourological Society Ureteroscopy Global Study. World J Urol. 2015;33(12):2137–2144. doi:10.1007/S00345-015-1582-8.
15. Berquet G, Prunel P, Verhoest G, Mathieu R, Bensalah K. The use of a ureteral access sheath does not improve stone-free rate after ureteroscopy for upper urinary tract stones. World J Urol. 2014;32(1):229–232. doi:10.1007/S00345-013-1181-5.
16. Huang J, Zhao Z, AlSmadi JK, et al. Use of the ureteral access sheath during ureteroscopy: A systematic review and meta-analysis. PLoS One. 2018;13(2):e0193600. doi:10.1371/JOURNAL.PONE.0193600.
17. Cristallo C, Santillán D, Tobia I, Tirapegui FI, Daels FP, González MS. Flexible ureteroscopy without ureteral access sheath. Actas Urológicas Españolas (English Edition). 2022;46(6):354–360. doi:10.1016/J.ACUROE.2021.12.006.
18. Yitgin Y, Yitgin E, Verep S, Gasimov K, Tefik T, Karakose A. Is Access Sheath Essential for Safety and Effective Retrograde Intrarenal Stone Surgery? J Coll Physicians Surg Pak. 2021;31(10):1202–1206. doi:10.29271/JCPSP.2021.10.1202.
19. Acar C, Cal C. Impact of residual fragments following endourological treatments in renal stones. Adv Urol. Published online 2012. doi:10.1155/2012/813523.
20. Ghani KR, Wolf JS. What is the stone-free rate following flexible ureteroscopy for kidney stones? Nature Reviews Urology 2015 12:5. 2015;12(5):281–288. doi:10.1038/nrurol.2015.74

OLGU SUNUMU / *CASE REPORT*

Acute Myeloid Leukemia (M4)/Myeloid Sarcoma Presenting with Hyperleukocytosis, 47,XX + mar Case

Akut Miyeloid Lösemi (M4)/Hiperlökositoz ile Kendini Gösteren Miyeloid Sarkom, 47,XX + mar Vakası

Mustafa Ozay[1]

[1]*Ataturk University, Faculty of Medicine, Department of Paediatrics, Division of Paediatric Haematology-Oncology, Erzurum, Turkiye*

ABSTRACT

Hyperleukocytosis is defined as a blood blast count >100.000/mm3 and may occur most commonly in monocytic (M4) acute myeloid leukemia (AML). Hyperleukocytosis is a medical emergency associated with lung and central nervous system leukostasis. An 18-month-old female patient was brought to our clinic with anemia, thrombocytopenia, and leukocytosis with bilateral palpebral swelling/proptosis, a palpable mass in the midline, and lymphadenopathy in the neck. Myeloid sarcoma was suspected. The patient had AML M4 morphological features, and 47,XX + mar was detected in bone marrow karyotype analysis. She had complications such as hyperleukocytosis, leukostasis (blurring of consciousness, tachypnea/tachycardia), tumor lysis syndrome, and disseminated intravascular coagulation. In addition to low-dose cytoreduction chemotherapy, leukocyte apheresis was performed. All symptoms and complaints of the patient disappeared. Therefore, myeloid sarcoma should be considered in young children with orbital swelling/proptosis, an abdominal mass, high leukocyte count at diagnosis, AML M4 morphological features, and diffuse intravascular coagulation.

Keywords: acute myeloid leukemia; myeloid sarcoma; hyperleukocytosis; disseminated intravascular coagulation

Keywords: *acute myeloid leukemia; myeloid sarcoma; hyperleukocytosis; disseminated intravascular coagulation*

ÖZET

Hiperlökositoz 100.000/mm3'ten yüksek bir kan blast sayısı olarak tanımlanır ve en sık olarak monositik (M4) akut miyeloid lösemi (AML)'de meydana gelebilir. Hiperlökositoz, akciğerlerde ve santral sinir sisteminde lökostaz ile ilişkili olduğu için tıbbi bir acil durumdur. On sekiz aylık kız hasta kliniğimize anemi, trombositopeni, lökositoz, bilateral palpebral şişlik/proptozis, orta hatta ele gelen kitle ve boyunda lenfadenopati şikâyetleri ile getirildi. Akut miyeloid lösemi M4 morfolojik özelliklere sahip olan hastada miyeloid sarkom düşünüldü ve kemik iliği karyotip analizinde 47,XX+mar tespit edildi. Hiperlökositoz, lökostaz (bilinç bulanıklığı, takipne/taşikardi), tümör lizis sendromu ve yaygın damar içi pıhtılaşması gibi komplikasyonları vardı. Düşük doz sitoredüksiyon kemoterapisine ilaveten, lökosit aferezi yapıldı. Hastanın tüm semptom ve şikâyetlerinin kayboldu. Sonuç olarak; orbital şişlik/proptozis ve batında kitle ile gelen, tanı anında yüksek lökosit sayısı, AML M4 morfolojik özelliklere sahip, yaygın damar içi pıhtılaşması olan ve küçük yaştaki bir çocuk hastada miyeloid sarkom akla gelmelidir.

Anahtar Kelimeler: *akut miyeloid lösemi, miyeloid sarkom, hiperlökositoz, yaygın damar içi pıhtılaşması*

Introduction

Hyperleukocytosis is defined as a blood blast count >100,000/mm^3 and may occur most commonly in monocytic (M4) acute myeloid leukemia (AML). Hyperleukocytosis is a medical emergency associated with lung and central nervous system leukostasis. It causes respiratory failure and often rapidly fatal intracerebral hemorrhage[1,2]. Acquired coagulation disorders are a common complication in patients with AML. Although it is common in acute promyelocytic leukemia (APL), coagulation abnormalities occur in other subtypes of AML, particularly myelomonocytic differentiation, and may present with both hemorrhagic and thromboembolic events. While hemorrhage occurs in 60% of patients with AML at first admission, venous thromboembolism (VTE) develops in 10%. Bleeding in patients with AML may result from disease or treatment-related thrombocytopenia and complex systemic coagulation disorders such as excessive fibrinolysis, disseminated intravascular coagulation (DIC), or nonspecific proteolysis. In this context, abnormal

İletişim/Contact: *Mustafa Özay, Atatürk University, Faculty of Medicine, Department of Paediatrics, Division of Paediatric Haematology-Oncology, Erzurum, Türkiye* • ***Tel:*** *0532 717 2491* • ***E-mail:*** *mustafaaryaozay@gmail.com* • ***Geliş/Received:*** *07.12.2022* • ***Kabul/Accepted:*** *28.12.2022*

ORCID: *Mustafa Özay, 0000-0002-5656-9867*

tissue factor (TF) expression by transformed myeloblasts or proinflammatory monocytes may contribute significantly to the procoagulant state[3].

An 18-month-old female patient who presented to our clinic with bilateral orbital swelling and proptosis, abdominal mass, hyperleukocytosis, disseminated intravascular coagulation, and bone marrow karyotype analysis 47,XX, + mar was diagnosed with acute myelomonocytic leukemia (M4) and treated.

This report aimed to present a patient with a positive bone marrow karyotype analysis of 47,XX, + mar, diagnosed with acute myelomonocytic leukemia (M4), who presented to our clinic with bilateral orbital swelling and proptosis, abdominal mass, hyperleukocytosis, and disseminated intravascular coagulation.

Presentation of the Case

An 18-month-old female patient was referred to us with the suspicion of malignancy, as anemia, thrombocytopenia, and leukocytosis were detected as a result of the examinations performed at the health center they went to due to swelling on her face. In the physical examination of the patient, pallor, clouding of consciousness, tachypnea/tachycardia, swelling and proptosis in the bilateral palpebral region, diffuse distention in the abdomen, and a palpable mass of approximately 8×8 cm in the midline, lymphadenopathy of 1.5×1 cm in the right submandibular and 2×1.5 cm in the left submandibular were present. The patient's laboratory results were as follows: leukocytes, 153.75×103/μL; hemoglobin, 8.0 g/dL; hematocrit, (%), 23.5; mean corpuscular volume, 80.5 fL; platelet, 74×103/μL; lactate dehydrogenase, 1,513 U/L (135–214); uric acid, 14.2 mg/dl (2.4) -5.7; total protein, 5.15 g/dL (6–8); albumin, 2.61 g/dL (3.8–5.4); sodium, 138 mEq/l (136–145); potassium, 4.1 mEq/l (3.5–5.1); calcium, 7.9 mg/dL (8.8–11); phosphorus, 6.28 mg/dL (2.5–4.5); D-dimer, 2,325 ng/ml (0–500); PT, 38.7 sec (12–16); activated partial thromboplastin time (aPTT), 43.9 sec (25–35); and fibrinogen, 40 mg/dl (245–400). In the abdominal ultrasonography performed urgently, a mass of approximately 11×13×9 cm was observed in the midline. In the peripheral smear, blasts with monocyte character were seen at a rate of 50%. Considering acute myelomonocytic leukemia, allopurinol was started at 10 mg/kg (3 doses) by adding 3,000 cc/m^2/day fluid + 40 mEq/L $NaHCO_3$. Erythrocyte and platelet suspension, 2×15 ml kg/dose fresh frozen plasma (FFP), and 5 mg vitamin K were administered.

The patient was transferred to the pediatric intensive care unit because of tachypnea/tachycardia and the need for leukapheresis. A catheter was inserted through the femoral vein, and leukapheresis was performed once under intensive care. Multiple FFP infusions were performed because of low fibrinogen levels and a long PT and aPTT. Bone marrow aspiration was performed in the patient with blasts in a peripheral smear. Flow cytometry findings were HLA-DR 53%, CD11C 95%, CD 64 97%, CD11B 93%, CD 4 94%, CD 13 79%, CD 14 30%, CD 15 26%, CD 33 98%, and Anti-MPO 18%. Disseminated intravascular coagulation laboratory findings (PT and aPTT length, low fibrinogen, increase in fibrin degradation products) were observed in the patient, and AML (M4) myeloid sarcoma was suspected together with clinical, morphological, and flow cytometry findings. Because the leukocyte count was >100.000 x 103/μL, 20 mg/m2 cytarabine, 2 x 20 mg/kg hydroxyurea, and 20 mg/m2 thioguanine were administered as pre-phase treatment according to the BFM AML-2019 protocol. The patient underwent leukapheresis once, and leukocyte count decreased below 100 x 103/μL (65 x 103/μL), fibrinogen and PT/aPTT values returned to normal, and then was transferred to the ward. Acute myeloid leukemia (M4) myeloid sarcoma was suspected, and the first induction was initiated according to the BFM AML-2019 protocol. Meanwhile, thrombosis developed in the femoral vein of the patient from which the catheter was removed. Enoxaparin at 2 x 100 μ/kg was administered to the patient for 14 days, and it was observed that the thrombosis resolved. After the second induction, swelling/proptosis in the bilateral palpebral region, abdominal distention, midline mass (11×13×9 cm), and lymphadenopathy completely disappeared. The patient's genetic result at the time of diagnosis (47,XX, + mar) was 46,XX after induction therapy. Before all chemotherapy cycles, a blast count <5% was considered for remission. The maintenance treatment was initiated according to the BFM AML-2019 protocol.

Discussion

Acute myeloid leukemia is a highly aggressive hematological malignancy characterized by clonal expansion of transformed myeloblasts. Patients with AML are at high risk for hemorrhagic and thromboembolic

complications. In addition to disease or treatment-induced thrombocytopenia, patients with AML may suffer from complex systemic coagulation disorders such as overt disseminated intravascular coagulation, excessive fibrinolysis, or nonspecific proteolysis[4].

Disseminated intravascular coagulation is more common in AML than ALL and is most common in APL. Almost all patients with APL have DIC at presentation. The incidence of DIC in AML other than APL is between 10% and 30%. Disseminated intravascular coagulation is thought to be caused by the release of tissue factor-like procoagulants from azurophilic granules within leukemia cells. Disseminated intravascular coagulation presents clinically with bruising and, when severe, bleeding from multiple sites. Laboratory findings include thrombocytopenia, hypofibrinogenemia, elevated fibrin breakdown products, and deficiency of clotting factors, including factor V and factor VIII. Other mechanisms, such as excessive fibrinolysis and secretion of interleukin (IL)-1 by AML cells, may contribute to bleeding[1]. Our patient was diagnosed with AML-M4. Due to the PT and aPTT length, low fibrinogen, and increase in fibrin degradation products, treatment for disseminated intravascular coagulation was arranged. It was observed that disseminated intravascular coagulation improved with both supportive treatment and chemotherapy.

While 60% of patients with AML experience bleeding at first admission, 10% have been reported to develop VTE[3]. Thrombosis that developed after catheter removal from our patient's femoral vein responded dramatically to subcutaneous enoxaparin treatment in addition to chemotherapy, and it was observed that the thrombosis disappeared in 14 days. The fact that our patient had AML M4 (myelomonocytic) and that thrombosis was observed in the femoral vein, albeit associated with DIC and catheter, is consistent with the literature regarding its dramatic response to treatment.

Hyperleukocytosis was defined as a blast count >100.000/mm^3. This condition is associated with increased morbidity and mortality and can induce leukostasis, tumor lysis syndrome, and DIC, especially in patients with acute leukemia. In some leukemias, hyperleukocytosis is more common in certain subsets of patients. Hyperleukocytosis in AML appears to be associated with monocytic differentiation[5]. The fact that our patient had AML M4 and hyperleukocytosis was consistent with the literature.

The exact prevalence of hyperleukocytosis in acute leukemia is unknown, but it probably occurs in 5–10% of patients with AML and is slightly higher (>20%) in acute lymphoblastic leukemia. However, acute complications of hyperleukocytosis are closely linked to leukostasis and are most pronounced in cells that show signs of myeloid differentiation. The organs most frequently affected are the central nervous system (CNS), including the lungs and retina[5]. Hyperleukocytosis is a medical emergency associated with leukostasis in the lungs and CNS, causing respiratory failure and often rapidly fatal intracerebral hemorrhage. Pulmonary leukostasis manifests as dyspnea, tachypnea, rales, interstitial infiltrates, and respiratory failure. Central nervous system leukostasis manifests as headaches, blurred vision, somnolence, obtundation, ischemic stroke, and intracerebral hemorrhage[6]. Therefore, the main goal of the initial treatment of hyperleukocytosis and/or leukostasis is to reduce the number of circulating leukemia cells, thus preventing the development of organ failure. The most common method for rapid cytoreduction is leukapheresis, which can be combined with chemotherapy[5]. Interventions with more universal support include coagulation, hyperhydration, optimization of urate oxidase administration, and avoidance of red cell suspension transfusions, which can increase blood viscosity. However, initial treatment with hydroxyurea or low-dose chemotherapy and other interventions involving exchange transfusion or leukapheresis are controversial. Low-dose chemotherapy with hydroxyurea, cytarabine, etoposide, and 6-thioguanine has been used to achieve more gradual cytoreduction. In contrast, leukapheresis has been used to achieve faster cytoreduction, potentially reducing tumor lysis syndrome[7]. Our patient received low-dose chemotherapy with hyperhydration, allopurinol, hydroxyurea, cytarabine, and thioguanine. Since our patient had symptoms, a more gradual cytoreduction was achieved with leukapheresis once, in addition to chemotherapy, to avoid complications of hyperleukocytosis.

Myeloid sarcoma (MS), also known as chloroma, refers to the accumulation of myeloid blasts outside the bone marrow that can cause the destruction or compression of normal tissue. Myeloid sarcoma sites commonly include the CNS, skin, orbit, and bone. The incidence of MS in pediatric patients with AML is approximately 10%. Myeloid sarcoma is more common in patients with high leukocyte counts, younger age, t (8; 21), and AML M4/M5 morphological features at diagnosis[8,9]. Some studies in adults have shown higher relapse rates

and lower survival rates in patients with MS. In children, the prognostic impact of MS appears to depend on its site of involvement[8–10]. Pediatric patients with MS and CNS or orbital involvement showed better survival than those without CNS or orbital involvement and patients without MS. In contrast, relapse rates are higher in children with chloromatous skin involvement. Extramedullary relapses are more common in patients with extramedullary disease at diagnosis[8,11]. Our patient was 18 months of age. She had hyperleukocytosis, AML M4, bilateral proptosis, an abdominal mass, and 47,XX, + mar positivity. However, no t (8; 21) chromosomal translocations were observed. Bilateral proptosis and the abdominal mass disappeared completely after induction treatment. We believe that myeloid sarcoma may be due to the complete disappearance of orbital and abdominal masses with chemotherapy.

Marker chromosomes are defined in the International System for Human Cytogenetic Nomenclature (ISCN=International System for Human Cytogenetic Nomenclature) as an "abnormal chromosome of unknown origin, often found in the karyotype of patients with cancer and patients with structural genetic disorders"[12]. Genetic results of our patient at the time of the first diagnosis: 47,XX, + mar came in as 46,XX after induction therapy.

Therefore, myeloid sarcoma should be considered in young children with orbital swelling/proptosis, abdominal mass, high leukocyte count at diagnosis, AML M4 morphological features, and diffuse intravascular coagulation.

References

1. Emadi A, Baer MR. Acute myeloid leukemia in adults. In: Greer JP, Arber DA, Glader B, List AF, Means Jr RT, Paraskevas F, Rodges GM. Wintrobe's Clinical Hematology, 13th ed. Philadelphia: Lippincott Williams & Wilkins. 2014: 3591-3695.
2. Creutzig U, Ritter J, Budde M, Sutor A, Schellong G. Early deaths due to hemorrhage and leukostasis in childhood acute myelogenous leukemia. Associations with hyperleukocytosis and acute monocytic leukemia. Cancer. 1987; 60:3071.
3. Beckmann L, Rolling CC, Voigtländer M, Mäder J, Klingler F, Schulenkorf A et al. Bacitracin and rutin regulate tissue factor production in inflammatory monocytes and acute myeloid leukemia blasts. Cancers (Basel). 2021 Aug 4; 13(16):3941
4. Dicke C, Amirkhosravi A, Spath B, Jiménez-Alcázar M, Fuchs T, Davila M et al. Tissue factor-dependent and -independent pathways of systemic coagulation activation in acute myeloid leukemia: a single-center cohort study. Exp Hematol Oncol. 2015 Aug 6; 4:22.
5. Bruserud Ø, Liseth K, Stamnesfet S, Cacic DL, Melve G, Kristoffersen E et al. Hyperleukocytosis and leukocytapheresis in acute leukaemias: experience from a single centre and review of the literature of leukocytapheresis in acute myeloid leukaemia. Transfus Med. 2013 Dec; 23(6):397-406.
6. Ganzel C, Becker J, Mintz PD, Lazarus HM, Rowe JM. Hyperleukocytosis, leukostasis and leukapheresis: practice management. Blood Rev. 2012; 26:117.
7. Oberoi S, Lehrnbecher T, Phillips B, Hitzler J, Ethier MC, Beyene J et al. Leukapheresis and low-dose chemotherapy do not reduce early mortality in acute myeloid leukemia hyperleukocytosis: a systematic review and meta-analysis. Leuk Res. 2014 Apr; 38(4):460-8.
8. Dusenbery KE, Howells WB, Arthur DC, Alonzo T, Lee JW, Kobrinsky N et al. Extramedullary leukemia in children with newly diagnosed acute myeloid leukemia: a report from the Children's Cancer Group. J Pediatr Hematol Oncol. 2003; 25:760.
9. Shimizu H, Saitoh T, Hatsumi N, Takada S, Yokohama A, Handa H et al. Clinical significance of granulocytic sarcoma in adult patients with acute myeloid leukemia. Cancer Sci. 2012; 103:1513.
10. Johnston DL, Alonzo TA, Gerbing RB, Lange BJ, Woods WG. Superior outcome of pediatric acute myeloid leukemia patients with orbital and CNS myeloid sarcoma: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2012; 58:519.
11. Hall MD, Chen YJ, Schultheiss TE, Pezner RD, Stein AS, Wong JY. Treatment outcomes for patients with chloroma receiving radiation therapy. J Med Imaging Radiat Oncol. 2014; 58:523.
12. Liehr T, Claussen U, Starke H. Small supernumerary marker chromosomes (sSMC) in humans. Cytogenet Genome Res. 2004; 107:55-67.

DERLEME / *REVIEW*

The Hypothesis of a New Extrachromosomal Approach to Cancer Treatment

Kanser Tedavisine Yeni Bir Ekstrakromozomal Yaklaşım Hipotezi

Abdullah Dogan[1]

[1]*Kafkas University, Faculty of Veterinary Science, Department of Pharmacology and Toxicology Kars, Turkiye*

ABSTRACT

There are important unexplained points in cancer formation and its treatment with drugs. Some of the cancer drugs used in the treatment affect the genetic material of cancer cells. These types of drugs have a high toxicity. Despite important drugs used in cancer treatment have been developed today, there are serious problems in developing a drug with high specificity. This is because the pharmacological action points where drugs can affect cancerous cells and which are different from normal cells have not been fully determined. The current article reveals hypotheses about some extrachromosomal action points that may be beneficial in cancer treatment. Depending on the proposed hypothesis, information about the chemicals to be investigated is given.

Key Words: *antineoplastic drugs; Warburg hypothesis; aromatic amino acid; aromatic alpha-keto acid; Coenzyme Q10*

ÖZET

Kanserin oluşumu ve ilaçlarla tedavisinde aydınlatılmamış önemli noktalar bulunmaktadır. Tedavide kullanılan kanser ilaçlarının bir kısmı kanser hücrelerinin genetik materyaline etki etmektedir. Bu tip ilaçlar yüksek toksisiteye sahiptirler. Günümüzde kanser tedavisinde kullanılan önemli ilaçlar geliştirilmiş olmasına rağmen, henüz spesifitesi yüksek bir ilaç geliştirilmesi konusunda ciddi sorunlar vardır. Bunun nedeni kenserli hücrelere ilaçların etki edebileceği normal hücrelerden farklı farmakolojik etki noktalarının tam olarak tespit edilememiş olmasıdır. Bu makalede kanserin tedavisinde faydalı olabilecek bazı ekstrakromozomal etki noktaları ile ilgili hipotezler ileri sürülmüştür. Önerilen hipoteze dayanılarak araştırılması gereken kimyasal maddeler hakkında bilgiler verilmiştir.

Anahtar kelimeler: *antineoplastik ilaçlar; Warburg hipotezi; aromatik aminoasit; aromatik alfa-keto asit; Coenzyme Q10*

Introduction

Chemical carcinogens, known as an important cause of cancer (70%), develop tumors, shorten the emergence time of the tumor, and promote metastasis. Primary carcinogens directly initiate cancer, and secondary carcinogens initiate by reacting with the genetic structure via their metabolites. Co-carcinogens facilitate the promotion and progression of the tumor. Tumor cells, which form by the effect of chemical carcinogens, go through the stages of initiation, promotion, and progression[1,2].

Drugs used in cancer treatment may affect the tumor cell (internally: genetic and other functions) and the surrounding of the tumor (externally)[3].

Genetic Targets

Among the genetic targets of the drugs, mutant oncogenic genes and epigenetic and transcriptional conduction irregularities take place. RAS proteins coded[3] by the RAS gene (membrane-associated G-proteins: HRAS, KRAS, NRAS) are protooncogenic, and they have GTPaz activity. Its GPT-related form transfers the signals, stimulating cell division, from the cell membrane to the nucleus[4]. BRAF gene (Ras Associated Factor) codes a protein that controls cell division. Point mutations of the BRAF gene cause the activation of tyrosine kinases related to the membrane, such as MEK (MAPKK), ERK (MAPK), SRC, and BCR/ABL[4]. Mitogen-activated protein kinase (MAPK) has serine/treonine kinase (in the cytoplasm) activity that plays a role in the intracellular signal pathway (MAPKsi, AKT). Drugs such as vemurafenib, dabrafenib, trametinib, and cobimetinib inhibit BRAF mutation[3]. PI3K (phosphatidylinositol 3-kinase) is activated by the mutations of PIK3CA (phosphatidylinositol 3-kinase, catalytic, α-polypeptide). PI3K inhibitors are tried on PIK3CA-mutation cancers[3].

İletişim/Contact: *Abdullah Doğan, Kafkas University, Faculty of Veterinary Science, Department of Pharmacology and Toxicology Kars, Türkiye* • ***Tel:*** *0507 365 5313* • ***E-mail:*** *adogankars@hotmail.com* • ***Geliş/Received:*** *29.04.2022* • ***Kabul/Accepted:*** *18.10.2022*

ORCID: *Abdullah Doğan, 0000-0003-2008-6713*

The tumor is located between the suppressor genes Gatekeeper (APC, p53, Rb) and Caretaker (TP53). Point mutation, loss of heterozygosity (LOH), and increased methylation are seen in these genes in cancer[4]. Mutations causing loss of function in ubiquitin ligase CBL increase the signal on the thyrosine kinase pathway. The mutations in PTEN inactivating the phosphatase activity increase signal on the PI3K pathway. Drugs restoring the normal function of mutant TP53 have been studied. A bisindolylmaleimide-derivative drug has been discovered that regains the interaction between SMAD4 and SMAD3 mutations, which are cell growth-suppressing genes. Poly (ADP-ribose) polymerase (PARP) enzyme activity increases when BRCA1 and BRCA2, DNA repair and tumor suppressor genes, are mutated. Inhibition of these enzymes increases success in the treatment. Inhibition of CYCLOPS genes causes a loss in the number of copies. This induces death in the cells that do not contain the corresponding tumor suppressor gene (paralog)[3].

Extragenic Targets

Tumor microenvironment, differentiation in the immune cells and stromal cells such as fibroblasts, abnormal endocrine signals, and microbiome occur in the environmental targets of antineoplastic drugs. Antiangiogenic treatments have been developed that target the vascular endothelial growth factor (VEGF), one of the external proteins of normal cells. It is thought that antibodies inhibiting immune checkpoints, such as PD-1/PD-L1 and CTLA-4, may effectively treat some types of cancer. Chimeric antigen receptor T-cell (CAR-T) infusion has been used in hematologic malignancy. Antibodies of multiple cell surface receptors (ex., Klgr1 and TIGIT) blocking metastatic colonization have been detected. Some antibodies are effective against proteins inhibiting the immune responses, such as programmed cell death protein 1 (PD-1)[3]. Mitosis inhibitors, hormones and antagonists, enzymes (asparaginase), tyrosine kinase blockers (imatinib), growth receptor inhibitors (trastuzumab), and vascular endothelial growth factor inhibitors (bevacizumab) are used in the treatment[1,2]. In addition, studies on the correlation between energy and synthesis have been conducted.

Warburg Effect

Otto Heinrich Warburg determined that the tumor cells convert glucose to lactic acid over pyruvic acid under aerobic conditions. Due to this finding, also known as Warburg effect, the researcher won the Nobel prize in 1924[5–8]. In healthy cells, pyruvic acid, composed of glucose, is transported to the mitochondria, converted to Acetyl CoA, and decomposed in the TCA cycle. Meanwhile, 36 ATP are produced from a glucose molecule (38 ATP in total). Tumor cells convert pyruvic acid into lactic acid via glycolysis in the cytoplasm under aerobic conditions and produce 2 ATP from one glucose molecule (4 ATP in total)[5,6,8–12].

Pyruvic acid is degraded with 95% oxidative phosphorylation and 5% aerobic glycolysis in healthy cells[5]. Cancer cells are degraded with approximately 85% aerobic glycolysis and 15% oxidative phosphorylation[11]. Oxidative phosphorylation in healthy cells is 19 times more than aerobic glycolysis (95/5). According to the rates mentioned above, healthy cells obtain 36.3 ATP from one mole of glucose, and cancer cells obtain a total of 9.1 ATP.

Reason for Cancer and Aerobic Glycolysis According to Warburg

According to Warburg, cancer is caused by anoxemia and function disorder in mitochondria[10,12]. Cells that adapt to low-oxygen environments are converted into cancer cells by fermentation. Non-adapted ones are subject to apoptosis[5]. As the mitochondria of cancer cells cannot function, apoptosis is not observed, and they continuously generate[8]. Fermentation developing in cancer is irreversible[5,6]. Pyruvic acid and alpha-ketoglutarate are converted into Acetyl CoA by dehydrogenases using thiamine pyrophosphate as co-enzymes[2]. This data supports Warburg effect.

Cancer cells are thought to retain their ability to ferment in the evolutionary process by inheriting from bacteria[6,9]. Besides cancer cells, fermentation is also seen in all the healthy cells (immune system cells in case of infection, healing wounds, embryonic cells) that generate rapidly[10]. Fermentation also occurs in the muscle cells as a result of excessive physical activity[6,10,13]. However, Warburg effect seen in normal cells is reversible[10,12].

Studies have indicated that most cancer cells do not impair mitochondrial function. Tumors can also be seen in lungs rich in an oxygenated environment. Thus, the idea that cancer arises from impaired aerobic respiration in mitochondria is not entirely accepted[11].

Metabolites, occurring due to Warburg effect, are required for angiogenesis required by the cancer cells[6]. Metabolites help the synthesis of agents such as

protein, lipid, and nucleic acid[10,11]. NADPH synthesis reproduces upon the Warburg effect. Glutamine, synthesized by transamination, contributes to NADPH production by catabolizing malate dehydrogenase into lactate[11]. NADPH acts as a reductant in the synthesis of fatty acids[10]. Modulation of pyruvate kinase facilitates re-directing pyruvic acid to pentose phosphate, nucleotide, and amino acid biosynthesis pathways[9–11]. The cells convert lactate, which is generated in the tissues by Cori cycle, back to glucose in the liver. In addition, they convert alanine back to glucose. One glucose molecule may provide 30 ATP and 2 NADPH if it enters the pentose phosphate pathway or 6 carbons for the synthesis of macromolecules if it does not enter the pathway[11]. If a glucose molecule degrades in TCA, it provides 5 times the ATP needed to generate a 16-carbon fatty acid chain. However, 7 glucose molecules are required to generate NADPH in the same synthesis[9,11]. Thus, aerobic glucose develops to provide elements to the cell rather than energy.

Lactic acid, emerging due to the Warburg effect, reduces pH of the surrounding tissues. This facilitates the invasion of cancer[5,6,10]. Lactic acid increases the vascularization of the tissues and encourages metastasis. It is also efficient by developing the tissue fibers acting in metastasis, such as collagen[10].

The Use of Warburg Effect in the Diagnosis of Tumor

In Positron Emission Tomography (PET), used for tumor diagnosis, fluorodeoxyglucose (FDG), which is a radioactive fluorine (^{18}F) compound, is used. It was detected by PET that tumor cells use an excess amount of glucose[8–10]. Cancer cells use glucose approximately 20 times more than healthy cells[6,8].

Causes of Cancer and Use of Metabolic Differences in Cancer Treatment Today

The cause of cancer is explained by the activated oncogenic genes and inactivated tumor suppressor genes related to the mutations[10].

It can be considered that reduction of glucose uptake may be beneficial in the treatment of cancer (apoptosis). This study determined that cancer is less seen in approximately 30 thousand patients with Type 1 diabetes mellitus, followed up for 30 years, than in healthy people[6].

In normal cells, p53 gene inhibits excess glucose uptake, lipogenesis, NADPH synthesis, and cell proliferation. In cancer, this gene is mutated, thus it cannot function accordingly[10]. Expression of TIGAR gene in cancer inhibits phosphofructokinase. It directs glucose to the pentose phosphate pathway and generates NADPH in glutathione synthesis. In healthy cells, high oxidative phosphorylation and ROS generation induce apoptosis[11].

Cell growth and glucose metabolism are controlled by insulin-like growth factor (IGF)– Phosphoinositide 3-kinase/Protein kinase B (PI3K/AKT) pathway[9]. PI3K signal pathway promotes the amino acids enter in protein synthesis via mTOR (mammalian target of rapamycin). PI3K signal increases the expression of glucose-transporting molecules via AKT. It stimulates hexokinase and phosphofructokinase activity and increases the use of glucose. Thus, small molecules degrading PI3K signal cause the tumor to regress[11].

Cells using aerobic glycolysis have a high ATP/ADP and NADH/NAD+ ratio. If ATP decreases, the cells undergo apoptosis. Adenylate kinase contributes to ATP production by converting two ADPs into one ATP and one AMP. The resulting AMP activates the protein kinase (AMPK) that is activated with AMP. Protein kinase activates various structures in the cell via phosphorylation (tumor suppressor protein LKB1). Metformin and phenformin activate AMPK in the cell. It is reported that adding metformin in cancer treatments may be effective in the prevention and treatment of cancer[11].

Oncogenes stimulate thyrosine kinase (in the cytoplasm) enzyme acting in cell proliferation. Activated tyrosine kinase regulates glucose metabolism (not seen in normal cells)[9–12].

Proliferating cells express the M2 (PK-M2) isoform of pyruvate kinase, a glycolytic enzyme[11]. PK-M2 enzyme is only present in cancer and rapidly dividing cells. It is not present in other cells. This enzyme accelerates the conversion of glucose to pyruvic acid in cancer cells. When the synthesis of PK-M2 enzyme is inhibited, enzyme passes into another form. This may prevent growth in cancer cells[8].

Pyruvate dehydrogenase enzyme complex in the mitochondria consists of three enzymes; pyruvate dehydrogenase, dihydrolipoyl methylase, and dihydrolipoyl dehydrogenase[6]. Pyruvate dehydrogenase enzyme is converted into inactivated form via phosphorylation by pyruvate dehydrogenase. Phosphatase enzyme converts the inactivated pyruvate dehydrogenase into active form. Active pyruvate dehydrogenase converts pyruvate into Acetyl CoA and provides it to be degraded with oxidative phosphorylation in TCA. Pyruvate dehydrogenase

kinase inhibitors prevent pyruvate dehydrogenase from being converted into inactivated form. Among them, drugs such as SB-204990, 2-deoxy-D-glucose, 3-bromopyruvate, bromopyruvic acid, 3-bromo-2-oxopropyonate-1-propyl ester, 5-thioglucose, and dichloroacetic acid are developed. This lowers the aerobic glucose level in the cytoplasm of cancer cells[8].

It is asserted that cancer can also be seen depending on the insufficiency of enzyme (citrate synthase) that converts pyruvic acid into citric acid[6]. Isocitrate dehydrogenase-1 (IDH1) and Isocitrate dehydrogenase-2 (IDH2) enzymes convert the isocitrate in cytoplasm to alpha-ketoglutarate via NADP+/NADPH. Mutation was determined in the gene coding cytosolic IDH1 in 12% of glioblastoma multiforme[3,11]. D-2-hydroxyglutarate, emerging depending on mutation, inhibits TET2 protein function, which is efficient on epigenetic mechanisms. Suppression of TET2 activation causes abnormal DNA methylation[3,10].

Mutations in enzymes involved in the TCA cycle, such as succinate dehydrogenase (converts succinate to fumarate) and fumarate hydratase (fumarate malate), are identified in human renal cancer. As a result of these mutations, Hif1α-mediated glucose use is activated[11].

In cancer cells, majority of the pyruvic acid is converted to lactic acid by the enzyme lactate dehydrogenase (LDHA) in the cytoplasm. In most human cancers, the LDHA amount is found to be higher than in healthy tissues. Inhibition of enzymes can be used in cancer treatment[6].

Cancer cells need glutamine, glycine, serine, and aspartate to synthesize the building blocks[3]. Cancer cells ferment glutamine, the most abundant amino acid in the blood, into lactate (ATP). It has been determined by the PET scans that some cancer cells use radioactive glutamine more than radioactive glucose (10 times more other amino acids)[9]. Human tumor cells, whose growth is directed by the MYC oncogene (mutated), are susceptible to glutamine deficiency[9,11]. The growth of tumors containing mutations in PIK3CA mostly depends on aspartate. Some tumors elevate the serine levels due to NRF2 and ATF4 signaling or oncogenic signaling as a result of the hypoxia responses. In this type of tumor, suppression of serine metabolism regresses the tumor. The tumorigenic potential of the cells initiating metastasis depends on their fatty acid uptake via CD36, which is the fatty acid receptor. Thus, lipid synthesis can be targeted in tumors containing high amounts of polyunsaturated lipids[3].

Hypothetical Points Recommended to be Investigated in Cancer Treatment

Phenylalanine is an essential aromatic amino acid[14,15]. It enters into the synthesis of protein and sympathetic amines in the body[1]. Tyrosine is chemically p-hydroxyphenylalanine[14]. Plants and bacteria can synthesize tyrosine (phenylalanine) from prephenate, released as an intermediate product in the shikimate pathway. Melanine, sympathetic amine, and thyroid hormones are synthesized from tyrosine in the body. Tryptophan is an essential aromatic amino acid, and it is glycogenic and ketogenic[14,15]. Plants and bacteria may synthesize tryptophane from shikimic acid or anthranilate[15]. Serotonin, niacin[14], kynurenine, and auxin are synthesized from tryptophane.

Phenylalanine, tyrosine, and tryptophan are absorbed from the digestive tract, used in protein synthesis, and metabolized. Phenylalanine is slowly and irreversibly converted to tyrosine by phenylalanine hydroxylase in the liver (75%)[1,14,16]. Phenylalanine is converted to phenylpyruvate via transamination. Phenylpyruvate is converted to either o-hydroxy phenylacetate or phenylactate by dehydrogenase enzyme[16]. Phenyllactic acid is oxidized in the body and is converted to phenylacetic acid. This product is conjugated with amino acids (glutamine, glycine) and excreted from the body[14,16,17]. Phenylalanine is converted to phenylethylamine by decarboxylation. This substance is converted to phenylacetylglutamate over phenylacetate and excreted in urine[16]. Benzene ring of phenylalanine is opened too little and then decomposed[18].

Tyrosine is decarboxylated (tyramine) and transaminated. Tyrosine transaminase enzyme that transfers the amine group in tyrosine to alpha-ketoglutarate converts tyrosine to p-hydroxyphenylpyruvate. This metabolite is converted to p-hydroxyphenyllactate and then to p-hydroxyphenylacetate. P-hydroxyacetate is excreted by conjugating with glycine and glutamine. In the digestive tract, tyrosine is converted to p-hydroxyphenylpyruvate by the deamination of its side chain under anaerobic conditions via the effect of intestinal bacteria. Then, p-hydroxyphenylacetic acid, p-cresol, and phenol are generated. Cresol (methylphenol) and phenols are absorbed by the intestines and then excreted by urine after being conjugated in the liver. Decomposition of the benzene structure of tyrosine is slow and rarely seen (fumarate, malate, acetoacetate)[14].

Tryptophan is converted to serotonin via hydroxylation and decarboxylation[14,18]. It is degraded by decomposing

to kynurenine, then to the products such as formic acid, alanine, xanthurenic acid, nicotinic acid, α-ketoadipic acid, Glutaryl-CoA, and Acetyl-CoA. Tryptophan is converted to indolepyruvate by oxidative deamination via tryptophanase enzyme secreted by *E. coli* in the intestine. Indolepyruvate is converted to indoleacetate and methylindol (scatol) by decarboxylation. Indole is formed from scatol in the liver. Indole is oxidized and converted to indoxyl and then to indoxyl sulphate and excreted by urine[14].

Phenylalanine, tyrosine, and tryptophan are converted to keto-acids (phenylpyruvate, hydroxyphenylpyruvate, indole pyruvate, respectively) by deamination or transamination in the body and some of them are degraded in TCA[14]. However, since TCA cannot serve with full efficiency in the tumor cells, the degradation rates are low by this pathway.

Ammonia is combined mostly with glutamate (glutamine synthetase) and converted to glutamine in the blood. In the muscles, it is transferred to pyruvate (alanine aminotransferase) and alanine is synthesized. Glutamine and alanine come to the liver. Alanine transfers ammonia to alpha-ketoglutarate and converts it to glutamate (transamination) and is converted to glucose via pyruvate[14,19,20]. Glucose enters the pentose phosphate pathway (NADPH production) or is degraded again to pyruvate via glucose-6-phosphate. Thus, it is used in the synthesis of serine (glycine and cysteine from serine), alanine, valine leucine and isoleucine, glutamate (then glutamine, pyrroline, arginine) and aspartate (then asparagine, methionine, threonine, lysine)[19,20]. In the tissues other than the liver, glutamine is converted to glutamate by deamination. Glutamate is included in the cell. It is converted to alpha-ketoglutarate and aspartate by giving the amine group to oxaloacetate[20]. Glutamine, glycine, and aspartate enter the synthesis of purine, glutamine, and aspartate pyrimidine (folic acid is also important)[14,20].

Degradation of DNA of the cells initiates cancer. However, degradation of its metabolism is required for progress. Lactic acid formed from glucose in the cancer cells, is converted to alanine (transamination) in the liver. Alanine synthesizes with Acetyl CoA, and thus the fatty acids via lactic acid and pyruvic acid[20]. The conversion of alanine to glucose and aliphatic amino acids provides the need for genetic base, amino acid, fatty acid, and NADPH of the tumors. Aliphatic amino acids such as glycine are conjugated with metabolites such as phenylacetic acid (can cause loss of aromatic amino acids). Disruption of this cycle can suppress the growth of cancer cells (Fig. 1).

Aromatic amino acids are converted to aromatic a-keto acids. Aromatic keto acid reductase (80%) and lactate dehydrogenase (20%) enzymes take place in the reduction of phenylpyruvic acid and other alpha-keto acids to phenyllactic acid (and its derivatives)[21]. Part of phenylpyruvic acid is converted to phenylacetic acid and excreted from the organism by conjugating with aliphatic amino acids such as glutamine and glycine in the body. Aromatic alpha-keto acids can prevent the conversion of pyruvic acid to lactic acid in the tumor cells as they use lactate dehydrogenase enzyme, which converts pyruvic acid to lactic acid. Lactic acid and alanine cannot be synthesized from pyruvic acid. Adequate glucose cannot be formed in the liver due to decreased alanine. Alpha-keto acids lower aliphatic amino acids such as glutamine and glycine, which enter into DNA synthesis, as they cause their excretion by conjugation. As a result, they less convert to pyruvate, glucose, and aliphatic amino acids (glutamine, glycine, aspartate). This may cause tumorostatic effect by suppressing DNA synthesis and cell proliferation in cancer cells. Besides the degradation of DNA, the reason of cancer may be associated with the lack of aromatic amino acids or their alpha-ketoacid metabolites (which may also be transaminase or oxidative deaminase enzyme deficiency).

Low level of tyrosine may sufficiently prevent the synthesis of Coenzyme Q10. This may explain the low oxidative phosphorylation rate in cancer cells. In addition, tyrosine also participates in the structure of thyroid hormones that produce energy in mitochondria (vast ATP production). If mitochondria do not show activity, cells enter into apoptosis (cannot make aerobic respiration). Thus, aerobic glycolysis is required not to have apoptosis in cancer cells (less ATP and less free radicals).

The absorption and distribution of aromatic amino acids taken in certain rates together with food is regulated (abundance of one reduces the passage of the other through the membranes.) by other neutral amino acids (alanine, asparagine, glutamine, glycine, isoleucine, leucine, valine, serine, pyrroline, threonine, methionine, and cysteine). Thus, amino acids in food are taken to the body at a fixed rate. Metabolites of aromatic amino acids taken in the body via food at a fixed rate do not prevent the use of aliphatic amino acids, of which synthesis has increased in the cancer cells, DNA, and other building blocks. Thus, the hypothesis can be proposed stating that aromatic amino acids or their

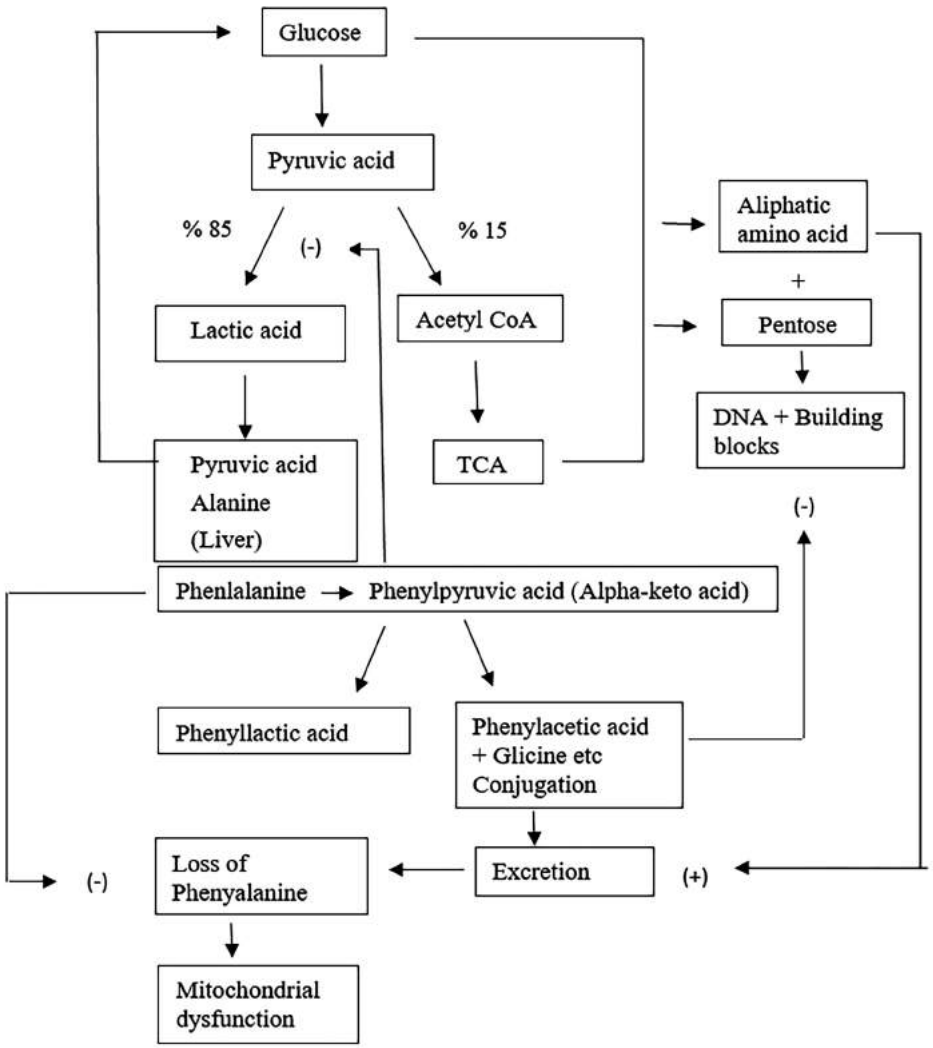

Figure 1. *Hypothetical action points of aromatic amino acids and aromatic alpha-keto acids (aromatic amino acid derivatives) in cancer cells.*

aromatic alpha-ketoside derivatives (including their analogs) should be administered externally for prophylactic or therapeutic purposes.

When aromatic amino acids are administered in high doses, they can also be efficient by decreasing the absorption of other neutral amino acids via gastrointestinal tract.

Sodium phenylpyruvate showed cytotoxic effect in lung (A549) and breast adenocarcinoma (MDA-MB-231) cell cultures (as far as is known, the hypothesis is passed for the first time)[22]. 4-Phenylbutyrate is a modulator that can cause differentiation or apoptosis in the cancer types such as prostate, ovarian, melanoma, glioma, and leukemia. 4-Pheynlbutyrate causes the excretion of glutamine from the body. Phenylbutyrate and phenylacetate are in the trial stage in treatment of Hodgkin's and non-Hodgkin's acute myeloid leukemia[23]. Phenylpyruvic acid is chemically similar to phenylbutyrate and is converted to phenylacetate. These studies support this hypothesis.

Fish are ammonotelic animals and they give the ammonia forming in their bodies directly into water[14]. The reason why cancer is not seen in sharks (not known in other fish) may be associated with the suppression of glutamine and DNA synthesis as a result of giving ammonia to the water. In such animals, cancer cells may not meet the increasing amine needs.

Body cells primarily subject the amino acids to deamination (keto acids are released). Bacteria primarily convert amino acids into polyamines by decarboxylation. Aerobic glycolysis of cancer cells is similar to bacteria.

Synthesis of serotonin, product of decarboyxlation, increases in carcinoid tumors[14]. This information is compatible with the hypothesis.

The substances recommended in this hypothesis are amino acids or the substances that can be converted into amino acids. Thus, their possibility of cell proliferation should also be considered.

Other hypothetical points to be investigated include aromatic amino acids and their analogs of alpha keto acid derivatives, prevention of pyruvate synthesis from lactic acid, prevention of alanine synthesis from lactic acid (lactic acid analogs), and supporting the mitochondrial functions.

Supporting Mitochondrial Functions

Coenzyme Q10 and aromatic amino acids such as phenylalanine and tyrosine, are involved in its synthesis, and unsaturated long chain fatty acids can support mitochondrial functions.

Coenzyme Q10

Coenzyme Q10 was primarily isolated from the mitochondria in bovine heart by Dr. Frederic Crane in 1957[7,24–26]. The ubiquinone that is known as Coenzyme Q10 is chemically 2.3-dimethoxy-5-methyl-6-decaprenyl-1.4-bensoquinone[25]. It is in the form of Coenzyme Q10 in humans, Coenzyme Q9 in mice, Coenzyme Q8 in E. coli, and Coenzyme Q6 in Saccharomyces cerevisiae[13].

The side chain of ubiquinone and cholesterol synthesis initiate from Acetyl-CoA and continue over mevalonic acid and isopentenyl diphosphate. Cholesterol, ubiquinone, vitamins A, E, K and terpenes are synthesized from isopentenyl diphosphate[27]. Aromatic ring of Coenzyme Q10 is synthesized from tyrosine. For its synthesis, B2, B3, B6, B12, C, folic acid, pantothenic acid, and some nutrient components are required[13,24–26]. It can be produced synthetically at a laboratory. Coenzyme Q10 can be produced in bacteria such as *Pseudomonas denitrificans* and *Agrobacterium tumefaciens* and numerous yeast media such as *Neurospora crassa and Aspergillus fumigatus*[24].

Coenzyme Q10 is found in sesame seeds, broccoli, soybeans, peanuts, cauliflower, oranges, strawberries, fish, meat, hearts, livers, kidneys, and eggs (all the animals)[24–26,28,29]. Food containing Coenzyme Q10 is divided in two as the ones containing more than 20 μg/g and less than 20 μg/g. Coenzyme Q10 is between 260–280 μg/g in pig heart, 8–200 μg/g in red meat and 4–64 μg/g in fish[24].

Danish people get 3–5 mg of Coenzyme Q10 from meat and poultry every day[7]. Swedish people get averagely 2–20 mg of Coenzyme Q10 every day, Japanese people get averagely 4.48 mg of Coenzyme Q10 every day in total. It is considered that men get 5.4 mg of Coenzyme Q10 and women get 3.8 mg of Coenzyme Q10 every day. It has been reported that frying calf heart decreases the amount of Co-enzyme Q10 by 30.58±1.37%, frying calf liver by 23.62±2.18% and boiling calf meat by 22.81±2.66%[24].

Aging, stress, and malnutrition reduce Coenzyme Q level in the body[7,24]. Coenzyme Q10 consumption increases by vigorous exercises, hypermetabolism, and acute shock situations. HMG CoA reductase inhibitors decrease the cholesterol and Coenzyme Q10 level[25].

In energy generation in mitochondria, enzymes such as Complex I (NADH-ubiquinon oxidoreductase: nicotinamide adenine dinucleotide dehydrogenase), Complex II (succinate-ubiquinon oxidoreductase: succinate dehydrogenase), Complex III (ubiquinol: ferrocytochrome C oxidoreductase: ubiquinon-cytochrome c reductase), Complex IV (ferrocytochrome c: oxygen oxidoreductase or cytochrome C oxidase), and Complex V (ATP synthase) take place[13,24]. Coenzyme Q10 is the co-enzyme of Complex I, II and III enzyme systems. These enzymes take part in electron transport and ATP synthesis[24,25]. Ubiquinone is converted to hydroxyquinon by receiving 2e in its quinone ring[24].

When Coenzyme Q10 is administered in pure form, it is absorbed orally at a low rate. When it is dissolved in fat and administered, its absorption rate increases. Its absorption occurs via passive diffusion[24,30]. Oral intake of ubiquinole oxidizes in ubiquinone in the stomach. After ubiquinone is reduced to ubiquinol in the intestines, it is absorbed from the small intestines in the form of chylomicrons and passes into the lymph circulation[13]. After it is converted to lipoproteins in the liver (VLDL, LDL), it mixes with blood[24,31]. When it is found mostly in the form of ubiquinone in the brain and lungs, it is found mostly in the form of ubiquinol in the blood (90–95%) and other tissues[13].

Fatty dispersions, emulsions, semi-emulsified systems, water-soluble powder formulations, and cyclodextrin complexes can be applied. It is known that the administration of Coenzyme Q10, in emulsified systems, and food increases bioavailability 3 times[24]. Oral

bioavailability of nanoparticles of Coenzyme Q10 is 4.28 times higher than its free form[30]. Also, cyclodextrins increase the oral bioavailability of Coenzyme Q10[24,30].

Coenzyme Q10 is efficient as an antioxidant[25,28]. Coenzyme Q10 inhibits lipid peroxidation by binding oxygen-derived radicals. Unstable free radicals become stable by receiving an electron from ubiquinol[24]. They act in membrane stability, cell signal, gene expression, cell proliferation, and control of apoptosis[13,24]. It slows down the aging process. It is protective against geriatric brain diseases. It modulates the gene expression of Coenzyme Q10 and repair DNA damage and mutations[28,29]. It strengthens the musculature and immune system[24]. It has been shown that Coenzyme Q10 reduces oxidative stress in diabetic patients, provides glycemic control, and decreases the HbA1 c levels. It is also reported that it prevents cardiovascular and neurodegenerative diseases and supports their treatment[24,25]. Coenzyme Q10 decreases the frequency of migraine attacks[26]. It is effective in mitochondrial encephalopathies[25] and Alzheimer[24]. It provides recovery in the symptoms of Parkinsonism[24,25,30].

In the patients with breast, lung, prostate, cervix, colon, rectal, and stomach cancer, it is reported that plasma-tissue Coenzyme Q10 level is low[7,29,32,33]. Low Coenzyme Q10 in the body emerges before malignancy[29]. The studies have revealed that Coenzyme Q10 supplementation increases the survival rate in breast, lung, ovary, kidney, brain, esophagus, stomach, and pancreas cancer[30]. In a survey conducted by naturopathic doctors in North America in 2002, it was reported that Coenzyme Q10 treated 77% of breast cancers. Coenzyme Q10 increases tumor regression and survival rate when taken together with food in addition to oral tamoxifen treatment[7]. Complete regression of tumor was observed after the administration of 90 mg/day Coenzyme Q10 to the patients with breast cancer[31]. Coenzyme Q10 with a dose of 600 mg daily was shown to be beneficial for older women with breast cancer. It needs to be clarified whether or not it is beneficial in the patients with terminal prostate cancer[34]. It was shown that the level of Coenzyme Q10 lowered in the blood of mice infected with the leukemia virus, and the mortality rate in mice treated with Coenzyme Q10 was 50% less than in untreated mice[32]. Coenzyme Q administered with diet to mice with dibenzpyrene-induced tumors delayed tumor formation and reduced tumor size and mortality rate[32,35]. It was found that co-administration of coenzyme Q10 and tamoxifen to rats with dimethylbenzanthracene (DMBA)-induced breast carcinoma increased antioxidant activity and decreased the risk of cancer recurrence and metastasis[31]. Coenzyme Q10 decreases MMP-2 activity, a metastatic protein, proportional to the dose and suppresses metastasis[36].

Compared to non-malignant cells, Coenzyme Q increases free radical production in malignant cells[30]. It has been shown that Bleomycin (BLM) treatment increases the content of Coenzyme Q10 in normal liver tissues of hamsters. This partially supports the idea that it may effectively protect against BLM-induced cytotoxicity[37].

100 mg Coenzyme Q10 was administered twice daily to 10 of 20 children with acute lymphoblastic leukemia or Hodgkin's lymphoma (180 mg/m^2 in total) and their electrocardiograms were examined. According to the study results, it is suggested that Coenzyme Q10 may protect myocardial toxicity[33]. It is thought that the agents such as Coenzyme Q10 may reduce tumor-related damage by inhibiting the effects of cytokines promoting tumor development[32]. Coenzyme Q10 strengthens the immune system. It is also revealed that it may increase immunoglobulin G and T4/T8 lymphocytes[33]. Coenzyme Q10 is beneficial in reproductive diseases[30]. Experimental data on the effects of co-enzymeQ10 in cancer treatment are important. Despite these data, its use in cancer treatment is unclear. It has the potential to be used as a preventive and supportive treatment.

Coenzyme Q10 may be administered via oral and intravenous route[7]. It is recommended to administer a dose of 10–100 mg per day[33]. When 100 mg Coenzyme Q10 is taken daily, this increases 1 μg/ml, which is its normal level in the blood, to 2 μg/ml[13,33]. It is reported that high toxicity will occur when 300 mg is administered per day[33]. However, some authors have reported that the toxicity of Coenzyme Q10 is low and doses up to 400–500 mg/day do not cause any clinically visible side effect[13,32]. Among the side effects, dizziness, headache, reflux, nausea, insomnia, fatigue, irritability, mild sensitivity, abdominal pain, and elevated liver enzymes can be listed[7]. Warfarin may reduce its anticoagulant effects[33]. Its effect in pregnant and breastfeeding women has not been known yet[25].

Conclusion

It is recommended to investigate whether the aromatic amino acids and their alpha-keto acid derivatives (including their analogs), as asserted in the hypothesis, have antitumoral effects through in vitro and in vivo methods.

References

1. Doğan A. Veteriner Farmakoloji. Eser Basım Yayın Dağıtım Matbaacılık, Erzurum, 2017.
2. Doğan A. Veteriner Toksikoloji. Eser Basım Yayın Dağıtım Matbaacılık, Erzurum, 2016.
3. Hahn WC, Bader JS, Braun TP, Califano A, Clemons PA, Druker BJ, Ewald AJ, Fu H, Jagu S, Kemp CJ, Kim W, Kuo CJ, McManus M, Mills GB, Mo X, Sahni N, Schreiber SI, Talamas JA, Tamayo P, Tyner JW, Wagner BK, Weiss WA, Gerhard DS. An expanded universe of cancer targets. Cell. 2021;184(4):1142–1155.
4. Protoonkogen onkogen tümör supresör genler, Ankara. [cited 2021 Sept 20]; Available from: https://acikders.ankara.edu.tr
5. Antón JFR. Warburg Effect: Metabolism in cancer cells. [cited 2021 Apr 2]; Available from: https://josefelixrodriguezantonweb.com/2016/09/10/warburg-effect-metabolism-in-cancer-cells/
6. Devic S. Warburg Effect-A consequence or the cause of carcinogenesis? J Cancer. 2016;7(7):817–822.
7. Mathews M, White S, Xue Y. The effects of coenzyme Q10 on women with breast cancer: Systematic review protocol. JBI Database Syst Rev Implement Rep. 2014;12(8):127–144.
8. Warburg effect (oncology). [cited 2021 Jun 12]; Available from: https://en.wikipedia.org
9. Fung J. The paradox of cancer's Warburg Effect. [cited 2021 Apr 8]; Available from: https://medium.com/@drjasonfung/the-paradox-of-cancers-warburg-effect- 7fb572364b81.
10. Kiriş HT. Warburg etkisi ve kanserde meydana gelen metabolik değişimler. [cited 2021 Apr 6]; Available from: https://evrimagaci.org/warburg-etkisi-ve-kanserde-meydana-gelen-metabolik-degisimler-7901Yayınlanma Tarihi 30/08/2019 12:48. 24.
11. Mathew G, Vander Heiden Lewis C and Craig BT. Understanding the Warbung effect: The metabolic requirements of cell proliferation. Sci. 2009;324(5930):1029–1033.
12. Warburg O. On the Orgine of Cancer Cells. Sci. 1956;123(3191):309–14.
13. Şahin Ş. Ubikinol mü? Ubikinon mu? [cited 2021 Jun 12]; Available from: http://eczacininsesi.com/?yon=haber&id=10429.
14. Altınışık M. Protein ve aminoasit metabolizması. [cited 2021 May 11]; Available from: https://www.mustafaaltinisik.org.uk/89-1-19.pdf
15. Aromatic aminoacide. [cited 2021 May 16]; Available from: https://en.wikipedia.org
16. Erdem Ş. Fenilalanin hidroksilaz geninde görülen yaygın mutasyonların taranması. Yüksek Lisans Tezi. Erciyes Üniversitesi Sağlık Bilimleri Enstitüsü Tıbbi Genetik Anabilim Dalı. Kayseri, 2013.
17. Fernandez-Lafuente R, Rodriguez V, Guisan JM. The coimmobilization of D-amino acid oxidase and catalase enables the quantitative transformation of D-amino acids (D-phenylalanine) into a-keto acids (phenylpyruvic acid). Enzyme Microb Technol. 1998;23(1):28–33.
18. Chandler JP, Lewıs HB. Comparatıve studıes of the metabolısm of the amino acıds. V. The oxıdatıon of phenylalanıne and phenylpyruvıc acıd in the organism of the rabbit. J Biol Chem. 1932;96(3):619–636.
19. Altınışık M. Esansiyel olmayan aminoasitlerin biyosentezi. [cited 2021 May 10]; Available from: https://www.mustafaaltinisik.org.uk
20. Aminoasit biyosentezi-Avesis. [cited 2021 May 16]; Available from: https://avesis.yildiz.edu.tr
21. Webert WW, Zannonı VG. Reduction of phenylpyruvic acids to phenyllactic acids in mammalian tissues. J Biol Chem. 1966;241(6):1345–1349.
22. Doğan A, Doğan ANC. Investigation of the effects of sodium phenylpyruvate on pulmonary adenocarcinoma (A549) and mammary adenocarcinoma (MDA-MB-231) on cell lines. Cauc J Sci. 2022;9(1):20–34.
23. Liu M, Brusilow WSA, Needleman R. Activity of the yeast Tat2p tryptophan permease is sensitive to the anti-tumor agent 4-phenylbutyrate. Curr Genet. 2004;46:256–268.
24. Ercan P, El SN. Koenzim Q10'un beslenme ve sağlık açısından önemi biyoyararlılığı. Tübav Bilim Derg. 2010;3(2):192–200.
25. Etkin bir antioksidan koenzim q10. [cited 2021 Jun 6]; Available from: https://www.centro.com.tr/wp-content/uploads/2019/05/Centro-Koenzim-Q10-Bilimsel-B%C3%BClten.pdf
26. Koenzim Q10. [cited 2021 Jun 6];Available from: https://www.wikizero.com/tr/ koenzim_q10.
27. Fidancı U.R. Kolesterol biyosentezi. 20.04.2009 [cited 2021 Jun 10]; Available from: http://80.251.40.59/veterinary.ankara.edu.tr/fidanci/Ders_Notlari/LM Kolesterol_Biyosentezi.html
28. Durmuş M. Ko-enzim Q10 gerçeği ve statinler. [cited 2021 Jun 2]; Available from: https://www.iyibilgi.com/?haber, 90391.
29. Palan PR, Mikhail MS, Shaban DW, Romney SL. Plasma concentrations of coenzyme Q10 and tocopherols in cervical intraepithelial neoplasia and cervical cancer. Eur J Cancer Prev. 2003;12(4):321–326.
30. Paroha S, Chandel AKS, Dubey RD. Nanosystems for drug delivery of coenzyme Q10. Environ Chem Lett. 2018;16(2018):71–77.
31. Sachdanandam P. Antiangiogenic and hypolipidemic activity of coenzyme Q10 supplementation to breast cancer patients undergoing Tamoxifen therapy. BioFactors. 2008;32(2008):151–159.
32. Hodges S, Hertz N, Lockwood K and Lister R. CoQ10: could it have a role in cancer management? BioFactors. 1999;9(1999):365–370.
33. Roffe L, Schmidt K and Ernst E. Efficacy of Coenzyme Q10 for Improved Tolerability of Cancer Treatments: A systematic review. J Clin Oncol. 2004;22(21):4418–4424.
34. Eric Yarnell E and Abascal K. Holistic approaches to prostate cancer. Altern Complemen Ther. 2008;14(4):164–180.
35. Quilesa JL. Farquharson AJ, Ramırez-Tortosaa MC, Grant I, Milne L, Huertasa JR, Battinoc M, Mataixa J and Wahleb KWJ. Coenzyme Q differentially modulates phospholipid hydroperoxide glutathione peroxidase gene expression and free radicals production in malignant and non-malignant prostate cells. BioFactors. 2003;18(2003):265–270.
36. Bahar M, Khaghani S, Pasalar P, Paknejad M, Khorramizadeh MR, Mirmiranpour H, Nejad SG. Exogenous coenzyme Q10 modulates MMP-2 activity in MCF-7 cell line as a breast cancer cellular model. Nutrition Journal. 2010;9(62):1–9. [cited 2021 Jun 10]; Available from: http://www.nutritionj.com/content/9/1/62.
37. Yen H-C, Li S-H, Majıma HJ, Huang Y-H, Chen C-P, Liu, C-C, Tu Y-C, Chen C-W. Up-regulation of antioxidant enzymes and coenzyme Q 10 in a human oral cancer cell line with acquired bleomycin resistance. Free Radic Res 2011;45(6):707–716.

DERLEME / *REVIEW*

Underrated Diagnosis: Prenatal Depression

Göz Ardı Edilen Tanı: Prenatal Depresyon

Ozgur Kocak[1], Sabina Kocak[1]

[1]*Hitit University Faculty of Medicine, Department of Obstetrics and Gynecology, Corum, Türkiye*

ABSTRACT

Mental health disorders characterized by emotional lability, difficulty in concentrating, hopelessness, low energy level, irritability, food intake disorder, and changes in sleep patterns are called depression. To be diagnosed with depression according to the DSM-5, the following five or more symptoms must be present for at least 2 weeks, and at least one of the symptoms must be depressed mood or loss of interest or pleasure. Others include weight loss without dieting, decreased physical activity, fatigue or loss of energy, feelings of worthlessness, decreased ability to think or concentrate, and recurrent thoughts of death. The detection of antenatal depression may have many clinical implications because; it was associated with poor obstetric, neonatal outcomes, postpartum depression, preterm birth and low birth weight, small for gestational age, suicidal attempts, higher incidence of cesarean section, prolonged labor, more painful labor, operative delivery and it was also associated with a low APGAR score. While Covid 19 treatment is certain for pregnant women, we think it is useful to remember the treatment of anxiety and depression, which is more important and has increased prevalence during Covid 19 pandemics. The treatment options are Psychotherapy, Acupuncture, Bright light therapy, Exercise/yoga, Massage therapy, Family/couples therapy, Folic acid, Omega-3 fatty acids, S-adenosyl methionine, and medical Antidepressant treatment. In this review, current treatment methods used in the treatment of pregnant depression are summarized in detail.

Keywords: *pregnancy; depression; Covid 19; pandemic; SSRI*

ÖZET

Duygusal değişkenlik, konsantrasyon güçlüğü, umutsuzluk, düşük enerji seviyesi, sinirlilik, besin alım bozukluğu ve uyku düzenindeki değişiklikler ile karakterize ruh sağlığı bozukluklarına depresyon denir. DSM-5'e göre depresyon tanısı koymak için en az iki haftalık süre ile aşağıdaki beş veya daha fazla semptom olmalı ve semptomlardan en az biri depresif duygudurum veya ilgi kaybı veya zevk kaybı olmalıdır. Diğerleri ise diyet yapmadan kilo kaybı, fiziksel harekette azalma, yorgunluk veya enerji kaybı, değersizlik hissi, düşünme veya konsantre olma yeteneğinde azalma ve tekrarlayan ölüm düşünceleridir. Doğum öncesi depresyonun tespitinin birçok klinik anlamı olabilir çünkü; kötü obstetrik sonuçlar ve kötü neonatal sonuçlar, doğum sonrası depresyon, erken doğum ve düşük doğum ağırlığı, gebelik yaşına göre küçük fetüs, intihar girişimleri, daha yüksek sezaryen insidansı, uzamış doğum, daha ağrılı doğum, operatif doğum ve ayrıca düşük APGAR skoru ile ilişkilidir. Gebeler için Covid 19 tedavisi standart olmakla birlikte, Covid 19 pandemileri sırasında daha önemli olan ve prevalansı artan anksiyete ve depresyonun tedavisini hatırlamakta fayda olduğunu düşünüyoruz. Tedavi seçenekleri Psikoterapi, Akupunktur, Parlak ışık tedavisi, Egzersiz/yoga, Masaj terapisi, Aile/çift terapisi, Folik asit, Omega-3 yağ asitleri, S-adenosil metiyonin ve tıbbi Antidepresan tedavisidir. Bu derlemede gebe depresyonunun tedavisinde kullanılan güncel tedavi yöntemleri detaylı olarak özetlenmiştir.

Anahtar Kelimeler: *gebelik; depresyon; Covid 19; pandemi; SSRI*

Introduction

Mental health disorders characterized by emotional lability, difficulty concentrating, hopelessness, low energy level, irritability, food intake disorder, and changes in sleep patterns are called depression[1]. However, it is expected that the detection frequency of mental disorders in studies has been reported differently. Moreover, with the new coronavirus (2019-nCoV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2019, a new pandemic is observed globally, and public health is at risk every respect[2].

İletişim/Contact: *Özgür Koçak, Hitit University Faculty of Medicine, Department of Obstetrics and Gynecology, Çorum, Türkiye* • ***Tel:*** *0532 642 39 24* • ***E-mail:*** *dr.ozgur@hotmail.com* • ***Geliş/Received:*** *09.11.2021* • ***Kabul/Accepted:*** *14.02.2023*

ORCID: *Özgür Koçak, 0000-0002-3906-9422* • *Sabina Koçak, 0000-0002-1997-4951*

Kafkas J Med Sci 2023; 13(1):100–108
doi: 10.5505/kjms.2023.21033

Generalized anxiety disorder (GAD) is characterized by a hard-to-control, distressing, constant anxiety that lasts less than six months. Other features include physical anxiety symptoms, such as increased fatigue and muscle tension. Unipolar major depression (major depressive disorder) is at least one major depressive episode without a history of mania or hypomania[3]. According to DSM 5 (The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition), an episode of unipolar major depression lasts at least two weeks, with five or more of the following nine symptoms: loss of interest or pleasure in most or all activities, depressed mood, changes in appetite or weight, insomnia or hypersomnia, psychomotor retardation, or agitation, poor concentration, low energy, guilt or thoughts of worthlessness, and recurrent thoughts about death or suicide. In one study, it has been reported that in 10% of developed countries and 25% of developing countries, women suffer from mental health problems during pregnancy and after childbirth[4]. A meta-analysis reported that the average prevalence of prenatal mental disorders in low and middle-income countries was 15.6%[5]. In many studies, the prevalence of depression has been reported at different rates, and the incidence varies greatly from study to study. In studies, depression was reported between 11.7%–39%[6–8], while anxiety was reported between 54.2%–55.7%[8,9].

In a study, it was found that the rate of depression decreases as the gestational week increases. In this study, the depression was 11% in the first trimester and 8.5% in the second and third trimesters[10]. Pregnancy is a condition that increases the risk of depressive attacks, and more than 10% of women experience depressive episodes during pregnancy[11] and in adolescence, rising to 17%[12]. In addition, it was reported that depression, anxiety, and stress symptoms changed during pregnancy, and anxiety and stress increased in advanced gestational weeks when depression was observed in early pregnancy[13]. The prevalence of perinatal depression has been between 2 and 21% in international studies[14,15].

The detection of such high rates of antenatal depression may have many clinical implications because; it was associated with poor obstetric, neonatal outcomes[16], postpartum depression[17], preterm birth and low birth weight[18,19], small for gestational age[20], suicidal attempts[11,21,22], higher incidence of cesarean section, prolonged labour[23,24], more painful labour, perative delivery[25] and it was also associated with a low APGAR score in one study[26]. In another study, women anxious during pregnancy may feel more pain during labour, thus requesting more for analgesia[27].

Prenatal distress affects child development[28,29]. A review shows that pregnancy distress is related to mental health in the offspring later in life.

From a neurobiological viewpoint, anxiety and depression are thought to be effective on maternal-placental-fetal neuroendocrine mechanisms. Anxiety increases catecholamine release. The high catecholamine concentration has been associated with poor uterine contractility and prolonged labour. For all these reasons, the need for oxytocin increases[26]. Along with the serotonin system, corticotropin-releasing hormone (CRH) can affect prenatal stress and anxiety, fetal development, and infant and child development[30,31]. From a psychological view, depressive symptoms are associated with cognitive function that plays a significant role in pain control. If the cognitive function is labile, pain is viewed as intolerable and uncontrollable, and as a result, pain anticipation and attention to pain increases, and women experience childbirth more painful[32].

Many studies report that Covid 19 pandemics increased depression and anxiety among healthcare professionals. Some studies offer strategies to improve mental health that should be provided to healthcare professionals. Social isolation due to Covid 19 pandemic causes a feeling of loneliness and increases the risk of mental disorders (depressive and anxiety disorders) and even substance use disorder[33]. Studies have shown that anxiety, depression, fear, stress, and sleep problems are more common during the COVID-19 outbreak.

In a study, generalized anxiety disorder (GAD) was as high as 35.1% during a pandemic. It is also reported that younger people have a significantly higher prevalence of depressive and GAD symptoms than older people. In another study, females' anxiety risk was found to be approximately 3 times higher compared to males. For people younger than 40; the anxiety risk was 2.5 times higher than for those above 40 years old. In a study in Türkiye, it is shown that 23.6% of the population scored above depression, and 45.1% scored above the cut-off point for anxiety in the Hospital Anxiety and Depression Scale (HADS). In the same study, risk factors for anxiety were female gender, living in urban areas, and previous psychiatric illness[34]. Pregnant and non-pregnant women reproductive-aged have comparable clinical courses and outcomes when infected with

SARS-CoV-2. Vertical transmission of COVID-19 in the third trimester is not shown yet[35].

Measures to prevent Covid 19 transmission are the same for pregnant and non-pregnant people. These measures are to maintain social distance, use masks in public areas, pay attention to hand hygiene and disinfect surfaces. In a meta-analysis that examined 33 studies and 356 pregnant women, the most common symptoms in pregnant women infected with Covid 19 were fever (67%) and cough (66%)[36].

In many studies reporting a few cases, it has been reported that pregnancy and birth do not increase the risk of getting SARS-CoV-2 infection and do not worsen the clinical course of Covid-19 compared to non-pregnant individuals of the same age[37–41].

In a study examining 51 pregnant patients with Covid-19, it was reported that 39 percent of pregnant gave birth before the 37th gestational week and 96 percent delivered by cesarean section[42]. In another study in which 252 pregnant Covid-19 patients were examined, 15% of pregnant women were delivered before 37 weeks, and the cesarean rate was 70% in the same group of patients[36]. Guidelines published by the Society for Maternal-Fetal Medicine and The American College of Obstetricians and Gynecologists (ACOG) are available for treating pregnant women infected with Covid 19[43,44].

While Covid 19 treatment is specific for pregnant women, we think it is helpful to remember the treatment of anxiety and depression, which is more important and has increased prevalence during Covid 19 pandemics. Although, as mentioned above, many studies are showing that the prevalence of anxiety and depression increased during the COVID pandemic, we could not find a study on pregnant women in this regard in the literature[44].

It would not be wrong to say that anxiety and depression may increase in pregnant women during the Covid pandemic. For this reason, we wanted to contribute to this current issue by giving current treatment information on anxiety and depression in pregnant women. With these treatments, we think that some of the results of anxiety and depression can be prevented, maybe some of the preterm birth.

Pathophysiology of Perinatal Depression

Impact of Depression During Pregnancy

The pathophysiology of depression is not well known, and it has a complex etiology. Biological, social, and psychological factors may contribute to depression[45,46].

Because of studies conducted on animals and humans, the causes of mood disorders in the perinatal period are due to hormonal disorders, abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, and genetic and epigenetic factors. The main female reproductive steroid hormones, estrogen, and progesterone have some reproductive functions; they also affect nonreproductive behaviors, including mood and cognition[47]. Brain sensitivity to steroids increases after adolescence, and evidence suggests steroids have long-term effects on the brain[47,48]. The brain affected by these steroids may be more vulnerable to depression.

High estrogen and progesterone levels stimulate the HPA axis in the third trimester, and plasma cortisol levels increase accordingly[49]. Immediately after birth, estrogen and progesterone levels decrease rapidly, and the hypothalamic corticotropin-releasing hormone (CRH) is suppressed and gradually returns to standard[50]. Corticotropin-releasing hormone is secreted from the paraventricular nucleus of the hypothalamus; this hormone stimulates the secretion of the adrenocorticotropic hormone (ACTH) from the anterior pituitary and triggers the stimulation of cortisol from the adrenal cortex. This hormonal system is regulated by negative feedback with cortisol receptors and CRH autoreceptors. Maternal depressed infants are exposed to higher cortisol concentrations than infants of mothers who are not depressed in intrauterine life[51].

The regulation of the HPA axis is impaired in patients with depression. The same deterioration in pregnancy also explains the tendency to depression[52]. Interestingly, the HPA axis also affects other endocrine systems. One study reported that with lower total and free thyroxine concentrations in euthyroid patients, the risk of developing postpartum depressive symptoms might be higher even if the patient is euthyroid[53]. The field of epigenetics investigates heritable phenotypic variations without a change in the DNA sequence[54]. Most involve changes that affect gene activity and expression. Studies have shown that epigenetic changes effectively affect maternal behaviour in animal models. Although

there are not enough human data, they are likely to be effective[55–57].

Choosing Treatment

Psychotherapy

When choosing the treatment method, it is always necessary to decide according to the patient's previous history, the condition of the patient, and the severity of the disease. Structured psychotherapy can be tried as an initial treatment, such as cognitive-behavioural therapy (CBT) or interpersonal psychotherapy. If the patient was previously treated with psychotherapy and provided treatment, the same method can be tried while pregnant. If the patient has previously benefited from pharmacotherapy, the same drug can be used.

Many authorities primarily recommended psychotherapy. However, there are no well-designed randomized controlled studies on this subject. The reasons for the difficulties are it is difficult to diagnose, decide the severity of the disease, and evaluate the treatment's effectiveness.

Starting treatment with antidepressant drugs is an acceptable option in some cases[58,59].

- If the patient does not accept psychotherapy
- If the patient prefers pharmacotherapy
- If patients have a history of severe depression

In a prospective study, 41 women at 16 weeks of gestation without clinical depression but at risk of depression were randomized. Cognitive-behavioral was the intervention group. In follow-up, the depression rate was 14% in the intervention group, while 25% was in the control group[60].

Non pharmacological methods can be used alone or in combination in the treatment of depression. By adjunctive treatment, fetal exposure to medications may be minimized. Pregnant women may also prefer psychotherapy as the first-line treatment[61]. In a meta-analysis, psychotherapy methods were moderately effective in pregnant women and the postpartum period[62]. Cognitive-behaviour therapy (CBT) was reported to be effective in the same meta-analysis[62]. Exercise may also be effective[63].

Other Options

Some of the adjunctive interventions can be added to the primary treatment:

- Acupuncture
- Bright light therapy
- Exercise/yoga
- Massage therapy
- Family/couples therapy
- Folic acid
- Omega-3 fatty acids
- S-adenosyl methionine

Acupuncture: Evidence is insufficient to use acupuncture for depressed patients. Randomized studies have reported that acupuncture can effectively treat antenatal depression treatment[64].

Bright light therapy: Bright light therapy may be helpful in depression[65].

Yoga and massage: Maybe a treatment option[66,67].

Family/couples therapy: Family therapy may be an option for primary or adjunctive treatment.

Folic Acid: Folic acid is recommended for all pregnant women to prevent neural tube defects and many anomalies such as cardiac. Additionally, some studies show that folic acid can also help to treat depression[68].

Omega-3 Fatty Acids: The use of omega-3 fatty acids is recommended for all populations. It is the same in pregnant women. In randomized studies, it has been shown that omega-3 fatty acids can be effective as an add-on therapy for depression[69].

S-adenosyl methionine: S-adenosyl methionine may be helpful in the treatment of depression[70].

Antidepressant Treatment of Anxiety and Depression During Pregnancy

Approximately 7% of pregnant women in the United States use selective serotonin reuptake inhibitors (SSRIs)[71]. Another study reported that about 13 % of women used antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), during pregnancy[72]. If it is thought that psychiatric diagnoses are made less than it is, on the other hand, the actual number is more remarkable. Because there is an underestimation and underreporting of psychiatric disorders.

Table 1. *Relative Risks of Commonly Used SSRI*

	Spontaneous abortion	Hypertensive disorders of pregnancy	Postpartum hemorrhage
Paroxetine	No Risk	Unclear	RR:1.4
Fluoxetine	No Risk	No Risk	RR:1.5
Sertraline	No Risk	No Risk	RR:1.4
Fluvoxamine	No Data	No Risk	No Data
Citalopram	No Risk	No Risk	RR:1.5
Escitalopram	No Risk	No Risk	RR:1.6

RR: relative risk.

It is a difficult decision to prescribe medication for anxiety and depression during pregnancy, and it is necessary to consider the potential risks and benefits for the baby and mother. However, the most prescribed drug group in pregnancy is selective serotonin reuptake inhibitors (SSRI)[73]. Commonly used SSRI relative risksiz are Shown in Table 1

Studies have shown that stopping antidepressant treatment with a previous history of depression leads to a relapse of symptoms in as many as 60% to 70% of pregnant women[74,75].

Antidepressants cross the placenta and cross the fetal blood-brain barrier. Therefore, prenatal exposure to antidepressants involves risks of teratogenesis, low birth weight, preterm birth and pregnancy complications (e.g., postpartum haemorrhage and spontaneous abortion), and postnatal effects (e.g., persistent pulmonary hypertension).

However, maternal antidepressant usage during pregnancy has been associated with persistent pulmonary hypertension of the newborn (PPHN) and neonatal withdrawal/toxicity syndrome. Persistent pulmonary hypertension of the newborn is a rare condition, and it is prevalence in seen 1–2 infants out of 1000 normal populations and is affected by many conditions such as diabetes, meconium aspiration, cesarean section, and sepsis[76].

If SSRI is thought to increase the risk of PPHN 6–12 times, the probability of not having PPHN in the fetus of a pregnant woman using SSRI is 99%[77].

Prenatal Exposure to Antidepressants

Prenatal exposure to SSRIs may affect the serotonin system by reducing the calcium-binding protein specific to astroglia cells or by altering genes encoding the serotonin transporter protein[30,78]. Serotonin may also influence the HPA axis[78]. A recent study reported a 12% rate of spontaneous abortion when exposed to antidepressants, the relative risk 1.14 (95% CI 1.10–1.18. Selective serotonin reuptake inhibitor treatment during pregnancy significantly increases the risk of premature birth by 1.55–1.96[79–82]. However, studies have reported that preterm birth was just 3–5 days before, and its effect is minimal[83].

Although studies have shown a slightly increased risk of major congenital malformations with SSRI exposure, this may not be clinically important[84,85]. Therefore, SSRIs are not accepted as major teratogens[83,86].

Tricyclic Antidepressants (TCAs) During Pregnancy

Major congenital anomaly risk is not associated with TCA[87,88]. However, TCAs are associated with an increased risk of low birth weight and Preterm birth[87]. Nortriptyline and desipramine are the first-line TCAs in pregnancy due to low toxicity and low withdrawal risk[88].

Long-Term Effects of Antidepressants During Pregnancy

There are inconsistencies in the long-term outcomes of prenatal exposure to antidepressants in studies[89]. Although there are negative effects associated with the use of antidepressants, they improve over time and it is difficult to distinguish these effects from other factors such as asfiksia[89,90]. A study reported that untreated depression exposure in prenatal periods increases the risk of behavioural or emotional problems at 4–5 years of age compared to prenatal antidepressant use[91]. It was shown that children exposed to SSRIs and non-treated control group children have similar full-scale IQ, and depressed mothers' children may be at risk of future psychopathology[92].

Studies have claimed a relationship between SSRI exposure during pregnancy and autism spectrum disorder[93,94], as well as studies claiming the opposite[95,96].

It is possible to say the same for neonatal mortality. Studies have reported that it increases[97,98], and studies claiming that it has no effect[99,100].

Selective Serotonin Reuptake Inhibitors (SSRIs)

Research questions in perinatal psychiatry have been focused mainly on risks of medication exposure instead of risks of disease exposure for the mother and fetus.

Conclusions

The screening of psychiatric disorders and their identification is critical at prenatal visits and needs improvement. The diagnosis of depression is difficult for many reasons, and if the patient is pregnant multidisciplinary approach is necessary to optimize care. The treatment option decision is difficult for pregnant women. Untreated anxiety and depression and exposure to the fetus may have short-term and long-term adverse effects. Antidepressant treatment during pregnancy may increase the risk of miscarriage, probably a slight increase in the risk of congenital cardiac malformations, PTB, PPHN, and transient neonatal symptoms.

There may be a risk of delayed motor development. However, current medical data is unclear about the benefits or harms of antidepressant medications for infants and mothers. In decision making, the symptom severity is the primary determining factor. Nonpharmacological strategies can be helpful to women with mild or moderate depression. However, women with severe depression or recurrent depressive attacks should consider maintaining antidepressant treatment during pregnancy. Treatment modalities must be individualized. A multidisciplinary approach should be done, and decisions should be made with the clinicians, the patient, and her partner. During Covid 19 pandemic, this issue gained more importance.

References

1. Al Thomali A, Daghestani MH, Kaya N, Warsy A. Polymorphic Variations In Vdr Gene In Saudi Women With And Without Polycystic Ovary Syndrome (PCOS) And Significant Influence Of Seven Polymorphic Sites On Anthropometric And Hormonal Parameters. J Med Biochem. 2018;37:415–25.
2. Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). Indian journal of pediatrics. 2020;87:281–6.
3. Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub; 2013.
4. Organization WH. Maternal mental health and child health and development in low and middle income countries: report of the meeting, Geneva, Switzerland, 30 January-1 February, 2008. 2008.
5. Fisher J, Tran T, Tran TD, Dwyer T, Nguyen T, Casey GJ, et al. Prevalence and risk factors for symptoms of common mental disorders in early and late pregnancy in Vietnamese women: a prospective population-based study. J Affect Disord. 2013;146:213–9.
6. Hartley M, Tomlinson M, Greco E, Comulada WS, Stewart J, le Roux I, et al. Depressed mood in pregnancy: prevalence and correlates in two Cape Town peri-urban settlements. Reprod Health. 2011;8:9.
7. Felice E, Saliba J, Grech V, Cox J. Prevalence rates and psychosocial characteristics associated with depression in pregnancy and postpartum in Maltese women. J Affect Disord. 2004;82:297–301.
8. Alipour Z, Kheirabadi GR, Eslami AA, Kazemi A. Psychological profiles of risk for antenatal depression and anxiety in Iranian sociocultural context. J Educ Health Promot. 2018;7:160.
9. Nath A, Venkatesh S, Balan S, Metgud CS, Krishna M, Murthy GVS. The prevalence and determinants of pregnancy-related anxiety amongst pregnant women at less than 24 weeks of pregnancy in Bangalore, Southern India. International journal of women's health. 2019;11:241.
10. Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson TJO, et al. Perinatal depression: a systematic review of prevalence and incidence. 2005;106:1071–83.
11. Melville JL, Gavin A, Guo Y, Fan M-Y, Katon WJJO, gynecology. Depressive disorders during pregnancy: prevalence and risk factors in a large urban sample. 2010;116:1064.
12. Viguera AC, Tondo L, Koukopoulos AE, Reginaldi D, Lepri B, Baldessarini RJJAJoP. Episodes of mood disorders in 2, 252 pregnancies and postpartum periods. 2011;168:1179–85.
13. Rallis S, Skouteris H, McCabe M, Milgrom J. A prospective examination of depression, anxiety and stress throughout pregnancy. Women and birth: journal of the Australian College of Midwives. 2014;27:e36–42.
14. Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR. Prevalence of depression during pregnancy: systematic review. Obstetrics & Gynecology. 2004;103:698–709.
15. Gaynes BN, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner G, et al. Perinatal depression: Prevalence, screening accuracy, and screening outcomes: Summary. AHRQ evidence report summaries: Agency for Healthcare Research and Quality (US); 2005.

16. Alderdice F, McNeill J, Lynn F. A systematic review of systematic reviews of interventions to improve maternal mental health and well-being. Midwifery. 2013;29:389–99.
17. Hartmann JM, Mendoza-Sassi RA, Cesar JA. Postpartum depression: prevalence and associated factors. Cadernos de saude publica. 2017;33:e00094016–e.
18. Davalos DB, Yadon CA, Tregellas HC. Untreated prenatal maternal depression and the potential risks to offspring: a review. Archives of women's mental health. 2012;15:1–14.
19. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJJAogp. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. 2010;67:1012–24.
20. Szegda K, Markenson G, Bertone-Johnson ER, Chasan-Taber LJTJoM-F, Medicine N. Depression during pregnancy: a risk factor for adverse neonatal outcomes? A critical review of the literature. 2014;27:960–7.
21. Mauri M, Oppo A, Borri C, Banti SJAowsmh. SUICIDALITY in the perinatal period: comparison of two self-report instruments. Results from PND-ReScU. 2012;15:39–47.
22. Newport DJ, Levey L, Pennell P, Ragan K, Stowe ZNJAowsmh. Suicidal ideation in pregnancy: assessment and clinical implications. 2007;10:181–7.
23. Nasreen HE, Kabir ZN, Forsell Y, Edhborg M. Low birth weight in offspring of women with depressive and anxiety symptoms during pregnancy: results from a population based study in Bangladesh. BMC Public Health. 2010;10:515.
24. Niemi M, Falkenberg T, Petzold M, Chuc NT, Patel V. Symptoms of antenatal common mental disorders, preterm birth and low birthweight: a prospective cohort study in a semi-rural district of Vietnam. Trop Med Int Health. 2013;18:687–95.
25. Alhusen JL, Alvarez C. Perinatal depression: A clinical update. The Nurse Practitioner. 2016;41:50.
26. Smorti M, Ponti L, Tani F. The effect of maternal depression and anxiety on labour and the well-being of the newborn. Journal of Obstetrics and Gynaecology. 2019;39:492–7.
27. Rhudy JL, Meagher MW. Fear and anxiety: divergent effects on human pain thresholds. Pain. 2000;84:65–75.
28. Bergman K, Sarkar P, O'CONNOR TG, Modi N, Glover V. Maternal stress during pregnancy predicts cognitive ability and fearfulness in infancy. Journal of the American Academy of Child & Adolescent Psychiatry. 2007;46:1454–63.
29. Glover V. Maternal depression, anxiety and stress during pregnancy and child outcome; what needs to be done. Best Pract Res Clin Obstet Gynaecol. 2014;28:25–35.
30. Hanley GE, Oberlander TFJBDRPAC, Teratology M. Neurodevelopmental outcomes following prenatal exposure to serotonin reuptake inhibitor antidepressants: a "social teratogen" or moderator of developmental risk?. 2012;94:651–9.
31. Graignic-Philippe R, Dayan J, Chokron S, Jacquet A, Tordjman SJN, reviews b. Effects of prenatal stress on fetal and child development: a critical literature review. 2014;43:137–62.
32. Flink IK, Mroczek MZ, Sullivan MJ, Linton SJ. Pain in childbirth and postpartum recovery-The role of catastrophizing. European Journal of Pain. 2009;13:312–6.
33. Balanzá-Martínez V, Atienza-Carbonell B, Kapczinski F, De Boni RB. Lifestyle behaviours during the COVID-19 - time to connect. Acta Psychiatr Scand 2020.
34. Özdin S, Bayrak Özdin Ş. Levels and predictors of anxiety, depression and health anxiety during COVID-19 pandemic in Turkish society: The importance of gender. International Journal of Social Psychiatry;0:0020764020927051.
35. Qiancheng X, Jian S, Lingling P, Lei H, Xiaogan J, Weihua L, et al. Coronavirus disease 2019 in pregnancy. International journal of infectious diseases: IJID. official publication of the International Society for Infectious Diseases 2020.
36. Elshafeey F, Magdi R, Hindi N, Elshebiny M, Farrag N, Mahdy S, et al. A systematic scoping review of COVID-19 during pregnancy and childbirth. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2020.
37. Breslin N, Baptiste C, Gyamfi-Bannerman C, Miller R, Martinez R, Bernstein K, et al. COVID-19 infection among asymptomatic and symptomatic pregnant women: Two weeks of confirmed presentations to an affiliated pair of New York City hospitals. Am J Obstet Gynecol MFM 2020:100118.
38. Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of Coronavirus spectrum infections (SARS, MERS, COVID 1 -19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM 2020:100107.
39. Khan S, Jun L, Nawsherwan, Siddique R, Li Y, Han G, et al. Association of COVID-19 with pregnancy outcomes in health-care workers and general women. Clin Microbiol Infect 2020.
40. Li N, Han L, Peng M, Lv Y, Ouyang Y, Liu K, et al. Maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia: a case-control study. Clin Infect Dis 2020.
41. Schwartz DA. An Analysis of 38 Pregnant Women with COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes. Arch Pathol Lab Med 2020.
42. Della Gatta AN, Rizzo R, Pilu G, Simonazzi G. COVID19 during pregnancy: a systematic review of reported cases. Am J Obstet Gynecol 2020.
43. https://www.smfm.org/covid19 (Accessed on May 13 2021).
44. https://www.acog.org/ (Accessed on May 13 2021).
45. Yonkers KA, Vigod S, Ross LEJF. Diagnosis, pathophysiology, and management of mood disorders in pregnant and postpartum women. 2012;10:51–66.
46. Roy A, Campbell MKJC, medicine i. A unifying framework for depression: bridging the major biological and psychosocial theories through stress. 2013:E170-E90.
47. Rubinow DJAowsmh. Reproductive steroids in context. 2005;8:1.

48. Phoenix CH, Goy RW, Gerall AA, Young WCJE. Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. 1959;65:369–82.
49. Nolten We, Lindheimer Md, Rueckert Pa, Oparil S, Ehrlich Enjtjoce, Metabolism. Diurnal patterns and regulation of cortisol secretion in pregnancy. 1980;51:466–72.
50. Magiakou M, Mastorakos G, Rabin D, Dubbert B, Gold P, Chrousos GJTJoCE, et al. Hypothalamic corticotropin-releasing hormone suppression during the postpartum period: implications for the increase in psychiatric manifestations at this time. 1996;81:1912–7.
51. Essex MJ, Klein MH, Cho E, Kalin NHJBp. Maternal stress beginning in infancy may sensitize children to later stress exposure: effects on cortisol and behavior. 2002;52:776–84.
52. Gold PW, Gabry KE, Yasuda MR, Chrousos GPJE, Clinics M. Divergent endocrine abnormalities in melancholic and atypical depression: clinical and pathophysiologic implications. 2002;31:37–62.
53. Pedersen CA, Johnson JL, Silva S, Bunevicius R, Meltzer-Brody S, Hamer RM, et al. Antenatal thyroid correlates of postpartum depression. 2007;32:235–45.
54. Dupont C, Armant DR, Brenner CA. Epigenetics: definition, mechanisms and clinical perspective. Seminars in reproductive medicine. 2009;27:351–7.
55. Curley JP, Davidson S, Bateson P, Champagne FAJFibn. Social enrichment during postnatal development induces transgenerational effects on emotional and reproductive behavior in mice. 2009;3:25.
56. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, et al. Epigenetic programming by maternal behavior. 2004;7:847–54.
57. Champagne FAJFin. Epigenetic mechanisms and the transgenerational effects of maternal care. 2008;29:386–97.
58. Stewart DE. Clinical practice. Depression during pregnancy. The New England journal of medicine. 2011;365:1605–11.
59. Chaudron LH. Complex challenges in treating depression during pregnancy. The American journal of psychiatry. 2013;170:12–20.
60. Muñoz RF, Le H-N, Ippen CG, Diaz MA, Urizar Jr GG, Soto J, et al. Prevention of postpartum depression in low-income women: Development of the Mamás y Bebés/Mothers and Babies Course. 2007;14:70–83.
61. Dimidjian S, Goodman SHJBr, therapy. Preferences and attitudes toward approaches to depression relapse/recurrence prevention among pregnant women. 2014;54:7–11.
62. Stuart S, Koleva HJBP, Obstetrics RC, Gynaecology. Psychological treatments for perinatal depression. 2014;28:61–70.
63. Daley A, Foster L, Long G, Palmer C, Robinson O, Walmsley H, et al. The effectiveness of exercise for the prevention and treatment of antenatal depression: systematic review with meta-analysis. 2015;122:57–62.
64. Smith CA, Hay PP, Macpherson H. Acupuncture for depression. The Cochrane database of systematic reviews 2010: Cd004046.
65. Lieverse R, Van Someren EJ, Nielen MM, Uitdehaag BM, Smit JH, Hoogendijk WJ. Bright light treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-controlled trial. Archives of general psychiatry. 2011;68:61–70.
66. Deligiannidis KM, Freeman MPJBP, Obstetrics RC, Gynaecology. Complementary and alternative medicine therapies for perinatal depression. 2014;28:85–95.
67. Field T, Diego M, Delgado J, Medina LJCticp. Tai chi/yoga reduces prenatal depression, anxiety and sleep disturbances. 2013;19:6–10.
68. Chong MF, Wong JX, Colega M, Chen LW, van Dam RM, Tan CS, et al. Relationships of maternal folate and vitamin B12 status during pregnancy with perinatal depression: The GUSTO study. Journal of psychiatric research. 2014;55:110–6.
69. Su KP, Huang SY, Chiu TH, Huang KC, Huang CL, Chang HC, et al. Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial. The Journal of clinical psychiatry. 2008;69:644–51.
70. Hardy ML, Coulter I, Morton SC, Favreau J, Venuturupalli S, Chiappelli F, et al. S-adenosyl-L-methionine for treatment of depression, osteoarthritis, and liver disease. Evidence report/technology assessment (Summary) 2003:1-3.
71. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernández-Díaz S, et al. Medication use during pregnancy, with particular focus on prescription drugs:1976-2008. 2011;205:51. e1-. e8.
72. Cooper WO, Willy ME, Pont SJ, Ray WAJAjoo, gynecology. Increasing use of antidepressants in pregnancy. 2007;196:544. e1-. e5.
73. Andrade SE, McPhillips H, Loren D, Raebel MA, Lane K, Livingston J, et al. Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. 2009;18:246–52.
74. Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. 2006;295:499–507.
75. Cohen LS, Nonacs R, Bailey J, Viguera A, Reminick A, Altshuler L, et al. Relapse of depression during pregnancy following antidepressant discontinuation: a preliminary prospective study. 2004;7:217–21.
76. Hernández-Díaz S, Van Marter LJ, Werler MM, Louik C, Mitchell AAJP. Risk factors for persistent pulmonary hypertension of the newborn. 2007;120:e272–e82.
77. Rubinow DR. Antidepressant treatment during pregnancy: between Scylla and Charybdis. Am Psychiatric Assoc; 2006.
78. Gur TL, Kim DR, Epperson CNJP. Central nervous system effects of prenatal selective serotonin reuptake inhibitors: sensing the signal through the noise. 2013;227:567–82.
79. McDonagh MS, Matthews A, Phillipi C, Romm J, Peterson K, Thakurta S, et al. Depression drug treatment outcomes in pregnancy and the postpartum period: a systematic review and meta-analysis. 2014;124:526–34.

80. Huang H, Coleman S, Bridge JA, Yonkers K, Katon WJGhp. A meta-analysis of the relationship between antidepressant use in pregnancy and the risk of preterm birth and low birth weight. 2014;36:13–8.
81. Ross LE, Grigoriadis S, Mamisashvili L, VonderPorten EH, Roerecke M, Rehm J, et al. Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. 2013;70:436–43.
82. Huybrechts KF, Sanghani RS, Avorn J, Urato ACJPO. Preterm birth and antidepressant medication use during pregnancy: a systematic review and meta-analysis. 2014;9.
83. Yonkers KA, Blackwell KA, Glover J, Forray AJArocp. Antidepressant use in pregnant and postpartum women. 2014;10:369–92.
84. Roerecke M, Rehm J, Dennis C-L, Koren GJJCP. Antidepressant Exposure During Pregnancy and Congenital Malformations: Is There an Association? A Systematic Review and. 2013;74:e293–e308.
85. Byatt N, Deligiannidis KM, Freeman MPJAPS. Antidepressant use in pregnancy: a critical review focused on risks and controversies. 2013;127:94–114.
86. Huybrechts KF, Palmsten K, Avorn J, Cohen LS, Holmes LB, Franklin JM, et al. Antidepressant use in pregnancy and the risk of cardiac defects. 2014;370:2397–407.
87. Gentile SJEoods. Tricyclic antidepressants in pregnancy and puerperium. 2014;13:207–25.
88. Osborne LM, Birndorf CA, Szkodny LE, Wisner KLJAowsmh. Returning to tricyclic antidepressants for depression during childbearing: clinical and dosing challenges. 2014;17:239–46.
89. El Marroun H, White T, Verhulst FC, Tiemeier HJEc, psychiatry a. Maternal use of antidepressant or anxiolytic medication during pregnancy and childhood neurodevelopmental outcomes: a systematic review. 2014;23:973–92.
90. Gentile SJD, anxiety. Neurodevelopmental effects of prenatal exposure to psychotropic medications. 2010;27:675–86.
91. Pedersen LH, Henriksen T, Bech B, Licht R, Kjaer D, Olsen JJAps. Prenatal antidepressant exposure and behavioral problems in early childhood-a cohort study. 2013;127:126–35.
92. Nulman I, Koren G, Rovet J, Barrera M, Pulver A, Streiner D, et al. Neurodevelopment of children following prenatal exposure to venlafaxine, selective serotonin reuptake inhibitors, or untreated maternal depression. 2012;169:1165–74.
93. El Marroun H, White TJ, van der Knaap NJ, Homberg JR, Fernandez G, Schoemaker NK, et al. Prenatal exposure to selective serotonin reuptake inhibitors and social responsiveness symptoms of autism: population-based study of young children. 2014;205:95–102.
94. Rai D, Lee BK, Dalman C, Golding J, Lewis G, Magnusson CJB. Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. 2013;346:f2059.
95. Sørensen MJ, Grønborg TK, Christensen J, Parner ET, Vestergaard M, Schendel D, et al. Antidepressant exposure in pregnancy and risk of autism spectrum disorders. 2013;5:449.
96. Hviid A, Melbye M, Pasternak BJNEJoM. Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism. 2013;369:2406–15.
97. Colvin L, Slack-Smith L, Stanley FJ, Bower CJCd. Early Morbidity and Mortality Following In Utero Exposure to Selective Serotonin Reuptake Inhibitors. 2012;26:e1–e14.
98. Ban L, Tata LJ, West J, Fiaschi L, Gibson JEJPo. Live and non-live pregnancy outcomes among women with depression and anxiety: a population-based study. 2012;7.
99. Stephansson O, Kieler H, Haglund B, Artama M, Engeland A, Furu K, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of stillbirth and infant mortality. 2013;309:48–54.
100. Jimenez-Solem E, Andersen JT, Petersen M, Broedbaek K, Lander AR, Afzal S, et al. SSRI use during pregnancy and risk of stillbirth and neonatal mortality. 2013;170:299–304.

Kafkas Tıp Bilimleri Dergisi / Kafkas Journal of Medical Sciences

İçindekiler / *Contents*

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

OLGU SUNUMU / *CASE REPORT*

DERLEME / *REVIEW*