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Magnetic resonance imaging findings in patients with cerebral palsy in Duhok, Iraq: Case series

Duhok, Irak'taki serebral palsili hastaların manyetik rezonans görüntüleme bulguları: Olgu serisi

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Abstract

Aim: Magnetic resonance imaging is an important technique for evaluating structural abnormalities in the brain. Many neurologists and pediatricians refer cerebral palsy patients to conventional magnetic resonance imaging. The objective of this study was to assess magnetic resonance imaging findings in children with cerebral palsy and to research whether it can predict the etiology or pathogenesis of this disease.

Methods: This case study was carried out at Azadi General Hospital from the 1st of July 2016 until the 28th of February 2017. A total of 48 patients who were diagnosed with cerebral palsy were included in the study. They all underwent cranial magnetic resonance imaging under general anesthesia, and results were compared statistically.

Results: The male to female ratio was 2.4:1. Magnetic resonance imaging was abnormal in 87.5%. Diffuse encephalopathy was seen in 56.2% of cases, periventricular leukomalacia was detected in 18.8%, changes of ischemic lesion were seen in 4.2 %, congenital malformations in 8.3% and normal scan was seen in 12.5% of cases. Among the clinical sub-types of cerebral palsy, spastic diplegia was the most common (47.9%), followed by spastic quadriplegia (35.4%), spastic hemiplegia (10.4%), and choreoathetoid cerebral palsy (6.3%).

Conclusions: This study concluded that brain changes in magnetic resonance imaging can detect the pathogenesis of cerebral palsy and is diagnostic in congenital brain malformations.

Keywords: Magnetic resonance imaging, Cerebral palsy

Öz

Amaç: Manyetik rezonans görüntüleme beyindeki yapısal anormallikleri değerlendirmek için önemli bir tekniktir. Birçok nörolog ve çocuk doktoru serebral palsi hastalarını konvansiyonel manyetik rezonans görüntülemeye yönlendirir. Bu çalışmanın amacı serebral palsili çocuklarda manyetik rezonans görüntüleme bulgularını değerlendirmek ve bu hastalığın etiyolojisini veya patogenezini öngörüp öngöremeyeceğini araştırmaktır.

Yöntemler: Bu vaka çalışması 1 Temmuz 2016 - 28 Şubat 2017 tarihleri arasında Azadi Genel Hastanesi'nde gerçekleştirildi. Serebral palsi tanısı alan toplam 48 hasta çalışmaya dahil edildi. Hepsine genel anestezi altında kraniyal manyetik rezonans görüntüleme yapıldı ve sonuçlar istatistiksel olarak karşılaştırıldı.

Bulgular: Erkek/kız oranı 2,4:1 idi. Manyetik rezonans görüntüleme hastaların %87,5'inde anormaldi. Olguların %56,2'sinde diffüz ensefalopati, %18,8'inde periventriküler lökolazi, %4,2'sinde iskemik lezyon değişiklikleri, %8,3'ünde konjenital malformasyon ve %12,5'inde normal tarama saptandı. Serebral palsi klinik alt tipleri arasında en yaygın spastik dipleji (%47,9), ardından spastik kuadripleji (%35,4), spastik hemipleji (%10,4) ve koreoetotoid serebral palsi (%6,3) gözlendi.

Sonuç: Bu çalışma manyetik rezonans görüntülemede beyin değişikliklerinin serebral palsi patogenezini tespit edebildiği ve konjenital beyin malformasyonlarında tanısal olduğu sonucuna varmıştır.

Anahtar kelimeler: Manyetik rezonans görüntüleme, Serebral palsi

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Introduction

Cerebral Palsy (CP) occurs due to a defect or lesion in the developing brain, which may have had its onset in the prenatal, perinatal, or postnatal period [1]. It is important to know the onset of the brain injury, as it is significant in the assessment of recurrence risk and the implementation of prevention programs [2].

Two large meta-analyses have attempted to document the extent and spectrum of central nervous system abnormalities found on Magnetic Resonance Imaging (MRI) in children with CP. Ashwal et al. [3], who studied data involving 644 children with CP, and found abnormal MRI in 89%, concluded that neuro-pathologic changes seen in MRI can be linked to the gestational ages of the infant at the time of brain injury.

In Ashwal et al.'s [3] study, periventricular leukomalacia (PVL) was the commonest MRI abnormality in preterm patients, while diffuse encephalopathy (cortical/subcortical atrophy/ventriculomegaly) was mostly detected in term infants. The second meta-analysis conducted by Krägeloh-Mann and Horber [4], who found 86% of the patients showed abnormal MRI findings, concluded that PVL was mostly seen in the early third trimester and the prematurely born infant, while cortical and subcortical atrophy, damage to the basal ganglia and thalamus were more commonly observed towards the end of the third trimester, during the perinatal period and in the term infant. In another study carried out at Al-Kindy Teaching hospital, 91 CP cases underwent computerized tomography (CT) scans, among which cortical and subcortical brain atrophy were the commonest findings [5].

An important point is that an abnormality on MRI does not necessarily mean that the etiology of the motor deficit has been established. For example, diffuse cortical atrophy and delayed myelination are non-specific findings which only suggest that a CNS disturbance occurred and may not reveal the underlying cause [3].

The present study aims to assess the cranial MRI findings in children with CP in terms of abnormalities and pathogenesis and compare them along with the demographic data and subtypes of disease.

Materials and methods

This case study was approved by the Scientific Research Committee of the Faculty of Medicine and the Ethics Committee of the Directorate of Health. Oral and written consent forms were obtained from parents of all patients.

The study was conducted at the radiology department/MRI unit in Azadi general hospital in Duhok governorate over a period of 8 months, between 01/07/2016 and 28/02/2017.

This study included 48 children younger than 5 years of age, referred by either the Pediatrician or the neurologist from the Early Detection and Rehabilitation center. All children were clinically diagnosed CP patients whose physician asked for MRI scans. Children older than 5 years of age with determined CP etiologies and those not fit to receive general anesthesia were excluded.

History regarding gestational age was obtained from the patients' patients, after which all patients were categorized into three groups as Preterm (born before 37 gestational weeks), Term (born between the 37^{th} and 42^{nd} gestational weeks) and Post-term (born after the 42^{nd} gestational week). History of any maternal diseases during pregnancy was reported, including hypertension, heart diseases, blood incompatibility disorders and others like diabetes mellitus. Any admission to neonatal care unit for asphyxia and or convulsion was recorded. The CP clinical sub types (i.e. topographic distribution of motor involvement) were reported by the referred physician and categorized as spastic or non-spastic. Types of spastic CP included diplegic, quadriplegic, or hemiplegic CP while non-spastic CP comprised the chorea athetotic type.

Parents were informed to keep their children fasted for 4 hours as directed by the anesthesiologist. In the radiology department, all patients were examined by the anesthesiologist, who was responsible for administration of general anesthesia, along with his/her assistant. The cranial diffusion weighted MRI was obtained using the 1.5 Tesla Philips machine.

The axial diffusion weighted sections used the following parameters: TR 5067ms repetition time, TE 156ms echo time, 23 cm field-of-view, -10^{o} flip angle, 152x105 acquisition matrix. 20 contiguous slices of about 5 mm thickness were interpreted. T1W was obtained with TR 596 ms, TE 15ms, T2W with TR 4855ms, TE 110ms and FLAIR with TR 6000ms, TE 120ms.

Coronal, axial and sagittal views were examined. The child remained still over a period of 10 to 15 minutes. Findings obtained on the MRI were classified into 6 patterns of abnormality as defined and described by Ashwal et al. [3], as follows: Normal: No abnormality detected on MRI. PVL: Signal abnormality and/or volume loss in the periventricular and/or deep white matter, may include scalloping of the ventricles, ventricular dilatation, or periventricular cysts. Diffuse encephalopathy: Global/diffuse signal abnormality and/or volume loss involving the cortex/sub cortex, deep grey matter (basal ganglia and/or thalamus), and white matter/multicystic encephalomalacia. Focal ischemic or hemorrhagic lesions: Signal change, volume loss, or porencephaly in an established vascular territory with or without other focal ischemic or hemorrhagic lesions. Brain malformations: Cortical dysplasia, polymicrogyria, lissencephaly, pachygyria, heterotopias, schizencephaly, polymicrogyria, cerebellar hypoplasia or dysgenesis, holoprosencephaly, and hydranencephaly. Unclassified group: Any MRI abnormality that is unable to be classified into one of the above groups.

Statistical analysis

Collected data were entered into an Excel 2013 workbook and then converted into SPSS version 24 for analysis.

Results

The total number of patients was 48, 70.8% of total patients were males and the male to female ratio was 2.4:1. The mean age was 1.8 years. About 22.9% of patients in the study were preterm while 77.1% were term and post-term. The demographic characteristics of all patients are presented in Table 1. The most common clinical subtype of CP was spastic diplegia

(47.9%), followed by spastic quadriplegia (35.4%), hemiplegic CP (10.4%), and chorea-athetotic CP (6.3%).

Among all patients, 62.5% had no risk factors in contrast to 37.5% who did. Prematurity was the commonest risk factor in the study group, accounting for 32.2% of all risk factors, followed by prenatal maternal diseases (29.4%). Maternal hypertension was the commonest maternal disease. Perinatal asphyxia contributed to 23.5%, followed by twin gestation (8.8%) and neonatal hyperbilirubinemia, which constituted about 6% of all risk factors.

Abnormal MRI was detected in 87.5% of cases, diffuse encephalopathy was the commonest pattern observed (56.2%). PVL was observed in 18.75%, congenital brain malformation was seen in 8.33% and ischemic brain injury was detected in 4.16%. The remaining 12.5% had unremarkable brain MRIs. The MRI pattern differences between the preterm and full-term infants are presented in Table 2. All preterm patients had abnormal MRI findings. About 45.5% of preterm infants showed PVL. Ischemic causes were more common in preterm infants than term ones.

In term and post-term children, the most common MRI finding was diffuse encephalopathy, which was seen in the form of cortical and sub-cortical atrophy, and multicystic encephalomalacia. All patients with congenital malformations and those with normal MRIs were in the term and post-term groups.

The MRI findings according to the clinical subtypes of CP are presented in Table 3. Diffuse encephalopathy was seen in the MRI scan in 52% of patients with spastic diplegia, and 30.4% showed PVL. A relatively large percent of patients with spastic quadriplegia (64.7%) and 60% of patients with hemiplegia showed diffuse encephalopathy.

Table 1: Demographic characteristics of all patients

		n	%
Age (years)	< 1 year	7	14.6
	1 - 3 years	31	64.6
	3 - 5 years	10	20.8
Gender	Male	34	70.8
	Female	14	29.2
Gestational age	Preterm	11	22.9
	Term and Post-term	37	77.1
Type of CP	Spastic diplegia	23	47.9
	Spastic quadriplegia	17	35.4
	Hemiplegia	5	10.4
	Chore-athetosis	3	6.3
Total		48	100

Table 2: The distribution of CP patients according to MRI findings and gestational age at delivery

Gestational age at delivery	Normal n (%)	PVL n (%)	Diffuse encephalopathy n (%)	Ischemic cause n (%)	Congenital malformation n (%)	Total n (%)
Pre-term	0	5 (45.5)	4 (36.4)	2 (18.2)	0	11 (100)
Term and post-term	6 (16.2)	4 (10.8)	23 (62.2)	0	4 (10.8)	37 (100)
Total	6	9	27	2	4	48

n: Number of patients, PVL: Periventricular leukomalacia

Table 3: MRI patterns according to cerebral palsy subtypes

MRI pattern types	Spastic diplegia n (%)	Spastic quadriplegia n (%)	Hemiplegia n (%)	Non-spastic n (%)	Total n (%)
Normal	3 (13.0)	-	1 (20.0)	2 (66.7)	6 (12.5)
PVL	7 (30.4)	2 (11.8)	-	-	9 (18.8)
Diffuse encephalopathy	12 (52.2)	11 (64.7)	3 (60.0)	1 (33.3)	27 (56.2)
Ischemic cause	-	1 (5.9)	1 (20.0)	-	2 (4.2)
Congenital malformation	1 (4.4)	3 (17.6)	-	-	4 (8.3)
Total	23 (100)	17 (100)	5 (100)	3 (100)	48 (100)

n: Number of patients, PVL: Periventricular leukomalacia

Discussion

In the present study, there was male predominance (70.8%). A slightly lower percentage (68%) was reported in a study carried out in Australia [6]. Some authors reported that male gender is a risk factor for CP [7]. Factors playing role in the etiology of CP interact with each other. A relatively large percentage of the cases in this study had no prenatal risk factors (62.5%). The rest 37.5% had one or more risk factors. The commonest risk factor was prematurity followed by maternal diseases, perinatal asphyxia, twin gestation and neonatal hyperbilirubinemia. It is presumed that certain radiological findings are suggestive for birth asphyxia, such as PVL, cystic encephalomalacia, localized atrophy, and gliosis with or without basal ganglia involvement [8].

The most common clinical type of CP was spastic diplegia, seen in 48% of cases. This figure is close that in a study performed at the Neurosciences Hospital of Baghdad, in which spastic diplegia constituted about 43% of all CP cases [9]. These results were also similar to studies conducted in the developed countries [2,10]. Spastic quadriplegia (35%) was the next most common type in the current study. In a study carried out in Indian, Spastic quadriplegic involvement was the most common type of CP [8]. In two separate studies conducted at Al-Kindy and AL-Mansour teaching hospitals in Baghdad, the quadriplegic CP was the most common type [5,11]. One can conclude that, the clinical spectrum of CP is different in developing countries compared to developed countries, but the result of our study was closer to that of developing countries. Hemiplegic CP is not common in our study, and accounted for 10.4%, which was higher than that reported by other authors [12]. Convulsion abnormalities were reported in 18% of our patients; higher percentages were reported by others [10].

In different European studies, the MRI abnormalities ranged from 86% to 89% [4,10,13]. This was in agreement with our current results (87.5%). Unlike these results, Benini and Shevell [14] found that 29% of the examined patients had normal MRI findings, which was dominated by dyskinetic CP. The results of the current study showed a higher proportion of diffuse encephalopathy and periventricular white mater disease, and a lower proportion of malformations and ischemic lesions.

Data from previous researches showed that the less severely affected children were more likely to have a normal MRI. Spastic monoplegia and diplegia were the commonest types of CP in the Robinson study [2]. PVL is the commonest MRI abnormality in developed countries. In 3 different studies, PVL constituted 56% (4), 42.5% (10), and 31.2% [2] of all MRI abnormalities, respectively. In the current study, diffuse encephalopathy was the commonest MRI abnormality, constituting 56.2% of all MRI abnormalities. Most of them (88%) showed cortical and sub cortical atrophy, and (11%) of them showed multi-cystic encephalomalacia. The multi-cystic encephalomalacia is more often found in term than preterm newborns and the prognosis is unfavorable [15].

Congenital brain malformations develop during the 1st and 2nd trimesters [16]. In this study, brain malformations were observed in 4 children (8.3%), all were full-term babies, and 75% showed quadriplegic type of CP. Ischemic/hemorrhagic lesions, seen only in 2 cases (4.2%), both occurred in pre-term

babies. They are seen on MRI as post-hemorrhagic or post-infarction porencephaly. This is thought to be the result of perinatal stroke. Previous studies showed more cases of focal ischemic lesions: the rates were 16.2% in Robinson et al [2] and 7.4% in Bax et al. [10].

Limitations

Children were imaged over a wide age range, which can affect the interpretation of MR images. The machine used for MR imaging had field strength of 1.5 Tesla only, and the head coil used was designed for adults. Complications during the administration of general anesthesia ended with discontinuation of the MRI scan. Many cases were postponed due to chest infections, which are common among children. National obstetrics and the neonatal medical record systems were insufficient, which is a pressing problem in most of the developing countries.

Conclusions

This study concluded that diffuse encephalopathy is a common MRI abnormality in children with CP. MRI in children with CP is relatively of value in understanding the pathogenesis of CP and it is diagnostic in congenital brain malformations. Neuro-radiological classification of CP can be applied to all patients and CP is more common among the male gender.

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Electron microscopic examination of needles used in infraclavicular brachial plexus block

İnfraklaviküler brakial pleksus bloğunda blok iğnelerinin elektron mikroskobik incelenmesi

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Abstract

Aim: The application of peripheral block is frequently used in anesthesia practice. One of the most significant complications of this procedure is peripheral nerve damage that can develop due to the needles used. The aim of this study was to determine the presence of tissue residue on the needle and to obtain information about damage to surrounding tissues during this procedure by examining the needles used in brachial plexus block with electron microscopy.

Methods: This prospective-cohort study included patients who were to undergo forearm or hand surgery in the Orthopedics Clinic under anesthesia with infraclavicular brachial plexus block performed with 2 different techniques: The local anesthetic agent was administered to the subclavian artery at 6 and 9 o'clock levels in Group 1 and 2, 6 and 9 o'clock levels in Group 2. The needles used during the block were preserved in glutaraldehyde solution then examined with electron microscopy. The presence of tissue on the needles was recorded and statistical evaluations were made.

Results: The needles used in two different techniques of infraclavicular brachial plexus block were examined under scanning electron microscope. The amount of tissue residue remaining on the needle in Group 1 was significantly less than that in Group 2 (P<0.001).

Conclusion: When it is considered that ultrasound provides a 2-dimensional image, the fewer the number of needle manipulations made during the procedure of brachial plexus block application, the less damage will be made to the surrounding tissues, thus reducing the possibility of mechanical nerve damage.

Keywords: Infraclavicular block, Electron microscopy, Neuronal damage

Öz

Amaç: Periferik blok uygulamaları anestezi pratiğinde sıklıkla kullanılmaktadır. Bu işlemin en önemli komplikasyonlarından biri de kullanılan iğnelere bağlı gelişebilecek periferik sinir hasarıdır. Çalışmamızda brakial pleksus blok işlemlerinde kullanılan iğnelerin işlem sonrası elektron mikroskobisi ile incelenerek iğne üzerinde kalan doku parçalarının varlığı ile iğnenin işlem sırasında çevre dokulara verdiği hasar hakkında bilgi sahibi olmak amaçlanmıştır.

Yöntemler: Prospektif kohort olarak planlanan çalışmamızda ortopedi kliniğinde ön kol veya el cerrahisi yapılacak hastalara farklı iki teknik ile infraklaviküler brakial pleksus bloğu ile anestezi yapıldı. İnfraklaviküler blok; Grup 1'de subklavian arterin saat 6 ve 9 hizasına lokal anestezik verilerek, Grup 2'de subklavian arterin saat 2, 6 ve 9 hizasına verilerek uygulandı. Blok sırasında kullanılan iğneler glutaraldehit solüsyonunda korunarak sonrasında elektron mikroskobik olarak incelendi. İğne üzerinde doku varlığı kaydedildi, istatistiksel olarak değerlendirildi.

Bulgular: İnfraklaviküler brakial pleksus bloğunda iki farklı teknikte kullanılan iğnelerin SEM değerlendirilmesinin yapıldığı çalışmamızda. Grup 1'de iğne üzerinde kalan doku kalıntısı miktarı grup 2'den daha az saptanmıştır (P<0,001).

Sonuç: Ultrasonun iki boyutlu görüntü vermesi göz önüne alındığında brakial pleksus blok uygulamalarında işlem sırasında iğne yönlendirme sayısı ne kadar az olursa çevre dokulara daha az zarar verilecektir dahası muhtemel mekanik sinir hasarı olasılığı da azalacaktır.

Anahtar kelimeler: İnfraklaviküler blok, Elektron mikroskopi, Nöronal hasar

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Introduction

Applications of peripheral block are frequently used in anesthesia practice. Over time, the use of ultrasound has gained a stronger ground in regional anesthesia applications, in which various effects such as shortening the time to onset of the block [1], high rates of block success [2], and postoperative analgesia [3,4] have been reported. Furthermore, with the use of ultrasound during the procedure, there are advantages such as reducing the number of needle manipulations and shortening the duration of the procedure. There are limited data related to the occurrence and frequency of neurological complications. In peripheral block applications, the nerve to be blocked is located with the neurostimulation technique and ultrasound guidance with the aid of peripheral block needles. Peripheral block applications, both with the use of the neurostimulation technique and the use of ultrasound under current conditions, are performed more safely and with lower complication rates. However, as ultrasound provides a 2-dimensional image of the vascular, neural, and muscular structures together, complications such as vascular access, direct nerve damage with the needle and intraneural injection may be seen [5]. It has been reported that fewer needle manipulations during peripheral block under ultrasound guidance will reduce the risk of mechanical nerve damage [6,7].

The use of electron microscopy has been helpful for better understanding of the ultrastructure and associated details related to peripheral nerves. Findings obtained with electron microscopy can be of guidance in physiological, pharmacological, and mechanical complications related to regional and peripheral blocks [8].

In the current study, two techniques used in infraclavicular brachial plexus block were compared. The aim was to evaluate which technique caused less tissue damage through post-procedural examination of the peripheral block needles used during the procedures under an electron microscope.

Materials and methods

This study included 30 patients aged between 18-70 years who were to undergo elective forearm or hand surgery with infraclavicular brachial plexus block. Patients were excluded from the study if they did not wish to participate, if they were pregnant, had neuromuscular disease, a history of infraclavicular region surgery, nerve damage or neurological disease, bleeding disorder or coagulopathy, a history of allergy to local anesthetic drugs, an infection in the needle entry site or any contra-indications to regional anesthesia.

Block administration protocol

Patients were admitted to the preoperative block room, intravenous vascular access was obtained from the back of the hand, through which an infusion of 0.9% NaCl was started at the rate of 3ml/kg/hour. Throughout the procedure, nasal O_2 (2L/min) was administered and patients were monitored with electrocardiography, pulse oximetry, and non-invasive blood pressure measurements. All blocks were performed by a single anesthetist (BB), using a 21-gauge 100 mm peripheral block needle (Stimuplex® A, B. Braun Melsungen AG, Germany). During administration of the peripheral block, an ultrasound device (Esaote MyLab Five, Italy) with a 10MHz linear probe was used. The ultrasound probe was placed parasagittally immediately medial to the coracoid process using the previously described coracoid technique [9]. After visualization of the subclavian artery and the surrounding brachial plexus cords, 25 ml of 0.5% bupivacaine was administered to the subclavian artery at 6 and 9 o'clock levels in Group 1 and 2, 6 and 9 o'clock levels in Group 2. The duration of the block procedure, time to onset, and complications such as vascular punction during the procedure and paresthesia were noted. After completion of the peripheral block application, the peripheral block needle used was numbered and prepared for electron microscopic examination.

Electron microscopic examination of the block needles

The needles used in the peripheral block application were fixed in 2.5% glutaraldehyde for 24 hours, washed in phosphate buffer (pH: 7.4), then dehydrated in increasing concentrations of acetone. They were then post-fixed in 1% osmium tetroxide for one hour, washed in phosphate buffer (pH: 7.4), and dehydrated again in increasing concentrations of acetone. The samples were then attached to metal stubs with double-sided adhesive bands. Using a BIO-RAD (England) sputter apparatus, the samples to be examined were coated with gold at a thickness of 100 Angstrom. The prepared materials were examined with a Fesem Zeiss Gemini 500 (Germany) scanning electron microscope. Photographs were taken at x60, x1000, and x5000 magnification, numbered and examined by another researcher (ÖFB). Evaluations were made with respect to the deformation of the needle surface on the images at x60 and x1000 magnification. The amount of soft tissue remaining on the tip of the needle was evaluated under x5000 magnification and classified using a 5-point Likert scale (1: none, 2: minimal, 3: moderate, 4: mostly, 5: completely).

Statistical analysis

Data obtained in the study were analyzed statistically using IBM SPSS v. 22 software (IBM SPSS for Windows, IBM Corporation, Armonk, NY, USA). Conformity of the data to normal distribution was assessed with the Shapiro-Wilk test. Group comparisons of variables showing normal distribution were made using the Independent Samples t-test. Statistical parameters were stated as mean and standard deviation mean (SD) values. For comparisons of variables not showing normal distribution, the Mann Whitney U-test was applied. Statistical parameters were stated as median (25%-75% quartiles) values. The relationships between group distributions of categorical variables were examined with the Chi-square test and the Fisher Exact test. A value of $P<0.05$ was considered statistically significant.

Results

Scanning electron microscopic evaluation made of the needles used in 2 different techniques of infraclavicular brachial plexus block showed that the amount of tissue residue remaining on the needle in Group 1 was significantly less than that in group 2 ($P<0.001$). Duration of procedure was shorter in Group 1 ($P=0.025$). The onset time of the block was less in group 2 ($P=0.001$) (Table 1). No deformation or breakage of the needle

surface were determined on the images at x60 and x1000 magnification in either one of the groups (Figure 1). Findings of tissue residue were observed on all the needles on images magnified at x5000 (Figure 2). Paresthesia was observed during the procedure in 2 patients in Group 2.

Table 1: Patient and block characteristics, tissue residue on the needles

		Group 1	Group 2	*P*-value
Procedure time [b] min	Median(Q1-Q3)	4.00(3.00-4.00)	4.00(4.00-5.00)	0.025*
Block onset time [b] min	Median(Q1-Q3)	14.00(13.00-14.00)	12.00(12.00-12.00)	0.001*
Gender[c] Female	n(%)	7(46.7)	5(33.3)	0.456
Male	n(%)	8(53.3)	10(66.7)	
Tissue residue [b]	Median(Q1-Q3)	2.00(2.00-3.00)	4.00(4.00-4.00)	<0.001*

[a] Independent samples t test, [b] Mann-Whitney U test, [c] Chi-Square test, [d] Fisher exact test, * Difference between the groups is statistically significant; Median(Q1-Q3): Median (25% quartile-75% quartile)

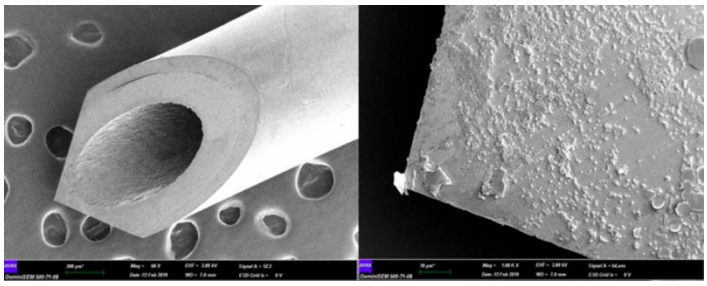

Figure 1: Images of a Group 1 needle at x60 and x1000 magnification. At x1000 magnification, mostly epithelial residue can be seen on the needle tip

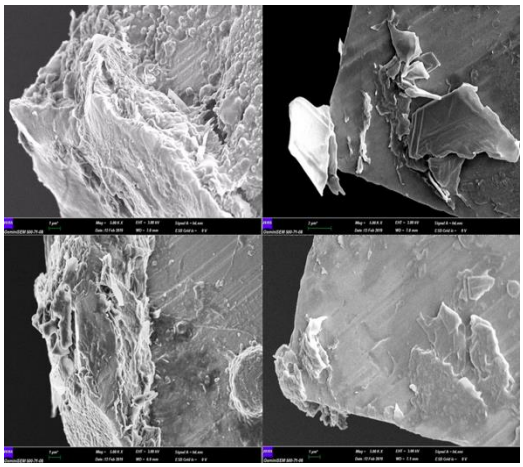

Figure 2: Electron microscope image of needle tips at x5000 magnification

Discussion

In peripheral blocks administered under ultrasound guidance, one of the most significant complications is mechanical nerve damage related to the needles used. When it is considered that ultrasound provides a 2-dimensional image, the fewer the number of needle manipulations made during the procedure of brachial plexus block application, the less damage will be made to the surrounding tissues, thus reducing the possibility of mechanical nerve damage.

With ultrasound guidance it is usually difficult to differentiate neural structures from other soft tissues, and despite real-time ultrasonographic imaging in clinical practice, it may not be possible to prevent complications such as contact of the needle to the nerve and epineurium injury. In the literature related to peripheral blocks with ultrasound guidance, there are studies that have reported peripheral nerve damage, unintended intraneural injections, and the anatomic and histological properties of these nerves [10,11]. Hara et al. [12] reported the frequency of unintended intraneural injection as 16.3% in sciatic nerve block administered under ultrasound guidance in subgluteal approach. In a study of interscalene and supraclavicular brachial plexus blocks, Liu et al. [13] reported unintended intraneural injection at the rate of 17%. In both studies, the intraneural injections in these patients did not reportedly result in clinical neural injury during the postoperative period. The most likely reason for this was stated as the fact that intraneural injections were made within the neural connective tissue and there was no damage to the neural fascicles. In this study, electron microscope examination of the needles used in infraclavicular block showed that the tissue residue on the needle tips, as seen at x5000 magnification in both groups, was of connective tissue in character.

Previous studies have not shown any superiority between the methods of single, double or triple injections [14,15]. Bowens et al. [16] reported that the single injection technique used in the posterior cord in the infraclavicular block had high success rates. In accordance with these data in literature, by examining the block needles used in infraclavicular blocks achieved with double and triple injections, the effects formed in the neural structures or soft tissues during these procedures were evaluated. In the electron microscopic examination of the needle tips of Group 2 at x5000 magnification, where triple injections were made, a significantly greater amount of tissue residue was observed on the needle tips. When the course of the brachial plexus in the upper extremity and the surrounding soft tissue and the proximity to vascular structures are taken into consideration, it can be said that if the number of needle manipulations is reduced during block application, less damage will be incurred.

In a cadaver study of upper extremity blocks administered under ultrasound guidance, Sermeus et al. [17] found the incidence of intraneural injection higher in procedures performed with a direct approach with ultrasonographic guidance to the target nerve compared to those performed with a tangential approach. In the current study, the possibility of needle contact with the brachial plexus was increased in Group 2, where local anesthetic agents were administered at 2, 6 and 9 o'clock levels of the subclavian artery. Especially in maneuvers which consider the medial cord as the target, the risk of direct contact with the medial cord increases. Paresthesia was observed in 2 patients in Group 2 in this study.

Limitations

Limitations of this study include the lack of histological examination of tissue residues at the tip of the needle. Further randomized controlled studies may be planned in the future.

Conclusion

In peripheral blocks administered under ultrasound guidance, it is recommended to use additional techniques such as real-time peripheral nerve stimulator, injection pressure monitorization and hydro-localization to reduce the incidence of intraneural injection. Decreasing needle manipulations will prevent damaging of the surrounding connecting tissue and lessen the possibility of the needle causing mechanical damage in the peripheral nerves.

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Hydatidiform mole in Duhok, Iraq: Frequency, types and histopathological diagnostic features

Irak, Duhok'ta hidatidiform mol: Sıklığı, tipleri ve histopatolojik tanısal özellikler

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Abstract

Aim: There is a worldwide variation in the distribution of molar pregnancy with respect to its type. Difficulties in obtaining accurate data about miscarriage make the precise incidence uncertain. The aim of this study was to estimate the frequency of Hydatidiform mole among the miscarriages and deliveries in Duhok province, estimate their main types, partial or complete, and correlate them with histopathological diagnostic features.

Methods: This cross-sectional study was conducted between June 1, 2016 and September 1, 2019 and included Hydatidiform mole cases from the main histopathological centers in Duhok and Zakho. All childbirths and miscarriages were evaluated within the same areas and during the same period. Samples were examined histologically and divided into three groups as partial, complete, and indeterminate molar types, after which their correlation with the main histopathological features were examined. Additional efforts were made to identify the indeterminate cases, like the use of P57 marker.

Results: The frequency of Hydatidiform mole was less than 1%. Complete type represented 43% of the cases with a relatively high percentage of indeterminate molar pregnancies (26%). The highest percentage of women belonged to the 20-30 years-old group. The most common histological feature was circumferential trophoblastic proliferation.

Conclusion: The frequency of Hydatidiform mole in Duhok was within the world range, with a relatively high percentage of indeterminate types. More efforts should be made to establish an accurate diagnosis depending on histopathological features and additional markers like P57 should be used.

Keywords: Hydatidiform mole, Frequency, Types, Histopathology

Öz

Amaç: Molar gebeliğin türüne göre dağılımında dünya çapında bir farklılık vardır. Düşükle ilgili doğru veri elde etmedeki zorluklar, kesin insidansı belirsiz kılar. Bu çalışmanın amacı, Duhok eyaletindeki düşükler ve doğumlar arasındaki Hidatidiform mol sıklığını tahmin etmek, ana tiplerini, kısmi, tam veya belirsiz olarak sınıflamak ve histopatolojik tanı özellikleri ile ilişkilendirmekti.

Yöntemler: Bu kesitsel çalışma, 1 Haziran 2016 ile 1 Eylül 2019 tarihleri arasında Duhok ve Zakho'daki ana histopatolojik merkezlerden Hydatidiform mol vakalarında yapıldı. Tüm doğumlar ve düşükler aynı bölgelerde ve aynı dönemde değerlendirildi. Örnekler histolojik olarak incelendi ve kısmi, tam ve belirsiz molar tipler olarak üç gruba ayrıldı, daha sonra ana histopatolojik özelliklerle korelasyonları incelendi. Belirsiz vakaları tanımlamak için, P57 markörünün kullanımı gibi ek tetkikler uygulandı.

Bulgular: Hidatidiform mol sıklığı % 1'den azdı. Tam tip, nispeten yüksek oranda belirsiz molar gebeliklere (% 26) sahip olguların % 43'ünü temsil etmekteydi. Kadınların çoğunlukla 20-30 yaş grubundaydı. En sık görülen histolojik özellik çevresel trofoblastik proliferasyon idi.

Sonuç: Duhok'taki Hydatidiform mol sıklığı, belirsiz türlerin nispeten yüksek bir yüzdede görülmesiyle, dünya aralığındadır. Histopatolojik özelliklere bağlı olarak doğru tanı koymak için daha fazla çaba gösterilmeli ve P57 gibi ek belirteçler kullanılmalıdır.

Anahtar kelimeler: Hydatidiform mole, Frekans, Tipleri, Histopatoloji

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Introduction

There are broad variations in the distribution of Hydatidiform mole (HM) pregnancy worldwide, with higher incidences in certain parts of Asia, Africa and other developing countries. However, the methodological problems in obtaining curettage samples from all patients with miscarriage make the accuracy of the incidence and rates unclear [1]. In developed countries, the incidence of complete Hydatidiform mole (CM) is around 1–3/1000 pregnancies and those of partial Hydatidiform mole (PM) is approximately 3/1000 pregnancies [2]. The primary estimated frequency in developing countries 10 times less than some Asian or African countries [3,4].

The CM type is associated more with invasive subsequent complication compared to PM, which is probably correlated with the male origin of the DNA [5,6]. The complete type carries about 15% increased risk of developing malignancy, while the same risk for the partial type is considerably lower [7]. Management, including the use of chemoprophylaxis treatment after evacuation and follow-up, differ according to the subtype of molar pregnancy [8]. Therefore, distinguishing between these two types is significant to prevent the unnecessary use of chemotherapy or malignant changes.

This study aimed to estimate a primary frequency of HM among the miscarriage cases and labors in Duhok province and the surrounding districts including Zakho, detect the percentages of the subtypes and correlate them with age and important histopathological features.

Materials and methods

Ethical approval was obtained from the official Ethics Committee for Research in Duhok and scientific approval was obtained from the Scientific Committee for Research in College of Medicine/ University of Duhok.

HM cases from different histopathological centers in Duhok and the surrounding districts including Zakho were collected between June 01, 2016 and September 01, 2019 for retrospective evaluation. All diagnosed HM cases were included without any exclusion criteria. All recorded miscarriages and the number of childbirths were counted within the same areas during the same period, including alive and still births, based on the official center of health protection in Duhok to estimate the frequency of HM.

Samples were divided according to histological examination into partial, complete, and unclassified types, which were considered as indeterminate HM. The histopathological features present in the report and used for diagnosis included cistern formation, trophoblastic and circumferential proliferation, and presence of gross, grapelike vesicles. All these correlated with various subtypes of HM. Additional efforts were made to identify indeterminate cases, such as the use of P57 as a marker.

Statistical analysis

All obtained data were analyzed using the IBM SPSS software (Version 22). Descriptive data were presented as numbers and percentages. Cross table tests were performed with P-value at <0.05 indicating a significant difference.

Results

The total number of the HM diagnosed and confirmed by histopathology centers, collected from June 1,2016 until September 1, 2019 was 140. The number of miscarriages was 610, while there were 146,015 births recorded during the same period (Officially obtained from the Preventive Affairs Directorate in Duhok which included Duhok province and the surrounding villages and districts, including Zakho, and the refugee camps). Based on these numbers, the frequency of HM would approximately be 0.095%, which is less than 1%.

There were 43 partial HM and 61 CM cases, in addition to the 36 indeterminate HM cases. Figure 1 presents the percentages of these 3 diagnoses.

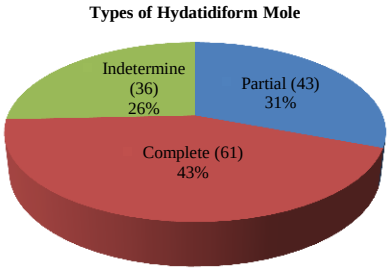

Figure 1: The frequencies and percentages of the diagnosed types of hydatidiform mole

The mean age of all patients at time of diagnosis was 27.6 years. The mean age of PM at diagnosis was 25.1 years, while that of CM was 28.1 years. The highest percentages of HM, PM, and CM (53.6%, 62.8% and 50.8% respectively) were seen in the age group between 20 and 30 years, as seen in Table 1.

Table 1: The types of Hydatidiform mole in relation to the age of the patient

Age	Partial		Complete		Indeterminate		Total	
	n	%	n	%	n	%	n	%
>20	7	16.3	13	21.3	4	11.1	24	17.1
20-30	27	62.8	31	50.8	17	47.2	75	53.6
30-40	7	16.3	7	11.5	9	25	23	16.4
40-50	2	4.6	10	16.4	6	16.7	18	12.9
Total	43	100	61	100	36	100	140	100

The major features used in the histological reports for the diagnosis of HM and differentiation between PM and CM are listed in Table 2. Except for circumferential trophoblastic proliferation and gross vesicle formation, all other features were seen in relatively high percentages in all types of HM and no statistically significant difference was detected among distinct types. Vesicles were seen grossly in 46.5% and 68.9% of PM and CM cases respectively, while circumferential trophoblastic proliferation were encountered histologically in 2.3% and 55.7% of PM and CM cases, respectively. These values were statistically significant. Out of 140 cases, P57 was used only in 3 cases (2.1%) to confirm the type of HM.

Table 2: The main gross and histological features used for the diagnosis and the differentiation of Hydatidiform mole types

Gross and histological features	Partial		Complete		*P*-value[1]	Indeterminate	
	n	%*	n	%**		n	%***
Gross Vesicles	20	46.5	42	68.9	0.01 Significant	20	55.6%
Cistern formation	41	95.3	54	88.5	0.20 Not significant	20	55.6%
Trophoblastic proliferation	43	100	56	91.8	0.10 Not significant	36	100%
Circumferential trophoblastic proliferation	1	2.3	34	55.7	0.05 Significant	14	38.9%

*Frequency of encounter among partial Hydatidiform moles (43), ** Frequency of encounter among complete Hydatidiform moles (61), *** Frequency of encounter among indeterminate moles (36), [1] *P*-value: between partial and omplete types

Discussion

This study examined the diagnosis and registration of HM cases in Duhok province including Zakho, and the refugee camps, to establish a primary frequency of HM, its types, and the accuracy of diagnosis. The strength of this study lied in the collaboration from different official registration centers.

The main limitation to this study was the probable shortage of obtaining data from all miscarriages. Although there are strict orders from the directory of health to send the products of conception of all miscarriages to histopathology laboratories, the private clinics do not usually comply. However, the same problem is encountered throughout many areas all over the world [1-4,9-12]. The incidence of HM in this study was approximately 0.095%, which is less than 1%. Some authors reported a wide range of incidence of HM, from 23 to 1299 cases per 100,000 pregnancies [13], while others found a significantly lower incidence in Europe and the United States than that from Asia, Africa and South America [2,3-14].

Joneborg et al. [9] stated the following: [We found evidence of a significant temporal increase in the incidence rate of HM, which could not fully be explained by an increase in maternal age over time. Changes in diagnostic methods probably contributed to the increased incidence rate of PM]. Even if the causes of varying incidences have not been clear, there were different explanations. Brown et al. [10] suggested that dietary and nutritional causes may affect the etiology. It is hard to compare the incidences of molar pregnancy from different types of studies, which is why several studies proposed diverse reasons: the inadequate description of the population at risk, the differences in the definition of the disease, the frequent changes in the diagnostic tools over time and the variation in the methodological designs [9-12].

CM was the commonest type in this study (43%) followed by PM (31%). HM was mostly seen in the age group of 20-30 years, with a mean age of 27.6 years. The fact that HM is more common at the extremes of reproductive age and that women under 20 or over 40 years of age have a higher risk [15] may change. Recently, and in agreement with our result, a Swedish study conducted in Stockholm found a significant increase in the age of HM diagnosis [9]. Similarly, another study determined the median maternal age of molar pregnancy as about 27 years and nearly 91% of cases occurred in females aged 18 to 40 years [16].

In the current study more than quarter of the cases (26%) were diagnosed as HM without determining the type. The diagnosis and sub-classification of HM is becoming more difficult due to the early pregnancy ultrasound examinations, which leads to the early evacuation of HM before the development of trophoblast proliferation [17]. Several authors have concluded that the diagnosis of HM depending on morphological features alone is defective and personally variable [18,19].

The histological features of circumferential trophoblastic proliferation and gross vesicle formation were seen more in CM, as well as in other types. No other features were significantly different among subtypes. Despite the relatively high percentage of indeterminate HM, p57 test was performed to only 3 out of 140 HM cases (2.1%).

The risk of gestational trophoblastic neoplasms, including choriocarcinoma, is much higher after the CM (reaching to 30 %) than PM (about 0.5–5 %), which renders accurate diagnosis important [18-20].

Limitations

People who live in Duhok belong to different castes. Plenty refugees from other parts of Iraq and Syria who escaped adjacent war-torn areas live in Duhok as well, but samples were collected from different Histopathology centers in Duhok and Zakho centers only. Refugees in different camps with complaints of bleeding were referred to specialized private Obstetrics and Gynecology Centers to undergo curettage. Unfortunately, there is no specialized hospital inside the camps for refugees. In this study, we were unable to address patients directly. Most cases weren't included in this study due to the need of obtaining a special and formal permit to research or enter refugee camps, which is difficult.

Conclusions

The correct diagnosis may strongly require additional immunohistochemical techniques to perform the p57 marker [20] test or molecular analysis including flow-cytometry, hybridization, or polymerase chain reaction (PCR) [17]. For all these reasons, it is highly recommended to use more of these above-mentioned techniques, especially the PCR, to establish diagnosis in problematic cases.

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Prevalence of human pseudocholinesterase (butyrylcholinesterase) deficiency in central Anatolian people: A cross-sectional study

Orta Anadolu toplumunda human psödokolinesteraz (butirilkolinesteraz) eksikliğinin yaygınlığı

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Abstract

Aim: Human pseudocholinesterase (PChE) is an enzyme responsible for hydrolysis of the muscle relaxant drugs like succinylcholine and mivacurium. PChE deficiency, which may lead to prolonged apnea, may occur due to hereditary or acquired causes. In our study, we aimed to investigate the prevalence of human pseudocholinesterase (PChE) enzyme deficiency around the central Anatolia region and present our results in light of the literature.

Methods: This cross-sectional study included 936 patients (age 18-70 years) who underwent any elective surgery under general anesthesia between August 2015 and September 2019. Human PChE level, plasma PChE activity, the human PChE activity/albumin, serum liver and kidney function tests were analyzed from blood samples. Human PChE enzyme deficiency and possible association of the PChE deficiency with other values was also investigated. The normal value of PChE was considered to range from 4650 U/L to 10,440 U/L.

Results: PChE activity was decreased in 19 (1.9%) of the 936 patients (442 males and 494 females). There was no statistically significant difference between the PChE levels in terms of gender (P=0.236). The mean human PChE activity of all patients was 7.490 (0.980). The PChE activity of 22 (2.35%) and 58 patients (6.4%) were below 5.000 U/ml and 6.000 U/, respectively. A statistically significant difference was found between serum urea, creatinine and human PChE levels (P=0.034, P=0.236, respectively). However, PChE deficiency had no correlation with liver function tests such as AST and ALT (P=0.432, P=0.022, respectively).

Conclusion: PChE deficiency can be observed in preoperatively evaluated patients and may cause serious life-threatening conditions, including respiratory failure and prolonged apnea.

Keywords: Human butyrylcholinesterase, Central Anatolian people, Pseudocholinesterase deficiency, Succinylcholine

Öz

Amaç: Human psödokolinesteraz (PChE), süksinilkolin ve mivakuryum gibi kas gevşeticilerin yıkımından sorumlu bir enzimdir. PChE eksikliği genetik kökenle veya edinilmiş sebeplerle ortaya çıkabilir ve bu durum uzamış apneye yol açabilir. Biz çalışmamızda, orta Anadolu bölgesinde Human psödokolinesteraz (PChE) enzim eksikliğinin sıklığını araştırmayı ve literatür ışığında sunmayı amaçladık.

Yöntemler: Bu enine-kesitsel çalışmada, Ağustos 2015 ve Eylül 2019 arasında genel anestezi altında herhangi bir elektif cerrahi geçiren 18-70 yaş arasındaki toplam 936 hasta çalışmaya dahil edildi. Hastaların kan örneğinde human PChE düzeyi, plazma PChE aktivitesi, human PChE aktivitesi / serum albümin düzeyi, serum karaciğer ve böbrek fonksiyon testleri analiz edildi. Human PChE enzim eksikliği ve serumda ölçülen diğer değerler ile muhtemel ilişkisi de ayrıca araştırıldı. PChE normal değeri 4650 U/L-10440 U/L olarak kabul edildi.

Bulgular: PChE enzim aktivitesi, toplam 936 hastanın (442 erkek, 494 bayan) 19'unda (%1,9) normalin altındaydı. Cinsiyet açısından PChE düzeyleri arasında anlamlı fark yoktu (P=0,236). Hastaların 22'sinde (%2,35) PChE aktivitesi 5,000 U/ml' in altındaydı. 58 (%6,4) hastada ise PChE aktivitesi 6,000 U/L' in altında ölçüldü. Human PChE seviyesi ile serum üre ve kreatinin arasında istatistiki olarak önemli fark saptandı (sırasıyla, P=0,034, P=0,236). Ancak PChE enzim eksikliğinin AST ve ALT gibi karaciğer fonksiyon testleri ile ilişkisi saptanmadı (sırasıyla, P=0,432, P=0,022).

Sonuç: Psödokolinesteraz enzim eksikliği preoperatif hastalarda gözlenebilir ve uzamış apne ve solunum desteği dahil yaşamı tehdit eden ciddi sonuçlara sebep olabilir.

Anahtar kelimeler: Human bütirilkolinesteraz, Orta Anadolu toplumu, Psödokolinesteraz eksikliği, Süksinilkolin

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Introduction

Human pseudocholinesterase (PChE), also known as butyrylcholinesterase (BChE) or plasma cholinesterase is a drug metabolizing enzyme responsible for hydrolysis of the muscle relaxant drugs like succinylcholine and mivacurium [1,2]. PChE deficiency is rare condition which may occur due to hereditary or acquired causes and is typically diagnosed only after exposure to succinylcholine or mivacurium. Although many physiopathological conditions may affect BChE synthesis or activity, the main cause of BChE deficiency is hereditary. Succinylcholine is short-time anesthetic agent used for rapid intubation, which normally provides motor block lasting for 10-12 minutes when used in standard doses (1 mg/kg, IV). PChE deficiency leads to prolonged motor block associated with succinylcholine and mivacurium. The major presenting symptom is prolonged skeletal muscle paralysis including the diaphragm and intercostal muscles, which are required for spontaneous breathing [3]. Deficiency due to any cause can lead to prolonged apnea and paralysis following administration of succinylcholine and mivacurium [4]. Patients with PChE deficiency will often be admitted to the intensive care unit and need continuous ventilator support postoperatively until muscle strength is restored [5]. Human PChE is a glycoprotein enzyme that is synthesized by the liver and immediately released into the plasma [6]. The plasma half-life has been estimated as approximately 12 minutes. Initial dose of succinylcholine is rapidly hydrolyzed by PChE within 10 to 13 minutes during which 90 % of the muscle strength is restored. Deficient PChE activity is usually considered to be caused by several allelic mutations in butyrylcholinesterase (BChE) gene, which provides instructions on how to make the enzyme pseudocholinesterase [7]. This study was designed to evaluate the PChE deficiency in middle Anatolian people for the first time. In addition, changing PChE levels were investigated with regards to liver and kidney function tests. In this study, we aimed to make anesthesiologists, specially trained nursing staff, and physicians of the intensive care unit aware of PChE deficiency and the significance of anesthetic management.

Materials and methods

This cross-sectional study was conducted between August 12, 2015, and September 20, 2019, and approved by the Ethics committee of the Bozok University Medical Faculty (date: 08/06/2015, number: 27/09). Preoperatively assessed 936 patients (442 men and 494 women) with a mean age of 44.85 years (18-70 years) were enrolled in the study group. The study was performed in the Central Anatolia Region of Turkey.

The participants were fully informed about the aim and scope of the study and the tests to be performed. Informed consent forms were obtained from all participants. Patients aged 18-70 years scheduled for any elective surgery under general anesthesia were included. Patients who use acetylcholinesterase inhibitors, anticholinesterases, cytotoxic agents, metoclopramide, steroids, ester-type local anesthetics, hexafluronium, pancuronium, oral contraceptives, or antidepressants, those with liver or renal diseases, malnutrition, malignancy, extensive burn injuries, pregnant patients and those who underwent cardiopulmonary bypass were excluded. After physical examination, venous blood samples were collected for total blood count and biochemical tests (AST, ALT, albumin, BUN, urea and creatinine clearance). Fasting blood samples were drawn from all subjects between 7:00 AM and 8:00 AM, and immediately sent to the hospital laboratory for evaluation. A specimen of clotted blood was centrifuged at 3.000 g for 10 minutes for serum assessment, which was stored at –70°C until analysis.

Laboratory analysis for PChE activity was conducted by obtaining the plasma sample and performing a qualitive test of PChE activity. Moreover, quantitative testing via colorimetry was performed to determine the actual amount of PChE present in the sample.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc, Chicago, IL, USA). Data was reported as mean (standard deviation) or percentages (number of patients) as appropriate unless otherwise specified. The Kolmogorov–Smirnov goodness-of-fit test was used to evaluate normality of the data. Correlation coefficients were derived by using Pearson's correlation test.

In the power analysis based on the data of previous studies and the population of region, a sample size of 866 patients were needed with 90% power (1-β err prob=0.90) and 5% error margin (α err prob=0.05). 936 patients were enrolled in the study after taking possible loss of data into consideration.

Results

Nine hundred thirty-six preoperative subjects (442 males and 494 females) were recruited, with a mean age of 44.85 years (18-70 years). Demographic characteristics of the patients are presented in Table 1.

Among all patients, the PChE values of 19 individuals (1.9 %) were below normal (range: 4650 U/L to 10,440 U/L). No significant difference was found between PChE levels in terms of gender (P=0.236) (Table 2).

Table 1: Demographic data of the patients

	Gender					
	Male (n=442)		Female (n=494)		Total (n=936)	
Age (years)	n	%	n	%	n	%
≤15	64	14.4	56	11.3	120	12.8
16-40	213	48.3	246	49.8	459	49.1
41-64	119	26.9	154	31.2	273	29.2
≥65	46	10.4	38	7.7	84	8.9

Table 2: Comparison of Pseudocholinesterase (PChE) values in terms of gender

	PChE (ng/ml)				
	Normal		Low		*P*-value
Sex	n	%	n	%	
Male (n=442)	431	97.5	11	2.5	0.236
Female (n=494)	486	98.4	8	1.6	

The mean human PChE activity of all patients was 7.490 (0.980). The PChE activity of 22 (2.35%) and 58 patients (6.4%) were below 5.000 U/ml and 6.000 U/, respectively. PChE activity measurements are presented in Table 3.

Table 3: Pseudocholinesterase activity measurements

	PChE activity (U/ml)					
Value (U/ml)	<4.8	4.8-6	6-7	7-8	8-9	>9
Number	18	62	176	352	294	34
%	1.9	6.6	18.8	37.6	31.4	3.63

PChE: Pseudocholinesterase

The mean value for human PChE activity/albumin ratio of all patients was 1.657. The PChE activity/albumin ratio was measured under 1.200 in 12 (1,28%) patients and under 1,300 in 28 (2,99%) patients (Table 4).

Human PChE activity was found to significantly and positively correlate with plasma PChE levels, albumin, PChE activity/albumin ratio, urea and creatinine levels. Similarly, the human plasma PChE levels correlated with PChE activity, albumin, and creatinine. A statistically significant difference was found between serum urea, creatinine and human PChE levels (P=0.034, P=0.236, respectively). Serum creatinine, albumin, PChE activity, urea, alanine aminotransferase (ALT), aspartate transaminase (AST), and PChE measurements are presented in Table 5.

Table 4: The human Pseudocholinesterase (PChE) activity / albumin values

	PChE activity / albumin					
Range	<120	120-130	130-140	140-180	180-200	>200
Number	12	28	58	622	160	56
%	1.28	2.99	6.19	66.45	17.09	5.98

PChE: Pseudocholinesterase

Table 5: Evaluation of blood creatinine, albumin, PChE activity, urea, ALT, AST, PChE

	Minimum	Maximum	Mean (SD)	*P*-value
Creatinine (mg/dl)				
Male (n=442)	0.43	5.23	0.79 (0.33)	0.236
Female (n=494)	0.38	4.92	0.72 (0.38)	
Albumin (g/dl)				
Male (n=442)	3.01	6.39	4.55 (0.55)	0.654
Female (n=494)	3.34	7.12	5.15 (0.68)	
PChE activity (U/L)				
Male (n=442)	4.42	9.59	7.49 (0.98)	0.124
Female (n=494)	4.16	8.64	6.86 (0.77)	
Urea (mg/dl)				
Male (n=426)	5	92	14.12 (7.29)	0.034
Female (n=452)	6	98	17.42 (8.42)	
ALT				
Male (n=430)	6	331	21.93 (21.6)	0.022
Female (n=474)	8	298	17.83 (18.5)	
AST				
Male (n=432)	7	395	23.71 (22.97)	0.432
Female (n=488)	8	356	22.63 (20.81)	
PChE (ng/ml)				
Male (n=442)	9.51	75.57	25.68 (10.13)	0.452
Female (n=494)	8.63	72.43	24.57 (9.18)	

PChE: Pseudocholinesterase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Discussion

The normal value of plasma PChE value ranged from 4650 U/L to 10,440 U/L [8]. The main result of our study was that, of all 936 patients, 19 patients (1.9%) had decreased PChE values. In our country, a study on PChE deficiency was conducted by Yildirim et al. [9] in 2009, in which the incidence enzyme deficiency was reported as 3.77% in Sivas province.

We performed a qualitative test to determine PChE activity in the patients' plasma samples and used quantitative testing by colorimetry to detect the actual amount of PChE. The dibucaine inhibition test is one of the most used tests, and measures PChE inhibition by dibucaine. Dibucaine, an aminoamide local anesthetic, may be used to determine the activity of the atypical variants of the PChE. Although dibucaine will inhibit of the normal variant of the PChE by 80%, it will reduce the activity of the atypical variants of the PChE to much smaller degrees (heterozygotes by 60%, homozygotes by 30%) [10].

PChE deficiency is usually genetic in origin, and arises from inherited, acquired, and iatrogenic causes [6]. In inherited PChE deficiency, succinylcholine and mivacurium cannot be hydrolyzed by atypical PChE. The majority of people (96%) are homozygous for the normal PChE genotype and the remaining individuals (4%) carry 1 or much more of the atypical gene alleles [11]. A small minority of the people (0.2%, 1 per 480) carry both enzymes (heterozygous), and these patients hydrolyze succinylcholine in a longer time. The ratio of carrying homozygous and heterozygous alleles for abnormal PChE is 1 per 3200 and 1 per 500, respectively, and these patients cannot break down the succinylcholine and mivacurium [12]. Homozygotes may present with neuromuscular blockade for clinically significant longer durations, such as 3 hours after standard succinylcholine dosing [13]. Patients with atypical homozygous genotype do not only have reduced serum cholinesterase activities but also their elimination rate for some pharmacologically potent drugs decrease drastically [14].

A recent study revealed that there is a close relationship between number of multiple mutations in the collagen Q (COLQ) gene. A large number of multiple mutations in the COLQ gene may cause an abnormal release of cholinesterase, resulting in decreased serum PChE content associated with PChE deficiency [15].

Butyrylcholinesterase gene (BChE) is located at chromosome 3 (3q26.1-26.2) and has newly discovered significant variants such as the atypical (A-variant), the Kalow (K-variant), the fluoride (F-variant) and the silent (S-variants) variants. Atypical (A-variant) and Kalow (K-variant) are the most common BChE gene variants in the white population. Especially the atypical variant is most frequently related to prolonged apnea. Recent studies have revealed that new variants of the BChE gene may cause PChE deficiency and lead to the prolonged effect of succinylcholine or mivacurium eventually [2]. Atypical BChE gene is two times more common in males than in females (1/2 ratio) [16]. The patient's ethnic origin plays a significant role in PChE deficiency. Ethnic populations with the highest prevalence for PChE deficiency are Caucasian males of European descent, native Alaskan ethnicities, and Persian Jewish community [17].

Drugs that inhibit the enzyme's activity include acetylcholinesterase inhibitors (neostigmine, pyridostigmine, physostigmine, and edrophonium), anticholinesterases (especially echothiophate), cytotoxic agents such as cyclophosphamide, steroids, ester-type local anesthetics, pancuronium, oral contraceptives and antidepressants (fluoxetine, sertraline) [18]. Acquired causes, including chronic infections, liver disease, renal disease, malnutrition, pregnancy, malignancy, hemodialysis, extensive burn injuries, and myocardial infarction or cardiopulmonary bypass, can reduce PChE levels [19,5]. In patients with PChE deficiency, the use of cocaine can lead to sudden cardiac death. In these patients, the non-depolarizing muscular blocker mivacurium should not be used during anesthesia induction, but other non-depolarizing muscular blockers such as rocuronium, vecuronium and atracurium may be used safely in this period [18]. When prolonged neuromuscular paralysis associated with the use of succinylcholine or mivacurium occurs, complete recovery is generally achieved following the spontaneous return of muscle function in patients with careful monitoring and mechanical respiratory ventilation support [20]. Patients should be sedated during mechanical ventilator support. Fresh frozen plasma may also be administered to these patients to facilitate the recovery of muscle function [21]. In BChE deficiency, the use of Recombinant BChE injection is an interesting approach, but it is not performed in daily practice due to production difficulties and non-cost-effectiveness [22].

A peripheral nerve stimulator can be used for repeated evaluation of motor function [13]. Since PChE deficiency is associated with inheriting an abnormal variant of the BChE gene, family members of patients with PChE deficiency should be recommended to undergo laboratory testing. Moreover, the Association of Anesthesiology of Great Britain and Ireland require the usage of neuromuscular blockade monitoring devices throughout all anesthetic procedures, including regional and sedative anesthesia [23].

One of the main results in our study is the significant positive correlation of PChE activity with plasma PChE, albumin, BChE activity/albumin, and creatinine. PChE activity is not significantly correlated with liver function tests, which can be derived from the advanced liver failure patients who were excluded from this study. A recent study conducted by Abdullayev et al. [24], investigating the likely relationship between pseudocholinesterase deficiency and other laboratory tests, revealed a significant relationship between AST, urea levels and PChE. However, they could not detect any relationship between PChE and ALT, INR, aPTT and creatinine levels. They concluded that enzyme deficiency incidence was 4.5 times higher in patients with high AST levels, and 9-fold higher among patients with high urea levels. Yildirim et al. [9] revealed that a decrease in PChE levels is related to older age, male gender, AST, ALT, urea, creatinine, PT and aPTT elevation. The incidence of PChE deficiency was observed to be three times higher in high AST levels, and 5 times higher in case of urea and creatinine elevation in blood sample.

PChE deficiency can be confused with different diagnoses such as residual neuromuscular blockade, the effect of residual fentanyl, myasthenia gravis, hypokalemia and hypermagnesemia [25]. Since PChE deficiency can be fatal if not recognized and treated properly, the pre-operative assessment should include family history of a genetic origin [5].

Limitations

No further genotype examination via genetic tests was performed in patients with PChE deficiency detected by laboratory testing. In patients with PChE deficiency, whether the failure is caused by hereditary or acquired etiology has not been investigated. Moreover, due to limited conditions, we did not have possibility to determine the plasma cholinesterase levels of family members of patients with PChE deficiency.

Conclusions

Anesthesia providers should familiarize themselves with the significance of a PChE deficiency, because PChE deficiency may become a life-threatening condition if the patient must undergo general anesthesia for surgery. For this reason, the anesthesiologist, specially trained nursing staff, and physicians of the intensive care unit should always consider using less neuromuscular blocking agents such as succinylcholine and mivacurium. Necessary measures should be taken for ventilator support due to the possibility of prolonged apnea. The patient with PChE deficiency and family members should be also educated about future anesthetic practices. Patients should be registered in a database for PChE deficiency.

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The effect of dexpanthenol on the formation of epidural fibrosis in an experimental laminectomy model in rats

Deneysel epidural fibrosis modelinde dextpanthenol'ün epidural fibrosis oluşumu üzerine etkisi

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Abstract

Aim: Epidural fibrosis, which develops after spinal surgery, is one of the factors which reduce the chances of successful surgery in the medium and long term by tightly surrounding the dura and spinal roots. In this experimental study, the aim was to compare the effects of local and systemic administration of dexpanthenol on epidural fibrosis formation in rats.

Methods: Twenty-eight rats were randomly divided into 4 equal groups (control, Spongostan, local dexpanthenol and systemic dexpanthenol) and laminectomy was performed at the T11 level. Local dexpanthenol (500mg/kg) was administered with Spongostan, and systemic dexpanthenol (500 mg/kg) was administered once a day for three weeks. Epidural fibrosis, arachnoidal involvement, fibroblast cell count, vascular endothelial growth factor, and hydroxyproline levels were evaluated.

Results: The grade of epidural fibrosis, fibroblast cell counts, and hydroxyproline levels were significantly lower in the systemic dexpanthenol groups (P=0.025).

Conclusion: Dexpanthenol may be used as potential agent for reducing epidural fibrosis. However, it should be administered more than once for it to take effect.

Keywords: Laminectomy, Epidural fibrosis, Fibroblast, Dexpanthenol, Rat

Öz

Amaç: Spinal cerrahi sonrası gelişen epidural fibrosis dura ve spinal köklerin çevresini sıkıca sararak orta ve uzun vadede cerrahinin balşarı şansını azaltan nedenlerden biridir. Bu nedenle, bu deneysel çalışmada, ratlarda local ve sistemik dekspanthenol uygulamasının epidural fibrosis oluşumu üzerine etkisini karşılaştırmak amaç edinilmiştir.

Yöntemler: Yirmi sekiz adet sıçan rastlantısal olarak 4 eşit gruba ayrıldı (Kontrol, spongostan, local dekspanthenol ve sistemik dekspanthenol) ve bütün sıçanların torakal 11 düzeyine laminektomi yapıldı. Local olarak dexpanthenol 500 mg/kg dan spongostan ile uygulandı. Sistemik olarak dexpanthanol, 500 mg/kg dan günde bir defa olmak üzere 3 hafta boyunca uygulandı. Epidural fibrosis, araknoid tutulum, fibroblast hücre sayısı, vasküler endotelyal büyüme faktörü ve hidroksiprolini çeriği değerlendirildi.

Bulgular: Epidural fibrosis derecesi, fibroblast hücre sayısı ve hidroksiprolin düzeyi istatistiksel olarak anlamlı düzeyde sistemik dekspanthenol grubunda düşüktü (P=0,025).

Sonuç: Dekspanthenol epidural fibrosisi azaltmak için potansiyel bir ajan olabilir, fakat bu etkinin ortaya çıkması için birden fazla sayıda verilmesi gereklidir.

Anahtar kelimeler: Laminektomi, Epidural fibrosis, Fibroblast, Dekspanthenol, Sıçan

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Introduction

Failed back surgery syndrome (FBSS) is described as chronic back pain which persists after spinal surgery, with or without radicular pain [1]. In the literature, the main reported factor in the development of FBSS is extensive fibrotic tissue formation in the epidural distance after surgery, causing widespread adhesions and retractions that involve the neuronal roots and dura [2-4]. It has been reported that epidural fibrosis (EF) occurs after lumbar disc surgery at rates varying between 5% and 33%, and that it can vary depending on the surgery type [5]. Although it is not currently an effective treatment method, the best protection against EF is decreasing its formation [2,6,7]. Many etiological factors which could influence the formation of EF include epidural hematoma, removal of the epidural fat tissue, and paraspinal muscular fiber invasion.

Although the mechanism of EF formation has not been understood, many authors have shown the effect of fibroblast cell proliferation on formation of EF, focusing to decrease fibroblast proliferation and its production. In these studies, free fat grafts, anti-neoplastic and anti-inflammatory agents, Adcol-L, and numerous chemical agents were investigated. However, no standard treatment protocol has been established for humans [2,8-11]. Studies on EF continue to be conducted.

Dexpanthenol, also known as provitamin B5, is an alcohol analogue of pantothenic acid. Following oral or parenteral administration, it is transformed into pantothenic acid in the tissues and has frequently been used to enhance the recovery of skin injuries. Studies on dexpanthenol have shown its anti-oxidative and anti-inflammatory activity [12-15]. There is no information related to effect of dexpanthenol on EF formation.

In this study, we investigated the effects of the local and systemic administration of dexpanthenol in an empirical EF model and discussed the results in the light of the available literature.

Materials and methods

Animals

After receiving the approval of the Animal Ethics Committee (Approval Number 64583101/2017/090), all experimental protocols were followed according to the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals. Twenty-eight adult female Wistar albino rats weighing 300 ± 50 g were used in this study, and they were housed under environmentally suitable conditions at 21–25°C with 50% humidity and a 12-hour light/dark cycles. The rats were provided with free access to food and water.

Groups

The rats were randomly divided into the following four groups (n=7 each) and were treated as indicated.

Group 1: Control (C). T11 total laminectomy was performed and the site was washed with saline.

Group 2: Spongostan (S), T11 total laminectomy was performed and saline was administered with spongostan on the laminectomy area.

Group 3: Local Dexpanthenol (D). T11 total laminectomy was performed and 500 mg/kg dexpanthenol (Bepanthen injectable solution, Bayer Turk Chemical Co., Turkey) was applied with spongostan.

Group 4: Systemic Dexpanthenol (SD). T11 total laminectomy was performed, saline was applied with spongontan, and 500 mg/kg dexpanthenol was administered once a day for a total period of three weeks.

Surgical procedure and sample preparation

Intraperitoneal (IP) injection of a mixture of 10 mg/kg xylazine hydrochloride (BIOVETA plc, Czech Republic) and 50 mg/kg ketamine HCl (Ketasol, Richter Pharma, Austria) were administered for anesthesia five minutes before the surgery. The body temperatures of the rats were maintained at 37°C, and they were placed in the prone position. The laminectomy areas were shaved and disinfected with povidone-iodine. The same surgeon carried out all surgical procedures. An incision was performed through the skin along the T8–L3 levels. The thoracolumbar fascia and paravertebral muscles were dissected in a sub-periosteal manner, reaching the T10–L2 laminae. Total laminectomy was performed at the T11 level. Cotton pads and water were applied to maintain hemostasis. The wounds were sutured in anatomical layers using a 5-0 polypropylene suture after administration of dexpanthenol. On postoperative day 21, the rats were euthanized by cervical dislocation under deep anesthesia. The vertebral columns of the rats were removed *en bloc* between T8 and L3.

Histopathological evaluation

The vertebral column from T9 to L1 including the paraspinal muscles and epidural scar tissue was removed *en bloc* and fixed in 10% neutral-buffered formalin solution. The samples were decalcified in 10% formic acid for approximately 10 days, after which tissue samples were collected from the laminectomy areas, washed with tap water, and routinely processed. Subsequently, the specimens were embedded in paraffin. The upright T11 vertebra was cut into 12 continuous transverse sections of 4 µm, among which six sections were stained with hematoxylin and eosin (H&E), and the other six with Masson's trichrome stains. The H&E and Masson's trichrome-stained fibrous tissue sections were examined using an Olympus BX52 microscope, and images were captured with an Olympus DP 25 camera. The presence of arachnoidal involvement was also identified, and the extent of the EF and the dura mater was graded according to the following scale described by He et al. [16]. Grade 0: the dura mater was free of scar tissue; Grade 1: only thin fibrous bands were observed between the scar tissue and dura mater; Grade 2: continuous adherence was observed in less than two-thirds of the laminectomy defect; Grade 3: scar tissue adherence was considerable, affecting more than two-thirds of the laminectomy defect or the adherence extended to the nerve roots. At 400x magnification, fibroblast density was calculated in three fields of the laminectomy sites from each section.

Immunohistochemistry

The immunostaining was conducted at room temperature using a DAKO autostainer universal staining system (Autostainer Link 48 DAKO, Glostrup, Denmark). The 4-μm thick paraffin-embedded sections were mounted on positively charged slides, deparaffinized in xylene, and subsequently dehydrated using a graded series of ethanol solutions. Then,

antigen retrieval was performed at 96°C in a 10 mM/L citrate buffer (pH 6) for 40 min in a thermostatic water bath (PT Link). The sections were incubated with vascular endothelial growth factor (VEGF) (RB-9031, NeoMarkers, Fremont, CA, USA) for 60 minutes at room temperature. Positive and negative controls were included for each antibody and each batch of stained tissue. A streptavidin-biotin enhanced immunoperoxidase technique (K8000 Envision Flex, DAKO, Glostrup, Denmark) was used to detect the immunoreactions using an automated system. The sections were incubated with 3,3'-diaminobenzidine (DAB) and counterstained lightly with hematoxylin to demonstrate the binding. Finally, the sections were dehydrated and mounted onto the slides. The positively immunostained slides were used as positive controls. Normal rabbit serum IgG was used to replace primary antibody as a negative control.

Evaluation of immunostaining

The slides were examined at low magnification (100x), areas that exhibited the highest staining intensity were considered "hot spots" and were further evaluated at high magnification (200x). The stained cell ratio was determined by counting at least 200 cells. When ≥10% of the cells were stained with the marker, the staining was considered positive. The staining intensity at different magnifications was evaluated using the following scale: "weak," "moderate," and "strong;" visible at 200x, 100x, and 40x magnifications, respectively.

Hydroxyproline content analysis

Total collagen was determined by measuring the concentration of hydroxyproline in each specimen as described by Reddy et al. [17]. The samples (40 mg) homogenized in 100 µl 2N NaOH were hydrolyzed by autoclaving at 120°C for 20 min. Then, 450 µl chloramine-T was added to the hydrolysate, mixed gently, and oxidation was allowed to proceed for 25 min at room temperature. 500 µl of Ehrlich's aldehyde reagent was added to each sample, mixed gently, and the chromophore was developed by incubating the samples at 65°C for 20 minutes. Absorbance of each sample was read at 550 nm using a spectrophotometer. Unknown concentrations of hydroxyproline in each tissue specimen were deduced from a standard calibration curve using L-hydroxyproline. The content of total collagen was calculated assuming that 14 percent of the total amino acids of collagen were hydroxyproline.

Statistical analysis

Kolmogorov-Smirnov test was used to determine whether the variables were normally distributed among groups. One-way ANOVA test was used in the groups showing normal distribution. Kruskall-Wallis H test was used if the group was non-normally distributed. Bonferroni corrected post-hoc test and Tamhane's T2 test were used for pairwise comparisons. Descriptive statistics for the variables were presented as median (25.-75. percentile) and Mean (Standard Deviation). *P-value* of less than 0.05 was considered significant.

Results

Complications associated with wound recovery and medical practice

Dexpanthenol did not induce any adverse effects in the wound area or peripheral tissues. In addition, no infections, cerebrospinal fluid collections or hematoma were seen in the wound area.

Histopathological results

Grade 3 EF (Figures 1A and 1B) was observed in groups C, S, D and SD in five rats, two rats, five rats and one rat, respectively. Grade 2 EF (Figure 2A and 2B) was observed in groups C, S, D and SD in two, five, two and six rats, respectively. These results were significantly different between the groups (P=0.025) (Table 1). In addition, there was a statistically significant difference between groups D and SD.

Arachnoidal involvements were observed in two, one, two and one rats in groups C, S, D and SD, respectively, the difference between which was not significantly different (P=0.756).

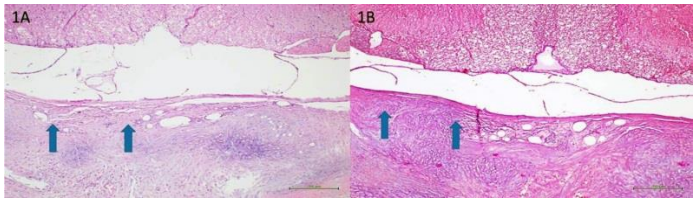

Figure 1: (A) Hematoxylin and eosin (H&E) and (B) Masson trichrome (both 100x magnification) staining of the epidural fibrosis in the laminectomy sites. Grade 3 fibrosis: scar tissue completely covered the laminectomy defects and adhered to the underlying dura mater (arrows)

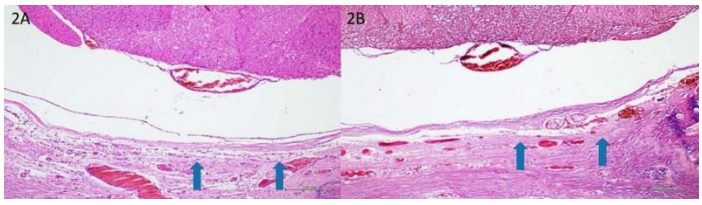

Figure 2: (A) Hematoxylin and eosin (H&E) and (B) Masson trichrome (both 100x magnification) staining of the epidural fibrosis in the laminectomy sites. Grade 2 fibrosis: scar tissue adhered to the underlying dura mater and covered less than two-thirds of the laminectomy sites (arrows)

Fibroblast count results

Fibroblast counts were 197.5 (190 - 200.5), 181 (173.5 - 188.5), 195.5 (193 - 196.5), and 171 (169.5 - 175.5), respectively, in groups C, S, D, and SD. These results were significantly different between the groups (P<0.001) (Figure 3A, 3B, 3C and 3D) (Table 2).

Immunohistochemistry results

The VEGF levels were evaluated in each group according to strong, moderate, and weak staining levels. Weak (Figure 4A) and moderate (Figure 4B) levels were observed in four and three rats in Groups C and S, respectively. Weak, moderate, and strong (Figure 4C) staining levels were observed in two, three, and two rats in Group D, respectively. Moderate and strong staining was observed in three and four rats in group SD, respectively. There was no statistically significant difference between the groups (P=0.068).

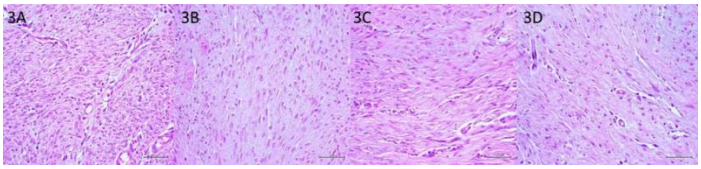

Figure 3: Fibroblast numbers of Control (3A), Spongostan (3B), local dexpanthenol (3C), and systemic dexpanthenol (3D) were expressed as number per counting area (400x).

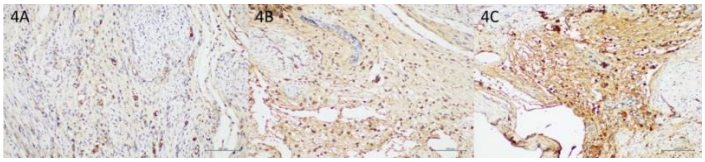

Figure 4: Vascular endothelial growth factor (VEGF) immunostaining of the epidural fibrosis in the laminectomy sites. (4A) Weak, (4B) moderate, and (4C) strong staining (200x magnification).

Hydroxyproline results

Hydroxyproline values were found as 1.556 (1.081) μgHyp/mg wet weight, 0.701 (0.309) μgHyp/mg wet weight, 1.520 (0.346) μgHyp/mg wet weight, and 0.414 (0.104) μgHyp/mg wet weight, respectively, in groups C, S, D, and SD, which significantly differed *(P*=0.002) (Table 3).

Table 1: The grades of epidural fibrosis (EF) according to the He et al. [16]

	C (n=7)	S (n=7)	D (n=7)	SD (n=7)	*P*-value
EF grade	3 (3-3)a	2 (2-3)b,c	3 (2-3)a,b	2(2-2)b,c	0.025

Descriptive statistics for the variables were given as median (25.-75. percentile). Similar letters in the same line represent similarity, and different letters represent dissimilarity.

Table 2: Fibroblast counting in epidural fibrosis tissue

	C (n=7)	S (n=7)	D (n=7)	SD (n=7)	*P*-value
Fibroblast Counting	197.5 (190-200.5)^{a}	181 (173.5-188.5)^{b,c}	195.5 (193-196.5)^{a,b}	171 (169.5-175.5)^{c}	<0.001

Descriptive statistics for the variables were given as median (25.-75. percentile). Similar letters in the same line represent similarity, and different letters represent dissimilarity.

Table 3: Hydroxyproline content of the groups

	C (n=7)	S (n=7)	D (n=7)	SD (n=7)	*P*-value
Hydroxyproline Content	1.556 (1.081)^{a,b,c,d}	0.701 (0.309)^{b}	1.520 (0.346)^{c}	0.414 (0.104)^{b,d}	0.002

Descriptive statistics on variables were given as mean (standard deviation). Similar letters in the same line represent similarity, and different letters represent dissimilarity.

Discussion

The effects of local and systemic administration of dexpanthenol on EF grade were demonstrated in this study. According to our results, EF grades decreased after systemic administration of dexpanthenol compared with local administration and control group. The decrease in hydroxyproline levels in group SD was a factor which reduced EF grades. However, many factors may be responsible for these results.

In the literature, a study conducted by Ermis et al. [13] using a bleomycin-induced lung fibrosis model showed that leukocyte infiltration and lung fibrosis rates were decreased in the dexpanthenol and bleomycin-treated group compared with the group treated with bleomycin alone. They also reported that this effect could be attributed to the combined anti-inflammatory and antioxidant effects of dexpanthenol [13]. Previous studies supported the idea that dexpanthenol may have an effect in decreasing EF formation. In the literature, various studies have shown that decreases in the pro-inflammatory cytokines TNF-α, IL-6, and transforming growth factor β particularly, might decrease the proliferation and differentiation of fibroblasts and EF [1,18-20]. However, in our study, local dexpanthenol was shown to increase the formation of EF, whereas systemic administration decreased it. In fact, our study results are not contrary to those in the literature because there are numerous possible explanations for these results. One of the probable causes is the method of administration. In a study by Ulger et al. [21] which investigated the effects of the local application of nebivolol and dexpanthenol on wound healing, it was reported that although this administration significantly decreased inflammation compared with the control group, fibrosis in the dexpanthenol-treated group was higher. The same study also reported that granulation and angiogenesis rates did not differ significantly between the control and dexpanthenol groups [21]. The study emphasized that local administration of dexpanthenol might increase fibrosis by supporting tissue fibroblasts despite its anti-inflammatory effects. The results of our study support those of Ulger et al. [21], because we have shown that local administration of dexpanthenol increases the level of hydroxyproline and fibroblast cell count in the laminectomy area. Moreover, in the previous study, authors reported that hydroxyproline levels indicate the amount of collagen and increased hydroxyproline levels are considered one of the most important signs in formation of EF. Therefore, our opinion is that increased level of hydroxyproline related to the local application of dexpanthenol might cause increased EF grade.

Another reason may be that the dose of dexpanthenol is responsible for the observed results. A previous study, conducted by Yardimci et al. [22], who showed that the administration of substantial amounts, even at the same dosage, might induce more obvious anti-fibrotic activity, supports this view. In our study, we also showed that the administration of substantial amounts of dexpanthenol caused a decrease in the level of hydroxyproline and fibroblast cell count in EF tissue. Our opinion is that when dexpanthenol is systemically administered more than once, it may be effective not only at a single stage of inflammation but at many stages at once. This is because a decrease in hydroxyproline levels suggests that inflammation and proliferation phases can be affected. The proliferation phase may be affected indirectly because fibroblasts, which are altered due to decreased pro-inflammatory cytokines, are more prominent in the proliferation phases of the inflammation. In the literature, previous studies have also reported that decreasing tumor necrosis alpha (TNF-α), interleukin (IL)-6, and transforming growth factor β particularly, might decrease the proliferation and differentiation of fibroblasts and EF [1,18-20]. In addition to this, authors have stated that the use of dexpanthenol decreased TNF-α and IL-1β levels, neutrophil flow, and IL-6 synthesis [15,23].

Limitations

Although we showed for the first time that administration of systemic dexpanthenol had a negative effect of formation of epidural fibrosis, the study had some limitations. Firstly, different doses of dexpanthenol were not administered. Secondly, the molecular mechanisms were not investigated to reveal the action mechanism of dexpanthenol. Third, our sample size was small.

Conclusion

We demonstrated that dexpanthenol should be given more than once for its anti-inflammatory effect, for which the decrease of hydroxyproline and fibroblast cell count may be responsible. Also, dexpanthenol may be effective at various stages of inflammation and a potential agent for reducing EF.

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Increased post-voiding residue and recurrent acute epididymitis: Are they causally related?

Rezidü idrar miktarı ve tekrarlayan akut epididimit arasında sebep-sonuç ilişkisi var mı?

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Abstract

Aim: It is known that recurrent urinary tract infection (rUTI) is associated with increased post-voiding residue (PVR), however, the same relationship is yet to be shown in adults for recurrent acute epididymitis. To the best of our knowledge, there are inadequate studies on this subject and they are mainly focused on the retrograde flow of the infected urine into the ejaculatory duct in terms of pathophysiology. In this study, we aimed to evaluate the causal relationship between recurrent acute epididymitis and increased post-voiding residue.

Methods: In this retrospective cohort study, the data of 388 patients who received treatment for epididymitis in our polyclinic between 2015 and 2018 were evaluated to determine that 72 were examined for lower urinary tract symptoms (LUTS). Age, PSA level, Qmax value, uroflowmetric pattern, post-voiding residual volume, International Prostate Symptom Scores (IPSS), and prostate volumes were recorded. Patients were divided into acute (n=38, Group 1) and recurrent acute (n=34, Group 2) epididymitis groups for analysis. The patients in Group 2 were treated for epididymitis at least two times in the last six months or thrice a year. The patients in Group 1 were treated only once in a year. Chi-square (Fisher's exact test) and Student's t-test were used to compare categorical variables. A value of $P<0.05$ was considered the threshold of statistical significance.

Results: Age, PSA level, prostate volume, IPSS score, and peak flow did not significantly differ between the two groups. However, there were significant differences in terms of post-voiding residual urine volumes ($P=0.029$). The mean post-voiding residual volumes in patients with acute and recurrent acute epididymitis were 47.3 (16.2) ml and 178.2 (23.6) ml, respectively.

Conclusion: There is a relationship between increased post-voiding residual urine volume and recurrent acute epididymitis. Patients who present with recurrent acute epididymitis should be scanned for urological pathologies which may cause increased PVR.

Keywords: Epididymitis, Post-voiding residue

Öz

Amaç: Tekrarlayan idrar yolu enfeksiyonunun artmış rezidü idrar ile ilişkili olduğu biliniyor. Yetişkinlerde tekrarlayan akut epididimit için ise böyle bir durum henüz gösterilmemiş. Bildiğimiz kadarıyla bu konuyla ilgili çok fazla çalışma yok ve bu yapılan kısıtlı sayıdaki çalışmaların çoğunda etyolojide ejekülatör kanala retrograd idrar akışı üzerinde durulmuş. Bu çalışmada tekrarlayan akut epididimit ile artmış rezidü idrar (PVR) arasındaki olası nedensel ilişkiyi incelemeyi amaçladık.

Yöntemler: Çalışma retrospektif kohort olarak tasarlandı. 2015-2018 yılları arasında polikliniğimizde epididimit tedavisi gören 388 hastanın verileri retrospektif olarak incelendi. Bu hastaların 72'si aynı zamanda alt üriner sistem semptomları (AÜSS) açısından da incelenmişti. Yaş, PSA düzeyi, Qmax değeri, üroflowmetrik patern, işeme sonrası rezidüel hacim, IPSS Skorları ve prostat hacimleri kaydedildi. Hastalar, dahil edilme kriterlerine göre akut ve tekrarlayan akut epididimiti olanlar olarak iki gruba ayrıldı. Analiz için hastalar akut (n=38, Grup 1) ve rekürren akut (n=34, Grup 2) epididimit olarak iki gruba ayrıldı. Grup 2'deki hastalar epididimit için son altı ayda iki veya son bir yılda üç defa tedavi edildi. Grup 1'deki hastalar yılda sadece 1 kez tedavi edildi. Kategorik değişkenleri karşılaştırmak için ki-kare (Fisher's exact test) ve Student t-testi kullanıldı. $P<0.05$ değeri istatistiksel anlamlılık eşiği olarak kabul edildi.

Bulgular: Yaş, PSA düzeyi, prostat hacmi, IPSS skoru ve pik akım iki grup arasında anlamlı farklılık göstermedi. Bununla birlikte, işeme sonrası rezidüel idrar hacimleri açısından anlamlı farklılıklar vardı ($P=0.029$). Akut ve rekürren akut epididimitli hastalarda ortalama işeme sonrası rezidüel hacimler sırasıyla 47.3 (16.2) ml ve 178.2 (23.6) ml idi.

Sonuç: Artan işeme sonrası rezidüel idrar hacmi ile tekrarlayan akut epididimit arasında bir sebep-sonuç ilişkisi vardır. Tekrarlayan akut epididimit ile başvuran hastalar, artmış PVR'ye neden olabilecek ürolojik patolojiler için taranmalıdır.

Anahtar kelimeler: Epididimit, Artmış rezidü idrar

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Introduction

Epididymitis is an inflammation of the coiled tube (epididymis) at the back of the testicle that stores and carries sperm. Its incidence ranges from 25 to 65 cases per 10.000 adult males per year [1]. Signs and symptoms of epididymitis might include a swollen, hyperemic, or warm scrotum, scrotal pain, tenderness usually on one side, painful urination, an urgent or frequent need to urinate, and less commonly, fever. It can be acute, chronic, or recurrent [1,2]. Acute epididymitis is a clinical syndrome consisting of pain, swelling, and inflammation of the epididymis that lasts for less than 3 months. Chronic epididymitis is characterized by symptoms of discomfort and/or pain in the scrotum, testicle, or epididymis for more than 3 months [2]. Recurrent epididymitis considered as chronic epididymitis, but according to some authors, it is a clinical condition involving pain, swelling, hyperemic and warm scrotum, tenderness, fever lasting for less than 3 months like acute epididymitis, that is treated with antibiotics but can recur due to urological pathologies and anomalies after clinical recovery [7-9]. The pathophysiology of epididymitis remains unclear, although it is postulated to occur secondary to retrograde flow of infected urine into the ejaculatory duct [2]. Chronic infectious epididymitis is most frequently seen in conditions associated with a granulomatous reaction. Mycobacterium tuberculosis (TB) is the most common granulomatous disease affecting the epididymis and should be suspected, especially in men with a known history of or recent exposure to TB [3]. The most common isolated pathogens are C. trachomatis and N. gonorrhoeae along with sexually and non-sexually transmitted pathogens [4,5]. Non-sexually transmitted infectious causes of acute epididymitis are uncommon and include obstructive urinary disease, urinary tract surgery, prostate biopsy, urinary tract catheterization, systemic disease, and/or immunosuppression [5]. Epididymitis is diagnosed with clinical findings, but urine dipstick test, urine culture, urethral smear, and scrotal ultrasonography are helpful [5]. The treatment of epididymitis includes bed rest, scrotal elevation, analgesics, nonsteroidal anti-inflammatory drugs, empirical antibiotics, correcting the underlying cause, and surgery [1,6]. To the best of our knowledge, there are a few published studies about the underlying causes of recurrent acute epididymitis in adults. Due to inadequate studies on this subject and the fact that authors are mainly focused on the retrograde flow of the infected urine into the ejaculatory duct in pathophysiology, we aimed to determine underlying causes of recurrent acute epididymitis and its relationship with post-voiding residual urine volume in order to choose the best treatment for patients and avoid epididymectomy.

Materials and methods

In this retrospective cohort study, 388 patients treated for epididymitis between June 2015 and May 2018 were evaluated. Patients who were older than 18 years of age were all included in this study. All patients had low urinary tract symptoms and were diagnosed by ultrasonography, urinalysis, and physical examination. All patients had swollen, hyperemic or warm scrotums, testicle pain, tenderness, and positive urine culture for bacteria or fungi. The patients in Group 2 (recurrent acute epididymitis, n=34) were treated for epididymitis at least two times in six months or thrice a year. The patients in Group 1 (acute epididymitis, n=38) were treated only once in a year. Patients younger 18 years, those with chronic epididymitis, sexually transmitted epididymitis, and negative urine cultures were excluded from the study. A total of 72 patients were included based on the inclusion and diagnostic criteria, thirty-four of which were treated for epididymitis at least two times in six months or three times in a year (Group 2). There is no definitive description of recurrent acute epididymitis. Therefore, we classified the patients into two groups based on the definition of recurrent urinary tract infection in the EAU guideline [13,14]: Acute epididymitis (n=38, Group 1) and recurrent acute epididymitis (n=34, Group 2). Age, PSA level, Q_{max} value, uroflowmetric pattern, post-voiding residual urine volume, IPSS scores, prostate volume, and underlying causes were recorded.

Statistical analysis

Statistical analysis was performed with SPSS v25.0 for Windows (IBM Corp. Released 2018). Chi-square (Fisher's exact test) and Student's t-test were used to compare categorical variables. $P<0.05$ was considered statistically significant.

Results

The mean ages of the first and second groups were 56.2 (15.2) years and 68.3 (14.6) years, respectively. The incidence of recurrent acute epididymitis was insignificantly higher in the older group ($P=0.29$). Epididymitis is more common between the ages of 18-50 [12]. The reason for the higher age average is that only patients with lower urinary tract symptoms were included in our study, who were all above 40 years of age. Mean PSA levels were 3.67 (1.26) and 3.09 (2.11) ng/mL in the first and second groups, respectively, which were similar ($P=0.47$). There were no significant differences in terms of prostate volumes, IPSS scores, and peak flow between the two groups ($P=0.26$, $P=0.18$, $P=0.21$), although mean prostate volume and IPSS score were greater in recurrent acute epididymitis patient group, in which all patients had severe LUTS. Most patients had normal voiding patterns and Q_{max} values were lower in patients with recurrent acute epididymitis. The mean post-voiding residual volumes in patients with acute and recurrent acute epididymitis were 47.3 (16.2) ml and 178.2 (23.6) ml, respectively ($P=0.029$). In addition, there were more underlying causes in patients with recurrent acute epididymitis ($P=0.039$): 1 patient had undergone transurethral resection of the prostate (TURP), 2 patients had undergone hypospadias repair and 1 patient had urethritis secondary to urethral stricture. 5 patients had neurogenic bladder, 11 patients had benign prostate hyperplasia and 6 patients had prostatic surgeries, such as transurethral electrovaporization of the prostate, TURP, or biopsy. The results and the underlying causes are summarized in Table 1 and Figure 1, respectively.

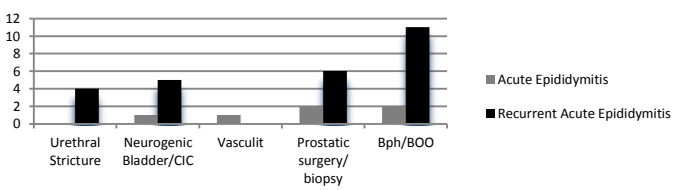

Figure 1: Underlying causes of AE and RAE (p=0.039) (AE: Acute Epididymitis, RAE: Recurrent acute epididymitis)

Table 1: Characteristics of the acute and recurrent group

Parameters	Acute epididymitis (n=38) Mean	n	Recurrent acute epididymitis (n=34) Mean	n	*P*-value
Age	56.2(15.2)		68.3(14.6)		0.29
PSA Level (ng/mL)	3.67(1.26)		3.09(2.11)		0.47
Prostate volume (mL)	44.41(23.1)		61.33(21.95)		0.26
IPSS	8.1(4.7)		13.7(6.23)		0.18
Mild=0-7		16		12	
Moderate=8-19		19		12	
Severe=20-35		3		10	
Peak Flow (Q max)	18.2(11.1)		13.2(9.6)		0.21
Normal >15		30		21	
Obstructive<15		8		13	
Post voiding residual urine volume (mL)	47.3(16.2)		178.2(23.6)		0.029
Underlying causes		6		26	0.039
Urethral stricture		-		4	
Neurogenic bladder/CIC		1		5	
Vasculitis		1		-	
Prostatic surgery		1		5	
Following prostate biopsy		1		1	
BPH/BOO		2		11	

BOO: Bladder outlet obstruction, CIC: Clear intermittent catheterization, BPH: Benign prostatic hyperplasia, n: Number of patients

Discussion

Residual urine is defined as the volume of urine left in the bladder following urination. It is measured by the help of a catheter or ultrasonography. Catheterization allows for safer evaluation of PVR, however, it is time-consuming and carries complication risks, such as urethral injury, urinary tract infection and urethrorrhagia. Ultrasonographic examination of the bladder is a noninvasive, basic and easily-accessible method that requires a well-trained radiologist. However, its results depend on the performer, and it does not provide a definite result for PVR. Normal PVR urine volume is ≤50 ml, but there is no consensus on cut-off values. Increased PVR volume indicates problems with the emptying of the bladder. In men, it may be caused by various pathologies, such as benign prostate hyperplasia, bladder outlet obstruction, urethral or meatal stricture, underactive bladder, and neurogenic bladder [17]. The PVR volume significantly affects the quality of life due to the fact that increased PVR may reduce functional bladder capacity and cause symptoms of the lower urinary tract [21]. Current studies have shown that it is associated with many complications ranging from a simple lower urinary tract symptom to acute and chronic renal failure [24]. It is also reportedly associated with recurrent urinary tract infections. Dray et al. [23] reported that increased post-void urine residue was found to aggravate incontinence, as measured by the M-ISI (Michigan Incontinence Symptom Index) score and increase the risk of recurrent UTIs in selected MS (Multiple sclerosis) patients with LUTS. A PVR volume greater than 50 ml is considered an independent risk factor for rUTIs [18]. Some studies have shown that clinically asymptomatic adult men with a PVR of 180 ml or greater are at higher risk for bacteriuria [19]. High post-void residual (PVR) volumes can function as a reservoir for microorganisms because the infected urine cannot be emptied completely [20]. The pathophysiology of both acute and recurrent acute epididymitis remains unclear, but the theory of ‘‘retrograde flow of infected urine into the ejaculatory duct’’ is the most current one. All these studies and the pathophysiology of epididymitis suggest that there may be a relationship between the increased amount of residual urine and the development or recurrence of epididymitis. Some congenital abnormalities and low urinary tract pathologies have been associated with recurrent acute epididymitis in pediatric populations [7-10]. In adults, there are a few studies on recurrent acute epididymitis [15,16]. Hoeppner et al. [16] reported that among 336 men aged over 60 years presenting with acute/recurrent acute epididymitis, lower urinary tract obstruction was identified in 187(56%) patients, which was caused by benign prostate hyperplasia, prostate cancer, and/or urethral stricture. Our study is important for the following two reasons: First of all, to the best of our knowledge, there is no sufficient study to date on recurrent acute epididymitis and secondly, we found a relationship between residual urine volume and recurrent acute epididymitis, which confirms the theory of “retrograde flow of infected urine into the ejaculatory duct” in pathophysiology.

Limitations

However, our study has some limitations: Some data were missing due to its retrospective nature. Residual urine volume was measured only in patients with low urinary tract system symptoms, which decreased our sample size. Some of the patients in Group 1 may have had acute epididymitis attacks more than once, and it may not be recorded in the hospital registry, which may have led to statistically significant differences. It is not known whether the patients in Group 2 were previously treated for the pathologies leading to increased residual urine volume.

Conclusion

Based on our study, we believe that solving the underlying pathology which increases PVR will be the best treatment choice in patients with recurrent acute epididymitis. It is possible that microorganisms migrate from the bladder due to high post-voiding residual urine increase in patients with recurrent acute epididymitis. Evaluating the PSA level, prostate volume, IPSS, peak flow and post-voiding residual volume in patients with recurrent acute epididymitis will determine the correct approach to treatment, even if there are no lower urinary tract symptoms. Further, prospective studies with large patient series are required to shed light on the issue.

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Ovarian reserve testing in the prediction of recurrent pregnancy loss

Tekrarlayan gebelik kaybını öngörmede over rezerv testlerinin kullanılması

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Abstract

Aim: Approximately 1-2% of reproductive women have faced recurrent pregnancy loss (RPL). Ovarian reserve testing in the prediction of recurrent pregnancy loss is not usually performed. In this study, we aim to evaluate whether there were any differences between patients with and without a history of recurrent pregnancy loss (RPL) with regards to anti-Mullerian hormone (AMH), follicle stimulating hormone (FSH), luteinizing hormone (Lh), estradiol (E2) levels and basal follicle count.

Methods: This case-control study was conducted between 1 January 2013 and 1 January 2015 in the Gynecology and Obstetrics Clinic of Adana Numune Training and Research Hospital. A total of 370 patients aged 17-37 years with a diagnosis of RPL during that 2-year period were contacted by telephone. Further evaluation was made of 40 patients who met the study criteria and gave verbal consent. Patients were called to the Gynecology Polyclinic for assessment on the 3rd day of their menstrual cycle, and a control group was formed of 40 patients with similar demographic characteristics who were referred to the Gynecology Polyclinic and met the study criteria.

Results: The mean basal follicle count was determined as 9.4 (2.7) in the study group and 8.9 (2.5) in the control group (P=0.092). The mean AMH values in the RPL and control groups were 3.50 (1.92) ng/mL and 3.66 (2.14) ng/mL, respectively (P=0.718). The mean FSH values in the RPL and control groups were 6.77 (1.87) mIU/mL and 7.01 (1.90) mIU/mL, respectively (P=0.494). Mean LH values were measured as 5.6 (1.8) mIU/mL in the study group and 4.9 (1.7) mIU/mL in the control group. Mean E2 values were 87.7 (83.9) pg/mL and 48.4 (27.9) pg/mL in the study and control groups, respectively.

Conclusion: While no difference was found between the RPL and control groups in respect of AMH and FSH values in the ovarian reserve tests, the basal follicle count of the patients with recurrent pregnancy loss was found lower than that of the control group.

Keywords: Recurrent pregnancy loss, Ovarian reserve, AMH, Basal follicle count, FSH

Öz

Amaç: Üreme çağındaki kadınlarının yaklaşık %1-2'si tekrarlayan gebelik kaybı (RPL) ile karşı karşıyadır. Tekrarlayan gebelik kaybının öngörülmesinde yumurtalık rezerv testi genellikle yapılmaz. Bu çalışmamızda Antimüllerian hormon, follikül stimulant hormon, Lüteinizan hormon, Estradiol ve Bazal follikül sayısının tekrarlayan gebelik kabı olan ve olmayan hastalar arasında farklı olup olmadığının değerlendirilmesi amaçlanmıştır.

Yöntemler: 2 yıllık sürede tekrarlayan gebelik kaybı tanısı konulan, yaşları 17-37 yaş arası 370 hasta telefonla aranarak ayrıntılı sorgulama sonucu çalışma kriterlerine uyan ve sözlü onamları alınan 40 hasta tekrar değerlendirilmek üzere mensrüel siklusun 3. günü jinekoloji polikiniğe davet edildi. Çalışma grubu olarak alınan hastalarla aynı gün jinekoloji polikliniğine başvuran benzer demoğrafik özellikteki çalışma kriterlerine uyan 40 hasta kontrol grubu olarak oluşturuldu.

Bulgular: Tekrarlayan gebelik kaybı olan grupta ortalama bazal follikül sayısı 9,4 (2,7) adet, kontrol grubunda 8,9 (2,5) adet olarak ölçüldü. (P=0,092). Tekrarlayan gebelik kaybı olan grupta ortalama AMH değeri 3,50 (1.92) ng/mL, kontrol grubunda 3,66 (2,14) ng/mL, (P=0,718), FSH değeri tekrarlayan düşük yapan grupta 6,77 (1,87) mIU/mL, kontrol grubunda 7,01 (1,29) mIU/mL (P=0,494), LH değeri sırasıyla 5,6 (1,8) mIU/mL ve 4,9 (1,7) mIU/mL, E2 değeri sırasıyla 87,7 (83,9) pg/mL, 48,4 (27,9) pg/mL olarak ölçüldü.

Sonuç: Over rezevr testlerinden tekrarlayan gebelik kaybı olan grup ile kontrol grubu arasında AMH, FSH değerleri arasında fark bulunmazken, tekrarlayan gebelik kaybı olan grupta estradiol seviyesi daha yüksek, bazal follikül sayısı ise daha düşük bulundu.

Anahtar kelimeler: Tekrarlayan gebelik kaybı, Over rezervi, AMH, Bazal follikül sayısı, FSH

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Introduction

The terminology of recurrent pregnancy loss (RPL) has still not been fully defined. To remove this confusion, in 2005, The European Society of Human Reproduction and Embryology (ESHRE) recommended that the definition of RPL be accepted as 3 or more consecutive pregnancies lost before the 22nd week [1]. Several factors have been held responsible in the etiopathogenesis.

The factors which are primarily thought to be responsible are maternal and paternal chromosomal anomalies (this risk is greater in cases of marital consanguinity), auto-antibodies, natural killer cell dysfunctions, abnormal HLA-G expression, hereditary or acquired thrombophilia, thyroid auto-antibodies, polycystic ovary disease (PCOD), sperm DNA fragmentation, impaired endometrial receptivity, uterine malformations and lifestyle-associated problems such as excessive alcohol consumption or obesity [2].

Anti-Mullerian hormone (AMH), glycoprotein in structure, prevents the development of paramesonephric canals (Mullerian canals) in a male embryo and is encoded by the AMH gene in the transforming growth factor (TGF-beta) family. In the female fetus, it initiates the proliferation of granulosa cells of the preantral and small antral follicles towards the end of fetal life and particularly postnatally [3].

As females age, AMH within the follicle decreases along with AMH serum concentrations. Aging cases a gradual deterioration in oocyte quality. A stronger correlation is shown of oocyte quality and basal follicle count compared to E2 and FSH in this drop in AMH levels [4].

The formation of maternal non-disjunctions during oogenesis and the emergence of chromosomal abnormalities in the embryo which have developed as a result of impairments in the spindles may cause embryo and fetus losses [5,6]. In parallel with a decreasing ovarian reserve, the increasing rate of aneuploidy in oocytes has been shown to cause miscarriages as well as reduced fertility [7-9].

The aim of this study was to reveal whether or not there was a relationship between falling AMH levels due to a diminishing ovarian reserve and recurrent pregnancy loss. It was thought that different results may emerge as few previous studies have been made with selection and randomization of the study groups, and control groups have included very high AMH values such as in PCOD.

Materials and methods

This prospective case-control study was conducted between 1 January 2013 and 1 January 2015 in the Gynecology and Obstetrics Clinic of Adana Numune Training and Research Hospital. Patients aged 17-37 years with a diagnosis of recurrent pregnancy loss during that 2-year period were included as the study group, and contacted by telephone and recalled to the Gynecology Outpatient clinic for assessment on the 3rd day of their menstrual cycles. Of the total 370 patients with RPL in the previous 2 years, 158 presented at the outpatient clinic. A detailed anamnesis was taken from each patient. The previous tests were recorded and family history was questioned. A detailed gynecological examination was performed with transvaginal ultrasonography using a 5-7 MHz vaginal probe (TV-USG Mindray, DC-7 Nanshan Shenzhen P.R. China).

On day 3 of the menstrual cycle, between 08:00 and 12:00, a fasting venous blood sample was withdrawn into a sterile tube containing no other material (Becton-Dickinson, Vacutainer, Z). After waiting for 30 minutes, serum was separated by centrifugation at 2000 rpm. Analysis was made with chemoluminescence immunoassay method for endocrine tests such as FSH, LH, PRL, T3, T4, TSH (thyroid auto-antibodies were requested from those with impaired thyroid tests) (Roche Cobas 6000 e601, Roche Diagnostics, Mannheim, Germany).

A blood sample was concurrently obtained from all patients for AMH measurement. Serum was separated by centrifugation at 2000 rpm then stored at -20° until analysis. The AMH concentration was measured with the ELIZA enzyme immunoassay method (Immunotech, Beckman Coulter, Marseilles, France). Antiphospholipid antibody, HgbA1c (glycolised hemoglobin), liver function tests, hemogram and spermiogram tests were performed.

Exclusion criteria from the study included patients who were pregnant, smoked cigarettes or drank alcohol, those with marital consanguinity, with abnormal karyotype analyses, abnormal findings on trans-vaginal ultrasonography (an appearance consistent with endometrioma, hydrosalpinx, etc), a previous diagnosis of endometriosis, with partners with abnormal spermiograms, connective tissue or immunological diseases, systemic diseases (diabetes mellitus, hypertension, PCOD – according to the Rotterdam criteria) or other endocrinological disorders, those without low values in 3 or more of the ESHRE criteria, those with an abnormal finding on hysterosalpingography (HSG), body mass index (BMI) >30, a history of gynecological surgery or if consent was not given for participation in the study.

The control group consisted of patients of similar age and demographic characteristics who attended the Gynecology outpatient and had no history of pregnancy loss, did not have PCOD and had a regular menstrual cycle. Fasting blood samples were drawn from both the patient and control groups in the morning of the 3rd day of the menstrual cycle.

Approval for the study was granted by the Ethics Committee of Adana Numune Training and Research Hospital. After detailed explanations, informed consent was obtained from all participants. In the control group, a record was made for each participant of age, menstrual status, number of pregnancy losses, smoking habits and alcohol habits. BMI was calculated from the height and weight values.

Forty patients and 40 control groups subjects who all met the study criteria were evaluated.

Statistical analysis

Statistical analysis was performed with Statistics Package for Social Sciences (SPSS) [SPSS 21 Inc., Chicago, IL, USA] software. Independent groups were compared with the Independent samples t-test. For non-parametric data, the Mann Whitney U-test and the Chi-square test were used. A value of $P < 0.05$ was considered statistically significant.

Results

The study included 40 patients with recurrent pregnancy loss (RPL) and a control group of 40 healthy volunteers. The mean age was 30.2 (4.5) years in the study group and 28.3 (5.7) years in the control group. The mean BMI value was calculated as 22.6 (1.9) in the study group and 21.7(1.7) in the control group. The number of pregnancy losses was recorded as 3 in 27 patients, 4 in 9 patients, 5 in 3 patients and 6 in 1 patient. None of the study or control group subjects smoked cigarettes or consumed alcohol. The demographic characteristics and the laboratory findings of both groups are shown in Table 1.

The mean basal follicle count was measured as 9.4 (2.7) in the study group and 8.9 (2.5) in the control group, which were similar (P=0.092).

The mean AMH value was determined as 3.50 (1.92) ng/mL in the study group and 3.66 (2.1) ng/mL in the control group (P=0.718). The mean FSH value was determined as 6.77 (1.87) mIU/mL in the study group and 7.01 (1.29) mIU/mL in the control group (P=0.494). The distribution of the basal follicle count and AMH values is shown in Figure 1.

Table 1: Distribution of the demographic and laboratory values of both groups

	Control group n=40	Study group n=40	Total	*P*-value
Age (years)	28.3 (5.7)	30.2 (1.9)	29.3 (5.2)	0.149
AMH Level (ng/mL)	3.66 (2.1)	3.50 (1.9)	3.6 (2.0)	0.718
FSH Level (mIU/mL)	7.0 (1.3)	6.7 (1.8)	6.9 (1.6)	0.494
LH Level (mIU/mL)	4.5 (1.7)	5.6 (1.8)	5.3 (1.8)	0.607
E2 Level (pg/mL)	48.4 (27.9)	87.7 (89.9)	68.0 (65.2)	<0.001
Basal follicle count	9.4 (2.8)	8.9 (2.5)	9.2 (2.6)	0.092
BMI	21.7 (1.7)	22.6 (1.9)	22.2 (1.8)	0.227

Data as presented mean (SD), SD: Standard deviation, BMI: Body mass index

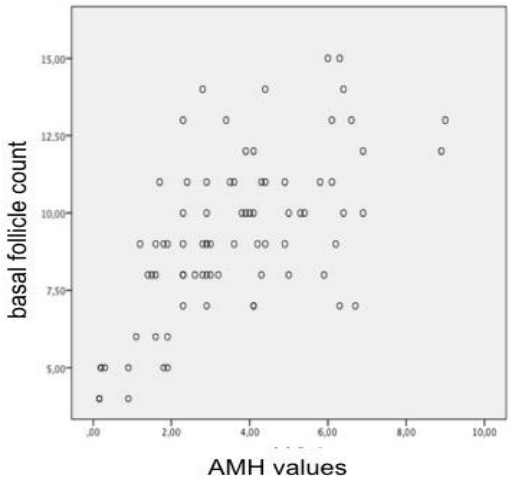

Figure 1: Distribution of basal follicle count and AMH values

Discussion

Reduced rates of becoming pregnant, together with increased rates of the birth of infants with anomalies and rates of miscarriage are seen with increasing age and decreasing ovarian reserve [10,11]. The probable reason for this is thought to be the diminished quality of the eggs remaining in the reduced ovarian reserve associated with increasing age [12]. The extended exposure of eggs to toxic mutant agents due to increased maternal age may be the cause of a deterioration in quality due to DNA damage and the formation of DNA methylation [13].

Basal follicle count and 3rd day FSH values have been used for many years in the determination of ovarian reserve. AMH measurement, which is strongly correlated with antral follicle count, has started to be used routinely in many clinics at the start of IVF treatment besides the determination of ovarian reserve, especially in patients with PCOD and before endometrioma surgery [14]. As AMH measurement can be made on any day of the cycle, it has the advantage of facilitating analysis in patients where the ovarian reserve is evaluated. Previous studies related to AMH have generally been conducted on infertile patient groups [4].

Most studies of patients with a diagnosis of endometriosis have included a pre and post- surgical evaluation of ovarian reserve. In studies by Chang et al, the relationship between laparoscopic cystectomy and ovarian reserve was investigated with 3D-USG evaluation of the ovarian volume and AMH levels. A decrease in serum AMH levels on the 7th postoperative day was determined in both groups of patients with ovarian cysts and no endometrioma. At the 3rd postoperative month, this fall in the AMH levels had increased to 65% of the preoperative level. However, in that study, no detailed information was available with respect to the history of pregnancy loss [15].

The vast majority of these cases of RPL may be due to reasons such as defective chromosomes carried by the mother or father, genetic damage occurring in the formation of the embryo, maternal metabolic or endocrine diseases, maternal hereditary or acquired thrombophilic diseases, functional or structural defects in the uterus or endometrium or maternal immune disorders. Despite a comprehensive investigation of patients, the etiology of recurrent miscarriage is not identified in 50% of cases [16].

Furthermore, it has recently been shown that apoptosis mechanisms play a significant role in placental development and differentiation and tissue homeostasis. The interaction of Fas ligand (fasL) with decidual cells in the uterine wall internal layer was seen to provide down-regulation on the active leukocytes in that area. This adjusts the levels of cytokines such as TGF-beta and IL-10 and provides trophoblastic invasion in an appropriate form. Leukocyte infiltration into the implantation area occurs when this substance is absent or decreased in decidual cells [17].

It has been suggested in previous research that the inhibition of trophoblastic invasion with this mechanism could be a possible reason for recurrent pregnancy loss. Some studies have also implied that the decrease in bcl-2 expression and increase in bax expression in decidual cells could be the reason for RPL [18]. Studies on the subject will shed light on the molecular mechanism and treatment choices in RPL.

In patients with high AMH levels, a greater number of follicles can be obtained with gonadotropin stimulation in IVF treatment. The rate of success with live births can be predicted when the AMH cut-off level is taken as 7.5pmol/L (1.05ng/mL). A relationship has been shown between AMH and oocyte quality which is not affected by the age of the woman. This relationship has been shown to be particularly stronger with follicular fluid AMH level rather than serum AMH level [19].

Prior studies have suggested that low anti-Mullerian hormone level (≤0.4ng/mL) is associated with an increased risk of miscarriage [20]. In the current study, a statistically significant relationship was determined between AMH and the antral follicle count. Similarly, in another study, a statistically significant correlation was found between the AMH level and antral follicle count [21]. Studies have been conducted on the correlation of premature ovary ageing and RPL, the reduction shown in oocyte

number and quality with this ageing of the ovaries and the level of serum FSH as an indirect indicator of this disorder [22]. In a study where young oocytes were donated to patients over 40 years of age who were undergoing IVF treatment, the rate of pregnancy loss was determined as 11.1% in the follow-up of those who became pregnant. This finding suggests that maternal and paternal factors together could play a role in spontaneous abortion [23]. Despite the reporting of various data regarding Y-chromosome micro-deletions, sperm DNA fragmentation due to oxidative stress, sperm morphological impairments, reduced concentration and impaired sperm motility which could cause RPL, no clear findings have emerged of the role of sperm in unexplained RPL [24]. In the current study, as it was considered that impaired sperm parameters could be associated with the result, RPL patients with impaired spermiogram parameters were excluded from the study.

Previous results reveal that maternal diminished ovarian reserve and low AMH level is related with increased risk of embryo aneuploidy in women of advanced age [25]. On the contrary, recent studies concluded that maternal serum AMH levels may not be a marker for fetal aneuploidy and healthy fetuses [26].

In another study of the relationship of AMH level and pregnancy loss, one hundred fifty-five RPL patients were examined. In a univariate logistic regression, AMH value <1 ng/mL was found related to diminished likelihood of live birth (OR 0.38; CI 0.16-0.87, P=0.03) [27]. Although the AMH level of the RPL group was slightly lower, it was not statistically significant.

In our present study, estradiol levels were found to be statistically significant between the study and control groups. We believe that this difference should be investigated in large patient populations whether the difference is incidental or not from the study group.

Several studies have researched the correlation between AMH and other markers of ovarian reserve. The correlation of AMH and different sizes of antral follicle has been previously investigated and the strongest correlation was found to be between AMH and antral follicles >5-6 mm in size, with the correlation coefficient reported to be as low as 0.41. The lack of an international assay standard for AMH measurements may explain these different results [28].

Limitations

One of the limitations of the study was the relatively small number of patients and the fact that it was single-centered.

Conclusion

While a significant correlation was determined between RPL and antral follicle count, the fact that no significant correlation was determined between high serum FSH level and low serum AMH level suggests that several complex agents other than diminished ovarian reserve could play a role in recurrent pregnancy loss. There is a need for further studies including molecular and genetic examinations to clarify the etiopathogenesis.

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Imaging-guided percutaneous vertebral and paravertebral lesion biopsy: A single center experience

Görüntüleme eşliğinde perkütan vertebral ve paravertebral lezyon biyopsileri: Tek merkez deneyimi

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Abstract

Aim: Percutaneous needle biopsy has been used successfully in the diagnosis of vertebral, paravertebral and disc diseases in recent years as it is a minimally invasive, safe, and effective method. The aim of this study was to share our experience with imaging-guided percutaneous vertebral and paravertebral biopsies.

Methods: Images and data of 10 patients who underwent percutaneous vertebral and paravertebral biopsies between January 2018 and December 2019 were screened retrospectively through the hospital registry. The anatomical location of the lesion, guideline imaging method, number of samples taken, whether there were any complications after the procedure, needle diameter used, hemoglobin (Hb) values before and after the procedure were recorded.

Results: Among 10 patients included in the study, 3 (30%) were male and 7 (70%) were female. The mean age of the patients was 63.5 (8.6) years. Biopsies were performed under computerized tomography and ultrasound guidance in nine patients and one patient, respectively. The lesion was located at the thoracic level in 4 patients (40%) and at the lumbar level in 6 patients (60%). Two samples were obtained from all patients. There were no complications. The mean Hemoglobin (Hb) values before and after the procedure were 10 (1.1) mg/dL and 10.2 (1.4) mg/dL, respectively, which were similar (P=0.91). 18G needle was used in all patients.

Conclusion: Imaging-guided percutaneous vertebral and paravertebral biopsy is a safe and effective method which allows sampling for cytological, histological, and microbiological analysis. In the future, imaging techniques and biopsies will be increasingly used in the diagnosis of vertebral and paravertebral lesions.

Keywords: Percutaneous biopsy, Vertebrae, Imaging

Öz

Amaç: Bu çalışmadaki amacımız giderek daha yaygın olarak kullanılan görüntüleme eşliğindeki perkütan vertebral ve paravertebral biyopsi deneyimimizi paylaşmaktır.

Yöntemler: Ocak 2018 - Aralık 2019 tarihleri arasında görüntüleme eşliğinde perkütan vertebral ve paravertebral biyopsi yapılan toplam 10 hastaya ait görüntüler ve veriler hastane bilgi sistemi üzerinden retrospektif olarak tarandı. Lezyon anatomik lokasyonu, kılavuz görüntüleme yöntemi, örnek alınma sayısı, işlem sonrası komplikasyon olup olmadığı, kullanılan iğne çapı, işlem öncesi ve sonrası hemoglobin (Hb) değerleri kaydedildi.

Bulgular: Çalışmaya dahil edilen 10 hastadan 3'ü (%30) erkek, 7'si (%70) kadındı. Hastaların yaş ortalaması 63,5 (8,6) idi. 9 hastaya BT kılavuzluğunda, 1 hastaya ise USG kılavuzluğunda işlem yapılmıştı. 4 hastada (%40) lezyon torakal seviyede iken 6 hastada lezyon lomber seviyede idi (%60). Hastaların tamamından 2 kez örnek alınmıştı. Hiçbir hastada komplikasyon mevcut değildi. İşlem öncesi ortalama Hb değeri 10 (1,1) iken işlem sonrası Hb değeri 10,2 (1,4) olarak bulundu. İşlem öncesi ile sonrası saptanan Hb değerleri arasında anlamlı farklılık saptanmadı (P=0,91). Hastaların tamamında 18G iğne kullanıldı.

Sonuç: Görüntüleme eşliğinde perkütan vertebral ve paravertebral biyopsiler güvenli ve etkin bir yöntem olup sitolojik, histolojik ve mikrobiyolojik analiz için örnek alınmasına imkan sağlamaktadır. Gelecekte görüntüleme yöntemleri ve biyopsi sistemlerinde yaşanacak gelişmelerle birlikte görüntüleme eşliğinde yapılan biyopsiler vertebral ve paravertebral lezyonların tanısında giderek daha fazla tercih edilecektir.

Anahtar kelimeler: Perkütan biyopsi, Vertebra, Görüntüleme

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Introduction

Percutaneous needle biopsy has been used successfully in the diagnosis of vertebral, paravertebral and disc diseases in recent years as it is a minimally invasive, safe, and effective method. Thanks to the advances in needle technology from past to present, enough specimens have been obtained for pathological examination. In addition, multiple biopsies can be obtained from the same site thanks to the coaxial technique. Guiding imaging methods include fluoroscopy, computed tomography (CT), ultrasonography (US) and magnetic resonance imaging (MRI) [1].

Although advances in technology in imaging modalities increase lesion detectability, due to the low specificity of these methods, histological confirmation is still required in many uncertain cases [2]. In addition, the presence of specific gene mutations in metastatic lesions or the detection of microbial agents in infective pathologies change treatment plans and prognosis [3]. Advantages of percutaneous biopsies include lower morbidity and mortality rates compared to open surgical biopsies, being cheaper and taking shorter. In that regard, imaging-guided percutaneous biopsy should be the first method for tissue sampling. Percutaneous biopsy of bone lesions can be performed under the guidance of various imaging methods such as fluoroscopy, computed tomography (CT), ultrasonography (US) and magnetic resonance (MR). CT is the most widely used guide imaging method in spinal biopsies [4].

The aim of this study was to share our experience with imaging-guided percutaneous vertebral and paravertebral biopsies, which are more widely used every day.

Materials and methods

This retrospective cohort study has been approved by the local ethics committee (Sakarya University Faculty of Medicine Ethics Committee, 26/12/2019, E16091) and conducted in accordance with the Declaration of Helsinki (2000). Informed consent was waived because of the retrospective nature of the study.

Images and data of 10 patients who underwent percutaneous vertebral and paravertebral biopsy performed in the interventional radiology department of Sakarya University Training and Research Hospital between January 2018 and December 2019 with various indications were reviewed retrospectively on the hospital registry. The anatomical location of the lesion, guideline imaging method, number of samples taken, whether there were any complications after the procedure, needle diameter used, hemoglobin (Hb) values before and after the procedure were recorded.

Biopsies were performed under CT or US guidance. Modality selection was made according to the location of the lesion. Before the procedure, routine blood tests and bleeding parameters were requested from the patients. Patients were all monitored during the procedure. 2% prilocaine was used for local anesthesia (Citanest, AstraZeneca, Turkey).

CT-guided biopsies were performed on a 64-detector device (Aquilion64, Toshiba Medical Systems, Japan). Prebiopsy images were obtained after the patient was placed on the table in prone form. According to this image, radiopaque grid was placed on the patient's skin. Local anesthesia was administered after the site was cleaned. All biopsies were performed with the coaxial bone biopsy system (Ostycut, Bard Biopsy, USA). The specimens were fixed with formalin. US-guided biopsy was performed using a 3.5MHz convex probe with the Esaote MyLab 50 device (Esaote S.p.A, Italy). Biopsy was obtained with 18G fully automatic biopsy needle (Geotek, Turkey). The specimens were fixed with formalin.

Statistical analysis

MedCalc (Medcalc ver.12, Ostend, Belgium) was used for statistical analysis. Descriptive statistics were presented as median (minimum – maximum) and mean (standard deviation). Categorical variables were stated as frequencies and percentages. Correlation analysis was performed using the Pearson correlation coefficient. The Independent samples t-test was used for comparison of continuous variables with normal distribution in the Kolmogorov-Smirnov and Shapiro-Wilk tests. A value of $P<0.05$ was considered statistically significant.

Results

Among 10 patients included in the study, 3 (30%) were male and 7 (70%) were female. The mean age of the patients was 63.5 (8.6) years. Nine patients underwent CT-guided and 1 patient underwent US-guided percutaneous lesion biopsy (Figure 1, 2). The lesion was at the thoracic level in 4 patients (40%) and the lumbar level in 6 patients (60%). Two samples each were obtained from all patients. There were no procedure-related complications in any patient. The mean Hb values before and after the procedure were 10 (1.1), 10.2 (1.4) mg/dL, respectively, which were similar ($P=0.91$). 18G needle was used in all patients. The indication for biopsy was spondylodiscitis in 6 patients (60%) and metastasis in 4 patients (40%). Patient data are summarized in Table 1.

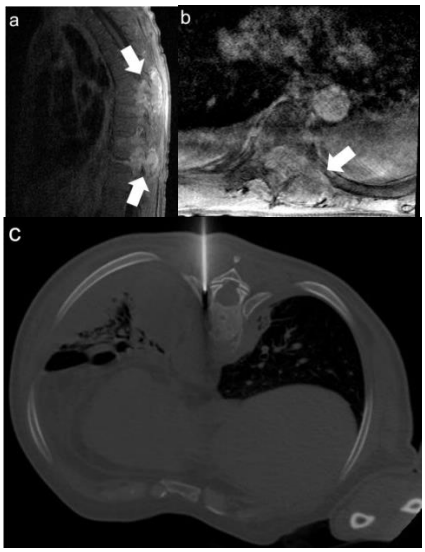

Figure 1: Sagittal (a) and axial (b) postcontrast fat-suppressed T1-weighted magnetic resonance images show contrast enhancement at two different levels (arrows). The same patient underwent computed tomography-guided percutaneous biopsy (c)

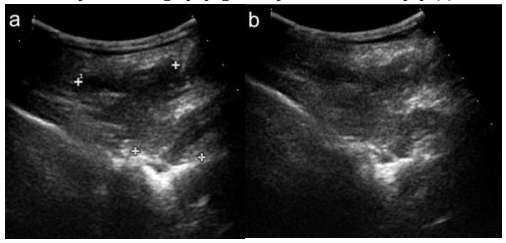

Figure 2: Ultrasonographic image of the paravertebral mass (a) and percutaneous biopsy procedure (b).

Table 1: Patient data

Patient no	Age	Gender	Modality	Location	Indication
1	67	F	CT	T10-11	Spondylodiscitis
2	54	F	CT	L4-5	Spondylodiscitis
3	56	F	CT	L3-4	Spondylodiscitis
4	80	F	CT	L2	Spondylodiscitis
5	62	F	CT	L3-4	Suspected metastasis
6	63	M	CT	T8-9	Suspected metastasis
7	66	M	CT	L3-4	Spondylodiscitis
8	79	F	CT	T12-L1	Spondylodiscitis
9	59	F	CT	L1-2	Suspected metastasis
10	64	M	US	T11	Suspected metastasis

CT: Computed tomography, US: Ultrasonography

Discussion

The most important result in our study was that there were no complications after the procedure and no decrease in hemoglobin compared to pre-procedural values. Percutaneous biopsy of the musculoskeletal system has a lower complication rate than open biopsies [1]: Complications are less than 1% in percutaneous vertebral biopsies [5]. Most of the complications occur in the thoracic vertebra due to the proximity of major vascular structures, pleura, lung and posterior mediastinum [6]. Percutaneous biopsy of vertebral, paravertebral and disc diseases may cause hemorrhage due to vascular structures such as the aorta and its branches (such as vertebral arteries, segmental arteries) and venous plexuses (internal and external venous plexuses, azygos system). In addition, spinal root injuries and adjacent organ (lung, kidney, etc.) injuries, fractures, bone and soft tissue infections, pneumothorax, spinal cord injury, meningitis may also be seen [7].

There are many studies in the literature about percutaneous vertebral biopsies performed with the help of imaging. In a recent study by Yang et al. [4], including 247 spinal tumor biopsies, the diagnostic success rate was 80%. This rate was 77% in the study of Wu et al. [8] and 77.14% in the study of Puri et al. [9]. The factors affecting diagnostic success were listed as size, bone matrix and definitive diagnosis of lesion in the study of Yang et al. [4]. In the study of Gul et al. [10], the success rate was found to be 80% and the only factor that had a significant relationship with success was reported as lesion histopathology. In a recent study by Kasalak et al. [11], which included 64 patients with suspected spondylodiscitis, only 31.3% had culture positivity. However, 96.9% of culture positive patients were treated appropriately. Therefore, the importance of biopsy has been emphasized in guiding the treatment [11]. In the meta-analysis performed by Pupabiool et al. [12], the sensitivity and specificity of the imaging-guided biopsies performed for spontaneous vertebral osteomyelitis were reported as 52.2% and 99.9%, respectively. Therefore, it can be considered that this method should be used especially in the presence of strong clinical suspicion.

As with all biopsies, the most crucial step in vertebral biopsies is correct planning. Meticulously planned and performed biopsy is essential for accurate diagnosis. Before the procedure, the patient and all imaging studies should be evaluated in detail. Additional imaging studies should be performed if necessary. As a result of these evaluations, the necessity of biopsy should be decided by considering the right indication and contraindicated conditions or profit-loss ratio. After the biopsy decision is taken, the most appropriate biopsy site should be determined with convenient imaging modality [13]. The approach depends on the location of the lesion, which should be adapted for each patient. The patient should be informed about the procedure and detailed information should be given before, during, and after the procedure and written consent must be obtained. Laboratory parameters related to coagulation of the patient should be at optimal values and the anticoagulant used should be discontinued before the procedure. If necessary, preprocedural sedation should be administered [14].

Depending on the localization of the pathology, in vertebral biopsies, the patient is usually placed in the prone position on the processing table. CT images are obtained, and a radiopaque marker is placed on the skin above the localization of the pathology. To reach the pathology, the optimal cross-section and angle away from the neurovascular bundle is determined over the skin. This area is cleaned and covered. After local anesthesia, a small skin incision is performed. The biopsy needle is directed towards the lesion under CT control. The type of needle used depends on the character of the lesion and the preference of the treating physician. In general, the needle should be of sufficient length to reach the lesion and of sufficient diameter to receive a sufficient amount of sample. Coaxial technique is generally used for sampling. Thus, multiple samples can be made using the same entry point. The distance of the needle to adjacent tissues should be checked by CT to avoid possible complications. Once the lesion is reached, sampling should be performed with aspiration or tru-cut needles [12,15].

Limitations

There were some limitations of our study: The first was the small number of patients included in the study, and the second was its retrospective nature. More comprehensive and prospective studies can be planned with regards to this subject. Another important limitation is that the biopsy and microbiological results of the patients could not be obtained, hence, could not be included in the study.

Conclusion

Imaging-guided percutaneous vertebral and paravertebral biopsies are safe and effective methods which allow sampling for cytological, histological, and microbiological analyses. The teamwork of patients, interventional radiologists, pathologists, oncologists, and surgeons is important in the application of this method. In the future, imaging techniques and biopsies will be increasingly used in the diagnosis of vertebral and paravertebral lesions.

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Evaluation of anxiety sensitivity, depression, and personality characteristics in chronic subjective dizziness patients

Kronik subjektif dizziness hastalarında anksiyete duyarlılığı, depresyon ve kişilik özelliklerinin değerlendirilmesi

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Abstract

Aim: Dizziness and vertigo are among the most common symptoms in otolaryngology, neurology and psychiatry clinics. In this study, it was aimed to evaluate anxiety sensitivity, depression and personality traits in patients who were followed up with chronic subjective dizziness.

Methods: Fifty-one patients with dizziness complaints for at least 3 months and no history of peripheral vestibular disease were enrolled to the patient group, and 51 healthy controls were enrolled to the control group of this case-control study. Anxiety Sensitivity Index-3 (ASI-3), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI) and Eysenck Personality Questionnaire (EPQ) scale forms were applied to the patient and control groups by a psychiatrist.

Results: There was no statistically significant difference in ASI-3 between the groups (P=0.119). In the patient group, the BAI values were found higher than the control group (P<0.001). While BDI values between the patient and control groups were similar, there was a trend for higher depression scores in the patients compared with the healthy individuals (P=0.052).

Conclusion: As a result, the presence of anxiety symptoms and neurotic personality characteristics may worsen dizziness development or disease progression. In the treatment of dizziness patients without neurological and otologic problems, a multidisciplinary approach will provide positive contributions to the course of the disease and to the quality of life of the patients.

Keywords: Dizziness, Anxiety sensitivity, Personality traits, Depression

Öz

Amaç: Dizziness ve vertigo otolaringoloji, nöroloji ve psikiyatri kliniklerinde en sık görülen semptomlar arasındadır. Bu çalışmada kronik subjektif dizziness hastalarında anksiyete duyarlılığı, depresyon ve kişilik özelliklerinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Periferik vestibüler hastalık hikayesi olmayan en az 3 aydır süren subjektif dizziness şikayeti olan 51 hasta ile 51 sağlıklı gönüllü çalışmaya dahil edildi. Anksiyete Duyarlılığı İndeksi-3 (ASI-3), Beck Anksiyete Ölçeği (BAI), Beck Depresyon Ölçeği (BDI) ve Eysenk Kişilik Envanteri (EPQ) psikiyatri uzmanı tarafından hasta ve kontrol grubuna uygulandı.

Bulgular: Gruplar arasında anksiyete duyarlılık indeksi-3 ölçeğinde anlamlı farklılık bulunmadı (P=0.119). Hasta grubunda BAI değerleri kontrol grubuna göre istatiksel olarak anlamlı yüksekti (P<0.001). BDI değerleri hasta grubunda kontrol grubuna göre daha yüksek olmasına rağmen aradaki fark istatiksel olarak anlamlı değildi (P=0.052).

Sonuç: Sonuç olarak anksiyete semptomu ve nevrotik kişilik özelliklerinin varlığı dizziness gelişimini ya da hastalığın seyrini kötüleştirebilir. Nörolojik ve otolojik problemi olmayan dizziness hastalarının tedavisinde multidisipliner yaklaşım hastalığın seyri ve hastaların yaşam kalitesi üzerine olumlu katkılar sağlayacaktır.

Anahtar kelimeler: Dizziness, Anksiyete duyarlılığı, Kişilik özellikleri, Depresyon

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Introduction

Dizziness and vertigo are among the most common symptoms in otolaryngology, neurology, and psychiatry clinics, which affect the daily activities of patients and decrease their quality of life. Chronic subjective dizziness (CSD) can be defined as chronic non-vertiginous dizziness syndrome or unsteadiness that is present throughout the day for 3 months or more [1]. Patients complain of dizziness when they are standing and vertigo when they walk. Patients' complaints increase at shopping centers where they are exposed to visual stimuli, while looking at the computer screen or reading books [2]. Patients' own movements and visual environmental stimuli usually activate dizziness.

Dizziness is the general name of the sense of disorientation. Vertigo is the subgroup of dizziness, which can be expressed as a misperception of the movement itself or object, which is the incompatibility between vestibular, visual, and somatosensory systems. Dizziness is often called non vertiginous imbalance [3]. Prospective studies have also reported that acute anxiety and hypervigilance lead to persistent dizziness [4].

Anxiety sensitivity is a fundamental fear that persists in the character of a person. People with elevated levels of anxiety sensitivity are immediately alerted to their fears when they experience anxiety, which in turn exacerbates their anxiety [5]. Some authors describe anxiety sensitivity as a "fear of fear" or "fear of anxiety" [6]. It has been stated that people with high anxiety may have low anxiety sensitivity or vice versa [7]. The view that anxiety sensitivity is different from anxiety is more consistent and matches with personal observations.

In approximately 30–50% of patients with vertigo/dizziness, complaints are not fully explained by a vestibular deficit or a defined organic illness, but instead are related to psychiatric disorders [8]. In a study of 189 patients with dizziness who had anxiety disorder in terms of psychiatric subgroups, they found anxiety and phobic disorder in 56 patients, somatoform disorder in 53 patients and depressive disorder in 20 patients [9].

Anxiety was investigated in normal subjects with postural control, along with those with anxiety disorder and vestibular disorder. Patient with anxiety disorder have more balance disorders than normal individuals. It has been reported that balance disorders are improved when anxiety disorders of these patients are treated [10].

While assessing the personality traits, different measurement scales can be used, such as Temperament and Character Scale (TCS), which is another scale for measuring personality traits that was used by Akçay et al. [11] in one of their studies. We used the Eysenck Personality Questionnaire (EPQ) for this study, and aimed to evaluate anxiety sensitivity, depression symptoms and accompanying personality factors in patients with complaints of dizziness lasting for at least 3 months.

Materials and methods

Fifty-one patients with dizziness complaints lasting for at least 3 months and 51 healthy volunteers aged between 18-65 years were included in this study between April-December 2017. It was conducted at department of otolaryngology. Informed consents were obtained from all participants. Patients with systemic diseases such as hearing loss, tinnitus, diabetes mellitus, hypertension, coronary heart disease in addition to dizziness complaint, and those who had previously experienced head and ear trauma, ear surgery, those with peripheral vestibular disease history, alcohol consumers and smokers were not included in the study. A complete head and neck examination was performed in all participants. Audiometry, tympanometry, acoustic reflex, spontaneous nystagmus and Dix Hallpike tests and ear Magnetic Resonance Imaging (MRI) results were normal in both the patient and control groups. Anxiety Sensitivity Index-3 (ASI-3), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI) and EPQ scale forms were applied to the patient and control groups by a psychiatrist.

Anxiety Sensitivity Index-3 (ASI-3)

This a self-assessment scale used to measure anxiety sensitivity with its physical, social, and cognitive aspects. It is easily applicable, short, and understandable. Subjects may fill it out themselves. A five-point Likert type (0=very small, 4=very large) scale is used for 18 items. The total score of the scale is the sum of the scores of each item. High scores indicate increased anxiety sensitivity and Turkish form has no cut-off score. ASI-3 showed a high internal consistency, Cronbach's alpha coefficient was calculated as 0.930, and test-retest reliability was found to be very good (r=0.64, $P<0.001$). Taylor et al. [12] developed the test, after which Mantar et al. [13] adapted it for Turkey.

Eysenck Personality Questionnaire

Francis et al. [14-16] reviewed the EPQ and the short form (48 items) of same questionnaire and created the reviewed short form, which consists of 24 items and assesses personality in 3 main factors: extroversion, neuroticism, psychoticism. In this questionnaire where each factor is evaluated with 6 items, participants are asked to answer Yes (1) - No (0) to 24 questions. Points for each personality attribute range from 0 to 6. Turkish validity and reliability study was performed by Karancı et al. [17].

Beck Depression Inventory

It was developed by Beck et al. [18] to assess somatic, emotional, cognitive, and motivational symptoms seen in depression. The BDI is a scale consisting of 21 self-assessment sentences and each symptom category has four options. Each item is scored between 0-3 points, and the total score ranges between 0-63. Turkish validity and reliability studies were conducted [19], for which the cut-off point was determined as 17.

Beck Anxiety Inventory

It was developed by Beck et al. [20] to measure the prevalence of anxiety symptoms experienced by the individual. BAI, based on self-reporting, consists of 21 items. Each item is scored between 0 and 3 and the total score ranges from 0 to 63. The high scores on the scale indicate the severity of the anxiety experienced by the individual. Turkish validity and reliability study was conducted by Ulusoy et al. [21].

Statistical analysis

Data analysis was performed using the IBM SPSS statistics 22.0 software (IBM Corp., Armonk, NY). Descriptive

statistics methods were used to evaluate frequency, percentage, mean, standard deviation, median, quaternary separation. Chi-square (χ^2) test was used to evaluate qualitative data. The conformity of data to normal distribution was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. Independent Samples t-test and Mann-Whitney U tests were used for continuous normally distributed data and non-normally distributed data, respectively. Spearman Rho correlation test was utilized to evaluate interrelationships between variables. *P*-values <0.05 are considered significant.

Power analysis was conducted with G*Power 3.1.9.2 software. The power of this data was calculated as 1-β=0.99 with n1=51, n2=51, α=0.05 and an effect size of d=1.0.

Results

Fifty-one patients with dizziness and 51 healthy individuals were included in this study as the patient and control groups, respectively. The number of females and males in the control and study groups were 33 (64.7%), 18 (35.2%) and 37 (72.5%), 14 (27.5%), respectively, with a significant dominance of females in both groups (*P*=0.009). Groups were similar in terms of age (*P*=0.258) and ASI-3 (*P*=0.119) scores. Mean BAI scores (68.6%) were higher in the patient group (*P*<0.001) (Figure 1). There was a trend for higher BDI values in the patient group compared to the control group (*P*=0.052). There was no statistically significant difference in EPQ neuroticism, extraversion and psychoticism between the patient and control groups (*P*=0.334, *P*=0.789, *P*=0.116 respectively) (Table 1).

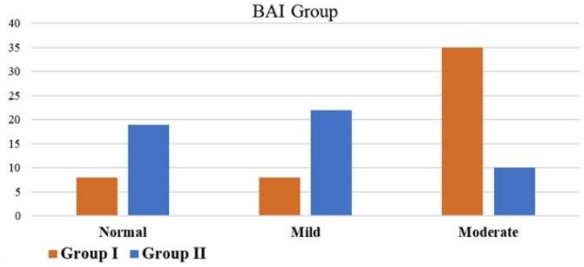

Figure 1: Comparison of Beck Anxiety Index between groups (Group I: Patients, Group II: Control)

Table 1: Sociodemographic data and scale results in patient and control group

		Patient (n=51)	Control (n=51)	*P*-value
Gender	Female	37 (72.5%)	33 (64.7%)	0.009 [a]
	Male	14 (27.5%)	18 (35.2%)	
Age (Year)		45.1(13.3)	42.3(11.1)	0.258 [b]
ASI-3		22 (16 - 39)	17 (10 - 34)	0.119 [c]
BAI		23 (12 - 32)	10 (5 - 14)	0.000 [c]
BAI Group	Normal	8 (15.7%)	19 (37.3%)	0.000 [a]
	Mild	8 (15.7%)	22 (43.1%)	
	Moderate	35 (68.6%)	10 (19.6%)	
BDI		14 (7 - 21)	9 (4 - 14)	0.052 [c]
BDI Group	Normal	19 (37.3%)	29 (56.9%)	0.070 [a]
	Mild	18 (35.3%)	15 (29.4%)	
	Moderate	11 (21.6%)	3 (5.9%)	
	Severe	3 (5.9%)	4 (7.8%)	
EPQ	Neuroticism	4 (2 - 5)	3 (2 - 5)	0.334 [c]
	Extraversion	4 (2 - 5)	4 (2 - 5)	0.789 [c]
	Psychoticism	2 (1 - 3)	1 (1 - 2)	0.116 [c]

Mean (SD), EPQ: Eysenck Personality Questionnaire, BDI: Beck Depression Inventory, ASI-3: Anxiety Sensitivity Index-3, BAI: Beck Anxiety Inventory, [a]: Chi-Square Test (n/%), [b]: Independent Samples T Test, [c]: Mann-Whitney U Test [Median (Interquartile Range)]

When the patient group was evaluated among itself, a positive correlation was detected between the female gender and ASI-3(*P*=0.006, r=-0.379), BAI (*P*=0.005, r=-0.391), BDI (*P*=0.001, r=-0.468) scores, and neuroticism (*P*=0.008, r=-0.366). ASI-3 and BAI (*P*<0.001, r=0.665), BDI (*P*<0.001 r=0.607), neuroticism (*P*<0.001 r=0.506) were also found to positively correlate, along with BAI, BDI (*P*<0.001 r=0.679), and neuroticism (*P*<0.001, r=0.600). BDI and neuroticism were positively correlated as well (*P*<0.001, r=0.674).

When the control group was evaluated among itself, a positive correlation was detected between the female gender and neuroticism (*P*=0.005, r=-0.388). ASI-3 and BAI (*P*<0.001, r=0.545), BDI (*P*=0.001, r=0.438), neuroticism (*P*=0.029, r=0.306) were also found to positively correlate, along with BAI, BDI (*P*=0.001, r=0.467), neuroticism (*P*<0.001, r=0.637), and extraversion (*P*=0.006, r=-0.378). BDI was found to positively correlate with neuroticism (*P*=0.003, r=0.413) and psychoticism (*P*=0.027, r=0.309), while neuroticism negatively correlated with extraversion (*P*=0.006, r=-0.381) (Table 2).

Table 2: Relations between variables according to groups

		Gender	Age	Anxiety Index-3	Sensitivity	Beck Anxiety Inventory	Beck Depression Inventory	EPQ Neuroticism	EPQ Extraversion	EPQ Psychoticism
Patient Group										
Gender	r	1.000								
	P-value	.								
Age (Year)	R	-0.158	1.000							
	P-value	0.267	.							
Anxiety Sensitivity Index-3 (ASI-3)	R	-0.379	0.161	1.000						
	P-value	0.006	0.258	.						
Beck Anxiety Inventory (BAI)	r	-0.391	0.213	0.665		1.000				
	P-value	0.005	0.134	0.000		.				
Beck Depression Inventory (BDI)	R	-0.468	0.299	0.607		0.679	1.000			
	P-value	0.001	0.033	0.000		0.000	.			
EPQ Neuroticism	R	-0.366	-0.005	0.506		0.600	0.674	1.000		
	P-value	0.008	0.974	0.000		0.000	0.000	.		
EPQ Extraversion	R	0.164	-0.110	-0.087		-0.147	-0.240	-0.219	1.000	
	P-value	0.251	0.442	0.543		0.304	0.089	0.123	.	
EPQ Psychoticism	R	0.122	-0.106	-0.042		0.004	0.091	0.006	0.096	1.000
	P-value	0.395	0.461	0.768		0.980	0.525	0.965	0.504	.
Control Group										
Gender	R	1.000								
	P-value	.								
Age (Year)	R	-0.151	1.000							
	P-value	0.289	.							
Anxiety Sensitivity Index-3 (ASI-3)	R	-0.048	0.155	1.000						
	P-value	0.737	0.279	.						
Beck Anxiety Inventory (BAI)	R	-0.142	0.081	0.545		1.000				
	P-value	0.320	0.570	0.000		.				
Beck Depression Inventory (BDI)	R	-0.233	-0.012	0.438		0.467	1.000			
	P-value	0.099	0.932	0.001		0.001	.			
EPQ Neuroticism	R	-0.388	-0.116	0.306		0.637	0.413	1.000		
	P-value	0.005	0.416	0.029		0.000	0.003	.		
EPQ Extraversion	R	-0.112	-0.022	-0.074		-0.378	-0.065	-0.381	1.000	
	P-value	0.435	0.876	0.608		0.006	0.652	0.006	.	
EPQ Psychoticism	R	0.274	-0.127	0.050		0.129	0.309	-0.001	-0.057	1.000
	P-value	0.052	0.374	0.727		0.366	0.027	0.993	0.692	.

*: Spearman's Rho Correlations

Discussion

Symptoms of dizziness usually consist of nonspecific complaints. Otolaryngologists often direct their attention to inner ear pathologies, however, neurological, cardiological and psychiatric pathologies underlying dizziness should be taken into consideration for correct diagnosis and treatment. Dizziness can be seen at various ages from adolescents to elder adults. It is usually seen between the ages of 40-50 with most of the patients (60-70%) being females [22]. The mean age of the patients in our study was 45.1 (13.3) years. The greater number of women in our study can be explained by the fact that dizziness is more common in women than in men.

Although the relationship between visual, vestibular symptoms and anxiety has been studied recently, the relationship between anxiety and visio-vestibular system has been known for many years [23].

Anxiety's effect on postural control was investigated in normal subjects, and in those with anxiety and vestibular disorders. In patients with anxiety disorder, balance disorder is seen more than normal individuals. It has been reported that balance disorders are cured when anxiety disorders of these patients are treated [10].

Studies in vestibular and psychiatric patients have supported the relationship between balance control systems and anxiety [24]. In addition, patients with vestibular dysfunction are more susceptible to anxiety development than patients without vestibular dysfunction [25]. Patients with chronic dizziness also have higher anxiety levels than patients with other vestibular disorders [10].

In a study of the role of emotional disorders in the extent of dizziness, Roh et al. [26] found that chronic dizziness patients had higher anxiety depression levels and emotional distress and stated that emotional distress extends the duration of dizziness.

The long duration of dizziness complaints affects patients' daily physical activities, work life and quality of life. Dizziness may cause anxiety development or anxiety can cause extension of dizziness. Dizziness, vertigo, and imbalance are also complaints that can be seen in anxiety disorders. One of the main symptoms of panic attacks is dizziness. Therefore, in recent years, the relationship between vestibular functions and anxiety and the psychological factors that cause CSD to appear and continue have been studied [27]. In a study of 105 patients with dizziness diagnosis, Odman et al. [28] found that 79.3% of the patients also had anxiety and/or depression.

Staab et al. [1] found that hospital anxiety depression scores were higher in the CSD group in their study evaluating anxiety and personality characteristics in 40 patients. A study in which Chiarella et al. [29] assessed personality factors in patients with CSD found that anxiety, neuroticism, and openness scores were higher in CSD patients.

In this study, BAI was found significantly higher in the patient group. BDI showed a trend for higher depression scores in patients compared with the healthy group.

Best et al. [25] reported that in a study of psychiatric morbidity and comorbidity in patients with vestibular disorders, these psychiatric disturbances were reactivated after the onset of vestibular symptoms in patients with depression and somatoform disorders. In addition, psychiatric evaluation was deemed necessary to maintain the treatment more effective in dizziness patients with known psychiatric disorders.

The combination of anxiety and dizziness is one of the areas of common interest of otolaryngology and psychiatry. Until recently, the nature of the relationship between these two conditions has not been fully elucidated. The findings of the multidisciplinary study of the otorhinolaryngology, neurology and psychiatry can solve the complexity of "dizziness-anxiety-personality traits" by providing a better understanding of the pathophysiology.

Limitations

The limitations of the study include the fact that the sample group was relatively small. The psychiatric evaluation was not made by face-to-face interviews with these patients, and no evaluation regarding treatment was made. There is a need for prospective studies involving treatment for a longer period with a broader sample group.

Conclusion

The presence of anxiety symptoms may play a role in worsening of the course of the disease in dizziness. Using a multidisciplinary approach in the treatment of dizziness patients without neurological and otologic problems, and the use of treatment options such as drugs or cognitive behavioral therapies in the treatment of psychiatric patients will contribute positively to the chronicity of the disease, hospitalizations and the quality of life of the patients.

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Beta hemolytic *Streptococci* strains isolated from clinical specimens, their characteristics and antibiotic susceptibility

Klinik örneklerden izole edilen beta-hemolitik *Streptokok* suşları, özellikleri ve antibiyotik duyarlılığı

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Abstract

Aim: Beta Hemolytic Streptococcus (BHS) species play a role in many infections, such as urinary tract infection, skin/soft tissue infections, neonatal meningitis, sepsis, pneumonia as well as upper respiratory tract infections like tonsillopharyngitis. The aim of this study was to determine the types of BHS species, their infectious characteristics and antibiotic susceptibility profiles in clinical specimens.

Methods: In this cross-sectional study, infectious features of 1276 streptococcus strains isolated from 1110 (87%) outpatients and 166 (13%) inpatients between January 2014 and June 2019 at our laboratory and antimicrobial susceptibility of the 320 strains were analyzed retrospectively.

Results: Retrospective analysis of 1276 BHS isolates revealed that 48.6% were group B, 33.9% were group A, 9.6% were group F, 5.7% were group C and 2.2% were group G BHS. Among isolated BHS infections, 42.9% caused urinary tract infection, 34.6% caused tonsillitis/tonsillopharyngitis, 15.7% were isolated from skin/soft tissue infections, 3% were found in the bloodstream, and 1% in meningitis, pneumonia, conjunctivitis, and peritonitis. About 2.8% Group B Streptococcus were considered vaginal colonization. Among all patients, 11.2% had more than one underlying disease. All isolates were susceptible to penicillin, vancomycin, linezolid and tigecycline. Erythromycin, clindamycin, and tetracycline resistance rates were determined as 5%, 2%, 40% respectively for Group A and 34%, 11%, 90%, respectively for Group B Streptococcus.

Conclusion: Early diagnosis and appropriate antibiotherapy are important parameters in the management of streptococcal infections. Although there is no penicillin resistance in beta-hemolytic *streptococci*, we think that antibiotic susceptibility should be closely monitored due to increasing clinical failures, penicillin Minimal inhibitory concentration (MIC) values, and macrolide and fluoroquinolone resistance, especially in Group B Streptococcus.

Keywords: Antibiotic susceptibility, Infection, Beta hemolytic Streptococcus spp

Öz

Amaç: Beta Hemolitik Streptococcus (BHS) türleri, idrar yolu enfeksiyonu, cilt/yumuşak doku enfeksiyonları, tonsillofarenjit gibi üst solunum yolu enfeksiyonları, yenidoğanda menenjit, sepsis ve pnömoni gibi birçok enfeksiyonda rol oynar. Bu çalışmanın amacı klinik örneklerden izole edilen BHS türlerini, enfeksiyon özelliklerini ve antibiyotik duyarlılık profillerini belirlemektir.

Yöntemler: Laboratuvarımızda Ocak 2014 - Haziran 2019 tarihleri arasında, 1110 (%87) ayaktan ve 166 (%13) yatarak tedavi gören hastadan izole edilen 1276 beta hemolitik streptokok (BHS) suşu, özellikleri ve 320 suşun antimikrobiyal duyarlılığı retrospektif olarak incelendi. Çalışmanın tipi kesitsel çalışmadır.

Bulgular: Toplam 1276 BHS izolatının; %48,6 grup B, %33,9 grup A, %9,6 grup F, %5,7 grup C ve %2,2 grup G BHS idi. İncelenen BHS enfeksiyonlarının; %42,9'u idrar yolu enfeksiyonu, %34,6'sı tonsillit/tonsillofarenjit, %15,7'si cilt/yumuşak doku enfeksiyonu, %3'ü kan dolaşımı enfeksiyonu ve %1'i menenjit, pnömoni, konjonktivit ve peritonit idi. %2,8 Grup B Streptokok izolatı vajinal kolonizasyon olarak kabul edildi. Hastaların %11,2'sinde birden fazla altta yatan hastalık vardı. Tüm izolatlar penisilin, vankomisin, linezolid ve tigesikline duyarlıydı. Eritromisin, klindamisin ve tetrasiklin dirençi Grup A Streptokok ve Grup B Streptokok için sırasıyla %5, %2, %40 ve %34, %11, %90 olarak belirlendi.

Sonuç: Erken tanı ve uygun antibiyoterapi streptokok enfeksiyonlarının tedavisinde önemli parametrelerdir. Beta-hemolitik streptokoklarda penisilin direnci olmasa da, klinik başarısızlıkların varlığı, özellikle Grup B Streptokok 'da penisilin Minimal İnhibitör Konsantrasyonu (MİK) değerlerinin artışı, makrolid ve florokinolon direncinin artması nedeniyle antibiyotik duyarlılığının yakından izlenmesi gerektiğini düşünüyoruz.

Anahtar kelimeler: Antibiyotik duyarlılığı, Enfeksiyon, Beta hemolitik Streptococcus spp

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Introduction

Streptococcus spp are common in nature. They can also be found in the normal flora of the human mouth, pharynx, lower gastrointestinal tract and vagina. *Streptococci* can cause serious life-threatening infections such as necrotizing fasciitis, endocarditis, newborn meningitis, sepsis and pneumonia, as well as upper respiratory infections such as tonsillopharyngitis. Among *streptococci*, beta hemolytic *streptococci* (BHS) constitute an important group causing invasive infections. They are divided into sera-groups (A through H and K through V) by antigenic differences in their cell wall carbohydrates by Lancefield, and the most common causative agents of infection in humans are the A, B, C and G groups [1]. The increase in invasive BHS infections worldwide has increased the importance of early diagnosis and treatment in life-threatening infections [2,3]. In this study, we aimed to evaluate the clinical characteristics and determine the antibiotic susceptibility patterns of patients with BHS isolated in their clinical specimens.

Materials and methods

In this study, infectious features of 1276 streptococcus strains isolated from 1110 (87%) outpatients and 166 (13%) inpatients between January 2014 and June 2019 at the medical microbiology laboratory of our hospital and antimicrobial susceptibility of the 320 strains were analyzed retrospectively.

Samples were fixed in 5% sheep blood agar medium and placed in a waxed jar, which would provide 5-10% CO2 medium, and incubated in 37 °C oven for 24 hours. At the end of incubation, colonies with β-hemolysis were evaluated. Of these colonies, gram positive cocci that formed chains and were negative for catalase were grouped with streptococcal slide agglutination kit (Streptococcal latex test, Plasmatec, UK). 5% sheep blood Müeller Hinton Agar was used for antibiotic susceptibility test. The prepared suspension from 24-hour pure cultures of strains at 0.5 McFarland tube turbidity was spread on the medium. For penicillin G sensitivity, the gradient test strip (ETEST, Biomerieux, France) and discs for other antibiotics (BD BBL Sensi-Disc, USA) were placed in the medium with the help of dispenser at enough distances from each other. The petri dishes were incubated in a 37 °C oven for 24 hours and the disc diffusion results were evaluated by measuring zone diameters. The points where the inhibition ellipse formed around the gradient test strip intersect with the E test strip were determined as the minimum inhibitory concentration (MIC) of the antibiotic. Evaluations were made according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria [4]. Penicillin G MIC values were recorded in all BHS isolates. The highest and lowest MIC values were defined as MIC range. MIC values that inhibited 50% and 90% of BHS growth were considered MIC_{50} and MIC_{90}, respectively. D test was used to determine erythromycin-inducible clindamycin resistance (MLS_B). %5 sheep blood Mueller-Hinton agar, erythromycin (15 µg) and clindamycin (2 µg) discs were placed at a distance of 12-15 mm between the outer edges of each other. Inducible MLS_B was defined as a bulging on the side facing erythromycin within the clindamycin zone and D test was considered positive. If the strains were resistant to both erythromycin and clindamycin, they were regarded as $CMLS_B$ phenotype. The M phenotype was considered erythromycin-resistant and clindamycin-susceptible if there was no bulging on the zone [5].

Statistical analysis

The total number of beta hemolytic streptococci, the biological samples they produced within the specified period and antibiotic susceptibility were calculated and percentages were found for each.

Results

Among 1276 strains in the study, 48.6% (n=620) were as Group B Streptococcus (GBS), 33.9% (n=432) were Group A Streptococcus (GAS), 9.6% (n=123) were Group F Streptococcus (GFS), 5.7% (n=73) were Group C Streptococcus (GCS) and 2.2% (n=28) were defined as Group G Streptococcus (GGS) (Figure 1). Among determined BHS infections, 42.9% (n=547) were urinary tract infections, 34.6% (n=441) were tonsillitis/tonsillopharyngitis, 15.7% (n=200) were skin/soft tissue infections, 3% (n=39) were bloodstream infections, and 1% (n=13) were meningitis, pneumonia, conjunctivitis and peritonitis (Table 1). Among GBS isolates, 2.8% (n=36) were considered vaginal colonization.

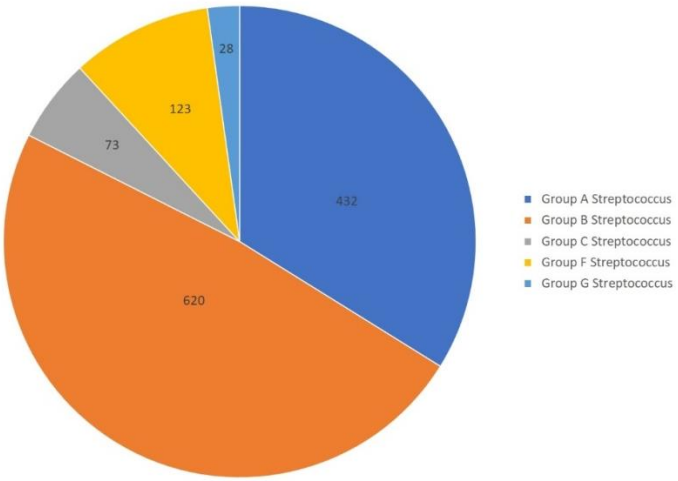

Figure 1: Distribution of *Streptococci* subgroups

Upon evaluation of the reproduction of BHS in blood and cerebrospinal fluid (CSF) samples, which were considered invasive infections, 42 (3.3%) patients had sepsis/bacteremia and meningitis. Seven of these patients had neonatal sepsis and 3 had neonatal meningitis. Diagnoses of inpatients were skin and soft tissue infection in 45.7%, sepsis/bacteremia in 23.4%, genitourinary tract infection in 21.9%, respiratory tract infection in 6%, meningitis in 1.8%, conjunctivitis and peritonitis in 1.2%. Outpatients included in the study were diagnosed with genitourinary system infection (48.8%), tonsillitis/tonsillopharyngitis (37%) and skin and soft tissue infections (14.2%).

Table 1: Distribution of isolated BHS strains

Material	GAS (n=432)	GBS (n=620)	GCS (n=73)	GFS (n=123)	GGS (n=28)	Total (n=1276)
Throat	312	2	30	79	18	34.6% (n=441)
Urine	9	533	0	5	0	42.9% (n=547)
Tissue /Abscess	94	25	43	30	8	15.7% (n=200)
Blood	8	21	0	8	2	3.0% (n=39)
Vagina	0	36	0	0	0	2.8% (n=36)
Sputum	8	0	0	0	0	0.06% (n=8)
CSF	0	3	0	0	0	0.02% (n=3)
Sterile body fluid	1	0	0	1	0	0.02% (n=2)

CSF: Cerebrospinal fluid

The rate of patients with more than one underlying disease was 11.2% (n=143). It was diabetes in 32.2% (n=46), kidney and ureteral stones in 21% (n=30), trauma and surgery in 20.3% (n=29), malignancy in 16% (n=23), renal failure in 6.3% (n=9), autoimmune diseases in 3.5% (n=5) and HIV in 0.7% (n=1). Among 9992 throat cultures, 4.4% (n=437) had BHS growth. Among strains, 70.5% were GAS, 18.0% were GFS, 6.9% were GCS, 4.1% were GGS, and 0.5% was GBS.

Antibiotic susceptibility testing was performed for 200 GBS, 100 GAS and 20 GCS, GGS, and GFS BHS isolates over a five-year period. All isolates studied for antibiotic susceptibility were susceptible to penicillin, vancomycin, teicoplanin, linezolid and tigecycline. Penicillin G minimal inhibitory concentration (MIC) results of 320 BHS strains and their erythromycin, clindamycin, tetracycline, levofloxacin, and nitrofurantoin disc diffusion results are shown in Table 2. Since all BHS isolates were susceptible to vancomycin, teicoplanin, tigecycline and linezolid by disc diffusion method, they are not shown in table 2. In five erythromycin resistant GAS, two $CMLS_B$, two M phenotypes and one $IMLS_B$ were identified. Sixty-eight erythromycin resistant GBS isolates consisted of 38 $IMLS_B$, 21 $CMLS_B$ and 9 M phenotypes. One $CMLS_B$ was detected among GCS and two $CMLS_B$ and one M phenotype were identified among three erythromycin resistant GGS.

Table 2: Antimicrobial resistance pattern in Beta-hemolytic *Streptococci* (n=320)

	MIC value (µg/ml)			Disc diffusion		
	MIC range	MIC_{50}	MIC_{90}	Susceptible (%)	Intermediate (%)	Resistant (%)
GAS (n=100)						
Penicillin G	0.004-0.047	0.008	0.023	100	-	-
Erythromycin	-	-	-	95	0	5
Clindamycin	-	-	-	98	0	2
Tetracycline	-	-	-	54	6	40
Levofloxacin	-	-	-	97	2	1
Nitrofurantoin	-	-	-	100	0	0
GBS (n=200)						
Penicillin G	0.016-0.125	0.047	0.094	100	-	-
Erythromycin	-	-	-	64	2	34
Clindamycin	-	-	-	89	0	11
Tetracycline	-	-	-	9.5	0.5	90
Levofloxacin	-	-	-	74	1	25
Nitrofurantoin	-	-	-	99	0	1
GCS (n=4)	-					
Penicillin G	0.012-0.047	0.012	0.032	100	-	-
Erythromycin	-	-	-	75	0	25
Clindamycin	-	-	-	75	0	25
Tetracycline	-	-	-	50	0	50
Levofloxacin	-	-	-	100	0	0
Nitrofurantoin	-	-	-	100	0	0
GFS (n=8)	-					
Penicillin G	0.016-0.047	0.023	0.023	100	-	-
Erythromycin	-	-	-	100	0	0
Clindamycin	-	-	-	100	0	0
Tetracycline	-	-	-	50	0	50
Levofloxacin	-	-	-	100	0	0
Nitrofurantoin	-	-	-	100	0	0
GGS (n=8)	-					
Penicillin G	0.008-0.047	0.012	0.016	100	-	-
Erythromycin	-	-	-	62.5	0	37.5
Clindamycin	-	-	-	75	0	25
Tetracycline	-	-	-	50	0	50
Levofloxacin	-	-	-	100	0	0
Nitrofurantoin	-	-	-	100	0	0

GAS: Group A Streptococcus, GBS: Group B Streptococcus, GCS: Group C Streptococcus, GFS: Group F Streptococcus, GGS: Group G Streptococcus, MIC: Minimal inhibitory concentration

Discussion

In this study, we analyzed the general clinical features and antibiotic susceptibility pattern of BHS in a tertiary center and determined that the most common isolates were GBS and GAS; the most common infections were urinary tract infection and tonsillitis/tonsillopharyngitis, and among throat cultures the most common group was GAS. All BHS isolates were susceptible to vancomycin, teicoplanin, linezolid and tigecycline.

Invasive GAS infections continue to be associated with increased morbidity and mortality rates worldwide. There are an estimated 10649- 13434 cases in the United States that result in 1136-1607 deaths each year. It is similar to the incidence of invasive GAS in Canada (4.3/100000) and to many European countries (2–4/100000). In the same study, they found that in the presence of underlying comorbid diseases, mortality rates increased in elderly and long-term patients in nursing homes [6]. In another study, it was emphasized that bacteremia due to GAS most commonly developed secondary to soft tissue infections, and diabetes mellitus was the most common comorbidity [7]. Similarly, in our study, diabetes was the most common comorbidity for all infections. In another study examining GAS, GBS, GCS and GGS bacteremia, cardiovascular diseases, malignancy, and diabetes mellitus were the most common underlying diseases. They concluded that the most common infection was skin/soft tissue infections and moreover, urinary tract infections were more common in the GBS group (12.4%) than the other groups [8]. In a study of Topkaya et al. [9] including 46 microbiology laboratories from different regions, only 65 invasive GAS isolates were identified within a year, and they concluded that invasive GAS infection incidence was low in Turkey. We detected invasive BHS infections in 3.3% of 1276 streptococcus strains. In a recent meta-analysis, clarithromycin was reported as a valid, effective, and largely well-tolerated treatment option for GAS pharyngitis patient who cannot benefit from other agents [10]. In our study, in five erythromycin resistant GAS, two $CMLS_B$, two M phenotypes and one $IMLS_B$ were identified.

In the study conducted by Unlu et al. [11], 9 (5.6%) of the 161 *streptococci* strains isolated from the throat samples were GAS, 64 (39.7%) were GBS, two (1.2%) were GCS and three (1.8%) Type D, two (1.2%) GGS, 57 (35.4%) were viridians *streptococci* and 24 (14.9%) were pneumococci. Among isolated *streptococci*, the most common infections were urinary tract infections (n=52; 32.2%), skin/soft tissue infection (n=48; 29.8%) and pneumonia (n=25; 15.5%). They detected more than one underlying disease in 87 (54%) patients. Penicillin resistance was found to be 0% and 4.9% in GAS and GBS isolates, respectively. Similarly, in our study, the most frequently isolated group was GBS, and the most common infections were urinary tract infection and skin/soft tissue infection. In our study, an underlying disease was detected in 11.2% of the patients, while this rate was 54% in the above-mentioned study. In our study, the absence of *viridians streptococci* and *pneumococci*, and the inclusion of throat samples may cause this rate to be low. Almost all of our throat specimens were isolated from outpatients who had no underlying disease. In recent years, GBS has been identified as one of the most common pathogens responsible for maternal and neonatal infections.

Although there is not enough data about GBS colonization in developing countries, it is known that 20-30% of women are colonized by GBS in developed countries. Maternal intrapartum GBS colonization is the primary risk factor for early-onset GBS infection in infants. It is estimated that 1-2% of infants born from colonized mothers with GBS will develop early-onset GBS infection, including neonatal pneumonia, sepsis and meningitis, when untreated or inadequate measures are

taken. Severe GBS infections may result in neonatal mortality or permanent damage [12]. In a study of Karadag et al. [13] GBS colonization was detected in 3% of 300 pregnant women in labor in Turkey. Antibiotic susceptibilities of the strains isolated in the same study were studied. While resistance to penicillin G, ampicillin, meropenem and vancomycin was not detected, they found 89% resistance to tetracycline and 22% resistance to erythromycin and clindamycin. In the study of Karadeniz et al. [14], the prevalence of GBS was found to be 8% in pregnant women and 5% in newborn babies, and they reported that none of the newborns with GBS colonization developed infection in one month following birth. In our study, three neonatal meningitis and seven newborn sepsis cases due to GBS were detected. However, colonization in mothers is unknown. In our study, in almost all patients with streptococcal genitourinary tract infection, GBS were found responsible. The presence of an underlying urological pathology was found in many of the cases followed up for urinary tract infections. In a study of Shayanfar et al. [15], the prevalence of GBS in females with urinary tract infection was 8.92% and GBS was highly susceptible to cephalothin, norfloxacin, ampicillin, nitrofurantoin and vancomycin. In our study, GBS isolates were highly susceptible to Penicillin G, nitrofurantoin and clindamycin.

In recent years, the incidence of invasive infections involving GCS and GGS has increased. They lead to clinical infection presentations like GAS [16]. In our study, GCS and GGS were isolated from soft tissue infections, similar to GAS. Bacteremia due to GGS was secondary to the internal prosthesis device. In a recent study from India, Srilaka et al. [17] reported that the highest percentage of *streptococci* isolated was from throat swabs (35.5%), followed by sputum (15.9%), urine (14.1%), blood (10.5%), pus(8.6%), cerebrospinal fluid (6.4%), bronchoalveolar lavage (5.9%) and endotracheal tips (3.2%). The highest percentage of BHS belongs to GCS (74, 33.6%), followed by GGS (51, 23.2%), GBS (42, 19.1%), GFS (28, 12.7%), GAS (21, 9.5%) and GDS (4, 1.8%). Shahin et al. [18] reported that GCS, GFS, and GGS were common pathogens in patients with an underlying malignancy, and they are usually associated with other pathogens requiring combinatorial therapeutic strategies.

In our study, it was found that 31.6% (n=25) of GFS positive throat isolates were from Family Medicine clinics and isolated from routine samples taken during the recruitment examinations. This may suggest that GFS are colonized in the throat and not clinically important in this population. However, lung abscess associated with GFS has been reported in literature and for that reason, clinicians should be aware of more dangerous infections associated with GFS [19].

All BHS were susceptible to penicillin. In a recent review, after 70 years of use, penicillin was still defined as universally active against GAS, GCS and GGS. However, therapeutic failures were recorded in 2-28% of pharyngitis cases [20]. On the other hand, GBS with reduced susceptibility to penicillin were described in previous literature [21]. Levofloxacin resistance in GBS may also cause important clinical problems in future. In this study we defined a high levofloxacin resistance rate of 25% in GBS. Previously some genetic mutations were reported to be associated with fluoroquinolone resistance in GBS [22]. Lee et al. [23] reported the levofloxacin resistance as 4.8% in 188 GBS isolates. However, Wang et al. [24] reported that 40 GBS isolates recovered from infected neonates less than 3 months of age were susceptible to levofloxacin. Recently Seki et al. [21] reported an increased tendency to multidrug resistance (to both macrolides and fluoroquinolones) reaching approximately 10% in GBS.

Limitations

There are some limitations of this study. First this is a single center, retrospective study. Secondly, the number of isolates with antibiotic susceptibility results was low. Although penicillin resistance was not found in among BHS, we think that antibiotic susceptibility should be closely monitored due to the increased clinical failures, penicillin MIC values, macrolide, and fluoroquinolone resistance, especially in GBS.

Conclusions

As a result, infections due to *streptococci* may be seen in a wide variety ranging from tonsillitis, tonsillopharyngitis, necrotizing fasciitis, and sepsis to invasive infections such as meningitis. These invasive infections may result in serious mortality and morbidity, especially in the presence of underlying comorbid diseases. Early diagnosis and appropriate antibiotherapy are important parameters in the management of streptococcal infections. It should be noted that soft tissue infections such as surgical site infection and necrotizing fasciitis due to GAS may progress rapidly. Newborn infections are especially important for GBS. Therefore, vaginal and rectal colonization should be investigated during pregnancy and necessary precautions should be taken according to the result.

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The relationship between maternal and neonatal vitamin B12 and folate levels, anthropometric measurements, and metabolic indicators

Annelerdeki vitamin B12 ve folat düzeylerinin, yenidoğanlardaki vitamin B12 ve folat düzeyleri, antropometrik ölçümler ve metabolik belirteçlerle ilişkisi

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Abstract

Aim: The nutritional imbalances in pregnancy may lead to metabolic problems in newborns, which may cause obesity during childhood and later in life. It is aimed to determine the maternal levels of folate, vitamin B12 at birth and to investigate the correlation between neonatal anthropometric measurements, and metabolic indicators such as serum lipid profile and insulin resistance.

Methods: A total of 102 mothers and newborns were enrolled in this prospective cohort study. The demographic, obstetric features, serum levels of vitamin B12, folate, glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, cholesterol, insulin, homocysteine, and homeostatic model assessment (HOMA-IR) were noted. For vitamin B12, levels, ≥191 ng/L were accepted as normal. The correlation between maternal levels of vitamin B12, folate, anthropometric measurements, and metabolic indicators of newborns were evaluated.

Results: Body mass index (P=0.004), serum insulin levels (P=0.012), HOMA-IR (P=0.001), and homocysteine (P=0.001) were increased in neonates born from mothers with lower serum levels of vitamin B12. The maternal vitamin B12 levels were positively, strongly correlated with neonatal vitamin B12 levels (r=0.719, P<0.001). There was an inverse, weak correlation between maternal vitamin B12 levels and neonatal serum insulin levels (r=-0.221, P=0.025), HOMA-IR (r=-0.249, P=0.011), and homocysteine (r=-0.394, P<0.001). Maternal folate levels were strongly, positively correlated with neonatal folate (r=0.735, P<0.001); weakly, positively correlated with neonatal vitamin B12 (r=0.327, P=0.001); moderately, inversely correlated with neonatal homocysteine (r=-0.505, P<0.001).

Conclusion: Optimizing intake of these vitamins levels during pregnancy is important to reduce the neonatal metabolic abnormalities, which may lead to obesity later in life.

Keywords: Pregnancy, Vitamin B12, Folate, Neonates, Insulin resistance, Metabolic indicators

Öz

Amaç: Gebelikteki besin dengesizlikleri yenidoğanın gelecek yaşamında obeziteye neden olan metabolik problemlere yol açabilir. Çalışmamızda, gebeliğin sonunda annelerdeki folik asit, B12 vitamini düzeylerini belirlemek, yenidoğanın antropometrik ölçümleri, serum lipit profili, insülin direnci gibi metabolik göstergeleri arasındaki ilişkiyi araştırmak amaçlandı.

Yöntemler: Toplam 102 anne ve bebek prospektif kohort çalışmaya dahil edildi. Demografik, obstetrik özellikler, serum B12 vitamini, folat, glikoz, yüksek yoğunluklu lipoprotein (HDL), düşük yoğunluklu lipoprotein (LDL), trigliseritler, kolesterol, insülin, homosistein ve homeostatik model değerlendirmesi (HOMA-IR) not edildi. B12 vitamini için, ≥191 ng/L seviyeleri normal olarak kabul edildi. Maternal vitamin B12 ve folat seviyeleri ile yenidoğanların metabolik göstergeleri, antropometrik ölçümleri arasındaki ilişki araştırıldı.

Bulgular: Serum vitamin B12 düzeyi düşük olan annelerden doğan bebeklerde vücut kitle indeksi (P=0,004), serum insülin düzeyleri (P=0,012), HOMA-IR (P=0,001) ve homosistein (P=0,001) düzeyleri artmış olarak saptandı. Maternal B12 vitamini düzeylerinin, yenidoğan B12 vitamini düzeyleri ile kuvvetli korelasyon (r=0,719, P<0,001); serum insülin (r=-0,221, P=0,025), HOMA-IR (r=-0,249, P=0,011), homosistein (r=-0,394, P<0,001) seviyeleri arasında ters zayıf bir korelasyon saptandı. Maternal folat düzeyleri neonatal folat düzeyleri ile kuvvetli pozitif (r=0,735, P<0,001); yenidoğan B12 vitamini düzeyleri ile zayıf pozitif (r=0,327, P=0,001); neonatal homosistein seviyeleri ile orta derecede ters korelasyon gösterdi (r=-0,505, P<0,001).

Sonuç: Gebelik döneminde annelerde vitamin değerlerinin optimal seviyelerde tutulması, bebeklerin gelecek yaşamlarında obeziteye yol açabilecek metabolik dengesizliklerini azaltmak açısından önemlidir.

Anahtar kelimeler: Gebelik, Vitamin B12, Folat, Yenidoğan, İnsülin direnci, Metabolik belirteçler

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Introduction

Obesity is a major cause of morbidity and mortality worldwide [1]. The prevalence of obesity in the pediatric population exhibits a noteworthy, global increase. Childhood obesity is linked with not only obesity in adulthood, but also increased risk for various metabolic disorders. The nutritional imbalances in pregnancy may lead to decreased serum levels of high-density lipoproteins (HDL), increased triglyceride levels as well as abnormal birth weight [2]. These alterations may enhance the occurrence of obesity, coronary heart disease, type 2 diabetes mellitus (DM) and deterioration of cognitive functions in the later life [3].

Maternal nutritional habits and vitamin deficiencies at the beginning of pregnancy may be related to imbalances of vitamin B12 and folate metabolism [4]. The low levels of vitamin B12, and elevated levels of folate may lead to insulin resistance and metabolic disorders in infants [5-7]. Experimental studies demonstrated that deficiency of vitamin B12 was accompanied by high adiposity, insulin resistance, high blood pressure, and impaired lipid metabolism [8-10]. Low levels of vitamin B12 during pregnancy may alter the methylation pattern of insulin-like growth factor-2 (IGF-2) and influence fetal growth [11], while also restricting the synthesis of S-adenosylmethionine (SAMe), thus leading to increased biosynthesis of cholesterol [12].

Recent studies indicated that vitamin B12 insufficiency during pregnancy was common even in non-vegetarian populations, and that the concentrations of vitamin B12 decreased from the first to the third trimester. No consistent association was reported between vitamin B12 deficiency and birth weight, and the metabolic indicators of newborn such as insulin resistance and blood lipid profiles [13,14].

Our purpose was to assess the correlation between the maternal levels of vitamin B12 and folate, fetal anthropometric measurements at birth, and metabolic indicators such as blood lipid profile, insulin resistance.

Materials and methods

Study design

This prospective cohort was implemented between January 2016 and April 2016 in the pediatric departments of our tertiary care center following the approval of Ethical committee of our institution (Ethic committee of Memorial Hospital-29.01.2016-No:2016/1). Written informed consent was obtained from every participant. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendment or comparable ethical standards.

Initially, 125 women admitted for pregnancy follow-up were enrolled in the study. Since 23 pregnant women declined to participate in the trial, our study group comprised 102 cases with a mean age of 29.15 (4.52) years. A questionnaire form that reviews the socio-demographic features (age, education level, body height, pre-pregnancy body weight, gravida, parity and gestation age, lifestyle, pregnancy history, comorbidities before pregnancy, use of medications before and during pregnancy, family history, and nutritional habits) were filled for every participant. The body-mass indices (BMI) of the pregnant women at the beginning of pregnancy and on the day of labor were noted. Blood samples were collected from brachial veins after at least six hours of fasting and centrifuged within 5 min at 4000 rpm and 4°C. The sera were stored at −80°C until analysis. The serum levels of vitamin B12, folate, glucose, high-density lipoproteins (HDL), low-density lipoprotein (LDL), triglycerides, cholesterol, insulin, and homocysteine were measured in pregnant women. Homeostatic model assessment insulin resistance (HOMA-IR) was evaluated for every participant.

The data on anthropometric measurements of the newborns, including birthweight (g), length (cm) and head circumference, were recorded immediately after birth by a trained assistant. The serum levels of vitamin B12, folate, HDL, LDL, triglycerides, glucose, cholesterol, insulin, and homocysteine were measured from the cord blood of newborns. HOMA-IR levels were assessed for every newborn.

Serum studies

Serum levels of glucose, cholesterol, triglycerides, HDL, and LDL were studied by a commercially available kit (GMI Inc., Bunker, Minnesota, USA). Fried Ewald formula was employed for measurement of LDL cholesterol, whereas HOMA-IR was assessed with Homeostasis Model Assessment 2 computer model (HOMA 2), based on fasting blood glucose and insulin levels [15-17].

Electrochemiluminescence immunoassay method was utilized for studying serum levels of insulin, vitamin B12 and folate (Roche Cobas e411 Immunology Analyzer, Roche Diagnostics, Basel, Switzerland). For vitamin B12, levels ≥191 ng/L were accepted as normal. The homocysteine levels from serum and cord blood were investigated using the microparticle enzyme immunoassay (MEIA) method (Abbot IMX®, Abbott Lab., Abbott Park, IL, USA).

Exclusion criteria were unwillingness to participate, presence of a chronic disease and use of medications other than multivitamin or folate supplements for the mothers, and congenital anomalies and prematurity for the newborns.

Statistical analysis

Analysis of data was performed by IBM Statistical Package for Social Sciences (SPSS) Statistics v.21 software (SPSS Inc., Chicago, IL, USA). Quantitative variables are presented as mean (standard deviation) or median, minimum, and maximum values, while categorical variables are expressed as number and percentage. The assumption of normality needed for the utility of parametric tests has been investigated with the Shapiro – Wilks test. The significance of the difference between two groups was evaluated with either T-test or Mann Whitney U test. The significance of the correlation between variables was assessed using Pearson or Spearman correlation coefficient. *P*-value <0.05 was considered statistically significant.

Results

A total of 102 mothers and their newborns were analyzed. An overview of maternal and neonatal baseline descriptive data is presented in Table 1. The mean maternal age was 29.15 (4.52) years (range: 19-49); the mean BMI values before and at the end of pregnancy were 25.1 kg/m^2 (3.9) and

30.5 kg/m^2 (3.7), respectively. While none of the mothers used vitamin B12 supplements, 55.4% of the mothers used folate supplements, and 5 (4.9%) of the mothers were vegetarian. The mean vitamin B12 level of the mothers were 228.3 ng/ml; 32 (31.4%) mothers had low vitamin B12. The mean folate level was 15.1 µg /ml. None of the mothers had low folate levels. The mean gestational age of the newborns was 38.8 (0.8) weeks. The mode of delivery was cesarean section (C/S) in 73 cases (71.6%), and vaginal delivery (28.4%) in 29 cases.

The baseline descriptive data for neonates is presented in Table 2. The pregnant women gave birth to 45 female (44.1%) and 57 male (55.9%) neonates. The average BMI of neonates was 13.18 (1.27) kg/m^2.

Table 3 displays the serum maternal and neonatal levels of vitamin B12, folate and other markers. The mean serum levels of vitamin B12 in the mother and newborn were 246.37 ng/ml (99.12) and 460.7 ng/ml (339.95), respectively. The mean maternal and neonate folate levels were 15.89 µg /ml (4.36), and 18.90 µg /ml (2.22), respectively.

Table 1: Baseline descriptive data of mothers in our series (n=102)

Variable		Mean (SD)	Min – Max
Age		29.15 (4.52)	19 – 49
BMI (before pregnancy)		25.12 (3.93)	43 – 86
BMI		30.6 (3.79)	22 – 42
Gravidity		1.64 (1.04)	1 – 7
Gestational age (weeks)		38.77 (0.82)	38 - 41
		Number	Percentage
Educational level	PS	7	6.9
	SS	49	48.0
	University	46	45.1
Mode of delivery	Vaginal	29	28.4
	C/S	73	71.6
Folate use	No	45	44.1
	Yes	57	55.9
Vegetarian	No	97	95.1
	Yes	5	4.9
Smoking	No	94	92.2
	Yes	8	7.8

BMI: body-mass index, PS: primary school, SS: secondary school, C/S: cesarean section

Table 2: Baseline descriptive information for newborns in our series (n=102)

Variables		Mean (SD)	Min – Max
Body-mass index (kg/m^2)		13.18 (1.27)	10.15 – 16.55
Head circumference (cm)		34.24 (1.52)	30 - 37
		Number	Percentage
Sex	Female	45	44.1
	Male	57	55.9

SD: Standard deviation

Table 3: Serum levels of laboratory parameters under investigation

Variable	Maternal	Neonatal
Vitamin B12 (ng/ml)	246.37 (99.12)	460.7 (339.95)
Folate (µg/ml)	15.89 (4.36)	18.90 (2.22)
Glucose (mg/dl)	82.36 (16.17)	71.75 (26.42)
Cholesterol (mg/dl)	258.67 (45.76)	60.93 (15.65)
TG (mg/dl)	265.72 (89.23)	28.82 (16.01)
HDL (mg/dl)	73.93 (19.51)	29.91 (10.83)
LDL (mg/dl)	134.73 (41.98)	25.25 (8.44)
Insulin (mIU/l)	20.12 (19.43)	12.16 (11.55)
HOMA-IR	4.31 (6.33)	2.34 (2.89)
Homocysteine (µmol/l)	5.46 (2.75)	5.53 (1.56)

TG: triglyceride, HDL: high-density lipoprotein, LDL: low-density lipoprotein, HOMA-IR: homeostasis model assessment insulin resistance

The distribution of maternal serum parameters with respect to cut-off points is shown in Table 4. The results indicated that 32 pregnant women (31.4%) had low levels of vitamin B12 (<191 ng/ml). Notably, serum folate levels were sufficient (≥4.9 µg/ml) in all pregnant women.

Table 4. The distribution of maternal serum parameters with respect to cut-off points

Variable		Number	Percentage
Body-mass index (kg/m^2)	18.5 - 24.9	6	5.9
	25 – 29.9	39	38.2
	≥ 30	57	55.9
Vitamin B12 (ng/ml)	< 191	32	31.4
	≥ 191	70	68.6
Folate (µg/ml)	< 4.9	0	0.0
	≥ 4.9	102	100.0
Glucose (mg/dl)	≤ 125	99	97.1
	> 125	3	2.9
Cholesterol (mg/dl)	≤ 200	5	4.9
	> 200	97	95.1
TG /mg/dl)	≤ 150	9	8.8
	> 150	93	91.2
HDL (mg/dl)	≤ 40	1	1.0
	> 40	101	99.0
LDL (mg/dl)	< 130	50	49.0
	≥ 130	52	51.0
Insulin (mIU/l)	< 10	29	28.4
	≥ 10	73	71.6
HOMA-IR	< 2	34	33.3
	≥ 2	68	66.7
Homocysteine (µmol/l)	≤ 15	101	99.0
	> 15	1	1.0

TG: triglyceride, HDL: high-density lipoprotein, LDL: low-density lipoprotein, HOMA-IR: homeostasis model assessment insulin resistance

Table 5 demonstrates a comparative analysis of descriptive and laboratory parameters with respect to maternal and newborn serum vitamin B12 levels. In terms of maternal vitamin B12 levels, BMI, serum vitamin B12, insulin, homocysteine and HOMA-IR were found to differ significantly in neonates. Newborns of mothers with lower serum vitamin B12 levels (<191 ng/ml) had remarkably higher BMI (P=0.004), higher levels of insulin (P=0.012), HOMA-IR (P=0.001), homocysteine (P=0.001) and lower levels of serum vitamin B12 (P<0.001).

Table 5: Comparative analysis of descriptive and laboratory parameters with respect to maternal and newborn serum vitamin B12 levels

	Maternal		*P*-value	Neonatal		*P*-value
	<191 ng/ml	≥191 ng/ml		<191 ng/ml	≥191 ng/ml	
Age	28.59 (3.93)	29.40 (4.77)	0.406	-	-	-
BMI	25.45 (3.83)	24.97 (3.99	0.570	-	-	-
BMI**	30.83 (3.52)	30.5 (3.93)	0.681	13.70 (1.10)	12.93 (1.27)	0.004
Folate	15.30 [5 - 20]	18.25 [7 - 20]	0.097	20 [10 - 20]	20 [13 - 20]	0.230
Glucose	82 [50 - 186]	81.5 [60 - 126]	0.845	63 [48 - 156]	65.5 [26 - 156]	0.405
Cholesterol	251.53 (35.48)	261.93 (49.65)	0.289	61.81 (14.63)	60.53 (16.18)	0.703
TG	290.19 (109.77)	254.53 (76.40)	0.061	26.5 [11 - 99]	25 [7 - 84]	0.662
HDL	71.16 (18.08)	75.20 (20.12)	0.334	27.5 [10 - 55]	28 [11 - 66]	0.806
LDL	124.81 (36.71)	139.26 (43.67)	0.107	25.09 (6.07)	25.33 (9.36)	0.880
Insulin	14.5 [2 - 114]	13.95 [2 - 112]	0.968	11.25 [4 - 65]	8.45 [0 - 68]	0.012
HOMA-IR	3.15 [0 - 52]	2.60 [0 - 25]	0.700	2.2 [0 - 15]	1.20 [0 - 20]	0.001
Homocysteine	5.65 [2.8 – 29.6]	4.9 [2.9 – 8.8]	0.109	6.27 (1.73)	5.19 (1.36)	0.001

BMI*: body-mass index before pregnancy, BMI**: BMI on the day of labour, TG: triglyceride, HDL: high-density lipoprotein, LDL: low-density lipoprotein, HOMA-IR: homeostasis model assessment insulin resistance

Table 6: An overview of maternal and neonatal serum vitamin B12 and folate levels with respect to various characteristics of the mother

		Maternal				Neonatal			
		Vitamin B12	*P*-value	Folate	*P*-value	Vitamin B12	*P*-value	Folate	*P*-value
Mode of delivery	V	211 [99 - 571]	0.873	14.8 [5 - 20]	0.013	373 [123 - 1916]	0.659	20 [14 - 20]	0.280
	C/S	227 [59 - 563]		18.9 [7 - 20]		368 [98 - 1983]		20 [10 - 20]	
Folate use	No	224 [59 - 571]	0.928	15.5 [5 - 20]	0.151	378 [98 - 1916]	0.835	20 [13 - 20]	0.652
	Yes	227 [99 - 563]		18.6 [7 - 20]		368 [123 - 1983]		20 [10 - 20]	
Vegetarian	No	227 [59 - 571]	0.125	17.5 [5 - 20]	0.887	371 [98 - 1983]	0.303	20 [10 - 20]	0.718
	Yes	158 [120 - 370]		14.1 [11 - 20]		231 [182 - 1715]		20 [14 - 20]	
Smoking	No	227 [59 - 571]	0.463	16.9 [5 - 20]	0.097	366 [98 - 1983]	0.538	20 [10 - 20]	0.317
	Yes	195 [99 - 352]		19.85 [11 - 20]		389 [123 - 771]		20 [14 - 20]	

V: vaginal, C/S: cesarean section

An outline of maternal and neonatal serum vitamin B12 and folate levels with respect to various characteristics of the mother is given in Table 6. Notably, mothers who gave birth via C/S had higher levels of folate than those who underwent vaginal delivery (P=0.014). Interestingly, folate supplementation did not yield a significant difference in neither maternal (P=0.151) nor neonatal (P=0.652) serum folate levels.

The results of correlation analysis for maternal serum levels of folate and vitamin B12 and neonatal biomarkers is shown in Table 7. We noted that maternal vitamin B12 levels was positively and strongly correlated with neonatal vitamin B12 levels (r=0.719, P<0.001). There was an inverse and weak correlation between maternal vitamin B12 levels and neonatal serum levels of insulin (r=-0.221, P=0.025), HOMA-IR (r=-0.249, P=0.011) and homocysteine (r=-0.394, P<0.001). Maternal folate levels were strongly and positively correlated with neonatal folate (r=0.735, P<0.001), weakly and positively correlated with neonatal vitamin B12 (r=0.327, P=0.001), moderately and inversely correlated with neonatal homocysteine (r=-0.505, P<0.001).

Table 7: Analysis of the correlation between maternal serum levels of vitamin B12 and folate and neonatal variables under investigation

	Maternal vitamin B12		Maternal folate	
Neonatal	r	*P*-value	r	*P*-value
Vitamin B12	0.719	<0.001	0.327	0.001
Folate	0.118	0.236	0.735	<0.001
Glucose	0.062	0.538	0.007	0.947
Cholesterol	0.004	0.971	0.073	0.463
TG	0.035	0.728	-0.165	0.097
HDL	-0.049	0.623	0.077	0.441
LDL	0.078	0.434	0.043	0.668
Insulin	-0.221	0.025	0.084	0.400
HOMA-IR	-0.249	0.011	0.050	0.617
Homocysteine	-0.394	<0.001	-0.505	<0.001

TG: triglyceride, HDL: high-density lipoprotein, LDL: low-density lipoprotein, HOMA-IR: homeostasis model assessment insulin resistance, correlation coefficients (r): 1 - 0.90: very strong association; 0.89 – 0.70: strong association; 0.69 – 0.40: moderate association; 0.39 – 0.20: weak association; 0.19 – 0.0: no associations

Discussion

Suboptimal concentrations of vitamin B12 may be independently associated with abnormal birth weight, an adverse lipid profile, and higher insulin resistance in neonates. Therefore, that may serve as surrogate markers for metabolic disorders such as obesity, type 2 diabetes, and metabolic syndrome in later life in many populations [2]. We investigated the serum levels of vitamin B12 and folate in pregnant women to investigate whether they are correlated with metabolic indicators and fetal anthropometric measurements at birth. Results of the current study imply that low levels of maternal vitamin B12 were associated with an increased likelihood of obesity and glucose intolerance in neonates.

There is an association between vitamin B12 levels and indicators of metabolic risk (such as lipid profiles) at birth [2]. The increased levels of homocysteine in the patients with low vitamin B12 suggest that these low levels can be clinically significant and represent a frank insufficiency at the tissue level [2,15]. The recent studies have reported a rate of 40% for low vitamin B12 level in mothers, which was attributed to hemodilution, changes in binding proteins, active transport to the fetus as well as consumption of processed foods and improved hygiene [2,18].

Adaikalakoteswari et al. [2] proposed that decreased levels of maternal vitamin B12 were linked with fetal insulin resistance, lower HDL and higher triglycerides. Similarly, an experimental study demonstrated that adverse lipid profile was detected in rats born to vitamin B12 restricted dams [19]. It can be postulated that low maternal vitamin B12 status may unfavorably influence the lipid profile in the newborn. We observed that maternal vitamin B12 levels were positively correlated with neonatal vitamin B12 levels and inversely correlated with neonatal insulin, HOMA-IR, and homocysteine levels. On the other hand, no remarkable association could be established between maternal and neonatal lipids. Further trials are warranted to unveil the roles of lipids in vitamin B12, folate and glucose metabolism during pregnancy.

Supplementation of vitamin B12 and folate in pregnant women may be useful for reduction of metabolic risks for neonate and achievement of more favorable perinatal outcomes. Our data is important since we observed that maintenance of sufficient folate levels in the mother was accompanied with adequate folate level and diminution of homocysteine in the neonate. Maternal vitamin B12 levels were inversely correlated with neonatal head circumference and neonatal triglyceride levels. Thus, we speculate that maternal vitamin B12 supplementation is crucial for regulation of favorable fat and glucose metabolisms in the newborn.

Interestingly, the relationship between maternal folate and neonatal homocysteine became insignificant when maternal homocysteine level was included in the analysis. Hence, the effect of folate on neonatal homocysteine may be mediated through maternal homocysteine while the impact of vitamin B12 may be partly independent of it. In accordance with this data, low levels of maternal vitamin B12 were predictive for hyperhomocysteinemia in both the newborns and the mothers [20].

Vitamin B12 is supposed to be the strongest driver of homocysteine, and an established metabolic risk factor [5,21]. There is a strong inverse correlation between maternal vitamin B12 and neonatal homocysteine levels [2]. In the relevant literature, BMI was higher in patients with low vitamin B12 [22]. However, the causality of this association has not been yet elucidated. The biochemical basis for increased metabolic risk due to low vitamin B12 may be due to 2 pathways: Vitamin B12 is a cofactor for conversions of homocysteine to methionine and methyl malonyl Co-A to succinyl Co-A. Thus, oxidation of free fatty acids will be impaired, and lipogenesis will occur in the case of deficiency of vitamin B12 [5]. Low maternal vitamin B12 and high folate status may be involved in the epidemic of adiposity and type 2 DM. Our data is coherent with these results.

Our results imply that the dietary supply of methyl donors like folate and vitamin B12 during pregnancy is necessary for normal growth, development, and physiological functions of newborn. Maternal deficiency of vitamin B12 was reflected as higher BMI, increased levels of insulin, HOMA-IR and homocysteine in neonates. Therefore, we suggest that monitorization of maternal vitamin B12 and replacement of any deficiency detected during pregnancy may avoid further adverse metabolic consequences in the newborn. Deficiency of vitamin B12 is particularly associated with altered lipid profile and increased metabolic risk [12]. Sukumar et al. [23] suggested that vitamin B12 insufficiency during pregnancy was common even in non-vegetarian populations and there was no clear association

between vitamin B12 and low birth weight. Vitamin B12 exhibits a crucial function in adipose metabolism, and its deficiency causes increased levels of homocysteine and cholesterol. There were remarkable associations of vitamin B12 deficiency with BMI, triglycerides, and total cholesterol [12]. Thus, maintenance of adequate levels of vitamin B12 during periconceptional period is important and special risk groups such as vegetarians and patients with malabsorption need to be evaluated carefully [12]. However, we did not come across any adverse metabolic outcome due to a vegetarian diet.

Experimental studies have shown that maternal folic acid supplementation can alter DNA methylation and gene expression in the developing fetus, which may confer disease susceptibility later in life. Maternal folic acid supplementation affects tissue folate concentrations, DNA methylation and gene expression in the offspring in a gestation-period-dependent and organ-specific manner [24]. Even though low maternal folate levels were initially correlated with metabolic risk markers in the newborn, these associations became invisible after regression analysis [2]. A folate supply may contribute to the implantation and development of the placenta and improvement of the endothelial function [25]. There is a remarkable interaction between metabolisms of folate and vitamin B12, and a high folate intake may hinder the hematologic and neurodegenerative symptoms of vitamin B12 deficiency. The investigation of the link between sociodemographic factors with vitamin B12 status revealed that gender and income were not associated with serum vitamin B12 levels. On the other hand, obesity was negatively correlated with vitamin B12 status [26]. We suggest that maternal supplementation of vitamin B12 and folate may be the initial step in the combat with obesity and DM.

Limitations

The modest sample size and data restricted to the experience of a single institution. Furthermore, the impact of confounding variables such as social, environmental, genetic, metabolic, and ethnic factors may have affected our results. Hence, interpretation of our results must be made cautiously. Further multi-centric trials on larger series are warranted to identify the consequences of deficiencies of folate and vitamin B12 in pregnant women.

Conclusion

The main strength of this study was the investigation of the relationship between multiple metabolic indicators and folate, vitamin B12. In conclusion, we suggest that the achievement of optimal serum levels of vitamin B12 and folate during pregnancy are important for reducing the likelihood of neonatal DM and obesity. Identification of deficiency of these vitamins in the periconceptional period is important to provide adequate nutritional support to avoid obesity and related metabolic morbidities. Levels of vitamin B12 may have a significant potential to affect the health of future offspring. Policies and recommendations should be developed for food fortification and supplement use to decrease risks for metabolic hazards such as type 2 DM, obesity, and cardiovascular diseases.

The achievement of optimal serum levels of vitamin B12 and folate during pregnancy are important for reducing the likelihood of neonatal glucose metabolism abnormalities and obesity in later life. Identification of deficiency of these vitamins during the periconceptional period is important to provide adequate nutritional support to avoid obesity and related metabolic morbidities.

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Risk factors for bacteremia following endoscopic retrograde cholangiopancreatography

Endoscopic retrograde cholangiopancreatography sonrası gelişen bakteriyemide eşlik eden risk faktörleri

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Abstract

Aim: Bacteremia after endoscopic retrograde cholangiopancreatography (ERCP) is a serious complication, but its risk factors have not yet been clearly defined. In this study, we aimed to determine the incidence of bacteremia and associated risk factors after ERCP.

Methods: This retrospective-cohort study was conducted between January 2017 and December 2018. Patients who had no signs of infection before the procedure and who developed bacteremia after the procedure were included in the study. For each patient who developed bacteremia, two randomized control patients who underwent ERCP and did not develop bacteremia were selected to compare risk factors, clinical and laboratory findings.

Results: A total of 91 bacteremia attacks were detected in 86 of the 4237 patients who underwent ERCP procedure. Bacteremia rate after ERCP was 2%. In multivariate analysis, the age of the patient, presence of biliary tract cancer, cholecystitis / cholangitis, pancreatitis and biopsy were determined as significant risk factors for post-ERCP bacteremia (P=0.009, P<0.001, P=0.008, P=0.002 and P=0.014 respectively).

Conclusion: The development of bacteremia after ERCP significantly increases the risk of mortality. The mean age of the patients who died was older. This result supports the use of prophylactic antibiotics especially in elderly patients. We think that knowledge of potential ERCP complications and risk factors may help reduce the incidence and severity of complications.

Keywords: Endoscopic retrograde cholangiopancreatography, Bacteremia, Risk factors

Öz

Amaç: Endoskopik retrograd kolanjiyopankreatografi (ERCP) sonrası bakteriyemi ciddi bir komplikasyondur, ancak bu komplikasyon için risk faktörleri henüz net olarak tanımlanmamıştır. Bu çalışmada ERCP sonrası bakteriyemi ve ilişkili risk faktörlerinin insidansını belirlemeyi amaçladık.

Yöntemler: Bu retrospektif-kohort çalışma Ocak 2017-Aralık 2018 tarihleri arasında yapıldı. İşlem öncesi enfeksiyon belirtisi olmayan ve işlem sonrası bakteriyemi gelişen hastalar çalışmaya alındı. Bakteriyemi gelişen her hasta için ERCP uygulanan ve bakteriyemi geliştirmeyen iki randomize kontrol hastası risk faktörlerini, klinik ve laboratuvar bulgularını karşılaştırmak için seçildi.

Bulgular: ERCP prosedürü uygulanan 4237 hastanın 86'sında toplam 91 bakteriyemi atağı tespit edildi. ERCP sonrası bakteriyemi oranı % 2 olarak bulundu. Çok değişkenli analizde, hastanın yaşı, safra yolları kanseri, kolesistit / kolanjit, pankreatit ve biyopsi bakteriyemi için anlamlı risk faktörleri olarak bulundu (sırasıyla P=0,009, P<0,001, P=0,008, P=0,002 ve P=0,014) .

Sonuç: ERCP sonrası bakteriyemi gelişimi mortalite riskini önemli ölçüde artırmaktadır. Çalışmamızda, kaybedilen hastaların yaş ortalaması daha büyüktü. Bu sonuç, özellikle yaşlı hastalarda profilaktik antibiyotik kullanımını destekler niteliktedir. Potansiyel ERCP komplikasyonları ve risk faktörleri hakkındaki bilgi sahibi olmanın, komplikasyon insidansını ve şiddetini azaltmaya yardımcı olabileceğini düşünüyoruz.

Anahtar kelimeler: Endoscopic retrograde cholangiopancreatography, Bakteriyemi, Risk faktörleri

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a complex interventional procedure that is frequently used for diagnosis and treatment of pancreatic-biliary diseases [1-2]. Although the scope of its use increases daily due to advances in technology, ERCP remains an invasive procedure with potential complications including infection, bleeding, pancreatitis, and perforation [3]. Approximately 500,000 ERCP procedures are performed annually in the United States, with an ERCP-related complication rate of 4% to 10.3% and a mortality rate between 0.05% and 1% [4]. The most serious complication following ERCP is bloodstream infections (BSI). Although the actual incidence of BSI after ERCP is unknown, researchers have reported the incidence of bacteremia in different populations as ranging between 2.2% and 21% [4-6]. Enteric bacteria enter the biliary tree hematogenously or after endoscopic or radiological manipulation [7]. It has been reported that septic complications after ERCP are more common in patients with obstructed biliary ducts and inadequate drainage during the procedure [4,8]. ERCP bacteremia is reportedly more common during combined use of percutaneous and endoscopic procedures, placement of stent for malignant stenosis, presence of jaundice, in case of incomplete or unsuccessful biliary drainage or when the procedure is performed by less experienced doctors [7-9]. Sepsis is the most common cause of death associated with ERCP [8]. Risk factors need to be well known to improve the reliability of the ERCP procedure [10].

Few data are available on the rates of post-ERCP bacteremia. In this study, we aimed to determine the frequency of bacteremia after ERCP and associated risk factors in a tertiary branch hospital.

Materials and methods

This study was conducted between January 2017 and December 2018 in a tertiary branch hospital where ERCP was performed intensively. A total of 4237 ERCP procedures performed during this period were evaluated. Patients who did not have any pre-procedural sepsis-related symptoms and signs or any microorganism reproduction in their blood culture were included in the study. Patients did not receive routine empirical antibiotic treatment before ERCP. Bacteremia was defined as the presence of positive bacterial cultures (excluding contamination) in blood samples obtained from patients with postoperative fever, according to the definition of blood stream infection by the National Health Safety Network (CDC-NHSN) [11]. Patients with a fever of > 38.0 ºC, tremors in the first 30 days after ERCP procedure and positive blood cultures were included in the study. Patients with a proven infection at another site after ERCP were excluded. Age, ERCP indication, isolated microorganisms, and risk factors for bacteremia were recorded. For the identification of microorganisms, Phoenix 100 (Becton Dickinson, USA) automated system was used.

The distribution of microorganisms in patients who developed bacteremia after ERCP was evaluated. The characteristics of patients who developed and died of bacteremia after ERCP were compared with those of patients who lived.

For each patient who developed bacteremia, two randomized patients who underwent ERCP with no post-procedural bacteremia were selected as controls. A total of 172 patients were included in the control group. Patients with and without bacteremia after ERCP were compared in terms of risk factors, clinical and laboratory findings, and mortality rates.

Statistical analysis

Differences were assessed using a Pearson χ^2 test or Fisher's exact test (when expected cell frequencies were <5) in categorical variables and independent t-test in non-categorical variables. SPSS version 20.0 was used for all statistical analyses. *P*-value of <0.05 was considered statistically significant.

Results

A total of 4237 ERCP procedures were performed in our hospital between January 2017 and December 2018 under elective conditions, during which 91 bacteremia attacks in 86 patients were detected after the procedure. The rate of bacteremia after ERCP was 2%. Among 86 patients who developed post-ERCP bacteremia, 31 were female (36%) and 55 were male (64%). The patients' ages ranged from 20 to 95 years with a mean age of 65.36 (16.2) years. The median time for development of bacteremia after ERCP was 6 days. When bacteremia episodes were analyzed, it was found that 79% were gram-negative and 21% were gram-positive bacteremia. The most frequently isolated agent was Escherichia coli (32 isolates, 35%), followed by Klebsiella pneumonia (19%) with 18 isolates and Pseudomonas aeruginosa (18%) with 17 isolates (Table 1).

The most common risk factors in patients who developed bacteremia after ERCP were history of prior ERCP (52%), presence of a biliary stone (51%), stent (48%), cholecystitis / cholangitis (37%) and diabetes (31%). The distribution of microorganisms in patients with bacteremia after ERCP, according to the most common risk factors, is shown in Table 2.

Table 1: Distribution of the microorganisms in patients who developed bacteremia after ERCP

Microorganisms	No (%) of microorganisms
Gram positive microorganisms	
Enterococcus spp	8/91 (8.79%)
Staphylococcus spp	8/91 (8.79%)
Streptococcus spp	3/91 (3.30%)
Gram negative microorganisms	
Escherichia coli	32/91 (35.16%)
Klebsiella pneumonia	18/91 (19.78%)
Pseudomonas aeruginosa	17/91 (18.68%)
Acinetobacter baumannii	2/91 (2.20%)
Stenotrophomonas maltophilia	2/91 (2.20%)
Proteus spp	1/91 (1.10%)

Table 2: The most common microorganisms according to risk factors in patients with bacteremia after ERCP

Microorganism	Risk Factors						Exitus (n:20)
	Malign biliary stricture (n:33)	DM (n:27)	Stent (n:42)	Prior ERCP (n:45)	Biliary stone (n:44)	Cholecystitis / cholangitis (n:32)	
E. coli	10 (30%)	14 (52%)	15 (36%)	18 (40%)	15 (34%)	12 (37.5%)	2 (10%)
Klebsiella spp.	8 (24%)	4 (15%)	11 (26%)	11 (24%)	8 (18%)	7 (21.9%)	4 (20%)
Pseudomonas spp.	9 (27%)	2 (7%)	12 (29%)	12 (27%)	8 (18%)	6 (18.8%)	4 (20%)
Enterococcus spp.	6 (18%)	-	2 (5%)	2 (4%)	3 (7%)	2 (6.2%)	2 (10%)
Staphylococcus spp.	1 (3%)		2 (5%)	2 (4%)	6 (14%)	4 (12.5%)	2 (10%)

The mean age of patients with post-procedural bacteremia was higher than those without (*P*=0.007). There was no difference in terms of gender between those with and without bacteremia. The risk of bacteremia was 5.7 fold higher in the presence of biliary tract cancer (*P*<0.001), (OR: 5.7, 95% CI: 2.925-11.017), 2.1 fold higher in the presence of cholecystitis / cholangitis (*P*=0.01) (OR: 2.09, 95% CI: 1.186 -3.682) and 3.5 fold higher in patients with cirrhosis, which was not statistically

significant (P=0.122) (OR: 3.5, 95% CI: 0.811-14.908). Bacteremia risk significantly increased in patients with pancreatitis (P=0.003). The risk of bacteremia was 2.9 times higher in patients who underwent diagnostic biopsy of intrahepatic or extrahepatic biliary tracts during ERCP, which was significant (P=0.03). In those with bacteremia, mortality risk was 25.8 times higher (P<0.001) (OR: 25.8, 95% CI: 5.857-113.274), CRP elevation was 49 fold (OR: 49.1, 95% CI: 6.677-361.460), WBC elevation (leukocytosis), 8.7 fold (OR: 8.7, 95% CI: 4.207-18.067), bilirubin elevation, 8.7 fold (OR: 8.7, 95% CI: 4.723-16.093) and ALP elevation, 4.2 fold (OR: 4.2, 95% CI: 2.277-7.763) (P<0.001 for all) (Table 3).

Multivariate analysis showed that the age of patients, presence of biliary tract cancer, cholecystitis / cholangitis, pancreatitis and biopsy were significant risk factors for the development of bacteremia (P=0.009, P<0.001, P=0.008, P=0.002 and P=0.014, respectively).

Among 86 patients who developed bacteremia after ERCP, all-cause 30-day mortality rate was 23% (n: 20). Of the 20 patients who died within 30 days, 11 had malignant biliary stenosis (55%). Klebsiella, Pseudomonas (each in 4 patients, 20%) and E. coli (in 2 patients, 10%) were the most common causative agents.

In terms of gender, no difference was found between patients who lived and those who died within 30 days (p> 0.05). The mean age of non-survivors (71.9 (12.2) years) was higher than survivors (63.3 (16.8) years) (P=0.039). In patients who died, the incidences of biliary tract cancer was 2.4 times higher, diabetes mellitus, 1.6 times higher, and biopsy, 1.8 times higher than those who lived; however, no statistically significant difference was found between non-survivors and survivors in terms of risk factors or laboratory findings (Table 4).

Table 3: Comparison of baseline characteristics, laboratory findings, risk factors and mortality

Characteristic	Patients with bacteremia (n:172) %	Patients without bacteremia (n:86) %	*P*-value
Age, mean	59.05	65.36	0.007
Male sex	55.2	64	0.181
Biliary tract cancer	9.9	38.4	<0.001
Diabetes mellitus	24.4	31.4	0.233
Common bile duct stone	56.4	51.2	0.426
Cholecystitis/cholangitis	22.1	37.2	0.010
Pancreatitis	8.1	24.4	0.003
Liver cirrhosis	1.7	5.8	0.122
Presence of stent	52.3	48.8	0.597
ERCP before processing	55.2	52.3	0.659
Biopsy	5.2	14	0.030
Exitus	1.2	23.3	<0.001
Laboratory findings			
Increased white blood cell (N: 3.9-11.7 x103/µL)	7.0	39.5	<0.001
Increased C-reactive protein (N: <5 mg/L)	63.4	98.8	<0.001
Increased total bilirubin (N: 0.3-1.2 mg/dl)	30.2	79.1	<0.001
Increased alkaline phosphatase (N: 30-120 U/L)	51.2	81.4	<0.001
Increased amylase (N: 28-100 U/L)	28.5	10.5	0.002
Mean white blood cell	7.3	10.8	<0.001
Mean C-reactive protein	24	141	<0.001
Mean total bilirubin	2.03	6.02	<0.001
Mean alkaline phosphatase	194	306	0.006
Mean amylase	103	70	0.074

Table 4: Comparison of the baseline characteristics, laboratory findings, risk factors for bacteremia between living and deceased patients

Characteristic	Living patients (n:66) %	Deceased patients (n:20) %	*P*-value
Age, mean	63.38	71.90	0.039
Male sex	68.2	50.0	0.223
Biliary tract cancer	33.3	55.0	0.138
Diabetes mellitus	28.8	40.0	0.502
Common bile duct stone	54.5	40.0	0.376
Cholecystitis/cholangitis	36.4	40.0	0.976
Pancreatitis	10.6	0	0.193
Liver cirrhosis	6.1	5.0	1.000
Presence of stent	51.5	40.0	0.518
ERCP before processing	57.6	35.0	0.130
Biopsy	12.1	20.0	0.462
Laboratory findings			
Increased white blood cell (N: 3.9-11.7 x103/µL)	39.4	40.0	1.000
Increased C-reactive protein (N: <5 mg/L)	98.5	100	1.000
Increased total bilirubin (N: 0.3-1.2 mg/dl)	80.3	75.0	0.844
Increased alkaline phosphatase (N: 30-120 U/L)	81.8	80.0	1.000
Increased amylase (N: 28-100 U/L)	10.6	10.0	1.000
Mean white blood cell	10.6	11.2	0.609
C-reactive protein mean	137.9	150.6	0.586
Mean total bilirubin	6.2	5.4	0.647
Mean alkaline phosphatase	280.8	389.3	0.370
Mean amylase	2.1	61.4	0.742

Discussion

Although ERCP is a semi-critical procedure, various instruments such as wire, stent, and balloon are pushed along a long duodenoscope through an elevator mechanism to enter a sterile ductal environment [12]. The colonization and incomplete sterilization of the complex mechanism at the end of this duodenoscope used in the procedure has been held responsible for the transmission of infections [12]. In recent years, multidrug resistant microorganisms and carbapenem-resistant Enterobacteriaceae (CRE) have been reported to cause duodenoscope-related infections [12]. In our study, we found carbapenem resistance in 61.1% (11/18) of Klebsiella spp. isolates. Four of these 11 patients died. Three of the 32 E. coli isolates were also resistant to carbapenem (9.4%).

Our incidence of bacteremia after ERCP was 2%, which was similarly reported as 3.1% in the study of Kwak et al. [3], 2.24% in that of Anderson et al. [5] and 3.56% in that of Du et al. [6]. Worldwide, ERCP mortality ranges from 0 to 1.5% and can be caused by any complication. Mortality rate is generally high in therapeutic procedures [13]. In the study performed by Borges et al. [13], infection rate after ERCP was reported as 3%, bacteremia rate as 0.5% and mortality rate as 1.5%. In a 10-year retrospective study by Coelho-Prabhu et al. [4], post-ERCP infection and 30-day mortality rates were 1.5% and 2.4%, respectively. Although the reported frequency of clinically significant iatrogenic infections after ERCP is limited (1-3%), sepsis represents a common cause of death [14]. In our study, 30-day mortality rate was 23% in patients who developed bacteremia after ERCP. In a study by Novello et al. [15] including 2010 patients who underwent ERCP, septic complications were reported in 51 patients (2.5%), and 16 patients (31%) with tumor obstruction died within 30 days after ERCP.

The microorganisms responsible for infection after ERCP are Enterobacteriaceae (especially Escherichia coli and Klebsiella spp), alpha hemolytic streptococci, Pseudomonas aeruginosa, Enterococcus spp and Staphylococcus epidermidis

[8]. In our study, analysis of the bacteremia episodes after ERCP revealed that 79% were gram negative and 21% were gram positive bacteremia. The most isolated microorganisms were E. coli (35.16%), Klebsiella pneumonia (19.78%) and Pseudomonas aeruginosa (18.68%). In the study of Kwak et al. [3], the most common microorganisms in bacteremia episodes after ERCP were listed as E. coli, Klebsiella and Pseudomonas, akin to our study. Novello et al. [15] reported that P. aeruginosa was the most common causative agent, with a rate of 30%. Blockage of the bile duct system due to strictures, stones and tumors has been shown to be associated with bacteriobilia. Increasing the intrabiliary pressure (>25 mmHg) results in biliovenous reflux and bacteremia in patients with infected bile [16]. Specific risk factors for post-procedural infection include stenting in malignancy, presence of obstructed ducts and jaundice, combined percutaneous endoscopic procedures, primary sclerosing cholangitis, and incomplete or unsuccessful biliary drainage [14]. In our study, malignant biliary stenosis, pre-existing stents, recurrent ERCP procedures, and presence of stones in the biliary system were the most common risk factors in patients with post-ERCP bacteremia. Contaminated duodenoscopes, biliary stent placement, diagnosis of cholangiocarcinoma and active inpatient status were reported as risk factors for transmission of CRE infection in a single-center case series of 115 patients with ERCP-associated CRE bacteremia [12]. In patients with cholangiocarcinoma, there is a risk of sepsis, especially when intrahepatic biliary tract cannot be drained, in which case administration of intrahepatic contrast agent should be avoided [8-9]. It has been reported that the best predictor for development of infectious complications after ERCP is the confirmation that biliary tract obstruction is not fully resolved, and prophylactic antibiotic treatment reduces the risk of bacteremia after ERCP but does not affect overall mortality [17]. Dutta et al. [18] reported that sepsis may develop in the presence of abnormal biliary and pancreatic ducts after ERCP and appropriate antibiotic treatment should be initiated after the procedure.

Routine prophylactic antibiotics were not administered before ERCP in our center. In meta-analyses, the benefit of routine prophylactic antibiotic use before ERCP was not shown [9]. A retrospective review of 11,484 ERCPs over a 11-year period in a single institution assessed the role of antibiotics in cholangitis prevention, and showed that although the rate of routine prophylactic antibiotic use decreased from 95% to 25% over the years, the reduction of infection rate was limited (0.48% to 0.25%). In the multivariate analysis of the study, the risk of infection was found to be high only in transplant recipients who underwent biliary intervention [9]. The American Society for Gastrointestinal Endoscopy (ASGE) also does not recommend antibiotic prophylaxis in patients with biliary obstruction in which complete biliary drainage was provided by ERCP [8]. However, Thosani et al. [19] recommend the use of prophylactic antibiotics before the procedure, especially in elderly patients, patients who had been previously stented and those who underwent intraductal stone lithotripsy.

In our study, the presence of presence of biliary tract cancer, cholecystitis / cholangitis and pancreatitis, as well as biliary biopsy obtained during the procedure were found to be associated with the development of post-ERCP bacteremia. In a prospective study, Mollison et al. [20] reported that patients with biliary obstruction and those who underwent therapeutic endoscopic procedures were at the highest risk for bacteremia. In their study including 55 patients who developed sepsis after ERCP, Deviere et al. [21] reported that the incidence of septicemia was more prominent in malignant obstruction than in benign obstruction (% 21 versus % 3; $P<0.01$) mainly due to drainage problems associated with tumor infiltration. They also stated that the previous diagnostic ERCP procedure without drainage was associated with the development of septicemia after therapeutic ERCP. In our study, WBC, CRP, bilirubin, and alkaline phosphatase levels were significantly higher in patients who developed post-ERCP bacteremia. In their study, Kwak et al. [3] reported that alkaline phosphatase level was high in post-ERCP bacteremia. Motte et al. [22] did not detect any statistically significant difference between WBC, bilirubin, and alkaline phosphatase levels in patients with sepsis after endoscopic biliary stent implantation. In a study in which Rupp et al. [23] investigated risk factors associated with biliary infection, they found that serum CRP levels were increased in patients with bactobilia.

Limitations

The principal limitation of our study is its retrospective nature. In addition, the synergistic effects of multiple risk factors which may have led to post-ERCP complications were not analyzed. The third limitation was the usage of a single center's patient data, which increased the possibility of selection bias.

Conclusions

The development of bacteremia after ERCP significantly increases the risk of mortality. The mean age of the patients who died was older. This result supports the use of prophylactic antibiotics, especially in elderly patients. We think that knowledge of potential ERCP complications and risk factors may help reduce the incidence and severity of complications.

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Vertebral fractures and spinopelvic parameters in patients with osteoporosis

Osteoporozlu hastalarda vertebral kırıklar ve spinopelvik parametreler

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Abstract

Aim: Bone mineral density (BMD) generally assesses fracture risk in the elderly but is not included in assessment of vertebral fracture status. In this study we aimed to investigate spinal alignment and pelvic orientation in patients with osteoporosis and identify indicators of vertebral fractures (VFs).

Methods: Seventy patients above 50 years of age with osteoporosis were included in this retrospective cohort study. Patients were allocated to two groups comprising 29 patients with and 41 patients without VFs. Demographic and clinical characteristics and back pain scores evaluated by Visual Analogue Scale were obtained by scanning patient files. Sagittal vertebral axis (SVA), spinal and pelvic parameters were evaluated with lateral radiography. All parameters and their effect of VFs were compared in both groups.

Results: Femoral neck BMD, sacral slope, lumbar lordosis, and pain scores were significantly different in patients with and without VFs (P=0.016, P=0.032, P=0.010, P<0.001, respectively). However, no significant difference was observed in terms of lumbar spine BMD, pelvic tilt, pelvic incidence, and thoracic kyphosis (P=0.394, P=0.313, P=0.258, P=0.341, respectively). Sacral slope and lumbar lordosis were positively correlated in patients with and without VFs (r=0.54, P=0.003 and r=0.50, P=0.001, respectively). SVA>50 mm and pain scores were predictors of VFs according to results of logistic regression.

Conclusion: The spinal deformity in patients with osteoporosis may be explained by the spinal parameters. In our study, we concluded that pain and sagittal imbalance in osteoporosis patients are important parameters for vertebral fractures.

Keywords: Osteoporosis, Sagittal balance, Spinopelvic parameters, Vertebral fracture

Öz

Amaç: Kemik mineral yoğunluğu (KMY) genellikle yaşlı bireylerin kırık riski değerlendirmesini gösterir ancak vertebral kırık durumunun değerlendirilmesini içermez. Biz bu çalışmada osteoporozlu hastalarda spinal sagital denge bozukluğu ve pelvik uyum bozukluklarını araştırmayı ve vertebral kırıkların (VK) tahmini göstergelerini tanımlamayı amaçladık.

Yöntemler: Bu retrospektif kohort çalışmada 50 yaş üzeri 70 osteoporoz hastası dahil edildi. Hastalar vertebral kırıkları olan; 29 VK(+) ve olmayan; 41 VK(-) olmak üzere iki gruba ayrıldı. Demografik ve klinik özellikler ile Görsel Analog Skala ile ölçülen sırt ağrısı skorları dosya taraması yolu ile elde edildi. Lateral radyolojik inceleme ile sagital vertebral aks (SVA), spinal ve pelvik parametreler değerlendirildi. Tüm parametreler her iki grupta da karşılaştırıldı ve bu parametrelerin VK üzerindeki etkisi analiz edildi.

Bulgular: Vertebral kırığı olan ve olmayan hastalarda femur boynu KMY, sakral eğim, lomber lordoz ve ağrı skorlarının anlamlı derecede farklı olduğu bulundu (sırasıyla P=0.016, P=0.032, P=0.010, P<0.001). Bununla birlikte, lomber omurga KMY, pelvik tilt, pelvik insidans ve torakal kifoz açısından anlamlı bir fark gözlenmedi (sırasıyla P=0.394, P=0.313, P=0.258, P=0.341). Sakral eğim ile lomber lordoz arasında pozitif anlamlı bir korelasyon bulunmuştur (sırasıyla r=0.54, P=0.03 ve r=0.50, P=0.001). Lojistik regresyon sonuçlarına göre SVA >50 mm ve ağrı skorları VK'ın belirleyicileriydi.

Sonuç: Osteoporozlu hastalarda omurga deformitesi omurga parametreleriyle açıklanabilir. Çalışmamızda osteoporoz hastalarında ağrı ve sagital dengesizliğin, vertebral kırıkların göstergeleri olduğu sonucuna varıldı.

Anahtar kelimeler: Osteoporoz, Sagital denge, Spinopelvik parametreler, Vertebral kırık

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Introduction

Osteoporosis leading to an increased risk of fracture and poor posture is a global health problem involving more than 200 million people, the incidence of which is predicted to considerably increase by the year 2050 [1]. Impaired spinal biomechanics and spinal imbalance are important causes of vertebral fractures (VFs) and morbidity in patients with osteoporosis [2]. Studies have shown that when a vertebral fracture develops, the fracture risk increases more with the number of previous vertebral fractures, especially within the first year [3,4]. The increased fracture risk may not always be explained by low bone mineral density (BMD) [5]. Spinal curvature and load-bearing capacity of the spine are also thought to contribute to VFs [6]. On the other hand, thoracic kyphosis is another risk factor for a new vertebral fracture independent of BMD [7,8].

Various postural changes, such as increase in lumbar lordosis, posterior tilt or rotation of the pelvis, extension of the hip, flexion of knees and dorsiflexion of ankles, may occur due to an increase in thoracic kyphosis [9-14]. Additionally, patients with sagittal malalignment often present with pain, poor balance, and gait disturbance [15]. Numerous studies on spinopelvic parameters have shown that these measurements may change with age, gender, weight, and pelvic morphology [16,17].

Sagittal imbalance causes displacement of the sacrum and pelvis in case of loss of normal lumbar lordosis, or an increase in thoracic kyphosis, or both [18]. Many studies on spinal sagittal imbalance and radiographic spinopelvic parameters have investigated older populations but there are few studies on the effect of these parameters on VFs in osteoporotic patients.

In our study, we aimed to determine the importance of sagittal balance, lumbar lordosis, and thoracic kyphosis in patients with osteoporosis and whether these parameters in the osteoporotic spine are predictive factors in the development of spontaneous VFs.

Materials and methods

Patients who were referred to SANKO University, Sani Konukoğlu Research and Practice Hospital, Physical Medicine and Rehabilitation outpatient clinic between May-October 2018 were included in this retrospective cohort study. A total of 70 (67 females; 3 males) patients underwent BMD measurement and digital x-rays radiographs. Back pain scores, previously evaluated by visual analogue score (VAS) (0-10 cm) [19], were recorded from patient files. All subjects were diagnosed with osteoporosis based on BMD diagnostic criteria [20]. Radiographic investigation of the anteroposterior and lateral whole spine, including hip joints, were investigated to assess VFs. Demographic and anthropometric measurements consisting of age, gender, height, and weight were obtained from the patient files. Body mass index values (BMI) [21] were calculated from measured BMD scans. The patients were divided into two groups as those with and without at least one vertebral asymptomatic collapse fracture (VFs (+) group and VFs (-) group, respectively). We excluded patients with a history of VFs secondary to trauma or an accident, who underwent instrumented fusion surgery, immobile patients, those with concomitant medical conditions such as metastatic disease or hyperparathyroidism, chronic alcohol users, smokers and those using corticosteroids for more than 3 months. Patients with documented VFs within the last 6 months were also excluded to avoid biased results in pain scores.

Bone mineral density measurement

Lumbar spinal bone mineral density (LSBMD) and femoral neck bone mineral density (FNBMD) of the non-dominant proximal femur were measured by dual-energy X-ray absorptiometry (DEXA) (GE-Lunar DPX). BMD measurements (g/cm^2) at the lumbar spine and hip were used to diagnose osteoporosis [22]. T-score of at least -2.5 standard deviations or below were considered as the presence of osteoporosis.

Spinal and pelvic parameters

Lumbar lordosis, thoracic kyphosis, pelvic tilt, pelvic incidence, and sacral slope were measured using a picture achieving computer system (Angora Viewer Version 2.1.11, Data-med).

Lumbar lordosis is defined as the angle between superior endplate of L1 and the superior endplate of S1, and thoracic kyphosis is measured from the superior endplate of T4 to the inferior endplate of T12 using Cobb's method [23].

The three pelvic parameters measured in this study included pelvic tilt, pelvic incidence, and sacral slope. Pelvic tilt (PT) is a positional pelvic parameter represented by the angle between the line joining the bicoxofemoral axis with the midpoint of the S1 endplate. Pelvic incidence (PI) is a morphologic parameter to define lumbar alignment. PI angle indicates the ability of posterior pelvic rotation, which is determined by the angle between the line joining hip axis, center of the S1 endplate and the line orthogonal to the S1 endplate. The pelvic retroversion of patients with small PI has a small compensatory mechanism to achieve sagittal balance. Sacral slope is a positional parameter, as well as the PT. SS is measured by the angle between the sacral endplate and the horizontal plane (Figure 1) [24].

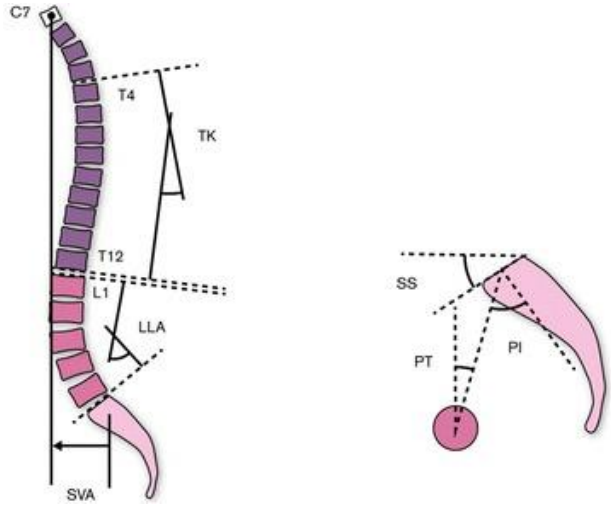

Figure 1: Sagittal curvatures of the spine and pelvic parameters: Lumbar lordosis angle (LLA) and thoracic kyphosis (TK), sacral slope (SS), pelvic tilt (PT), pelvic incidence (PI), sagittal vertical axis (SVA) and C7 plumb line [24]

Sagittal global balance of the spine

Sagittal balance is most often assessed by determining the sagittal vertical axis (SVA) which corresponds to the horizontal distance between the C7 plumb line and the postero-superior S1 corner (Fig 1) [24]. Osteoporotic patients were

separated into the sagittal balance and sagittal imbalance group based on SVA (SVA≤50 mm, SVA>50 mm, respectively) [25]. Demographic and radiological measurements were compared between the groups.

Vertebral fractures

The thoracolumbar spine lateral view x-rays (T4 to L5) were interpreted by radiologists. Genant's method was used to quantify the VFs of the patients [26]. In this classification, vertebral fracture is based on the vertebral shape, with respect to vertebral height loss involving the anterior, posterior, and/or middle vertebral body.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 23. In univariate analysis, independent samples t-test and Mann-Whitney U tests were used for normally and non-normally distributed data, respectively. Descriptive statistics were expressed as median (minimum-maximum) values. Chi-square test with continuity correction was used for categorical variables. A multiple logistic regression was performed to identify indicators of VFs. After univariate analysis, variables with *P*-values <0.10 were included in the logistic model [27]. Forward conditional multiple logistic regression analysis was used to develop a determinative model. *P*-values <0.05 were considered statistically significant.

Results

The mean ages of all osteoporotic patients, as well as those with and without VFs were 69.9 (9.4), 72.24 (9.44) and 68.17 (9.17) years, respectively. There was no statistically significant difference between two groups with respect to age (*P*=0.075). Our radiologists identified 29 patients with grade 2-3 fractured vertebrae on whole spine lateral radiography. Twenty-seven (40.3%) of 67 female patients and 2 of 3 male patients had VFs, among which 15 had thoracic, 11 had lumbar and 3 had both thoracic and lumbar VFs (Table 1).

Mean height, weight, and BMI values of the 70 patients were 153.7 (6.7) cm, 69.3 (12.5) kg and 29.4 (5.6) kg/m^2, respectively. Median VAS back pain score was 7 (3-10) for all patients. Parameters of patients with and without VFs and comparisons of two groups are summarized in Table 2. Patients with and without fractures were found to be significantly different in terms of FNBMD, sacral slope, lumbar lordosis, and VAS scores (*P*=0.016, *P*=0.032, *P*=0.010, *P*<0.001, respectively). In addition, the two groups significantly differed with respect to SVA>50 mm and ≤50 mm (*P*<0.001).

Correlation coefficients between sacral slope and lumbar lordosis both in patients with and without VFs were r=0.54; *P*=0.003 and r=0.50; *P*=0.001, respectively. There were no correlations between VAS score and the other spinopelvic parameters in patients with VFs (Table 3).

Based on univariate analysis, a multiple logistic regression was performed for age, FNBMD, sacral slope, lumbar lordosis, VAS and SVA>50mm, which showed that SVA>50 mm (*P*=0.003) and VAS (*P*=0.001) were predictors of vertebral fracture in osteoporotic patients (Table 4). The risk of VFs in patients with SVA>50 mm was approximately 10 times higher than for those with SVA≤50 mm. In patients with higher VAS scores, the risk was 2 times higher than in patients with lower VAS scores. Sacral slope was also statistically significant with an odds ratio of 1, which is why it may be considered ineffective on VFs.

Table 1: Distribution of levels in patients with vertebral fractures

Levels of vertebrae fractures	n (%)
T9	3 (5)
T10	10 (16)
T11	14 (22)
T12	10 (16)
L1	8 (13)
L2	5 (8)
L3	2 (3)
L4	9 (14)
L5	2 (3)

T: Thoracic vertebrae, L: Lumbar vertebrae, n: number (%)

Table 2: Characteristics of patients

	Vertebral fractures (+) (n=29)	Vertebral fractures (-) (n=41)	*P*-value
Age	72.24 (9.44)	68.17 (9.17)	0.075[a]
Height (cm)	153.59 (8.85)	153.76 (4.87)	0.926[a]
Weight (kg)	68.69 (12.82)	69.66 (12.41)	0.752[a]
BMI (kg/m²)	29.35 (6.23)	29.49 (5.23)	0.923[a]
Lumbar spine BMD	-2.7 (-4.4; 0)	-2.8 (-4.2; -1.5)	0.394[b]
Femoral neck BMD	-2.5 (-3.7; -0.3)	-1.6 (-4.0; 0.1)	0.016[b]
Sacral slope	38.31 (8.75)	43.63 (10.82)	0.032[a]
Pelvic tilt	18 (6; 36)	15 (7; 34)	0.313[b]
Pelvic incidence	58.07 (11.80)	61.29 (11.54)	0.258[a]
Thoracic kyphosis	40.34 (10.57)	37.83 (10.96)	0.341[a]
Lumbar lordosis	36.38 (12.68)	44.56 (12.81)	0.010[a]
SVA>50 mm	24 (82.8%)	14 (34.1%)	<0.001[c]
VAS Score	8 (4; 10)	5 (3; 10)	<0.001[b]

Mean (Standard Deviation, Median (Min; Max)), n: number (%), [a] Independent samples t-test, [b] Mann-Whitney U test, [c] Chi-square test with continuity correction, SVA: Sagittal vertebral axis

Table 3: Correlations between VAS and spinopelvic parameters in patients with vertebral fractures

		Sacral slope	Pelvic tilt	Pelvic incidence	Thoracic kyphosis	Lumbar lordosis	SVA (mm)
VAS	r	0.229	-0.151	0.058	0.022	-0.200	0.300
	p	0.232	0.435	0.765	0.909	0.918	0.114

SVA: Sagittal vertebral axis, VAS: Visual analogue score

Table 4: Results of logistic regression

Variables	Coefficient	Odds Ratio	95% Confidence Interval	*P*-value
Sacral slope	-0.101	0.904	0.842-0.970	0.005
SVA>50 mm	2.334	10.317	2.159-49.307	0.003
VAS	0.757	2.132	1.361-3.339	0.001
Constant	-2.677	2.034		0.154

SVA: Sagittal vertebral axis, VAS: Visual analogue score

Discussion

This study assessed VFs with or without sagittal balance and compared spine curvatures and pelvic parameters in osteoporotic patients over 50 years of age. We found that VFs significantly varied in patients with sagittal imbalance, FNBMD and pain. Lumbar lordosis and sacral slope were also found to differ significantly associated with VFs of the spine in osteoporotic patients.

Osteoporosis reduces trabecular thickness and connectivity in bone mass and microarchitecture leading to increased vertebral fragility and fracture risk [28]. Loss of physiological curves in the thoracic and/or lumbar spine causes an increase in the risk of vertebral fracture more than eight times in patients after the age of 50 years old [8].

It is not clear whether thoracic kyphosis is a potent determining factor for potential osteoporotic VFs [29]. In our study, it was found that there was no significant thoracic kyphosis in patients with VFs (+) compared to VFs (-) group.

Cortet et al. [30,31] examined the relationship between lordosis and osteoporosis, and found no difference in lumbar lordosis in patients with and without VFs. However, our results showed that lumbar lordosis has a strong impact on VFs: The VFs (+) group had a higher degree of lumbar lordosis than the VFs (-) group. This result suggests that hyperlordotic posture is a crucial factor which increases the risk of VFs. Besides, VF (-)

group had high sacral slope without high pelvic tilt compared to VF (+) group. This could be due to several reasons: First, sagittal alignment in the VFs (-) group is characterized by a compensatory mechanism. An imbalance in thoracic hyperkyphosis patients with VFs can be concealed by changes such as lumbar spine flattening and pelvic orientation to maintain postural harmony.

It is known that sacral slope angle is strongly correlated with lumbar lordosis [32]. Spinopelvic harmony has the capability to compensate for sagittal imbalance of the spine through pelvic retroversion with change in sacral slope. We showed that lumbar lordosis was proportional to sacral slope angle.

Pelvic incidence (PI) is an important link between pelvic and spinal alignment parameters determining the capability of rotation of the pelvis around the femoral head's axis, which is the optimal way of compensation of sagittal alignment [33]. However, there was no statistically significant difference in the compensatory ability of pelvis retroversion between the two groups in our study.

The optimal value of the SVA varies widely among populations. The International Spine Study Group defines the radiographic criterion for spinal imbalance as SVA≥50 mm [25]. As in many studies [33-35], we also considered SVA>50 mm as the threshold for predicting sagittal imbalance. This indicates that spinal imbalance can be evaluated from the SVA on a standing lateral radiograph of the whole spine to estimate VF development in osteoporotic patients.

It is shown that BMI>25 is related to a higher likelihood of developing VFs among post-menopausal women with osteoporosis [36]. In contrast, our data showed that being overweight (BMI>25) and VFs were not associated in any of the groups. As shown in Table 1, the mean BMI was 29.35 (6.23) in the VFs (+) group and similarly, 29.49 (5.23) in the VFs (-) group.

In the present study, SVA was a worse identifier of patients with VFs. In other words, sagittal imbalance was higher in the osteoporotic patients with VFs than in the osteoporotic patients with no VFs. Previous studies showed that spinal sagittal balance is closely related with osteoporosis [37], akin to our findings. To a certain degree, a decrease of lumbar lordosis can be obviated by a coinciding decrease in sacral slope to obtain the spinal curvature and congruent posture [38].

In patients with VFs secondary to osteoporosis, impairments in physical function, health, quality of life, and survival correlate with spinal deformity [39]. Glassman et al. [40,41] observed that sagittal balance is associated with pain and mechanical stress on the vertebrae. However, in our study, there was no significant correlation between VAS and spinopelvic parameters in patients with VFs.

Our multiple logistic regression analysis including FNBMD, sacral angle, lumbar lordosis, increasing age, SVA and VAS score showed that VAS and SVA>50 mm were important predictive factors of VFs in osteoporotic patients. However, in our study, the statistical significance of FNBMD in the univariate analysis revealed that it should be considered in evaluation of the risk of VFs, even if LSBMD is normal or close to normal.

In the literature, a significant relationship between age and spinal sagittal vertical axis has been reported; however, we found no such result [42]. In our study, the mean ages of patients with and without vertebral fractures were similar. Presumably, this is due to the fact that sagittal alignment is characterized by decrease in spinal mobility and compensatory mechanisms with aging.

Limitations

This study has some limitations regarding compensation of sagittal balance, spinal curvature and impact of osteoporotic VFs. First, we did not examine total countervailing changes like knee flexion and ankle extension. Second, since the spinal vertebral axis changes during walking, conventional radiography in standing position alone was not adequate for assessment of balance in patients. In addition, we carried out this study with a relatively small number of patients with osteoporosis. Therefore, further studies in larger populations are necessary to validate these findings.

Conclusions

This article shows that spinal imbalance and VAS are determining predictive parameters for VFs in patients with osteoporosis. The results suggest that clinicians should pay attention to sagittal imbalance, pain and FNBMD in osteoporotic patients even if they have normal LSBMD.

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Preoperative evaluation of the knowledge and concerns of gynecology patients regarding anesthesia: A questionnaire based observational study

Jinekoloji hastalarının preoperatif anestezi ile ilgili bilgi ve endişelerinin değerlendirilmesi: Bir anket çalışması

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Abstract

Aim: Anesthesiology is an advancing discipline that is progressively recognized by the society. Preoperative patients may have concerns about anesthesia as well as surgical operations. There are various surveys on this subject, in which the knowledge of the subjects about the anesthesiologist, anesthesia, and related concerns were questioned. In this study, we aimed to determine the knowledge, experiences and concerns of our female patients who were to undergo gynecological operations regarding the anesthesiologists and anesthesia with the questionnaire we conducted, and to contribute to the literature by evaluating our results and discussing the precautions to be taken.

Methods: A questionnaire-based observational study method was used in this study. The questionnaire, which was developed by the researchers, was conducted on the patients who were referred to the anesthesiology policlinic for gynecological operations and signed the informed consent forms. The patients were questioned in terms of knowledge and concerns about the anesthesiologist and anesthesia in general.

Results: This questionnaire was conducted on 150 patients. Seventy-eight percent of our patients were educated below high-school level, while 22% had high school diplomas or higher. 93.33% percent of our patients had already experienced anesthesia and 68% knew that it was administered by a specialist. The most common causes of worry on anesthesia and the operations included inability to regain consciousness (58%), followed by postoperative pain (52%). Less frequent anxiety factors were determined as nausea and vomiting after anesthesia and prior fasting.

Conclusion: As with all segments of the society, increasing the knowledge about anesthesia in women will reduce related anxiety. We believe that this information should be provided not only in polyclinic conditions but also through visual communication tools and brochures.

Keywords: Anesthesia, Worry, Females, Questionnaire

Öz

Amaç: Anesteziyoloji günümüzde ilerlemekte olan ve toplum tarafından giderek de tanınan bir bilim dalıdır. Cerrahi öncesi hastaların cerrahi operasyonlar kadar anestezi uygulamaları konusunda da endişeleri olabilmektedir. Bu konuda yapılmış anket çalışmaları mevcuttur. Bu çalışmalarda bireylerin anestezist, anestezi hakkındaki bilgisi ve anestezi ile ilgili kaygıları sorgulanmıştır. Biz de Jinekolojik operasyon geçirecek ve anestezi uygulanacak kadın hastalarda yaptığımız anket çalışmasıyla hastalarımızın anestezi doktoru ve anestezi ile ilgili bilgi ve deneyimlerini ve endişe nedenlerini belirlemeyi amaçladık. Sonuçlarımızı değerlendirmek ve alınabilecek önlemleri de tartışarak literatüre katkıda bulunmayı da amaçladık.

Yöntemler: Bu araştırma bir anket çalışması olarak planlanmıştır. Araştırmacılar tarafından geliştirilen anket anesteziyoloji polikliniğine jinekoloji operasyonu için başvuran ve bilgilendirilmiş onamları alınan hastalar üzerinde uygulanmıştır. Anket formu ile olguların anestezist ve anestezi ile ilgili bilgi ve kaygı nedenleri sorgulanmıştır.

Bulgular: Anket çalışması toplam 150 hastaya uygulandı. Eğitim durumuna göre hastaların oranları %78 lise altı, %22 lise ve üstü saptandı. Anestezi deneyimini yaşayan hastalarımızın oranı %93.33'tür. Anestezi uygulamasının uzman doktor tarafından yapıldığı yanıtı ise %68 şeklindedir. Anestezi ve ameliyathane ile ilgili en fazla endişe veren durum %58 oranı ile uyanamama; ikinci sıklıkta endişe nedeninin de %52 oranı ile postoperatif ağrı olduğu saptandı.

Sonuç: Toplumun her kesiminde olduğu gibi kadınlarda da anestezi uygulamaları hakkında bilgiyi artırmak anestezi ile ilgili kaygı veren durumları da azaltacaktır. Bu bilgilendirmenin yalnızca poliklinik koşullarında değil görsel iletişim araçları ve broşürler yoluyla da olması gerektiğini düşünüyoruz.

Anahtar kelimeler: Anestezi, Endişe, Kadın, Anket

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Introduction

The struggle against pain in human history has been quite challenging and the point we have reached today has been gained after long wars and experiences. In this process, any surgical experience was painful for the patient, and a major challenge for the surgeon. The first treatments for pain relief were alcohol, and opium-dipped sponges.

Joseph Priestley's description of oxygen in 1774 and his discovery of nitrous oxide in 1776 were turning points in the history of anesthesia. Horace Wells also performed painless tooth extraction using nitrous oxide in 1844. In 1913, Karl Connell developed the anesthesia machine [1,2]. The period of modern anesthesia developed between 1920 and 1940 and since 1937 "Anesthesiology" has been accepted as a scientific discipline globally [2].

Anxiety is a common emotional disorder among patients. There have been several studies related to anxiety for various types of diagnoses [3,4]. Since the 1970s, studies have been conducted on the level of knowledge on anesthesiologists and anesthesia applications, onto which research regarding patient satisfaction, measurement of preoperative anxiety and causes were added during later years [5-7]. With this in mind, we aimed to determine the knowledge and experiences of our female patients, who play significant roles in the upbringing of new generations, about anesthesiologists and anesthesia, and their causes of concern. Our purpose was to contribute to the literature by evaluating our results and discussing the precautions to be taken.

Materials and methods

The study was conducted after the approval of the local ethics committee (Bursa Yüksek Ihtisas Training and Research Hospital, Health Sciences University Ethical Committee of Clinical Research, 2011-KAEK-25 2019/06-11) was obtained, and consisted of patients who were to undergo elective gynecological operations under anesthesia in Bursa Yüksek İhtisas Training and Research Hospital. GPower 3.1 program was used to determine sample size, which revealed that 80 participants were needed for 0.5 effect size. Hence, we included 150 patients who were referred to our polyclinic for pre-anesthesia examination. Female patients who were older than 18 years with informed consent were included in the survey. The exclusion criteria included refusing to participate, a history of emergency surgery or a known psychiatric disorder, and lack of literacy.

Previous experience, information on the duties of anesthesiologists and causes of concern related to anesthesia were questioned in patients who were referred to the anesthesia outpatient clinic for preoperative examination. Participants were given a questionnaire which was developed by the researchers and were able to answer the questions without any influences. The questionnaire (Table 1), namely, Preoperative Evaluation of The Knowledge and Concerns of Gynecology Patients Regarding Anesthesia, was developed by the researchers based on the literature view [8-10]. A pilot study was done with 15 participants to evaluate the questionnaire's clarity. A revision was made due to feedbacks. The participants were told that they did not need to sign their names on the questionnaire, that their answers would not affect the service they would receive and were asked to express their real thoughts.

Statistical analysis

SPSS 21.0 (Statistic Inc. version Chicago, IL, USA) software was used for statistical analysis of the data. Descriptive statistics were expressed as mean (standard deviation) for continuous variables, and number of patients (%) for nominal variables. The results were considered statistically significant within a 95% confidence interval when *P*- value <0.05.

Table 1: Items of the questionnaire

Questionnaire
Gender:
Age:
Educational Level: □Below High School □High School Degree and Above
Do you have a previous experience of anesthesia?
a) Yes b) No
Is there a family member who underwent anesthesia?
a) Yes b) No
Did you have any problems related to anesthesia?
a) Yes b) No
Do you know why you were referred to the anesthesia polyclinic?
a) Yes b) No
Were you informed about anesthesia?
a) Yes b) No
Who administers anesthesia in the operation rooms?
a) Specialist b) Technician c) Nurse d) No idea
Where does an anesthesiologist work?
a) Operating rooms b) Operating rooms, polyclinics, and intensive care units c) No idea
Do you know what the definition of an anesthesiologist is?
a) Follows weakness and vital signs of the patient b) Administers anesthesia to the patient c) No idea
What anesthetic method/s do you know?
a) General b) Local/Regional c) General/Local/Regional d) No idea
Circle the most suitable option which reflects your anxiety and concern level about anesthesia
a) Not anxious b) A little anxious c) Anxious d) Very anxious
Circle the most suitable option which reflects your anxiety and concern level about inability to regain consciousness
a) Not anxious b) A little anxious c) Anxious d) Very anxious
Circle the most suitable option which reflects your anxiety and concern level about fasting before anesthesia
a) Not anxious b) A little anxious c) Anxious d) Very anxious
Circle the most suitable option which reflects your anxiety and concern level about postoperative pain
a) Not anxious b) A little anxious c) Anxious d) Very anxious
Circle the most suitable option which reflects your anxiety and concern level about nausea/vomiting after anesthesia
a) Not anxious b) A little anxious c) Anxious d) Very anxious

Results

A total of 150 patients were surveyed. The mean age of the patients was 45.37 (10.79) years. All our patients were female. Among them, 78% were educated below high school, and 22% had high school degrees and above. Approximately 93% had previous anesthesia experience and 76% experienced it through a family member. Ninety-four of the cases stated that they did not experience any problems during general anesthesia while 6% stated that they did. Eighty-eight percent knew why they were referred to the anesthesia clinic while 12% did not. 54% patients stated that they were informed before referral to our clinic while 46% stated they were not (Table 2).

Of all patients, 68% stated that anesthesiologists administered anesthesia in the operation rooms ($P<0.001$), 16% stated that it was the technicians, 2% stated it was the nurses and 14% of patients had no idea (Figure 1). Sixty-six percent stated that anesthesiologists worked in the operating rooms only ($P<0.001$), while 12% wrote that they worked in the polyclinics and intensive care units along with the operating rooms. Twenty-two percent had no idea. The following answers were given question regarding the job of the anesthesiologist in the operation rooms: Follows wakefulness and vital signs (44%), administers anesthesia to the patient (42%), no idea (14%) ($P=0.829$).

Regarding the information of anesthetic methods, 56% knew about general anesthesia, 24% had information on local/regional anesthesia, 16% knew about both and 4% had no

idea (Figure 2). General anesthesia was the significantly most commonly known among all (P<0.001).

The most common cause of concern regarding anesthesia was inability to regain consciousness (58%), followed by postoperative pain. The causes of concern and rates are presented in Table 3. Chi-square tests measuring anxiety levels regarding anesthesia revealed that there were significant differences between anxiety levels (P<0.001).

Table 2: Evaluation of patients' anesthetic histories and general information on anesthesia

	Yes		No		*P*-value
	n	%	n	%	
Do you have a previous experience of anesthesia?	140	93.33	10	6.67	<0.001
Is there a family member who underwent anesthesia?	114	76	36	24	<0.001
Did you have any problems related to anesthesia?	9	6	141	94	<0.001
Do you know why you were referred to the anesthesia polyclinic?	132	88	18	12	<0.001
Were you informed about anesthesia?	81	54	69	46	0.424

Table 3: Evaluation of causes of concern and anxiety levels regarding anesthesia and the operation

	Not anxious		A little anxious		Anxious		Very anxious	
	n	%	n	%	n	%	n	%
Regarding anesthesia	23	15.33	24	16	31	20.67	72	48
Regarding inability to regain consciousness	24	16	18	12	21	14	87	58
Regarding prior fasting	45	30	69	46	27	18	9	6
Regarding postoperative pain	15	10	28	18.67	29	19.33	78	52
Regarding nausea/vomiting after anesthesia	14	9.33	104	69.33	25	16.67	7	4.67

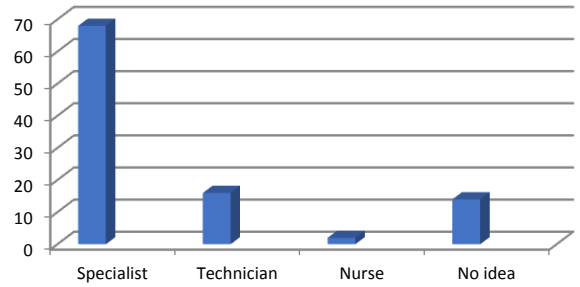

Figure 1: The answers of the question regarding who administers anesthesia

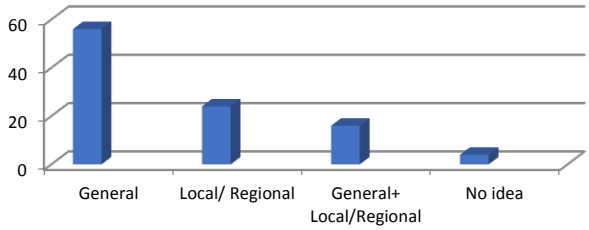

Figure 2: Answers to the question about knowledge of anesthesia methods

Discussion

Preoperative evaluation, a clinical examination which is the responsibility of the anesthesiologist, is performed prior to the anesthesia in the patient to be operated [11]. However, there is little information about the anesthesiologist and various studies have shown that people believe that the anesthesiologist is not a medical doctor [8,9].

In a study conducted on 800 patients in 1991, Shevde et al. [5] reported the rate of knowing the role of the anesthesiologist as 68%. In another study, the rate of knowing that the anesthesiologist was a specialist was found to be 58%, and it was reported that this rate was lower compared to other specialties [12]. This can be attributed to the pre-operative exposure of patients to a complex environment. Many patients do not remember the anesthesiologist because they encounter a large number of hospital staff [13,14].

In our study, the mean age of the patients was 45.37(10.79) years. The fact that 92% of our patients had previous experiences with anesthesia and 76% had experiences with a family member can be attributed to the lack of young patients. Despite the high rate of anesthesia experience, the question of who administers anesthesia in the operating room was not answered with "a specialist physician" by 32%. Only 68% gave the answer of an anesthesiologist. A statistically significant majority of the patients knew why they came to the anesthesia outpatient clinic. We thought that the high rate of prior anesthesia experience was effective in this result.

Various studies have been conducted on questioning the working places of anesthesiologists and results have been shared in the literature [9]. Demir et al. [9] argued that most of the patients knew that the anesthesiologist also worked outside the operating room (polyclinic, intensive care, pain treatment). In other studies, it was found that the patients thought that the anesthesiologists would only work in the operating room and did not know about other work areas, such as the intensive care unit, pain clinic, and interventional procedures [15-17]. The reasons may include the fact that anesthesia is a newly-recognized branch compared to other sciences, the anesthesiologists usually work as consultant physicians outside the operating room and consequently, they are rarely seen and recognized, and finally, that new working areas of the anesthesiologists have recently been added. In a different study, it was questioned whether the anesthesiologist had any other duties outside the operating room, and 19.6% patients responded "Yes" while 80.4% responded "No" [18]. In our study, 66% of our patients gave the response "operating room" while 22% of the patients stated that they had no idea. Only 12% of the patients reported knowing about outpatient clinics and intensive care units in addition to the operating room. These results are incompatible with the results of Demir et al. [9] and consistent with other study results.

We believe that the socioeconomic and educational level of the survey population are key factors in these differences. In their study, Tuba et al. [8] concluded that the accuracy of the answers given to the questions about the anesthesiologist and anesthesia increased with the level of education.

In our study, 78% were educated below high school, 22% had high school diplomas and above. This situation and the fact that the non-operating working areas are known at a rate of 12% makes the education level important, in accordance with the study performed by Tuba et al. [8].

In their study, Hariharan et al. [19] questioned the work performed by the anesthesiologist in the operating room, and 75% answered with consciousness follow-up and 62.8%, with vital signs follow-up. In our study, 44% stated that anesthesiologists follow wakefulness and vital signs, 42% stated that they administer anesthesia to the patients,14% had no idea.

It is reported that general anesthesia, which is one of the anesthesia methods, is more widely known than local and regional anesthesia [9]. In addition, Demir et al. [9] state that women's knowledge level is higher than that of men's. The knowledge about general anesthesia was significantly higher in our patient group compared to local and regional anesthesia methods.

Patients are often anxious prior to anesthesia and operation. Concerns about surgical intervention and anesthesia

practice adversely affect the intraoperative period as well as postoperative recovery process [11]. In preoperative evaluation, diagnosis, general condition, comorbidities, medications, laboratory results and anesthesia risk are determined, and physical examination is performed. In addition, the psychological state of the patient is evaluated, and it is aimed to reduce the anxiety by giving information [11].

When the causes of anxiety related to anesthesia and operating room were questioned in our patients, it was found that the most worrying situation was the fear of not being able to regain consciousness. The second most frequent cause of anxiety was postoperative pain. Similar to these results, there are also reports in the literature that indicate fear of not being able to regain consciousness and postoperative pain are important causes of anxiety [6,18,19].

In their study in 1998, Chew et al. [6] reported pain as the most important cause of anxiety, while Hume et al. [20] reported waking up during surgery as an important cause of concern. While postoperative pain continues to be a cause of anxiety today, we believe that waking up during surgery is not a cause of concern due to the development of anesthetic agents.

Weis et al. [21] showed that the detailed information provided to the patients decreased anxiety in the preoperative and postoperative periods and that the recovery in the postoperative period was faster and less painful.

Different studies measuring preoperative patient satisfaction, causes and degrees of anxiety conclude that providing information is useful [11,22]. The introduction of the anesthesiologist and the information provided about anesthesia applications during preoperative examination plays a key role.

Increased treatment costs shorten the duration of hospital stay. Also, the fact that anesthesiologists do not visit the patients after the surgery prevents postoperative encounter. This is caused by the increased workload of anesthesiologists, like all healthcare workers, and because postoperative visits are not routine procedures.

Limitation

The limitation of our study is the lack of a postoperative survey conducted on the same patients. It is our belief that planning future studies in this regard will highly contributes to the literature.

Conclusion

This study shows that preoperative process is highly stressful for most patients. The lack of information about the above-mentioned concepts may be considered as one of the reasons of observed anxiety. Patients may be informed about anesthesiologists and their applications to reduce stress. Pre-operative visits and visual communication tools and brochures may reduce the anxiety of patients regarding anesthesia and related processes. It is also expected to contribute positively to the recognition of the rapidly developing branch of anesthesiology and the anesthesiologists.

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Research article
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Evaluation of deep vein thrombosis incidence with respect to age and gender in light of regional factors in central Anatolia: A population-based study

Bölgesel etmenlerin ışığında iç anadolu bölgesinde derin ven trombozu insidansı ile yaş ve cinsiyete açısından değerlendirilmesi: Nüfus bazlı çalışma

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Abstract

Aim: Deep vein thrombosis (DVT) is a prevailing cause of serious complications such as pulmonary thromboembolism, venous ulcer, chronic venous insufficiency, venous gangrene and post-thrombotic syndrome, and significantly increased hospitalization costs. The aim of this study is to determine the incidence of DVT and regional effects for its development as well as evaluate its distribution in terms of age and gender in Yozgat, a city with a population of more than 500.000 people, which is considered to fairly represent Central Anatolia with regards to geography, economy, industry, age distribution, morbidity and mortality.

Methods: For this cross-sectional study, we included all DVT cases aged 15 years and older from Yozgat diagnosed in Bozok University, Faculty of Medicine, Research and Application Hospital and Yozgat State Hospital between September 2012-September 2016. Patients and diagnostic characteristics were retrieved from medical records. The distribution of DVT cases were evaluated in terms of age and gender according to the data derived from address-based population registration system of Turkish Statistical Institute (TUSI) 2016.

Results: One thousand two hundred and eighty-seven patients were enrolled in this research. DVT incidence increased with age and substantially accelerated above the age of 40. The overall DVT incidence was 1:1000 persons per year and slightly higher among the female population (1:1000 persons/year vs 0.9:1000 persons/year) (P=0.924). According to TUSI 2016, the mean body mass index (BMI) of females was significantly higher than that of males (29.2 (5.3) kg/m² and 26.7 (3.6) kg/m², respectively, P<0.001). In the region comprising Yozgat, Sivas and Kayseri, labor-force participation rate of females and males were 28% and 49.6%, respectively, which was a significant regional risk factor for DVT development.

Conclusion: It would be possible to decrease the incidence of DVT and the high hospitalization costs of related complications, most of which can be avoided with suitable prophylaxis based on more reliable results obtained from further research. Appropriate precautions should be taken after considering regional socioeconomic and sociocultural values.

Keywords: Deep vein thrombosis, Incidence, Yozgat, Age, Gender, Body mass index

Öz

Amaç: Derin ven trombozu pulmoner tromboemboli, venöz ülser, kronik venöz yetmezlik, venöz gangren ve posttrombotik sendrom gibi ciddi komplikasyonların güncel bir sebebini oluşturmaktadır. Bu çalışmanın amacı 500.000'den fazla nüfusa sahip, gerek coğrafik, ekonomik, endüstriel ve yaş dağılımı gerekse morbidite ve mortalite oranları açısından İç Anadolu Bölgesi'nin temsil edebilecek özelliklere sahip Yozgat ilinde derin ve trombozu (DVT) insidansını tanımlamak ve DVT gelişim üzerinde etkisi olan bölgesel etmenler üzerine vurgu yapmaktır.

Yöntemler: Bu araştırma kesitsel bir çalışma olarak planlanmıştır. Yozgat ilinde ikamet eden Bozok Üniversitesi Tıp Fakültesi Araştırma ve Uygulama Hastanesi ile Yozgat Şehir Hastanesi'nde 2012 ve 2016 yılları arasında DVT tanısı almış 15 yaş ve üzeri bireyler çalışmaya dahil edildi. Hastalar ve hasta verileri medikal kayıtlardan elde edildi. DVT dağılımı, Türkiye İstatistik Kurumu'na (TUSI) ait adrese dayalı nüfus dağılımı verileri kullanılarak yaş ve cinsiyet açısından değerlendirildi.

Bulgular: Çalışmaya 1287 hasta dahil edilmiştir. DVT dağılımı yaşlanma ile artış göstermekte özellikle 40 yaş üzerinde ciddi bir ivmelenme göstermektedir. Genel DVT insidansı 1/1000 hasta/yıl olarak belirlendi ve kadın nüfusta 1/1000 hasta/yıl iken erkek nüfusta 0.9/1000 hasta/yıl olarak tespit edildi (P=0,924). TUSI 2016 verilerine göre Yozgat, Sivas ve Kayseri illerinde ortalama beden kitle indeksi (BKI) kadın popülasyonda erkeklere göre daha yüksek idi, kadın popülasyonsa 29,2 (5,3) kg/m² iken erkek popülasyonda 26,7 (3,6) kg/m² (P<0,001) ve işgücü katılım oranı kadınlarda %28 iken erkeklerde %49,6 olarak tespit edildi. Bu durum DVT gelişiminde bölgesel etmenlerin etkinliğini ortaya koymaktadır.

Sonuç: Bölgesel sosyoekonomik ve sosyokültürel realiteler göz önünde bulundurularak ve daha geniş çaplı çalışmalar ile elde edilecek veriler ışığında önceden alınacak önlemler ile DVT insidansını ve uygun profilaktik yaklaşımlar ile birçoğu önlenebilir olan ve yüksek sağlık giderlerine sebep olan ilgili komplikasyonların önüne geçmek mümkündür.

Anahtar kelimeler: Derin ven trombozu, İnsidans, Yozgat, Yaş, Cinsiyet, Beden kitle indeksi

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Introduction

Deep vein thrombosis (DVT) is the third most common cardiovascular disease, after ischemic cardiac diseases and stroke [1]. Despite many improvements in both medical and surgical management, DVT remains the cause of various serious complications, such as pulmonary thromboembolism, venous ulcer, chronic venous insufficiency, venous gangrene and post-thrombotic syndrome, along with significantly increased hospitalization costs [2,3].

DVT is rarely observed under the age of 20. However, its incidence gains significant acceleration after the age of 40 and peaks after the age of 70 [4-8]. The incidence of DVT is similar between males and females, although it remains slightly higher among the reproductive female population, which evens out after menopause [4,7,9,10].

To the best of our knowledge, no extensive research has been conducted in Turkey on DVT incidence to this date, however, it is possible to see many examples in the literature from different countries. In this article, we aimed to research the incidence of DVT and evaluate its distribution with respect to gender and age in Yozgat, a city with a population of more than 500,000 people, which is thought to represent Central Anatolia in terms of geography, economy, industry, age distribution, morbidity, and mortality.

Materials and methods

DVT cases were classified as idiopathic and secondary. Any DVT caused by malignancy, trauma, surgery, immobility (due to paresis, paralysis, prolonged bedrest) within the last 3 months, pregnancy or puerperium at the time of the event, or oral contraceptives used at the time of the event or up to 1 month before the event was regarded as secondary DVT. A DVT case was regarded as idiopathic DVT in case of the absence of precipitating factors for a secondary DVT.

This cross-sectional study was conducted in Bozok University, Faculty of Medicine, Research and Application Hospital and Yozgat State Hospital, the only centers of cardiovascular surgery in Yozgat city, with the approval obtained from Local Health Authority in Yozgat Governorship (no: 21143511-030.04.01). Ethics committee approval was not received due to the retrospective study design.

One thousand two hundred eighty-seven patients who were referred to Bozok University, Faculty of Medicine, Research and Application Hospital and Yozgat State Hospital between September 2012-September 2016, diagnosed with DVT based on physical examination and imaging (colored Doppler ultrasonography (CDUS) and venous computerized tomographic angiography) and treated either as an outpatient or inpatient, were enrolled in this research. The patients under the age of 15 and those who were not diagnosed in Yozgat were excluded. The medical records of the patients were reviewed retrospectively by getting the official permissions of related clinics.

Demographic data (age, gender, coexisting diseases and body mass index (BMI)) and the distribution of DVT cases were evaluated in terms of age and gender according to the data of address-based population registration system of Turkish Statistical Institute (TUSI) in 2016.

In both Cardiovascular Surgery Departments, the routine DVT treatment protocol was the same as that stated in "National Treatment Guide of Peripheral Artery and Vein Diseases, 2016" published by Turkish Cardiovascular Surgery Association and National Vascular and Endovascular Surgery Association. Each DVT patient was treated with subcutaneous low molecular weight heparin (LMWH) for at least five days and per oral vitamin K antagonist (VKA) starting at the time of diagnosis. International normalized ratio (INR) was monitored each day and when INR level reached 2-3 on two consecutive measurements, LMWH was stopped and treatment was continued with VKA alone. Each patient used compression socks with a pressure of 20-30 mmHg and frequent mobilization was advised. VKA treatment was stopped in patients whose INR level could not provide the set point on four consecutive measurements, and new oral anticoagulant (NOAC) therapy was ordered in the presence of normal values of liver and renal function tests.

Pharmacomechanic thrombectomy procedure was performed to two patients with iliac vein thrombosis following gastrointestinal carcinoma and a major abdominal surgery.

Statistical analysis

To calculate incidence rates of first DVT event, we used the observed number of cases of first DVT as the numerator and the sum of individuals per year as the total resident population as the denominator. This data was obtained from the data of address-based population registration system of Turkish Statistical Institute (TUSI) in 2016

Incidence rates for DVT were standardized by using the direct method, applying the age-specific rates in each 5-year age group to the world (Segi) standard population aged 15 years and above.

All analyses were performed using MINITAB™ Version 16. The Chi-square square test was used for the analysis of categorical data by creating crosstabs. Descriptive statistics were presented as frequency and percentages. For all tests, *P*-value <0.05 was considered statistically significant. Two samples test and t-test were used for demographic variables.

Results

The total sample comprised 1287 patients. Regarding the distribution of gender, 695 (54%) were female and 592 (46%) were male. The mean age of males and females were 54 (3.6) and 51 (2.3) years, respectively. Ninety-six (13.8%) females and 68 (11.4%) males were treated as in-patients (Table 1).

Accompanying diseases of the patients were shown in Table 1. There was not any statistically significant difference among the male and female patients in terms of diabetes mellitus (DM) (P=0.147), hypertension (HT) (P=0.074), cerebrovascular accident (CVA) (P=0.877), chronic renal failure (CRF) (P=0.162), peripheral arterial disease (PAD) (P=0.074), and left heart failure (LHF) (patients with left ventricle ejection fraction ≤30% in transthoracic echocardiography) (P=0.987). However, among those with chronic obstructive pulmonary disease (COPD), male patients had a significantly higher incidence of DVT compared to female patients (P=0.024). There was no

statistically significant difference between inpatient males and females (P=0.209).

The mean BMI of females and males were 29.2 (5.3) kg/m² and 26.7 (3.6) kg/m² respectively, (P<0.001) (Table 1).

Based on the data derived from TUSI, the overall incidence of DVT in Yozgat was one per 1000 persons-year, which was similar with the literature. DVT incidence increased with age and accelerated substantially especially above the age of 40 (Table 2).

DVT incidence was slightly higher among the female population (1:1000 persons/year vs 0.9:1000 persons/year) (P=0.924).

Table 1: Demographic data of DVT patients

	n (%)	*P*-value
Age		
Female	51 (2.3)	0.501
Male	54 (3.6)	
Gender		
Female	695 (54)	0.924
Male	592 (46)	
Inpatient		
Female	96 (7)	0.209
Male	68 (5)	
DM		
Female	184 (14)	0.147
Male	136 (11)	
HT		
Female	206 (16)	0.074
Male	203 (16)	
COPD		
Female	33 (3)	0.024
Male	46 (4)	
CVA		
Female	27 (2)	0.877
Male	24 (2)	
CRF		
Female	11 (1)	0.162
Male	16 (1)	
PAD		
Female	35 (3)	0.074
Male	44 (3)	
LHF		
Female	53 (4)	0.987
Male	45 (3)	
Major surgery history		
Female	61 (5)	0.749
Male	55 (4)	
Malignancy		
Female	86 (7)	0.812
Male	79 (6)	
Immobility		
Female	176 (14)	0.629
Male	154 (12)	
BMI		
Female	29.2 (5.3) kg/m²	0.001
Male	26,7 (3,6) kg/m²	
DVT incidence		
Female	1/1000	0.924
Male	0.9/1000	

DVT: Deep vein thrombosis, DM: Diabetes mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease, CVA: Cerebrovascular accident, CRF: Chronic renal failure, PAD: Peripheral arterial disease, LHF: Left heart failure, BMI: Body mass index

Table 2: The distribution of DVT patients above 15 years of age in terms of age and gender according to the data derived from address-based population registration system of TUSI 2016

	The distribution of population over the age of 15 according to the data derived from address-based population registration system of TUSI 2016 (n/%)	The distribution of DVT patients above the age of 15 in terms of age and gender (n) - 4 years	The distribution of DVT patients above the age of 15 in terms of age and gender (Mean person/year)
The age of 15-39	157.455 / 47.9%	131	2/10000
Male	80.838 / 51.3%	58	1.7/10000
Female	76.617 / 48.7%	73	2.2/10000
The age of 40-49	49.879/ 15.2%	296	1.4/1000
Male	25.254/ 50.6%	136	1.3/1000
Female	24.625/ 49.4%	163	1.6/1000
The age of 50-59	48.761/ 14.8%	302	1.5/1000
Male	24.255/ 49.7%	145	1.5/1000
Female	24.506/ 50.3%	157	1.6/1000
The age of 60-69	40.335/ 12.3%	293	1.8/1000
Male	19.326/ 47.9%	132	1.7/1000
Female	21.009/ 52.1%	161	1..9/1000
Above the age of 70	32.464/ 9.9%	265	2/1000
Male	13.843/ 42.6%	123	2.2/1000
Female	18.621/ 47.4%	142	1.9/1000
Summary	328.894/ 100%	1287	1/1000
Male	163.516/ 49.7%	592	0.9/1000
Female	165.378/ 50.3%	695	1/1000

TUSI: Turkish Statistical Institute, DVT: Deep vein thrombosis

Table 3: Characteristics of 1287 patients with DVT

	Idiopathic, n (%)	Secondary, n (%)	Total, n (%)
DVT	676 (53)	611 (47	1287 (100)
Female	372 (55)	323 (52)	695 (54)
Male	304 (45)	288 (48)	592 (46)
Median Age			
Female	52 (1.8)	50 (2.6)	51 (2.3)
Male	54 (2.6)	53 (3.7)	54 (3.6)
Location			
DVT Upper Extremity	6 (1)	11 (2)	17 (1)
DVT Abdominal	4 (1)	7 (1)	11 (1)
DVT Lower Extremity			
Proximal	452 (67)	421 (69)	873 (68)
Distal	214 (31)	172 (28)	386 (30)

Discussion

The annual cost of DVT and related complications in United States of America (USA) is about 7.5-39.5 billion American dollars and the preventable amount of this cost is about 2.5-19.5 billion American dollars [11-13]. It is possible to prevent one of every six-thromboembolic events with appropriate prophylactic treatment, which is administered to less than 55% of the patients eligible for prophylaxis [14-15].

The incidence of DVT is one per 1000 person-year [4,7,8,14]. In our study, the incidence of DVT in Yozgat was found to be the same with the literature.

There are various risk factors affecting the development of DVT. Advanced age is one of the most important independent risk factors of DVT. DVT is rarely observed under the age of 20 but the incidence starts increasing, particularly above the age of 40 [4-8]. The annual incidence of DVT in terms of age are 2-3 per 10000 persons-year (30-49 years of age), 5 per 10000 persons-year (50-59 years of age), 10 per 10000 persons-year (60-69 years of age) and 20 per 10000 persons-year (70-79 years of age) [4-6,8]. In an extended research of DVT patients conducted in 50 States and 400 hospitals in the USA between 1979 and 1999, Stein et al reported that the incidence of DVT above the age of 70 was 4 times higher than that under the age of 50 [16]. In our study, the incidence of DVT under the age of 40 was found to be two per 10000 persons-year, and showed an increase after the age of 40, reaching two per 1000 persons-year above the age of 70.

DVT incidence in reproductive females might be slightly higher than males but would even out after menopause. However, the overall DVT incidence in terms of gender is reported as 1.3 per 1000 persons-year among males and 1.1 per 1000 persons-year among females [4,7-10,17,18]. In this study, DVT incidence was found as 1 per 1000 persons-year among females and 0.9 per 1000 persons-year among males. Although it was not meaningful statistically, this result was different from the literature as being higher in female population.

Obesity is defined as BMI ≥30 kg/m² and morbid obesity, as BMI ≥40 kg/m². It is a major but preventable risk factor of DVT development. Obesity increases the risk of DVT development 2-3-fold, which is further escalated in morbid obese persons [19]. According to the data derived from TUSI 2014, in Turkey, the overall obesity rate among the general population above the age of 15 was 19.9%, 15.9% among males and 24.5% among females. In our study conducted in Yozgat, the mean BMI values of females and males were 29.2 (5.3) kg/m², and 26.7 (3.6) kg/m² respectively, the difference between which was statistically significant.

According to the data of TUSI 2016, in the region consisting of Yozgat, Sivas and Kayseri, the labor-force participation rates of females and males were 28% and 49.6%, respectively. The number of females participating the labor-force is nearly the half of the male population in Central Anatolia Region, bringing forth a sedentary lifestyle, which would inevitably contribute to obesity development. Due to both high obesity and low labor-force participation rates of female population living in Yozgat, DVT incidence is higher in females than in males.

Although the physiomechanism has not been described properly, geographic circumstances have a considerable effect on DVT incidence. DVT is observed less in the seaside in comparison with inland [20,21]. Due to the harder environmental conditions, DVT incidence is observed 10-15% times higher in winter [22]. Given these circumstances, Yozgat has additional risk factors of DVT development, since it is away from the seaside with compelling winter conditions and a high altitude. That is why further larger-scale and comparative studies would provide more reliable and beneficial results.

COPD is a disease with acute exacerbations, most of which are related to infections. COPD is usually observed in advanced ages and is due to the lack of adequate mobilization and a strong history of tobacco consumption [23,24]. In a research conducted by Chen CY et al, the overall incidence rate of DVT was higher in patients with COPD, with 18.78 events per 10,000 persons-years [25]. In our study, male patients with COPD showed a significantly higher rate of DVT incidence in comparison with female patients with COPD. The higher rates of tobacco consumption starting from the childhood years among the male population might have been effective on this result. There was no statistically meaningful difference between male and female DVT patients in terms of other concomitant diseases.

Limitations

The main limitation of our study is misdiagnosed or undiagnosed DVT cases. Sometimes DVT, especially those with an atypical clinical progress, can be misdiagnosed and treated as soft tissue injury, myalgia, or orthopedic problems, etc. The thrombosis of gastrocnemius and soleus deep veins are responsible of approximately 60% of mid-calf deep vein thrombosis cases, which are reported as normal venous anatomy with CDUS.

Conclusion

DVT is a multifactorial disease capable of serious morbid or mortal complications. However, with proper precautions it is possible to prevent a remarkable amount of DVT cases and related complications. Thus, studies that consider the sociocultural, socioeconomic, and geographic data would provide more realistic results in terms of prevention and treatment of DVT and related complications.

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The effects of ozone therapy on postoperative adhesions and ovarian functions: An experimental study

Ozon terapinin postoperatif adezyon ve over fonksiyonları üzerindeki etkisi: Deneysel bir çalışma

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Abstract

Aim: Numerous methods are used to prevent the development of postoperative adhesion formation. There are few studies on the effects of ozone therapy on postoperative intraabdominal adhesions and ovarian functions. This study aimed to investigate the effects of ozone treatment on postoperative intraabdominal adhesions and ovarian roles in rats.

Methods: Twenty female Wistar albino rats were randomly allocated into two groups as laparotomy (Group 1, n: 10) and laparotomy + intraperitoneal ozone (Group 2, n: 10). After laparotomy, parietal peritoneum, uterus and adnexal surfaces were scraped in both groups. Follicle-stimulating hormone (FSH), Estradiol (E2), Lactate Dehydrogenase (LDH), Urea, and Creatinine levels were measured, and histopathological evaluation was performed. Both groups were compared concerning histopathological and biochemical findings.

Results: In the ozone-treated group, antioxidant levels (P=0.012) were significantly higher, and E2 levels (P=0.005) were substantially lower than the control group. There was no statistically significant difference between the two groups regarding FSH, Urea, Creatinine, and LDH (P=0.12, P=0.72, P=0.45, and P=0.79, respectively). Histopathologically, postoperative intraabdominal adhesion rates between the two groups were statistically similar.

Conclusion: Although there was no statistically significant difference, ozone therapy had a decreasing effect on severe fibrosis and congestion rates. Although there was no difference in FSH, low levels of E2 in Group 2 suggest that ozone treatment may have a protective effect on the ovaries. However, further studies are needed concerning adhesion formation and the impact on ovarian functions.

Keywords: Rats, Ozone, Adhesion

Öz

Amaç: Postoperatif adezyon gelişiminin önlenmesi için çok sayıda yöntem kullanılmaktadır. Ozon tedavisinin postoperatif batın içi adezyonlar ve over fonksiyonları üzerine etkileriyle ilgili literatürde az sayıda çalışma mevcuttur. Bu çalışma, ozon tedavisinin ratlarda postoperatif batın içi adezyonlar ve over fonksiyonları açısından etkilerini araştırmayı amaçlamıştır.

Yöntemler: Yirmi adet dişi Wistar albino rat, laparotomi (Grup 1, n:10) ve laparotomi + intraperitoneal ozon (Grup 2, n:10) olacak şekilde rastgele iki gruba ayrıldı. Laparotomi sonrası her iki grupta parietal periton, uterus ve adneksiyal yüzeyler kazındı. Folikül uyarıcı hormon (FSH), Estradiol (E2) ve Laktat Dehidrojenaz (LDH), Üre ve Kreatinin seviyeleri ölçüldü, histopatolojik değerlendirme yapıldı. Her iki grup histopatolojik ve biyokimyasal bulgular açısından karşılaştırıldı.

Bulgular: Ozon tedavi grubunda antioksidan seviyeleri (P=0,012), kontrol grubuna göre anlamlı derecede yüksek, E2 seviyeleri (P=0,005) ise anlamlı derecede düşük bulundu. İki grup arasında FSH, Üre, Kreatinin, LDH açısından istatistiksel olarak anlamlı fark bulunmadı (sırasıyla P=0,12, P=0,72, P=0,45, P=0,79). Histopatolojik olarak her iki grup arasında postoperatif intraabdominal adezyon oranları istatistiksel olarak benzer saptandı.

Sonuç: Her ne kadar istatistiksel olarak anlamlı fark olmasa da ozon terapinin şiddetli fibrozis ve konjesyon oranlarında azaltıcı etkisinin olduğu tespit edildi. FSH açısından fark bulunmasa da Grup2'de E2 seviyelerinin düşük tespit edilmesi, ozon tedavisinin over fonksiyonları üzerinde koruyucu etki oluşturabileceğini akla getirmektedir. Ancak adezyon oluşumu ve over fonksiyonları üzerindeki etkiler açısından daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Rat, Ozon, Adezyon

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Introduction

Adhesions in the peritoneum are abnormal bonds emerging between the omentum, bowel loops, and the abdominal wall [1]. The etiology of peritoneal adhesions can be either congenital or acquired; among the acquired reasons are inflammatory events and surgical interventions [2]. Although almost 90-95% of the intra-abdominal adhesions develop after surgery, this debilitating process can also be expected after an intra-abdominal inflammatory process such as pelvic inflammatory disease (PID), diverticulitis, or spontaneous bacterial peritonitis [3-5].

Trauma to the peritoneal epithelium is blamed as the primary mechanism of adhesion formation, results in fibrin matrix accumulation in the damaged intra-abdominal planes. As a fibrinolytic agent, plasmin is not sufficient to prevent the process after surgery. Thus, the degradation collected deposits convert eventually to adhesions [3]. Diamond et al. [6], categorize peritoneal adhesions as two distinct forms. Type 1 entities involve adhesions at sites without any previous adhesions. They include type 1A without any past operative procedures at the area of the problem and type 1B with some preceding operative procedures at the zone of adhesions. Surgeons define adhesions depending on personal factors based on individual experiences and proficiency [7].

Peritoneal adhesions can be associated with many diseases ranging from enduring abdominal pain to infertility [8]. One of the most prevalent ailments observed is incomplete or complete bowel obstruction, which is usually located in the small bowel area. Almost 79% of the intestinal obstructions are due to post-surgical procedures [9].

Many studies have investigated the formation of peritoneal adhesions. However, there is no particular approach to prevent their development; there are controversies regarding the usefulness of the current preventive methods. Additionally, the majority of research concentrates on gynecological cases. Thus, there is a need for trustworthy recommendations and guidelines for patients receiving abdominal surgical interventions [10].

Researchers have investigated many agents for the prevention of post-surgical peritoneal adhesions. The main strategies in this effort were concerning fibrinolysis, coagulation, inflammation, collagen synthesis, or creating barriers between wound surfaces. The preventive approaches included mechanical barrier such as crystalloids, dextran, hyaluronic acid, cellulose, polytetrafluoroethylene, pure olive and and chemical agents such as non-steroidal anti-inflammatory medications, corticosteroids, calcium channel blockers, histamine antagonists, antibiotics, fibrinolytic substances, anticoagulants, antioxidants, hormones, vitamins, colchicine, and selective immunosuppressors [10,11].

Postoperative adhesions frequently develop after surgical procedures, and they most commonly affect the ovaries [5]. It was demonstrated that the reduction of adhesion reformation is more challenging than the prevention of adhesion formation, which can cause infertility [12].

Ozone (O_3) is a colorless gas, consisting of three oxygen atoms and a characteristic odor at room temperature [13]. Medical ozone is always used as a combination of ozone and oxygen with a concentration of 1 to 100 μg/ml (0.05–5 O_3). Besides its bactericidal, fungicidal, virostatic, and antioxidant properties, ozone improves blood circulation and activates the immune system [13]. Ozone therapy (OT) is widely used in medicine, such as for cardiovascular diseases, subcutaneous tissues, peripheral vascular diseases, neurological diseases, head and neck problems, as well as ailments of the orthopedic, gastrointestinal, or genitourinary systems [13]. However, few studies investigated the effects of ozone treatment on preventing postoperative intraabdominal adhesions [14].

Biochemical and histopathological findings suggest that ozone is effective against ovarian ischemia/reperfusion injury [15]. Ozone therapy could have beneficial effect on tubal occlusion, could protect from endometritis and vaginitis, might protect ovaries from ischemia and oocyte loss, and finally might lead to less formation of pelvic adhesions [16].

We hypothesized that ozone can prevent postoperative adhesion formation by preventing tissue damage caused by surgical interventions. Especially its antioxidant effects may help to obtain the desired results for a new clinical use. Thus, this study aimed to investigate the effects of ozone treatment on postoperative intraabdominal adhesions and ovarian roles in rats.

Materials and methods

Study design

The study was conducted in experimental design, at the operating room and research laboratories of the Faculty of Veterinary Medicine of Kafkas University between October and December 2016. Study reporting was done per the PREPARE guideline [17]. The study protocol was approved by the Kafkas University Animal Experiments Local Ethics Committee (IRB number:115, Date: 10/27/2016). The rats received appropriate care per the institution's guidelines, as described in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health.

Twenty female Wistar rats weighing 200–240 g (4–6 months old, obtained from Atatürk University Experimental Animal Production and Research Center, Erzurum, Turkey), were used in the study.

Before commencing the experiment, the rats were fed with standard rat food and water as needed and housed in animal cages with controlled temperature and alternating 12h light/dark cycle for one week. They were randomly divided into two groups containing ten rats each: sham and OT groups. The sham group received no treatment in the postoperative period, while the OT group received ozone treatment as described below. The primary outcome variables of the study were the severity of inflammation and fibrosis in the endometrium and cervix.

The procedure

After general anesthesia, induced by 50 mg/kg ketamine (Ketalar; Parke Davis, Eczacıbaşı, Istanbul, Turkey), and 10 mg/kg xylazine (Rompun; Bayer AG, Leverkusen, Germany) (Figure 1), the abdominal area was shaved and disinfected with iodine. Under sterile conditions, the abdomen was opened with a 3cm incision at the midline (Figure 2). Then, laparotomy was performed on the parietal peritoneum, the surface of the uterus was scraped, and the abdomen was sutured according to the anatomical layers with 4/0 polyglycolic acid suture materials (Vicryl, Ethicon, Somerville, NJ). Right after closing the

abdomen, an ozone/oxygen mixture at a dose of 0.7 mg/kg was applied intraperitoneally once-a-day for consecutive 4 days, followed by a total of 8 doses of weekly intraperitoneal ozone. Later, all animals were put in a warm incubator at 33 C for two hours. After 2h, they were returned to their cages, where clear water was given as needed for 24h. Then, the animals were fed standard rat food and water ad libitum. Two months later, the rats were sacrificed by cervical dislocation.

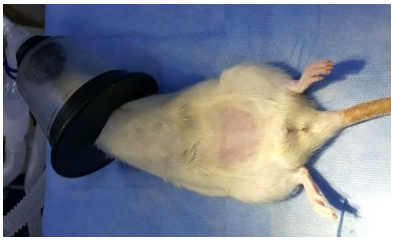

Figure 1: Administration of general anesthesia

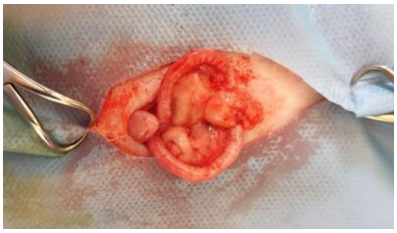

Figure 2: The surgical procedure

Ozone therapy

Ozone was produced by an ozone generator (Ozonosan Photonic 1014; Hansler GmbH, Iffezheim, Germany), permitting control of the gas flow rate and ozone concentration in real-time by a built-in UV spectrometer. The ozone flow rate was preserved at 3 L/min, representing a concentration of 60 mg/mL with a gas mixture of 97% oxygen+3% ozone. Tygon polymer tubes and single-use silicon-treated, ozone-resistant polypropylene syringes were used throughout the reaction to guarantee ozone containment and sustained concentrations.

Blood and tissue sampling

Blood samples were collected from sacrificed rats in the sham and OT groups. Antioxidant (Mm), follicle-stimulating hormone (FSH) (ng/mL), estradiol (E2) (ng/mL), urea (mg/dL), creatinine (mg/dL), and lactate dehydrogenase LDH (U/L) levels were measured.

The abdomen was re-opened to obtain tissue samples. The uterus, tubes, and ovaries were harvested and stowed at -80 C until histopathological examination. The tissues were homogenized in phosphate buffer (pH 7.4) employing a homogenizer (Heidolph Diax 900; Heidolph Elektro GmbH, Kelhaim, Germany) on an ice cube. The homogenized tissues were centrifuged at 7 530x*g* in 4 C for 10 minutes.

Variables

The primary outcome variables of the study were the severity (mild/moderate/severe) of inflammation and fibrosis in the endometrium and cervix. The secondary outcome variables were the macroscopic appearance of tuba, ovary, and intraabdominal adipose tissues. The independent study variable was study groups (sham and OT).

Statistical analysis

Data was entered into the computer and analyzed using the SPSS 25.0 software (SPSS Inc., Chicago, IL, USA). The findings were presented as frequencies, percentages, median, and Interquartile range (IQR). The normal distribution of the numerical data was analyzed by the Kolmogorov-Smirnov test. The homogeneity of the variances was examined by the Levene's test. For the comparison of sham and OT groups, the independent samples Mann-Whitney U test was used for antioxidant, FSH, E2, urea, creatinine, and LDH levels, while the Fisher's Exact Test was used for comparing the severity of inflammation, congestion, and fibrosis. All hypotheses were two-sided, and a *P*-value of <0.05 was considered statistically significant.

Results

Biochemical results

On the 19th day in the ozone-treated group and on the 11th day in the sham group, one rat died. Data of 9 rats in the ozone group and 9 in the sham group were analyzed. Antioxidant levels were significantly higher in the ozone group (median: 4.12, IQR: 0.93) than in the sham group (median: 2.86, IQR: 1.05) (Z=2.517, *P*=0.01). E2 levels were significantly lower in the ozone group (median: 108.96, IQR: 8.80) than in the sham group (median: 127.64, IQR: 17.77) (Z=2.782, *P*=0.005). There was no statistical difference between the other blood values between the groups (*P*>0.05). The comparison of biochemical blood values in the ozone and sham groups is given in Table 1.

Histological results

No statistically significant difference was found between the severity of congestion, inflammation, and fibrosis in the endometrium, cervix, and ovaries, in the ozone-treated and sham groups (*P*>0.05) (Table 2). Histological demonstrations of endometrium and cervix are shown in Figure 3A-D.

The appearance of all tubes was normal. Intraabdominal adipose tissues in the ozone and sham groups looked similar.

Table 1: Comparison of biochemical blood values in the ozone-treated and sham groups

	Groups					
	Ozone therapy		Sham			
	Median	IQR	Median	IQR	Z	*P*-value
Antioxidant (Mm)	4.12	0.93	2.86	1.05	2.52	0.012
FSH (ng/mL)	68.42	9.61	63.12	22.08	1.55	0.12
E2 (ng/mL)	108.96	8.80	127.64	17.77	2.78	0.005
Urea (mg/dL)	38.00	7.50	38.00	9.50	0.36	0.72
Creatinine (mg/dL)	0.50	0.08	0.47	0.04	0.75	0.45
LDH (U/L)	884.00	254.50	868.00	117.00	0.265	0.79

IQR: Interquartile range

Table 2: Comparison of inflammation, congestion, and fibrosis of tissues of ozone therapy, and sham groups

		Groups				
		Ozone therapy		Sham		
		n	%	n	%	*P*-value*
Endometrial inflammation	Mild	0	0.0	3	33.3	0.37
	Moderate	7	77.8	5	55.6	
	Severe	2	22.2	1	11.1	
Endometrial congestion	Mild	6	66.7	2	22.2	0.26
	Moderate	1	11.1	3	33.3	
	Severe	2	22.2	4	44.4	
Endometrial fibrosis	Mild	5	55.6	4	44.4	0.69
	Moderate	3	33.3	2	22.2	
	Severe	1	11.1	3	33.3	
Cervical inflammation	Mild	7	77.8	3	33.3	0.23
	Moderate	1	11.1	3	33.3	
	Severe	1	11.1	3	33.3	
Cervical fibrosis	Mild	5	55.6	4	44.4	0.69
	Moderate	3	33.3	2	22.2	
	Severe	1	11.1	3	33.3	
Ovarian congestion	Mild	3	33.3	5	55.6	0.35
	Moderate	0	0.0	1	11.1	
	Normal	6	66.7	3	33.3	

* Fisher's Exact Test

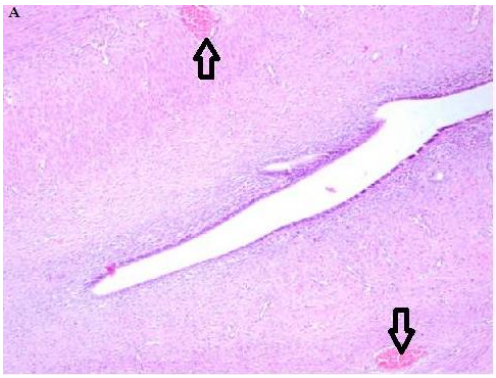

Figure 3A: Endometrial vascular congestion (black arrows) in SHAM group, H&E- 100x

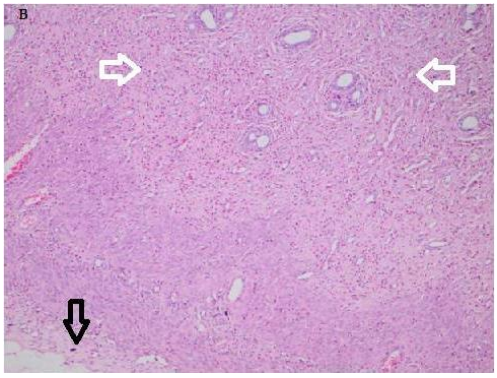

Figure 3B: Endometrial inflammation (white arrows) and fibrosis (black arrow) in the adhesion group, H&E- 100x

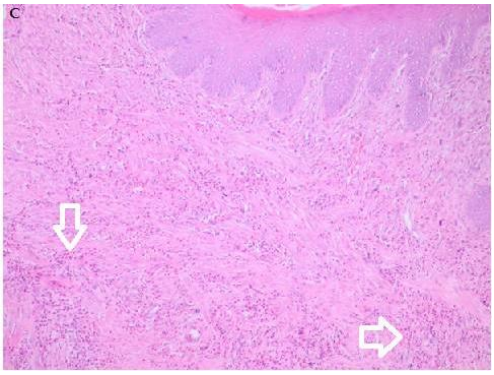

Figure 3C: Cervical inflammation (white arrows) in SHAM group, H&E- 100x,

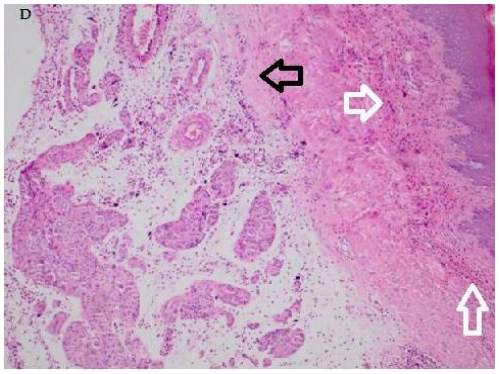

Figure 3D: Cervical inflammation (white arrows) and fibrosis (black arrow) in the adhesion group, H&E- 100x

Discussion

Our results showed significantly higher antioxidant levels in the OT group compared to the sham group. However, the E2 levels were meaningfully lower in the OT group. A recent study reported that SOD, CAT, and GPx activities increased, and MDA levels decreased in the ozone group [18]. These results suggest that ozone increases plasma antioxidant levels by triggering various biochemical pathways. Therefore, it is stated that ozone therapy can have positive impacts on preventing intraabdominal adhesions. In a study conducted in rats, it was reported that ozone exposure caused immunohistochemical staining for alpha and beta estrogen receptors, and dopamine beta-hydroxylase was reduced as were alpha and beta estrogen receptor protein levels [19]. Although ozone therapy is used in a broad spectrum of medical specialties [14], it is noteworthy that its effects on reproductive hormones have been under-examined.

Postoperative intraabdominal adhesion rates of the OT and sham groups were similar. A study conducted by Uysal et al. [14] reported that medical ozone treatment decreases postoperative uterine adhesions. Di Filippo et al. [20] reported the reduced formation of postoperative peritoneal adhesions after application of 300 Mm/kg ozone, associated with decreased levels of ubiquitin and 20S proteasome subunit within the adhered tissues.

Many agents were studied for their potential effects in preventing post-surgical peritoneal adhesions. The sought roles of these substances in achieving fibrinolysis, hindering coagulation, decreasing the inflammatory response, constraining collagen synthesis, or creating a boundary between neighboring wound surfaces. The preventive approaches are grouped into four categories: general principles, surgical techniques, mechanical barriers, and chemical agents [10]. Nonetheless, none of these methods were proven effective under all circumstances [21].

Our interpretations of this study confirmed that ozone improved oxidative stress and peritoneal adhesion formation in rats, which underwent a post-surgical experimental adhesion procedure. A possible explanation for the favorable effects of ozone is its modulation of oxidative and anti-oxidative status by stimulating endogenous superoxide dismutase (SOD) and glutathione peroxidase (GPX) [22-25]. In fact, the antioxidant effects of ozone administration are already proven in different organs such as the kidneys [24], esophagus [26], and intestines [27].

E2 levels in this study were significantly lower in the ozone group compared to the sham group. Although no studies could be retrieved concerning the effects of ozone, E2, and the ovaries, theoretically, hormonal alterations may be expected after procedures affecting the ovaries [28]. However, the connection of ozone treatment and decreased E2 levels in cases with peritoneal adhesions remains obscure.

Limitations

Our study has some limitations. The sample size is quite small. There are no human studies on the subject. In addition, our study is an experimental study and the follow-up period of the study was short.

Conclusion

Considering that the rate of endometrial and cervical fibrosis in our study was around 44%, it can be concluded that ozone application in postoperative intraabdominal adhesion is better than other methods, except for surgical treatment. Consequently, OT considerably prevents postoperative intra-abdominal adhesions in the experimental rat model. Thus, it seems logical that OT might be an add-on therapeutic modality in the prevention of postoperative intraabdominal adhesions. Nevertheless, further experimental, as well as clinical studies, are needed to determine the possible side effects and long-term

consequences before safely suggesting the use of ozone in the prevention of adhesions in humans.

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Research article
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Evaluation of hand anomalies in children admitted to a tertiary health center in eastern Anatolia

Doğu Anadolu bölgesinde bir üçüncü basamak sağlık merkezine başvuran el anomalili çocukların değerlendirilmesi

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Abstract

Aim: Identification and treatment management of congenital or acquired hand anomalies are serious problems for orthopedic and plastic surgeons. With the start of medical education in hand surgery as a subspecialty, the number of hand surgeons has increased, and this problem has partially been removed. This study aimed to contribute to the epidemiologic data of our country by sharing admission times and types, treatment management, and demographic data of children admitted with hand anomalies to a tertiary health center in the light of the literature.

Methods: Pediatric patients who were admitted with hand anomalies to the hand surgery clinic between 01.12.2018 and 01.12.2019 were included in this cross-sectional study. They were classified by extended OMT (Oberg, Manske, and Tonkin) classification by using the data obtained from the hospital registry. Patients' ages, genders, diagnoses, admission times, educational statuses, treatment plans and decisions of parents on the treatment were evaluated by a single hand surgeon available in the region.

Results: Out of approximately 1500 patients admitted to the hand surgery clinic, 49 patients between the ages of 0 and 18 with pediatric hand anomalies were included in the study. Out of 49 patients, 7 had acquired and 42 had congenital hand anomalies. The most common congenital anomaly was trigger finger. Eleven (22.5%) of the patients were at school age, 12 (24.5%) at pre-school age, and 26 (53%) were infants, aged 2 years and below.

Conclusion: It is highly important for patients with hand anomalies to reach the appropriate physician at the right time so that their treatment may be planned accordingly, the present anomaly does not delay the growth of the child, the deformity does not progress further and that these individuals can be brought into the society earlier. Therefore, we believe that the number of physicians should be increased due to the following reasons: Hand surgery is a new branch and these patients should be referred to subspecialists in accordance with the demands of the patients' parents. This branch is vital for the region, and there are patients still waiting for their already planned surgery.

Keywords: Congenital anomaly, Pediatric patient, Hand surgery

Öz

Amaç: Konjenital veya edinsel el anomalilerinin tanımlanması ve tedavi yönetimi ortopedik ve plastik cerrahlar için ciddi problemlerdir. El cerrahisinde tıbbi eğitimin bir alt uzmanlık olarak başlamasıyla, el cerrahlarının sayısı artmış ve bu sorun kısmen giderilmiştir. Bu çalışma, el anomalisi ile üçüncü basamak bir sağlık merkezine başvuran çocukların kabul tiplerini, tedavi yönetimini, kabul sürelerini ve demografik verilerini literatür eşliğinde paylaşarak ülkemizin epidemiyolojik verilerine katkıda bulunmayı amaçlamıştır.

Yöntemler: 01.12.2018 - 01.12.2019 tarihleri arasında el cerrahisi kliniğine el anomalisi ile başvuran pediatrik hastalar bu kesitsel çalışmaya alındı. Hastaların dosya kayıt sistemlerinden elde edilen veriler kullanılarak uzatılmış OMT (Oberg, Manske, and Tonkin) sınıflandırmasına göre sınıflandırıldı. Hastaların yaşı, cinsiyeti, tanısı, kabul süresi, eğitim durumu, tedavi planlaması ve ebeveynlerin tedaviye ilişkin kararları bölgede mevcut tek el cerrahı tarafından değerlendirildi.

Bulgular: El cerrahisi kliniğine başvuran yaklaşık 1500 hastadan 0 ile 18 yaşları arasında çocuk el anomalisi olan 49 hasta çalışmaya dahil edildi. 49 hastanın 7'sinde edinsel ve 42'sinde konjenital el anomalisi vardı. En sık görülen konjenital anomali tetik parmak idi. Hastaların 11'i (%22,5) okul çağında, 12'si (%24,5) okul öncesi yaşta ve 26'sı (%53) 2 yaş ve altı bebeklik döneminde idi.

Sonuç: El anomalisi olan hastaların uygun zamanda uygun doktora ulaşmaları, deformitenin uygun zamanda tedavi olması, mevcut anomalinin çocuğun gelişimini engellememesi, deformitenin daha da büyümemesi ve bu bireylerin topluma erkenden kazandırılması açısından çok önemlidir. El cerrahisinin bölgede yeni bir oluşum olması, bu hastaların yan dal olan el cerrahisine yönlendirilmesi, ebeveynlerin bu yönde taleplerinin olması, halen planlanan ameliyatlarını bekleyen hastaların olması nedeniyle bölgede el cerrahın olması çok önemlidir ve bu nedenlerden dolayı hekim sayısının artırılması gerektiği kanaatindeyiz.

Anahtar kelimeler: Konjenital anomali, Pediatrik hasta, El cerrahisi

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Introduction

Upper extremity has functionally had a crucial role in people's daily life, even in the development of civilization throughout history. Identification of functions and structure of the hand, which plays the main role in the functional structure of human, has always been an object of interest and many studies on identification of hand deformities (congenital or acquired), determination of their frequencies among different races and societies, and treatment modalities have been performed. This study aimed to identify the frequency of patients admitted to the hand surgery center of our hospital with hand anomalies (after the specialist hand surgeon was appointed) and share our knowledge in light of the literature. Upper and lower extremity anomalies vary widely and these anomalies, whether congenital or acquired, cause loss of function and many psychological problems, thereby impairing the quality of life [1]. A study [2] evaluating the distribution of patients admitted with upper extremity injuries to the hand surgery clinic in terms of whether they were emergent or elective was performed in the region, however, epidemiologic evaluation of pediatric patients with hand anomalies according to patient group was not performed. Many studies on hand anomalies and different incidences among different races and societies were reported in the literature [3-7].

This study aimed to identify the types of patients admitted with congenital [8] and acquired [9] anomalies within a year to the hand surgery clinic of a tertiary care university hospital serving approximately five cities. We believe that the data obtained from this study will be useful for future epidemiological studies and that knowledge of sociodemographic characteristics of these patients will be a guide in planning treatment services.

Materials and methods

This cross-sectional study was performed on patients admitted with congenital and acquired anomalies to our hand surgery clinic between December 2018-December 2019. Patients who were under the age of 18 and who did not complete the growth curve were included in the group. A total of 3 patients who were under the age of 18 with closed physes were excluded. In compliance with the distribution of the patients, patients admitted at the age of 1 month or below were evaluated as 1-month old patients as there would not be any delay at the time of treatment. The study was performed in accordance with the Declaration of Helsinki and approved by the local Ethics committee (no: 2019/18-09).

Data collection tools

Patients' ages, genders, diagnoses, etiologies, treatment statuses, the city where they came from, admission times, and whether there was any sequela due to delayed admission were recorded. Ages of all patients in the study were calculated in months. Diagnoses were classified according to the "Refinement of Oberg, Manske, and Tonkin (OMT) Classification (Extended Version)" (Table 1) [10,11]. Based on the treatment plan, patients were classified as the ones who were operated, the ones who refused treatment, the ones whose future surgery was planned and the ones with managed conservatively. Admission timing of the patients was divided into early, late, and normal timing for each patient group. Clinical evaluation was performed by a single physician with physical examination and comparative x-ray monitoring of both upper extremities.

Table 1: Refinement of Oberg, Manske and Tonkin (OMT) Classification (Extended Version)

1. Malformations
- **A. Failure of axis formation/differentiation— entire upper limb**
  - **1. Proximal-distal axis**
    - i. Brachymelia with brachydactyly
    - ii. Symbrachydactyly
    - iii. Transverse deficiency
      - Amelia
      - Clavicle
      - Long/short above elbow
      - Wrist
      - Proximal/distal carpal row
      - Metacarpal
      - Proximal/middle/distal phalanx
    - iv. Intersegmental deficiency
      - Phocomelia (total/proximal/distal)
  - **2. Radial-ulnar (anteroposterior) axis**
    - i. Radial longitudinal deficiency
      - Thumb hypoplasia (with proximal limb involvement)
    - ii. Ulnar longitudinal deficiency
    - iii. Ulnar dimelia
    - iv. Radioulnar synostosis
    - v. Humeroradial synostosis
      - Elbow ankyloses
  - **3. Dorsal-ventral axis**
    - i. Nail-patella, Fuhrmann, and Al-Awadi syndromes
    - ii. Arthrogryposis
    - iii. Absent/hypoplastic extensor/flexor muscles
  - **4. Unspecified axis**
    - i. Undescended shoulder (Sprengel)
    - ii. Abnormal shoulder muscles
- **B. Failure of axis formation/differentiation— hand plate**
  - **1. Proximal-distal axis**
    - i. Brachydactyly
    - ii. Symbrachydactyly
    - iii. Transverse deficiency
      - Wrist
      - Proximal/distal carpal row
      - Metacarpal
      - Proximal/middle/distal phalanx
  - **2. Radial-ulnar (anteroposterior) axis**
    - i. Radial (thumb) deficiency (no radius involvement, absent thumb, absent/hypoplastic thenar muscles
    - ii. Ulnar deficiency
    - iii. Radial polydactyly
    - iv. Triphalangeal thumb
    - v. Ulnar polydactyly
  - **3. Dorsal-ventral axis**
    - i. Dorsal dimelia (palmar nail)
    - ii. Hypoplastic/aplastic nail
    - iii. Arthrogryposis
  - **4. Unspecified axis**
    - **a. Soft tissue**
    - i. Syndactyly
    - ii. Camptodactyly
    - iii. Thumb in palm deformity
    - iv. Deviated finger without skeletal deformity
    - **b. Skeletal deficiency**
    - i. Clinodactyly
    - ii. Kirner deformity
    - iii. Metacarpal and carpal synostosis
    - **c. Complex**
    - i. Cleft hand
    - ii. Synpolydactyly—central
    - iii. Apert hand

2. Deformations
- **A. Constriction ring sequence**
- **B. Trigger digits**
- **C. Not otherwise specified**

3. Dysplasias
- **A. Hypertrophy**
  - **1. Whole limb**
    - i. Hemihypertrophy
    - ii. Aberrant flexor/extensor/intrinsic muscle
  - **2. Partial limb**
    - i. Macrodactyly
    - ii. Aberrant intrinsic muscles of hand
- **B. Tumorous conditions**
  - **1. Vascular**
    - i. Hemangioma
    - ii. Malformation
  - **2. Neurological**
    - i. Neurofibromatosis
  - **3. Connective tissue**
    - i. Juvenile aponeurotic fibroma
    - ii. Infantile digital fibroma
  - **4. Skeletal**
    - i. Osteochondromatosis
    - ii. Enchondromatosis
    - iii. Fibrous dysplasia
    - iv. Epiphyseal abnormalities
  - **4. Syndromes**

Statistical analysis

The required statistical analyses were performed with SPSS 23 statistical software. Numerical variables were defined as mean (standard deviation) while categorical variables were presented in number and percentile. One-way analysis of variance (One-way ANOVA) was used to determine whether there was a difference between the ages in different classifications. Duncan multiple comparison test was used to determine the classifications that were important after analysis of variance. Fisher Exact test was used to determine whether there was a relationship between classifications and admission times, classifications and treatment status, treatment status according to the cities and between admission times according to the cities.

Results

Forty-nine patients were included in our study. Seven of the patients had acquired and 42 had congenital anomalies. According to the extended OMT classification, only one of the patients among the ones with acquired anomalies had camptodactlia and was suitable for Benson's classification type II. Four (8.16%) patients had an anomaly related to the wrist-forearm and 45 (91.84%) patients had an anomaly on their hand. The youngest patient was newborn and the oldest was 15 years old. There were no patients over 15 years of age in the included age range (0-18). The difference between classifications in terms of mean month was statistically significant (P<0.001). The lowest and highest mean month values were obtained in 1.A.3.ii (Arthrogryposis) classification (mean: 1 month) and 3.A.2.i (Macrodactyly) classification (180 months/15 years), respectively. Eleven (22.5%) of the patients were at school age, 12 (24.5%) at pre-school age, and 26 (53%) were infants aged 2 years and below. Thirty-five (71.4%) patients were referred by another specialist physician, among which 13 were referred from pediatrics, 14 from plastic surgery and 8 from orthopedics. Other patients did not have any referral history. The evaluations of age distributions according to the classification are presented in Table 2.

Table 2: Age (month) distribution of our patients according to OMT Classification (Extended Version)

Diagnosis	n	Mean	SD	95% Confidence Interval for Mean		Minimum	Maximum
				Lower Bound	Upper Bound		
1.B.4.a.i	4	44.500	45.8	-28.367	117.367	10	108
acquired	6	42.167	24.6	16.406	67.927	1	72
2.B	8	18.500	12.4	8.173	28.827	5	36
1.B.2.iii	3	104	81.7	-98.910	306.910	12	168
1.A.2.i	2	4.500	2.1	-14.559	23.559	3	6
1.A.3.ii	3	1		1	1	1	1
1.A.1.ii	3	39	26.7	-27.238	105.238	9	60
3.A.2.i	2	180		180	180	180	180
1.B.4.a.ii	2	102	25.5	-126.712	330.712	84	120
3.B.1.i	2	168		168	168	168	168
1.B.2.iv	2	84		84	84	84	84
3.B.4.i	2	96		96	96	96	96
2.A	2	60		60	60	60	60
1.B.4.c.i	2	2		2	2	2	2
1.B.2.v	2	20		20	20	20	20
1.A.2.iii	2	4		4	4	4	4
1.b.1.İ	2	6		6	6	6	6
Total	49	50.3	54.6	34.609	65.962	1	180

A statistically significant relationship was found between the classification and admission times (P<0.001). Patients with 2.A (Constriction ring sequence) and 1.B.2.v (Ulnar polydactyly) classifications were generally at normal times, those with 1.A.2.i [Radial longitudinal deficiency, Thumb hypoplasia (with proximal limb involvement)], 1.A.2.iii (Ulnar dimelia), 1.A.3.ii (Arthrogryposis), 2.B (Trigger digits), 1.B.4.a.i (Syndactyly), and 1.B.4.c.i (Cleft hand) were early and patients with acquired anomalies, namely, 3.B.4.i (Osteochonromatosis), 3.B.1.i (Hemangioma), 3.A.2.i (Macrodactyly) and 1.B.2.iv (Triphalangeal thumb) were late in presentation. The evaluation of treatment status according to the classification is presented in Figure 1. The relationship between the classification and sequela occurence was significant (P<0.001). While there was sequela in patients with acquired anomalies, 3.A.2.i (Macrodactyly), 3.B.1.i (Hemangioma), 1.B.2.iv (Triphalangeal thumb), 3.B.4.i (Osteochonromatosis), and 1.B.4.c.i (Cleft hand), due to late admission, there was no sequela in other classifications. The relationship between classification and sequela is presented in Figure 2.

A significant relationship was found between the cities and admission times (P<0.001) (Figure 3). Patients coming from Bitlis and Igdir were gradually operated and those coming from Van and Hakkari were generally operated, or had their surgeries planned. The patient who were admitted with thumb hypoplasia and who came from Agri refused treatment, hence was not operated.

A statistically significant difference was found between the cities and admission times (P<0.001). Patients from Agri were admitted late, patients from Hakkari were mostly admitted early and patients from Van were mostly admitted late (Figure 4).

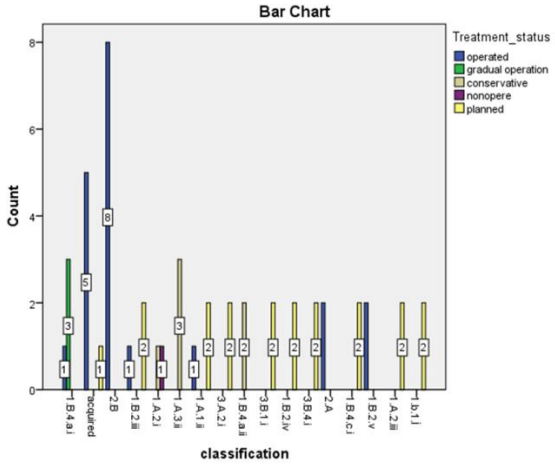

Figure 1: The evaluation of treatment status according to the classification

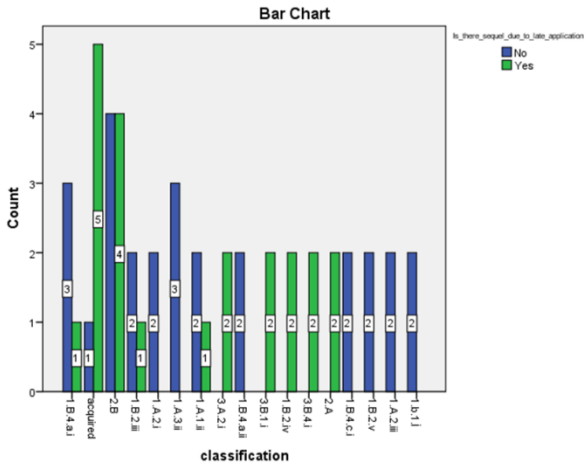

Figure 2: The relationship between the classification and occurrence of sequel

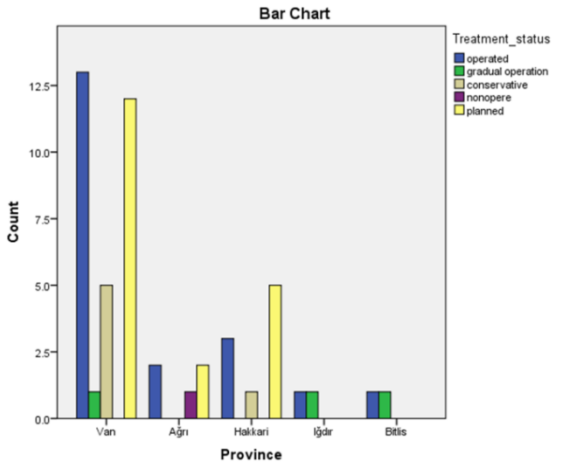

Figure 3: Relationship between the cities and admission times

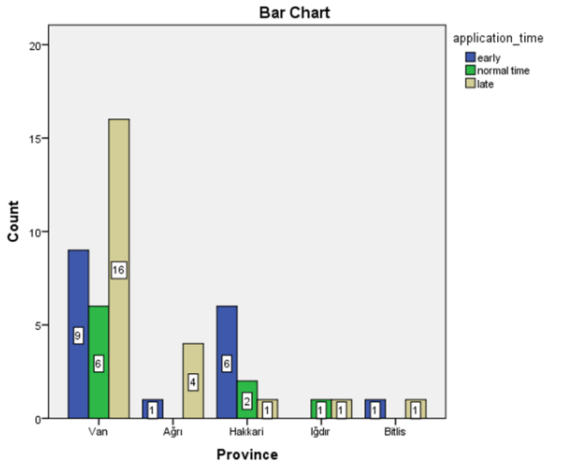

Figure 4: Difference between the cities and admission times

Discussion

The department of hand surgery provides the diagnosis and treatment of hand, wrist, forearm, shoulder, brachial plexus and peripheral nerve injuries and diseases and congenital anomalies of upper extremity [9,12]. The first hand surgery clinic at the level of Ministry of Health and University in our country was founded at Ankara Numune Training and Research Hospital in September, 2009. When a specialist hand surgeon was appointed to the Ministry of Health University in Van in September 2017, a hand surgery clinic was founded. Around 1500 patients are admitted to the Hand Surgery Clinic annually [2].

Hand Surgery is a field that has recently become a subspecialty in our country. Although studies identifying the clinical and sociodemographic characteristics of the patients admitted to hand surgery clinic have been performed in detail, there is not any detailed study on pediatric patients with hand anomalies, especially in the Eastern Anatolia Region of Turkey. Many age groups from birth to the end of childhood were admitted to our clinic with hand and wrist anomalies. Of these patients who had to be mostly operated at pre-school ages or in infancy, 22.5% were admitted at school ages. One hundred percent could not yet be reached in this patient group, who must be examined by a specialist physician and referred without missing the diagnosis. Admission times significantly differ according to patient groups, which is also related to the fact that the diagnosis can be recognized by both the patients' relatives and physicians. When the children with congenital hand anomalies are admitted later than the average surgical times of their present diseases, the functional and cosmetic success rate of the surgery decreases [13]. In the region, 22 (44.9%) of these patients with congenital hand anomalies exceeded this time. Sequelae were seen in patients with Madelung deformity, burn, contracture, swan neck deformity secondary to mallet finger, hemangioma in the wrist, triphalangeal thumb, osteochondromatosis and cleft hand due to late presentation. As patients in Hakkari, Van, Bitlis and Igdir preferred our clinic, most of them were either treated or their operations were planned. There was only one physician and some patients had to wait for their operations due to busyness. Patients from Hakkari were admitted early, while patients from Van and Agri were admitted late to our clinic in Van, which reveals that patients' relatives and/or physicians who would refer the patients are not aware enough. As the rate of being recognized in patients with additional pathology and syndrome was much, higher no delay was seen in their presentation. Presence of health insurance and parents being educated above high school have a positive effect on admission times. Congenital bilateral trigger finger was the most common anomaly. While especially grade 4 (Green Classification) presentations were more frequent, grade 2 and 3 were usually seen in the other finger. The possibility that this anomaly may be bilateral should be kept in mind in order to administer a complete treatment.

Limitations

The study was performed in a single center (as our clinic was the only hand surgery clinic in the region, no significant loss in the potential of patients was considered). Main limitations of our study may be that the number of patients was low, the 1-year duration of the study was short, and patients did not come from all Eastern Anatolia cities (due to probable conditions of transportation and closeness of other hospitals to other centers). Further studies are needed to contribute to the epidemiological data of our country in the future.

Conclusion

The facts that hand surgery is a new branch, patients in need of hand surgery should be referred from general examination to subspecialists, parents have demands on this direction, this branch with high work load and long learning-curve is extremely necessary for the region and that there are patients still waiting for their already planned surgery, suggest the need to increase the number of physicians. It is highly important for patients with hand anomalies to reach the appropriate physician at the right time so that their treatment can be planned to prevent the present anomaly from delaying the growth of the child without further progression. The aim is to bring these individuals into the society earlier. Therefore, we believe that identifying the frequency of these anomalies, increasing the awareness of the parents by improving the geographical as well as socioeconomic conditions, especially in rural areas, increasing the number admissions to the hospitals, evaluating the neonates in this regard and referring them to the related center early will contribute to the prevention of some progressive deformities and to the socioeconomic development of our country.

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Morphometry of the external auditory canal: Radiological study

Dış kulak yolunun morfometrisi: Radyoloji çalışması

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Abstract

Aim: Morphometry of the external auditory canal was not previously studied among the normal population in the literature. In this study we aimed to indicate normal values and age, gender, and side related changes of the external auditory canal of healthy individuals.

Methods: Computed Tomography (CT) images of 379 patients were evaluated in this cross-sectional study. Two diameters at three points were measured on sagittal images for each side: First point was at the level of the tympanic membrane where chorda tympani leaves the bony canal. The height (1a) and width (1b) were measured from the ground where the cylindrical view of EAC was most prominent. The second point was at isthmus level, where height (2a) and width (2b) were measured. The third point was the most lateral site of external auditory canal (EAC) at the level of the tympanomastoid suture where height (3a) and width (3b) were measured. Age, gender, and side related changes for each measurement were statistically analyzed.

Results: The diameter of each point in each direction was similar between the left and right sides. The median diameter of left 1a was 9.4 mm in males and 9.2 mm in females, which was significantly different. The "a" diameter of each point was higher in males than females for both sides. There was no significant difference between males and females in terms of b diameters. Diameter 1b was higher on the left side compared to the right side for females, while left-right side comparisons for other measurements were similar. None of the diameters differed between the left and right sides for males.

Conclusion: Normal measurements of EAC diameters and its age, sex and side related changes are important for surgeons, radiologists, and anatomists. Proper evaluation of EAC is critical for transcanal endoscopic ear surgery and early diagnosis of a pathology impairing the anatomy of EAC on radiologic images.

Keywords: External auditory canal, Temporal bone, Morphometry, Computed tomography

Öz

Amaç: Literatürde dış kulak yolu morfometrisi normal popülasyonda daha önce incelenmemiştir. Bu çalışmada, sağlıklı bireylerde dış kulak yolunun normal ölçümleri ve bu değerlerin yaş, cinsiyet ve taraflar arasında gösterdiği farklılıkları değerlendirmeyi amaçladık.

Yöntemler: Bu kesitsel çalışmada 379 hastanın bilgisayarlı tomografi (BT) görüntüleri incelendi. Her iki taraf için sagital görüntülerde üç noktada iki çap ölçüldü. 1.nokta, timpanik membran seviyesinde chorda tympani'nin kemik kanalından çıktığı noktaydı . Bu noktada dış kulak yolunun (DKY) silindirik görünümünün en belirgin olduğu yerden yükseklik (1a) ve genişlik (1b) ölçümleri alındı. 2.nokta isthmus seviyesindeydi ve bu noktadan yükseklik (2a) ve genişlik (2b) ölçümleri yapıldı. 3.nokta timpanomastoid sutur düzeyinde DKY'nun en lateral bölgesiydi. Bu noktadan da yükseklik (3a) ve genişlik (3b) ölçümleri yapıldı. Her ölçüm için yaş, cinsiyet ve tarafla ilişkili değişiklikler istatistiksel olarak analiz edildi.

Bulgular: Her bir nokta için her yönde yapılan ölçümler sol ve sağ taraflar arasında benzerdi. Erkeklerde sol 1a'nın ortalama uzunluğu 9,4 mm, kadınlarda 9,2 mm idi. Her noktanın 'a' uzunlukları erkeklerde her iki taraf için kadınlardan daha yüksekti. Erkekler ve kadınlar arasında 'b' uzunlukları açısından anlamlı bir fark yoktu. Kadınlarda 1b ölçümü sol tarafta sağ tarafa göre daha yüksekti, diğer ölçümler için sol-sağ taraf karşılaştırmaları anlamlı değildi. Ölçümlerin hiçbiri erkekler için sol ve sağ taraf arasında farklılık göstermemektedir.

Sonuç: DKY çaplarının normal ölçümleri ve bu ölçümlerin yaş, cinsiyet ve taraflar arasındaki farklılıkları cerrahlar, radyologlar ve anatomistler açısından önemlidir. Endoskopik kulak cerrahisi açısından ve radyolojik görüntülerde DKY anatomisini bozan bir patolojinin erken tanısı için DKY'nin doğru değerlendirilmesi önemlidir.

Anahtar kelimeler: Dış kulak yolu, Temporal kemik, Morfometri, Bilgisayarlı tomografi

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Introduction

External auditory canal (EAC) extends from the concha to the tympanic membrane. S-shaped EAC has a cartilaginous lateral part (one third) and medial bony part (two thirds), the lengths of which are 8mm and 16mm, respectively. Total length of EAC is around 2-3 cm. EAC narrows near the medial end of cartilaginous part and at the isthmus, which is 2 cm from the concha [1,2].

We encountered in vivo and in vitro measurements of EAC in the literature, for which the researchers used tympanometry, ear mold injections, computed assisted tomography (CAT), water injection and high-resolution computed tomography. EAC volume measured before canaloplasty operation is a predictor for post operation volume. It may also reveal efficacy of topical ear wax treatments [3-7].

EAC width, as well as its length and volume, are clinically important. Acquired or congenital stenosis of EAC leads to conductive or mixed hearing loss. Chronic otitis externa, cholesteatoma, exostoses are common reasons of acquired stenosis [8,9]. Bony ear canal opening equal or less than 2mm leads to cholesteatoma formation, which is a slow-growing destructive pathology [10]. It may develop in the middle ear cavity and communicate with EAC through a perforation on tympanic membrane or may individually develop in EAC [11]. Canaloplasty which consists of cholesteatoma removal and EAC enlargement is a common surgical procedure. Restenosis after canaloplasty is another cause of acquired EAC narrowing [7].

Proper understanding of EAC anatomy is essential for transcanal endoscopic ear surgery. Ayache et al. [12] reported that 89% of the patients had EAC narrowing in their study including 5000 patients.

An anatomical canal which has a tortuous path such as EAC should be analyzed on more than one point. In this study we aimed to present the detailed objective measurements and reveal normal morphometry of EAC diameters and its age, gender, and side-related changes. These measurements have both clinical and research applications.

Materials and methods

Ethics committee approval was received from Ankara Yıldırım Beyazıt University Yenimahalle Research and Training Hospital Clinical Research Ethics Committee. (Decision number: 2019/09 -90).

Computed Tomography (CT) images of 379 patients obtained for head and neck pathologies between February-September 2019 were evaluated in the radiology department. Patients with pathologies in the external auditory canal (atresia, fracture, foreign body, cholesteatoma, tumor, keratosis obturans, osteoma, exostoses, medial canal fibrosis, necrotizing external otitis) were not enrolled in this study. CT imaging was performed with the General Electric Revolution EVO CT device. Axial images were reformatted using high-resolution multiplanar reconstruction (MPR). Two dimensions at three points were measured on sagittal images for each side by the same radiologist, certified with 25 years' experience at head and neck imaging. The age, gender and side related changes for each measure were statistically analyzed.

Measurements were obtained from three points:

1st point: The level of the tympanic membrane where chorda tympani leaves the bony canal. The height (1a) and width (1b) were measured from the ground where the cylindrical view of EAC was most prominent (Figure 1A, Figure 1B).

2nd point: Height (2a) and width (2b) were measured at isthmus level (Figure 2A, Figure 2B).

3rd point: The height (3a) and width (3b) were measured from the most lateral site of EAC at the level of tympanomastoid suture. (Figure 3A, Figure 3B).

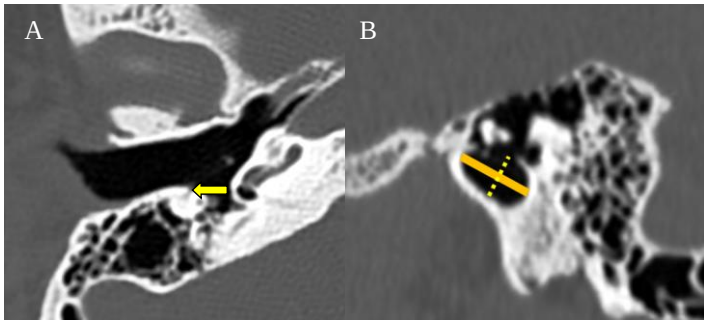

Figure 1A: Axial CT image of temporal bone. 1st measurement point is at the level of the tympanic membrane where chorda tympani leaves the bony canal (yellow arrow), 1B: Sagittal CT image of temporal bone diameters at the level of the tympanic membrane where chorda tympani leaves the bony canal (1a: non-interrupted line, 1b: interrupted line)

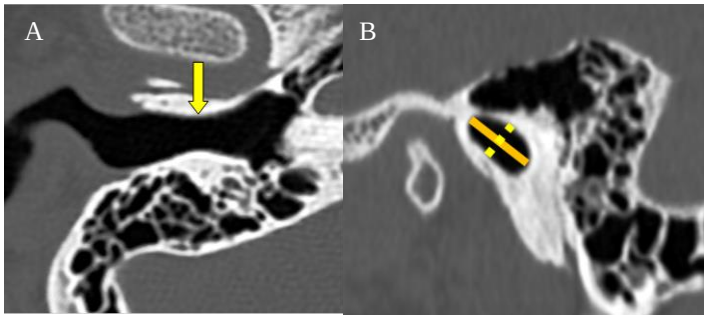

Figure 2A: Axial CT image of temporal bone. 2nd measurement point is at the level of isthmus (yellow arrow), 2B: Sagittal CT image of the temporal bone. Diameters at the level of the isthmus (2a: non-interrupted line, 2b: interrupted line)

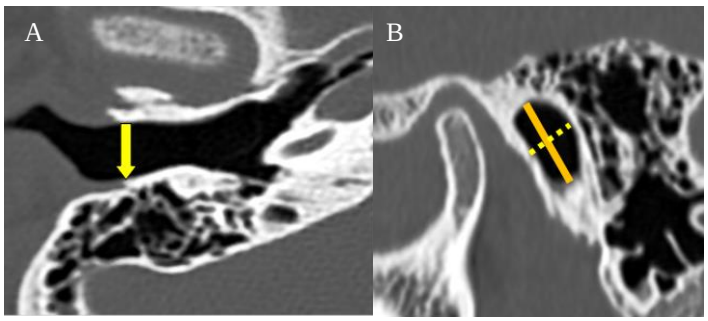

Figure 3A: Axial CT images of the temporal bone. 3rd measurement point is at the level of the tympanomastoid suture (yellow arrow), 3B: Sagittal CT image of the temporal bone. Diameters at the level of the tympanomastoid suture (3a: non-interrupted line, 3b: interrupted line)

Statistical analysis

Power analysis performed by G* Power (ver 3.1) revealed that the achieved power of this study was 98.4% (Cohen's d=0.423) with a Type 1 error rate of 0.05 and a sample size of 379 patients.

The distributions of the measurements were examined by the Shapiro-Wilk's test and the normality plots. Median (min-max) was reported for all metric variables, and gender was presented with frequency (%).

The left- and right-side measurements were compared by Wilcoxon signed-rank test within the whole sample. The Mann-Whitney U test was used to compare males and females

with respect to the diameter measurements. A *P*-value<0.05 was considered as statistically significant.

All statistical analyses and computations were performed via IBM SPSS Statistics 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Results

Three-hundred seventy-nine individuals were examined, out of which 46.4% (n=176) were male. The overall median age was 40 years (min-max:20-76). The median ages of males and females were both 40 years with a range of 20-75 years for males and 20-76 years for females. There was no significant difference between males and females with respect to age.

The median diameter of 1a was 9.3 mm (min-max:7.5-12.0) on the left and 9.3 mm (min-max:7.7-12.0) on the right (Table 1). The diameter of each point in each direction was similar between the left and right sides.

The median diameter of left 1a was 9.4 mm (min-max: 8.0-12.0) in males and 9.2 mm (min-max: 7.5-11.2) in females, resulting in a significant difference (Table 2). The "a" diameter of each point was higher in males than females for both sides. There was no significant difference between males and females in terms of "b" diameters.

Diameter 1b was higher on the left side compared to the right side for females, while left-right side comparisons for other measurements were similar (Table 2). All diameters were similar between the left and right side for males.

Table 1: The comparison of diameters between left and right ears

Diameters (mm)	Left Median (min-max)	Right Median (min-max)	*P*-value
1a	9.3 (7.5-12.0)	9.3 (7.7-12.0)	0.275
1b	6.1 (4.0-7.7)	6.0 (4.2-7.3)	0.348
2a	9.0 (6.9-12.1)	9.0 (6.8-12.1)	0.889
2b	5.4 (3.7-6.8)	5.3 (3.7-9.4)	0.308
3a	10.1 (7.8-13.5)	10.2 (7.4-13.9)	0.209
3b	6.3 (4.2-8.3)	6.3 (4.6-7.9)	0.550

1st point at the level of the tympanic membrane where chorda tympani leaves the bony canal. 1a: Height measured at 1st point, 1b: Width measured at 1st point, 2nd point at the level of isthmus, 2a: Height measured at the 2nd point, 2b: Width measured at 2nd point, 3rd point at the most lateral site of external auditory canal (EAC) at the level of tympanomastoid suture, 3a: Height measured at 3rd point, 3b: Width measured at the 3rd point.

Table 2: The comparison of measurements between males and females

Diameters (mm)	Males Median (min-max)	Females Median (min-max)	*P*-value
Left1a	9.4 (8.0-12.0)	9.2 (7.5-11.2)	0.009
1b	6.1 (4.1-7.7)	6.1 (4.0-7.7)*	0.695
2a	9.2 (7.0-12.1)	9.0 (6.9-11.7)	0.004
2b	5.5 (3.7-6.8)	5.3 (4.0-6.6)	0.155
3a	10.2 (7.9-13.5)	10.0 (7.8-12.7)	0.007
3b	6.4 (4.7-8.3)	6.3 (4.2-8.2)	0.137
Right1a	9.4 (7.9-12.0)	9.1 (7.7-12.0)	<0.001
1b	6.1 (4.6-7.3)	6.0 (4.2-7.3)*	0.216
2a	9.2 (6.9-12.1)	9.0 (6.8-11.8)	0.020
2b	5.4 (4.1-6.6)	5.3 (3.7-9.4)	0.355
3a	10.3 (7.4-13.9)	10 (7.5-13.5)	0.028
3b	6.3 (4.7-7.9)	6.2 (4.6-7.7)	0.251

**P*=0.019 for the comparison of left and right 1b in females. P>0.05 for other within-gender comparisons of left and right-sided measurements.

Discussion

Morphometric studies executed normal populations are valuable to distinguish abnormalities from normal ones. Knowledge of normal morphometry provides physicians a more constant ground when evaluating patients. An anatomical canal which has a tortuous path such as EAC should be analyzed on more than one point. Each of the points measured in the present study were revealed in detail on CT images.

Tsung et al. [13] created a three-dimensional ear canal model using CT on 40 individuals. They aimed to present proper data to ear plug producers and to protect workers from noise damage which leads to hearing loss. Studies analyzing the geometry of the ear canal among different populations may contribute to preventing workplace-related hearing problems which is a common health care issue worldwide. In our opinion these studies must be conducted with larger sample sizes. We included 379 patients in the present study.

Zemplenyi et al. [14] used an optical method to measure the ear canal length, and their results ranged from 2.2cm to 3cm. Djupesland et al. [15] also studied the length of the canal and found a mean value of 23mm. Due to bending of the ear canal, two dimensional radiologic images are insufficient to indicate accurate length. Experimental studies of Zempleyni et al. [14] and Djupesland et al. [15] contributed valuable data to literature but did not measure the diameters of the canal. Yu et al. [7] used high resolution computed tomography (HRCT), water injection and tympanometry on 9 male volunteers for EAC volume measurement. They created 3D images on HRCT images. In our opinion, it is not a practical method in routine radiology practice. As a contribution to the missing points of the mentioned studies diameters of ear canal were measured in our study. These measurements inform physicians about the narrowing of the canal, which are critical in approach to middle ear and eardrum. We measured the narrowest value at the transverse diameter of the isthmus (left:5.4mm and right 5.3mm).

Per-meatal, end-aural and post-auricular approaches are viable options for surgical access to eardrum and middle ear cavity in operations such as myringoplasty, tympanoplasty and stapedectomy. Each approach has limitations. A narrow EAC is a limitation for per-meatal approach [1,16]. Preoperative assessment of EAC is often underestimated. We believe that this study reveals sufficient anatomical data for surgeons in terms of per-meatal approach. End-aural and post auricular access are other alternatives if the EAC is not wide enough to allow per-meatal approach [1]. The post auricular approach has disadvantages in visualization of the posterior margin of tympanic membrane and end-aural approach limits the view of the anterior margin of tympanic membrane. [16].

Zhao et al. [17] declared that individuals with EAC less than 4 mm are considered to have congenital aural stenosis. They conducted their research on 10 children with a mean age of 12 years. Cole et al. [10] declared that patients with EAC less than 2mm were prone to developing cholesteatoma and should undergo surgery in late childhood before irreversible damage occurs. Because of the slow gradually growing pattern of cholesteatoma, most of the patients present with late complications such as discharge, hearing loss, facial paralysis, and intracranial complications in adulthood [18]. If undiagnosed, cholesteatoma may destroy EAC, skull base and temporal bone [19]. Randomly detected EAC narrowings in radiologic images may be valuable for differential diagnosis of such pathologies. We need scientific data on the normal values in the society to talk about narrowing. Clearly defined measurements based on large series are superior to subjective views. To the best of our knowledge, this study is the first to reveal measurements of EAC on clearly defined points in a large adult series. Individuals included in this study had no history of ear problems. From this

point of view, our study presents valuable data to the scientific literature.

Limitations

A study with a larger sample size would have been more significant. A comparative study between patient groups with normal morphology and EAC pathologies will contribute valuable data to literature. Comparative studies between imaging techniques and endoscopic techniques visualizing EAC will enlighten radiologists and otologists.

Conclusion

This study provides proper data to surgeons, radiologists and anatomists dealing with EAC. Thorough evaluation of EAC is critical for transcanal endoscopic ear surgery and helps radiologists in early diagnosis of a pathology impairing the anatomy of EAC.

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Evaluation of hospitalized newborns due to indirect hyperbilirubinemia: A cross-sectional study

Yenidoğan ünitesine indirekt hiperbilirubinemi nedeniyle yatan hastaların değerlendirilmesi

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Abstract

Aim: Indirect hyperbilirubinemia, a widespread problem in the newborn period, may need emergency treatment for prevention of neurological sequelae and mortality in some cases. We aimed to report the incidence, etiological factors, clinical findings, and the treatment of neonates with indirect hyperbilirubinemia.

Methods: Ninety-six cases of non-physiological indirect hyperbilirubinemia and prolonged jaundice which were followed-up in the Neonatology Unit of Kafkas University Hospital between January 2018-October 2019 were evaluated. The therapeutic approach was determined according to the recommendations of American Academy of Pediatrics in 2004.

Results: The incidence of IHB was 24.8% (n=96) among 387 hospitalized neonates. The mean gestational age, birth weight (BW), and bilirubin level on admission were 36.2 (2.5) weeks, 2628.9 (820) g, and 12.1 (5.29) mg/dL, respectively. Among all, vaginal delivery ratio was 38.5%, and cesarean delivery rate was 61.5%. About 34.4% were first-time mothers. The rates of breastfeeding and formula feeding were 39.6% and 1%, respectively. Around 59.4% were both breast- and formula-fed. The etiological factors of IHB were as follows: Prematurity and/or low birth weight (LBW) (20.9%), breast feeding jaundice (8.3%), ABO incompatibility (17.7%), Rh incompatibility (7.3%), ABO+Rh incompatibility (3.1%), cephal hematoma (2.1%), urinary infection (4.2%), sepsis (4.2%), pneumonia (2.1%), omphalitis (1%), subgroup incompatibility (1%), Glucose 6 phosphate dehydrogenase deficiency (1%) and unknown etiology (7.3%). Exchange transfusion rate was 1% (n=1), and 5 neonates (5.2%) were administered immunoglobulin therapy among 27 (28.1%) with hemolytic hyperbilirubinemia.

Conclusion: Indirect hyperbilirubinemia is an important risk factor for mortality and morbidity in newborn period. Defining the risk factors for non-physiologic indirect hyperbilirubinemia, adequate follow up and prompt treatment would reduce neurological sequelae and mortality rates.

Keywords: Newborn, Indirect hyperbilirubinemia, Etiology, Risk factors

Öz

Amaç: İndirekt hiperbilirubinemi yenidoğan döneminde sıklıkla görülen sorunlardan birisidir. Ciddi olgularda kalıcı nörolojik sekeller ve ölüme neden olduğu için acil müdahale gerektirir. Bu çalışmada; yenidoğanlarda indirekt hiperbilirubinemi (IHB) sıklığı, klinik özellikleri, altta yatan nedenleri ve tedavinin belirlenmesi amaçlandı.

Yöntemler: Ocak 2018- Ekim 2019 tarihleri arasında Kafkas Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları AD Yenidoğan Bölümünde patolojik indirekt hiperbilirubinemi ve uzamış sarılık nedeni ile takip edilen 96 olgu değerlendirilmeye alınmıştır. Olguların tedavi şekilleri Amerikan Pediatri Akademisi'nin 2004 yılında yayınlanan önerileri kapsamında total serum bilirübin düzeyleri, doğum tartıları ve doğum yaşlarına göre belirlendi.

Bulgular: Servisimizde izlenen 387 hastadan 96'sına (%24,8) İHB tanısı kondu. Olguların ortalama doğum ağırlıkları 2628,9 (820) gr, gestasyon haftaları 36,2 (2,5)hafta, doğum sonrası yaşları 3,1 (2,75), anne yaşları 30,1 (5,41), başvuru bilirubin düzeyi 12,1 (5,29), vaginal doğum oranı %38,5, sezaryen doğum oranı %61,5 di. Annenin ilk bebek olma oranı %34,4 olarak saptandı. Anne sütüyle beslenme oranı %39,6, formula ile beslenme oranı %1, anne sütü+ formula ile beslenme oranı %59,4. İHB nedenleri olarak Prematürite ve/veya düşük doğum ağırlığı %20,9, anne sütü sarılığı %8,3, ABO uyuşmazlığı %17,7, Rh uyuşmazlığı %7,3, ABO+Rh uyuşmazlığı %3,1, sefal hematom %2,1, idrar yolu enfeksiyonu %4,2, sepsis %4,2, pnömoni %2,1, omfolit %1, subgrup uyuşmazlığı %1, Glukoz 6 fosfat dehidrogenaz eksikliği %1 ve bilinmeyen nedenler %7,3 olarak saptandı. Kan değişimi 1 (%1) yenidoğana, hemolitik hiperbilirubinemisi olan 27 (%28,1) yenidoğandan 5'ine (%5,2) immünglobulin tedavisi uygulandı.

Sonuçlar: İndirekt hiperbilirubinemi yenidoğan döneminde görülen önemli bir mortalite ve morbidite sebebidir. Fizyolojik olmayan indirekt hiperbilirubinemide risk faktörlerinin saptanması klinik izlem ve erken tedavi yaklaşımı nörolojik sekel ve ölüm oranını azaltacaktır.

Anahtar kelimeler: Yenidoğan, İndirekt hiperbilirubinemi, Etiyoloji, Risk faktörleri

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Introduction

Indirect hyperbilirubinemia (IHB) is one of the most common problems encountered in newborns and jaundice is one of the most common reasons for referral to a doctor [1]. Between 60-70% of term newborns and almost all (90%) premature infants suffer from hyperbilirubinemia in the first days of life [2,3]. Although IHB occurs physiologically in most newborns, the rate of pathological hyperbilirubinemia requiring hospitalization is reportedly between 4.8% and 15.5% [4,5]. The cause of physiological jaundice is increased bilirubin load which occurs due to high erythrocyte mass in newborns, shorter erythrocyte life span, and relatively low enzyme activity in bilirubin metabolism [6]. Increased bilirubin production, inadequate hepatic uptake, and conjugation, and increased enterohepatic circulation are among the causes of pathological jaundice [7,8]. It has been shown that the severity and duration of IHB in newborns varies according to gestational age, birth weight, race, heredity, nutritional status and concomitant disease [6-8]. IHB may cause severe neurotoxicity, especially in the basal ganglia, therefore, it should be distinguished from mild and non-pathological IHB. Although pathological IHB can be treated with phototherapy in most cases, advanced treatment methods such as blood exchange may be needed.

The aim of this study was to determine the frequency, clinical characteristics, underlying causes and treatment modalities of newborns hospitalized for IHB.

Materials and methods

In this cross-sectional study, 96 neonatal patients who were hospitalized and treated at Kafkas University Health Application and Research Hospital, Neonatal Intensive Care Unit between January 2018 and October 2019 were evaluated. Newborns who were followed up for other reasons, such as dehydration, transient tachypnea of newborn, respiratory distress syndrome, or congenital anomalies were not included in the study. The underlying causes, clinical course, and treatments of newborns with IHB who were hospitalized in our ward were evaluated. In addition, by examining demographic characteristics, age and weight at admission, weight loss ratio, gestational ages, birth weights, maternal ages, birth types were determined. Indirect bilirubin levels above 12.9 mg/dl in term babies were considered as pathological jaundice and term babies with 8.8 mg/dl indirect bilirubin at the end of the second week were considered to have prolonged jaundice [9,10]. Pathologic jaundice in preterm infants was accepted as bilirubin values above the threshold for starting phototherapy [8]. The decision to start phototherapy and other forms of treatment were determined according to the recommendations of the American Academy of Pediatrics published in 2004 [9].

Hemogram, total serum bilirubin levels, peripheral blood smears, direct coombs tests, mother and infant blood groups and serum electrolytes and urea/creatinine values of infants with weight loss above 10% were evaluated.

Newborns with maternal blood type ‘O’, infant's blood type ‘A’, ’B’ or ‘AB’ and positive direct coombs test were accepted as ABO blood type incompatibility. Newborns with Rh positive blood groups whose mothers’ blood groups were Rh negative, those with positive direct coombs tests and decreased hematocrit in follow-up, and whose peripheral blood smear findings are compatible with hemolysis were considered Rh-incompatible. Maternal-infant subgroups, glucose-6 phosphate dehydrogenase enzyme levels, serum acute phase reactants and blood culture were studied in patients with unexplained indirect hyperbilirubinemia. Physical and laboratory findings were normal except for IHB and infants with jaundice lasting more than 14 days fed exclusively with breast milk were evaluated as late breast milk jaundice. Liver function tests, direct bilirubin levels, thyroid function tests, urine tests, sepsis parameters, reductant substances in urine, and osmotic fragility tests were evaluated in infants with prolonged jaundice (IHB lasting more than 14 days). Phototherapy was provided with blue halogen lamp phototherapy devices. If the serum total bilirubin level was close to the blood exchange limit or the bilirubin level continued to increase during the follow-up under phototherapy, slow infusion of intravenous immunoglobulin at 1g/kg dose was given in 4-6 hours in cases with direct coombs positivity due to immune-hemolytic anemia. The amount of donor blood required for blood exchange was adjusted to a double volume of 80cc/kg. Umbilical venous catheter was used for the procedure and the amount of blood to be taken and delivered at each cycle was 5cc/kg.

Statistical analysis

All obtained data were analyzed by using the statistical package for the social sciences (SPSS) version 22.0 software (SPSS,Inc Chıcago,IL,USA). The number (N), percentage (%), mean, standard deviation (SD), median, minimum and maximum values were presented for descriptive data. *P*-value <0.05 was considered statistically significant.

Results

The female-male ratio of our patients was 0.8. Socio-demographic characteristics, birth histories and nutritional status of our patients and their mothers are shown in Tables 1-2.

Table 1: Socio-demographic characteristics of patients and their mothers

Characteristics	Mean (SD)	(Min-Max)
Mother Age	30.1 (5.41)	(18-40)
Gestational week	36.2 (2.5)	(32-41)
Postnatal age	3.09 (2.75)	(1-21)
Birth weight	2628.9 (820)	(1505-4260)
Bilirubin level at admission (mg/dl)	12.1 (5.29)	(9-26)

SD: Standard deviation, Min: Minimum, Max: Maximum

Table 2: Birth and nutritional history of patients

Delivery Route	n	%
Vaginal	12 (Birth in house)	12.5
	25 (Birth in hospital)	26
Cesarean section	59	61.5
Number of living siblings		
1 Child	33	34.4
2 Child	27	28.1
> 2 Child	36	37.5
Feeding characteristic		
Breast milk (BM)	26	27.1
Formula (F)	1	1
Mixed(BM+F)	69	71.9

The main reasons of IHB are the insufficient feeding of the newborn with breast milk, prematurity (PM) and/or low birth weight (LBW). The causes of IHB in our newborn cases are shown in Table 3. Phototherapy was started in all cases admitted to our neonatology clinic. After 2-4 hours, control bilirubin levels were measured and bilirubin decline rates were evaluated.

Among 11 cases diagnosed with pathological jaundice on the first day of life, ABO, ABO and Rh, and Rh

incompatibility were detected in 5 (45.4%), 1 (9.1%) and 4 (36.4%) patients, respectively. Early neonatal sepsis was a risk factor in 1 (9.1%) patient.

Table 3: Causes of indirect hyperbilirubinemia (IHB) in newborns

Causes	n	%
Prematurity/Low birth weight	20	20.9
ABO incompatibility	17	17.7
Nutritional deficiency	19	19.8
Rh incompatibility	7	7.3
Late breast milk jaundice	8	8.3
Cephalo-hematoma	2	2.1
ABO+Rh incompatibility	3	3.1
Urinary tract infection	4	4.2
Subgroup mismatch	1	1
Sepsis	4	4.2
Pneumonia	2	2.1
Omphalitis	1	1
G6PD deficiency	1	1
Congenital hypothyroidism	-	0
Unknown causes	7	7.3
Total	96	100

The time of onset of hyperbilirubinemia was not different in patients with and without hemolytic jaundice. Blood exchange was performed in 1 (1%) of our patients with IHB and intravenous immunoglobulin treatment was administered in 5 (5.2%) neonates.

It was found that 11 newborns who could not be fed with adequate breast milk in the early period had lost 9.4% (3.1%) (4.2-23%) of their birth weight by the time they were admitted to our newborn clinic, while the same parameter was 4.9% (2.67%) (1.2-13%) for others. The weight loss of the patients who could not be breastfed in the early period according to birth weight was found to be significantly lower than the cases who were hospitalized due to other IHB reasons (P<0.001). The number of living children, prematurity, low birth weight and early gestational age were factors affecting postnatal weight loss.

Jaundice lasted more than two weeks in 14 of our cases who were followed-up and treated for IHB. Etiological causes of prolonged jaundice in these cases include late breast milk jaundice (n=5), urinary tract infection (n=1), prematurity/low birth weight (n=5), and glucose 6 phosphate dehydrogenase enzyme deficiency (n=1). No etiological cause was determined for 2 cases.

Among insufficiently breast-fed infants, cesarean section deliveries were numerically and insignificantly higher than normal spontaneous vaginal deliveries (P=0.256). We found the incidence of IHB is 24.8% in our study.

Discussion

IHB, which is frequently seen in the neonatal period, can cause serious health problems if it is not diagnosed and treated in time. Therefore, it is particularly important to distinguish between pathological and non-pathological causes of IHB [11,12]. Nowadays, the importance of breastmilk is understood. Increase in rates of breastfeeding, survival among premature and low birth weight infants, neonatology clinics and early discharge are among the reasons for the increase in admission and diagnosis rates of newborn infants with jaundice. The prevalence of the IHB is so high that it raises the importance of IHB in terms of its possible complications.

It is known that male gender is a risk factor for IHB and in our study, similar results were obtained with those conducted in our country. Ünal et al. [13] found male gender as 59%, Narlı et al. [14] as 56%, and Kılıç et al. [15] as 55%. Similarly, male gender (58%) was found to be higher in our study (M / F: 56/40).

In this study, the most common etiological cause of IHB was PM/LBW (20.9%), nutritional deficiency (19.8%) and ABO incompatibility (17.7%). Low bilirubin metabolism and transport in PM / LBW infants as well as delayed UDP-GT expression in the liver is the main cause of increased duration and severity of physiological jaundice [16].

In the early period of the newborn, insufficient breastfeeding is related to inappropriate breastfeeding techniques rather than the characteristics of breast milk. Early breast milk jaundice is seen due to inexperience of mother, low amount of milk and being the first-born baby. In our study, the rate of early breast milk jaundice was higher in the first infant (19.8%). It is particularly important to start early breastfeeding, teach the techniques, and emphasize the importance of the continuity of breastfeeding.

Late breast milk jaundice is characterized by hyperbilirubinemia, which has a slow rate of increase after the first week of life and is associated with certain substances in breast milk content. Bilirubin elevation in breast milk jaundice can last for 3 weeks-3 months and may take several months to return normal values. Diagnosis is made by ruling out other causes that may cause IHB [1,3,6,13]. In our study, late breast milk jaundice was 8.3% (Table 3).

Although there are many factors in the etiology of IHB, the most important one is hemolytic hyperbilirubinemia due to blood type incompatibility, the rate of which was reported as 7.9% for Rh, 2.9% for ABO + Rh incompatibility by Kılıç et al. [15], 13.2% for Rh, 10.4% for ABO + Rh incompatibility by Narlı et al. [14], 9.6% for Rh, 4.8% for ABO + Rh for incompatibility by Özkaya et al. [16], and 2.3% for Rh, 1.9% for ABO + Rh, 14.3% for ABO incompatibility and 0.9% for subgroup mismatch by Ünal et al. [13]. In our study, we found 7.3% Rh incompatibility, 3.1% ABO + Rh incompatibility, 17.7% ABO incompatibility and 1% subgroup mismatch. In light of the available data, it is necessary to determine the blood groups of newborns of O or Rh (-) mothers and be mindful of possible hemolytic IHB. It should also be remembered that subgroup mismatch is an etiology of hemolytic IHB of unknown origin.

Glucose 6 Phosphate Dehydrogenase (G6PD) enzyme deficiency should be evaluated in newborns with a family history, those of a specific ethnic-geographical origin (Mediterranean, Africa, Middle East, Southeast Asia, Arabic Peninsula) or those inadequately responsive to phototherapy. In our country, Büyükokuyan et al. [17] found that the rate of G6PD deficiency in newborns diagnosed with IHB was 3.8% in the Marmara region and 8.3% in the Çukurova region. In addition, G6PD deficiency was 3.85% in the IHB newborns studied by Atay et al. [18]. In our study, the G6PD deficiency rate was 1%. This low rate of G6PD deficiency can be explained by the determination of enzyme level in unexplained IHB cases, which was also low. In the study of Ünal et al. [13], G6PD enzyme deficiency rate was found as 0.5% in unexplained IHB cases, like our study. In the studies conducted in our country, the rate of urinary tract infection as the cause of prolonged IHB cases was reported as 7.8% by Bilgen et al. [19] (bag culture, 100,000 colonies / ml and above, only single species were considered significant), and 1% by Ünal et al. [13] (suprapubic

aspiration, single bacterium is considered significant). In our study, the rate of urinary tract infection as a cause of prolonged IHB was 4.2%. We think that the difference between our rates and the literature was due to the fact that we obtained urine cultures both with a bag and suprapubic aspiration.

In neonatal hyperbilirubinemia, the primary approach is to protect the central nervous system from the toxic effects of bilirubin and to protect the newborn from possible permanent damage to the neuromotor system. All patients admitted to our neonatology clinic with the diagnosis of IHB were treated with phototherapy. Blood exchange was performed in 1 (1%) newborn patient with severe hemolytic hyperbilirubinemia. Five (5.2%) patients received intravenous immunoglobulin therapy and 4 of these patients did not need blood exchange.

We found that infection was the cause of IHB in 7.3% of our cases (4.2% sepsis, 1% omphalitis, 2.1% pneumonia), while in their series, the rate of infection was reported as 7.2% (3.6% sepsis, 2.4% omphalitis, 1.2% pneumonia) by Tekinalp et al. [20] and 13.1% (sepsis 1.8%, omphalitis 11.3%) by Kılıç et al. [15]. The low rate of omphalitis in our series may be related to high-standard umbilical care due to elevated birth rate in the hospital.

As a result of this study, IHB was seen to accompany ABO/Rh incompatibility, neonatal infections, and enzymatic deficiencies. Early diagnosis of possible pathological conditions in the perinatal period will significantly reduce the mortality and morbidity rates of the newborn and prevent permanent damage to the newborn's central nervous system [21]. Close monitoring of newborns who are at risk of possible IHD is vitally important in this respect and adequate treatment of newborns with hyperbilirubinemia will contribute to the growth of healthy generations.

The most important limitation of our study is the low number of cases. We think that a larger sample size can eliminate the current limitation.

Conclusion

Indirect hyperbilirubinemia is an important risk factor for mortality and morbidity in the newborn period. Defining the risk factors for non-physiologic indirect hyperbilirubinemia, adequate follow up and prompt treatment would reduce neurological sequela and mortality rates.

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Determination of cancer progression in breast cells by fiber optic bioimpedance spectroscopy system

Fiber optik biyoimpedans spektroskopi sistemi ile meme hücrelerinde kanser gelişiminin belirlenmesi

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Abstract

Aim: It is well established that cancer can be most effectively treated when diagnosed at an early stage. Therefore, development, evaluation, and validation of new biomedical approaches for early detection of cancer and precancerous lesions are important priorities. Our aim was to distinguish low metastatic human breast cells from normal human breast cells using the Fiber Optic Bioimpedance Spectroscopy (FOBIS) system.

Methods: In the FOBIS system we developed, the diameters of the fibers and platinum wires are 50 and 25µm, respectively. The sensitivity of the system to differentiate different cell types was assessed with high metastatic (MDA-MB-231), low metastatic (MCF-7) and normal breast epithelial cells (MCF-10A). Statistical evaluation of data was performed by using Principle Component Analysis (PCA) and Linear Discriminant Analysis (LDA). Spectroscopic data obtained from FOBIS system on suspended human breast cells were evaluated by multivariate statistical analysis to obtain information about the cell type. Fiber optic and bioimpedance methods allow discrimination of different cell types based on their signature. By combining these two techniques, the sensitivity of the system to the differentiation of human breast cells was evaluated.

Results: The discrimination provided the sensitivity of 100% and specificity of 60% in distinguishing MCF-7 from MCF-10A cells.

Conclusion: A highly accurate distinction of breast cancer cells was achieved in cell culture by FOBIS system.

Keywords: Bioimpedance, Breast, Cell distinguish, Fiber optic, Spectroscopy

Öz

Amaç: Kanserin erken evrede teşhis edildiğinde en etkili şekilde tedavi edilebileceği iyi bilinmektedir. Bu nedenle, kanserin ve prekanseröz lezyonların erken tespiti için yeni biyomedikal yaklaşımların geliştirilmesi, değerlendirilmesi ve validasyonu önemli bir önceliktir. Amacımız, Fiber Optik Biyoimpedans Spektroskopisi (FOBIS) sistemini kullanarak düşük metastatik insan meme hücrelerini normal insan meme hücrelerinden ayırt etmekti.

Yöntemler: FOBİS sisteminde 50µm çaplı fiberler ve 25µm çaplı platin teller kullanılmıştır. Sistemin farklı hücre tiplerini ayırt etme duyarlılığı yüksek metastatik (MDA-MB-231), düşük metastatik (MCF-7) ve normal meme epitel hücreleri (MCF-10A) için hesaplanmıştır. Verilerin istatistiksel değerlendirmesi Temel Bileşenler Analizi (TBA) ve Doğrusal Ayırım Analizi (DAA) ile yapılmıştır. İnsan meme hücre kültürlerinde FOBİS sistemi ile elde edilen spektroskopik veriler, çok değişkenli istatistiksel analiz ile değerlendirilerek hücre tipi hakkında bilgi elde edilmiştir. Fiber optik ve biyoimpedans yöntemlerinden elde edilen spektroskopik veriler ile farklı hücre tipleri ayırt edilebilmektedir. Bu iki tekniğin birleştirilmesi ile sistemin insan meme hücrelerinin farklılaşmasına duyarlılığı test edilmiştir.

Bulgular: Buna göre %100 duyarlılık ve %60 seçicilik ile MCF-7 hücreleri MCF-10A hücrelerinden ayırt edilmiştir.

Sonuç: FOBİS sistemi ile hücre kültüründe meme kanseri hücreleri yüksek duyarlılıkla ayırt edilmiştir.

Anahtar kelimeler: Biyoimpedans, Meme, Hücre ayırımı, Fiber optik, Spektroskopi

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Etik Kurul Onayı: Bu çalışma, insan katılımcılarla yapılan bir çalışma değildir. Hayvanlar üzerinde deney yoktur. Bu çalışmada, insan katılımcıları veya yazarlar tarafından gerçekleştirilen hayvanlar üzerinde yapılan hiçbir çalışma yoktur. Katılımcıların tanımlayıcı bilgisi yoktur.

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Introduction

Probes with different diameters and geometries are designed to determine cancerous tissue in recent studies. Individually, fiber optic and impedance measurements are inadequate to detect precancerous lesions in the tissue. Intracellular ($R_{intracelular}$) fluids, extracellular ($R_{extracellular}$) fluids and ion channels ($R_{membrane}$) in the membrane are represented by resistance while the membrane itself is represented by a capacitor ($C_{membrane}$) in the electrical equivalent circuit model of the cell [1]. When an electrical potential is applied to tissue, the current flows through the intracellular and extracellular spaces at high frequencies and extracellular spaces at low frequencies [2]. The cell acts as an insulator in low frequency, and a conductor in high frequency. Current cannot enter the cell membrane and flows out of the cell at zero frequency. Resistance (R: the resistance of the body fluid) and reactance ($X_C=1/2\pi fC$: the resistance of the cell membrane and tissue interface) are components of impedance (Z), which is calculated for each frequency with the formula: $Z^2=X_C^2+R^2$. Reactance, related to the capacitance, causes the phase shift. This phase shift is defined by the Phase Angle (PA) which is calculated with arctan (X_C/R) [3, 4]. The impedance of the tissue varies with the frequency. The current applied to the tissue flows through extracellular fluid because cell membranes function as capacitors. At higher frequencies, this capacitive effect is lost, after which the current passes through the extracellular and intracellular fluid. Thus, the impedance shows a highly resistant characteristic without the reactive component.

Chromatin structure and mucosal integrity change, and cell volume expands, resulting in a decrease in extracellular space and nucleus growth when cancer develops in the tissue [5]. When malignant tumor cells develop in the tissue, various differentiations occur in the membrane and its contents. These differentiations are high aerobic lactate production, abnormal plasma membrane transitions, decreased cell connection, and new antigen formations. Neoplastic changes in the tissue affect sodium, potassium, and calcium ion ratios inside the cell that causes loss of shape, movement, and intercellular communication disorders. All these changes during cancer progression affect cell physiology and thus lead to changes in the electrical properties of the tissue.

Pathologists use morphological criteria like size, shape, nucleus-cytoplasm ratio and glandular structures of the cell during the diagnosis of the tissue. These structures vary in different types of cancer compared to normal tissue. The photons diffuse inside the tissue and some photons reflect from the surface. When light passes from one medium to another, a part of the energy is reflected from the surface of the medium, while another part passes through. When light enters the tissue, it is scattered from the cell membrane because of this difference. Scattering depends on the morphological structure of the tissue. In optical experiments, backscattered light from the tissue is collected as a spectrum, so diagnostic information is provided about the tissue. Salomon et al. [6] used triple spectroscopy technique, and the differentiation of benign and malignant prostate tissue was found with 75% sensitivity after validation. According to this study, the reason for high sensitivity in the differentiation of cancerous tissue was the addition of electrical impedance to the optic and laser system.

In the present study, we aimed to detect cancerous cell type in human breast cell culture in combination with Principle Component Analysis (PCA) and Linear Discriminant Analysis (LDA).

Materials and methods

FOBIS system consists of fiber optic and bioimpedance spectroscopy (Figure 1). Fiber optic part of the system consists of two fiber cables, and the bioimpedance part, two platinum wires. FOBIS system was used for getting optic and impedance spectral information. Current transferred to the media and information about the conductivity of the media was obtained via the bioimpedance part. Adjacent two fiber cables were used in the fiber optic part. Light sent to the media by the fiber that was connected to the light source, and backscattered light was collected with the other fiber for analysis. Since the diameter (50µm) and the numerical aperture (0.22) of the fibers were small (VIS-NIR low OH, 50-micron bare fiber, Ocean Optics), the backscattered light was detected from the surface of the medium. However, singly this optical information was not enough to detect precancerous lesions. For this reason, we added the bioimpedance part to our system. Electrode placement in bioimpedance measurement techniques affects the penetration depth of the signal. Bioimpedance information is obtained from the media surface with electrodes that are placed close to each other in our study. On the other hand, the signal goes more in-depth as the distance between the electrodes increases [7]. Hence, in the bioimpedance part of the system, the platinum wires were placed close to each other so that the bioimpedance information was obtained from the surface of the medium. These allow the optical and bioimpedance parts of the system to receive information from the same surface area in the medium.

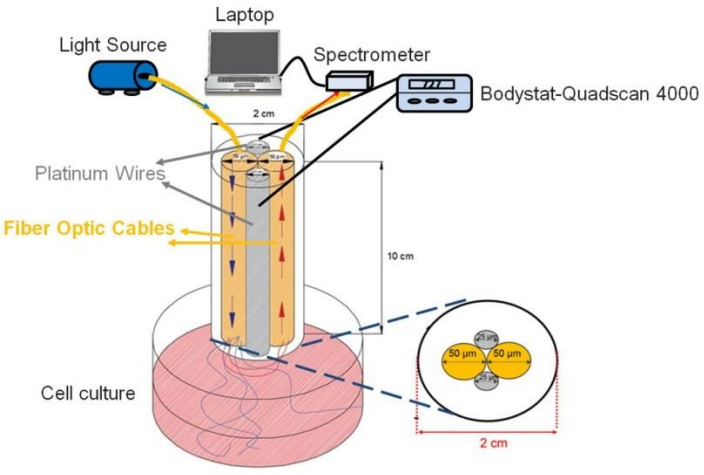

Figure 1: FOBIS system

Design of FOBIS system

Design of Fiber Optic Part: The Fiber Optic part of the system consists of a halogen-tungsten light source (HL-2000 Tungsten Halogen, Ocean Optics), a spectrometer (USB2000+ VIS-NIR Spectrometer, Ocean Optics), a laptop and two fiber optic cables with 50-micron diameter. These two fibers were centered with no distance between them, and all spectral signals were examined by IGOR program (Wavemetrics, Lake Oswego, OR, USA).

Design of Bioimpedance Part: In the second part of the FOBIS system, the 25-micron diameter platinum wires were combined with the optical part as represented in specified geometry in figure 1. To determine whether the platinum wires were in the defined geometry, the signal generator was connected for sending the signal to one end of the platinum wire, and the oscilloscope measured this signal from the other end of the same platinum wire. At the same time, to determine whether the platinum wires were isolated from each other inside the probe, the signal generator was connected for sending the signal to one of the two platinum wires, and the oscilloscope measured this signal from the end of the other platinum wire. In this procedure, the absence of the signal means that isolation was provided. Bioimpedance analyzer (Quadscan 4000, Bodystat Inc.) was connected to the platinum wires to send current to the medium and for impedance measurement. Currents sent in multiple (5, 50, 100 and 200kHz) frequencies and impedance measurements were obtained. Also, resistance, reactance and PA values were recorded at 50kHz frequency.

Calibration procedure of FOBIS system

Bioimpedance Calibration: The frequency versus impedance response of the saline solution is constant, platinum part of the FOBIS probe calibrated by using saline solutions for the known conductivity by using a conductivity meter. The principle of the calibration procedure was to relate the measured transfer impedance to a known uniform conductivity, using a calibration factor or probe constant for each measurement frequency.

Fiber Optic Calibration: Each spectrum was normalized to the integration time, and three spectra were measured for calibration. Firstly, we wanted to eliminate light as much as possible to gather a background spectrum. The tip of the FOBIS probe inserted to a black container which contains pure water and then we measured the back-reflection $R(\lambda)_{bg}$. Secondly, the spectral dispersion of the light source was measured $R(\lambda)_c$ from reflectance standard (Spectralon, Labsphere, Inc.). Confirmation of the calibration was done by observing Mie oscillation from the final spectrum, which was taken from polystyrene microspheres with 2 (0.02) micron diameter. After these calibration measurements, we obtained spectrum from cells, $R(\lambda)_s$ which were corrected by $R(\lambda)=[R(\lambda)_s - R(\lambda)_{bg}]/[R(\lambda)_c - R(\lambda)_{bg}]$.

Cell line

MDA-MB-231, MCF-7, and MCF-10A cells were obtained from the American Type Culture Collection (ATCC). MDA-MB-231 and MCF-7 cells were grown in DMEM supplemented with 4mmol/L L-glutamine and 5% to 10% fetal bovine serum. MCF-10A cells were grown in DMEM/Nut Mix F-12 supplemented with 4mmol/L L-glutamine, 5% serum, 10µg/mL insulin, 20ng/mL epidermal growth factor and 100ng/mL cholera toxins. Cells were chosen with a range of metastatic potential. The average surface area of each cell medium was determined with at least 30 measurements by using an ImageJ (Image Processing and Analysis in Java) open source program. Average surface area of MCF-10A, MCF-7 and MDA-MB-231 cells was calculated as 0.041 (0.019) mm^2, 0.064 (0.017) mm^2 and 0.09 (0.028) mm^2, respectively. Spectroscopic measurements were taken from MDA-MB-231, MCF-7 and MCF-10A cells by FOBIS system to detect the sensitivity to cell type. In order not to adversely affect the sterilization of culture media, FOBIS probe was sterilized with "Cidex-Opa" at each experimental stage.

Statistical analysis

PCA [8,9] followed by LDA [10] was performed to find specific patterns in the wavelength and frequencies for MDA-MB-231, MCF-7 and MCF-10A cells. PCA was used to identify and extract major trends within a given spectral data set. Optic and impedance spectroscopic data matrix "D" (I×C) contains the intensities of scattered light and impedance data from "I" spectra (3); the column number "C" is the number of points for each spectral data (965) and data matrix "D" is separated into several principal components (PCs). The result of PCA is a product of PC scores "S" and PC loadings "F" matrices plus the residue "k": $S= D.F \rightarrow D=S.F'+k=s_1f'_1+s_2f'_2+\ldots s_nf'_n+k$ where D: (IxC) initial data matrix (3x965); S: score $[s_1,s_2,s_3\ldots, s_n]$; F': Eigenvector matrix, loadings, variance; $[f'_1, f'_2, f'_3\ldots, f'_n]$; k: Residual matrix and n is the number of computed PCs. The purpose of PCA is reducing the dimension of observed variables into a relatively smaller number of components while maintaining as much information or variance. Afterward, the acquired components were analyzed by independent-sample t-test for each independent cell types. Statistically significant components were used in LDA to achieve the most precise differentiation of cells. While PCA finds basis vectors corresponding with the direction of the maximal variance of the variables in the data set, LDA searches for those vectors in the underlying space that best discriminates among classes of data and looks for linear combination of variables that best explain the data set [11]. Discrimination is done by setting the variate's weight for each variable to maximize the inter-class variance relative to the intra-class variance of the observation. For confirmation and validation of the analysis, leave-one-out cross-validation (LOOCV) was performed. The areas under the ROC curve (AUC) as well as the sensitivities and specificities for the optimal cut-points are calculated using the discriminant function scores which is obtained by LDA. We used the software package R-Studio Open Source Statistical Language for PCA, LDA and ROC analysis [12,13].

Results

Bioimpedance measurement results

It was found that the impedance value decreases in the suspended metastatic cancer cells in medium (Figure 2a). The reason for this is that the resistance value of the normal breast epithelial cells at lower frequencies is higher than the low and high metastatic resistance values at the same frequencies. The current at low frequencies is exposed to a long resistive pathway around the tight layer of the normal cells. However, the extracellular pathway decreases with the increase of surface area in cancerous cells that causes a decrease in impedance at low frequencies. In the same cell type, impedance was found high due to the strong dielectric properties of the cell membrane and the tissue interface acting as a capacitance in low frequency. However, impedance was found low due to the loss of this capacitive effect of the membrane at high frequencies.

PA values of all cell types were compared, and it was observed that this angle decreased from normal to high

metastasis in cell medium (Figure 2b). According to this finding, different cell types can be detected by using PA values of bioimpedance part of the FOBIS system in the medium.

Fiber optic measurement results

Spectra in the visible wavelength range were acquired from MCF-10A, MCF-7, and MDA-MB-231 cells by using fiber optic part of FOBIS system (Figure 3). At least 16 measurements were collected per cell. A total of 420 spectra were acquired from all cell types, and these spectra were analyzed. As shown in figure 3, the spectral data had different patterns, containing multiple and often overlapping peaks so they turned out to be not very distinct to differentiate cell types from each other. To overcome this limitation, advanced methods of analysis, PCA followed by LDA, were used to differentiate the cell types. In this analysis, firstly we performed a PCA to reduce the number of predictor variables, without much loss of optic and bioimpedance information, used for the differentiation of cell types, which was achieved by first finding the direction having the largest variance (PC1: 59%), and thereafter finding subsequent directions (PC2: 13%, PC3: 11%, PC4: 2%, PC5-15 together gives 1% or less of variance but still contributed significantly). Kruskal-Wallis H-test on all component scores showed that there were one most diagnostically significant (P<0.05) component (PC5) for discriminating cell types. Secondly, the significant component was used as the input variable of LDA. Finally, AUC, as well as the sensitivities and specificities for the optimal cut-points were calculated (Table 1-3).

Table 1: Specificity of FOBIS system for differentiating cell types

Specificity	MCF-10A	MCF-7	MDA-MB-231
MCF-10A	-		
MCF-7	0.60	-	
MDA-MB-231	0.80	0.80	-

Table 2: Sensitivity of FOBIS system for differentiating cell types

Sensitivity	MCF-10A	MCF-7	MDA-MB-231
MCF-10A	-		
MCF-7	1.0	-	
MDA-MB-231	1.0	0.80	-

Table 3: AUC of FOBIS system for differentiating cell types

AUC	MCF-10A	MCF-7	MDA-MB-231
MCF-10A	-		
MCF-7	0.76	-	
MDA-MB-231	0.80	0.76	-

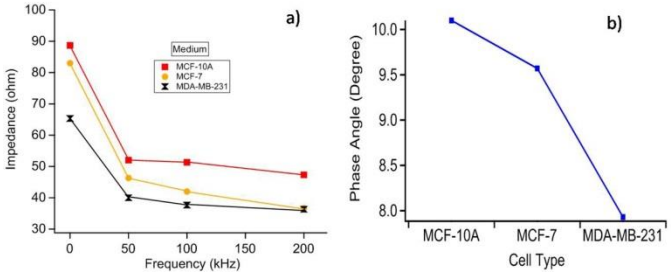

Figure 2: A: MCF-10A, MCF-7 and MDA-MB-231 cells impedance values at multiple frequencies in medium, B: PA values of different cell types in medium

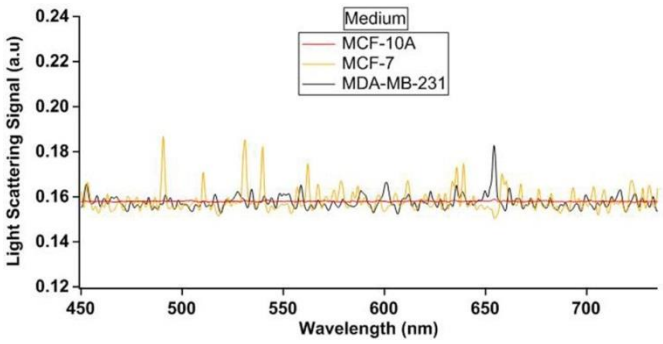

Figure 3: Light scattering signal in the visible range of different cell types in medium

In our study, ROC analysis further confirmed that PCA-LDA based diagnostic algorithms using the all spectral properties of FOBIS system can distinguish low metastatic cancer cells (MCF-7) from normal (MCF-10A) with a sensitivity of 100% and specificity of 60% as seen in figure 4.

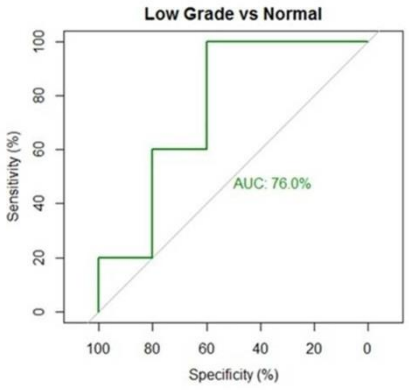

Figure 4: ROC curve comparing low metastatic cancer cell and normal

Discussion

Spectroscopic techniques are quantitative methods which yield more objective results than conventional approaches. In recent years, real-time and noninvasive diagnostic studies have been conducted using optical methods. Molecular and morphological changes in the tissue during the progression of cancer depend on the scatterers of tissue, including nucleus size, nucleus-cytoplasm ratio, and mitochondrial size than scattering and absorption coefficients. These parameters can be correlated with features that are used by pathologists during histological evaluation. The scattering of light from the tissue is more sensitive to changes in the cellular morphology than biochemical changes. Intracellular components such as cell nucleus, mitochondria, lysosomes, Golgi apparatus and the difference in Refractive Index (RI) of cytoplasm causes light scattering in biological tissues [14,15]. In the elastic light scattering, there is no difference between the wavelength of light, which is transmitted to the medium, and the wavelength of the backscattered light. Therefore, there is only the spatial dispersion of light in the medium. In our study, visible wavelength range (450-750 nm) light was used. Due to the small diameter of fibers (50µm) and numerical aperture (0.22), it was improbable that the photons, which were diffused in the medium, were collected by the adjacent optical fibers immediately, entering light into the medium re-collected from the surface of the medium without further deep penetration. With the fiber geometry that was determined in this study, the photons scattered only a few times in the medium were collected, and the sensitivity of the morphological changes in the cell was investigated with the obtained spectral information. With changing the particle size, alteration in the obtained spectra can be explained by Mie theory. According to this theory, the intensity of backscattered light from the medium depends on the scattering phase function (P (θ, λ)) and scattering coefficient $\mu_s(\lambda)$.

The structures in the cell function as biological scatterers. Light scattering occurs in the cell itself, nucleus, structures within organelle and organelle in mammalian cells. These cells are approximately 10-30µm diameter and have 3-10µm nucleus diameter [16]. The length of the mitochondria of these cells is about 1-4µm, and the diameter is around 0.3-0.7µm

[17]. Lysosomes and peroxisomes diameters of these cells are about 0.2-0.5μm [16]. The RI values of these organelles were determined as 1.35-1.36 for extracellular fluid [18], 1.36-1.375 for cytoplasm and 1.38-1.41 for nucleus [19], mitochondria and organelles [20] in the literature. RI value of normal epithelial cells that we studied was found as 1.34 for the growth medium, and RI value of its nucleus was found higher than the cytoplasm [21]. In a study, the RI values of MCF-7 and MDA-MB-231 cells were determined higher than the normal cells. Accordingly, the RI value was determined as 1.37 for normal, 1.401 for MCF-7 and 1.399 for MDA-MB-231 [22]. In our study, due to the difference of RI of the cells in the medium, the light scattering intensity which is obtained from the MCF-10A in which RI is close to the medium was found lower than MDA-MB-231 and MCF-7 which had high RI, consistent with the study in the literature [23].

It has been stated that the capacitive nature of the cell membrane causes the current flow into the surface of cells and the tight junctions act as a "short circuit" which in turn leads to a characteristic drop in impedance at high frequencies [24]. In our study, the impedance value decreased, while cancer progressed in the medium. Over the years, several *in-vitro* and *in-vivo* studies have been conducted to study the dielectric properties of cancerous and non-cancerous breast tissues. For instance, Chauveau et al. [25] conducted an *in-vitro* study of normal and cancerous breast tissues and observed significant differences in their dielectric properties. Surowiec et al. [26] conducted *in-vitro* dielectric studies in the tumor, surrounding the tumor and normal peripheral samples of breast tissues. They found that the tumor tissues had low frequency (100 kHz) conductivity which was higher than the conductivity of normal tissue and lower than that of the surrounding tissue. In another *ex-vivo* study, Fricke et al. [27] measured the parallel capacitance and resistance of the excised samples from the normal and carcinoma breast tissues. They found significantly higher permittivity of the tumor tissue at 20kHz as compared to the normal or benign tissues. PA values decreases from normal to cancer in the medium. The reduction in ionic conductivity and disorientation of cell integrity in cancer progression causes low reactance and low PA. This angle was found high in normal cells where membrane integrity was oriented, and reactance was high. Studies have shown that low PA is associated with the tumor, cell death or decreased cell integrity, but high PA is associated with the healthy cell or cell membrane [4,28-31].

Our results indicate that the FOBIS system can distinguish between MCF-10A and MCF-7 with a sensitivity of 100% and a specificity of 60%, MCF-10A, and MDA-MB-231 with a sensitivity of 100% and a specificity of 80%, MCF-7, and MDA-MB-231 with a sensitivity of 80% and a specificity of 80%. In the previous studies that used fiber optic and bioimpedance systems alone with different geometries, precancerous lesions were detected with low sensitivity [32,33].

Conclusion

It is well established that cancer can be most effectively treated when diagnosed at an early stage. Therefore, development, evaluation, and validation of new biomedical approaches for early detection of cancer and precancerous lesions are important priorities. The FOBIS system that we have developed in this study has been shown to distinguish low metastatic cells from normal cells with 100% sensitivity. Since the measurement takes a long time in this study, this is a constraint when the system is applied to the clinic *ex-vivo* experiments. To overcome this limitation, we are currently developing a scanning system with automation and interface. In this way, through probe tip of FOBIS system that has automation control, the tissue that has large surface area will be scanned in a short time with small steps so any region of the surface area will not be missed. It is planned that the management of the motor step movements, interface and the collection of spectroscopic signals will be performed on the same screen in the computer real time.

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Do inflammatory markers play a role in the detection of periprosthetic infections?

İnflamatuar belirteçlerin periprostetik enfeksiyonların belirlenmesinde rolü var mıdır?

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Abstract

Aim: Periprosthetic joint infection after total hip or knee arthroplasty is one of the most feared complications. The aim of this study was to evaluate the efficacy of inflammatory biomarkers in identifying periprosthetic joint infection.

Methods: This cross-sectional and bi-centered study included 131 patients, who had suspected prosthesis infection and underwent three-phase bone scintigraphy. Patients were divided into three groups according to the Musculoskeletal Infection Society criteria and scintigraphic study results: Group 1 comprised cases with prosthetic infection, Group 2 included aseptic loosening cases and Group 3 included cases with healthy prostheses.

Results: White blood cell average was 11.5 (3.2) 10^9/L in group 1, 8. (2.1) 10^9/L in group 2 and 7.9 (2.1) 10^9/L in group 3, among which it was significantly higher in Group 1 compared to Groups 2 and 3, (P<0.001, P<0.001), while there was no significant difference between groups 2 and 3 (P=0.753). C reactive protein values (CRP) were 46.6 (50.0) mg/L in group 1, 18.8 (17.5) mg/L in group 2 and 15.3 (17.1) mg/L in group 3, significantly higher in group 1 than the other groups (P<0.001, P<0.001), and similar in Groups 2 and 3 (P=0.876). The mean erythrocyte sedimentation rate values did not differ significantly between the groups.

Conclusion: The use of three-phase bone scintigraphy and inflammatory biomarkers such as C reactive protein and white blood cell have been shown to be effective in predicting prosthetic infection.

Keywords: White blood cell, Biomarker, C-reactive protein, Prosthetic infection

Öz

Amaç: Total kalça veya diz artroplastisi sonrası periprostetik eklem enfeksiyonu en korkulan komplikasyonlardan biridir. Bu çalışmanın amacı, inflamatuar biyobelirteçlerin periprostetik eklem enfeksiyonunun tanımlanmasındaki etkinliğini değerlendirmektir.

Yöntemler: Çalışma kesitsel ve iki merkezli planlandı. Protez enfeksiyonundan şüphelenilen ve üç fazlı kemik sintigrafisi uygulanan 131 hasta dahil edildi. Hastalar Kas İskelet Enfeksiyonları Derneği kriterlerine ve sintigrafik çalışma sonuçlarına göre üç gruba ayrıldı: Grup 1 protez enfeksiyonu olan olgular, Grup 2 aseptik gevşemesi olan olgular, Grup 3 sağlıklı protezleri olan olgulardan oluşmaktadır.

Bulgular: Beyaz küre sayısı ortalaması grup 1'de 11,5 (3,2) 10^9/L, grup 2'de 8,3 (2,1) 10^9/L ve grup 3'de 7,9 (2,1) 10^9/L bulundu. Beyaz küre sayısı değerleri grup 1'de diğer gruplara göre istatistiksel olarak anlamlı derecede yüksek bulundu (P<0,001, P<0,001), grup 2 ve 3 arasında anlamlı fark yoktu (P=0,753). C-reaktif protein değerleri grup 1'de 46,6 (50,0) mg/L, grup 2'de 18,8 (17,5) mg/L ve grup 3'de 15,3 (17,1) mg/L olarak bulundu ve C-reaktif protein değerleri gruplar arasında karşılaştırıldığında istatistiksel olarak anlamlı derecede yüksek bulundu. Grup 1'de diğer gruplara göre (P<0,001, P<0,001) ve grup 2 ile 3 arasında anlamlı fark yoktu (P=0,876). Ortalama eritrosit sedimantasyon hızı değerleri karşılaştırıldığında gruplar arasında anlamlı fark bulunmadı.

Sonuç Üç fazlı kemik sintigrafisi, C-reaktif protein ve beyaz küre sayısı gibi inflamatuar biyobelirteçlerin kullanılmasının, protez enfeksiyonunu öngörmede etkili olduğu gösterilmiştir.

Anahtar kelimeler: Beyaz küre sayısı, Biyobelirteç, C-reaktif protein, Protez enfeksiyonu

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Introduction

The prolongation of life expectancy and increase in living standards of humans have led to a significant increase in orthopedic prosthesis operations in recent years [1]. Joint replacement in cases of hip and knee osteoarthritis is one of the most cost-effective and safe surgical procedures that relieve or improve the pain symptoms of the patients, restore joint function and improve quality of life [2,3].

Periprosthetic joint infection (PJI) is one of the most terrible complications after total hip arthroplasty or total knee arthroplasty, and has a very negative impact on the physical, emotional, social and economic aspects of the patient's life [4,5].

Early diagnosis is a positive factor for preserving prosthesis and joint function. It has been shown that a mix of multiple tests positively improves diagnostic accuracy, as any test or indicator used in the clinic or laboratory does not provide ideal sensitivity and specificity for PJI diagnosis [6].

The aim of this study was to assist early diagnosis and treatment by determining the sensitivity of inflammatory biomarkers in identifying PJI.

Materials and methods

Data from the Kahramanmaras Sutcu Imam University Medical Faculty Hospital and Kahramanmaras Necip Fazıl City Hospital in the same province were used. A hundred thirty-one patients with suspected prosthesis infections who underwent three-phase bone scintigraphy between January 2015 and June 2017 were included in this study, and divided into three groups: The patients with PJI were classified as Group 1, patients with aseptic loosening (AL) were classified as Group 2 and those with healthy prosthesis were classified as Group 3. Kahramanmaras Sutcu Imam University Medical Faculty Clinical Research Ethics Committee approval was received for the study (Session: 2019/2, Date: 06.02.2019, Decision no: 11).

Demographic data, laboratory results and three-phase bone scintigraphy results were recorded using patient files and hospital database. Patients whose examination findings and laboratory results were not available were excluded from the study, even if their three-phase bone scintigraphy could be reached. Three-phase bone scintigraphy was performed to strengthen the diagnosis in patients suspected of prosthesis infection by physical examination and laboratory results. According to these results, joint aspiration was performed.

White blood cells (WBC) (normal range: 3.5-8.9 10^9/L), C-reactive protein (CRP) (normal range:0-5 mg/dL), and erythrocyte sedimentation rate (ESR) (normal range:0-20 mm/h) were used for as inflammatory markers. The white blood cells, CRP and ESR were analyzed using the Beckman coulter LH 750, Beckman coulter image 800 and Thermo linear devices respectively, according to the guidelines of the producer firms.

The diagnosis of PJI was made by evaluating the Musculoskeletal Infection Society (MSIS) criteria (Table 1) and scintigraphy results [7]. In joint aspirations, twice culture positivity was observed in twelve patients. Twenty-seven patients were determined to have periprosthetic infection with minor criteria. Five patients had fistula tract. The inclusion of types of group 1 according to MSIS criteria and typing of reproductive microorganisms are shown in Table 2. Group 1 was formed according to these results. Two-stage revision knee arthroplasty was performed in 26 patients and revision surgery could not be performed in 14 patients due to additional diseases. Four patients refused surgical treatment in Group 1. Eighteen patients in the aseptic loosing group underwent single-stage revision surgery and 16 patients rejected the revision surgery in Group 2.

Table 1: MSIS Workgroup standard definition for PJI

One of the following must be met for diagnosis of PJI

1. There is a sinus tract communicating with the prosthesis
2. A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint
3. Four of the following six criteria exist:
   - Elevated ESR and CRP (ESR>30 mm/hour; CRP>10 mg/L)
   - Elevated synovial fluid WBC count (>3000 cells/L)
   - Elevated synovial fluid neutrophil percentage (>65%)
   - Presence of purulence in the affected joint
   - Isolation of a microorganism in one periprosthetic tissue or fluid
   - Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at 9400 magnification.

MSIS: Musculoskeletal Infection Society, PJI: Periprosthetic joint infection, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, WBC: White blood cell

Table 2: Group 1 according to MSIS criteria

		n (%) n=44
A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint	MRSE+MRSE: 4 MRSA+MRSA:3 MRSE+ESBL (+)*Escherichia coli*: 2 Gr (+) coccus non-typable: 2 CNS+CNS: 1	12 (27.2)
There is a sinus tract communicating with the prosthesis		5 (11.4)
Minor criteria of MSIS		27 (61.4)
Elevated ESR and CRP (ESR>30 mm/hour; CRP>10 mg/L)	n:24	
Elevated synovial fluid WBC count (>3000 cells/L)	n:21	
Elevated synovial fluid neutrophil percentage (>65%)	n:21	
Presence of purulence in the affected joint	n:26	
Isolation of a microorganism in one periprosthetic tissue or fluid	Gr (+) coccus non-typable: 8 Gr (-) bacilli: 2 MRSE:3 MSSA:2 ESBL (+) *Escherichia coli*: 1 ESBL (+) *Klebsiella pneumoniae*: 1 *Streptococcus agalactiae*:1 *Streptococcus pyogenes*:1	
Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at 400 magnification	-	

MRSE: Methicillin Resistant *Staphylococcus epidermidis*, MRSA: Methicillin Resistant *Staphylococcus aureus*, ESBL: Extended Spectrum Beta-Lactamase, CNS: Coagulase Negative Staphylococcus, MSSA: Methicillin Sensitive *Staphylococcus aureus* MSIS: Musculoskeletal Infection Society

E-Cam double-headed Gamma Camera (Siemens, Erlangen, Germany) was used for the evaluation of three-phase bone scintigraphy, and interpretations in favor of infection were divided into three groups as mild, moderate, and high probability.

Statistical analysis

SPSS 22.0 package program was used for statistical evaluation of the data obtained from the study (SPSS Inc, Chicago, Illinois, USA). Continuous data were summarized as mean, standard deviation while categorical data were summarized in numbers and percentages. Student t test was used to compare continuous variables in independent groups. For comparisons between the groups, chi-square (χ^2) test was used to evaluate two categorical independent groups. The mean values of continuous variables were compared with one-way ANOVA, and post-hoc Tukey test was used to compare the groups. Receiver operating characteristic (ROC) curve was used to evaluate the markers' ability to predict prosthetic infection. *P*-value <0.05 was considered statistically significant.

Results

A total of 131 patients (38.2% (n=50) male) were included in the study, the mean age of which was 64.8 (15) years (min-max: 20-90 years). The groups were similar in terms of age and gender (P values for age and gender, respectively; Group 1-2: 0.369, 0.586, Group 1-3: 0.961, 0.609; Group 2-3: 0.449, 0.330).

The findings of Group 1 according to MSIS criteria were presented in Table 2.

Of the three-phase bone scintigraphies, 49.6% (n=65) were for knee prosthesis and 50.4% (n=66) were for hip prosthesis. More than half (55%) of the prostheses were applied to the right knee and hip while 37.4% (n=49) were applied to the left knee and hip, and 7.6% (n=10) were applied bilaterally.

It was found that 33.6% (n=44) of the three-phase bone scintigraphies performed for various reasons were compatible with infection while 26% (n=34) were compatible with loosening, whereas 40.5% (n=53) were intact.

The degree of infection was evaluated according to the level of radioactive material uptake in perfusion, soft tissue and bone phase. Accordingly, 59% (n=26) of 44 cases were found to be mild, 20.5% (n=9) were moderate and 20.5% (n=9) were high. The laboratory values of all three groups are presented in Table 3.

Cut-Off, sensitivity, specificity, AUC, 95% confidence interval and p values of the ability of inflammatory markers to predict prosthetic infection are presented in Table 4 and the image of the ROC curve is shown in (Figure 1).

Table 3: Laboratory values of cases

	Group 1 (n=44)	Group 2 (n=34)	Group 3 (n=53)	*P*-value 1-2	1-3	2-3
WBC (10^9/L)	11.5 (3.2)	8.3 (2.1)	7.9 (2.1)	<0.001	<0.001	0.753
CRP (mg/L)	46.4 (50.0)	18.8 (17.5)	15.3 (17.1)	0.001	<0.001	0.876
ESR (mm/sa)	36.7 (18.6)	38.7 (23.5)	28.6 (17.9)	0.900	0.111	0.055
NLR	2.8 (1.8)	3.1 (1.7)	2.8 (2.0)	0.756	1.000	0.748
PLR	165.8 (75.6)	185.0 (67.7)	143.0 (66.4)	0.452	0.251	0.019
MPV (fL)	9.9 (1.1)	10.0 (1.0)	10.0 (1.1)	0.886	0.894	0.997

* ANOVA test and posthoc Tukey test were used to compare the groups. Group 1: Prosthesis infection, Group 2: Aseptic loosening, Group 3: Intact Prosthesis, WBC: White Blood Cell, CRP: C-reactive protein, NLR: Neutrophile-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, MPV: Mean Platelet Volume, *P*<0.05 value was considered statistically significant

Table 4: Cut-Off, sensitivity, specificity, AUC, 95% confidence interval and p values of ESR, CRP, WBC, MPV, NLO, and PLO for predicting prosthetic infection

	Cut-off	Sensitivity %	Specificity %	AUC	%95 CI	*P*-value
WBC (10^9/L)	8.6	91	61	0.845	77.7-91.4	0,001
CRP (mg/L)	12.2	84.1	55.2	0.777	69.2-86.1	0.001
ESR (mm/sa)	19.5	84.8	34.5	0.589	48.9-68.9	0.097
NLR	2.4	50	36.8	0.457	35.2-56.1	0.419
PLR	138.3	59.1	49.4	0.527	42.2-63.2	0.612
MPV (fL)	10.1	50	55.2	0.492	38.7-59.6	0.878

* ROC curve was used to calculate the values, ANOVA test and posthoc Tukey test were used to compare the groups. Group 1: Prosthesis infection, Group 2: Aseptic loosening, Group 3: Intact Prosthesis, WBC: White Blood Cell, CRP: C-reactive protein, NLR: Neutrophile-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, MPV: Mean Platelet Volume, *P*<0.05 value was considered statistically significant

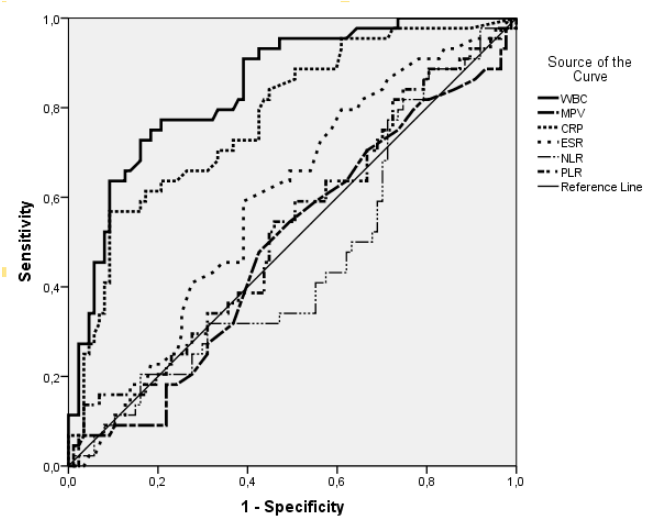

Figure 1: ROC curve of patients with prosthetic infection

Discussion

The number of joint prostheses is increasing due to increased life expectancy, lifestyle changes in the elderly population, and increased expectations such as mobility at an older age. With increasing prosthesis application, the lifetime of prosthesis in the body is prolonged. As a result, the possibility of hematogenous infections and AL increases during its lifetime [8].

Hip and knee arthroplasties are successful elective surgical procedures and have a survival rate of over 95% at 10-year follow-up [9]. Complications may be observed, although not often. Painful orthopedic prosthesis can be caused by intraarticular (infection, instability, AL) or extraarticular (tendinitis, periprosthetic fracture, degenerative joint disease, neurological problems) causes [1,10,11].

Early diagnosis is a positive factor for preserving prosthesis and joint function. Despite its clinical importance, difficulties remain in the emergency diagnosis of orthopedic prosthesis infection, and definitive diagnostic testing is still lacking. Although many serologic markers for PJI have been evaluated in the past including interleukin-6 (IL-6), ESR, and CRP are often used as a screening test since they are more susceptible to infection, faster, cheaper and more cost-effective than other serological biomarkers. Radiological methods also have a limited contribution to the diagnostic evaluation of infection. So, co-evaluation of multiple tests and radiology may reasonably improve diagnostic accuracy [7,12,13].

In the study of Xiong et al. [14] comparing PJI and AL groups, it was found that ESR values were 40.0 and 13.9 mm/h respectively and were significantly higher in the PJI group. In another study, it was found that the cut-off value of the ESR was 41 mm/h and significantly higher in the PJI group compared to the AL group. In the same study, sensitivity for ESR was 63.6%, specificity was 70.2% and AUC:0.719 [15]. In our study, the mean ESR, cut-off value, sensitivity, specificity, and AUC values were very low compared to the literature. This was related to the fact that most of the patients in our study group had chronic infection.

Abnormal CRP increases after primary arthroplasty were evaluated in a retrospective study by Tae Won Kim et al. [16]. While 24% of the cases had CRP elevation associated with

PJI, 56% of the cases had CRP elevation due to non-prosthetic reasons (paralytic ileus, upper respiratory tract infection, deep vein thrombosis, acute renal failure). However, in 20% of cases, the cause could not be determined. When Marcus Lensky et al. [17] retrospectively evaluated a total of 719 patients, they showed that the mean CRP of 67 patients diagnosed with PJI was 10.6 (9.7) mg/dL (sensitivity 91.7%; specificity 15.4% and AUC:0.746). In another study by Alijanipour et al. [18] 84 patients with PJI and 1962 AL cases were compared. When the cut-off value for CRP was 23.5 mg/dL, the sensitivity was 87%, the specificity was 94%, and the AUC value was 0.950. In the study by Leilei Qin et al. [15] it was determined that CRP values were significantly higher in PJI group than AL group. In conclusion, it was emphasized that CRP is a good biomarker in predicting the correct diagnosis. Our results for CRP were similar to the literature.

Clinical studies have shown that CRP and ESR are rarely normal in the presence of infection. Hence, in patients suspected of infection or planned for revision arthroplasty for any reason, these should be screened before surgery [19].

Although the number of white blood cells (WBC) in synovial fluid is one of the minor criteria for the diagnosis of PJI according to MSIS criteria, serum WBC value may be helpful in the diagnosis of infection. While Friedrich et al. [20] were using microbiology and histology data as reference test in the prospective evaluation of 120 patients who underwent total knee or hip revision, they found 21% sensitivity and 94% specificity for serum WBC. Bottner et al. [21] reported that in a prospective study of 78 patients who underwent revision total knee or hip arthroplasty, the sensitivity and specificity for WBC were 70% and 60%, respectively, and these results limit the utility of WBC in the diagnosis of PJI. In another study, they reported that WBC average was 11 (6.4) 10^9/L, cut-off value was 11.5 10^9/L, sensitivity was 92.3% in patients with PJI and had good diagnostic potential (AUC:0.751). As a result of the study, it was found that WBC has diagnostic potential equivalent to CRP [16]. In our study, WBC average was significantly higher in PJI group compared to AL and healthy prosthesis groups.

Limitations

The retrospective design and the fact that some of the cases did not have culture results are the limitations of our study.

Conclusions

The use of three-phase bone scintigraphy and inflammatory markers such as CRP and WBC have been shown to be important in the diagnosis of prosthetic infection.

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Case report
Olgu sunumu

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Congenital isolated asplenia accidentally discovered during acute peritonitis

Akut peritonit sırasında tesadüfen fark edilen konjenital izole asplenia

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Abstract

An extremely rare condition, congenital asplenia has 2 distinct types: heterotaxy syndromes and isolated congenital asplenia (ICA). Ivemark syndrome is one of the heterotaxy syndromes characterized by asplenia, malformations of the heart, and malposition of internal organs in the chest and abdomen. ICA cases are also fatal in childhood, but there are reported living adult cases. Those affected are typically at increased risk for fulminant sepsis and carry a higher risk of noninfectious complications, such as thrombocytosis and mesenteric thrombosis. We herein report the unusual case of a patient with congenital asplenia, which was discovered fortuitously during an emergency laparotomy for peritonitis due to ulcer perforation.

Keywords: Congenital isolated asplenia, Adult peritonitis

Öz

Çok nadir görülen bir durum olan konjenital aspleninin 2 farklı tipi vardır: heterotaksi sendromları ve izole konjenital aspleni (ICA). Ivemark sendromu, asplenia, kalbin malformasyonları ve göğüs ve karındaki iç organların malpozisyonu ile karakterize heterotaksi sendromlarından biridir. ICA vakaları çocuklukta da ölümcüldür, ancak bildirilen canlı yetişkin vakaları mevcuttur. Etkilenenler tipik olarak fulminan sepsis için yüksek risk altındadır ve trombositoz ve mezenterik tromboz gibi bulaşıcı olmayan komplikasyon riski daha yüksektir. Burada ülser perforasyonuna bağlı peritonit için acil bir laparotomi sırasında tesadüfen saptanan doğuştan asplenisi olan bir hastanın olağandışı olgusunu sunuyoruz.

Anahtar kelimeler: Konjenital izole asplenia, Yetişkin peritoniti

Introduction

Isolated congenital asplenia is an exceptional form, and rare cases have been reported in the literature (Table 1) [1-4]. It is usually diagnosed after the onset of severe infections in infants. In adults without a history of severe sepsis in infancy, the presenting sign may be thrombocytosis [5]. Our case shows that congenital isolated asplenia patients can remain asymptomatic for a long time, or even lead normal lives.

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Hasta Onamı: Yazar çalışmada görüntüleri sunulan hastadan yazılı onam alındığını ifade etmiştir.

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Table 1: Classification of asplenia

• Congenital	• Acquired
Isolated	Splenectomy
Familial	Trauma
Non-familial	Hemolytic anaemia
	ITP
	Malignancy
• Syndromatic	• Functional/hyposplenism
Ivemark	HbSS/Sickle-cell anaemia
Storkmorken	Portal hypertension
Kartagener	Storage diseases (Amyloidosis, M. Gaucher)
Meckel	Iatrogenic (radiotherapy)
Pallister-Hall	
Cystic liver, kidney, pancreas	
MLRD (microgastria-limb reduction defects association)	
Smith – Fineman – Meyers	
Schmidt	

ITP: idiopathic thrombopenic purpura

Case presentation

A 65-year-old male patient of Moroccon origin, a chronic smoker without a pathological personal or family history, was consulted urgently due to diffuse abdominal pain. Physical examination revealed a conscious, febrile, dehydrated patient who was hypotensive with a blood pressure of 90/60 mmHg. He had generalized abdominal defense of the left pelvis and iliac fossa and diffuse tenderness in all four abdominal quadrants. Laboratory results showed leukocytosis at 18 g/L, C-reactive protein at 250 mg/L, slight thrombocytosis at 500 g/L, and acute renal failure. Hepato-pancreatic functional tests were normal. Lung radiograph showed pneumoperitoneum right below the diaphragm, consistent with perforation of a hollow organ, after which we decided to operate on the patient. An urgent laparotomy was performed, which revealed the presence of about 1 L of pus intraabdominally, and anteriorly perforated duodenal bulbus. The perforation was sutured, and intraabdominal lavage and drainage were done. During abdominal exploration, no spleen was observed in the left hypochondrium (Figure 1). Postoperative follows-up were uneventful. Subsequently, a thoraco-abdominopelvic CT scan was obtained, which confirmed the absence of the spleen, and excluded any other abdominal or thoracic malformation (Figure 2).The postoperative hematologic assessment revealed the presence of Howell-Jolly corpuscles confirming functional asplenia.

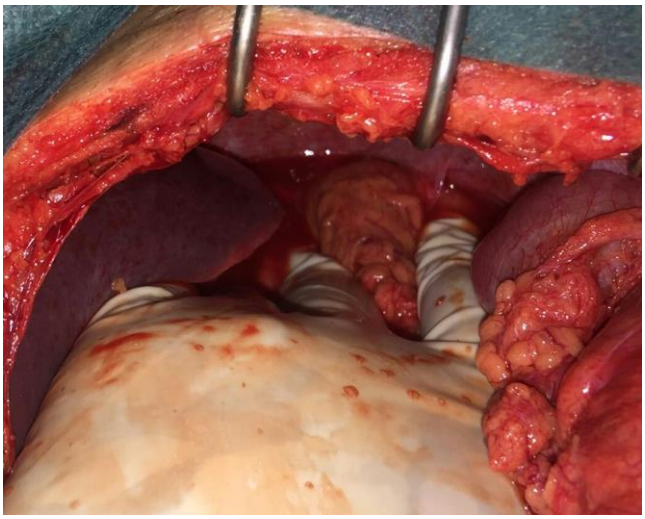

Figure 1: Per operatory image shows an absence of spleen in a left hypochondrium

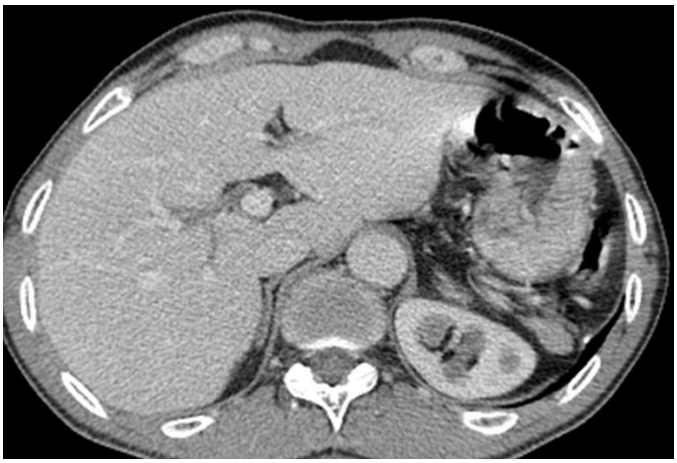

Figure 2: CT image shows an Empty splenic lodge occupied by the tail of the pancreas

Discussion

Congenital asplenia, a poorly understood and rare form of primary immunodeficiency, is either associated with malformation syndromes such as heterotaxia, or presents as an isolated finding, as was the case in our patient [2]. Heterotaxia syndrome with situs abnormalities (Ivemark syndrome) is a sporadic, autosomal recessive syndrome seen in cases of parental consanguinity. Patients with Ivemark syndrome generally die by the age of 6 months. On the other hand, ICA, with the plausible autosomal dominant mode of inheritance, is often fatal in early childhood or complicated with life-threatening infections such as meningitis and purpura fulminans or noninfectious complications such as thrombocytosis and mesenteric thrombosis [6,7].

Bolze et al. [7] studied 33 patients with isolated congenital asplenia from 23 families, including 5 families previously reported by Mahlaoui et al. [6] and those described Ferlicot et al. [8], and suggested that heterozygous coding mutations in RPSA on chromosome 3p21 underlie most cases of isolated congenital asplenia, with apparently complete penetrance. RPSA is not likely to have been identified through a candidate-gene approach, as RPSA is ubiquitously expressed and is not known to be involved in spleen development [7].

The clinical record that we report is interesting since this patient had congenital isolated non-syndromic asplenia, discovered incidentally at the age of 65 years. The anamnesis was negative for any septic episode or other anomalies. Prolonged survival in the absence of cardiopulmonary and infectious complications is therefore possible in patients with congenital asplenia. Rare cases, to our knowledge, have been reported [9]. But in most cases, in the absence of cardiac malformations, asplenia is discovered at autopsy, as mentioned in the case of a child who died from pneumococcal sepsis [10].

This prompted our comprehensive literature search of adult ICA cases that presented with complications other than those related to infection [2]. Eighteen adult cases of ICA were identified and analyzed since the first report of Myerson and Koelle in 1956. Eleven of the 18 reported cases were sporadic and the remaining were familial. Familial cases are generally asymptomatic and usually diagnosed after a close family member/child suffers a life-threatening or fatal infection secondary to congenital asplenia. Associated findings include thrombocytosis, mesenteric vein thrombosis, chronic thromboembolic pulmonary hypertension, and pneumococcal

sepsis (Table 2). Seven adult patients with ICA had invasive bacterial infections [6-12]. In addition, there were 5 adult cases of ICA with thrombocytosis but no infectious events were found [13,14].

Table 2: Adult isolated congenital cases reported from 1956 till 2015

Case No.	Familial or sporadic	Age at diagnosis/gender	Clinical presentation	Outcome
1	Sporadic	36 years/Male	Pneumococcal sepsis/Waterhouse-Friderichsen syndrome	Deceased
2	Sporadic	37 years/Male	Thrombocytosis	Alive
3	Sporadic	56 years/Female	Thrombocytosis/myocardial infarction	Alive
4	Sporadic	56 years/Male	Thrombocytosis	Alive
5	Sporadic	60 years/Female	Pneumococcal sepsis	Alive
6	Sporadic	77 years/Male	Mesenteric vein thrombosis	Alive
7	Sporadic	52 years/Female	Pneumococcal sepsis	Deceased
8	Sporadic	72 years/Male	Thrombocytosis	Alive
9	Familial	20 years/Female	Pneumococcal sepsis/2 children affected	Alive
10	Familial	35 years/Male	Asymptomatic/5 children affected	Alive
11	Familial	45 years/Male	Meningitis-pneumococcal/2 children affected	Alive
12	Familial	Unknown/Male	Asymptomatic/1 child affected	Alive
13	Familial	25 years/Male	Thrombocytosis/1 child affected	Alive
14	Familial	Unknown/Female	Asymptomatic/2 children affected	Alive
15	Familial	27 years/Male	Asymptomatic/sister affected with AVM	Alive
16	Adopted	22 years/Male	Small bowel AVM bleed, Mycoplasma pneumonia	Alive
17	Sporadic	28 years/Male	Streptococcal pneumonia/ulcerative colitis	Alive
18	Sporadic	44 years/Female	Thrombocytosis/Chronic thromboembolic pulmonary hypertension	Alive
19	Sporadic	67 years/Female	Waterhouse-Friderichsen syndrome/lung fibrosis	Deceased

Reflecting another risk associated with thrombocytosis in adults, Takahashi et al. [15] also described the case of a 44-year-old female with ICA who had chronic thromboembolic pulmonary hypertension. The diagnosis of functional asplenia was confirmed by the analysis of the peripheral blood smear, which revealed the presence of Howell-Jolly corpuscles [10]. The diagnosis of isolated congenital asplenia is confirmed apart from any infectious complication or cardiovascular malformation which probably explains the prolonged survival in our patient. Finally, the interest of vaccination against pneumococcal infections and even long-term antibiotic prophylaxis was discussed, but vaccination did not seem justified in this very particular situation [9].

Conclusion

This clinical presentation suggests that isolated congenital asplenia is compatible with a normal and prolonged existence in the absence of any infectious complications, and cardiovascular and digestive tract malformations.

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Primary rectal linitis plastica: Report of two cases and a review of the literature

Primer rektal linitis plastika: İki olgu sunumu ve literatürün gözden geçirilmesi

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Abstract
Primary rectal linitis is a rare tumor which mostly affects young patients. The definite diagnosis is based on the histologic examination of deep biopsy samples. It is mostly diagnosed in advanced stages, which worsens the prognosis. In this report, two cases of primary rectal linitis plastica will be presented and discussed in light of the literature.
Keywords: Plastic linitis, Primary rectal tumor

Öz
Primer rektal linit, çoğunlukla genç hastaları etkileyen nadir bir tümördür. Kesin tanı derin biyopsi örneklerinin histolojik incelemesine dayanır. Çoğunlukla ileri aşamalarda teşhis edildiğinden, prognozu kötüdür. Bu raporda, iki primer rektal linitis plastica olgusu literatür eşliğinde sunulacak ve tartışılacaktır.
Anahtar kelimeler: Plastik linit, Primer rektal tümör

Introduction

The conventional definition of plastic linitis, a.k.a. “scirrhous carcinoma”, is a tumor that massively infiltrates the entire thickness of the wall of a hollow organ. Histologically, it corresponds to an adenocarcinoma of independent cells with a signet ring appearance, and usually affects the stomach. The involvement of another digestive organ is often secondary. In fact, the primary rectal linitis is a rare entity [1].

Below are presented two patients diagnosed with primary rectal linitis.

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Case presentation

Case 1

A 31-year-old female patient, who was operated for an ovarian cyst in 2015, was admitted with progressive hematochezia lasting for two months and severe weight loss. At 2 cm from the anal margin (AM), we palpated a circumferential, stenosing and obstructive mass fixed to the anterior and posterior planes. On examination, the posterior wall of the vagina was thick and rough. Biopsies revealed rectal carcinoma with independent cells in a signet-ring appearance (Figure 1). The thoraco-abdomino-pelvic computerized tomography (CT) revealed a thickening 3 cm proximal to the AM, extending for 10 cm and infiltrating the perilesional fat, along with adjacent lymphadenopathy (Figure 2). The patient underwent an esophagogastroduodenoscopy (EGD) and a colonoscopy to search for a primary source of tumor, which both turned out normal, hence the diagnosis of primary rectal linitis. The patient received a long-term radiotherapy protocol with concomitant chemotherapy. The disease progressed, as marked by local extension of the tumor which was deemed unresectable, and the patient was referred for palliative chemotherapy.

Case 2

A 38-year-old male patient with no medical history was admitted for rectal bleeding, proctalgia, and transit disorder with a weight loss of 10 kg evolving for six months. The abdominal examination was normal, and digital rectal examination was very painful. The patient underwent a rectoscopy on sedation, which revealed an infiltrated, stenotic mucosa 4 cm proximal from the AM (Figure 3). The biopsies were reported as undifferentiated and infiltrative carcinoma with signet ring cells. A thoraco-abdomino-pelvic CT scan showed a tumoral thickening of the lower rectum with secondary iliac lymphadenopathies. The patient underwent an EGD which was normal, then received radiotherapy concurrent with chemotherapy. Magnetic resonance imaging (MRI) scan revealed a posterior hemicircumferential lower rectum mass, infiltrating the rectal mucosa along with the internal and external sphincters, without prostatic or bladder involvement (Figure 4). Intraoperative exploration revealed an unresectable tumor. A sigmoidostomy was performed, after which the patient was referred for palliative chemotherapy.

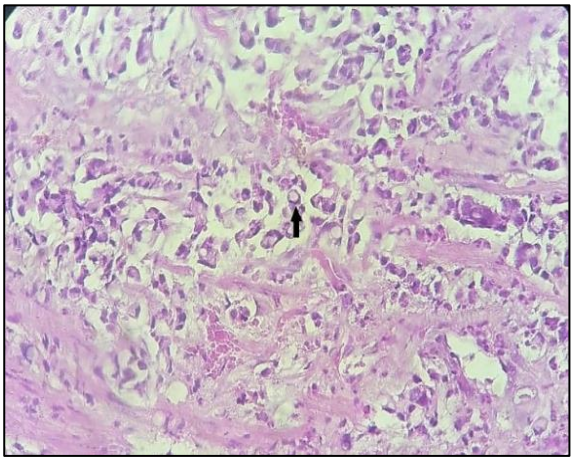

Figure 1: Microscopic image shows the histological appearance of rectal linitis: rectal carcinoma with independent cells

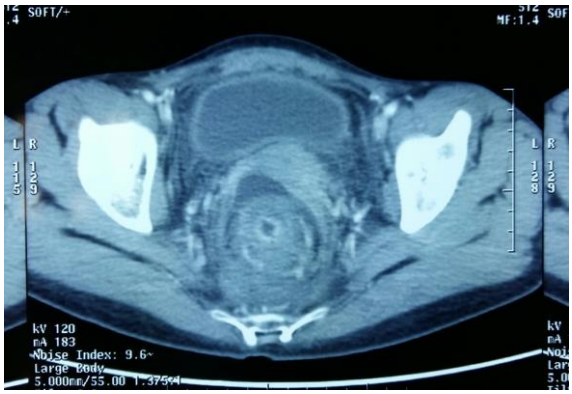

Figure 2: CT image shows the local extension of rectal linitis

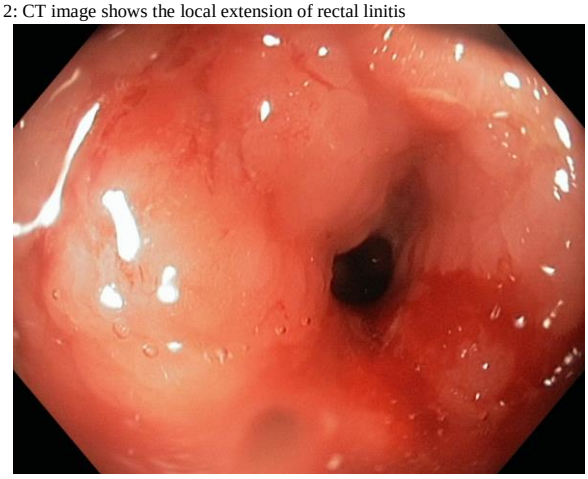

Figure 3: Rectoscopy shows the infiltrating and stenosing aspect of rectal linitis

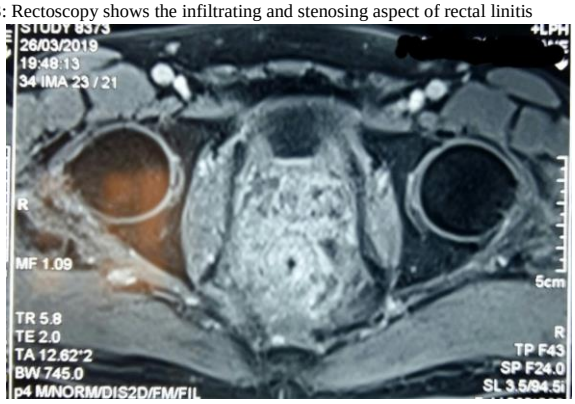

Figure 4: Image of MRI shows a rectal process with internal and external sphincter invasion

Discussion

Rectal primary plastic linitis, accounting for 1/1,000 for colonic and rectal cancers, is rare [1], and more common in men (sex ratio M/F: 1,3). Most authors insist on the occurrence of linitis at an early age [1,2], which is the case of our two patients. It does not share the same characteristics and etiopathogenic factors with conventional adenocarcinomas. Indeed, genetic predisposition or malign transformation of an adenomatous polyp have not been established for this kind of tumor. A relationship between colorectal linitis and inflammatory bowel disease, particularly Crohn's disease, has been reported [2, 6]. The revealing symptoms, such as transit disorders, bowel obstruction, abdominal pain, weight loss or hematochezia, are not specific [2-4]. The diagnosis is often late. In most of cases, digital rectal examination reveals in infiltrating mass and a fixed rectal ampulla [4]. Upon endoscopic exploration, the mucosa is seen intact with a narrowed or obstructed lumen. The biopsies results are negative in 50% of the cases, which necessitates the need for deep or surgical biopsies [2]. Endoscopic ultrasonography assists in the diagnosis by guiding biopsies and

revealing a circumferential thickening reaching the mucosa and the muscular mucosa in a concentric, hypoechoic sleeve around the ultrasound probe. It plays a significant role in not only preoperative assessment and staging, but also in follow-up by measuring the regression of lesions under radiotherapy and chemotherapy [5,6]. Computed tomography and magnetic resonance imaging show locoregional and distant invasion [7]. Definite diagnosis is based on histological examination: Macroscopically, a thickening of the wall and circumferential involvement of the rectum, engulfing the mesorectum, with a most often normal mucosa [2-1] is seen. Microscopically, we find abundant (50%) signet ring cells within a dense fibrous stroma infiltrating the rectal wall [1].

The search for a primary extra-rectal tumor, especially gastric, must be systematic, because only its negativity affirms the primitive nature of the lesion. Secondary rectal linitis is more frequent, most often corresponding to the metastasis of a gastric cancer, and more rarely, to cancers of gall bladder, breast, or prostate [8,9]. Linitis has a predominantly locoregional extension to the lymphatic (lymphadenopathy: 86%), pelvic (ovary, trunk, and uterus: 58%) and peritoneal (47%) areas. Hepatic metastases are exceptional (17%). Metastases to the bone are present in 12% of patients and other sites, 6% of patients. Aggressive treatment with ganglion dissection is performed if the extension allows. Combination of radiotherapy with a chemotherapy combining 5-fluorouracil and cisplatin appears to provide better outcomes in long term survival [1]

The prognosis of primary rectal linitis is poor, since lymphatic metastases are often found immediately at diagnosis. Survival is variable from one month to two years [2-8].

Conclusion

Primary rectal linitis is a rare and an extremely aggressive tumor, diagnosed most often at advanced stages, which worsens prognosis. The definite diagnosis is based on histological examination of deep biopsy samples.

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Auditory, visual and tactile hallucinations in a 16-year-old adolescent with high-dose duloxetine at one time

16 yaşındaki ergende tek seferde yüksek doz duloksetin kullanımı ortaya çıkan işitsel, görsel ve dokunsal halüsinasyonlar

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Abstract
Duloxetine is a dual-acting serotonin-noradrenaline reuptake inhibitor. It has FDA approval for the diagnosis of Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), Diabetic Neuropathic Pain, Fibromyalgia, Chronic Skeletal Muscle Pain in adults, and GAD in children and adolescents. This article presents a 16-year-old female patient referred to the emergency department with hallucinations starting after she took a total of 330 mg/day duloxetine for headaches. It is thought that her experienced hallucinations may be due to increased dopamine, as a result of inhibition of serotonergic system and noradrenaline transport system. It is thought that this article will contribute to the literature in terms of pharmacokinetic and pharmacodynamic effects of duloxetine in children and adolescents.
Keywords: Duloxetine, Hallucination, Adolescent

Öz
Duloksetin dual etkili serotonin-noradrenalin geri alım inhibitörüdür. Erişkinlerde Major Depresif Bozukluk (MDD), Yaygın Anksiyete Bozukluğu (GAD), Diyabetik Nöropatik Ağrı, Fibromiyalji, Kronik İskelet Kas Ağrısı tanılarında, çocuk ve ergenlerde GAD için FDA onayı vardır. Bu yazıda, baş ağrıları olduğu için toplam 330 mg/gün duloksetin içen sonrasında halüsinasyonları başladığı için acil servise başvuran 16 yaşındaki kadın hasta sunulacaktır. Halüsinasyonların serotonerjik sistem ve noradrenalin transport sisteminin inhibisyonu sonucunda dopamin artışına bağlı olabileceği düşünülmektedir. Bu yazı, duloksetinin, çocuk ve ergenlerdeki farmakokinetik ve farmakodinamik etkileri açısından literatüre katkı sağlayacağı düşünülmüştür.
Anahtar kelimeler: Duloksetin, Halüsinasyon, Ergen

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Introduction

Duloxetine is a serotonin-noradrenaline reuptake inhibitor [1]. It has FDA approval for the diagnosis of Major Depressive Disorder, Generalized Anxiety Disorder, Diabetic Neuropathic Pain, Fibromyalgia, Chronic Skeletal Muscle Pain in adults, and GAD in children and adolescents older than 7 years old [2]. It has been reported that no dose adjustment is needed in children and adolescents, and that the dose is similar to that used with adults [3]. In a study conducted on the pharmacokinetics of duloxetine in children and adolescents, no clinically significant difference was found when compared with adults [4]. The most common side effects associated with duloxetine are nausea, dry mouth, dizziness, decreased appetite, constipation, and insomnia [5]. The most common psychiatric side effects are increased suicidal ideation, suicidal behavior, shift to mania, and hypomania [1]. In this article, a case with visual, auditory, and tactile hallucinations that occurred after 330 mg/day duloxetine use will be presented.

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Case presentation

A 16-year-old female patient was referred to our clinic from the emergency services for our evaluation. It was learned that no pathologies were found to explain hallucinations in cardiological, neurological examinations, blood (complete blood count, liver function tests, kidney function tests, electrolytes, glucose, blood lipids, thyroid function tests, and imaging tests (MR) before she was referred. The patient stated that she used one duloxetine 30 mg capsule (Cymbalta® 30 mg capsule), which her mother used for headaches; she then took 11 tablets in a row as one did not have any effect upon her. It was approved by her and her family that she had used a total of 330 mg. It was learned that she tried to sleep when it did not work; she woke up approximately five hours later and saw someone in the room. It was learned that her family waited, thinking that it would pass; however, a few hours later, she stated that the person she saw talked by touching her back. She communicated to her father by making a sign of a telephone with her hand, and was then referred to the emergency service with her family. The patient stated that, in addition to hallucinations, she had a tingling sensation in her feet and hands, a sense of flushing, difficulty in urinating, and feelings of palpitations. It was observed that the patient had difficulty sitting and following the speech content during the examination. She stated she was worried about hallucinations and that she saw the person she had seen before during the examination. She stated that she took the large quantity of drugs as she believed they would work if she took more. Although this situation suggests a suicide attempt, it was learned that there were no significant complaints from neither the patient's statements, nor the Beck Depression Scale and STAI-II scales she completed during the examination. At the same time, the history taken from her family revealed that she had no previous suicide attempts and self-injurious behavior. The fact that she did not have psychiatric complaints, depressive symptoms, suicidal thoughts, and active suicide plans, and that her hallucinations started all of a sudden after she took medication suggested that she did not have a psychiatric disease. The case was followed up without medication due to the uncommon hallucinations, their sudden onset and her good family functioning. With a close follow-up, it was observed that the hallucinations regressed after five days and that there were no active complaints. When psychopathologies were re-evaluated in the control appointment two weeks later, it was concluded that there was no active psychopathology.

When she was assessed with Naranjo Adverse Drug Reactions Probability Scale, she recorded six points, which suggested that the association of this adverse effect with duloxetine was “probable” [6]. It was thought that the hallucinations were an adverse effect of the high duloxetine. For this reason, considering the possible contribution to the literature, a case report was made upon the completion of a consent form from the patient and her family.

Discussion

Duloxetine, which is rarely used in Turkey since there is no reimbursement by insurance in children and adolescents, is thought to be safe in children and adolescents [7]. It is frequently preferred in the treatment of children and adolescents, as well as resistant MDD and GAD cases [8,9]. Although there are case reports in the literature that conclude duloxetine causes hallucinations [10–12], only one case report of hallucinations in children and adolescents was sourced [13]. It was reported that the case was followed up to observe any GADs, and that the hallucinations had started on the fifth day following when the duloxetine dosing commenced.

In case reports, there is no clear information in the literature about how duloxetine causes hallucinations. Since DAT is not very high in the prefrontal cortex, dopamine is removed from the synaptic space via NET [14]. It is thought that, increased dopamine in the synaptic range, alongside the NET inhibition of SNRIs, may cause hallucinations [15]. It is also emphasized that serotonin may cause hallucinations as a result of increased dopamine in the ventral striatum via 5HT2 and 5HT3 receptors, as a consequence of the inhibition reuptake [16–18]. It is also said that even if the SNRIs are weak, they can increase the dopamine level by inhibiting the dopamine reuptake pump (dopamine transporter) [14].

The presence of multiple drug use in some reports and the presence of an underlying psychopathology in some reports may be considered as a confusing factor in the relationship between hallucinations and duloxetine. In the present study’s case, the lack of underlying psychopathology provides an opportunity to say something more clearly about the relationship between hallucination and duloxetine. In addition, the fact that duloxetine was reportedly used within the appropriate dose range in cases in which it is reported to cause hallucinations, as well as that it was not within the appropriate dose range in our case suggests that this adverse effect is dose-independent.

Conclusions

Hallucinations occurring in the onset of treatment and in dose changes suggest that there is a need to be wary and conscious of hallucinations in every stage of the treatment in cases that use duloxetine.

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Perinephric abscess as a rare cause of acute abdomen: A case report

Akut batının nadir bir nedeni olarak perinefrik apse: Olgu sunumu

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Abstract
Renal and perinephric abscesses are usually confined within the Gerota's fascia and treated with conservatively. We herein present a case with peritonitis caused by the spillage of perinephritic abscess into the abdomen through the Gerota's fascia, which is clinical outcome. A 41-year-old female patient was admitted to emergency room with complaints of abdominal pain, bloating, fever, and fatigue. During the operation, an abscess of approximately 20x15cm in size was observed to extend into the abdominal cavity through the Gerota's fascia, causing secondary peritonitis. On the 20th postoperative day, the patient was uneventfully discharged. Delay in diagnosis of renal and perinephric abscesses can lead to fatal complications. Laparotomy is a life-saving approach in cases that cannot be treated with percutaneous drainage, when the abscess is large and causes complications such as strictures, fistulas, or secondary peritonitis, by extension through the Gerota's fascia, as in our case.
Keywords: Perinephric abscess, Renal abscess, Secondary peritonitis, Acute abdomen

Öz
Renal ve perinefrik apseler genellikle Gerota fasyasında sınırlı kalırlar ve konservatif yöntemlerle tedavi edilirler. Bu çalışmada perinefritik apsenin nadir görülen klinik bir sonucu olarak Gerota fasyasından karın içerisine açılması sonucu sekonder peritonite sebep olduğu olguyu sunmayı amaçladık. 41 yaşında kadın hasta karın ağrısı, karında şişlik, ateş ve halsizlik şikayetleriyle hastanemiz acil servisine başvurdu. Acil opere edilen hastada Gerota fasyasından karın içine uzanan yaklaşık 20x15 cm çapında apse ve sekonder peritonit saptandı. Postoperatif 20. gün hasta şifa ile hastaneden taburcu edildi. Perinefritik apselerin tanısında gecikme olması öldürücü komplikasyonlara yol açabilir. Gerota fasyasını aşan, striktür, fistül veya bizim olgumuzda olduğu gibi sekonder peritonitin geliştiği ve perkütan drenajla tedavi edilemeyen geniş apselerde laparotomi hayat kurtarıcıdır.
Anahtar kelimeler: Perinefrik apse, Renal apse, Sekonder peritonit, Akut karın

Introduction

Renal and perinephric abscesses are two major clinical problems in hospitalized patients, with a prevalence of 1 to 10 per 10,000. The prevalence is approximately same in males and females [1]. When the renal abscess develops, the suppurative material encases the renal parenchyma and the capsule. The abscess is usually confined within the Gerota's fascia. The most common condition associated with abscess formation is the spreading of lower urinary tract infections to the kidney, which develop due to gram-negative bacteria [2,3]. These abscesses are treated with conservative methods, such as antibiotic treatment and percutaneous drainage, and can lead to flank, scrotal, or subphrenic abscesses and occasionally, colonic fistulae [4,5]. According to the literature, expansion of the perinephric abscess into the mediastinal and epidural space has also been reported [6]. Our case manifests a rare condition of secondary peritonitis caused by perinephric abscess extending through Gerota's fascia and spilling into the abdominal cavity.

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Case presentation

A 41-year-old female patient was admitted to the emergency room with complaints of abdominal pain, bloating, fever, and fatigue. The abdominal pain had lasted for a week and worsened in the last 2 days. The patient had Type 1 Diabetes and received insulin treatment. On physical examination, blood pressure was 110/60 mmHg, pulse rate was 96/min, and body temperature was 37.9^{o}C. There was severe distention, abdominal guarding and rebound in all quadrants of the abdomen, particularly in the left upper and lower quadrants. Leukocyte count (WBC) was 13.84 x 109/L, hemoglobin value was 10.73 g/dL (14-18 g/dL), hematocrit, 34.31, C-reactive protein (CRP), 20.7 (40-53%), blood glucose, 287, and serum albumin, 2.3 g/dL (3.5-5 g / dL). All other biochemical parameters were within normal limits. Respiratory and cardiac examination revealed no pathology. Emergency ultrasound examination (US) revealed an intense lesion measuring approximately 185 x 99 mm and a thick wall in the left renal pouch, indicating pyonephrosis and an abscess. Extensive free fluid was seen in the abdomen and edema was observed in abdominal submucosal fat planes. Upon these findings, an abdominal tomography (CT scan) was performed, which revealed a fluid collection measuring approximately 129x114 mm with air and septae, indicating an abscess and emphysematous pyelonephritis, surrounding the left kidney with borders undistinguishable from the left kidney. The lesion pushed the left kidney anteroinferiorly. It has been reported that contrast enhancement was observed on the peritoneal surfaces in the pelvic region, pointing to peritonitis, as evidenced by the distorted appearance of mesenteric tissue and omentum in the lower quadrant of the abdomen. Axial and coronal section plane abdominal CT findings are shown at Figure 1 and Figure 2.

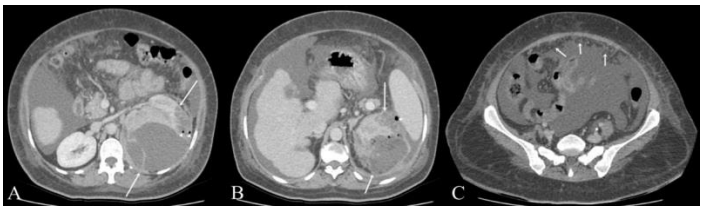

Figure 1: A: IV contrast abdominal computerized tomography showed dense fluid collection with septae displacing the left kidney anteriorly (long arrows), air images inside the fluid collection (short arrows) and intraabdominal free fluid in the axial plane B: dense fluid collection with septae including air images in the left kidney region (long arrow), intraabdominal free fluid and free air adjacent to the spleen (short arrow), C: Intraabdominal omental thickening – contamination (arrows) and widespread intraabdominal free fluid

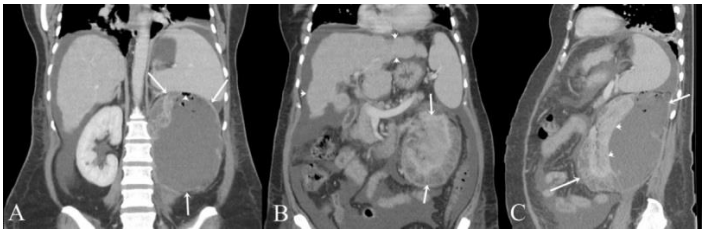

Figure 2: A: IV contrast abdominal computerized tomography showed a dense fluid collection around the left kidney, air images superior to the fluid collection (short arrows) and intraabdominal free fluid in the coronal plane, B: dense fluid collection with septae displacing the left kidney inferiorly (long arrows), lobulated liver contours (short arrows) and intraabdominal free fluid, C: dense fluid collection with septae displacing the left kidney anteriorly (long arrows), air images superior to the fluid collection (short arrows) and intraabdominal free fluid

With these findings, the patient was urgently operated on. During the operation, approximately 4 liters of infected fluid (ascites) was aspirated from the abdominal cavity. Exploration of the abdomen revealed an abscess measuring approximately 20x15 cm in size, extending into the abdominal cavity through Gerota's fascia. The omentum and small intestines were edematous and conglomerated in the lower quadrants. Purulent fluid was present in the pelvic, perihepatic, perisplenic areas and lower right quadrant regions of the stomach. The peritoneum was thickened and edematous in the left upper and lower quadrants, due to secondary peritonitis. The liver also appeared extremely fibrotic and cirrhotic. Gerota's fascia was dissected and patchy, necrotic areas were observed in the superior kidney parenchyma. The abscess pouch was opened, a culture was obtained and approximately 400 cc of purulent fluid was aspirated. The purulent fluid in the abdomen, approximately 600 cc, was aspirated and the abdominal cavity was irrigated with abundant saline. Due to edema in the intestines and peritonitis findings, the fascia could not be closed, and the operation was terminated after closure of the skin. The patient was monitored in the intensive care unit with the support of a ventilator. Blood, fresh frozen plasma, and albumin replacements were administered, and antibiotic therapy (meropenem) was started. On the first postoperative day, peritoneal lavage was performed due to purulent discharge from the surgical drains. Monitoring with the support of a ventilator was continued and blood, fresh frozen plasma and albumin replacements were administered periodically. Peritoneal lavage was performed, and fascia was closed on the 4th postoperative day. Monitoring was continued in the intensive care unit. The patient was extubated on the 6th postoperative day and she was discharged from the intensive care unit on the 9th postoperative day. On the 20th postoperative day, the patient was uneventfully discharged. Written and verbal informed consent forms were obtained from patient.

Discussion

Renal and perinephric abscesses are two major clinical problems that result from lower urinary tract infections ascending to the kidney. They often develop due to gram-negative bacteria, E. coli being the most common [2,7]. Early start of appropriate antibiotic therapy is important in treating urinary tract infections and preventing complications such as renal abscess [8]. Perinephric abscesses occur as a result of parenchymal damage due to severe pyelonephritis and elevation in the intrapelvic pressure, usually caused by stone-related obstruction. The most important predisposing factors are a combination of conditions that lead to immunosuppression, such as stone-induced obstruction accompanied by urinary tract infection, uncontrolled diabetes, and the use of intravenous drugs [9]. Our patient was receiving insulin treatment due to Type 1 diabetes, and liver cirrhosis was found during abdominal CT scan and following the operation.

Renal and perinephric abscesses usually manifest by varying degrees of discomfort and pain in the flank area, fever, fatigue, loss of appetite, nausea, weight loss and sometimes permanent hiccups [9]. Since the findings of lower urinary tract infections are common in patients admitted to the hospital, the diagnosis of pyelonephritis and perinephric abscesses are often delayed until the occurrence of major findings [10]. These abscesses, usually confined within the Gerota's fascia at the time of diagnosis, can occasionally spread beyond it and extend to the pararenal area. This can result in strictures and fistulas in the surrounding organs (bowel, pancreas, liver, spleen, pleural space, gall bladder, vertebra, prostate, etc.) due to the collection of purulent fluid [4-6,9]. Therefore, the most crucial factor in

treating renal and perinephric abscesses is early diagnosis [11]. In our case, the abscess caused a rare clinical finding of secondary peritonitis due to extension through the Gerota's fascia to the peritoneum.

It is particularly important to evaluate patients with renal and perinephric abscesses carefully in terms of clinical symptoms, findings of urosepsis, age, general condition and presence of comorbid diseases [10]. In laboratory findings, high CRP and BUN levels are correlated with poor prognosis [12]. With the use of modern imaging techniques, such as high-resolution ultrasound, computed tomography and MRI, renal and perinephric abscess-related mortality has declined from 40-50% to 1.5-15% in the last 30 years [13]. The first line modality for diagnosis of renal and perinephric abscesses is ultrasound, with a sensitivity ranging between 70 and 86%. Sensitivity of CT scan is higher, between 96 and 100%. Although sensitivity of an MRI is higher than that of a CT scan, it is not the preferred imaging method. However, it reduces the amount of radiation in cases where clinical follow-up is required [10]. In our patient, the ultrasound revealed a collection of fluid with intense content at the left renal pouch, leading to the pre-diagnosis of pyelonephrosis and an abscess. The CT scan showed an abscess and emphysematous pyelonephritis.

The empirical antibiotic therapy commonly used in the treatment of renal and perinephric abscesses involves fluoroquinolones. Also, aminopenicillins, group 2 and group 3a cephalosporin combinations, or aminoglycosides can be used [2]. It is reported that invasive procedures should be avoided in cases of small or medium-sized abscesses, which measure less than 5 cm in diameter, and in abscesses which regress within four weeks of antibiotic therapy [14]. Invasive treatment should be performed in patients with abscesses larger than 5 cm in diameter, unopened to abdominal cavity, uncomplicated, and not responding to antibiotic treatment. The first-line treatment method in these cases is percutaneous drainage. This process is curative in 60-93% of cases [11]. In the last decade, renal and perinephric abscesses have been treated with percutaneous drainage in 52-84% of cases and open surgical procedures have been performed in only 6% of patients [15]. Factors that can limit percutaneous drainage include multilocular abscesses and abscesses with a diameter larger than 5 cm. The success rate may be reduced due to the need for multiple drainage procedures in the multilocular abscesses. Success rate of percutaneous drainage in abscesses with a diameter ≤5 cm was reported as 92%, while those with a diameter of >5 cm was only 33%. Rate of open surgical procedure was reported as 37% in the latter group [16].

Conclusion

Delay in diagnosis of renal and perinephric abscesses can lead to fatal complications. Laparotomy is a life-saving approach in cases that cannot be treated with percutaneous drainage or when the abscess is large and causes complications such as strictures, fistulas, or secondary peritonitis caused by extension through the Gerota's fascia, as in our case.

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Abscess and bronchobiliary fistula following percutaneous hydatid cyst treatment: A case report

Perkütan kist hidatik tedavisi sonrasi apse ve bronko-bilier fistül: Olgu sunumu

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Abstract

Clinical course and treatment are uncomplicated in majority of hepatic hydatid cyst cases. However, in hydatid cysts involving percutaneous intervention, occult biliary fistulas can drain into the cavity due to a decrease in intracystic pressure, and the cyst can become complicated. Complicated cysts may be treated using non- invasive and minimally invasive methods. The cyst must be closely observed in terms of its size and location and the patient's place of residence. Delayed surgical treatment of hydatid cysts with percutaneous intervention and abscess development leads to high morbidity and mortality. Ultrasonography-guided PAIR (puncture – aspiration– injection – respiration) was performed on a patient with a Gharbi type 1 hydatid cyst, 150x110 mm in size, located in the right hepatic lobe. Since the cyst was contiguous with the bile ducts, a percutaneous catheter was inserted and endoscopic retrograde cholangiopancreatography (ERCP) was performed. We report a case of hydatid cyst involving open surgical drainage following cavity infection and postoperative bronchobiliary fistula and pneumonia at follow-up. Patients developing percutaneous treatment-related cavity infection have worse hospital stays, treatment costs, disease-related morbidity and mortality than those undergoing open surgery. We think that patients developing cavity infection should be closely observed and that the surgical procedure should be performed without delay.

Keywords: Hydatid cyst of the liver, PAIR, Cavity infection, Bronchobiliary fistula

Öz

Hepatik kist vakalarının çoğu komplike olmayan klinik seyir ve tedavi göstermektedir. Perkütan müdahale edilen kistlerde, kist içerisindeki basıncın düşmesi ile gizli olan safra fistülleri kavite içerisine drene olabilir ve kist komplike hale gelebilir. Komplike hale gelmiş olan kistler non invaziv ve minimal invaziv yöntemlerle takip ve tedavi edilebilir. Ancak kistin yerleşim yeri, büyüklüğü ve hastanın yaşadığı yer göz önünde bulundurularak yakından takip edilmesi gerekir. Perkütan müdahale edilen ve apse gelişmiş kist hidatiklerde cerrahi tedavide geç kalmak, yüksek morbidite ve mortalite oranlarına neden olmaktadır. Karaciğer sağ lopta 150x110 mm ebadında Gharbi tip 1 kist hidatik lezyonu olan hastaya ultrasonografi eşliğinde PAIR (puncture – aspiration – injection – respiration) yapılmıştı. Kistin safra yolları ile iştirakli olması üzerine perkütan kateter takılmış ve endoskopik retrograd kolanjiopankreatografi (ERCP) yapılmıştı. Takiplerinde kavite enfeksiyonu gelişmesi üzerine açık cerrahi drenaj yapılan, ameliyattan sonra bronko-bilier füstül ve pnömoni gelişen Kist hidatik olgusu sunulmuştur. Perkütan tedaviye bağlı kavite enfeksiyonu gelişen hastaların, hastanede kalış süresi, tedavi maliyetleri ve hastalığın morbiditesi açık cerrahi yapılan hastalara göre daha kötü sonuçlara yol açmaktadır. Kavite enfeksiyonu gelişen hastaların yakın takip edilmesini ve gecikmeden cerrahi işlem yapılmasının daha uygun olduğunu düşünüyoruz.

Anahtar kelimeler: Karaciğer kist hidatik, PAIR, Kavite enfeksiyonu, Bronkobilier fistül

Introduction

Hydatid cyst is a zoonosis caused by the larvae of Echinococcus granulosus. The disease is endemic in several countries of the world, including Turkey. Approximately 4000 patients are diagnosed with hydatid cyst in Turkey every year, mainly in rural areas [1]. The larvae most commonly cause disease by settling in the liver and lungs. Depending on the size and location of the cyst, the most common finding is nonspecific abdominal pain. Anaphylactic shock may develop as a result of cyst perforation or during surgery [2]. Diagnosis is made by visualizing the cyst using imaging methods such as ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI). Serological tests may sometimes be required to confirm the diagnosis. Surgical and percutaneous treatment (PT), which have been increasingly used in recent years, are widely employed in treatment in suitable cases.

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Gharbi type 1-2 and some type 3 cysts respond well to PT [3,4]. Fine-needle aspiration and sclerosis (puncture – aspiration – injection – respiration [PAIR]) are sufficient in small cysts and those not involving the bile ducts (<5 cm, 5- 10 cm). Percutaneous catheter drainage, Modified Catheterization Techniques (MoCat) or Percutaneous Evacuation (PEVAC) are required in large cysts and those involving the bile ducts (>10 cm) [5,6]. Hilar and large-diameter cysts can lead to cysto-biliary fistulas by exhibiting destructive effects on the bile ducts. Stent insertion, sphincterotomy with percutaneous catheterization and with endoscopic retrograde cholangiopancreatography (ERCP) can be performed in these cases [7]. However, percutaneous catheter use and ERCP can lead to cavity infection and abscess. Cavity infections developing into abscesses may be treated by catheter insertion, but these need to be closely monitored based on the cyst's location, size, and the patient's place of residence. Delayed surgical treatment of hydatid cysts with percutaneous intervention and abscess development leads to high morbidity and mortality among patients.

Case presentation

A percutaneous catheter was inserted in a 46-year-old male patient due to a Gharbi type 1 hydatid cyst of 150x110 mm in size, filling segments 6, 7, and 8 of the right hepatic lobe. The biliary fistula did not decrease in size with percutaneous catheterization, and a stent was inserted in the main bile duct with endoscopic retrograde cholangiopancreatography (ERCP) on day 22 after the procedure. Cavity infection developed at follow-up, and the patient presented to the general surgery clinic with a recommendation of surgery on day 70 after the procedure. A 140x100 mm abscess with air bubbles was present in segments 6, 7, and 8 of the hepatic right lobe at abdominal tomography (Figure 1).

The patient's laboratory values were as follows: WBC: 9.000 µL, Hg: 10.6 g/dl, CRP: 44.8 mg/L, ALP: 331 U/L, GGT: 228 U/L, D.DIL: 0.32 mg/L, T.BIL: 0.9 mg/L, AST: 44 U/L, and ALT: 49 U/L. The patient was explored with a median and right lateral incision. Approximately 1000-1500 cc hemorrhagic purulent necrotic material and infected malodorous fluid was aspirated from the cyst with cystotomy. The cyst cavity was necrotic and hemorrhagic secondary to inflammation. No biliary fistula was observed, and the case was concluded with unroofing and drainage (Figure 2).

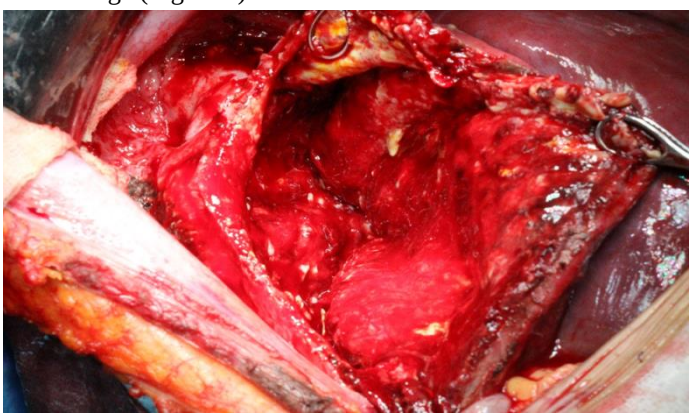

Figure 2: Appearance of the hydatid cyst abscess cavity in hepatic segments 7 and 8

Purulent and necrotic material drainage continued postoperatively. Approximately 100 ml of bile was drained on the 6th postoperative day. Thoracic CT performed on the 10th postoperative day revealed fluid in the right hemithorax, and a chest tube was inserted (Figure 3). About 1000 ml of impure biliary fluid drained from the chest tube. Two days after chest tube insertion, diffuse pneumonic foci developed in this patient with biliary fistula. Sepsis and pneumonia developed, and the patient was intubated. The pulmonary consolidations contracted at follow-up. The biliary drainage from the chest tube persisted for a further 15 days, and the patient was uneventfully discharged on the 60th postoperative day.

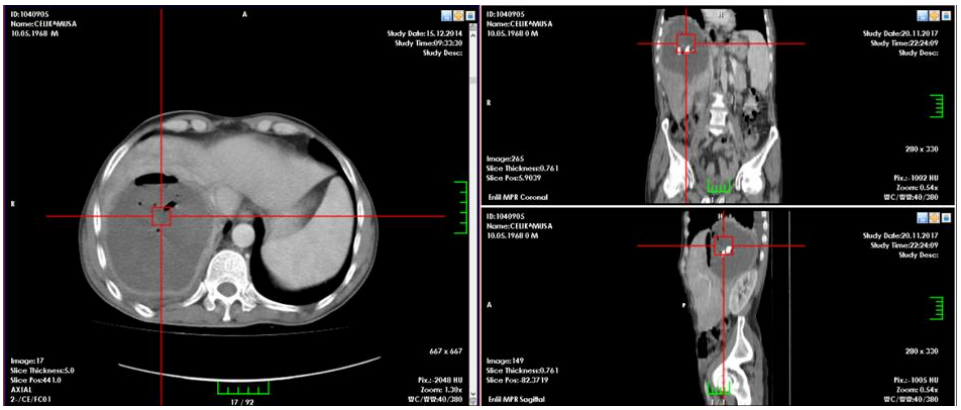

Figure 1: Abscess in the hydatid cyst cavity. The catheter is visualized within the cyst.

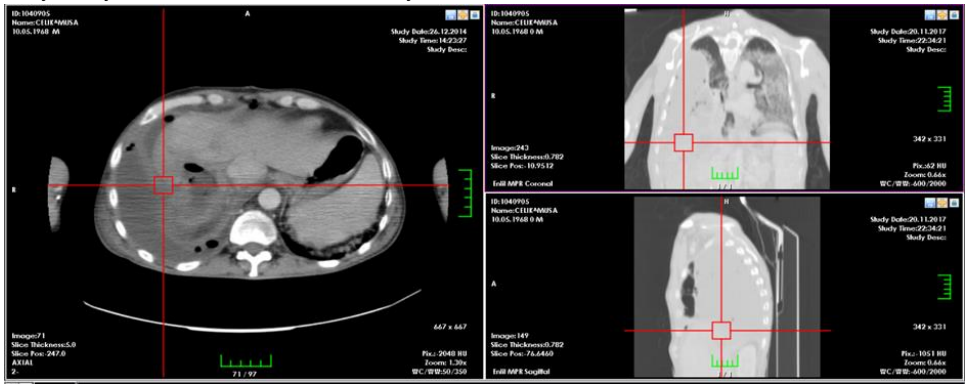

Figure 3: Fluid in the right hemithorax and pneumonia in the left lung at abdominal and thoracic CT scans

Discussion

Gharbi type 1-2 and some type 3 cysts respond well to percutaneous therapy. Percutaneous treatment of hydatid cyst of the liver is performed with PAIR and percutaneous catheter, MoCat, and PEVAC drainage. PAIR can be used if the cyst is smaller than 5-6 cm in diameter and if there is no biliary fistula. Cysts exceeding 5-6 cm, some type 3 and 4 cysts, and those with biliary fistula are treated with a catheter [3-5,8]. Even if drainage ceases in large cysts treated with percutaneous catheterization, the catheter must still be left in place for at least one week, since cystobiliary fistula may develop at follow-up [9]. In that case, papillotomy with ERCP and stent are performed [7]. However, both percutaneous catheter insertion and papillotomy with ERCP and stent placement can lead to the development of refractory inflammation in the cyst cavity. Care must therefore be taken with appropriate patient selection considering the location, diameter and content of the cyst for percutaneous catheter procedures [10].

A percutaneous catheter was inserted in this patient with a 150 x110 mm cyst in segments 6, 7, and 8 of the right hepatic lobe. The cystobiliary fistula persisted at follow-up, and a stent was placed with ERCP on postprocedural day 22. Cavity infection developed, and the patient was operated on day 70 following the percutaneous procedure.

Since the cyst cavity was covered in intensely inflammatory and hemorrhagic necrotic tissue, intraoperative biliary fistula repair was not possible. The cyst wall adhered to the diaphragm due to inflammation. Abscess drainage and unroofing were performed. Biliary fistula developed in the cyst cavity on the 6^{th} postoperative day. Approximately 250-300 ml of biliary drainage was observed daily. Respiratory distress developed on the 10^{th} postoperative day, on which diffuse fluid was determined in the right pleural area at abdominal and thoracic CT. A chest tube, which drained infected bile, was inserted. Manifestations of pneumonia and sepsis developed in this patient at follow-up. The patient was connected to a ventilator, after which pulmonary infection improved. He was uneventfully discharged on the 60^{th} postoperative day.

Conclusion

Percutaneous therapy is successfully performed in hydatid cysts of the liver of selected patients. Percutaneous intervention in hydatid cysts of the liver lowers treatment costs and shortens hospital stay compared to surgical procedures. However, patients developing intracavitary infection associated with percutaneous treatment have longer hospital stays, higher treatment costs and disease morbidity than those undergoing open surgery. Care must therefore be taken over patient selection for percutaneous procedures. Attention must be paid to the size and location of the cyst and the patient's place of residence in subjects developing cavity infection. Patients must be followed-up at frequent intervals. We think that surgical procedures are more appropriate, particularly in patients living in rural areas and who cannot be followed-up on a regular basis.

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