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TIP DALLARINDAKİ GELİŞMELERİN TARİHİ

EDİTÖRLER

HAKAN ERTİN, AHMET SALDUZ
ZEYNEB İREM YÜKSEL SALDUZ

Tıp, saf bilimden ziyade, bilim ile sanatın birleşmesiyle oluşan bir disiplindir. Pozitif bilimlerin çoğu alanını tanımlamayı amaçlarken, tıp bilimsel metod ve prensipleri insanlığın yararına kullanılan bir maharete dönüştürür. Bir başka deyişle, tıp başlı başına bir şifa verme sanatıdır.

Hekimlik mesleğini bütün bu öğeleri ile hakkını vererek yapabilme, yaşadığımız anı idrak edebilme, geçmişte yapılan hataları tekrarlamama ve bir ölçüde ileriyi öngörebilme söz konusu olduğunda tıp tarihine vakıf olmanın önemi inkar edilemez. Mesleğinin teknik yönleri kadar tarihini de öğrenmek için çaba gösterenler başarıya ulaşma yolunda bir adım önde olacaklardır. Herakleitos'un yüzyıllar öncesinden ifade ettiği *'Değişmeyen tek şey değişimin kendisidir'* sözü uyarınca bilginin de dönüşüp değiştiği, zaman içinde evrildiği aşikardır. Bir bilimi oluşturan teoriler, keşifler, yenilikler insanlığın binlerce yılda oluşturduğu bilgi birikiminin ürünüdür. Günümüz tıbbı da geçmişten bu yana basamak basamak çıkılan bir merdiven gibi, gerçeğe ulaşan yoldaki tüm bilgi ve tecrübelerin sentezidir. Yarının bilimine ise bugünden aktardığımız bilgi ve tecrübelerimiz temel olacaktır.

Alanında ehil, değerli bilim insanı hocalarımızın katkılarıyla ortaya çıkan ve tıp dallarının tarihini hekim gözüyle anlatmayı hedefleyen bu kitabın tıbba, hekimliğe ve sağlığa ilgi duyan tüm okurlar için bir kaynak eser olmasını umuyoruz.

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HAYAT SAĞLIK VE SOSYAL HİZMETLER VAKFI

Değerli Yazar ve Okurlarımız,

Bilim, sonsuz bir yolculuktur; bazen kesin doğrulara ulaşırken, bazen de yeni soruların peşine düşeriz. Tıpkı keşfedilmemiş denizlerde rotasını arayan bir gemi gibi, bilim insanları da bilinmeyenin derinliklerine cesaretle yelken açar. Ancak bu yolculuk, yalnızca bilgiye ulaşmaktan ibaret değildir; etik değerler çerçevesinde ilerlemek, bilimi anlamlı ve sürdürülebilir kılan en önemli unsurdur. Bilimin ışığını karanlıkta güvenle taşımak, ancak dürüstlük, şeffaflık ve etik sorumluluk ilkelerine bağlı kalmakla mümkündür.

Anadolu Kliniği Tıp Bilimleri Dergisi olarak, bu bilimsel yolculukta araştırmacılarımızın özverili çalışmalarını, hakemlerimizin titiz değerlendirmelerini ve yayın kurulumuzun disiplinli çabalarını büyük bir takdirle karşılıyoruz. Her bir araştırma, bilimin engin denizine bırakılan bir pusula misali, yön gösterir, ufkumuzu genişletir ve insanlığa değer katar.

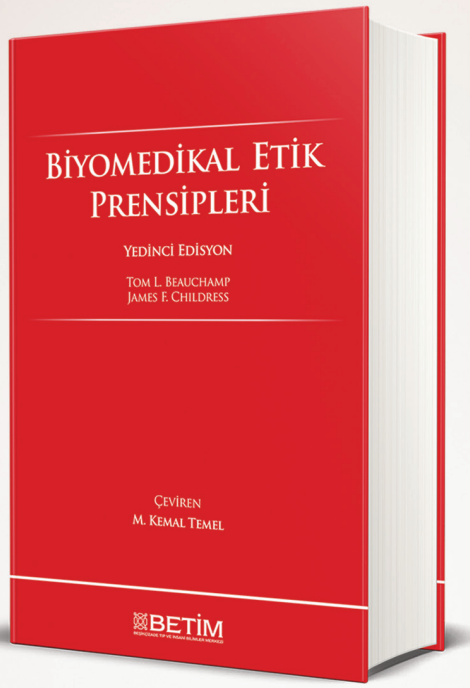
Bu doğrultuda, dergimizde yayımlanan her çalışmanın yalnızca bilimsel katkı sağlamakla kalmayıp, aynı zamanda etik ilkeler doğrultusunda yürütüldüğünü bir kez daha vurgulamak isteriz. Çünkü bilimsel ilerlemenin temeli, etik değerlerle harmanlandığında kalıcı ve güvenilir hale gelir. Açık erişimli yayıncılık anlayışımızla bilgiye erişimi kolaylaştırırken, bilginin doğruluğunu ve güvenilirliğini de en üst seviyede tutmaya devam ediyoruz.

Bilim yolculuğunda etik ilkeleri kendine rehber edinerek özveriyle yayıncılığını sürdüren dergimiz, siz değerli okuyucularımıza 15 araştırma makalesi, 1 olgu sunumu ve 2 derlemeden oluşan yeni sayımızı sunmanın gururunu yaşamaktadır.

Değerli yazarlarımız, hakemlerimiz ve okuyucularımız; bilime olan katkılarınız ve destekleriniz için en içten teşekkürlerimizi sunuyor, bu yolculukta sizlerle birlikte ilerlemekten duyduğumuz mutluluğu paylaşmak istiyoruz. Yeni yılın hepimize sağlık, mutluluk ve huzur getirmesini temenni ediyoruz.

Saygılarımızla,

Doç. Dr. Sedat Akbaş



BİYOMEDİKAL ETİK PRENSİPLERİ

YEDİNCİ EDİSYON

TOM L. BEAUCHAMP - JAMES F. CHILDRESS

ÇEVİREN
M. KEMAL TEMEL

Amerikan filozoflar Tom L. Beauchamp ve James F. Childress tarafından yazılmış olan ve birçok ülkede benimsenen ana akım tıp etiği paradigmasının temelini oluşturan Biyomedikal Etik Prensipleri, Türkiye'de de klinik uygulama ve araştırmalarda, tıp eğitimi, etiği ve hukukunda esas alınan başlıca ilkelerin kaynağıdır. Bu kitap, İngilizce temel eserin yedinci edisyonu ve ilk Türkçe baskısıdır. İstanbul Tıp Fakültesi Tıp Tarihi ve Etik Anabilim Dalı mensubu Uzm. M. Kemal Temel tarafından tercüme edilmiş ve üç yıllık kusursuz bir çalışma sonucunda basılmıştır. Başta tıp ve insani bilimler olmak üzere, Türkiye'de bilimsel gelişim ve üretime adanmış bir kurum olan, Hayat Sağlık ve Sosyal Hizmetler Vakfı bünyesindeki Beşikçizade Tıp ve İnsani Bilimler Merkezi—BETİM, bu tercümeyi Türk akademisyen ve okurların istifadelerine iftiharla sunar.

BETİM KİTAPLIĞI

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The OGG1 Ser326Cys polymorphism and its association with DNA damage and DNA repair in papillary thyroid cancer

OGG1 Ser326Cys polimorfizmi ve papiller tiroid kanserindeki DNA hasarı ve DNA onarımı ile ilişkisi

Abstract

Aim: Hydrogen peroxide locally produced during thyroid hormone synthesis, leads to oxidative stress in the thyroid gland. Defective repair of oxidative DNA lesions contributes to tumor development. This study aimed to understand the importance of DNA damage and repair on thyroid cancer development through the impact of the DNA repair gene OGG1 Ser326Cys polymorphism that has clinical significance in untreated patients with papillary thyroid cancer.

Methods: The study was performed with 70 patients with papillary thyroid cancer and 73 volunteers as control. In lymphocytes, endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair were determined by comet assay. The polymerase chain reaction-restriction fragment length polymorphism method was performed for OGG1 genotyping.

Results: Endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair were higher in patients with thyroid cancer than in the controls (P<0.001). An association was determined between the OGG1 Cys326 allele and increased risk for the development of papillary thyroid cancer. No significant difference was determined between cases carrying different OGG1 genotypes for endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair in the study groups.

Conclusions: Endogenous DNA damage and cell susceptibility to oxidation increase, and DNA repair is impaired in patients with papillary thyroid cancer. However, the OGG1 Ser326Cys polymorphism is not responsible for the DNA repair defect.

Keywords: DNA damage; DNA repair; polymorphism; thyroid neoplasm

Öz

Amaç: Tiroit hormonu sentezi sırasında lokal olarak üretilen hidrojen peroksit, tiroit bezinde oksidatif strese yol açmaktadır. Oksidatif DNA lezyonlarının kusurlu onarımı tümör gelişimine katkıda bulunur. Bu çalışmada, tedavi edilmemiş papiller tiroit kanserli hastalarda, DNA hasarı ve DNA onarımının tiroit kanseri gelişimindeki rolünün, klinik önemi olan DNA onarım geni OGG1 Ser326Cys polimorfizminin üzerinden belirlenmesi amaçlandı.

Yöntem: Çalışma papiller tiroit kanserli 70 hasta ve kontrol grubu olarak 73 gönüllü ile gerçekleştirildi. Lenfositlerde endojen DNA hasarı, H_2O_2 ile indüklenmiş DNA hasarı ve onarım sonrası DNA hasarı Comet yöntemi ile belirlendi. OGG1 genotiplemesi için polimeraz zincir reaksiyonu-kısıtlama fragman uzunluğu polimorfizmi yöntemi uygulandı.

Bulgular: Tiroit kanserli hastalarda endojen DNA hasarı, H_2O_2 ile indüklenmiş DNA hasarı ve onarım sonrası DNA hasarı kontrollere göre daha yüksekti (P<0.001). OGG1 Cys326 aleli ile papiller tiroit kanseri gelişme riskinin artması arasında bir ilişki belirlendi. Çalışma gruplarında farklı OGG1 genotipi taşıyan olgular arasında endojen DNA hasarı, H_2O_2 ile indüklenmiş DNA hasarı ve onarım sonrası DNA hasarı açısından anlamlı bir fark saptanmadı.

Sonuç: Papiller tiroit kanserli hastalarda endojen DNA hasarı ve hücrenin oksidasyona duyarlılığı artmakta, DNA onarımı bozulmaktadır. Ancak OGG1 Ser326Cys polimorfizmi DNA onarım defektinden sorumlu olmadığı gösterilmiştir.

Anahtar Sözcükler: DNA hasarı; DNA onarımı; polimorfizm; tiroid kanseri

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INTRODUCTION

The most prevalent endocrine system cancer is thyroid cancer. Thyroid tumors develop due to point mutations frequently in Rat sarcoma (RAS) or B-Raf Proto-Oncogene, Serine/Threonine Kinase (BRAF) genes, and translocations in RET/PTC or PAX8/PPARγ genes (1, 2). The most important mutagenic factor for thyrocytes is radiation, which causes tumor development through the excessive production of reactive oxygen species (ROS). The thyroid gland produces large amounts of hydrogen peroxide (H_2O_2) to oxidize iodide for thyroid hormone biosynthesis. This creates a potentially mutagenic environment through ROS production (3, 4). By attacking DNA, ROS causes oxidative DNA damage. Base oxidation and DNA strand breaks occur due to oxidative DNA damage. The most common and harmful oxidative DNA damage is 8-hydroxydeoxyguanosine (8-OHdG). Oxidized guanine can lead to GC-TA transversion mutation (5).

DNA repair plays a pivotal role in the maintenance of genetic integrity. Defective DNA repair is a contributory factor in carcinogenesis. A low DNA repair potential is attributed to an increased risk for many cancers, including thyroid cancer (6,7). There are individual differences in cancer risk. These differences may arise from single nucleotide polymorphisms in DNA repair genes. 8-OHdG is repaired by the base excision repair system. 8-oxo-deoxyguanosine DNA glycosylase 1 (OGG1) excises 8-OHdG adducts. 8-OHdG appears in the bloodstream and is excreted in the urine (8). The Ser326Cys; rs1052133, is the most common OGG1 gene polymorphism. The polymorphic OGG1-Cys326 protein has lower enzymatic activity than the common OGG1-Ser326 protein (9). This means that more mutations may accumulate due to oxidative stress in individuals homozygous for OGG1-Cys326.

There is no study investigating the association between Ser326Cys polymorphism and OGG1 DNA damage in patients with papillary thyroid cancer. In the present study; firstly, the determination of endogenous DNA damage, susceptibility to *in vitro* oxidation by H_2O_2, and repair level after H_2O_2 treatment in patients with papillary thyroid cancer. Secondly, the influence of OGG1 Ser326Cys polymorphism on all these parameters was evaluated.

MATERIAL AND METHODS

This study was approved by Istanbul University Cerrahpasa Medical Faculty Ethics Committee (date: 02.04.2013, decision no:A-33). All individuals signed informed consent.

70 patients with papillary thyroid cancer were recruited from the Department of General Surgery, Cerrahpasa Medical Faculty Hospital. The number of samples was approximately determined with G*Power 3.1.9.7 software. Using a T-test with α error = 0.05 and a power of 1-β = 0.95, we determined that the required sample size for each study group was 71 individuals, and the total sample size was 142. Based on this calculation, we formed a control group of 73 healthy volunteers who matched our exclusion criteria and a patient group of 70 volunteers who were diagnosed with papillary thyroid cancer for the first time. All patients were newly diagnosed, and none of them had undergone anti-cancer therapy previously. The diagnosis of thyroid cancer was based on ultrasound and fine-needle aspiration and confirmed by the pathology reports after resection of the tumors. The control group was composed of 73 patients who were age and gender-matched, had no history of cancer, and had no family history of any cancer. Patient and control features are presented in Table 1. Subjects with acute or chronic inflammatory diseases, infectious diseases, liver and kidney dysfunction were excluded from the study. None of the study cases were smokers and were taking antioxidant supplements.

Lymphocyte isolation

Blood samples were taken into heparinized tubes by venipuncture before the surgical operation. Lymphocyte isolation was performed immediately. For isolation, gradient density centrifugation was performed using histopaque 1077 (Sigma-Aldrich 10771, Germany). The collected lymphocytes were washed with phosphate-buffered saline solution and then suspended in Roswell Park Memorial Institute medium (RPMI 1640) (Sigma-Aldrich 10771, Germany) containing 10% dimethyl sulfoxide (DMSO) (Sigma-Aldrich 10771, Germany) and 60% fetal bovine serum (FBS) (Sigma-Aldrich 10771, Germany). The trypan blue exclusion assay evaluated cell viability (10).

Endogenous DNA damage

Endogenous DNA damage in lymphocytes was evaluated for strand breaks by applying the comet assay as described previously (11). In brief, the cells mixed with low-melting-point agarose were placed on the agarose gel layer on a microscope slide. The lysis was performed with non-ionic detergent and hypertonic lysis solution. After washing steps, the microscope slide was treated with a high alkaline solution (pH > 11) to unwind supercoiled loops.

Strand breaks appear alkali labile sites. Subsequently, electrophoresis was carried out. The breaks migrated towards the anode, giving a comet-tail appearance, whereas undamaged DNA remained within the comet head. Comet images were visualized using the fluorescent staining method. After staining with ethidium bromide, comet images were detected with a camera-equipped fluorescence microscope (Olympus BX51T-32H01). Tail moments were measured with the image analysis software package (Metasystems, Germany). Two slides were studied for each case. A single observer blinded to the subject's diagnosis scrutinized 50 randomly selected cells on each slide (100 cells in total). The tail moment, which is the product of the tail length and the percentage of total DNA in the tail, was used to express the DNA damage.

H_2O_2-induced DNA damage and DNA damage after repair

As is customary in the comet assay, cells were implanted in an agarose layer on two distinct microscope slides to assess H_2O_2-induced DNA damage and DNA damage after repair. The slides were incubated on ice with 50 mM H_2O_2 in phosphate-buffered saline solution for 40 min. The slides were washed to remove H_2O_2 and then put into lysis solution. After washing one of the slides were treated with OGG1 enzyme a damage-specific repair endonuclease for 1 hour at 37°C, whereas latter was not threated. This enzyme generates additional breaks at sites containing 8-OHdG. After the enzyme treatment the slides were washed, electrophoresis was applied as previously mentioned.

Every slide was produced twice for every case. For every slide, the mean values of the tail moment of the cells were computed for every research group.

Genotyping of OGG1 codon 326

A Nucleo-Spin DNA purification kit (Macherey–Nagel GmbH, Duren, Germany) was used to extract genomic DNA from lymphocytes. The OGG1 Ser326Cys polymorphism was determined by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method, as previously described (12). The sequences of the primers were HOGG1F:5'-GGAAGGTGCTTGGGGAAT-3' and HOGG1R:5'-ACTGTCACTAGTCTCACCAG-3'. The amplification process involved a 5-minute denaturation at 95°C, followed by 30 cycles of 95°C for 30 seconds, 58°C for 30 seconds, and 72°C for 1 minute each. After the reaction, a 7-minute incubation step at 72 °C was added. The PCR product is 200 bp long and digested with SatI at 37 °C for 16 hours, yielding a single 200-bp band for the homozygous Ser/Ser hOGG1 variant, a single 100-bp band for the homozygous Cys/Cys hOGG1 variant, and double bands of 200 and 100 bp for the heterozygous Ser/Cys hOGG1 variant. The fragments were separated using a 3% high-resolution metaphor agarose gel. Figure (Figure 1) illustrates the gel showing the genotypes of OGG1 Ser326Cys. Finally, the PCR-RFLP results were validated using the real-time PCR method.

Statistical analysis

IBM Statistical Package for the Social Sciences package program version 22.0 (SPSS Inc., Chicago, IL, USA) for Windows was used for statistical analysis. Because the data were not normally distributed, variables were reported as median (min-max). The measured parameters in the thyroid cancer and control groups were compared with the Mann-Whitney U test. The differences between endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair in each group were compared with the Kruskal-Wallis test. Then, binary data were compared with the Mann-Whitney U test. The Pearson Chi-Square or Fisher's exact tests (two-sided) were used to determine the relationship between genotypes and alleles in the control and thyroid cancer groups and the deviation of genotype distribution from the Hardy–Weinberg equation. The combined odds ratio (OR) with a 95% confidence interval (95% CI) was calculated to assess the asso-

ciation between the thyroid cancer risk and the Ser-326Cys genotype of the OGG1 gene. Spearman correlation coefficient was used to examine correlations between the variables. The P value less than 0.05 was considered statistically significant.

RESULTS

As shown in Table 2, endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair in peripheral lymphocytes of patients with thyroid cancer were found to be higher than those in the controls ($p<0.001$). The representative images of patients from the comet assay with their corresponding controls are shown in Figure 2. The Hardy-Weinberg equilibrium was observed in the dispersion of OGG1 Ser326Cys genotypes between thyroid cancer patients and controls ($p>0.05$). Significant differences existed between patients with thyroid cancer and control cases for the genotype distribution and allele frequencies. The distribution of OGG1 Ser326Cys genotypes in the thyroid cancer and control groups is given in the Table 3. OGG1-Cys326 allele and genotypes carrying this allele (Ser326Cys+Cys326Cys) were found to be associated with an increased risk for the development of papillary thyroid cancer. Neither in the patients with thyroid cancer nor the control group, a significant difference was determined between the OGG1 Ser326Cys genotypes for endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair (Table 4).

No significant correlation exists between thyroids hormones (T3, T4, TSH) and endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair.

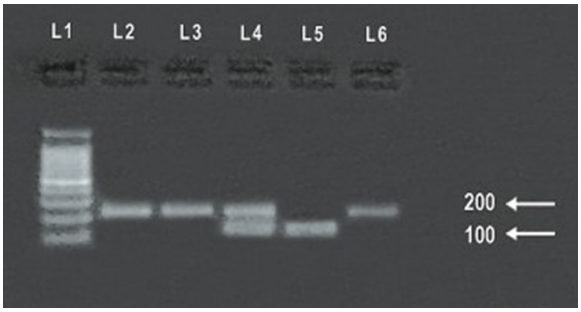

Figure 1. An illustration of the OGG1 Ser326Cys genotypes on the gel. For the 326Cys variation, the 200-bp PCR product is broken down into two 100-bp fragments by Fnu4HI, while the 326Ser allele remains undigested. Lane 1, 100-bp ladder size marker; Lane 2 and Lane 3, a Ser/Ser homozygote; Lane 4, a Ser/Cys heterozygote; Lane 5, a Cys/Cys homozygote; Lane 6, undigested products of PCR.

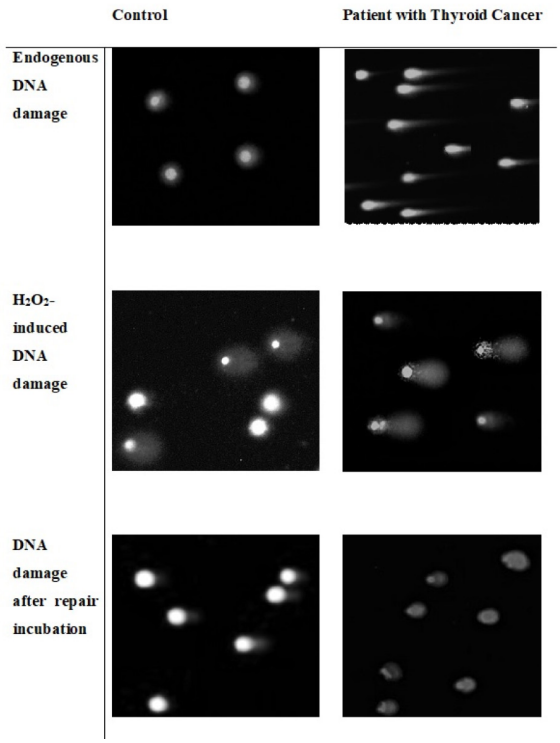

Figure 2. Representative comet assay images show endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair in the control and patients with thyroid cancer.

DISCUSSION

The thyroid gland may be exposed to more oxidative stress than other tissues. Because a high level of H_2O_2 is produced in the thyroid gland to act as a co-substrate in hormone biosynthesis. H_2O_2 is produced in the thyroid by one or two NADPH oxidases at the apical membrane of thyrocytes to oxidize iodide and then incorporate it into the thyroglobulin (3,13). On the other hand, H_2O_2 acts as an oxidant and induces the formation of ROS that constitute a potentially mutagenic environment in thyrocytes, leading to cancer development (4,14). Therefore, an efficient DNA repair is essential to prevent oxidative damage-induced mutagenesis in the thyroid gland. Unfortunately, compared to other tissues, thyroid tissue detected an 8-10-fold higher spontaneous mutation rate (15). This brings to mind defective DNA repair in thyrocytes. Masha et al.

Table 1. Demographic and clinical data of the study groups.

		Thyroid Cancer Group (n:70)	Control Group (n:73)	p
Age (year)		49 (24-79)	54 (20-69)	0.060
Gender	Men	15	23	
	Women	55	50	
T3 (pg/mL)		3.22 (0.26-4.25)[a]	1.20 (0.86-3.17)	0.000
T4 (ng/dL)		1.21 (0.05-2.54)	1.23 (0.98-1.60)	0,540
TSH (µU/ml)		1.84 (0.01-100.00)	2.13 (0.50-10.46)	0.096

[a] versus control group

T3: Triiodothyronine, T4: Tetraiodothyronine, TSH: Thyroid stimulating hormone, n: Number

Table 2. Endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair in the study groups.

	Thyroid Cancer Group (n:70)	Control Group (n:73)	p
Endogenous DNA damage (Tail Moment)	0.81 (0.36-1.63)[a]	0.32 (0.19-2.12)	0.000
H_2O_2-induced DNA damage (Tail Moment)	2.36 (0.91-5.70)[b]	1.81 (1.46-4.19)	0.003
DNA damage after repair (Tail Moment)	1.03 (0.43-1.83)[a]	0.52 (0.29-0.76)	0.000

[a] versus control group, [b] versus control group, n: Number

Table 3. Distribution of allele and genotype frequency of OGG1 Ser326Cys polymorphism in the study groups.

	Thyroid Cancer Group n (%)	Control Group (n%)	OR(95% CI)	p
OGG1-326				
Ser/Ser	30(43%)	44(60%)	Reference	
Ser/Cys +Cys/Cys	40(57%)	29(40%)	2.02(1.04-3.94)	0.037
Ser allele frequency	0.43	0.60	Ref	
Cys allele frequency	0.57	0.40	1.99(1.13-3.49)	0.016

Ser: Serine, Cys: Cysteine, OGG1: 8-oxo-deoxyguanosine DNA glycosylase 1, OR: odds ratio, n: Number

Table 4. Endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair according OGG1 Ser326cys genotypes.

	Endogenous DNA damage	H_2O_2-induced DNA damage	DNA damage after repair
Control Group			
Ser/Ser (n=44)	0.31 (0.19-0.40)	1.79 (1.49-4.19)	0.46 (0.21-0.76)
Ser/Cys+Cys/Cys (n=29)	0.32 (0.19-0.39)	1.82 (1.66-2.08)	0.49 (0.29-0.74)
p*	0.760	0.800	0.960
Thyroid Cancer Group			
Ser/Ser (n=30)	0.72 (0.40-1.56)	2.09 (1.26-4.36)	1.01 (0.55-1.83)
Ser/Cys+ Cys/Cys (n=40)	0.83 (0.360-1.630)	2.50 (0.91-5.70)	1.04 (0.43-1.53)
p*	0.630	0.250	0.640

* p values in each set refer to comparisons between cases with Ser/Ser and Ser/Cys+ Cys/Cys genotypes. Ser: Serine, Cys: Cysteine

(7) reported mismatch repair deficiency in papillary thyroid tumors. Karger et al. (16) determined downregulated DNA repair genes (OGG1, Mut Y homolog (MUTYH), and endonuclease III) and increased 8-OxoG in the nucleus of follicular thyroid carcinoma, compared with follicular adenoma. They suggested that oxidative stress and consequent transcriptional dysregulation in thyrocytes cause mismatch repair deficiency and potentiate papillary thyroid tumorigenesis. Similarly, we discovered in the current study that thyroid cancer patients had reduced *in vitro* repair of DNA damage caused by H_2O_2 treatment in peripheral lymphocytes compared to controls.

DNA repair deficiency may be derived from single nucleotide polymorphisms in DNA repair genes. The OGG1 Ser326Cys polymorphism was reported to modulate repair activity. Aka et al. (17) demonstrated that after challenging with 2 Gy of γ-rays, DNA strand break capacity is slower in peripheral blood lymphocytes of individuals with Ser/Cys or Cys/Cys OGG1 genotypes compared to those with the Ser/Ser OGG1 genotype. These findings agree with other studies. A higher level of DNA strand breaks was detected in the lymphocytes of agricultural workers exposed to pesticides (18) and male workers exposed to cobalt (19) in the presence of the OGG1 326Cys allele. The OGG1 Ser326Cys polymorphism has been widely evaluated in various case-control studies on cancer. Most studies examined the association between OGG1 Ser326Cys polymorphism increases/decreases cancer risk. OGG1 Cys326 allele was found to be associated with an increased risk of nasopharyngeal, esophageal, lung, stomach, prostate, and cervical cancers (20-25). As far as we know, only two groups investigated a potential association between OGG1 Ser326Cys polymorphism and thyroid cancer risk (26,27), and their results did not reveal a significant association. However, their findings were not evidenced by functional studies. None of the previous studies investigated the impact of OGG1 Ser326Cys polymorphism on DNA damage level or DNA repair activity in patients with thyroid cancer. Only García-Quispes et al. (28) examined a functional relationship between OGG1 Ser326Cys polymorphism. They looked into how various DNA repair gene polymorphisms (OGG1, XRCC1, XRCC2, and XRCC3) affected the frequency of micronuclei (MN) in the lymphocytes of a sample of thyroid cancer patients, both spontaneously and through stimulation. They stated that only OGG1 Ser326Cys polymorphism is able to affect MN frequency. It should be noted that this impact was seen only at the spontaneous MN frequency and not at the MN frequency caused by treating lymphocytes with 0.5 Gy of γ-radiation. In our study, although the OGG1 Cys326 allele was found to be associated with an increased risk for the development of papillary thyroid cancer, no significant impact of the OGG1 Cys326 allele were observed on endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair. The lack of influence of the OGG1 Cys326 allele on DNA damage and repair can be attributed to extensive functional interactions between DNA repair proteins and overlapping specificity within the same repair pathway (29,30). The existing DNA damage may be repaired by an enzyme other than OGG1, and this repair may be deficient, so we observed high DNA damage. Alternatively, DNA repair capacity may be exceeded due to intensive damage. As a limitation of this study, we mainly focused on a DNA repair deficiency, so the requirement of measurement of antioxidant activity in the study groups escaped from our notice. Besides, the small number of study cases is another limitation of this study.

CONCLUSION

In the present study, we demonstrated for the first time that repair of DNA strand breaks is impaired in patients with papillary thyroid cancer, as evidenced by high endogenous DNA damage and high DNA damage after *in vitro* repair. The increased H_2O_2-induced DNA damage in the patients is also a novel finding and reflects an increased susceptibility to oxidation. Increased cell susceptibility to oxidation may occur due to defective antioxidant defense. Finally, this was a functional study to explain the possible role of DNA repair in the development of papillary thyroid cancer. We concluded that oxidative DNA damage and DNA repair deficiency may be critical events in thyroid tumorigenesis, but DNA repair gene OGG1 Ser326Cys polymorphism does not influence this pathogenic event.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. This study was supported and funded by the Istanbul University Scientific Research Projects Unit. (Project No: 31271).

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Opinions and considerations of obstetrics and gynecology specialists on cesarean section: A qualitative study in Sakarya province

Kadın hastalıkları ve doğum uzmanlarının sezaryen doğum yöntemi ile ilgili görüş ve düşünceleri: Nitel bir çalışma, Sakarya ili örneği

Abstract

Aim: While the ideal cesarean section rate should be 10-15% among all births, the cesarean section rate is increasing at an uncontrollable rate both in the world and in Turkey. In this study, we aimed to determine the reasons and solution suggestions for cesarean section rates in Turkey, based on the opinions of Gynecologists and Obstetricians.

Methods: Qualitative research method and phenomenological approach were used as the research design in this study. Participants were selected by convenience sampling method among Gynecology and Obstetrics specialists who resided in Sakarya/Turkey, worked as a
interviews between 01.02.2020 and 01.09.2020 and thematic content analysis was performed.

Results: As a result of in-depth interviews, 51 categories, 12 sub-themes from the categories and three themes from the sub-themes were created from the coded data. The three themes that emerged were: Causes of high cesarean rate, solutions for the increase in cesarean delivery rate, possible outcomes of cesarean delivery.

Conclusions: Since the factors affecting the cesarean section rate are multifaceted and interrelated, this versatility and correlation should be taken into account when taking measures to reduce the rates. We need to focus especially on cesarean births performed without medical indication, which has a large share in the increase in cesarean section rates.

Keywords: Attitude; cesarean section; obstetricians; qualitative research.

Öz

Amaç: İdeal sezaryen oranının tüm doğumlar arasında %10-15 olması gerekirken, sezaryen oranı hem dünyada hem de Türkiye'de kontrol edilemeyecek bir hızla artmaktadır. Bu çalışmada Kadın Hastalıkları ve Doğum hekimlerinin görüşlerinden yola çıkarak Türkiye'deki sezaryen doğum oranlarının nedenlerini ve çözüm önerilerini belirlemeyi amaçladık.

Yöntemler: Bu çalışmada araştırma deseni olarak nitel araştırma yöntemi ve fenomenolojik yaklaşım kullanılmıştır. Katılımcılar, Sakarya/Türkiye'de ikamet eden, en az 3 yıl uzman olarak çalışmış ve halen çalışmakta olan Kadın Hastalıkları ve Doğum uzmanları arasından kolay ulaşılabilir örnekleme yöntemi ile seçilmiştir. Veriler derinlemesine görüşmeler yoluyla sonra 01.02.2020 ile 01.09.2020 tarihleri arasında toplanmış ve tematik içerik analizi yapılmıştır.

Bulgular: Derinlemesine görüşmeler sonucunda kodlanan verilerden 51 kategori, kategorilerden 12 alt tema ve alt temalardan üç tema oluşturulmuştur. Ortaya çıkan üç tema: Yüksek sezaryen oranının nedenleri, sezaryen doğum oranının artmasına yönelik çözümler, sezaryen doğumun olası sonuçlarıydı.

Sonuçlar: Sezaryen oranını etkileyen faktörler çok yönlü ve birbiriyle bağıntılı olduğu için oranları düşürmeye yönelik önlem alınırken bu çok yönlülük ve bağıntı dikkate alınmalıdır. Özellikle sezaryen oranlarının artmasında büyük payı olan tıbbi endikasyon olmadan gerçekleştirilen sezaryen doğumlara ağırlık vermemiz gerekiyor.

Anahtar Sözcükler: Kadın hastalıkları ve doğum uzmanları; nitel araştırma; sezaryen; tutum.

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INTRODUCTION

Although Cesarean section is a procedure performed to save the fetus alive from a dying pregnant woman and has a high mortality rate, it has become a safer birth method since the 19th century as a result of advances in asepsis, anesthesia, surgical techniques and blood transfusion (1,2). The increase in the safety of cesarean section over the years has led to an alarming increase in cesarean section operations, especially in middle and high-income countries, in the absence of medical indication, without providing additional benefit to the mother and newborn (3,4).

As in many countries of the world, the cesarean section rate in Turkey has been increasing significantly over the years. According to the 2021 cesarean section rates published within the scope of the Organization for Economic and Development Cooperation Health Policy Studies, Turkey ranked first with 54.9 percent, while the countries closest to Turkey were Korea (45.0%) and Poland (38.9%) (5).

High cesarean section rates constitute an important public health problem due to maternal and perinatal complications, as well as long-term complications and increased costs (6). Cesarean section has many short-term maternal complications such as thromboembolism, postpartum hemorrhage, wound hematoma, and long-term complications such as intra-abdominal adhesions, ectopic pregnancy that may occur in subsequent pregnancies, placenta placement anomalies, etc (7). In addition, studies have shown that the risk of respiratory morbidity, including transient tachypnea of the newborn, respiratory distress syndrome, persistent pulmonary hypertension, increases in the short term, and the risk of obesity and asthma increases in the long term, especially in cesarean deliveries performed before the onset of labor (especially before 39-40 weeks) (8, 9,10). The high cesarean section rate not only creates negative health risk factors, but also imposes an extra financial burden on both the state economy and the family economy due to its higher cost compared to vaginal birth, especially in low- and middle-income countries (11). The cost of medication was found to be 4.4 times higher, the cost of testing 2.1 times, and the cost of medical supplies and disposable materials 2.8 times higher in cesarean births (12). Additionally, this financial burden resulting from the high rate of cesarean births acts as a barrier to needed health care and leads to health disparities, especially in low- and middle-income countries where medical care is purchased out-of-pocket (11). The increase in cesarean delivery rates causes similar problems in our country.

There are many studies in the literature on the factors affecting the high cesarean section rate. Mothers' concerns that their babies may be harmed during childbirth, the idea of not being able to control childbirth, the fear of episiotomy, cesarean section requests due to the idea that it may damage the perineum and sex life, and physicians' medicolegal concerns are the main factors that increase cesarean section rates (13-15).

In this study, considering that cesarean birth rates are increasing every year in Turkey and around the world, we aimed to determine the reasons for the rapidly increasing cesarean birth rates and possible solutions in line with the opinions of gynecologists.

MATERIAL AND METHODS

Statistical analyses / Research design

Phenomenological research design, one of the qualitative research methods, was used in the research. In this study, 'increased frequency of cesarean section' is considered as a phenomenon, and it is aimed to reach an explanation about this phenomenon through the experiences of Gynecologists and Obstetricians in similar professions.

Ethical approval

Ethical approval for this research was given by the ethics committee of the Sakarya University Faculty of Medicine (Date: 27.01.2020, decision no: 71522473). After explaining the topic and purpose of the research, the participants signed a voluntary consent form stating that any personal information they provided and their names would be kept confidential.

Population and sample

The study was carried out in Sakarya, one of Turkey's 30 metropolitan municipalities. In the selection of the study group, the Gynecology and Obstetrics specialists who received specialization education (at least for four years) in the branch of Obstetrics and Gy-

necology (OBGYN) and worked as a specialist physician for at least three years and are still working in a private hospital, state hospital or university hospital were preferred by using convenience sampling. Physicians who had been working for less than three years or were retired were excluded from the study. Since we wanted to interview physicians who were thought to have reached a certain understanding of medicine, we aimed to interview physicians who had at least 4 years of professional experience. Since the cesarean section rates started to increase over the years, interviews were planned with actively working physicians instead of retired physicians, whose opinions on this issue were thought to be more effective. In order to provide diversity with different experiences, people with different starting years and working in different institutions were included in the study (16).

Data collection tools

A semi-structured interview form was used to ask additional questions to the participants and to deeply examine the reasons underlying their answers. The first part includes six questions regarding sociodemographic characteristics, and the second part includes semi-structured questions prepared after literature review. The interview form was revised before application in line with the opinions of five specialist physicians with similar characteristics who were not included in the study group. Then, the interview form was given its final form.

After the subject and purpose of the research were explained to the participants, they were asked to sign a voluntary consent form stating that their personal information and names would be kept confidential. Appropriate day and time for the interview was determined by making an appointment with the participants. In-depth interviews were held with all participants between 01 February 2020 and 01 September 2020, mostly outside working hours and in their own offices. Permission was obtained from the participants for audio recording during the interview. Note-taking method was used in the interviews with six participants who did not allow audio recording. In order to keep the participants' names confidential, each participant was given a number. The study was completed with the participation of 17 experts.

The voice recordings taken during the interviews with the participants were transcribed one by one by the researcher using Microsoft Word Program, and the outputs were checked by the second researcher by listening to the recordings again. In the analysis of the data obtained from the in-depth interviews, the descriptive analysis technique with interesting quotes from the participants and the quotations that best summarize the subject or show the contradictory situations, and the thematic content analysis method of Braun and Clarke consisting of six steps were used (17). In this context, first of all, the data was extracted by reading the data repeatedly. It was then independently hand-coded by two researchers to increase its validity and reliability. Consistency between coders was calculated by including all codes in the coding lists in the denominator and common codes in the numerator, and the consistency was found to be 89%. After the common code lists were prepared, two researchers divided the codes into categories and divided the categories into subthemes and themes.

RESULTS

Participants and analysis

Of the 17 participants, 12 (70.6%) were male and 5 (29.4%) were female. The mean age of the participants was 59.64±6.7 (minimum 42 and maximum 68 years old). Eight (47.1%) of the participants stated that their income was good, and 9 (52.9%) stated that their income was moderate. The median value of working time as a specialist physician was 25 years, with a minimum of 9 and a maximum of 39 years (Table 1).

Participant interviews lasted a minimum of 20.5 minutes and a maximum of 59.0 minutes, and the mean duration was calculated as 37.0±2.8. Eight of the participants were working in their private offices, 5 in a private hospital, 1 in a university hospital, 1 in a medical center, 1 was working in a public hospital, and 1 was working in both a private office and a private hospital.

As a result of in-depth interviews, 51 categories, 12 sub-themes from the categories and three themes from the sub-themes were created from the coded data. Themes and subthemes are shown in Table 2.

Table 1. Characteristics of participants

	Participants (n = 17)
Age (years), mean±SD	59.64±6.7
Working time (years), min-median-max	9-25-39
Female, n (%)	5 (29.4)
Male, n (%)	12 (70.6)

n: number, SD: Standard Deviation , Min: Minimum, Max: maximum

Table 2. Themes and sub-themes of the study

Causes of high cesarean section rate	Solutions for the increase in cesarean birth rate	Possible consequences of cesarean delivery
Health system and health policies	Regulations in the midwifery system	On maternal health
Legal system	Updates to the judicial system	On baby health
Factors associated with the physician	Regulations in the health system	Other negatives
Patient-related factors	Support to physicians	
	Political solutions	

Theme 1 – Causes of high cesarean section rate

Sub theme 1 – Health system and health policies

Under this sub-theme, the participants expressed the contribution of the delivery room environments where the negative conditions in which pregnant women had to give birth by cesarean section were as follows: "People do not dare to give birth vaginally in the maternity hospital environment that looks like a tunnel of fear. What's happening; Let's go to the delivery room on an empty stomach at eight in the morning, go to the operating room an hour later, take our baby at 09.30, there is nothing left to do. Everyone is happy, there is no yelling in this conditions" (participant 8). Most of the participants expressed the inexperience of the new generation midwives and the difficulties they experienced while working with inexperienced midwives: "Since most new midwives are inadequate, when I hospitalize a patient who comes to give birth, I follow the patient myself. After the cervix is dilated five cm, I start standing next to the patient. The patient is lying in a room, and I am waiting for her to give birth in the next room" (participant 7). One participant pointed out the inadequacy of medical specialty training and stated that the new generation of physicians are hesitant about interventional deliveries: "I started specialization towards the end of 1992. We used a vacuum device in almost one in 10 births. Now our assistants graduate without using a vacuum device" (participant 8). Participants stated that they did not receive support from any institution or ministry in case of complications and that physicians were ignored: "Doctors are afraid to have a vaginal birth. Nobody gives medals to anyone just because they had a vaginal birth. But when you have problems with vaginal birth, you deal with a lot of things, but no one is there for you" (participant 12).

Sub theme 2 – Legal system

Participants stated that astronomical compensation cases are a nightmare for physicians and that this situation is abused by patients and their lawyers: "It is absurd to demand one million TL compensation from a patient for whom we earned five Turkish Liras (TL). There is nothing like this anywhere in the world. Salaries are Nigeria, compensations are America" (participant 15). "This situation is used for enrichment purposes, this is wrong" (participant 4). While the majority of the participants stated that they had medical-legal problems throughout their careers, some participants stated that they still had ongoing cases and could not receive support from the state in this process: "Three lawsuits have been filed, the fourth is currently ongoing. I had to hire a lawyer. "I did not receive financial support from any institution or ministry" (participant 3).

Sub theme 3 – Factors associated with the physician

Under this subtheme, one participant stated that physicians prefer cesarean section to spare more time for themselves: "It is easy for the doctor to adjust the

timing of a cesarean section. He leaves the operating room after 20-25 minutes. The doctor wants to make his plan" (participant 9) Participants stated that cesarean section saves doctors time, doctors are impatient, and too many interventions are made to shorten the birth process in vaginal birth: "As physicians, we are a bit impatient. It would be better if we didn't go into the delivery room. When we enter the delivery room, we perform a cesarean section once or twice and leave ☺ . If we do not enter, there may be more vaginal births" (participant 17).

Sub theme 4 – Patient-related factors

Participants stated that patients and their relatives put pressure on doctors to have a cesarean section and that they wanted guarantees to avoid any problems: "I talk to patients. Patients want to avoid problems. I'm talking about normal birth. The patient wants zero complications. This of course affects me. It's best not to do the job at all. "It's hard to say everything is okay." (participant 7). Participants expressed that they were afraid of being threatened and exposed to violence by patients and their relatives: "There is a risk of being beaten by the patient's relatives, there is a risk of being killed. They threaten to kill us if the baby dies. They say these words openly, without hesitation, without waiting for the court or anything like that ☺." (participant 7).

Theme 2 – Solutions for the ıncrease in cesarean birth rate

Sub theme 1 – Regulations in the midwifery system

Under this theme, participants emphasized the need for active, experienced, advanced, qualified midwives: "Midwives must have worked in the delivery room under the supervision of a gynecologist for at least four years (participant 4). Additionally, participants stated that midwives should be financially supported and receive the wages they deserve to encourage them to have vaginal births: "There should be a 25-30 percent difference between midwife salary and nurse salary. If we want midwives to give birth, we need to pay premiums per birth" (participant 7).

Sub theme 2 – Updates to the judicial system

The participants stated that compensation fees should be calculated in reasonable amounts taking into account their salaries and that interest should not be applied to the compensation fee over the years: "If there is abuse, of course there should be compensation. However, it should not be in a way that impoverishes those who pay and enriches those who earn." (participant 3). The participants stated that making a distinction between complications and malpractice in the laws will save physicians from a great pressure: "I think one of the most important reasons why physicians prefer cesarean section is the fear of malpractice. I think that if this burden on physicians is reduced by passing an appropriate malpractice law, cesarean section rates will be reached very easily to 30-35%" (participant 2).

Sub theme 3 – Regulations in the health system

The participants pointed out that it is important to educate pregnant women and their relatives: "It should start with the education of the people. Because they are very crowded. The public should be informed first, then the midwife should be included in the circle. After that, the physician must have received a good education. So it's like a pyramid. The lower part of the pyramid is the people, that is, the candidates for becoming mothers" (participant 6). Some participants mentioned the option of painless childbirth as a way to reduce their fear of childbirth: "I think most women would prefer a vaginal birth instead of a cesarean section if they could give birth painlessly. If the painless delivery option is offered to all women for free, I think we can reduce the cesarean section rate to 30-35% in Turkey" (participant 2).

Sub theme 4 – Support to physicians

Participants disagreed about increasing the costs of vaginal delivery in order to encourage doctors to perform a vaginal birth. A group of participants stated that the wage gap may encourage doctors to have a vaginal birth, while a group of participants stated that the problem is not wages, and an increase in fees will not solve the problems: "One of the ways to encourage vaginal birth in the capitalist system is to pay high fees

to doctors for vaginal birth, and this must be done" (Participant 10). "After all, I don't think any doctor would consider this from an economic point of view. So it is ethically wrong to compare money with this business. I don't think any doctor would think that. I even take it as an insult" (participant 5). Participants stated that the primary responsibility for births should be taken from doctors, they only want to intervene in complicated cases, and teamwork is advantageous: "As a doctor, I should enter into give birth if it is a complicated birth that the midwife cannot deliver, or if the patient insists on his own doctor entering into the birth"(participant 4).

Sub theme 5 – Political solutions

Participants stated that innovations should be made in health policies and that politicians have important responsibilities in this regard: "Policymakers should take the first step and stop pressuring OBGYN specialists" (participant 2).

Theme 3 – Possible consequences of cesarean delivery

Sub theme 1 – On maternal health

Participants stated that cesarean section protects the Genitourinary System more, it is a more comfortable delivery option because they do not suffer from labor pains and episiotomy: "I do not think that cesarean section has a negative impact on maternal health under today's modern operating room conditions, postoperative care and anesthesia conditions." (participant 16).

Sub theme 2 – On baby health

Some participants expressed that neonatal birth traumas are less common in cesarean deliveries and there is less likelihood of developing asphyxia: "The probability of the baby being without oxygen decreases. Birth is full of unknowns, anything can happen during this process. We eliminate them all." (participant 13). "I don't think there is anything negative about the baby. In other words, we have been giving birth for years, we have not encountered a negative situation just because there was a cesarean section" (participant 17).

Sub theme 3 – Other negatives

The participants expressed the difficulties that patients and physicians may experience due to repeated cesarean section operations as follows: "Yes, if we continue like this, the frequency of complications after cesarean section will increase a lot. Patients will bleed, maternal mortality will increase, and doctors will suffer more" (participant 13).

DISCUSSION

Based on the opinions of obstetricians and gynecologists due to the increase in the cesarean birth rate in Turkey and around the world, participants in this study, which aims to determine the causes of the increase in the cesarean birth rate and suggestions for solutions, stated that physically inadequate maternity ward conditions distract patients from vaginal childbirth. Similarly, another study indicated that inappropriate maternity ward conditions can negatively affect pregnant women's perspectives on vaginal delivery and decisions about the mode of delivery (14).

Participants stated that midwives are not effective in managing a normal birth, as stated in the studies in the literature, and physicians turn to cesarean delivery due to the inexperience of midwives (18,19).

It has also been stated in different studies that seeing a small number of complicated cases in assistant training is insufficient to develop technical skills, so they cannot trust themselves during clinical practice, and also legal fears distract them from interventional vaginal births and lead them to having a cesarean birth (20,21).

Cesarean births may be preferred as a result of having the advantage of planning the delivery time for the physician. There are also studies in the literature stating that physicians prefer cesarean delivery in order to save time and make personal plans (15,22,23,24). The fact that both planned and unplanned cesarean births, usually in the private sector, are mostly performed on weekdays and during working hours also points to the time factor (25,26). Similarly, some participants in our study pointed out the time factor as one of the reasons why physicians prefer cesarean section operations more and stated that cesarean section is seen as a procedure that consumes less time and makes it easier for the physician to make personal plans and programs.

The vast majority of the participants in the study stated that they turned to cesarean section more due to worries such as anxiety about encountering a negative result, violence, being threatened, lawsuits or complaints. In a study conducted by Cotzias et al. in 2001, 35% of physicians who performed cesarean sections at the request of the mother stated that they performed cesarean sections because of the fear of being sued (27).

Almost all of the participants in the study stated that they had experienced medicolegal problems during their professional lives, had to hire a lawyer, had ongoing lawsuits, did not receive support from the state during this process, and had individual struggles. In a study conducted with 1486 OBGYN specialists in which similar results were obtained to our study findings and medicolegal problems were questioned, 30.8% of the participants stated that they had been subjected to medical charges at least once, 13% had been sued at least once, and 42.8% had lost a case at least once (28).

All participants agreed that active, experienced, practical, qualified midwives were needed. Some participants stated that midwives should start working life after graduating from school, in busy environments such as a maternity hospital, or after gaining experience with a physician. In a qualitative study conducted in 2014, participants also pointed out the importance of qualified and skilled midwives in managing vaginal childbirth and the development of programs for the training of specialist midwives (18).

The majority of the participants emphasized the importance of improving the social and personal rights of midwives in encouraging midwifery. They stated that midwives could be included in the system by offering different options such as arranging midwives' salaries to be more than nurses' salaries or giving birth premiums. In a qualitative study conducted in 2018, a participating midwife stated that midwifery requires dedication, they are at greater risk, and therefore they should receive more salary than nurses, similar to our findings (29).

In our study, the participants emphasized that the distinction between complication and malpractice should be made absolutely, and that it would be important to regulate the laws on this issue. They also stated that compensation fees should be reasonable and standard. They expressed that the physician's salary should be taken into account when making the calculation, should be regulated within the framework of a certain quota and that interest should not be applied to these figures over the years. Studies offering similar solution suggestions have been found in the literature (29).

Another intervention study that should be carried out within the health system is to prepare pregnant women for vaginal birth. In the study, participants stated that patients who did not have sufficient knowledge about childbirth wanted more cesarean deliveries and therefore emphasized the importance of educating pregnant women and their relatives. Another study conducted in Turkey also concluded that effective training programs that can be offered by midwives and nurses from an early stage in the prenatal process can be useful in increasing vaginal birth rates (30).

In the bulletin of cesarean section on maternal request published by American College of Obstetricians and Gynecologists (ACOG) in 2013, it was stated that it is necessary to offer the appropriate analgesia option to women who request a cesarean section due to fear of pain (8). In our study, participants also stated that offering the option of painless delivery, especially to patients with fear of childbirth, will positively contribute to cesarean section rates. In a qualitative study conducted in 2014, 95% of the participants, consisting of midwives and physicians, stated that methods of reducing labor pain should be added to the health services delivery curriculum (18).

In addition to some participants who stated that keeping vaginal delivery fees higher than cesarean delivery fees could lead doctors to vaginal delivery, there were participants who stated that the problem of rising cesarean section rate could not be solved in this way, doctors did not turn to cesarean delivery because of money. They stated that fears cannot be overcome with money, and preventing doctors from turning to cesarean section can be solved not by giving them more money, but by removing the medicolegal pressures on them. In addition to the studies stating that there should be a wage gap in the literature, there are also studies stating that increasing vaginal delivery fees due to medicolegal concerns will not motivate physicians to have a vaginal birth (12,14,18,25) .

Participating physicians in the study stated that the pressure of primary responsibility in maternity cases should be removed, midwives can have uncomplicated births, and it would be more appropriate for them to intervene only in complicated cases. They noted that physicians receive training for complicated cases, that childbirth is the work that midwives know, and that their services should be refined. Similarly, in a study conducted in 2018, participants stated that midwives should be the primary responsibility in normal births, they can get support from obstetricians when complications occur, and thus the time pressure on doctors can be reduced and unnecessary cesarean sections can be prevented (25).

Participants stated that cesarean delivery prevents a number of complications that are likely to develop during vaginal delivery. One of the most frequently expressed complications was complications related to the Genitourinary System. They noted that the disadvantages such as urinary incontinence or vaginal relaxation are less common in women who have cesarean section. In a study conducted in 2014, participants also expressed that they believed that cesarean delivery was beneficial in reducing maternal complication rates in general (23). Although some of the participants in our study stated that cesarean delivery prevents a number of complications, cesarean section has many short-term maternal complications such as thromboembolism, postpartum bleeding, wound hematoma, and long-term complications such as intra-abdominal adhesions, ectopic pregnancy, and placental placement anomalies (7).

In the study, some participants who think that cesarean delivery is a more advantageous delivery method for newborns stated that cesarean delivery reduces the likelihood of asphyxia and birth traumas and increases the newborn's chances of survival. In a statement published in 2013, ACOG suggested that although the absolute risk difference is small, the possibilities of neonatal asphyxia, hypoxic ischemic encephalopathy (HIE) and birth trauma are the potential neonatal benefits of cesarean delivery (8). However, there are studies that show an increased risk of asthma and obesity in babies born by cesarean section in the long term (8,9,10).

Strengths

It is important that the opinions of physicians working in both public and private sectors were taken in the study in order to reflect the perspectives of physicians working in both institutions. In addition, the average professional experience of the participants in the study, which is 25 years, makes the results of the study strong. This situation strengthens the possibility of representing the views of obstetricians and gynecologists in general. The inferences obtained from the opinions and thoughts of the participants can be a guide for the steps planned to be taken for public health experts, health institution managers, policy makers In this context, we hope that our study will make important contributions to the literature.

Limitations

The statements obtained from in-depth interviews with 17 OBGYN specialists residing in Sakarya are specific to the participants, and should not be expected to represent the province or country where the study was conducted. Another element included in the limitations of the study is that only physicians were involved in the study among the determinants of cesarean delivery. The perspectives of pregnant women, midwives, health service managers and policy makers who have a role in the factors related to cesarean delivery rate have been excluded from the scope. In the study, some subcategories were created in accordance with the statements of one or two participants, and may be insufficient in terms of representing the views of the participant group.

CONCLUSION

Since the factors affecting the cesarean section rate are multifaceted and interconnected, this versatility and interconnection should be taken into account when taking precautions. We especially need to focus on cesarean births without medical indications, which have a large share in the increase in cesarean section rates. Additionally, distinguishing between complications inherent in the birthing process and malpractice can prevent unnecessary lawsuits against physicians.

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Obstrüktif uyku apne hastalarında kısa form-36 ve Dünya Sağlık Örgütü yaşam kalitesi ölçeklerinin karşılaştırılması

Comparison of short form-36 and World Health Organization quality of life scales in patients with obstructive sleep apnea

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Öz

Amaç: Bu çalışmada; Dünya Sağlık Örgütü Yaşam Kalitesi Ölçeği (WHOQOL –BREF) ve Kısa Form 36 (SF-36) anketlerinin obstrüktif uyku apne sendrom (OSAS)'lu hastalarda; yaşam kalitesini değerlendirmede güvenilirliğini ve etkinliğini karşılaştırmayı amaçladık.

Yöntemler: Bu çalışmaya Kocaeli Derince Eğitim ve Araştırma Hastanesi nöroloji kliniği uyku ve uyku bozuklukları merkezinde 25.11.2023-05.01.2024 tarihleri arasında OSAS tanısı alan 50 hasta ve polisomnografisi (PSG) normal saptanan 20 kişi kontrol grubu olarak alındı. Sigara kullanımı, eşlik eden hastalıklar (diyabet, hipertansiyon, hiperlipidemi), PSG'de apne-hipopne indeksi (AHI), rapid eye movement (REM) evresi, non-REM Evre 1 (N-REM 1), non-REM Evre 2 (N-REM 2), non-REM Evre 3 (N-REM 3) oranları, ortalama oksijen (O2) saturasyonu not alındı. Hastalara WHOQOL –BREF ve SF-36 anketleri, Beck depresyon ölçeği (BDI), Epworth Uykululuk Skalası (ESS) uygulanarak; WHOQOL –BREF ve SF-36 anketlerinin güvenilirliği ve etkinliği karşılaştırıldı.

Bulgular: Çalışma; %35,7'si (n=25) kadın ve %64,3'ü (n=45) erkek olmak üzere toplam 70 olguyla yapıldı. Olguların %28,6'sı (n=20) kontrol ve %71,4'ü (n=50) hasta grubu olarak alındı. İstatistiksel olarak anlamlı farklılık göstermese de; OSAS grubunda Epworth Uykululuk Skalası ve Beck depresyon ölçeği skorları daha yüksek saptandı (p>0,05). Gruplara göre olguların WHOQOL-BREF Ölçeği skorları istatistiksel olarak anlamlı farklılık göstermemekle beraber genel sağlık, fiziksel sağlık ve çevre skorları OSAS hastalarında daha düşük saptandı (p>0,05). SF-36 fiziksel fonksiyon skorları; istatistiksel olarak anlamlı olmasa da OSAS grubunda daha düşük saptandı. Erkeklerin SF-36 "Fiziksel fonksiyon" skoru kadınlardan istatistiksel olarak anlamlı olmamakla birlikte dikkat çekici düzeyde yüksek saptandı (p=0,054; p>0,05). Erkeklerin SF-36 "Fiziksel rol güçlüğü" skoru (p=0,009; p<0,01), "Emosyonel rol güçlüğü" skoru (p=0,025; p<0,05) ve "Sosyal işlevsellik" skoru (p=0,021; p<0,05) kadınlardan istatistiksel olarak anlamlı düzeyde yüksek saptandı.

Sonuç: Çalışma; OSAS hastalarında yaşam kalitesini değerlendirmede SF-36 ölçeğinin, WHOQOL–BREF ölçeğine göre daha iyi bir gösterge olduğunu gösterdi. OSAS hastalarında, iki yaşam kalite ölçeğinin tanıda ve tedavi verilecek hasta grubunu tespit etme konusunda karşılaştırılması yapılmadığı için, çalışmanın literatüre katkıda bulunacağını vurgulamak istiyoruz.

Anahtar Sözcükler: Dünya Sağlık Örgütü; ölçekler; tıkayıcı uyku apne sendromu; yaşam kalitesi

Abstract

Aim: In this study, the objective was to compare the reliability and effectiveness of the World Health Organization Quality of Life Scale (WHOQOL–BREF) and Short Form 36 (SF-36) questionnaires in assessing the quality of life in patients with obstructive sleep apnea syndrome (OSAS).

Methods: 50 patients diagnosed with OSAS, has been included in the study at the "Derince Training and Research Hospital's Neurology Clinic Sleep & Sleep Disorders Center" between November 25, 2023, and January 5, 2024, along with 20 individuals in the control group with normal polysomnography (PSG) results. Data, including smoking habits, comorbidities (diabetes, hypertension, hyperlipidemia), apnea-hypopnea index (AHI), rapid eye movement (REM) stage, non-REM stage 1 (N-REM 1), non-REM stage 2 (N-REM 2), non-REM stage 3 (N-REM 3) ratios, and average oxygen (O2) saturation, has been recorded from PSG. With applying the WHOQOL–BREF and SF-36 questionnaire, Beck Depression Scale (BDI), Epworth Sleepiness Scale (ESS) to the patients, the reliability and effectiveness of WHOQOL–BREF and SF-36 questionnaires were compared.

Results: The study was conducted with a total of 70 cases, consisting of 35.7% females (n=25) and 64.3% males (n=45). Of the cases, 28.6% (n=20) were categorized as the control group, and 71.4% (n=50) as the patient group. Although it does not show a statistically significant difference; Epworth Sleepiness Scale and Beck Depression Scale scores were determined to be higher in the OSAS group (p>0.05). However, despite no statistical significance, the WHOQOL-BREF Scale scores of the patients differed, with lower scores in general health, physical health, and environment (p>0.05). SF-36 physical function scores, while not statistically significant, were lower in the OSAS group. Men's SF-36 "Physical Function" score, while not statistically significant compared to women, was notably higher (p=0.054; p>0.05). Men had statistically significantly higher SF-36 scores in "Physical Role Limitations" (p=0.009; p<0.01), "Emotional Role Limitations" (p=0.025; p<0.05), and "Social Functioning" (p=0.021; p<0.05) compared to women.

Conclusion: The study demonstrated that the SF-36 scale is a better indicator for assessing quality of life in OSAS patients compared to the WHOQOL-BREF scale. We would like to emphasize that this study will contribute to the literature, as the comparison of these two quality of life scales in diagnosing and identifying the patient group for treatment in OSAS patients has not been previously made.

Keywords: Obstructive sleep apnea syndrome; questionnaires; quality of life; World Health Organization

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GİRİŞ

Obstrüktif uyku apne sendromu (OSAS), uykuda üst solunum yollarının kısmen veya tamamen obstrüksiyonu ile karakterize kronik inflamatuar bir hastalıktır (1,2).

OSAS'lı hastalar, sıklıkla yaşam kalitelerinde bozulmaya neden olan semptomlarla başvururlar. Son yıllarda, hastaların yaşam kalitesini değerlendiren farklı araştırmalar, OSAS hastalarının; OSAS olmayan hastalara göre daha düşük bir yaşam kalitesine sahip olduğunu göstermiştir (3). OSAS hastalarında yaşam kalitesini değerlendirmek için çeşitli ölçekler kullanılmıştır. En yaygın kullanılan ölçek, Short Form (SF-36) olmuştur (4). SF-36 ile Dünya Sağlık Örgütü Yaşam Kalitesi Ölçeği (WHOQOL–BREF) etkinlik ve güvenilirliliği bazı çalışmalarda incelenmiştir. Huang ve arkadaşları, her iki ölçeğin alt grupları arasındaki korelasyonların zayıf olduğunu belirtmiş, hem SF-36 hem de WHOQOL-BREF'in farklı yapıları ölçtüğü sonucuna varmış, SF-36'nın sağlıkla ilgili yaşam kalitesini ölçtüğünü vurgulamıştır (5). Hsiung ve ark. tarafından HIV enfeksiyonlu hastalar üzerinde yapılan başka bir çalışmada, her iki ölçeğin de yaşam kalitesini değerlendirmede güvenilir ve geçerli olduğu belirtilmiştir (6).

Çalışmamızda; OSAS hastalarında, SF-36 ve WHOQOL –BREF yaşam kalite ölçeklerini kullanarak bu iki testten hangisinin yaşam kalitesini daha iyi ölçtüğünü tespit etmeyi amaçlıyoruz. Bu sayede OSAS hastalarında yaşam kalitesini değerlendirerek; öncelikle tedavi vereceğimiz grubu daha iyi saptayabileceğimizi ve hastaların tedaviye uyumunu daha net değerlendirebileceğimizi düşünüyoruz. Literatürde, OSAS'lı hastalarda; WHOQOL-BREF ve SF-36 ölçekleri kullanılarak yaşam kalitesini aynı anda ölçen ve karşılaştıran az sayıda çalışmaya rastlanılmıştır. Bu nedenle çalışmamızın dikkate değer olduğunu düşünüyoruz.

GEREÇ VE YÖNTEMLER

Bu çalışma Kocaeli Derince Eğitim ve Araştırma Hastanesi nöroloji kliniği uyku ve uyku bozuklukları biriminde takipli polisomnografi (PSG)'si normal olan ve OSAS tanısı alan hastalar değerlendirilerek yapılmış prospektif tipte bir çalışmadır.

Hasta grubu olarak 25.11.2023-05.01.2024 tarihleri arasında Kocaeli Derince Eğitim ve Araştırma Hastanesi Nöroloji Kliniği uyku laboratuvarında yatırılmış ve uyku polikliniğinden takipleri yapılmış, OSAS tanısı alan 50 hasta, hasta grubu; PSG'si normal olan 20 hasta, kontrol grubu olarak alındı.

Sosyodemografik veriler (yaş, cinsiyet, boy, kilo, vücut kitle indeksi (VKİ), medeni durum, eğitim durumu, mesleki durum), OSAS için risk faktörleri (diyabet, hipertansiyon, kardiyak hastalık) analiz edildi. Rapid eye movement (REM) evresi, Non-REM 1 (N-REM 1), N-REM 2, N-REM 3 evrelerinin yüzdesi, apne hipopne indeksi (AHI), ortalama oksijen saturasyonu, sigara kullanımı not alındı. Hastalara, onamları alınarak; Epworth uykululuk skalası (ESS), Beck depresyon ölçeği (BDI), SF-36 VE WHOQOL-BREF yaşam kalite ölçeği anketleri uygulandı.

Narkolepsi ve hipersomni tanısı alan hastalar, pozitif havayolu basıncı (PAP) kullanımı sonucu yaşam kalitesinde düzelmeyle sonuçlanacağı için PAP tedavisi alan hastalar, OSAS dışındaki uykuda solunum bozukluğu olan hastalar, malignite, psikoz çalışma dışı bırakıldı. Çalışmaya OSAS tanısı alan hasta grubu ile polisomnografisi normal saptanan kontrol grubu alındı.

Etik onay

İnsan katılımcıları içeren çalışmalarda gerçekleştirilen tüm prosedürler, Sağlık Bilimleri Üniversitesi (SBÜ) Kocaeli Derince Eğitim ve Araştırma Hastanesi Bilimsel Araştırmalar Etik Kurulu'nun etik standartlarına uygundur ve 1964 Helsinki Bildirgesi'nin ilkelerine bağlı kalınmıştır. Etik kurul onayı Kocaeli Derince Eğitim ve Araştırma Hastanesi Bilimsel Araştırmalar Etik Kurulu tarafından 23.11.2023 tarihinde 2023-3 numaralı protokol numarası ile onaylandı.

Polisomnografi

Tüm hasta ve kontrollere uyku bozukluğu laboratuvarında tam gece PSG çekimi (Embla N7000-Philips-USA) yapıldı. PSG'de elektroensefalogram, elektrookülogram, çene ve bacak elektromiyogramı, elektrokardiyogram, horlama, termistör, nazal basınç transdüseri, parmak nabız oksimetresi, torasik ve abdominal solunum hareketleri ve vücut pozisyonu yer aldı. Skorlama 2017 Amerikan Uyku Tıbbı Akademisi kriterlerine göre yapıldı (7). Apne/hipopne indeksi

(AHI) ≥5/saat olan hastalar OSAS olarak kabul edildi. ≥5/saat ile <15/saat arası AHI değeri hafif, AHI değeri ≥15/saat ve 30/saatten az olanlar orta; AHI değeri ≥30/saat ise şiddetli OSAS olarak tanımlandı.

Beck depresyon ölçeği

Depresyonun; fiziksel, duygusal, bilişsel ve motivasyonel semptomlarını ölçer. Ölçeğin amacı depresyon tanısı koymak değil, depresyon belirtilerinin düzeyini ve şiddetindeki değişimi belirlemektir. 21 öz değerlendirme cümlesini içeren ve her belirti kategorisinin dört seçeneği olan bir ölçektir. Her madde 0 ile 3 arasında puanlanır ve toplam puan 0-63 arasında değişir. 0-9 arası minimal depresyonu, 10-16 arası hafif depresyonu, 17-29 arası orta depresyonu, 30-63 arası şiddetli depresyonu gösterir (8).

Kısa form-36 yaşam kalitesi anketi (sf-36)

SF-36; hastanın son 4 haftasını göz önünde bulundurarak yaşam kalitesini sorgulayan anket, 36 maddeden oluşmaktadır. Fiziksel-sosyal işlevler, fiziksel problemlere bağlı rollerde kısıtlanma, ağrı, ruhsal sağlık, duygusal sorunlara bağlı rollerde kısıtlanma, yaşam enerjisi ve genel sağlık olmak üzere sekiz alt kategorisi bulunmaktadır (9). Anketin total puanlaması yoktur. Alt kategorilerinin skorları 0 ile 100 arasında değişmektedir. 100 puan iyi sağlık durumuna, 0 ise kötü sağlık durumuna işaret etmektedir. Her soru maddesinde, işaret kutucuklarının yanında küçük harflerle yazılmış rakamlar bulunmaktadır. Hastanın işaretlediği şıkka ait rakam sabit yönergeye göre değiştirilerek kullanılır. Her bir alt kategori ile ilgili soruların puanları toplanıp sabit katsayıya bölünür. Çıkan değer her iki cinsiyet için sabit olan standart sapma değerlerine göre değerlendirmeye alınır.

WHOQOL-BREF kısa form

WHOQOL-100 içinden seçilen ve fiziksel sağlık, psikolojik sağlık, sosyal ilişkiler ve çevre alanı olmak üzere dört alandan oluşan 27 soru ile WHOQOL-BREF (WHOQOL-Kısa Form) oluşturulmuştur (10). Hastaların yaşam kaliteleri, sağlık ve kendi yaşamlarının diğer yönleri ile ilgili olarak son 2 haftadaki memnuniyetlerini 5 şıklı cevap içeren sorularla değerlendirmeleri istenmiştir. Alt parametrelere göre oluşturulan skorlama yönergelerine göre, elde edilen ham skordan en düşük skor çıkarılıp, skor aralığına bölünerek puanlama yapılmıştır. Puanlar 0-100 arasında değişmektedir. Yüksek puanlar yaşam kalitesi düzeyinin yüksek olduğunu gösterir.

Epworth uykululuk ölçeği

Epworth uykululuk ölçeği (ESS), uykululuğun bir ölçüsü olarak onaylanmış, yaygın olarak kullanılan bir ölçektir. Hastalara 8 farklı durum ile ilgili olarak uyuklama ihtimalleri sorulmuş, cevaplarına göre 0-3 arası puan verilmiştir. Toplam puanlamada; 0-5 arası; normal, 6-10 arası; normal ama artmış gün içi uykululuk, 11-12 arası; artmış ama ılımlı gün içi uykululuk, 13-15 arası; artmış orta düzeyde gün içi uykululuk, 16-24 arası; artmış şiddetli gün içi uykululuk olarak değerlendirilmiştir (11,12).

İstatistiksel analiz

Çalışmada elde edilen bulgular değerlendirilirken, istatistiksel analizler için NCSS (Number Cruncher Statistical System) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA) programı kullanıldı. Çalışma verileri değerlendirilirken, nicel değişkenler ortalama, standart sapma, medyan, min ve max değerleriyle, nitel değişkenler frekans ve yüzde gibi tanımlayıcı istatistiksel metodlar ile gösterildi. Verilerin normal dağılıma uygunluklarının değerlendirilmesinde Shapiro Wilks test ve Box Plot grafiklerden yararlanıldı.

Normal dağılım gösteren niceliksel iki grup değerlendirmelerinde Student t-test kullanıldı. Normal dağılım göstermeyen değişkenlerin iki gruba göre değerlendirmelerinde Mann Whitney-U test kullanıldı. Niteliksel verilerin karşılaştırılmasında ise Ki-Kare testi, Fisher Exact test ve Fisher's Freeman Halton test kullanıldı. Sonuçlar %95'lik güven aralığında, anlamlılık $p<0,05$ düzeyinde değerlendirildi.

BULGULAR

Çalışma 25.11.2023-05.01.2024 tarihleri arasında Kocaeli Derince Eğitim ve Araştırma Hastanesi'nde %35,7'si (n=25) kadın ve %64,3'ü (n=45) erkek olmak üzere toplam 70 olguyla yapılmıştır. Çalışmaya katılan olguların yaşları 17 ile 56 arasında değişmekte olup, ortalama yaş 43,03±8,75 olarak saptanmıştır. Olguların %28,6'sının (n=20) kontrol ve %71,4'ünün (n=50)

OSAS grubunda olduğu görülmektedir (Tablo 1, Şekil 1).

Çalışmaya katılan olguların vücut kitle indeksi (VKİ) olcumleri 22,5 ile 48,7 arasında değişmekte olup, ortalama VKİ 30,41±4,48 olarak saptanmıştır. Olguların %12,9'unun (n=9) bekar, %82,9'unun (n=58) evli ve %4,3'ünün (n=3) dul olduğu görülmektedir. Çalışmaya katılan olguların %57,1'inin (n=40) ilkokul/ortaokul, %24,3'ünün (n=17) lise ve %18,6'sının (n=13) üniversite mezunu olduğu görülmektedir. Olguların %70'inin (n=49) çalıştığı görülmektedir. Çalışmaya katılan olguların %38,6'sının (n=27) sigara kullandığı görülmektedir (Tablo 1, Şekil 2).

Gruplara göre olguların cinsiyet, yaş ve VKİ ölçümleri istatistiksel olarak anlamlı farklılık göstermemektedir (p>0,05). Gruplara göre olguların medeni durum, eğitim durumu, mesleki durum ve sigara kullanımı istatistiksel olarak anlamlı farklılık göstermemektedir (p>0,05) (Tablo 2).

Çalışmaya katılan olguların N-REM 1 (%) ölçümleri 0 ile 32,3 arasında değişmekte olup, ortalama N-REM 1 (%) 7,34±4,69; olguların N-REM 2 (%) ölçümleri 4,8 ile 77,3 arasında değişmekte olup, ortalama N-REM 2 (%) 38,86±19,34; olguların N-REM 3 (%) ölçümleri 0 ile 76,4 arasında değişmekte olup, ortalama N-REM 3 (%) 26,76±20,44; olguların REM evrelerinin yüzdesi 0 ile 50,5 arasında değişmekte olup,

Tablo 1. Tanımlayıcı özelliklerin dağılımları

		n (%)
Cinsiyet	Kadın	25 (35,7)
	Erkek	45 (64,3)
Yaş	Ort±SS	43,03±8,75
	Med (min-maks)	45 (17-56)
Grup	Kontrol	20 (28,6)
	OSAS	50 (71,4)
VKİ	Ort±SS	30,41±4,48
	Med (min-maks)	30,3 (22,5-48,7)
Medeni durum	Bekar	9 (12,9)
	Evli	58 (82,9)
	Dul/eşini kaybetmiş	3 (4,3)
Eğitim durumu	İlkokul/ortaokul	40 (57,1)
	Lise	17 (24,3)
	Üniversite	13 (18,6)
Mesleki durum	Çalışmıyor	21 (30,0)
	Çalışıyor	49 (70,0)
Sigara kullanımı	Yok	43 (61,4)
	Var	27 (38,6)

VKİ: Vücut kitle indeksi, OSAS: Obstrüktif Uyku Apne Sendromu, n: Olgu sayısı, %: Yüzde, Ort: Ortalama, SS: Standart sapma, med: Medyan, min: Minimum, maks: Maksimum

Tablo 2. Gruplara göre tanımlayıcı özelliklerin dağılımları

		Grup		
		Kontrol (n=20)	**OSAS (n=50)**	***p***
Cinsiyet	Kadın, n(%)	10 (50,0)	15 (30,0)	***[a]0,115***
	Erkek, n(%)	10 (50,0)	35 (70,0)	
Yaş	Ort±SS	39,70±11,87	44,36±6,84	***[b]0,112***
	Med (min-maks)	45 (17-53)	45 (28-56)	
VKİ	Ort±SS	29,20±4,37	30,89±4,48	***[b]0,154***
	Med (min-maks)	27,9 (22,5-36,3)	30,4 (23,7-48,7)	
Medeni durum	Bekâr, n(%)	6 (30,0)	6 (12,0)	***[c]0,088***
	Evli, n(%)	14 (70,0)	44 (88,0)	
	Dul/eşini kaybetmiş, n(%)	0 (0,0)	3 (6,0)	
Eğitim durumu	İlkokul/ortaokul, n(%)	10 (50,0)	30 (60,0)	***[c]0,295***
	Lise, n(%)	4 (20,0)	13 (26,0)	
	Üniversite, n(%)	6 (30,0)	7 (14,0)	
Mesleki durum	Çalışmıyor, n(%)	6 (30,0)	15 (30,0)	***[a]1,000***
	Çalışıyor, n(%)	14 (70,0)	35 (70,0)	
Sigara kullanımı	Yok, n(%)	12 (60,0)	31 (62,0)	***[a]0,877***
	Var, n(%)	8 (40,0)	19 (38,0)	

VKİ: Vücut kitle indeksi, OSAS: Obstrüktif Uyku Apne Sendromu, n: Olgu sayısı, %: Yüzde, Ort: Ortalama, SS: Standart sapma, med: Medyan, min: Minimum, maks: Maksimum

[a] Pearson Chi-Square, [b] Student-t Test, [c] Fisher Freeman Halton Test

Tablo 3. Polisomnografi verilerin dağılımları

		n (%)
AHI	Normal: AHI < 5	20 (28,6)
	Hafif düzeyde OSAS: 5 ≤ AHI < 15	24 (34,3)
	Orta düzeyde OSAS: 15 ≤ AHI < 30	7 (10,0)
	İleri düzeyde OSAS: AHI ≥ 30	19 (27,1)
Non-REM 1 (%)	Ort±SS	7,34±4,69
	Medyan (min-maks)	6,7 (0-32,3)
Non-REM 2 (%)	Ort±SS	38,86±19,34
	Medyan (min-maks)	42,6 (4,8-77,3)
Non-REM 3 (%)	Ort±SS	26,76±20,44
	Medyan (min-maks)	17,8 (0-76,4)
REM (%)	Ort±SS	14,09±8,82
	Medyan (min-maks)	13,2 (0-50,5)
Ortalama oksijen saturasyonu	Ort±SS	94,22±2,29
	Medyan (min-maks)	94,7 (80,9-97,2)

AHI: Apne-hipopne indeksi, OSAS: Obstrüktif Uyku Apne Sendromu, REM: Rapid Eye Movement, n: Olgu sayısı, %: Yüzde, Ort: Ortalama, SS: Standart sapma, min: Minimum, maks: Maksimum

Tablo 4. Eşlik eden hastalıkların dağılımı

		n (%)
DM	Yok	60 (85,7)
	Tip 1	10 (14,3)
HT	Yok	54 (77,1)
	Var	16 (22,9)
Kalp hastalığı	Yok	65 (92,9)
	Var	5 (7,1)
KOAH	Yok	67 (95,7)
	Var	3 (4,3)

DM: Diyabetes Mellitus HT: Hipertansiyon KOAH: Kronik obstrüktif akciğer hastalığı, n: Olgu sayısı, %: Yüzde

REM evrelerinin yüzdesi 14,09±8,82 olarak saptanmıştır. Olguların ortalama oksijen saturasyonu 80,9 ile 97,2 arasında değişmektedir (Tablo 3).

Olguların AHI grupları incelendiğinde; %28,6'sının (n=20) normal, %34,3'ünün (n=24) hafif derecede uyku apnesi (OSAS), %10'unun (n=7) orta derecede OSAS ve %27,1'inin (n=19) ileri derecede OSAS olduğu görülmektedir (Tablo 3, Şekil 3).

Olguların %14,3'ünde (n=10) diyabet, %22,9'unda (n=16) hipertansiyon, %7,1'inde (n=5) kalp hastalığı ve %4,3'ünde (n=3) kronik obstrüktif akciğer hastalığı (KOAH) olduğu görülmektedir (Tablo 4, Şekil 4).

Tablo 5. Gruplara göre Epworth uykululuk skalası ve Beck depresyon ölçeği skorlamalarının karşılaştırılması

		Grup		
		Kontrol (n=20)	OSAS (n=50)	*p*
ESS	Normal	7 (35,0)	11 (22,0)	[c]*0,432*
	Normal ama artmış gün içi uykululuk	7 (35,0)	16 (32,0)	
	Artmış ama ılımlı gün içi uykululuk	4 (20,0)	7 (14,0)	
	Artmış, orta düzeyde gün içi uykululuk	2 (10,0)	13 (26,0)	
	Artmış, şiddetli gün içi uykululuk	0 (0,0)	3 (6,0)	
BDI	Normal	9 (47,4)	27 (54,0)	[c]*0,551*
	Hafif ruhsal sıkıntı	5 (26,3)	7 (14,0)	
	Sınırda klinik depresyon	3 (15,8)	8 (16,0)	
	Orta depresyon	1 (5,3)	7 (14,0)	
	Ciddi depresyon	1 (5,3)	1 (2,0)	

OSAS: Obstrüktif Uyku Apne Sendromu ESS: Epworth Uykululuk Skalası BDI: Beck depresyon ölçeği, n: Olgu sayısı, %: Yüzde
[c] Fisher Freeman Halton Test

Tablo 6. Gruplara göre SF-36 ölçeği skorlarının karşılaştırılması

	Grup		
	Kontrol (n=20)	**OSAS (n=50)**	
	Ort±SS	Ort±SS	
	Med (min-maks)	Med (min-maks)	***P***
Fiziksel fonksiyon	60,75±24,67	57,10±23,69	[b]*0,567*
	65 (10-100)	60 (10-100)	
Fiziksel rol güçlüğü	42,08±39,50	49,33±41,40	[d]*0,418*
	50 (0-100)	50 (0-100)	
Emosyonel rol güçlüğü	38,30±31,09	45,37±33,55	[d]*0,403*
	33,3 (0-100)	33,3 (0-100)	
Enerji, canlılık, vitalite	57,00±11,40	58,19±12,80	[b]*0,718*
	60 (30-70)	60 (20-80)	
Ruhsal sağlık	45,40±12,53	47,14±14,77	[b]*0,644*
	44 (20-68)	48 (4-84)	
Sosyal işlevsellik	58,75±28,71	69,35±25,31	[d]*0,159*
	56,3 (12,5-100)	75 (12,5-100)	
Ağrı	42,25±29,94	48,15±31,05	[b]*0,471*
	45 (0-100)	45 (0-100)	
Genel sağlık algısı	35,25±17,05	41,00±19,82	[b]*0,259*
	32,5 (10-75)	40 (10-75)	

OSAS: Obstrüktif Uyku Apne Sendromu, SF-36: Short Form 36, n: Olgu sayısı, %: Yüzde, Ort: Ortalama, SS: Standart sapma, med: Medyan, min: Minimum, maks: Maksimum

b Student-t Test, d Mann-Whitney-U Test

Tablo 7. Gruplara göre WHOQOL-BREF ölçeği skorlarının karşılaştırılması

	Grup		
	Kontrol (n=20)	**OSAS (n=50)**	
	Ort±SS	Ort±SS	
	Med (min-maks)	Med (min-maks)	***P***
Genel sağlık durumu	51,25±14,57	45,75±18,83	[b]*0,245*
	50 (25-75)	50 (0-75)	
Fiziksel sağlık	59,75±20,15	53,57±18,34	[b]*0,220*
	60,7 (14-89,2)	50 (14-95,2)	
Psikolojik	55,39±22,12	56,30±20,33	[d]*0,839*
	62,5 (20,8-91,6)	62,5 (4,5-87,5)	
Sosyal ilişkiler	52,69±25,51	53,55±21,07	[d]*0,869*
	54,2 (0-83,3)	50 (0-100)	
Çevre	61,46±20,53	58,67±18,10	[d]*0,719*
	65,6 (9,3-93,7)	65,6 (21,8-96,6)	

OSAS: Obstrüktif Uyku Apne Sendromu, WHOQOL –BREF: Dünya Sağlık Örgütü Yaşam Kalitesi Ölçeği, n: Olgu sayısı, %: Yüzde, Ort: Ortalama, SS: Standart sapma, med: Medyan, min: Minimum, maks: Maksimum

[b] Student-t Test, [d] Mann-Whitney-U Test

Gruplara göre olguların Epworth Uykululuk Skalası ve Beck Depresyon Ölçeği skorlamaları istatistiksel olarak anlamlı farklılık göstermemektedir (p>0,05) (Tablo 5).

Gruplara göre olguların SF-36 Ölçeği skorları istatistiksel olarak anlamlı farklılık göstermemektedir (p>0,05) (Tablo 6).

Gruplara göre olguların WHOQOL-BREF Ölçeği skorları istatistiksel olarak anlamlı farklılık göstermemektedir (p>0,05) (Tablo 7).

OSAS'lı erkek hastaların SF-36 Ölçeği "Fiziksel fonksiyon" skoru, OSAS'lı kadın hastalardan istatistiksel olarak anlamlı olmamakla birlikte dikkat çeki-

Tablo 8. OSAS'lı hastalarda cinsiyete göre SF-36 ölçeği skorlarının karşılaştırılması

	Cinsiyet		
	Kadın (n=25) Ort±SS Med (min-maks)	**Erkek (n=45)** Ort±SS Med (min-maks)	***p***
Fiziksel fonksiyon	50,80±20,90 50 (10-100)	62,22±24,62 65 (10-100)	[b]*0,054*
Fiziksel rol güçlüğü	30,00±36,08 25 (0-100)	56,85±40,33 75 (0-100)	[d]*0,009***
Emosyonel rol güçlüğü	31,97±29,61 33,3 (0-100)	49,67±33,08 66,6 (0-100)	[d]*0,025**
Enerji, canlılık, vitalite	59,20±14,98 60 (25-80)	57,10±10,73 60 (20-75)	[b]*0,500*
Ruhsal sağlık	42,88±13,04 44 (4-60)	48,73±14,37 48 (20-84)	[b]*0,096*
Sosyal işlevsellik	56,00±27,51 50 (12,5-100)	72,06±24,47 75 (25-100)	[d]*0,021**
Ağrı	41,70±26,31 32,5 (0-100)	49,11±32,78 45 (0-100)	[b]*0,336*
Genel sağlık algısı	34,80±17,17 35 (10-70)	41,89±19,87 45 (10-75)	[b]*0,138*

OSAS: Obstrüktif Uyku Apne Sendromu, WH SF-36: Short Form 36, n: Olgu sayısı, %: Yüzde, Ort: Ortalama, SS: Standart sapma, med: Medyan, min: Minimum, maks: Maksimum

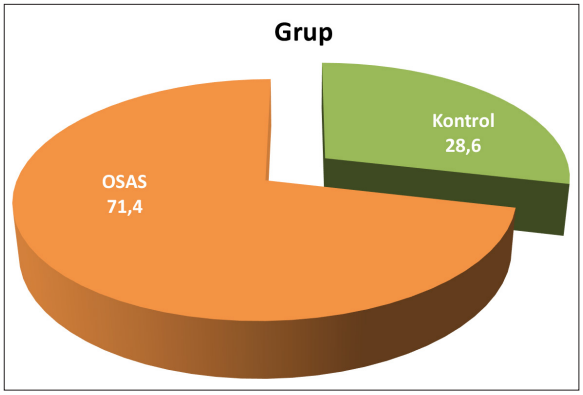
[b] Student-t Test, [d] Mann-Whitney-U Test, *p<0,05, **p<0,01

Tablo 9. OSAS'lı hastalarda cinsiyete göre WHOQOL-BREF ölçeği skorlarının karşılaştırılması

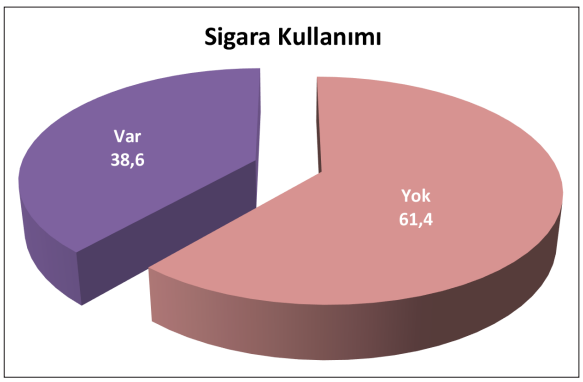
	Cinsiyet		
	Kadın (n=25)	**Erkek (n=45)**	***p***
Genel sağlık durumu	50,00±19,09 50 (0-75)	45,83±17,06 50 (12,5-75)	[b]*0,352*
Fiziksel sağlık	59,40±18,05 60,7 (14-89,2)	53,08±19,23 50 (14-95,2)	[b]*0,183*
Psikolojik	56,15±21,65 62,5 (4,5-87,5)	55,98±20,40 62 (20,8-91,6)	[d]*0,796*
Sosyal ilişkiler	51,68±24,65 50 (0-83,3)	54,21±21,01 50 (0-100)	[d]*0,906*
Çevre	60,80±20,48 65,6 (9,3-96,6)	58,72±17,86 65,6 (21,8-93,7)	[d]*0,621*

OSAS: Obstrüktif Uyku Apne Sendromu, WHOQOL –BREF: Dünya Sağlık Örgütü Yaşam Kalitesi Ölçeği, n: Olgu sayısı, %: Yüzde, Ort: Ortalama, SS: Standart sapma, med: Medyan, min: Minimum, maks: Maksimum

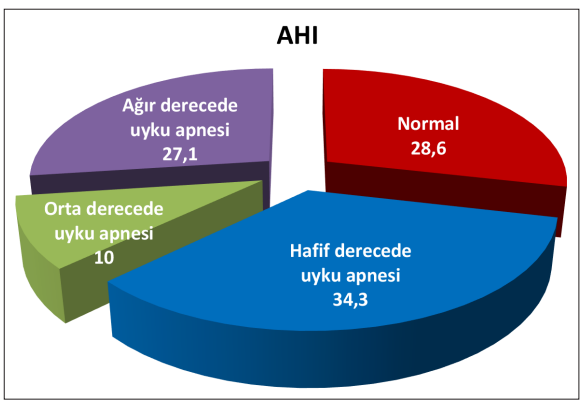
[b] *Student-t Test,* [d] *Mann-Whitney-U Test*



Şekil 1. Grupların dağılımı (%)

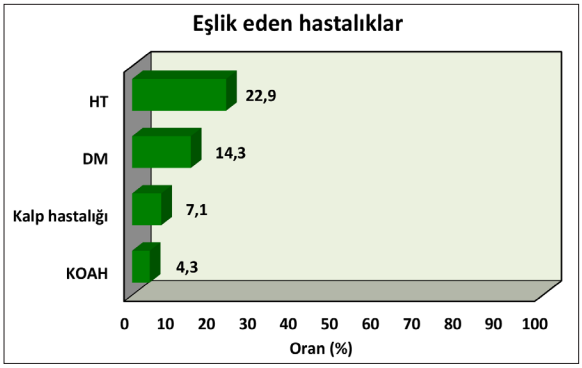


Şekil 2. Sigara kullanımının dağılımı (%)

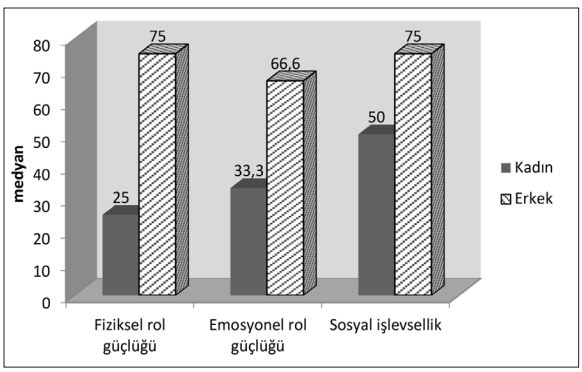


Şekil 3. Apne-Hipopne İndeksi dağılımı (%)

ci düzeyde yüksek saptanmıştır (p=0,054; p>0,05). OSAS'lı erkek hastaların SF-36 "Fiziksel rol güçlüğü" skoru (p=0,009; p<0,01), "Emosyonel rol güçlüğü" skoru (p=0,025; p<0,05) ve "Sosyal işlevsellik" skoru (p=0,021; p<0,05) OSAS'lı kadın hastalardan istatistiksel olarak anlamlı düzeyde yüksek saptandı (Şekil 5). Cinsiyete göre SF-36 Ölçeği "Ağrı" skoru ve "Genel sağlık algısı" skoru istatistiksel olarak anlamlı farklılık göstermemektedir (p>0,05) (Tablo 8).



Şekil 4. Eşlik eden hastalıkların dağılımı



Şekil 5. OSAS'lı hastalarda cinsiyete göre SF-36 ölçeği skorlarının karşılaştırılması

Cinsiyete göre WHOQOL-BREF Ölçeği skorları istatistiksel olarak anlamlı farklılık göstermemektedir (p>0,05) (Tablo 9).

TARTIŞMA

OSAS; yaşam kalitesini olumsuz etkiler ve komorbid hastalıkların riskini artırır (13). Yaşam kalitesi; tanıda ve tedavi aşamasında, hastalık sürecinin önemli bir göstergesidir (14). OSAS'lı hastalarda; SF-36 ve WHOQOL –BREF yaşam kalitesi ölçekleri ile; OSAS'ın hastanın genel sağlık durumuna ve yaşam kalitesine yansımasını saptamak mümkündür. Hafif derecede OSAS'ta PAP tedavisi vermediğimiz hasta grubu da mevcuttur. Yaptığımız çalışmada; kullandığımız her iki yaşam kalite ölçeğini değerlendirerek, sonuçta daha etkin olduğunu düşündüğümüz yaşam kalitesini ölçen test ile tedavi vereceğimiz hasta grubunu daha iyi tespit edebileceğimizi düşünmekteyiz. Çalışmamızın, her iki yaşam kalite ölçeğini OSAS'ta birlikte değerlendiren az sayıdaki literatüre katkıda bulunacağını düşünüyoruz.

Aşırı uykululuk, depresyon ve yaşam kalitesi arasındaki ilişki konusunda hala çelişkiler mevcuttur. Bir kohort çalışmasında, hafif OSAS'ı olan bireyler; OSAS'ı olmayanlara göre anlamlı düzeyde aşırı uykululuk, depresyon veya kötü yaşam kalitesi göstermemiştir (15). Çalışmamızda, gruplara göre olguların ESS ve BDI skorlamalarında istatistiksel olarak anlamlı farklılık görülmemiştir. Çalışmamız, bu açıdan belirttiğimiz kohort çalışması ile uyumlu bulunmuştur. Ancak istatistiksel olarak anlamlı olmasa da; çalışmamızda OSAS grubunda her iki ölçeğin skorları daha yüksek saptandı.

Yapılan çalışmalarda; OSAS'ın sosyal, duygusal ve fiziksel alanlarda, genellikle daha kötü bir yaşam kalitesi ile ilişkili olduğu saptanmıştır (16). Çalışmalar, şiddetli OSAS'ta daha düşük yaşam kalitesi saptamıştır (17,18). Çalışmamızda, gruplara göre olguların SF-36 ölçeği skorları istatistiksel olarak anlamlı farklılık göstermedi. Ancak fiziksel fonksiyon skorları; istatistiksel olarak anlamlı olmasa da; OSAS grubunda daha düşük saptandı.

Gruplara göre olguların WHOQOL-BREF ölçeği skorları, istatistiksel olarak anlamlı farklılık göstermemekle beraber; genel sağlık, fiziksek sağlık ve çevre skorları OSAS hastalarında daha düşük saptandı.

OSAS'ın kliniği ve PSG bulgularında cinsiyet farklılıkları olabilir. Erkeklerde kadınlardan iki ila üç kat daha fazla OSAS görüldüğü (19), erkeklerin daha erken yaşta OSAS ile başvurduğu (20) ve kadınlardan daha yüksek AHI'ye (21,22) sahip olduğu bildirilmiştir. Çalışmalar (23), OSAS'lı kadın hastalarda yaşam kalitesinin daha kötü olduğunu bildirmiştir. Bu durumun sebebi olarak; OSAS'lı kadın hastaların, yorgunluğu daha çok aşırı uyku hali olarak ifade etmeleri ve bu durumun da yaşam kalitesine yansıması olarak gösterilmiştir (24-26).

Çalışmamızda; OSAS'lı erkek hastaların SF-36 Ölçeği "Fiziksel fonksiyon" skoru, istatistiksel olarak anlamlı olmamakla birlikte OSAS'lı kadın hastalardan dikkat çekici düzeyde yüksek saptanmıştır. OSAS'lı erkek hastaların SF-36 ölçeği "Fiziksel rol güçlüğü, sosyal işlevsellik, emosyonel rol güçlüğü" skorları OSAS'lı kadın hastalardan istatistiksel olarak anlamlı düzeyde yüksek saptanmıştır. SF-36 ölçeği puanlamasında, kadın hastalarda genel olarak erkek hastalara göre skorlar daha düşük saptanmıştır. Çalışmamızda SF-36 ölçeği; OSAS'lı kadın hastalarda cinsiyetin yaşam kalitesine olan olumsuz etkisini daha etkili bir şekilde göstermiştir. Bu açıdan çalışmamız literatürle uyumlu bulunmuştur.

Cinsiyete göre WHOQOL-BREF Ölçeği skorları istatistiksel olarak anlamlı farklılık göstermemektedir. Erkek hastalarda fiziksel sağlık skorları; istatistiksel olarak anlamlı olmasa da daha düşük saptandı.

Bonomi ve arkadaşları (27) ; SF-36'nın fiziksel sağlık alt ölçeklerinin, WHOQOL-BREF'in hem fiziksel hem de psikolojik alt ölçekleriyle orta derecede ilişkili olduğunu bildirmiştir. Norholm (28) ve Skevington (29) SF-36'nın fiziksel alt ölçeklerinin, WHOQOL-BREF'in psikolojik alt ölçeklerinden çok fiziksel alt ölçekleriyle daha güçlü bir şekilde ilişkili olduğunu bildirmiştir. Çalışmamızda OSAS grubunda; istatistiksel olarak anlamlı olmasa da, SF-36 fiziksel fonksiyon skorları ile WHOQOL-BREF genel sağlık, fiziksel sağlık ve çevre skorları daha düşük bulundu.

OSAS'ta yaşam kalitesini değerlendirmek, OSAS kliniğinde kullanılmak üzere son zamanlarda sıklıkla başvurulan yöntemlerden biridir (3). OSAS hastaları, sıklıkla yaşam kalitesindeki bozulmayı gösteren semptomlarla başvurur. Yaşam kalitesindeki iyileşme, hastaların PAP tedavisine uyup uymadıklarının önemli bir göstergesidir. Bu durum, OSAS'ta klinik ve tedavi sonrası takipte yaşam kalitesini değerlendirmek için kullanılan ölçeklerin önemini artırır.

Örneklem sayısının azlığı, tek merkezde yürütülmüş olması, hastaların PAP tedavisi sonrası takiplerinin değerlendirilmemesi çalışmanın kısıtlılıklarıdır. OSAS tanısı ve tedavisi sonrası klinik takibinde SF-36 ve WHOQOL-BREF'in önemi; daha fazla sayıda hasta ve prospektif bir çalışma ile daha da pekiştirilebilir.

SONUÇ

Çalışmamız, SF-36 ve WHOQOL-BREF yaşam kalite ölçeklerinin OSAS tanısı ve tedavi aşamasında kullanılabileceğini; OSAS'lı kadın hastalarda, SF-36 ölçeğinin yaşam kalitesini değerlendirmede daha etkin olabileceğini göstermiştir. Çalışmamızın, OSAS'ta her iki yaşam kalite ölçeğini birlikte değerlendiren ve kadın hastalarda yaşam kalitesini değerlendirmede SF 36 ölçeğinin daha etkili olabileceğini gösteren az sayıda literatüre katkıda bulunacağını düşünüyoruz.

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Evaluation of family planning services: A district example in İstanbul

Aile planlaması hizmetlerinin değerlendirilmesi: İstanbul'da bir ilçe örneği

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Abstract

Aim: The aim of family planning services is to provide individuals with the information and support they need to make informed, safe, and healthy reproductive decisions. Furthermore, it provides women with the option to space out their pregnancies and offers protection from unplanned pregnancies. It is thought that family planning services could play a role in protecting maternal and child health, as well as improving the overall health level of society. The objective of this study was to gain insight into the family planning services provided to applicants at the Maternal Child Health and Family Planning (MCHFP) Centre in a district of İstanbul between 2018 and 2020.

Methods: The study population comprised individuals who had applied to the Eyüpsultan MCHFP Centre between 2018 and 2020. We are grateful to have had the opportunity to retrospectively analyze the data of 1,444 individuals.

Results: The study group had an average age of 33.95 years, with 45.2% of participants having completed primary education or below. It may be of interest to note that among the women who applied, 46.2% were in the age group of 35 years and above. It is worth noting that a significant proportion of the women who applied, namely 75.9%, were seeking to use a family planning method for the first time. It would seem that the age groups 29-34 and 35-40 saw the highest number of applications. It is notable that a relatively high proportion of women (49.4%) had not used any family planning method in the previous three months, compared to those who had employed other methods. It would seem that the intrauterine device is the most preferred family planning method across all age groups and education levels ($p<0.05$). It would seem that there is a difference between family planning methods before and after the AÇSAP application, according to years. Furthermore, it was observed that age group, educational level, and number of pregnancies were associated with the use of family planning methods ($p<0.05$).

Conclusion: In the study, the participants demonstrated a clear preference for modern family planning methods (86.1%) following the application period. It is recommended that individuals be provided with comprehensive family planning information and that awareness-raising activities be conducted in the local community. This will facilitate access to family planning services and improve attitudes and behaviors towards family planning.

Keywords: Child health; family planning; maternal health; maternal and child health centers

Öz

Amaç: Aile planlaması hizmetleri, bireylerin üreme ile ilgili kararlarını bilinçli, güvenli ve sağlıklı şekilde almalarını amaçlamaktadır. Ayrıca kadınların gebelikler arasındaki süreyi ayarlamalarına ve istenmeyen gebeliklerden korunmalarına olanak sağlayan bir uygulamadır. Aile planlaması hizmetleri ile anne ve çocuk sağlığı korunabilir ve toplumun sağlık düzeyi geliştirilebilir. Bu çalışmada İstanbul'un bir ilçesindeki Anne Çocuk Sağlığı ve Aile Planlaması (AÇSAP) merkezine 2018 ile 2020 yılları arasında başvuranlara verilen aile planlaması hizmetlerinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Tanımlayıcı tipteki araştırmanın evrenini Eyüpsultan AÇSAP Merkezi'ne 2018-2019-2020 yılları boyunca başvuran kişiler oluşturmuştur. Araştırma kapsamında 1444 kişinin verileri retrospektif olarak değerlendirilmiştir.

Bulgular: Araştırma grubunun yaş ortalaması 33,95 olup katılımcıların %45,2'sinin eğitim düzeyi ilköğretim ve altındadır. Başvuru yapan kadınların, %46,2'si ≥35 yaş grubundadır. Kadınların %75,9'u ilk defa aile planlaması yöntemi kullanmak için başvurumuştur. Yaş gruplarına göre en çok başvuru 29-34 yaş ve 35-40 yaş gruplarında gerçekleşmiştir. Son 3 ayda herhangi bir aile planlaması yöntemi kullanmayanların oranı (%49,4) diğer yöntemleri kullananlardan daha yüksek görülmüştür. AÇSAP Araştırma grubundaki kadınlardan tüm yaş gruplarında ve eğitim düzeylerinde en çok tercih edilen aile planlaması yöntemi Rahim İçi Araç olmuştur ($p<0,05$). Yıllara göre AÇSAP başvurusu öncesi ve sonrası aile planlaması yöntemleri arasında farklılık gözlenmiştir. Ayrıca yaş grubu, eğitim düzeyi ve gebelik sayısı ile aile planlaması yöntemi kullanımı arasında ilişkili tespit edilmiştir ($p<0,05$).

Sonuçlar: Araştırmada katılımcıların başvuru sonrası aile planlaması tercihi ağırlıklı olarak modern yöntemler (%86,1) olmuştur. Aile planlaması konusunda bireylerin desteklenmesi ve topluma yönelik farkındalık çalışmalarının yapılması, bireylerin aile planlaması hizmetlerine erişimini ve aile planlamasına yönelik tutum ve davranışlarının geliştirilmesine yardımcı olacaktır.

Anahtar Sözcükler: Aile planlaması; anne sağlığı; anne ve çocuk sağlığı merkezleri; çocuk sağlığı

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INTRODUCTION

Maternal and child health is one of the most significant determinants of the health levels of countries. The implementation of health improvement activities and the provision of health counseling prior to birth play a pivotal role in fostering the growth of a healthy population (1). Family planning (FP) services seek to ensure that individuals make informed, safe, and healthy reproductive decisions (2). The individual's knowledge, attitudes and beliefs, health literacy level, access to health services, and the ability to use the FP method correctly and effectively are among the determining factors affecting the use of sexual and reproductive health (3,4).

FP enables individuals to have children when and as many children as they want, the timing of pregnancy, and prevention of unwanted pregnancies. In this way, maternal and child health can be protected and the health level of society can be improved (5). In 2022, while the frequency of contraception use by women on a global scale is 65%, the rate of meeting the FP need of women of reproductive age with modern methods is 77.5%. While the rate of meeting the FP needs with traditional methods (coitus interruptus-withdrawal, calendar, vaginal douching, abstinence) is 7%, the unmet FP need is more than 15%. (6,7). According to Türkiye Demographic and Health Survey (TDHS) 2018 data, the rate of married women in Türkiye using any FP method is 70%, the rate of modern FP method use is 49%, and the unmet FP need is around 12% (7).

Globally, there are over one million new cases of sexually transmitted infections (STIs) diagnosed daily, with 370 million new cases reported annually (8). In 2020, approximately 287,000 women died from preventable causes related to pregnancy, childbirth, or puerperium, 95% of which occurred in low- and middle-income countries (9,10). In the same year, the maternal mortality rate was recorded at 223 per 100,000, reflecting a 34% decrease since 2000 due to the expansion of family planning services (9,11). In 2022, the maternal mortality rate in Türkiye was 12.6 per 100,000 (12). The global objective is to reduce this figure to below 70 per 100,000 by 2030 (9,10). Furthermore, additional antenatal care is a crucial aspect of ensuring optimal maternal and infant health outcomes. As reported by the World Health Organization (WHO), one million pregnancies occur globally on a daily basis. Of these, one-quarter are unplanned, one-third are unwanted pregnancies, and 29% result in miscarriage. Unsafe abortions, responsible for 45% of miscarriages, are a leading cause of maternal mortality (4,13,14). In Türkiye, high fertility rates and risky pregnancies, particularly among women under 20 and over 35, increase the risk of miscarriage. This emphasizes the importance of expanding reproductive health and family planning services (15,16).

Türkiye has been pursuing an antinatalist population policy and developing reproductive health and FP services since 1965 (17). The Ministry of Health facilitates citizens' access to reproductive health services, primarily through the provision of primary healthcare services. Counseling and services pertaining to reproductive health are provided at all family health centers. Furthermore, individuals applying to community health centers and district health directorates are provided with free reproductive health and FP services by units previously known as Maternal-Child Health and Family Planning (MCHFP) and currently designated as Child-Adolescent-Woman and Reproductive Health (CAWRH). The objective of these services is to provide education and counseling on reproductive health and sexually transmitted diseases, to ensure planned pregnancy, to provide healthy pregnancy and delivery services, to apply appropriate FP methods, and to reduce maternal-infant mortality (18,19).

The extent of unmet need for family planning services and the lack of knowledge of women in need of services are not fully known in the context of family planning services (20,21). Furthermore, the effects of cultural and religious factors on family planning services represent an important area for research (22). Conversely, the organization of health services and service quality are significant factors influencing citizens' access to family planning services (23). The objective of this study was to comparatively evaluate the sociodemographic characteristics, fertility characteristics, contraceptive method used, and type of service requested, by those who applied to MCHFP services in a district of İstanbul in 2018-2019 and 2020.

METHODS

The study employed a descriptive research methodology The study population comprised individuals who had submitted applications to the Eyüpsultan MCHFP Centre between the 1st of January 2018 and the 31st of December 2020. A total of 1,600 applications were submitted to the Eyüpsultan MCHFP Centre between 2018 and 2020, seeking FP-related services. Only the first applications of individuals in the same year were included in the study, with 140 duplicate applications made by the same individuals in the same year excluded. A total of 1460 individuals remained for analysis, with 16 cases excluded due to incomplete records. Consequently, the records of 1444 individuals were examined retrospectively. The examination of the records enabled the evaluation of the services received by the individuals, their use of FP methods, their change in the FP method they used, and the variables affecting these situations. The data on the time of application, demographic characteristics (age, gender, educational status), fertility characteristics (number of pregnancies, number of children born, number of living children, number of miscarriages, number of living children), and contraception characteristics (FP method used in the last three months, reason for application, change in the FP method used) were evaluated.

Statistical analyses

The statistical analysis of the study was performed using the Statistical Package for the Social Sciences package program version 24.0 (SPSS Inc., Chicago, IL, USA). Numerical variables were expressed as mean ± standard deviation (median, minimum, maximum), while categorical variables were expressed as numbers and percentages. The chi-square test was employed to ascertain the alterations within the parameters and the discrepancies between the groups in accordance with their distribution characteristics. A p-value of less than 0.05 was regarded as indicative of a statistically significant result.

Ethics committee permission

Ethics committee permission for the research was obtained from İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (date: 31.08.2023, decision no: 689).

RESULTS

The mean age of the study group was 33.9 years, with an application rate of 46.2% among those aged 35 years and over. The distribution of age, education level, number of pregnancies, and live births of those who applied to the MCHFP Center to receive FP services in 2018-2019-2020 is shown in Table 1.

While 75.9% (1096) of the women who applied to the MCHFP Centre did not use any FP method prior to the application, they commenced the use of an FP method following the application. Table 2 presents the distribution of the FP method use status of applicants to the MCHFP Centre before and after the application, as well as the FP methods used and switched to.

The highest number of applications was made in the 29-34 and 35-40 age groups. The distribution of applicants to the MCHFP Centre according to age groups and educational level is presented in Table 3.

Among the applicants to the MCHFP Centre, the proportion of those who did not use any FP method in the last 3 months was higher than those using the other methods. Furthermore, the most preferred FP method was the IUD. The distribution of applicants to the MCHFP Centre by year according to their characteristics related to fertility and FP, is shown in Table 4.

The most preferred FP method among women in the study group was IUD, regardless of age or education level ($p < 0.05$). The distribution of the FP methods that the women who applied to the MCHFP Centre subsequently initiated use of after their application, according to their sociodemographic characteristics, is presented in Table 5.

DISCUSSION AND CONCLUSION

In our study, the majority of the applicants were in the 29-40 age group, representing more than 50% of the total sample. Furthermore, the preference for traditional contraceptive methods and shorter-acting contraceptive use in the group below the age of 29 may be related to the desire to have a child. It is noteworthy that when the average age of mothers in Türkiye (29.0 years) is taken into consideration, it can be surmised that those in the study group mostly applied for FP methods after having a child (24).

Table 1. Sociodemographic and fertility characteristics of people applying to Maternal Child Health and Family Planning centres in 2018-2019-2020

		2018	2019	2020	Total
Age (Mean ± SD)		33,99 ± 7,75	33,68 ± 7,22	34,64 ± 7,39	33.95 ± 7.44
Number of Pregnancy (Mean ± SD)		2,91 ± 1,48	2,73 ± 1,38	2,77 ± 1,48	2.80 ± 1.41
Number of Live Births (Mean ± SD)		2,35 ± 1,071	2,27 ± 1,02	2,33 ± 1,16	2.32 ± 1.03
Number of Living Children (Mean ± SD)		2,30 ± 1,00	2,24 ± 0,97	2,27 ± 1,08	2.28 ±0.98
Number of Miscarriages (Mean ± SD)		0,56 ± 0,87	0,46± 0,80	0,44 ± 0,74	0.49 ± 0.81
		n	n	n	n (%)
Number of pregnancy (n=1444)	0	5	6	4	15 (1)
	1	56	85	60	201 (13.9)
	2-4	320	459	281	1060 (73.4)
	5 and above	61	67	40	168 (11.6)
Live births (n=1444)	0	6	6	5	17 (1.2)
	1	71	114	73	258 (17.9)
	2-4	350	478	294	1122 (77.7)
	5 and above	15	19	13	47 (3.3)
Total		442 (30.6)	617 (42.7)	385 (26.7)	1444 (100)

SD: Standart deviation, n: Number, %: Percentage

Table 2. Descriptive characteristics of people applying to Maternal Child Health and Family Planning centres in 2018-2019-2020 regarding Family Planning

		2018	**2019**	**2020**	**Total**	
		n (%)	**n (%)**	**n (%)**	**n**	**%**
Use of FP Method (n=1444)	Former User	100 (22.6)	160 (25.9)	88 (22.9)	348	24.1
	New User	342 (77.4)	457 (74.1)	297 (77.1)	1096	75.9
FP method used for the last 3 months at the time of application (n=1444)	Injection	6 (1.4)	30 (4.9)	27 (7.0)	63	4.4
	Oral Contraceptive	18 (4.1)	37 (6.0)	21 (5.5)	76	5.3
	Traditional Methods	64 (14.5)	63 (10.2)	4 (1.0)	131	9.1
	Condom	67 (15.2)	70 (11.3)	11 (2.9)	148	10.2
	IUD	107 (24.2)	110 (17.8)	96 (24.9)	313	21.7
	Does not use any method	180 (40.7)	307 (49.8)	226 (58.7)	713	49.4
FP method passed after the application (n=1444)	Traditional Methods	0 (0.0)	0 (0.0)	0 (0.0)	0	0.0
	Oral Contraceptive	13 (2.9)	6 (1.0)	23 (6.0)	42	2.9
	Injection	8 (1.8)	35 (5.7)	37 (9.6)	80	5.5
	Condom	45 (10.2)	63 (10.2)	0 (0.0)	108	7.5
	Does not use any method	71 (16.1)	56 (9.1)	74 (19.2)	201	13.9
	IUD	305 (69.0)	457 (74.1)	201 (65.2)	1013	70.2
Status of participants' changes in FP methods after application to Maternal Child Health and Family Planning. (n=1444)	No change	37 (8.4)	61 (9.9)	60 (15.6)	158	10.9
	Switching from any FP method to not using an FP method	71 (16.1)	56 (9.1)	74 (19.2)	201	13.9
	Switching from not using any FP method to using any method	180 (40.7)	307 (49.8)	226 (58.7)	713	49.4
	Change in the FP method used	154 (34.8)	193 (31.2)	25 (6.5)	372	25.8

FP: Family Planning, IUD: Intrauterine Device, n: Number, %: Percentage

Table 3. Distribution of applicants to Maternal Child Health and Family Planning centres by age and educational background by years

	2018	2019	2020	p
Age (n:1442)				
17-22	21 (4.8%)	34 (5.5%)	17(4.4%)	
23-28	102 (23.1%)	133 (21.6%)	73 (19.0%)	0.350
29-34	110 (24.9%)	186 (30.1%)	99 (25.8%)	
35-40	114 (25.9%)	146 (23.7%)	111 (28.9%)	
41 and above	94 (21.3%)	118 (19.1%)	84 (21.9%)	
Education Status (n:1444)				
Below primary education	43 (9.7%)	43 (7.0%)	35 (9.1%)	
Primary education	171 (38.7%)	221 (35.8%)	139 (36.1%)	
Secondary Education	87 (19.7%)	105 (17.0%)	67 (17.4%)	0.294
High School	84 (19.0%)	153 (24.8%)	91 (23.6%)	
Higher School and Bachelor's Degree	57 (12.9%)	95 (15.4%)	53 (13.8%)	
Total	442 (30.6%)	617 (42.7%)	385 (26.7%)	

n: Number

The health level of societies, the socioeconomic level of individuals, the socio-cultural structure, the provision of health services, and citizens' access to health services all exert an influence on family planning preferences. These factors also shape the preferences of individuals in relation to traditional or modern methods of family planning. Furthermore, they influence the choice of long- or short-acting family planning methods, depending on the desire to have children. The difficulties encountered in accessing healthcare services during the pandemic may have led women to opt for more traditional methods and condoms that could be purchased easily from pharmacies. The proportion of women who switched to a contraceptive method in the absence of protection prior to its initiation was found to be the highest in 2020. This indicates that women continue to seek and apply FP methods despite the difficulties encountered in accessing FP services provided by the Ministry of Health due to the pandemic. The period of the COVID-19 pandemic saw a number of factors impede individuals' access to and use of FP services. These included quarantine practices, women's access to primary healthcare services, the organization of healthcare services focused on the treatment of COVID-19, and problems in the supply of healthcare products (25-27). Furthermore, the suboptimal utilization of FP services during the course of the COVID-19 pandemic has had a detrimental impact on women's health, increasing the risk of unintended pregnancy and abortion in suboptimal circumstances (28). In the context of the ongoing global pandemic, it is of paramount importance to ensure the continuity of essential reproductive health services, including FP, through the utilization of diverse methodologies, with no interruption (29). In extraordinary situations such as pandemics, innovative services such as telemedicine and community/home-based services can be applied for antenatal and postnatal care and FP services to reduce the risk of exposure of healthcare personnel and individuals to the disease and to alleviate the burden on the healthcare system (30,31).

The level of education attained by an individual has an impact on their ability to access health services, their preferences regarding family planning, and their utilization of specific family planning methods. Despite the fact that those with a low level of education are situated within the lower sociocultural stratum of society, there is evidence to suggest that their utilization of family planning methods may vary. Given that women with low socioeconomic status tend to have larger families, they may represent a demographic with a heightened need for family planning services. Conversely, those with a low level of education tend to have limited health literacy, which in turn makes it more challenging for them to access health services. The fact that women with low education levels in the research group have less knowledge about FP methods

Table 4. Characteristics of fertility and Family Planning of people applying to Maternal Child Health and Family Planning. centres

	2018	2019	2020	p
Pregnancy (n: 1444)				
0	5 (1.1%)	6 (1.0%)	4 (1.0%)	
1	56 (12.7%)	85 (13.8%)	60 (15.6%)	
2-4	320 (72.4%)	459 (74.4%)	281 (73.0%)	0.663
5 and above	61 (13.8%)	67 (10.9%)	40 (10.4%)	
Number of live births (n:1444)				
0	6 (1.4%)	6 (1.0%)	5 (1.3%)	
1	71 (16.1%)	114 (18.5%)	73 (19.0%)	
2-4	350 (79.2%)	478 (77.5%)	294 (76.4%)	0.929
5 and above	15 (3.4%)	19 (3.1%)	13 (3.4%)	
FP Usage				
Former User	100 (22.6%)	160 (25.9%)	88 (22.9%)	
New Usser	342 (77.4%)	457 (74.1%)	297 (77.1%)	0.371
FP method used in the last 3 months before application (n:1444)				
Injection	6_a (1.4%)	30_b (4.9%)	27_b (7.0%)	
Oral Contraceptive	18_a (4.1%)	37_a (6.0%)	21_a (5.5%)	
Traditional Methods	64_a (14.5%)	63_a (10.2%)	4_b (1.0%)	**0.000**
Condom	67_a (15.2%)	70_a (11.3%)	11_b (2.9%)	
IUD	107_a (24.2%)	110_b (17.8%)	96_a (24.9%)	
Does not use any method	180_a (40.7%)	307_b (49.8%)	226_c (58.7%)	
FP method passed after the application (n:1444)				
Injection Moulding	8_a (1.8%)	35_b (5.7%)	37_b (9.6%)	
Oral Contraceptive	$13_{a.b}$ (2.9%)	6_b (1.0%)	23_a (6.0%)	
Condom	45_a (10.2%)	63_a (10.2%)	0_b (0.0%)	**0.000**
IUD	$305_{a.b}$ (69.0%)	457_b (74.1%)	251_a (65.2%)	
Does not use any method	71_a (16.1%)	56_b (9.1%)	74_a (19.2%)	
Changes in the FP method used after the application				
No change	37_a (8.4%)	61_a (9.9%)	60_b (15.6%)	
Switching from any FP method to not using an FP method	71_a (16.1%)	56_b (9.1%)	74_a (19.2%)	
Switching from not using any FP method to using any method	180_a (40.7%)	307_b (49.8%)	226_c (58.7%)	**0.000**
Change in the FP method used	154_a (34.8%)	193_a (%31.2)	25_b (6.5%)	

FP: Family Planning, IUD: Intrauterine Device, a, b: Statements of groups with significant differences between them, n: Number, %: Percentage

Table 5. Distribution of Family Planning methods started to be used by the applicants to Maternal Child Health and Family Planning. centres in 2018-2019-2020 according to sociodemographic characteristics

	Injection	Condom	Oral Contraceptive	IUD	Does not use any FP method	p
Age (n: 1442)						
17-22	1_{a} (1.4%)	4_{a} (5.6%)	0_{a} (0.0%)	63_{a} (87.5%)	4_{a} (5.6%)	
23-28	19_{a} (6.2%)	21_{a} (6.8%)	8_{a} (2.6%)	227_{a} (73.7%)	33_{a} (10.7%)	
29-34	25_{a} (6.3%)	21_{a} (5.3%)	11_{a} (2.8%)	284_{a} (71.9%)	54_{a} (13.7%)	**0.003**
35-40	22_{a} (5.9%)	32_{a} (8.6%)	13_{a} (3.5%)	255_{a} (68.7%)	49_{a} (13.2%)	
41 and above	$12_{a.b}$ (4.1%)	$30_{a.b}$ (10.1%)	$10_{a.b}$ (3.4%)	183_{b} (61.8%)	61_{a} (20.6%)	
Education Status (n:1444)						
Below primary education	6_{a} (5.0%)	9_{a} (7.4%)	0_{a} (0.0%)	88_{a} (72.7%)	18_{a} (14.9%)	
Primary education	21_{a} (4.0%)	46_{a} (8.7%)	14_{a} (2.6%)	363_{a} (68.4%)	87_{a} (16.4%)	
Secondary Education	13_{a} (5.0%)	20_{a} (7.7%)	8_{a} (3.1%)	182_{a} (70.3%)	36_{a} (13.9%)	**0.003**
High School	18_{a} (5.5%)	24_{a} (7.3%)	8_{a} (2.4%)	233_{a} (71.0%)	45_{a} (13.7%)	
Higher School and Bachelor's Degree	22_{a} (10.7%)	9_{b} (4.4%)	$12_{a.c}$ (5.9%)	$147_{b.c}$ (71.7%)	15_{b} (7.3%)	
Number of pregnancy (n:1444)						
0	$1_{a.b.c}$ (6.7%)	$4_{c.d}$ (26.7%)	6_{d} (40.0%)	1_{b} (6.7%)	$3_{a.c}$ (20.0%)	
1	18_{a} (9.0%)	11_{a} (5.5%)	7_{a} (3.5%)	131_{a} (65.2%)	34_{a} (16.9%)	**0.000**
2-4	55_{a} (5.2%)	76_{a} (7.2%)	29_{a} (2.7%)	755_{a} (71.2%)	145_{a} (13.7%)	
5 and above	6_{a} (3.6%)	17_{a} (10.1%)	0_{a} (0.0%)	126_{a} (75.0%)	19_{a} (11.3%)	

FP: Family Planning, IUD: Intrauterine Device a, b: Statements of groups with significant differences between them, n: Number, %: Percentage

may be related to the low rate of use. Furthermore, the fact that women with low educational levels were the most frequent applicants to the MCHFP unit in the study group may be related to the fact that this group prefers primary healthcare services where FP services are provided free of charge and access to these healthcare services is easier. The high rate of IUD use among women with a low level of education suggests that they have many children and wish to prefer long-term FP. In Türkiye, the reasons for women's preference for FP were determined to be reliability, cost-effectiveness, and accessibility, with minimal side effects (32). In another study conducted in Türkiye, the number of pregnancies and miscarriage rates of women with low education levels were found to be higher (33). It is acknowledged that the decision to utilize FP may not be straightforward for women, particularly given the multitude of factors that influence this decision. These factors include age, beliefs, educational and economic status, sociocultural values, thoughts about FP, and whether or not the woman has children (34-36). A meta-analysis conducted in Ethiopia determined the unmet need for FP to be between 26.52% and 36.39%. The determinants of this need were found to be the age at first marriage, the low educational level of the woman and her husband, and couples not discussing FP with each other (2). In a further meta-analysis, it was demonstrated that the unmet need for FP in sub-Saharan Africa was influenced by a number of factors, including the age of the woman, educational level, consent of the husband, accessibility of health facilities, and service provision (23).

The number of pregnancies and the number of children may influence women's preferences with regard to family planning. The average number of pregnancies and children in Türkiye varies across regions (33). In the study group, women who had experienced between two and four pregnancies and live births were more likely to submit applications. This suggests that families have an attitude about having as many children as they can care for, which leads them to apply for FP services. Furthermore, women with two or more pregnancies were more likely to opt for long-term contraceptive methods such as intrauterine de-

Table 6: Various family planning studies conducted in Türkiye

	Modern method	Traditional method	No method used
Değer at al. Maternal Child Health and Family Planning	86,1%	13,9%	0%
Mayda at al. (MCHFP)	82,6%	17,4%	0%
Doğru at al. (Hospital)	28,8%	26,7%	45,5%
Tekgündüz at al. (Hospital)	25,3%	10,0%	64,7%
Yücel at al. (Cross-sectional)	71,3%	26,5%	12,2%
Altuntaş at al. (Cross-sectional)	53,2%	19%	27,8%
Turkey Demographic and Health Survey - 2018	48,9%	20,9%	30,2%

vices (IUDs). In 2019 and 2020, women who had no pregnancy preferred oral contraceptives (OCs), while women who had two or more pregnancies preferred FP methods such as IUD. This indicates that women with no prior pregnancy prefer the FP method that they can discontinue more readily when they change their decision to have a child.

The majority of applicants to MCHFP centers express a desire to utilize a modern family planning method. Some of them apply to alter their family planning method. Indeed, the findings of our study indicate that the majority (75.9%) of applicants to MCHFP centers sought to utilize a novel FP method. In the global context, the proportion of women in the reproductive age group who have met their FP needs through modern contraceptive methods is 77.5%, while the unmet FP need is more than 15%, according to data from the 2018 TDHS. The rate of married women in Türkiye who use any FP method is 70%, while the rate of modern FP method use is 49.0%. The unmet FP need in all women is approximately 12.0% (6,7). In our study, the rate of use of any traditional or modern FP method by the applicants was 50.6%, which is below the average for Türkiye, while the rate of use of modern FP method after application was 86.1%, which is above the rates of use of any FP and modern FP method in Türkiye according to TDHS-2018 data. All of the FP methods used after application to our MCHFP unit are modern FP methods. The proportion of individuals who did not utilize any FP method following their visit to the MCHFP unit was 13.9%. A meta-analysis conducted on the FP attitudes of women in Türkiye revealed that the IUD (19.1%-25.2%), pill (13.9%-50.9%), and condom (13.2%-47.3%) were the most preferred modern methods, respectively. In contrast, withdrawal (9.1%-61.3%) was more commonly adopted among traditional methods. Furthermore, women with higher educational levels, those with social security, and working women exhibited more positive attitudes towards FP method use. (5).

Various FP studies conducted in Türkiye with community-based and different health facilities are shown in Table 6.

In community-based studies conducted with applicants to health facilities, the utilization of family planning methods exhibits variability according to the characteristics of the research group. In MCHFP centers, modern FP services, including IUDs, condoms and OCs, are provided with greater frequency. It may therefore be anticipated that the rate of uptake of modern FP methods among applicants to these centres will be high. This is because those who apply to MCHFP centers have already made the decision to use modern FP methods. Indeed, the prevalence of modern FP methods (82.6-86.1%) was observed to be higher in the studies conducted with those who applied to MCHFP centers in the table compared to the TDHS-2018 (15,35). Given that the majority of individuals seeking care at the hospital are there due to other health concerns, the utilization of FP methods may differ from the overall population average. As evidenced by the present study, the prevalence of modern FP method use (25.3-28.8%) was observed to be relatively low in comparison to other studies and the TDHS-2018. Furthermore, the proportion of hospital applicants who do not utilize any method (45.5-64.7%) is markedly higher than the TDHS data (15,37,38). In community-based cross-sectional surveys, appropriate sample selection allows for a more accurate representation of the status of FP method use in the community. As evi-

denced in the community-based FP studies presented in Table 6, the rate of modern FP method use (53.2-71.3%) exhibits variability, though it is lower than in our study and closer to the TDHS 2018 data (15,32,39).

FP is one of the most prominent primary healthcare practices. It is of the utmost importance to inform and guide women who require this service and to organize the necessary health system for them to receive this service. This is essential for improving the health level of society (40). It has been observed that disadvantaged groups, such as migrants and young people, have low levels of knowledge about and use of modern FP methods. This is due to cost and access to services (41,42). A study conducted in Şanlıurfa revealed that the prevalence of modern contraceptive use was 51.7%, with the most common reason for non-use being the unwillingness of the spouse (43). It is crucial to enhance the involvement of men as both users and beneficiaries to ensure the success of FP services (44). Furthermore, the provision of FP services in accordance with the privacy of individuals and without discrimination is an effective means of increasing individuals' access to services and FP preferences (45).

The unmet need for FP represents a significant public health concern, underscoring the inability of women to access this service (7). The quality and inclusiveness of FP services can be enhanced by increasing the level of awareness of the general public, particularly healthcare professionals, supporting those who require FP and identifying issues related to reproductive health (46,47). Furthermore, the diversification of contraceptive methods will facilitate the utilization of services by increasing the likelihood of individuals being able to make an informed choice. Furthermore, evidence indicates that informing and training activities targeting the general public, such as mass media, email, and text messages, have a positive effect on the utilization of FP services (48).

The provision of reproductive health and FP services is contingent upon the extent of coverage and utilization of the service (49). In Türkiye, the priority problems related to FP may include the following: the level of social awareness about FP varies significantly between regions; the social role of women; and the fact that all individuals do not have equal chances in accessing health services due to the low level of health literacy in our society (50). Conversely, person-centered sexual and reproductive health services that respect individuals' preferences, needs, and values and enable them to take responsibility for their own sexual and reproductive health are of critical importance for all women worldwide to benefit from these services (51).

Strengths and limitations of the study

The study has both strengths and limitations. It contributes to the existing body of literature on reproductive health and FP, which is an important determinant of maternal and child health and must be met. The fact that the study was conducted in a unit affiliated with the Ministry of Health is significant in that it provides citizens with the opportunity to evaluate the procurement of services from a public institution in the field of FP. Conversely, the fact that the study population consisted of those who had applied to the health facility represents a limitation. Furthermore, the fact that the study was conducted in a single center necessitates caution in generalizing the results to the wider population with regard to family planning.

The findings of our study indicate that the prevalence of modern FP methods among those who had undergone the application procedure was 86.1%. The preference for FP methods among applicants to the MCHFP center was found to be associated with their level of education, age group and number of pregnancies ($p < 0.05$).

The provision of support to individuals in the field of FP and the implementation of awareness-raising activities within the community will facilitate the accessibility of FP services and enhance the attitudes and behaviors of individuals towards FP. Furthermore, studies aimed at enhancing the health literacy of the population, expanding the range of contraceptive options, and adopting an individual-centered approach will facilitate individuals' access to and utilization of contraceptive services.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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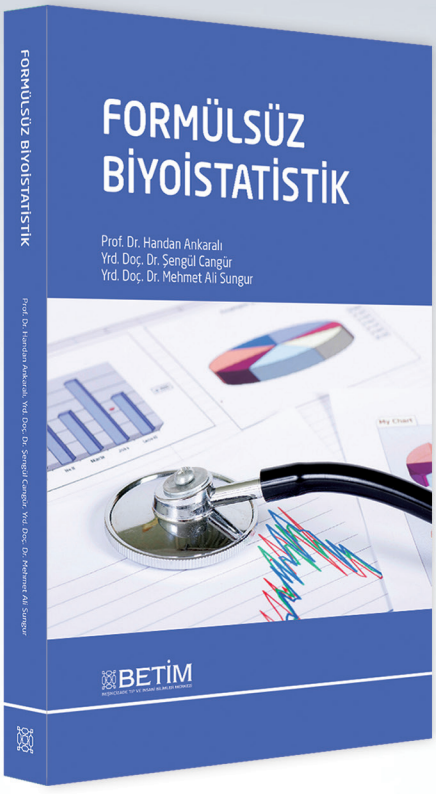

Formülsüz Biyoistatistik

Handan Ankaralı - Şengül Cangür - Mehmet Ali Sungur

Biyoistatistik yöntem ve prensiplerden yararlanırken önemli olan, doğru veriyi seçmek, doğru yerde kullanmak, doğru yöntemlerle değerlendirmek ve elde edilen sonuçları doğru bir şekilde sunmaktır. Bu bilgiler ışığında ve günümüz teknolojisi sayesinde elle çözüme neredeyse hiç ihtiyaç duyulmadığı gerçeğinden hareketle, bu kitapta yalın bir anlatım tekniği seçilmiş ve formül vermemek tercih edilmiştir. Bu anlatım tekniğiyle, biyoistatistik bilimi ve araçlarını, korkulacak bir bilim dalı olmaktan çıkararak sevilen ve ilgi duyulan bir bilim haline getirmek, ayrıca araştırmacıların temel düzeyde istatistik değerlendirmelerini yapabilecek donanıma sahip olmalarını sağlamak, en azından nerede yardım almaları gerektiği konusunda bilinç düzeylerini artırmak amaçlanmıştır.

BETİM KİTAPLIĞI

Clinical characteristics, outcomes, and prognostic factors of patients with systemic rheumatic diseases in medical intensive care unit: A retrospective single center study

Medikal yoğun bakım ünitesinde takip edilen sistemik romatolojik hastalığı olan hastaların klinik özellikleri, sonuçları ve prognostik faktörleri: Retrospektif tek merkezli çalışma

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Abstract

Aim: Systemic rheumatic diseases are a group of diseases that can affect several organs and occasionally need intensive care unit (ICU) admission due to the severity of diseases or complications. In this study, we aimed to investigate clinical features and factors associated with mortality in patients with systemic rheumatic diseases who were followed up in the medical ICU

Methods: This retrospective cohort study was conducted at a medical ICU, between January 1, 2018, and December 31, 2022. Patients who were 18 years older and with known or newly diagnosed systemic rheumatic diseases who were followed up in the ICU for more than 48 hours were included in the study. The cause of admission, clinical characteristics, and factors associated with mortality were evaluated.

Results: A total of 76 patients were included in the final analysis; the mean age was 60,8±15.0 years and rheumatoid arthritis (RA) (39%) was the most common systemic rheumatic disease. Acute respiratory failure (64%) was the most common reason for ICU admission, followed by septic shock (16%). A total of 41 (54%) patients died during their ICU stay. Non-survivor patients were older (mean age, 66.1 vs. 54.8 years, p=0.005) and had a higher APACHE-2 score than survivors (median, 24 vs. 14, p<0.001). APACHE-2 score ≥19 predicted mortality with 82% sensitivity and 80% specificity in patients with systemic rheumatic diseases.

Conclusions: ICU mortality was higher in patients with systemic rheumatic diseases. APACHE-2 score is a prognostic factor for ICU mortality in patients with systemic rheumatic diseases.

Keywords: APACHE II; intensive care units; mortality; rheumatic diseases

Öz

Amaç: Sistemik romatolojik hastalıklar, birçok organı etkileyebilen ve sıklıkla hastalığın şiddeti veya komplikasyonları nedeni ile yoğun bakım yatışı gereken bir grup hastalıktır. Bu çalışmada, medikal yoğun bakım ünitesinde (YBÜ) takip edilen sistemik romatolojik hastalık tanılı hastaların klinik özellikleri ve mortalite ile ilişkili faktörlerin değerlendirilmesini amaçladık.

Yöntemler: Bu retrospektif çalışma 1 Ocak 2018 ve 31 Aralık 2022 tarihleri arasında medikal YBÜ' de yapılmıştır. On sekiz yaş ve üzerinde bilinen veya yeni tanı almış sistemik romatolojik hastalığı olan ve YBÜ'de 48 saatten daha uzun süre takip edilen hastalar çalışmaya dahil edildi. Hastaların YBÜ'ye yatış nedenleri, klinik özellikleri ve mortalite ile ilişkili faktörleri değerlendirildi.

Bulgular: Çalışmaya dahil edilen 76 hastanın ortalama yaşı 60.8±15.0 yıldı ve en sık sistemik romatolojik hastalık romatoid artrit (%39) olarak tespit edildi. Yoğun bakıma en sık kabul edilme nedeni akut solunum yetmezliği (%64) ve septik şoktu (%16). Toplam 41 (%54) hasta YBÜ takipleri esnasında vefat etti. Vefat eden hastalar yaşayan hastalar ile karşılaştırıldığında daha ileri yaşta (ortalama yaş, 66.1 vs. 54.8 yıl, p=0.005) ve daha yüksek APACHE-2 skoruna (ortanca, 24 vs. 14, p<0.001) sahipti. APACHE-2 skorunun 19 ve üzeri olmasının %82 sensitivite ve %80 spesifite ile sistemik romatolojik hastalığı olanlarda mortaliteyi gösterdiği tespit edildi.

Sonuç: Sistemik romatolojik hastalığı olan hastalarda yoğun bakım mortalitesi yüksektir. APACHE-2 skoru YBÜ' de takip edilen sistemik romatolojik hastalığı olanlarda prognostik bir göstergedir.

Anahtar Sözcükler: APACHE II; ölüm oranı; romatizmal hastalıklar; yoğun bakım üniteleri

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INTRODUCTION

Systemic rheumatic diseases are a group of heterogeneous diseases that affect joints, soft tissues, and organs due to chronic inflammation. The severity of these diseases varies from mild symptoms to severe, threatening organ failure and usually requires immunosuppressive treatments. Previous studies have reported an increased risk of hospitalization due to the disease severity or complications of the immunosuppressive treatments (1,2).

Among systemic rheumatic diseases, systemic lupus erythematosus (SLE), systemic vasculitis, and rheumatoid arthritis (RA) are most prevalent in the ICU (3–5) including morbidity and mortality, were assessed in relation to the underlying diseases, treatments and complications. Results Overall, 48 patients with rheumatoid arthritis, five patients with spondyloarthritis, 14 patients with vasculitis, 30 patients with connective tissue diseases and 11 patients suffering from other rheumatologic conditions were admitted to the intensive care unit (ICU. In previous studies, respiratory failure was reported as the most common cause of ICU admission (4,6)59 years [interquartile range, 42-70 years]. Infections and exacerbations of lung involvement from systemic rheumatic diseases were the leading reasons for respiratory failure. Septic shock and acute kidney failure were reported as other frequent reasons for ICU admission in the rheumatologic population (4,5,7)carried out at a medical ICU in a military referral hospital. All adult ICU admissions with a known rheumatologic diagnosis were evaluated during 28 consecutive months. There were 48 ICU admissions available for review in 36 patients (1.33 ICU admissions/patient.

The rate of ICU mortality in rheumatologic population varied a wide range from 16% to 55% in previous studies (3,5,8,9)most importantly, long-term outcomes are scarce. Research Question: The aim of this study was to assess short and long-term outcome of patients with SRD who were admitted to the ICU. Study Design and Methods: All records of patients with SRD who were admitted to ICU between 2006 and 2016 were reviewed. In-hospital and one-year mortality rates were assessed, and predictive factors of death were identified. Results: A total of 525 patients with SRD were included. Causes of admission were most frequently shock (40.8%. In previous studies, advanced age, higher APACHE-2 scores, and receiving invasive mechanical ventilation (IMV) were reported as prognostic factors for mortality (4,5,8)47 females. Patients who were admitted to ICU for infections had a higher mortality rate than patients who were admitted to ICU for non-infectious reasons (4,10,11)including 23 patients who died in the ICU. Multivariable logistic regression showed that poor prior health status (Berdit's classification.

Few studies have examined the prognosis and mortality-related factors of patients with systemic rheumatic diseases who were followed up in the ICU. This study aimed to evaluate the demographic and clinical characteristics of patients with rheumatic diseases followed in medical ICU and to determine the factors associated with mortality in these patients.

MATERIAL AND METHODS

This retrospective cohort study was conducted at the University of Health Sciences Turkey, İzmir School of Medicine, Dr. Suat Seren Chest Disease and Surgery Training and Research Hospital, Intensive Care Unit, between January 1, 2018, and December 31, 2022. İzmir is the third-biggest city in Turkey and is in the western region of Turkey. Our unit is a respiratory ICU consisting of 23 beds and 600–700 adult admissions per year.

During the study period, patients aged 18 years and older with known or newly diagnosed systemic rheumatic diseases who were followed up in the ICU for more than 48 hours were included in the study. Patients with systemic rheumatic diseases who stayed in the ICU for less than 48 hours, pregnant patients, and patients without systemic rheumatic diseases (osteoarthritis, etc) were excluded from the final analysis.

The definition of newly diagnosed rheumatic diseases was made by a rheumatologist, and patients with known systemic rheumatic diseases were based on previous diagnoses by a rheumatologist. Demographic data, type of rheumatological treatment, clinical features, the reasons for ICU admission, APACHE-2 scores, ICU treatments, the need for IMV, renal replacement therapy (RRT), and therapeutic plasma exchange were obtained from hospital medical records. Primary outcome of the study was ICU mortality.

This study was approved by University of Health Sciences Turkey, Dr. Suat Seren Chest Disease and Thoracic Surgery Teaching and Research Hospital, Clinical Research Ethics Committee (Date: 20.09.2023, decision no: 2023/54-52).

Statistical Analysis

All statistical analyses were performed using SPSS 26.0 (Statistical Package for the Social Sciences. IBM Corp. Armonk, NY).

Patients admitted to ICU due to infectious reasons, and non-infectious reasons were compared for ICU mortality. Pneumonia, septic shock, or tuberculosis were defined as infectious reasons for ICU admission. Other reasons for ICU admission were defined as non-infectious reasons such as flares of rheumatic diseases, pulmonary thromboembolism, and acute kidney injury. To evaluate the effect of rheumatological treatment on intensive care unit mortality, patients who received biological disease modifying anti-rheumatic drugs (bDMARDs) were compared with those who did not. Comparisons were made with Chi-Square test for categorical data and with independent sample t-test or Mann-Whitney U test for continuous data. We also performed a receiving operating characteristics (ROC) analysis for the discriminative power of APACHE-2 for mortality. The post hoc power analysis of the study was tested using the G Power program based on the mean differences between the groups (31 vs. 45 patients). The analysis was single-ended. With an effect size of 0.6 and a margin of error of 0.05, a total sample of 76 patients reached a power of 0.81. The results suggested that the sample was of sufficient size The cut-off value was determined according to the maximum Youden index. A p-value <0.05 was accepted as statistically significant.

RESULTS

Seventy-six patients were included in the final analysis; 40 (52%) patients were female, and the mean age was 60,8±15.0 years. Rheumatoid arthritis (39%), granulomatosis with polyangiitis (14%), and spondyloarthropathies (12%) were the most common rheumatic diseases in patients who were followed up in the ICU, and the median duration of rheumatic disease was 11 years. Hypertension (39%) and diabetes mellitus (18%) are the most common comorbid diseases other than rheumatic diseases (Table 1). Rheumatic diseases were newly diagnosed in ten patients (13%) during their ICU stay.

Most patients were admitted to ICU due to acute respiratory failure (64%). Septic shock (16%) and acute kidney injury (12%) were other common reasons for ICU admission. Pneumonia and exacerbations of lung involvement of rheumatic diseases were the main causes of acute respiratory failure. Sixty-one patients (80%) were followed up under invasive mechanical ventilation (IMV) during their IUC stay. One in four patients needed renal replacement treatment (RRT), and nine (12%) patients required therapeutic plasma exchange (Table 1).

Forty-one (54%) patients died during their ICU stay. Non-survivor patients were older (mean age, 66.1 vs. 54.8 years, p=0.005) and had a higher APACHE-2 score than survivors (median, 24 vs. 14, p<0.001). Need for IMV (67.2% vs. 32.8%, p<0.001) and RRT (78.9% vs. 21.1%, p=0.009) were found to be associated with ICU mortality. Patients who were admitted to the ICU due to infectious reasons had a higher mortality rate than patients who were admitted to the ICU due to non-infectious reasons, but the difference was statistically insignificant (59% vs. 46%, p=0.604). The mortality rates were similar in patients who received bDMARDs and did not receive them (52% vs. 54%, p=0.378) (Table 2). ROC analysis showed that APACHE-2 score had good discriminative power for ICU mortality in patients with systemic rheumatic diseases (AUC: 0.91, 95% CI: 0.84 – 0.99, p<0.001) (Figure 1). The cut-off value of APACE-2 score for ICU mortality was 19, with 82% sensitivity and 80% specificity.

DISCUSSION AND CONCLUSION

The main findings of our study were that RA was the most frequent systemic rheumatic disease in our ICU, followed by granulomatosis with polyangiitis and spondyloarthropathies. Most patients with systemic rheumatic diseases were admitted to ICU due to respiratory failure. The ICU mortality rate was 54%; advanced age, a higher APACHE-2 score, and the need for IMV or RRT were found to be associated with mortality.

Table 1. Demographic and clinical features of patients

	Patients (n = 76)
Age, mean±SD, years	60,8±15.0
Gender, Female, n (%)	40 (52)
BMI, mean±SD, kg/m^2	26,4±5,1
Rheumatic Diseases, n (%)	
Rheumatoid Arthritis	30 (39)
Granulomatosis with Polyangiitis	11 (15)
Spondyloarthropathies	9 (12)
Ankylosing Spondylitis	6 (8)
Psoriatic Arthritis	2 (3)
Enteropathic Arthritis	1 (1)
Sarcoidosis	9 (12)
Systemic Lupus Erythematosus	6 (8)
Familial Mediterranean fever	4 (5)
Behçet's Disease	4 (5)
Dermatomyositis	2 (3)
Scleroderma	1 (1)
Duration of Rheumatic Diseases, median (IQR), years	11 (4 – 25)
Rheumatological Treatment, n (%)	
Only cDMARDs	32 (42)
cDMARDs plus Steroids	8 (11)
Only bDMARDs	17 (22)
bDMARDs plus cDMARDs	4 (7)
Only Steroids	5 (17)
Comorbid Diseases, n (%)	
Hypertension	30 (39)
Diabetes Mellitus	14 (18)
Chronic Obstructive Pulmonary Disease	11 (14)
Coronary Artery Disease	9 (12)
Congestive Heart Failure	7 (9)
Malignancy	3 (4)
Cause of ICU admission, n (%)	
Acute Respiratory Failure	55 (72)
Pneumonia	30 (39)
Flare of Lung Involvement	19 (25)
Pulmonary Thromboembolism	4 (5)
Tuberculosis	2 (3)
Septic Shock	12 (16)
Acute Kidney Injury	9 (12)
APACHE-2 Score, median (IQR),	19 (15 – 24)
Invasive Mechanical Ventilation, n (%)	61 (80)
Renal Replacement Therapy, n (%)	19 (25)
Therapeutic Plasma Exchange, n (%)	9 (12)
Mortality, n (%)	41 (54)
Length of Stay in ICU, median (IQR), days	9 (6 – 19)

APACHE: Acute physiology and chronic health evaluation, BMI: Body mass index, DMARDs: Disease modifying anti-rheumatic drugs, ICU: Intensive care unit, IQR: Interquartile range, SD: Standard deviation

Data were shown as mean±SD, median (IQR) or n (%), ±: Plus-minus, SD: Standard deviation, n: Number, %: Percentage

SLE was reported as the most common systemic rheumatic disease in previous studies. Arjmand et al. reported that 50 of 91 (54.9%) ICU patients with systemic rheumatic diseases had SLE (4)life-threatening organ involvement, or complication of treatment. The objective of this study is to determine the causes, outcome, and prognostic factors of patients with rheumatologic diseases admitted in teaching medical ICUs in

Table 2. Comparison of survivor and non-survivor patients

	Survivors (n=35)	Non-Survivors (n=41)	*p*
Age, mean±SD, years	54.8±14.1	66.1±13.9	0.005
Duration of rheumatic diseases, median (IQR), years	7 (3 – 15)	8 (4 – 19)	0.321
Rheumatological treatment, bDMARDs, n (%)	10 (47.6)	11 (52.4)	0.378
ICU admission due to infection, n (%)	18 (40.9)	26 (59.1)	0.604
Invasive mechanical ventilation, n (%)	20 (32.8)	41 (67.2)	<0.001
Renal replacement therapy, n (%)	4 (21.1)	15 (78.9)	0.009
Theurapeutic plasma exchange, n (%)	5 (55.5)	4 (44.5)	0.806
Duration of rheumatic diseases, median (IQR), years	7 (3 – 15)	8 (4 – 19)	0.321
APACHE-2	14 (10 – 17)	24 (20 – 29)	<0.001
Length of stay in ICU, median (IQR), days	9 (6 – 18)	9 (5 – 22)	0.846

APACHE: Acute physiology and chronic health evaluation, bDMARDs: Biologic disease modifying anti-rheumatic drugs, ICU: Intensive care unit, IQR: Interquartile range, SD: Standard deviation

Data were shown as mean±SD, median (IQR) or n (%), n: Number, %: Percentage

southern Iran. Methods: A retrospective case review of all patients with rheumatologic diseases admitted in the academic medical ICUs in two referral hospitals in southern Iran, from March 2015 to January 2020. Patients' data were documented from their hospital records and the cause of admission, in-hospital outcome, and prognostic factors was evaluated. Results: Ninety-one patients were included, of which 71.4% were female. Systemic lupus erythematosus (54.9%. Cavallasca and colleagues reported that 38% of ICU patients with systemic rheumatic diseases had SLE (5)most importantly, long-term outcomes are scarce. Research Question: The aim of this study was to assess short and long-term outcome of patients with SRD who were admitted to the ICU. Study Design and Methods: All records of patients with SRD who were admitted to ICU between 2006 and 2016 were reviewed. In-hospital and one-year mortality rates were assessed, and predictive factors of death were identified. Results: A total of 525 patients with SRD were included. Causes of admission were most frequently shock (40.8%. In our study, RA was the most common systemic rheumatic disease. Although the prevalence of rheumatic diseases showed geographical differences, RA is one of the most frequent systemic rheumatic diseases. Çakır et al. reported that RA had a higher prevalence rate than other systemic rheumatic diseases in western Turkey (12). While RA predominantly affects the joints, extra-articular involvement is not uncommon; the lungs are one of the most affected extra-articular organs (13,14)in Olmsted County, Minnesota, USA. Methods. Data on incident ExRA were abstracted from medical records of patients with RA - Olmsted County residents who first met the 1987 American College of Rheumatology criteria for RA between January 1, 1995, and December 31, 2007. Patients were followed until death, migration from Olmsted County, or December 31, 2008. ExRA were classified using the predefined criteria and compared to the corresponding 1985-1994 inception RA cohort (n = 147. In our study, respiratory failure was the main reason for ICU admission. The fact that rheumatoid arthritis is both common and frequently affects the lungs were considered to be the main reason for the most common systemic rheumatic diseases in our cohort. RA was also reported as one of the most frequent systemic rheumatic diseases in the ICU. Brünnler et al. reported that 108 patients with rheumatic diseases were followed up in ICU and 48 (44%) of them had RA (3)including morbidity and mortality, were assessed in relation to the underlying diseases, treatments and complications. Results Overall, 48 patients with rheumatoid arthritis, five patients with spondyloarthritis, 14 patients with vasculitis, 30 patients with connective tissue diseases and 11 patients suffering from other rheumatologic conditions were admitted to the intensive care unit (ICU. It is common for patients to receive their first diagnosis of systemic rheumatic diseases during ICU admission. The diagnosis of systemic rheumatic diseases was made during the ICU stay in 14% of patients in Larcher's study (6)59 years [interquartile range, 42-70 years]. Arjmand et al. reported that 20%

of patients were new cases of systemic rheumatic diseases (4)life-threatening organ involvement, or complication of treatment. The objective of this study is to determine the causes, outcome, and prognostic factors of patients with rheumatologic diseases admitted in teaching medical ICUs in southern Iran. Methods: A retrospective case review of all patients with rheumatologic diseases admitted in the academic medical ICUs in two referral hospitals in southern Iran, from March 2015 to January 2020. Patients' data were documented from their hospital records and the cause of admission, in-hospital outcome, and prognostic factors was evaluated. Results: Ninety-one patients were included, of which 71.4% were female. Systemic lupus erythematosus (54.9%. In our study, ten cases (13%) were diagnosed with systemic rheumatic diseases during their ICU stay, and all of them had granulomatosis and polyangiitis. Systemic vasculitis was more likely to be newly diagnosed in the ICU due to severe specific organ involvement and the need for organ support therapy (6)59 years [interquartile range, 42-70 years].

Respiratory failure was found to be the main reason for ICU admission in our study. Pneumonia and acute exacerbations of lung involvement were the most common reasons for the development of respiratory failure in our patients. In previous studies, patients with systemic rheumatic diseases were mostly admitted to ICU due to infectious reasons. Arjmand et al. reported that the majority of patients with systemic rheumatic diseases need ICU admission due to infectious reasons (4)life-threatening organ involvement, or complication of treatment. The objective of this study is to determine the causes, outcome, and prognostic factors of patients with rheumatologic diseases admitted in teaching medical ICUs in southern Iran. Methods: A retrospective case review of all patients with rheumatologic diseases admitted in the academic medical ICUs in two referral hospitals in southern Iran, from March 2015 to January 2020. Patients' data were documented from their hospital records and the cause of admission, in-hospital outcome, and prognostic factors was evaluated. Results: Ninety-one patients were included, of which 71.4% were female. Systemic lupus erythematosus (54.9%. Infections were also reported as one of the most common reasons for ICU admission in a multicenter study conducted by Larcher and

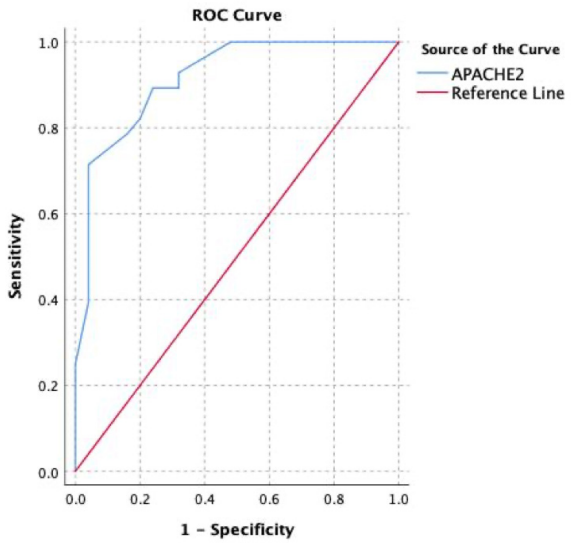

Figure 1. The Receiver operating characteristics analysis for intensive care unit mortality

colleagues (5)most importantly, long-term outcomes are scarce. Research Question: The aim of this study was to assess short and long-term outcome of patients with SRD who were admitted to the ICU. Study Design and Methods: All records of patients with SRD who were admitted to ICU between 2006 and 2016 were reviewed. In-hospital and one-year mortality rates were assessed, and predictive factors of death were identified. Results: A total of 525 patients with SRD were included. Causes of admission were most frequently shock (40.8%. In our study, more than half of the patients were admitted to ICU due to infectious complications such as acute respiratory failure due to pneumonia or septic shock. The risk of infection is increased in patients with rheumatic diseases because of an alternation of immunoregulation, comorbid diseases, or the use of immune suppressive treatments (15). Lungs were the main infection site in systemic rheumatic diseases such as RA and SLE (16,17)we performed a nested case-control study at the University of Toronto Lupus Clinic, with prospective follow-up according to a standard protocol since 1970. Cases were SLE patients seen between January 1987 and January 1992 who had documented infections and controls were patients without infection from the same cohort matched for age, gender and time of visit. The type, site and outcome of infection were recorded for each case. A conditional logistic regression analysis was

performed to compare factors associated with infection in cases and their controls. Ninety-three patients had 148 infection episodes; the majority were bacterial, but viral, fungal and protozoan organisms were also identified (multiple organisms in seven.

The ICU mortality of patients with rheumatic diseases varied widely in previous studies. The ICU mortality was reported at 16% by Brünnler et al. Larcher and colleagues reported that ICU mortality was 23.8%, and Cavallasca et al. reported 55% (3,5,9)including morbidity and mortality, were assessed in relation to the underlying diseases, treatments and complications. Results Overall, 48 patients with rheumatoid arthritis, five patients with spondyloarthritis, 14 patients with vasculitis, 30 patients with connective tissue diseases and 11 patients suffering from other rheumatologic conditions were admitted to the intensive care unit (ICU. We found the rate of ICU mortality was 54% in our study, slightly higher than that of the previous cohorts. Several factors were found to be associated with mortality in patients with systemic rheumatic diseases. A higher APACHE-2 score was one of the most important risk factors for ICU mortality in patients with systemic rheumatic diseases. The median APACHE-2 score was 12 in Brünnler's study, indicating that ICU mortality was lower (3)including morbidity and mortality, were assessed in relation to the underlying diseases, treatments and complications. Results Overall, 48 patients with rheumatoid arthritis, five patients with spondyloarthritis, 14 patients with vasculitis, 30 patients with connective tissue diseases and 11 patients suffering from other rheumatologic conditions were admitted to the intensive care unit (ICU. Aydın et al. reported that the mean APACHE-2 score was 24.7 and ICU mortality was 61% (18). The median APACHE score in our study was 19, which was higher than other studies and was thought to be the main reason for high mortality. APACHE-2 score had good discriminative power for mortality. Arjmand et al. reported that patients with an APACHE-2 score higher than 9 had a poor prognosis in ICU and the mortality rate with an APACHE-2 score above 9 was 96% (4)life-threatening organ involvement, or complication of treatment. The objective of this study is to determine the causes, outcome, and prognostic factors of patients with rheumatologic diseases admitted in teaching medical ICUs in southern Iran. Methods: A retrospective case review of all patients with rheumatologic diseases admitted in the academic medical ICUs in two referral hospitals in southern Iran, from March 2015 to January 2020. Patients' data were documented from their hospital records and the cause of admission, in-hospital outcome, and prognostic factors was evaluated. Results: Ninety-one patients were included, of which 71.4% were female. Systemic lupus erythematosus (54.9%. In our study, the cut-off value of APACHE-2 score for mortality was 19, with 82% sensitivity and 80% specificity. Need for IMV was another risk factor for ICU mortality. In previous studies, higher ICU mortality rates were reported in patients who were followed up with IMV (3,4)including morbidity and mortality, were assessed in relation to the underlying diseases, treatments and complications. Results Overall, 48 patients with rheumatoid arthritis, five patients with spondyloarthritis, 14 patients with vasculitis, 30 patients with connective tissue diseases and 11 patients suffering from other rheumatologic conditions were admitted to the intensive care unit (ICU. We found that the need for IMV was associated with ICU mortality; two of three patients who were followed up under IMV died during their ICU stay. In our study, most patients were followed up in the ICU due to respiratory failure, and the majority of patients (80%) needed IMV support, which was thought to be another reason for high mortality rate in our cohort. In previous studies, the mortality rate was reported to be higher in patients who were admitted to ICU due to infections (4,8)47 females. We found that patients who were admitted to the ICU for infectious reasons had a higher mortality rate than patients who were admitted for non-infectious reasons, but the difference was statistically insignificant. In our study, patients who received bDMARDs and patients who did not receive them had similar mortality rates. The effect of rheumatic treatment on ICU mortality is controversial. Godeu et al. reported that corticosteroid use was associated with poor prognosis; however, the use of corticosteroids or other immunosuppressive agents was not found to be associated with mortality by Moreels and colleagues (10,19).

Our study has several limitations. The results of our study cannot be generalized to all rheumatological populations because it is a single-center study. We assessed a limited number of parameters because our

study was retrospective. Most patients were admitted to the ICU for respiratory system-related complications such as respiratory failure because our center is specific to pulmonary intensive care. The severity of systemic rheumatic diseases may affect ICU outcomes. However, the severity of rheumatic diseases was unknown because the study was retrospective. Our study focused on the short-term outcomes of ICU patients with systemic rheumatic diseases; the long-term outcomes of these patients remain unclear.

In conclusion, patients with systemic rheumatological diseases have higher ICU mortality rates, and some of these patients may be diagnosed for the first time in the ICU. The APACHE-2 score may be useful for predicting mortality in patients with systemic rheumatologic diseases.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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Nadir bir orbital patoloji: Persistan hiperplastik primer vitreus

A rare orbital pathology: Persistent hyperplastic primary vitreous

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Öz

Amaç: Persistan hiperplastik primer vitreus (PHPV), embriyolojik primer vitreus ve hyaloid damar sisteminin gerilememesi nedeniyle ortaya çıkan konjenital bir anomalidir. Etkilenen gözlerde anatomik ve visual sonuç üzerinde önemli etkisi olabilir. Amacımız PHPV tanısı konulmuş hastaların Manyetik Rezonans Görüntüleme (MRG) özelliklerini sunmak ve literatürle karşılaştırmaktır.

Yöntemler: Çalışmamız retrospektif bir arşiv çalışması olup Ocak 2010-Ocak 2020 tarihleri arasında merkezimizde orbital MR çekimi yapılan ve görüntülemelerinde PHPV tanısı bulunan 9 hasta çalışmaya dahil edilmiştir. Hastalar yaş, cinsiyet, etkilenen orbita (sağ-sol, unilateral-bilateral), eşlik eden ek anomaliler açısından değerlendirildi.

Bulgular: Çalışmaya alınan 9 hastanın 8'i erkek 1'i kız idi. Hastaların yaş aralığı 3 ay-56 yaş olup yaş ortalaması 10,8 idi. Bilateral tutulum 2 (%22) hastada, unilateral tutulum 7 (%78) hastada (5 hastada sağ, 2 hastada sol) izlendi. Mikroftalmi 5 hastada, dismorfik orbita 2 hastada, retinal hemoraji-dekolman 3 hastada izlenmiştir. PHPV olgularına eşlik eden ek kranial patolojiler değerlendirildiğinde; 1 hastada lizensefali, 1 hastada porensefalik kavitasyon ve 2 hastada optik sinir periferinde sıvı artışı izlendi.

Sonuçlar: Sonuç olarak tek taraflı tutulum, mikroftalmi ve ön kamaranın kollabe olması PHPV ayırıcı tanısında en önemli klinik ipuçlarıdır. PHPV'den şüphelenildiğinde retrolental kitle ve huni şeklinde retina dekolmanı MR görüntülemede tanı koymada son derece önemli bulgulardır.

Anahtar Sözcükler: Manyetik rezonans görüntüleme; orbita hastalıkları; persistan hiperplastik primer vitreus; retinal hemoraji

Abstract

Aim: Persistent hyperplastic primary vitreous (PHPV) is a congenital anomaly that occurs due to failure of the embryological primary vitreous and hyaloid vascular system to regress. It may have a significant impact on the anatomical and visual outcome in the affected eyes. Our aim is to present the Magnetic Resonance Imaging (MRI) features of patients diagnosed with PHPV and compare them with the literature.

Methods: Our study is a retrospective archive study and 9 patients who underwent orbital MRI in our center between January 2010 and January 2020 and were diagnosed with PHPV on their images were included in the study. Patients were evaluated in terms of age, gender, affected orbit (right-left, unilateral-bilateral), and accompanying additional anomalies.

Results: Of the 9 patients included in the study, 8 were boys and 1 was a girl. The age range of the patients was 3 months-56 years and the average age was 10.8 years. Bilateral involvement was observed in 2 (22%) patients, and unilateral involvement was observed in 7 (78%) patients (right in 5 patients, left in 2 patients). Microphthalmia was observed in 5 patients, dysmorphic orbita in 2 patients, and retinal hemorrhage-detachment in 3 patients. When additional cranial pathologies accompanying PHPV cases are evaluated; lissencephaly was observed in 1 patient, porencephalic cavitation in 1 patient, and increased fluid in the optic nerve periphery was observed in 2 patients.

Conclusions: As a result, unilateral involvement, microphthalmia and anterior chamber collapse are the most important clinical clues in the differential diagnosis of PHPV. When PHPV is suspected, retrolental mass and funnel-shaped retinal detachment are extremely important findings in making the diagnosis on MR imaging.

Keywords: Magnetic resonance imaging; orbital disease; persistent hyperplastic primary vitreous; retinal hemorrhage

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GİRİŞ

Persistan hiperplastik primer vitreus (PHPV), embriyolojik primer vitreus ve hyaloid damar sisteminin gerilememesi nedeniyle ortaya çıkan konjenital bir anomalidir. Etkilenen gözlerde anatomik ve visual sonuç üzerinde önemli etkisi olabilir. Sonuçta fitizis bulbi ve tedavisi olmayan glokoma yol açabilir. Ayrıca, inatçı glokom ve klinik olarak şüphelenilen retinoblastom, enükleasyonun ana nedenidir (1,2). Çoğunlukla sağlıklı yenidoğanlarda görülür ve mikroftalmus, katarakt, retrolental fibrovasküler doku, persistan hiyaloid damarlanma ve tunica vasculosa lentis kalıntılarıyla ilişkilidir (1). Histolojik olarak bu süreçler retrolental kitlenin kenarlarına dahil edilir. Lens lifleri dejenere olur ve lens epitel hücreleri arkaya doğru göç eder. Lensin arka kapsülünün açılması sonucu spontan katarakt oluşabilir (1-3).

PHPV lökokori, mikroftalmi, katarakt, yaygın intravitreal kanama, hiyaloid arterin kalıcılığı, lensin şişmesi veya retrolental dokunun kontraktürünün neden olduğu sekonder glokom ve bazen de retina dekolmanı ile prezente olur (2,3). Tipik olarak tek taraflıdır; ancak iki taraflı olduğunda çoğunlukla trizomi 13, Walker Warburg sendromu ve Norrie hastalığı gibi diğer oküler ve sistemik konjenital sendromlar ile birliktelik gösterir (4). PHPV'nin karakteristik histopatolojik özelliği retrolental fibrovasküler membranın kalıcılığıdır. Uzatılmış siliyer süreçler küçük bir merceğin çevresi etrafında uzanabilir. Yaşlı hastalarda merceğin tamamen kalsifikasyonu, hatta kemikleşmesi gözlenebilir. Bazen merceğin retinası ayrılır, bazen de arka hyaloid membranın ayrılması olabilir. PHPV'nin MR görünümü oldukça değişken olabilir, embriyonik vitreus bileşenlerinin hiperplazisinin miktarına ve karakterine ve ikincil komplikasyonun kapsamına ve doğasına bağlı olarak değişir (5).

PHPV'nin Bilgisayarlı Tomografi (BT) görünümü, embriyonik vitreus bileşenlerinin hiperplazisinin miktarına ve karakterine, ikincil komplikasyonun boyutuna ve doğasına bağlı olarak oldukça değişken olabilir. PHPV tanısında Manyetik Rezonans Görüntüleme (MR) görüntüleme, BT'den üstündür. Üstün kontrast çözünürlüğüne sahip multiplanar görüntüleme intraorbital ve orbital yapıların biyokimyasal bileşimi hakkında fikir verir. Lensin, retrolental kitlenin ve buna bağlı retina - arka hyaloid dekolmanının görünümü, MR görüntülemede BT'ye göre daha iyi değerlendirilebilir. MR görüntülemenin hassasiyeti, yağ baskılı tekniklerinin kullanılması ve orbital yüzey koillerin kullanılmasıyla daha da artırılabilir. Postkontrast MR görüntülerinde, retrolental kitle içinde ve bazen ön kamarada anormal kontrastlanma tespit edilebilir (3-8).

Persistant hiperplastik primer vitreus hastalığının ayırıcı tanısı başvuru yaşına bağlıdır. Çocuklarda coast hastalığı, retinoblastom, prematüre retinopatisi (ROP), toksokora granülomu, ailesel eksüdatif vitreoretinopati dahil olmak üzere lökokori, şaşılık veya göz içi kitlelere neden olan diğer durumlar (Retinal anjiyomatozis, konjenital katarakt, Norrie hastalığı, inkontinentia pigmenti, endoftalmit ve pars planit) dikkate alınmalıdır (6).

Amacımız PHPV tanısı konulmuş hastaların MRG görüntüleme özelliklerini sunmak ve literatürle karşılaştırmaktır.

GEREÇ VE YÖNTEMLER

Çalışmamız retrospektif bir arşiv çalışması olup Ocak 2010-Ocak 2020 tarihleri arasında merkezimizde orbital MR çekimi yapılan ve görüntülemelerinde PHPV tanısı bulunan 9 hasta çalışmaya dahil edilmiştir. Hastalar yaş, cinsiyet, etkilenen orbita (sağ-sol, unilateral-bilateral), eşlik eden ek anomaliler açısından değerlendirilmiştir. Görüntülemede PHPV şüphesi bulunan ancak klinik açıdan doğrulanmayan hastalar, ön tanısında PHPV bulunan ancak görüntülemesinde belirgin patoloji saptanmayan, PHPV tanısı bulunan ancak görüntülemesi merkezimizde yapılmayan hastalar çalışma dışı bırakılmıştır.

Çalışmamız için yerel etik kurul onayı alınmıştır. (Dicle Üniversitesi Tıp Fakültesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu, Tarih: 25.10.2021, Sayı: 441)

Bu çalışmadaki tüm orbital MR görüntüler uzaysal çözünürlüğü iyileştirecek şekilde aksial ve koronal planda incelendi. Orbital T1 ağırlıklı görüntüler aşağıdaki parametreler kullanılarak elde edildi.(repetition time (TR): 600- 800 ms; echo time (TE): 20 ms; field of view (fov), 12-16 cm; kesit kalınlığı 3.0 mm; matrix, 256x192. Orbital T2 ağırlıklı görüntüler aşağıdaki parametreler kullanılarak elde edildi: TR, 1800-2500 ms; TE, 20-80 ms; field of view, 16 cm; kesit kalınlığı,

3.0 mm; matrix, 256x192; lezyonların sinyal intensitesi etkilenen veya karşı gözün vitreusu ile karşılaştırıldı.

PHPV MR bulguları anterior kamarada sığlaşma, retrolental vasküler membran. anterior segment anomalileri, tubuler görünüm, huni şeklinde retina dekolmanı, sıvı-sıvı seviyelenmeleri, retrolental kitle, vitreus hemorajisidir. Bu bulguları olan hastalar pozitif kabul edildi.

İstatistiksel analiz

İstatistiksel analizler icin ise SPSS (Statistical Package for the Social Sciences software for Windows, version 22.0, IBM, Chicago, IL, USA) programı kullanıldı. Çalışmamızda kullanılan istatiksel yöntemler; yaş, cinsiyet, etkilenen orbita, unilateral-bilateral etkilenme, eşlik eden ek bulgular parametresi için ortalama ve standart sapmalar kullanıldı. Verilerin normal dağılıma uyup uymadığı kontrol edildi ve normal dağılıma uyanlar için ikili karşılaştırmalarda independent sample t test ve normal dağılıma uymayanlarda Mann Whitney U test kullanıldı.

BULGULAR

Çalışmaya alınan 9 hastanın 8'i erkek 1'i kız idi. Hastaların yaş aralığı 3 ay (Olgu 1)-56 yaş olup yaş ortalaması 10,8 idi. Çalışmaya alınan hastaların 7'si (%78) çocuk-ergenlik dönemi (3 ay-7 yaş), 2'si (%22) erişkin (19 ve 56 yaş) yaş grubundaydı.

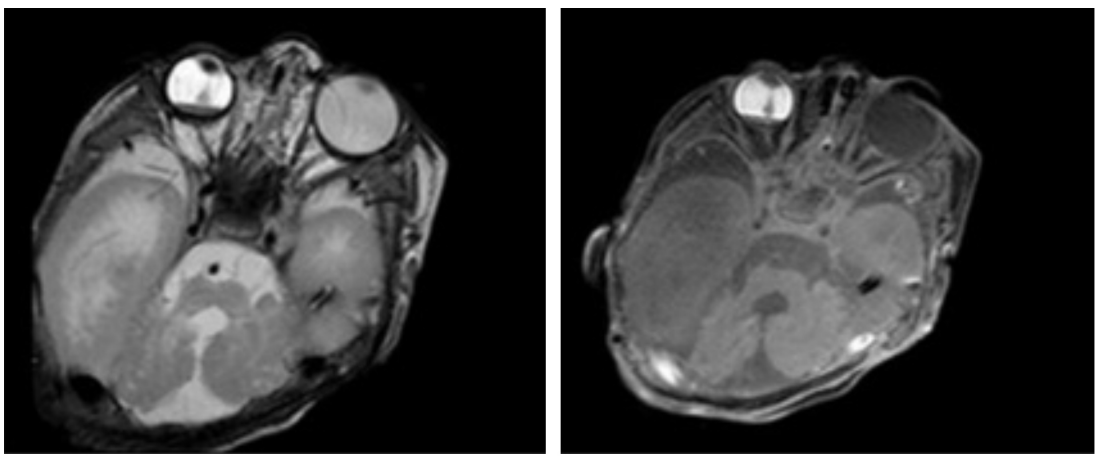
Bilateral tutulum 2 (%22) hastada, unilateral tutulum 7 (%78) hastada (5 hastada sağ, 2 hastada sol) izlendi.

Mikroftalmi (Olgu 2) 5 hastada (4 hastada PHPV olan orbitada,1 hastada PHPV olmayan orbitada), dismorfik orbita 2 hastada, retinal hemoraji (Olgu 3) bilateral tutulumu olan hastada bilateral izlenmişken 2 hastada PHPV olmayan orbitada izlenmiştir.

PHPV olgularına eşlik eden ek patolojiler değerlendirildiğinde; 1 hastada lizensefali (Olgu 4), 1 hastada porensefalik kavitasyon (Olgu 5) ve 2 hastada optik sinir periferinde sıvı artışı izlendi.

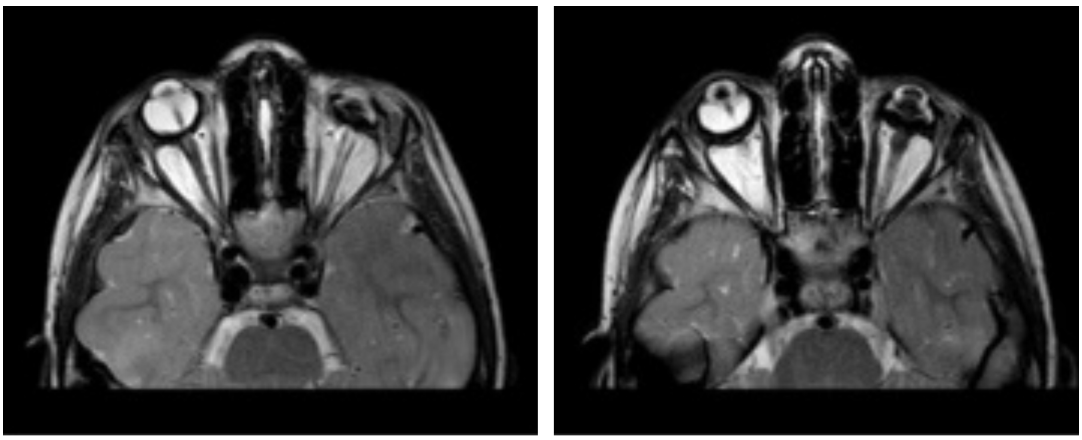
TARTIŞMA VE SONUÇ

Fetal intraoküler vasküler sistem anterior-posterior olarak ayrılır. Anterior sistem lensin anteriorundaki irisi beslerken; posterior sistem vitreusu besleyen ana hyaloid arter, vitreusun çevresini besleyen vasa hyloidea propia, iris ve merceği besleyen tunika vaskulosa lentisten oluşur (9,10). Anterior ve posterior hyaloid vaskuler sistem bağımsız geriler. Normal şekilde gerileyemezlerse PHPV oluşur. PHPV yenidoğan lökokorilerinin yaklaşık %5'inden sorumludur. Sıklıkla tek taraflı ve izoledir. PHPV çoğunlukla çocukluk çağında izlenir ancak geç tanı almış erişkinlerde de görülebilir. Çalışmamızdaki olguların çoğu (%78) literatür ile uyumlu olarak çocuk yaş grubuydu. Ayrıca literatürde bazı çalışmalarda erkek hakimiyetinin olduğu belirtil-



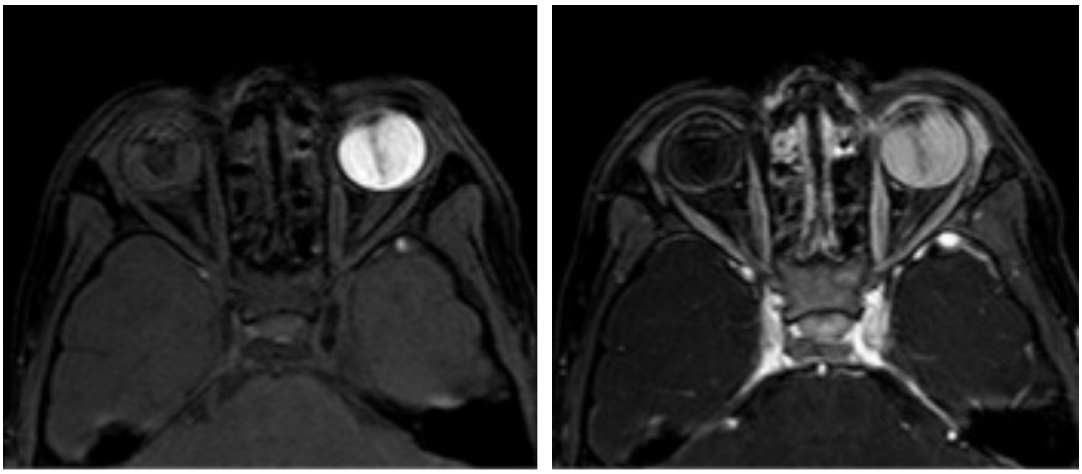
a **b**

Olgu 1: 3 ay erkek hasta, sağ lens posteriorunda optik sinir düzeyinde uzanan PHPV ile uyumlu fibröz bant görünümü ve seviyelenme veren hemoraji izlenmekte



a b

Olgu 2: 5 yaş erkek hasta, sağ lens posteriorunda optik sinir düzeyinde uzanan PHPV ile uyumlu fibröz bant görünümü, sol orbitada mikroftalmi ve dismorfik görünüm



a b

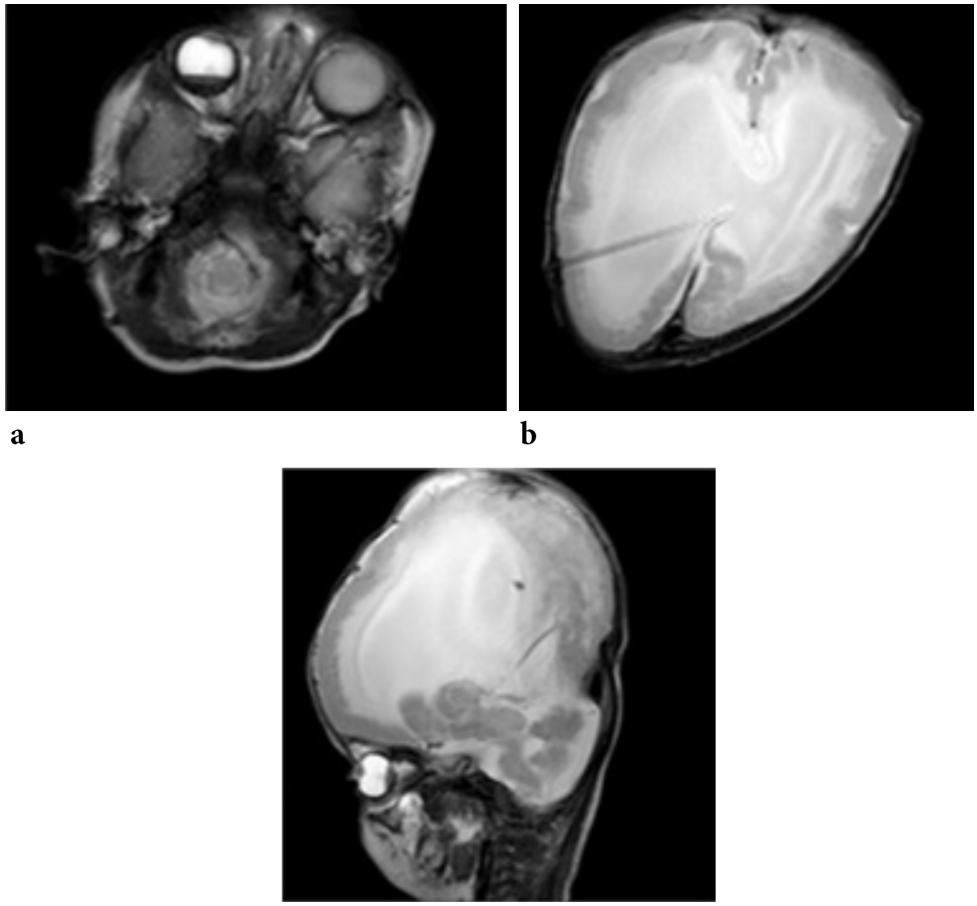
Olgu 3: 7 yaş erkek hasta, sağ orbitada retinal dekolman, sol orbitada PHPV ile uyumlu görünüm

miştir (7-13). Çalışmamızda erkek hasta sayısı oldukça yüksek oranda (%89) izlendi.

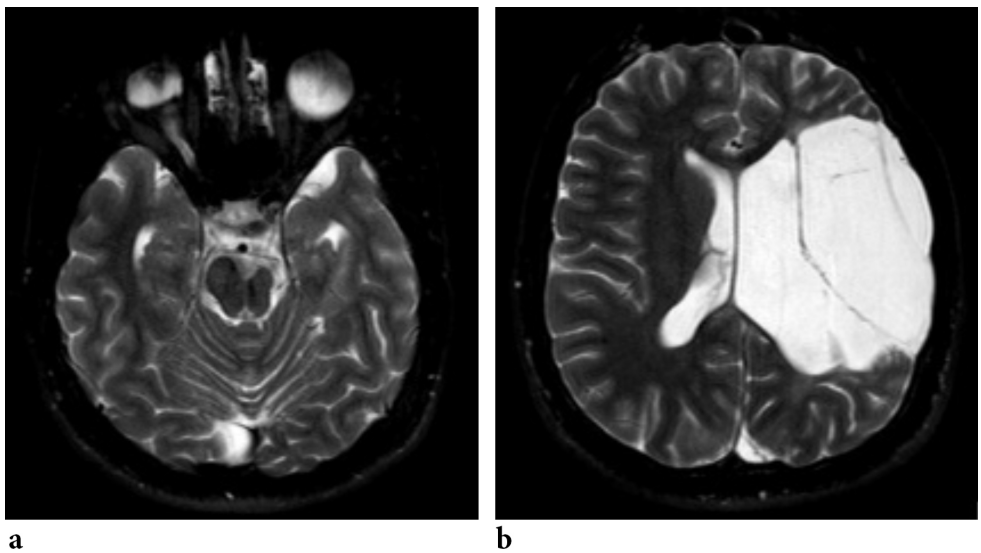
PHPV gelişimsel dönemde çoğunlukla tek orbitayı etkilediğinden genellikle patoloji tek orbitada izlenir. Ancak bazı sendromik durumlarda veya gelişimsel dönemde iki orbitanın etkilendiği durumlarda bilateral tutulum da izlenebilir (4-8). Çalışmamızda literatür ile uyumlu olarak (%78) unilateral tutulum sıklığı mevcuttu.

PHPV özellikle bilateral tutulumu olan olgularda bazı sendromlarla birlikte görülebilir. Bu tarz durumlarda orbital ve kranial ek bulgular izlenebilir. MR inceleme kranial ek bulgular açısından da oldukça önemlidir. Bilateral vakalara genellikle Norrie hastalığı, Warbur's hastalığı ve diğer intraorbital anomalililer gibi sistemik hastalıkların eşlik ettiği düşünülmektedir (3-6). Çalışmamızda PHPV olgularına eşlik eden ek patolojiler değerlendirildiğinde; %11 oranında lizensefali, %11 oranında lateral ventrikül kistik dilatasyonu ve %22 oranında optik sinir periferinde sıvı artışı izlendi. Lizensefalisi olan hasta Walker Walburg sendromu ile uyumlu idi.

Embriyolojik gelişim döneminde anomaliler bazen etkilenen veya etkilenmeyen orbitada ek anomalilere sebep olabilmektedir. MR görüntülemede orbital yapılar detaylı değerlendirilebilmektedir. MR görüntülemede orbital patolojilerin detaylı raporlanması tedavi



Olgu 4: 5 ay erkek hasta sağ orbitada PHPV görünümü ve lateral ventriküller ileri derecede dilatasyon, serebral fissür ve sulkuslarda gelişimsel anomali, gri cevher kalınlığında artış (komplet lizensefali)(Walker Walburg send-romu)



Olgu 5: 19 yaş erkek hasta, sağ orbitada PHPV görünümü, sol serebral hemisferde porensefalik kavitasyon

ve hastalık süreci açısından oldukça önemlidir (2-7). Çalışmamızda %55 oranında mikroftalmi mevcut olup, mikroftalmi en sık (%89) PHPV olan orbitada izlenmiştir. Bunu sırasıyla retinal hemoraji (%33) ve dismorfik orbita (%22) takip etmiştir.

Daha önceki literatür çalışmalarında PHPV'nin kalıtsal olmadığını bildiren yayınlar mevcut olmakla birlikte PHPV'si olan 3 aileden 8 vakanın bildirildiği ve hiyaloid arterin çift taraflı kalıcılık gösterdiği ortaya konmuştu (12). Bizim çalışmamızdaki hastalarda herhangi bir ailesel yakınlık yoktu. Bu da PHPV'nin kalıtsal yatkınlık olmayabileceğini desteklemektedir. Ancak daha geniş vaka serilerine ihtiyaç duyulmaktadır.

Çalışmamızın en önemli kısıtlılığı vaka sayısının nispeten az olmasıdır. Ayrıca çalışmamızdaki olgularda PHPV olgularının MR görüntüleri mevcut olup USG, BT görüntüleri çalışmada mevcut değildir.

Sonuç olarak tek taraflı tutulum, mikroftalmi ve ön kamaranın kollabe olması PHPV ayırıcı tanısında en önemli klinik ipuçlarıdır. PHPV'den şüphelenildiğinde retrolental kitle ve huni şeklinde retina dekolmanı MR görüntülemede tanı koymada son derece önemli bulgulardır.

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What have we learnt as orthopaedic surgeons? Pandemic surveillance of surgically treated fracture patients

Ortopedik cerrahlar olarak ne öğrendik? Cerrahi tedavi gören kırık hastalarının pandemik sürveyansı

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Abstract

Aim: To investigate the epidemiological and demographic data of the patients operated on during the first wave of the pandemic, and to analyze what the pandemic has taught orthopedic surgeons

Methods: In this retrospective analysis, 90 patients who were operated in our clinic were analyzed. Demographic data, injury mechanism, fracture site, anesthesia type, the number of consultations after admission, the comorbidities, average time between first admission to hospitalization, the length of stay in the intensive care unit (ICU), and neutrophil-lymphocyte ratio (NLR) were investigated.

Results: Higher incidence of hip fractures was observed in COVID-positive patients (p<0.001). The number of two or more consultations requested was significantly higher in COVID-positive patients (p=0.034). As the number of consultations requested increased, the mean time between the first admission and hospitalization also increased (p=0.036). Moreover, there was a significant association between COVID-positivity and the need for ICU follow-up (p=0.001). When the postoperative NLR was compared, it was found to be significantly different in COVID-positive patients compared to COVID-negative patients (p=0.005).

Conclusion: During the heart of disasters, patients with high comorbidity should not be made to wait for long periods in the emergency department. It is important to inform them and their relatives about the prognosis and possible ICU follow-up of these patients. It is important to consider that domestic injuries may increase. Additionally, it is important to note that parameters such as NLR, which are commonly used in routine follow-up, may be affected by infections.

Keywords: COVID-19; hip fracture; infection; intensive care unit

Öz

Amaç: Pandeminin ilk dalgası sırasında ameliyat edilen hastaların epidemiyolojik ve demografik verilerini araştırmak ve pandeminin ortopedik cerrahlara neler öğrettiğini analiz etmek

Yöntemler: Bu retrospektif analizde kliniğimizde ameliyat edilen 90 hasta incelendi. Demografik veriler, yaralanma mekanizması, kırık bölgesi, anestezi tipi, başvurudan sonraki konsültasyon sayısı, eşlik eden hastalıklar, ilk başvurudan hastaneye yatışa kadar geçen ortalama süre, yoğun bakım ünitesinde (YBÜ) kalış süresi ve nötrofil-lenfosit oranı (NLO) incelendi.

Bulgular: COVID-pozitif hastalarda daha yüksek kalça kırığı insidansı gözlenmiştir (p<0,001). İstenen iki veya daha fazla konsültasyon sayısı COVID-pozitif hastalarda anlamlı olarak daha yüksekti (p=0,034). İstenen konsültasyon sayısı arttıkça, ilk başvuru ile hastaneye yatış arasındaki ortalama süre de artmıştır (p=0,036). Ayrıca, COVID pozitifliği ile YBÜ takip ihtiyacı arasında anlamlı bir ilişki vardı (p=0,001). Ameliyat sonrası NLR karşılaştırıldığında, COVID-pozitif hastalarda COVID-negatif hastalara kıyasla anlamlı derecede farklı bulunmuştur (p=0,005).

Sonuç: Afetlerin merkezinde, yüksek komorbiditesi olan hastalar acil serviste uzun süre bekletilmemelidir. Bu hastaların prognozu ve olası YBÜ takibi hakkında kendilerini ve yakınlarını bilgilendirmek önemlidir. Ev içi yaralanmaların artabileceğini göz önünde bulundurmak önemlidir. Ayrıca rutin takipte sık kullanılan NLR gibi parametrelerin enfeksiyonlardan etkilenebileceği unutulmamalıdır.

Anahtar Sözcükler: COVID-19; enfeksiyon; kalça kırıkları; yoğun bakım ünitesi

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INTRODUCTION

About four years ago, our country and the whole world fought against the Coronavirus infection (COVID-19), which has been called "the pandemic of our time". While fever, cough, shortness of breath were the main symptoms, non-specific findings such as impairment of smell-taste, headache, weakness, and muscle aches could also be seen in COVID-19 infection. Although we recognize the pandemic of our time today, the fact that the treatment was not fully clarified at the time of its emergence and that the infection spread rapidly even without symptoms were the main problems in the management of this respiratory disease (1,2).

The rapid and uncontrolled spread of the infection has made it necessary to take urgent measures in our country, as in many other countries. One of the first moves made for this purpose was the concept of the "new normal", which included curfews, especially for risk groups, and the regulation of social rules (3). As orthopaedic surgeons, our main objective during this period was to determine the most appropriate management strategy in cases with fractures that need hospitalization. The importance of isolation of COVID-19-infected and COVID-suspected patients, proper management of hospital resources, and measures to prevent transmission were of maximum importance during this period (4-7). Therefore, considering the hospitals as the riskiest contamination places, elective surgeries were postponed to protect both patients and healthcare professionals, as many centers around the world (8-10). Moreover, all necessary measures were taken to prepare and perform trauma surgeries as quickly as possible and to ensure the early discharge of patients (11).

Today, we recognize, know, and manage COVID-19 infection. With precautions, proper treatments, and vaccines, we have brought the pandemic of our age under control and normalcy has returned. However, it should not be forgotten that COVID-variants continue to emerge and that coronavirus is not the only virus that carries the risk of a pandemic. Moreover, pandemics are not the only disasters that we need to manage as orthopedic surgeons, we must fulfill the responsibilities of our profession in all-natural disasters such as earthquakes and floods. Therefore, we must learn from the pandemic of our age. Our aim in this study, in which we investigated the epidemiological and demographic data of the patients we operated in our clinic during the first wave of the pandemic, was to analyze what the pandemic has taught orthopedic surgeons and how we should act in possible future pandemics.

MATERIAL AND METHODS

Patient Selection

Following the local ethical board approval (Ümraniye Education and Research Hospital Clinical Research Ethics Comittee, date: 12/05/2020, decision no: 160) and Turkish Ministry of Health Approval (02/05/2020), this study was conducted in a tertiary training and research hospital. Between the dates of March-May 2020, which is also called the first wave of the pandemic all orthopaedic trauma patients who applied to the emergency department and required surgical intervention were included in the study, regardless of the age (10). Patients who did not need surgery, patients who refused surgery and patients who followed up conservatively were excluded from the study. Considering these criteria, 90 patients were retrospectively analyzed.

Patient Management

In line with the recommendations of the Turkish Ministry of Health and the World Health Organization, all patients who were evaluated in the emergency room and planned to be hospitalized and surgically treated were evaluated for COVID-19 infection (12). Radiological and laboratory examination was performed on all the patients, and the diagnosis was made mainly based on performing thoracic computed tomography (CT) without waiting for PCR test results (Fig. 1) (13) and treatment strategy was planned accordingly (Fig.2). Suspicious or positive cases were quickly taken to the isolation areas. The patients were hospitalized as soon as possible, after their emergency interventions and consultations were completed. After hospitalization, patients with suspected or positive COVID-19 diagnosis were asked for a consultation from the Infectious Diseases Department and their treatment was arranged. To keep the duration of hospitalization shorter by speeding up the preoperative preparation period, as

suggested in the literature (4), preoperative preparation was completed as soon as possible under the supervision and management of the anesthesiologist.

Surgeries were performed in a separate operating room with negative pressure and HEPA filters. In an infected case, regional anesthesia techniques were preferred as much as possible due to the high risk of transmission with droplets and aerosols during intubation. In addition, regional anesthesia application is less likely to develop secondary pneumonia compared to general anesthesia (14). In patients undergoing general anesthesia, laryngeal mask airway was preferred to endotracheal intubation (15). During the anesthesia procedure, minimum healthcare professionals were kept in the operating room and after the anesthesia procedures were completed, surgeons and surgical nurses were taken into the operating room. All healthcare professionals were provided to use personnel protective equipment appropriately (1). Moreover, to achieve lesser exposure by shortening the operation time, two orthopaedic surgeons were enabled to work on the same case in the operating room. In terms of surgical technique, minimally invasive-closed techniques such as intramedullary nail applications were prioritized in order to reduce aerosol formation as much as possible and to provide less contact with the patient and shorter hospitalization time (15). The use of power tools such as electrocautery, drill, reamer, saw, and jet lavage, which has been shown to form aerosols, was tried to be reduced. In order to reduce the need for transfusion of patients, reduce hematoma formation and extra bleeding, diligent efforts were made to provide good intraoperative hemostasis (16)

Data Analysis

While analyzing data, demographic data such as age and gender, injury mechanism, fracture site, anesthesia type, the number of consultations after admission to the emergency department, the comorbidities, average time between first admission to hospitalization, and the length of stay (LOS) in the intensive care unit (ICU) were investigated. Also, considering the fact that in the majority of COVID-19 patients, neutrophil count increases, while the lymphocyte count decreases, and as a result, neutrophil-lymphocyte ratio (NLR) increases, patients preoperative and postoperative NLR were also investigated (4). All data were analyzed retrospectively, using the hospital information system and HSYS (Public Health Management System).

Statistical analyses

The database was created using Microsoft Excel and statistical analysis and visualizations were done using SciPy 1.4 software and Statistical Package for the Social Sciences package program version 23.0 (SPSS Inc., Chicago, IL, USA). Frequency and percentage were used as descriptive statistics in categorical data and mean and minimum-maximum range values were used to have an overview of the distribution of the variables. Since our data were found to be skewed distributed, the Mann-Whitney U test was used to compare the means of two groups of the variables age, NLR, and length of stay in ICU. The Spearman Correlation Analysis was used to investigate the association between the number of comorbidities and length of stay in the ICU and between the number of consultations and the average time of admission to hospitalization. For categorical data (gender, fracture site, injury energy, anesthesia type, number of consultations, number of comorbidities, and ICU follow-up requirement), the Chi-square test was used and in cases where the Chi-square assumption was not met, Fischer's exact test was used. For all the tests, significance was set at 0.05.

RESULTS

Among 90 patients who were treated surgically during the COVID-19 period, 16 (17.8%) patients had computed tomography findings compatible with pandemics. The mean age of all the patients was 42.5 (Range:4-95) years whereas the mean age of those with positive radiological findings compatible with pandemics was 70 (Range:24-95) years ($p=0.032$). In terms of fracture sites, a higher incidence of hip fractures was observed in COVID-positive patients ($p<0.001$). Detailed follow-up characteristics of surgically treated fracture patients in our clinic during the pandemic can be observed in Table 1.

When the number of consultations requested during the first emergency department admissions of the patients was analyzed, it was found that the number of two or more consultations requested was significantly

Table 1: Demographics and follow-up characteristics of surgically treated fracture patients during the COVID-19 pandemics

		COVID-positive (n=16)	COVID-negative (n=74)	Total (n=90)	p
Age (years)		70 years (24-95)	36.5 years (4-95)	42.5 years (4-95)	**0.032**
Gender	Female	10 (62.5%)	22 (29.7%)	32 (35.6%)	**0.013**
	Male	6 (37.5%)	52 (70.3%)	58 (64.4%)	
Fracture site	Upper limb	0	18 (24.3%)	18 (20%)	**<0.001**
	Lower limb other than hip	2 (12.5%)	42 (56.8%)	44 (48.9%)	
	Hip fracture	14 (87.5%)	14 (18.9%)	28 (31.1%)	
Injury energy	High-energy	2 (12.5%)	10 (13.5%)	12 (13.3%)	0.914
	Low-energy	14 (87.5%)	64 (86.5%)	78 (86.7%)	
Anesthesia type	General	5 (31.3%)	41(55.4%)	46 (51.1%)	0.080
	Regional	11 (68.7%)	33 (44.6%)	44 (48.9%)	
Number of consultations sent	<2	10 (62.5%)	64 (86.5%)	74 (82.2%)	**0.034**
	≥2	6 (37.5%)	10 (13.5%)	16 (17.8%)	
Comorbidity	<2	4 (25%)	52 (70.3%)	56 (62.2%)	**0.001**
	≥2	12 (75%)	22 (29.7%)	34 (37.8%)	
ICU Follow-up	No	6 (37.5%)	60 (81.1%)	66 (73.3%)	**0.001**
	Yes	10 (62.5%)	14 (18.9%)	24 (26.7%)	

n: number of patients; p: statistical significance value; Number of consultations sent: Number of consultations required at the first emergency admission; ICU: Intensive Care Unit.

higher in COVID-positive patients (p=0.034) (Table 1). There was also a significant correlation between the number of consultations requested and the average time between the first admission and hospitalization. It was observed that as the number of consultations requested increased, the mean time between the first admission and hospitalization also increased (p=0.036) (Fig 3).

When the relationship between the number of comorbidities and COVID diagnosis was examined, a significant association was found between COVID-positive patients and the presence of two or more comorbidities (p=0.001) (Table 1). Moreover, there was a significant association between COVID-positivity and the need for ICU follow-up (p=0.001). In the intensive care unit, the mean follow-up time was 1.62 (Range:0-6) days in COVID-positive patients, while it was 0.45 days (Range:0-2) in COVID-negative patients (p=0.007). The length of stay in the ICU of the COVID-positive patients with three or more comorbidities increased significantly compared to other patients (p=0.023) (Fig 4).

The preoperative mean NLR of all patients was 5.59 (Range:1.07-21.34), whereas postoperative NLR was 7.69 (Range:1.05-27.12). When the patients with COVID-19 were examined, the preoperative mean NLR was 9.2 (Range:1.66-21.34), whereas the postoperative NLR was 17.65 (Range:5.89-27.2). When the postoperative NLR was compared, it was found to be significantly different in COVID-positive patients compared to COVID-negative patients (p=0.005). The postoperative NLR of COVID-negative patients increased by an average of 43.5%, whereas an average of 178.3% increase was observed postoperatively among the COVID-positive patients (p=0.008)

DISCUSSION AND CONCLUSION

Orthopaedics and Traumatology is a branch that can be heavily impacted by natural disasters. Orthopaedic surgeons often play an active role in responding to disasters such as earthquakes, floods, and war situations (17). Additionally, the COVID-19 pandemic has highlighted the importance of orthopaedic surgeons during infectious pandemics (3,6,7). It is crucial to postpone elective cases and prioritize emergency cases based on infection status (7,9,10). Therefore, we must learn the necessary lessons from the pan-

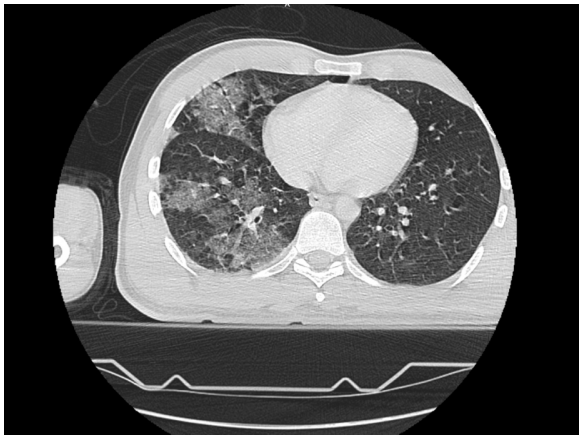

Figure 1: Computed tomography image of a COVID-positive patient

demic of our age and prepare for potential disasters. The study found that COVID-positive fractures were more common in women and the elderly, which is consistent with existing literature (2-6). The study also found a higher incidence of lower extremity fractures, particularly hip fractures, which is a common injury resulting from domestic accidents. Our study found that COVID-positive patients had significantly higher numbers of comorbidities, number of emergency consultations, duration between admission to hospitalization, and longer length of stay in ICU compared to COVID-negative fracture patients. Additionally, our study shows the preoperative and postoperative variation of NLR in COVID-positive and COVID-negative patients.

We spent most of our time in our homes due to the measures taken during the global COVID-19 pandemic. This can be interpreted as an increase in domestic accidents and related injuries, which is consistent with the literature (3,18). According to our data, fractures occur mainly in elderly patients with domestic falls, most often with falls from standing. 80% of the operated patients were lower extremity fractures and 31.1% of them were hip fractures. Gencer and Doğan conducted an epidemiological analysis of COVID-19 fracture patients in 2022 and reported a hip fracture incidence of 12.6%. The variation in rates may be related to regional differences, especially to the density of the elderly population. However, it is evident that increased time spent indoors results in a decrease in high-energy injuries and an increase in domestic injuries. In a study by Yanbin et al., it was stated that 72.7% of the fractures occurred especially in elderly patients with domestic falls, 89.4% of them were caused by falls from standing. They sug-

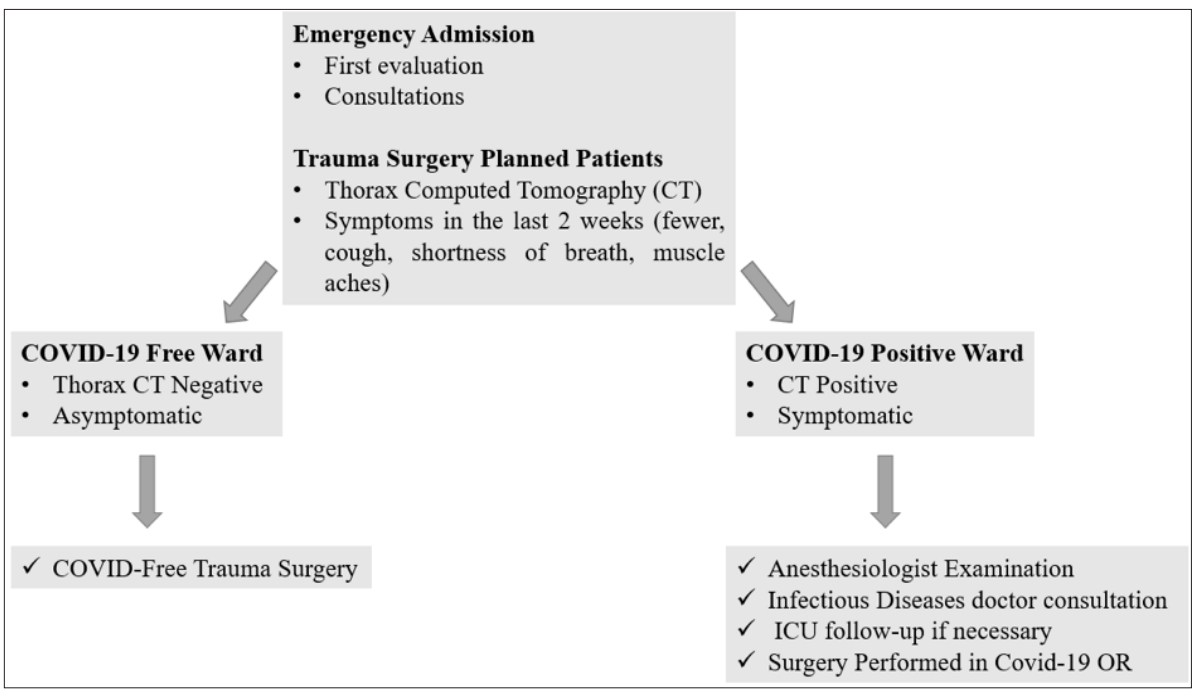

Figure 2: Treatment strategy in fracture patients admitted to our hospital during the pandemic
CT: computed tomography; OR: operations room

gest that the elderly must get up by 'holding on' after sitting or lying down for a long time (9). It is also important to investigate the causes of the higher incidence of COVID-19 positivity in hip fractures. Considering that COVID-19 infection is more common in people with weakened immune systems and in those who do not take adequate measures to prevent the risk of transmission, the susceptibility of the geriatric patient population to this infection due to both weakened immunity and inadequate precautions can be understood. The predisposition of the same population to hip fractures with domestic injuries may be the reason for the increased COVID-19 positivity in hip fractures.

According to our data, the average duration between admission to hospitalization is 339 minutes in cases where two or more consultations are requested in the emergency room and 109 minutes in cases where one consultation is requested (p=0.037). Keeping the patient in the emergency room for a long time will increase the probability of infection of the traumatized patient. In another possibility, if the patient is infected, it increases the likelihood of spreading to other people. The rational solution is to minimize the duration that the patient spends in crowded departments such as the emergency room (11). However, it is essential that a patient with both a trauma-related fracture and COVID-19 infection must be evaluated by the relevant clinics at the first admission, and it is urgent in terms of planning the treatment correctly and affecting the hospitalization of the patient. As a matter of fact, in our study, it was determined that the number of emergency consultations requested in COVID-positive patients was significantly higher. Undoubtedly, among the factors affecting this situation, the fact that COVID-positive patients are older and have more comorbidities is also important. Another important point to emphasize is that, during the pandemic, high-energy injuries decreased due to curfew restrictions, closure of some workplaces, and reduced traffic density. This situation can be considered as an advantage. Namely; the reduced patient load allowing the physician to perform consultations after hospitalization may reduce the need for additional consultations during pre-hospitalization process in traumatic patients. In any case, emergency department management becomes very important in emergencies such as

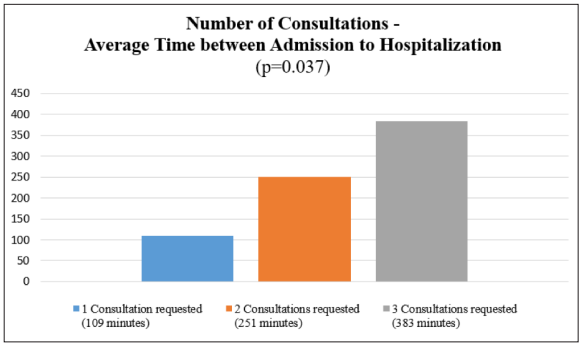

Figure 3: Association between the number of consultations requested in the emergency department and the average time between admission to hospitalization

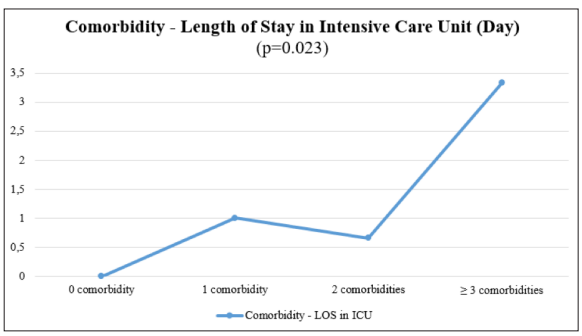

Figure 4: Association between the number of comorbidities and the length of stay in intensive care units

pandemics, and it is of utmost importance to manage the workforce correctly, to complete the absolute emergency procedures of the patients quickly and then to hospitalize them and to prevent overcrowding in emergency departments.

In our study, postoperative ICU requirement increases significantly in COVID-positive patients. Here, it is the factor that the infection disrupts respiratory functions and is more severe in patients with high comorbidities. In addition, we think that the surgery applied to the patient negatively affects the patient clinic by creating a second hit effect on the already traumatized patient. According to our data, 75% of infected patients have two or more comorbid diseases. In addition, in our study, COVID-positive patients with three or more comorbidities required longer follow-up in the ICU (p=0.023). Acknowledging the effect of comorbidity on fracture patients and especially the necessity of ICU follow-up is crucial for the optimal management of these patients and to correctly inform their relatives.

As stated in the current literature, COVID-19 infection decreases lymphocyte count, increases neutrophil count and increases NLR (14). The amount of this increase was found to be correlated with the severity of the disease and mortality rates (2, 15). In our patient group, we observed that the NLR in COVID-positive cases was higher than in COVID-negative patients. When we compare the preoperative and postoperative NLR; in COVID-positive cases, the mean NLR increased significantly higher whereas in COVID-negative patients the increase was relatively lower. It is important to know that the range of change of NLR is much wider in COVID-positive patients and that it increases both with infection and with trauma, fracture and surgery. When using this parameter in patient follow-up, it should be remembered that the patient's additional injuries and previous surgeries should be taken into consideration.

Our study has some limitations. Firstly, it was conducted in a single center and had a relatively low number of patients. Additionally, it was retrospective in nature. Another limitation is that the evaluation did not include asymptomatic cases that may have been overlooked, or cases in which conservative treatment was started but surgical treatment was required due to loss of reduction during outpatient follow-up. Furthermore, the process of the pandemic, injury, emergency admission, and operation is limited by several confounding factors and it is not possible to evaluate all. Despite its limitations, this single-center study examines variables related to patients operated on for fractures during the most active period of the pandemic. We believe that this study will contribute to the literature and that it is important to take action based on the findings. This will help us prepare for future disasters that may occur.

As orthopaedic surgeons, it is part of our job to work in the heart of disasters. During such times, it is important to make correct plans and ensure emergency admissions are met promptly. Patients with high comorbidity should not be made to wait for long periods in the emergency department. It is important to inform them and their relatives about the prognosis and possible ICU follow-up of these patients. It is important to consider that domestic injuries may increase. Additionally, it is important to note that parameters such as NLR, which are commonly used in routine follow-up, may be affected by infections. In conclusion, while planning the surgery during the pandemic, following the isolation rules, shortening the admission process, and striving to reduce mortality by closely monitoring patients with additional comorbidities is of utmost importance.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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The structural effects of transcranial magnetic stimulation on hippocampal subfields in Alzheimer's disease

Alzheimer hastalığında transkraniyal manyetik stimülasyonun hipokampal alt alanlar üzerindeki yapısal etkileri

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Abstract

Aim: This study investigates the structural effects of repetitive transcranial magnetic stimulation (rTMS) on hippocampal subfields and cortical shape metrics in Alzheimer's disease (AD) patients. Using high-resolution MRI segmentation and analysis via Hippunfold, we aim to elucidate TMS-induced structural changes and assess its potential neuroprotective role.

Methods: This retrospective study included 17 AD patients and 18 healthy controls (HC). AD patients underwent 20 Hz rTMS targeting the left lateral parietal cortex over 10 sessions across two weeks. Magnetic resonance imaging (MRI) data were acquired before and after rTMS and analyzed with Hippunfold to segment hippocampal subfields and extract cortical thickness and shape metrics. Statistical analyses were performed to compare subfield volumes and cortical metrics between groups and across time points.

Results: Hippocampal volumetric analysis revealed significant atrophy in subfields such as Cornu Ammonis 1, (CA1), CA2, CA4, dentate gyrus (DG), subiculum, and stratum radiatum-lacunosum-moleculare (SRLM) in AD patients compared to HC. Although no significant volumetric recovery was observed post-TMS, a further decline was noted in the right CA3 subfield ($p=0.005$), highlighting progressive atrophy. Cortical shape analyses showed significant reductions in hippocampal thickness ($p<0.001$) and surface area ($p<0.001$) in AD patients versus HC, with further cortical thinning in both hemispheres between pre- and post-TMS conditions. These findings suggest ongoing neurodegeneration despite TMS treatment.

Conclusion: TMS did not significantly reverse hippocampal atrophy or cortical thinning in this cohort. However, observed asymmetry in atrophy patterns, with relatively stable left hippocampal subfields compared to the right, suggests potential neuroprotective effects of TMS. These results highlight the need for prolonged and bilateral stimulation protocols to explore the therapeutic potential of TMS in mitigating AD progression.

Keywords: Alzheimer's disease; atrophy; hippokampus; transcranial magnetic stimulation

Öz

Amaç: Bu çalışma, Alzheimer hastalığı (AH) olan bireylerde tekrarlayan transkraniyal manyetik stimülasyonun (rTMS) hipokampal alt alanlar ve kortikal şekil metrikleri üzerindeki yapısal etkilerini araştırmaktadır. Yüksek çözünürlüklü MRI segmentasyonu ve Hippunfold analizi kullanılarak, TMS kaynaklı yapısal değişiklikleri incelemeyi ve TMS'nin olası nöroprotektif rolünü değerlendirmeyi amaçlıyoruz.

Yöntemler: Bu retrospektif çalışmada, 17 AH hastası ve 18 sağlıklı kontrol (SK) yer aldı. AH hastalarına, iki hafta boyunca toplam 10 seanslık sol lateral paryetal korteksi hedefleyen 20 Hz rTMS uygulandı. Tedavi öncesi ve sonrası MRI görüntüleri Hippunfold yazılımıyla analiz edilerek hipokampal alt alanlar segmentlendi ve kortikal kalınlık ile şekil metrikleri çıkarıldı. Gruplar arası ve zaman noktaları arasındaki karşılaştırmalar için istatistiksel analizler yapıldı.

Bulgular: Hipokampal volumetrik analiz, AH hastalarında Cornu Ammonis 1, (CA1), CA2, CA4, dentat girus (DG), subikulum ve stratum radiatum-lacunosum-moleculare (SRLM) gibi alt alanlarda belirgin atrofi olduğunu ortaya koydu. TMS sonrası anlamlı bir volumetrik iyileşme gözlenmese de, sağ CA3 alt alanında progresif atrofi tespit edildi ($p=0.005$). Kortikal şekil analizleri, AH hastalarında hipokampal kalınlıkta ($p<0.001$) ve yüzey alanında ($p<0.001$) sağlıklı kontrollere kıyasla anlamlı azalmalar olduğunu gösterdi ve her iki hemisferde de TMS öncesi ve sonrası arasında kortikal incelme görüldü. Bu bulgular, TMS tedavisine rağmen devam eden nörodejenerasyonu işaret etmektedir.

Sonuç: TMS, bu çalışmada hipokampal atrofiyi veya kortikal incelmeyi anlamlı şekilde tersine çevirmemiştir. Ancak, sol hipokampal alt alanların sağa göre daha stabil olması, TMS'nin potansiyel nöroprotektif etkilerini işaret etmektedir. Bu sonuçlar, TMS'nin AH progresyonunu hafifletme potansiyelini araştırmak için daha uzun süreli ve çift taraflı stimülasyon protokollerinin gerekliliğine dikkat çekmektedir.

Anahtar Sözcükler: Alzheimer hastalığı; atrofi; hipokampus; transkraniyal manyetik uyarı

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INTRODUCTION

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder that affects millions worldwide, posing a major health and social burden due to its progressive nature and irreversible cognitive decline. Characterized by memory loss, impaired executive function, and diminished daily functioning, AD primarily targets brain regions involved in memory and learning, particularly the hippocampus. The hippocampus is one of the earliest and most affected regions in AD, undergoing marked atrophy and cellular loss even in the initial stages of the disease. This atrophy is not uniform; it specifically impacts various hippocampal subfields, such as CA1, CA2, CA3, CA4, the dentate gyrus (DG), and the subiculum, which are each associated with different memory and cognitive functions (1). As the disease advances, structural deterioration in these subregions worsens, correlating strongly with the progressive cognitive decline observed in AD patients (2). Understanding the specific patterns of degeneration in hippocampal subfields may provide key insights into the progression of AD and help identify potential targets for intervention.

In recent years, Transcranial Magnetic Stimulation (TMS) has gained attention as a promising, non-invasive treatment modality for enhancing cognitive function in AD patients (3). TMS uses magnetic fields to stimulate neural activity, potentially altering brain circuits involved in cognitive processing. Studies suggest that TMS may offer neuroprotective benefits by promoting neural plasticity and reducing synaptic loss, thereby slowing the structural degradation associated with AD (4). Additionally, TMS has shown promise in modulating hippocampal activity, which could directly impact memory and cognitive functions (5–7). However, despite the potential of TMS, there is a lack of comprehensive studies examining its long-term structural effects on specific hippocampal subfields in AD. Understanding how TMS affects these subfields individually could clarify its potential as a targeted intervention in AD and offer insights into its underlying mechanisms.

In this study, we aim to investigate the impact of TMS on hippocampal subfield volumes in AD patients by employing Hippunfold, a cutting-edge software tool for high-resolution segmentation and analysis of hippocampal subfields (8). Hippunfold enables precise mapping of hippocampal regions, allowing us to assess structural changes with greater accuracy. By comparing MRI data from before and after TMS treatment in AD patients, alongside MRI data from age-matched healthy controls, we aim to elucidate any TMS-induced structural changes and evaluate their relevance in the context of AD. This approach not only enables us to assess the potential neuroprotective effects of TMS but also helps us identify disease-specific alterations in hippocampal subfields. We hypothesize that TMS treatment induces structural changes in the hippocampal subfields of AD patients, potentially preserving or enhancing the integrity of certain subfields compared to those of healthy controls. We further hypothesize that these changes will be more pronounced in regions typically affected by AD-related atrophy, such as the CA1 and DG subfields, thereby demonstrating the neuroprotective potential of TMS in mitigating hippocampal degeneration in AD.

MATERIALS AND METHODS

Participants

This retrospective study included 35 participants recruited from Istanbul Medipol University Mega Hospital, divided into two groups: 17 individuals diagnosed with Alzheimer's disease (mean age ± SD: 66.55 ± 5.52 years) and 18 age-matched healthy controls (mean age ± SD: 70.35 ± 7.82 years), with no significant age difference between the groups ($p = 0.109$). Alzheimer's disease was diagnosed based on standard clinical criteria, and all AD patients exhibited mild to severe cognitive impairment, as reflected by a Clinical Dementia Rating (CDR) score of 1 or higher. Each participant underwent a detailed medical history review, a thorough physical examination, and a cognitive assessment to ensure study eligibility and establish baseline cognitive status.

The Mini-Mental State Examination (MMSE) was administered to all participants as a measure of global cognitive function. AD patients exhibited MMSE scores consistent with their clinical diagnosis, ranging from mild to severe cognitive impairment, while healthy controls demonstrated normal cognitive function with no history of neurological or psychiatric

disorders. Healthy control participants were further screened to ensure they had no history of traumatic brain injury or neurological disease, allowing for a clear comparison between AD-affected and neurologically healthy brains.

This study was approved by Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (date: 03.12.2024, decision no: E-10840098-202.3.02-7360). All participants provided written informed consent prior to enrollment, in accordance with the Declaration of Helsinki.

TMS application

This study was conducted retrospectively, utilizing MRI data from before and after treatment of AD patients who had previously undergone repetitive transcranial magnetic stimulation (rTMS). The TMS protocol, as applied in our prior study (7), involved stimulation of the left lateral parietal cortex at a frequency of 20 Hz to target the left hippocampus indirectly, following a network-based targeting method (9). This approach leverages the connectivity between the parietal cortex and hippocampus, modulating hippocampal activity through its cortical network connections.

The rTMS treatment was administered over a two-week period, consisting of 10 daily sessions. Each session delivered a total of 1,640 magnetic pulses at an intensity of 100% of the patient's resting motor threshold to ensure effective cortical stimulation. MRI images were collected from each AD patient both before the initiation of TMS treatment and after the two-week intervention, allowing for pre- and post-intervention comparison of hippocampal subfield volumes.

Imaging acquisition

Structural and functional MRI data were acquired for each participant using a Philips Achieva 3 Tesla MRI scanner (Philips Medical Systems), ensuring high-resolution images suitable for detailed hippocampal subfield analysis. T1-weighted anatomical images were obtained to facilitate segmentation and volumetric analysis of hippocampal subregions.

The T1-weighted anatomical images were collected using high-resolution imaging parameters to enable detailed structural analysis. A total of 190 contiguous slices were acquired, covering a field of view (FOV) of 256 × 256 × 190 mm. The images were obtained with an isotropic voxel size of 1 × 1 × 1 mm, providing consistent spatial resolution across all axes. The imaging protocol used a repetition time (TR) of 8.1 ms, an echo time (TE) of 3.7 ms, and a flip angle of 8°, which together were optimized to enhance image clarity and structural delineation.

These imaging parameters were selected to optimize image quality, allowing for precise segmentation of hippocampal subfields and accurate assessment of structural integrity. The high isotropic voxel resolution (1 mm^3) facilitates detailed analysis of hippocampal morphology, which is essential for detecting subtle volumetric changes in AD-related atrophy and potential structural alterations due to TMS treatment.

Hippunfold analysis

Hippocampal subfields were segmented and analyzed using Hippunfold (version 1.3.x), a specialized software tool designed for the precise delineation of hippocampal subregions. Hippunfold enables high-resolution, automated segmentation of specific hippocampal subfields, including CA1, CA2, CA3, CA4, DG, subiculum, and the stratum radiatum-lacunosum-moleculare (SRLM).

Each participant's T1-weighted MRI images were input into the Hippunfold pipeline, executed by running the hippunfold command. This command utilizes advanced cortical unfolding algorithms to model and extract volumetric data from hippocampal subfields with high anatomical accuracy. The isotropic 1 × 1 × 1 mm resolution of the T1-weighted images was essential for reliable subfield segmentation, minimizing partial volume effects and ensuring high precision in volumetric measurements.

Upon completion, Hippunfold generated an output folder labeled anat, containing a file named desc-subfields_atlas-multihist7_volumes.tsv, which recorded the segmented left and right volumes of each hippocampal subfield. In addition to volumetric data, further cortical thickness and shape metrics were analyzed using files generated in the surf folder. Specific metrics included:

Left dentate gyrus metrics: L Dentate Gyrification shape, L Dentate Surfarea shape

Left hippocampus metrics: L Hipp Curvature shape, L Hipp Gyrification shape, L Hipp Surfarea shape, L Hipp Thickness shape

Right dentate gyrus metrics: R Dentate Gyrification shape, R Dentate Surfarea shape

Right hippocampus metrics: R Hipp Curvature shape, R Hipp Gyrification shape, R Hipp Surfarea shape, R Hipp Thickness shape

Scalar metrics for the dentate gyrus and hippocampus: Dentate Curvature dscalar, Dentate Gyrification dscalar, Hipp Curvature dscalar, Hipp Gyrification dscalar, Hipp Thickness dscalar

These surface-based metrics provided additional insights into cortical remodeling beyond volumetric changes, capturing features such as thickness, surface area, curvature, and gyrification. By comparing these metrics across pre-TMS and post-TMS scans of AD patients and the healthy control group, the analysis allowed for a more comprehensive evaluation of structural differences and potential effects of TMS on hippocampal architecture.

Following segmentation, thickness, and shape metric extraction, the data were statistically analyzed to identify significant differences between pre-, and post-TMS scans and between AD and control groups. These comparisons offered a detailed assessment of subfield-specific changes, cortical remodeling, and the potential structural impact of TMS on hippocampal subfields in AD.

Statistical analysis

Statistical analyses were conducted to evaluate group differences in hippocampal subfield volumes, with all analyses performed using Jamovi software (version 2.3.21.0) and a significance threshold set at $p<0.05$. Group comparisons included: (1) Healthy Controls vs. Pre-TMS AD, (2) Healthy Controls vs. Post-TMS AD, and (3) Pre-TMS vs. Post-TMS AD. Independent (unpaired) t-tests were used to assess differences in hippocampal subfield volumes between healthy controls and the AD groups (pre- and post-TMS), as these comparisons involved separate groups. For comparisons within the AD group (pre- vs. post-TMS), paired t-tests were employed to account for the repeated measures design and to evaluate changes in hippocampal subfield volumes following TMS treatment. In addition to p-values, t-statistic values were reported to provide further insight into the magnitude of group differences. To minimize inter-individual variability, volumetric data were standardized by dividing each subfield volume by the total hippocampal volume (sum of all seven subfields). This statistical approach enabled precise evaluation of TMS-induced changes in hippocampal subfields and facilitated a robust comparison with healthy controls, allowing us to assess the potential structural effects of rTMS treatment in Alzheimer's patients.

RESULTS

Hippunfold analysis revealed significant atrophy in several left hippocampal subfields in AD patients compared to healthy controls HC. The subiculum volume was significantly reduced in pre-TMS ($p<0.001$) and post-TMS ($p<0.001$) AD groups compared to HC. Similarly, the CA1 subfield exhibited significant reductions in pre-TMS ($p=0.001$) and post-TMS ($p<0.001$) conditions relative to HC. Significant reductions were also observed in the CA3 ($p<0.001$), CA4 ($p<0.001$), DG (p $p<0.001$), and SRLM ($p<0.001$) subfields in pre-TMS and post-TMS AD groups compared to HC. However, no significant changes in volumetric measures were observed between pre-TMS and post-TMS conditions for any of these subfields.

In the right hippocampus, similar patterns of atrophy were observed in AD patients. The subiculum and CA1 subfields were significantly reduced in both pre-TMS ($p<0.001$) and post-TMS ($p<0.001$) conditions compared to HC. The CA3 subfield showed progressive atrophy, with significant reductions in AD patients compared to HC (pre-TMS: $p=0.003$; post-TMS: $p<0.001$) and a further significant decrease between pre-TMS and post-TMS conditions ($p=0.005$). Significant reductions were also found in CA4 ($p<0.001$) and DG ($p<0.001$) volumes in pre-TMS and post-TMS AD groups compared to HC, but no significant differences were observed between pre-TMS and post-TMS conditions. The SRLM subfield was also significantly reduced in AD patients relative to HC ($p<0.001$), with no evidence of recovery post-TMS (Table 1 Fig. 3).

Cortical shape and thickness analyses revealed sig-

Table 1. Mean hippocampal subfield volumes (± SD) in healthy controls (HC), pre-TMS AD patients, and post-TMS AD patients.

Items	HC	pre TMS	post TMS	HC vs pre TMS	HC vs post TMS	pre TMS vs post TMS
	Mean ± SD	Mean ± SD	Mean ± SD	p (t)	p (t)	p (statistic)
L Sub	583.6 ± 86.1	412.1 ± 79.1	393.1 ± 68.3	<0.001 (6.143)	<0.001 (7.27)	0.225 (103)
L CA1	763.9 ± 95.9	573.0 ± 169.4	564.4 ± 138.8	0.001 (4.072)	<0.001 (4.92)	0.644 (87)
L CA2	131.4 ± 24.2	107.9 ± 40.7	108.7 ± 28.7	0.116 (2.068)	0.044 (2.52)	0.927 (74)
L CA3	208.8 ± 39.5	141.7 ± 48.4	151.5 ± 40.0	<0.001 (4.472)	<0.001 (4.26)	0.611 (65)
L CA4	271.5 ± 40.2	195.9 ± 53.4	202.1 ± 60.8	<0.001 (4.714)	0.001 (3.96)	0.378 (57)
L DG	126.9 ± 17.6	64.4 ± 30.7	65.4 ± 29.9	<0.001 (7.323)	<0.001 (7.35)	0.963 (78)
L SRLM	560.0 ± 67.5	359.3 ± 85.2	358.0 ± 92.8	<0.001 (7.69)	<0.001 (7.33)	0.611 (88)
R Sub	566.4 ± 79.7	387.5 ± 108.1	406.1 ± 112.2	<0.001 (5.548)	<0.001 (4.85)	0.109 (42)
R CA1	809.8 ± 95.5	607.5 ± 138.0	601.7 ± 145.2	<0.001 (5.015)	<0.001 (4.98)	0.207 (104)
R CA2	139.8 ± 19.6	122.0 ± 36.3	131.5 ± 40.5	0.195 (1.786)	0.728 (0.764)	0.89 (73)
R CA3	246.0 ± 40.1	185.6 ± 55.2	169.4 ± 52.5	0.003 (3.684)	<0.001 (4.83)	0.005 (134)
R CA4	259.5 ± 46.6	189.1 ± 48.8	186.6 ± 62.9	<0.001 (4.361)	0.002 (3.88)	0.89 (73)
R DG	134.3 ± 17.5	65.7 ± 32.5	63.2 ± 35.7	<0.001 (7.71)	<0.001 (7.42)	0.306 (99)
R SRLM	593.3 ± 73.2	371.8 ± 105.9	367.5 ± 113.0	<0.001 (7.156)	<0.001 (6.97)	0.353 (97

Volumetric differences between groups were analyzed using independent t-tests (Healthy Controls [HC] vs. pre-Transcranial Magnetic Stimulation [TMS] Alzheimer's Disease [AD] patients and HC vs. post-TMS AD patients) and paired t-tests (pre-TMS vs. post-TMS). The hippocampal subfields assessed include the left and right subiculum (L Sub, R Sub), CA1 (Cornu Ammonis 1; L CA1, R CA1), CA2 (L CA2, R CA2), CA3 (L CA3, R CA3), CA4 (L CA4, R CA4), dentate gyrus (L DG, R DG), and stratum radiatum-lacunosum-moleculare (L SRLM, R SRLM). Each cell presents the mean volume with standard deviation (Mean ± SD) followed by the p-value and t-statistic (p(t)) for each comparison. Significant p-values ($p < 0.05$) indicate notable differences in subfield volumes across conditions, highlighting potential TMS-induced structural changes in AD patients.

Table 2. Comparisons of cortical shape and thickness metrics between HC, pre-TMS, and post-TMS AD groups

Items	HC	pre TMS	post TMS	HC vs. pre TMS		HC vs. post TMS	
				Statistic	p	Statistic	p
L Dentate Gyrification shape	5.9553 ± 0.9931	4.2351 ± 1.5254	4.7 ± 1.7803	60	0.002	73	0.007
L Dentate Surfarea shape	0.1317 ± 0.0125	0.1009 ± 0.0165	0.1021 ± 0.0189	18	< 0.001	17	< 0.001
L Hipp Curvature shape	-0.0922 ± 0.0126	0.062 ± 0.7224	-0.0865 ± 14.2712	119	0.273	118	0.258
L Hipp Gyrification shape	2.133 ± 0.1845	1.7314 ± 0.3042	1.6633 ± 0.2916	43	< 0.001	34	< 0.001
L Hipp Surfarea shape	0.1515 ± 0.0126	0.1176 ± 0.0163	0.1153 ± 0.0161	13	< 0.001	12	< 0.001
L Hipp Thickness shape	1.3418 ± 0.0504	1.1711 ± 0.1506	1.1692 ± 0.1378	28	< 0.001	28	< 0.001
R Dentate Gyrification shape	6.1167 ± 1.1562	4.041 ± 1.5756	3.561 ± 1.5304	49	< 0.001	39	< 0.001
R Dentate Surfarea shape	0.1329 ± 0.0141	0.0986 ± 0.0177	0.0953 ± 0.0201	24	< 0.001	26	< 0.001
R Hipp Curvature shape	0.0841 ± 0.0173	2.6782 ± 12.4624	0.087 ± 0.0195	125	0.369	143	0.757
R Hipp Gyrification shape	2.229 ± 0.2136	1.7665 ± 0.3435	1.7661 ± 0.3115	41	< 0.001	32	< 0.001
R Hipp Surfarea shape	0.1582 ± 0.0126	0.1244 ± 0.0244	0.1175 ± 0.0204	40	<0.001	29	< 0.001
R Hipp Thickness shape	1.3399 ± 0.0516	1.1811 ± 0.1224	1.1883 ± 0.1095	39	< 0.001	20	< 0.001
Dentate Curvature dscalar	-0.0041 ± 0.0088	1.37 ± 6.5880	1.55 ± 7.1380	136	0.59	125	0.369
Dentate Gyrification dscalar	6.0360 ± 1.0406	4.14 ± 1.3250	4.12 ± 1.4610	42	< 0.001	42	< 0.001
Hipp Curvature dscalar	-0.0041 ± 0.0088	1.37 ± 6.5880	1.55 ± 7.1380	136	0.59	125	0.369
Hipp Gyrification dscalar	2.1810 ± 0.1758	1.75 ± 0.2920	1.73 ± 0.2740	39	< 0.001	26	< 0.001
Hipp Thickness dscalar	1.3409 ± 0.0458	1.18 ± 0.1270	1.17 ± 0.1160	29	< 0.001	20	< 0.001

The table presents the mean ± standard deviation (SD) for Healthy Controls (HC), pre-Transcranial Magnetic Stimulation (TMS) Alzheimer's Disease (AD) patients, and post-TMS AD patients across various metrics, including the dentate gyrus and hippocampal gyrification, surface area, curvature, and thickness. Statistical comparisons were performed to evaluate differences between HC vs. pre-TMS, HC vs. post-TMS, and pre-TMS vs. post-TMS groups. Significant results ($p < 0.05$) are highlighted. The metrics include hemisphere-specific measures (e.g., L Dentate Gyrification for the left dentate gyrus) as well as scalar metrics such as hippocampal thickness (Hipp Thickness dscalar) and dentate curvature (Dentate Curvature dscalar).

nificant differences between HC and AD patients, as well as between pre-TMS and post-TMS conditions in specific hippocampal subfields and cortical metrics.

For gyrification, surface area, and curvature measures, left dentate gyrus (L Dentate Gyrification shape) showed a significant reduction in pre-TMS (p=0.002) and post-TMS (p=0.007) AD groups compared to HC, while no significant changes were observed between pre-TMS and post-TMS conditions. Similarly, right dentate gyrus curvature (R Dentate Curvature shape) was significantly reduced in pre-TMS and post-TMS AD patients relative to HC (p<0.001), with no significant differences between pre- and post-TMS conditions. For surface area, significant reductions were also observed in both left hippocampal (L Hipp Surfacearea shape) and right hippocampal (R Hipp Surfacearea shape) metrics in AD patients compared to HC (p<0.001 for both).

In terms of hippocampal thickness, significant reductions were observed in the left hippocampal thickness (L Hipp Thickness shape) and right hippocampal thickness (R Hipp Thickness shape) in pre-TMS and post-TMS AD groups relative to HC (p<0.001). Notably, hippocampal thickness measures further declined significantly between pre-TMS and post-TMS conditions in both hemispheres (p<0.001), indicating progressive cortical thinning despite TMS treatment.

Finally, scalar measures of dentate gyrus curvature (Dentate Curvature dscalar) and hippocampal thickness (Hipp Thickness dscalar) showed significant reductions in AD patients compared to HC (p<0.001), with further reductions observed between pre-TMS and post-TMS conditions (p<0.001), emphasizing ongoing structural degeneration (Table 2).

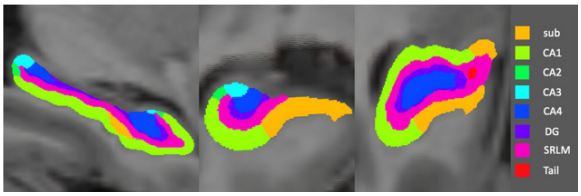

Figure 1. Segmented hippocampal subfields visualized on T1-weighted MRI images using the Hippunfold software. The image shows coronal, sagittal, and axial views of the hippocampus with color-coded labels for each subfield. Each color represents a distinct hippocampal subfield, facilitating detailed structural analysis and volumetric comparisons across different conditions. Sub: Subiculum, CA: Cornu Ammonis, DG: Dentate Gyrus, SRLM: Stratum Radiatum-Lacunosum-Moleculare, MRI: Magnetic Resonance Imaging

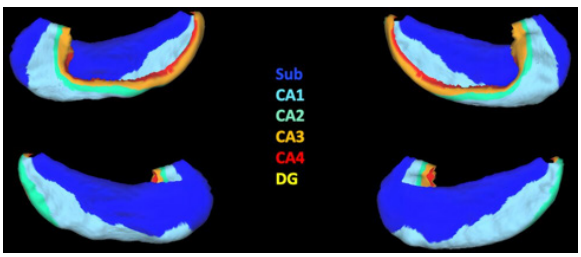

Figure 2. The figure depicts a 3D representation of hippocampal subfields segmented and color-coded using Hippunfold. Thickness is measured as the distance between the inner and outer surfaces of the hippocampal ribbon in each subfield. The visualization provides a clear spatial depiction of regional boundaries and structural properties, facilitating subfield-specific analyses of atrophy and cortical thinning in AD. Subfields are displayed bilaterally for both hemispheres, highlighting the utility of Hippunfold in quantifying structural metrics across the hippocampus. Sub: Subiculum, CA: Cornu Ammonis, DG: Dentate Gyrus, AD: Alzheimer's Disease

DISCUSSION

TMS and progression of atrophy

One notable observation was the persistent significant atrophy in most hippocampal subfields in AD patients compared to HC, particularly in the DG, CA1, CA3, CA4, and subiculum. Although rTMS did not cause volumetric recovery, the slight reduction in post-TMS comparisons (e.g. HC vs. post-TMS), which was not statistically significant, suggests that TMS may have modestly slowed the progression of hippocampal atrophy in certain regions. This subtle neuroprotective effect aligns with prior research suggesting that rTMS may promote neuroplasticity and enhance synaptic connectivity, potentially moderating the pace of structural degeneration (4). Long-term studies with extended TMS protocols are needed to clarify its effects on the trajectory of hippocampal atrophy.

Asymmetry in TMS effects: Left vs. Right hippocampus

The asymmetry in atrophy patterns between the left and right hippocampus was another key finding. TMS was administered to the left lateral parietal cortex, targeting the left hippocampus via network connectivity. Consequently, left hippocampal subfields, including the CA3, CA4, and DG exhibited a relatively stable profile compared to the right hippocampus, where at-

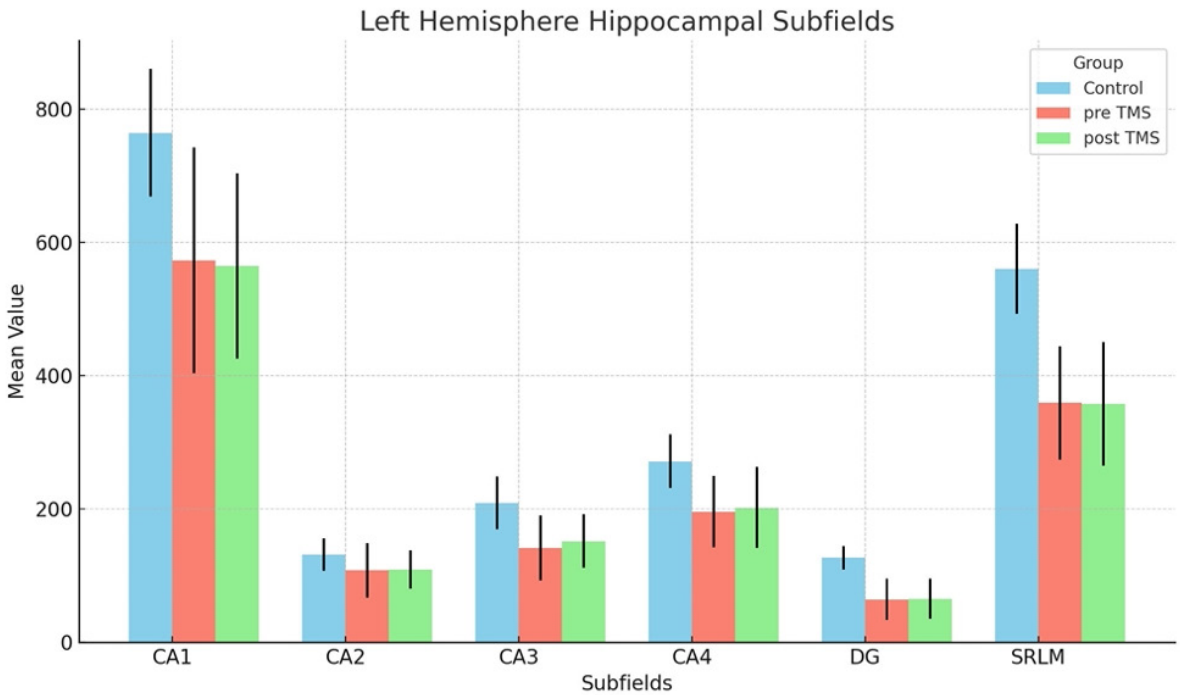

Figure 3. Mean hippocampal subfield volumes in the left hemisphere for healthy controls (blue), pre-Transcranial Magnetic Stimulation (TMS) Alzheimer's Disease (AD) patients (red) post-TMS AD patients (green). Subfields assessed include cornu ammonis 1 (CA1), CA2, CA3, CA4, dentate gyrus (DG), and stratum radiatum-lacunosum-moleculare (SRLM). Error bars represent standard deviations. This figure illustrates the volumetric differences in left hippocampal subfields across the three groups, highlighting potential changes following TMS treatment in AD patients as well as differences from the control group.

rophy appeared more pronounced, particularly in the CA3 subfield. This hemispheric difference supports the hypothesis that targeted stimulation provides some degree of structural preservation in the stimulated hemisphere, whereas the unstimulated side remains vulnerable to disease progression (10). Future research should explore the effects of bilateral stimulation to address this asymmetry and evaluate its potential to mitigate right hippocampal atrophy.

Vulnerability of specific subfields

The CA1 and SRLM subfields emerged as particularly vulnerable regions in AD. The significant reduction in CA3 volume in both hemispheres, with additional progressive atrophy observed in the right CA3 post-TMS, highlights its susceptibility to neurodegeneration. CA1 is critically involved in memory encoding and pattern separation, functions that are heavily impaired in AD (11). The pronounced decline in right CA3 volume underscores the importance of targeting this region in future interventions, potentially through bilateral or region-specific TMS protocols.

Similarly, the DG exhibited consistent atrophy in AD patients compared to HC, regardless of TMS intervention. This finding aligns with the DG's established role as a site of adult neurogenesis, which is impaired in AD (12). While no significant volumetric changes were observed post-TMS, prior studies suggest that TMS may enhance neurogenesis indirectly through increased neuroplasticity and cortical connectivity (13). Future research should evaluate whether prolonged or intensified rTMS protocols could stimulate neurogenic processes in the DG, potentially mitigating cognitive symptoms of AD.

Cortical thickness and shape metrics

Beyond hippocampal volumetry, cortical thickness, and shape analyses revealed additional structural insights into AD. Significant reductions in hippocampal thickness were observed bilaterally in AD patients compared to HC, with further thinning detected between pre-TMS and post-TMS conditions. These findings suggest that TMS may not halt cortical thinning in vulnerable subregions such as the left and right dentate

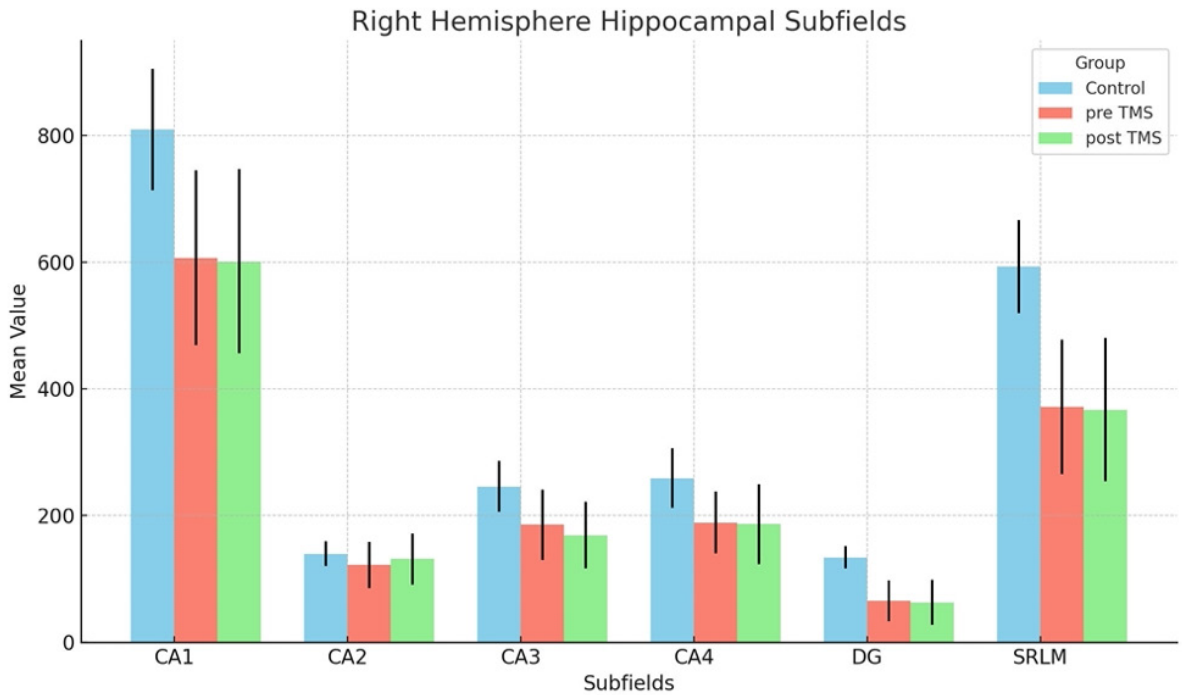

Figure 4. Mean hippocampal subfield volumes in the right hemisphere for healthy controls (blue), pre-Transcranial Magnetic Stimulation (TMS) Alzheimer's Disease (AD) patients (red) post-TMS AD patients (green). The same hippocampal subfields as in the left hemisphere are shown: Cornu ammonis 1 (CA1), CA2, CA3, CA4, dentate gyrus (DG), and stratum radiatum-lacunosum-moleculare (SRLM). Error bars represent standard deviations. This figure allows for comparison of right hippocampal subfield volumes across groups, providing insight into hemispheric differences and the effects of TMS in AD patients compared to healthy controls.

gyrus and hippocampal subfields. Cortical thinning in AD is consistent with the disease's well-documented progression, which involves synaptic loss and neuronal atrophy in regions critical for memory and learning, including the hippocampus (14).

Shape metrics, including curvature and surface area, also revealed distinct patterns of structural alterations. Notable reductions were observed in both the dentate gyrus and hippocampal surface, indicating continued degeneration in cortical and subcortical structures despite rTMS treatment. These changes highlight the complexity of structural remodeling in AD, as cortical atrophy is not limited to volumetric reductions but extends to changes in shape and connectivity (15). Such findings emphasize the need to explore whether longer or more targeted rTMS protocols could mitigate these progressive changes by promoting neuroplasticity and connectivity.

These results align with prior studies showing that cortical thickness and shape metrics provide sensitive markers of AD progression, even when volumetric recovery is absent. Importantly, changes in hippocampal thickness and shape metrics correlate strongly with cognitive decline, suggesting that these structural measures could serve as biomarkers for evaluating the efficacy of TMS and other therapeutic interventions (1,16).

Limitations

This study has several limitations that must be acknowledged. First, the relatively small sample size limits the generalizability of the findings and may reduce statistical power for detecting subtle structural changes. Larger sample sizes and multi-site studies are necessary to validate these results. The inclusion of a more diverse participant pool across multiple sites could also enhance the applicability of the findings to broader populations. Second, the absence of a sham (placebo) TMS group restricts the ability to attribute observed changes solely to TMS effects. Including a sham group in future research would provide critical controls for distinguishing between TMS-specific effects and natural variability in disease progression. The addition of alternative control conditions, such

as active or other forms of stimulation, could further strengthen causal inferences. Lastly, the short duration of the TMS protocol may have limited its potential to induce measurable volumetric changes. Extended protocols and longitudinal designs could better capture TMS's long-term structural effects. Future studies should also explore bilateral stimulation protocols, as unilateral approaches may not fully address asymmetrical patterns of hippocampal atrophy commonly observed in AD.

CONCLUSION

This study highlights the significant atrophy observed in hippocampal subfields and cortical thickness in AD patients and suggests that rTMS may modestly influence the progression of neurodegeneration. While no substantial recovery was observed, findings underscore the potential of rTMS as a neuroprotective intervention, particularly when applied bilaterally or over extended durations. Future research should focus on refining rTMS protocols to target specific hippocampal subfields, leveraging neurogenesis in regions like the DG, and addressing hemispheric asymmetry in treatment effects.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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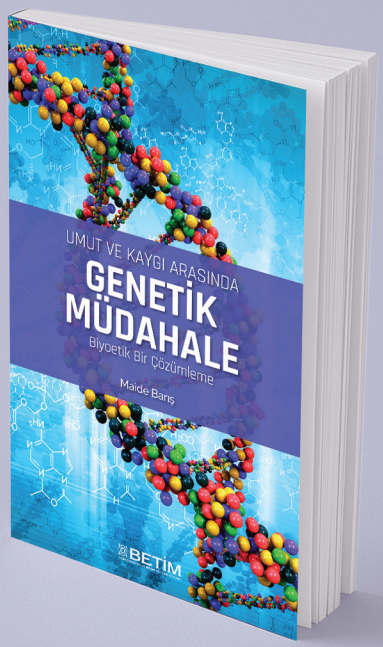

UMUT VE KAYGI ARASINDA

GENETİK MÜDAHALE

Biyoetik Bir Çözümleme

Maide Barış

Dünyadaki biyoetik literatürü genetik müdahale konusundaki tartışmalar bağlamında her geçen gün daha da zenginleşirken, Türkçe olarak yapılmış çalışmaların sayısı oldukça kısıtlıdır. Bu çalışma soy hattına yönelik genetik müdahalenin kategorik bir şekilde ahlaken yanlış olarak değerlendirilip değerlendirilemeyeceğine ilişkin kapsamlı bir tartışma yürütmektedir. CRISPR/Cas9 teknolojisinin geliştirilmesi ile birlikte pratik olarak mümkün hale gelen soy hattına yönelik genetik müdahaleler, laboratuvar dışına çıkmak (ve kliniğe doğru ilerlemek) için son hazırlıklarını tamamlamaktadır. Elinizdeki bu kitapta, tüm insanlığı ve gelecek nesilleri etkileme potansiyeli bulunan ve hem umut hem de kaygı kaynağı addedilen soy hattına yönelik genetik müdahale teknolojisi, dünya ile eş zamanlı olarak detaylı bir şekilde ele alınarak biyoetik bir analiz gerçekleştirilmiştir.

BETİM KİTAPLIĞI

Investigation of the effect of Severe Acute Respiratory Syndrome Coronavirus 2 pandemic on autoantibody positiveness evaluated by the indirect immunofluorescence assay

İndirekt immünofloresan testi ile değerlendirilen otoantikor pozitifliklerine Şiddetli Akut Solunum Yolu Sendromu Koronavirüsü 2 pandemisinin etkisinin araştırılması

Abstract

Aim: The aim of this study is to determine the possible relationship between Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) infection and systemic or organ-specific autoimmune diseases.

Methods: Serum samples sent to a Medical Microbiology Laboratory from patients in various clinics with preliminary diagnoses of autoimmune disease between March 2018 and March 2022 were included in our study. During this period, the indirect immunofluorescent antibody test results studied in our laboratory were obtained from the automation system of our hospital and evaluated retrospectively.

Results: In the two years before the Coronavirus Disease 2019 (COVİD 19) pandemic and the two years during the pandemic anti-nuclear antibody (ANA) positivity was detected in 2256 of 8325 patients who underwent indirect immunofluorescence assay (IIAF) evaluation [single pattern in 2038 patients (1363 speckled), multiple pattern in 218 patients]. When the change in autoantibody positivity over time was examined, it was determined that there was a statistically significant increase in the positivity rates of ANA, anti-double-stranded DNA antibody (anti-dsDNA), antigliadin,anti-islet cell antibody (anti -ICA) and anti-Gliadin autoantibodies in the first two years of the pandemic compared to the previous two years. No difference was observed in the positivity rates of anti-mitochondrial antibodies (AMA), anti-smooth muscle antibodies (ASMA), anti-endomysium, Antineutrophil cytoplasmic antibody (ANCA) autoantibodies before and during the COVID-19 pandemic.

Conclusion: The increase in the positivity rates of ANA, anti-dsDNA, anti-ICA, anti-Gliadin autoantibodies during the pandemic period suggested that the COVID-19 process may affect some autoimmune diseases.

Keywords: Autoantibodies; autoimmune diseases; indirect immunofluorescence assay; SARS-CoV-2

Öz

Amaç: Bu çalışmanın amacı Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) enfeksiyonu ile sistemik veya organa özgü otoimmün hastalıklar arasındaki olası ilişkiyi belirlemektir.

Yöntemler: Çalışmamıza Mart 2018 ile Mart 2022 tarihleri arasında çeşitli kliniklerden, otoimmün hastalık ön tanısı olan hastalardan Tıbbi Mikrobiyoloji Laboratuvarı'na gönderilen serum örnekleri dâhil edildi. Bu dönemde laboratuvarımızda çalışılan indirekt immünofloresan antikor test sonuçları hastanemiz otomasyon sisteminden elde edilerek retrospektif olarak değerlendirildi.

Bulgular: Coronavirus Disease 2019 (COVİD 19) pandemisinden önceki iki yılda ve pandemi dönemindeki iki yılda indirect immunofluorescence assay (IIAF) değerlendirmesi yapılan 8325 hastanın 2256'sında anti-nükleer antikor (ANA) pozitifliği saptandı [2038 hastada tekli patern (1363'ü benekli), 218 hastada çoklu patern]. Otoantikor pozitifliğinin zaman içindeki değişimi incelendiğinde, pandeminin ilk iki yıllık döneminde önceki iki yıla göre ANA, anti-double-stranded DNA antibody (anti-dsDNA), antigliadin,anti-islet cell antibody (anti -ICA) ve anti-Gliadin otoantikorlarının pozitiflik oranlarında istatistiksel olarak anlamlı bir artış olduğu tespit edildi. anti-mitochondrial antibody (AMA),, anti-smooth muscle antibody (ASMA), anti-Endomysium, anti-neutrophil cytoplasmic antibody (ANCA), otoantikorlarının ise pozitiflik oranlarında COVID-19 pandemi döneminde ve öncesinde farklılık gözlenmedi.

Sonuç: Pandemi döneminde ANA, anti-dsDNA, anti-ICA, anti-Gliadin otoantikorlarının pozitiflik oranlarının artması, COVID-19 sürecinin bazı otoimmün hastalıkları etkileyebileceğini düşündürdü.

Anahtar Sözcükler: İndirek immunfloresan ölçüm; otoantikorlar; otoimmün hastalıklar; SARS-CoV-2

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INTRODUCTION

Autoimmune diseases (AD) are caused by the development of immune responses against the organism own tissues and cells and autoantibodies are of great importance in the diagnosis of these diseases (1). Autoantibodies called anti-nuclear antibodies (ANA), which develop against nuclear structures in the cell nucleus and/or cytoplasm, are important diagnostic criteria in connective tissue diseases. Currently, there are many methods developed for the detection of ANA positivity (2). The gold standard method for ANA detection is the indirect immunofluorescence assay (IIFA) using Hep2 cells (1).

Many ADs are multifactorial, related to both genetic and environmental factors such as viral infections. Viruses are known to be among the most common exogenous factors that trigger the development of autoimmunity in genetically susceptible individuals (3). Specific virus types can promote the production of autoantibodies and cytokines by causing widespread non-specific B and T activation. For example, the presence of Epstein-Barr virus and Parvovirus B19 is associated with Hashimoto's thyroiditis, Human T-lymphotropic virus-1 with Graves disease and autoimmune encephalitis after infection with Herpes simplex virüs (4).

On 7 January 2020, the World Health Organization (WHO) announced that this agent was a new coronavirus that causes infection in humans. There is increasing evidence that SARS-CoV-2 infection is associated with the development of autoimmunity phenomena. The clinical spectrum of autoimmunity-related symptoms in COVID-19 patients ranges from organ-specific autoimmune diseases to systemic autoimmune and inflammatory diseases (5).

In this study, in order to investigate the effect of the COVID-19 pandemic period on the autoantibodies' positivity rates, it was aimed to examine the autoantibody test results evaluated by the IIFA method in the pre-pandemic period and during the pandemic period.

MATERIAL AND METHODS

In this study, serum samples sent to Düzce University, Medical Microbiology Laboratory between March 2018 and March 2022 with suspicion of ADs from patients in various clinics were included. IIFA parameters results of the samples were examined in our laboratory during this period were obtained from the automation system of our hospital and evaluated retrospectively.

Among the autoimmune test parameters; ANA, anti-double-stranded DNA antibody (anti-dsDNA), anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), anti-endomysium, anti-gliadin, anti-islet cell antibody (anti-ICA), perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA), cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA) tests were included in the study. For these tests, IIFA method was used according to the recommendations of the manufacturer (Euroimmun AG, Germany). EuroimmunEurostar (Euroimmun AG, Germany) fluorescence microscope was used.

This study was approved by the Düzce University Faculty Of Medicine Non-invasive Health Practices Ethics Committee (date: 10.17.2022, decision no: 2022/162.

Statistical analyses

Statistical Package for the Social Sciences software for Windows, version 22.0, was used for the statistical analysis (SPSS, Chicago, IL, USA). Appropriate descriptive statistics were calculated according to the type of data. The relationships between categorical variables were analysed by Chi-square, Fisher Freeman-Halton (post-hoc Bonferroni test) and Fisher's Exact tests. $p<0.05$ was considered statistically significant.

RESULTS

The study included 2448 patients who were found to be positive for any autoantibody among 8325 patients whose serum samples were sent to the microbiology laboratory for IIFA testing with suspicion of autoimmune disease in the two years before the COVID-19 pandemic and two years during the pandemic period.

Of the patients who were positive for IIFA, 1684 (68.80%) were female and 764 (31.20%) were male with a mean age of 41±19.44 years. The positivity rates of ANA, AMA, Anti-ICA tests were higher in women than in men. The evaluation of the positive tests of the patients according to gender is showmemran in Table 1.

Table 1. Evaluation of positive tests according to gender

	Female		Male		*p*
	n	%	*n*	%	
ANA	**1563/5076**	**30,80**	693/2600	26,66	***<0,001***
Anti-dsDNA	8/3139	0,25	0/1665	-	0,057
AMA	**17/601**	**2,82**	4/482	*0,82*	***0,024***
ASMA	12/673	1,78	12/535	2,24	0,569
ANCA	**34/988**	**3,44**	19/875	2,17	0,100
Anti-ICA	**7/205**	**3,41**	5/482	1,03	***0,030***
Anti- Endomisyum/Gliadin	43/1042	4,12	31/682	4,54	0,675
Total	**1684/5505**	**30,59**	764/2825	27,04	***0,001***

ANA: anti-nuclear antibodies, anti-dsDNA: anti-double-stranded DNA antibody, AMA: anti-mitochondrial antibody, ANCA: anti-cytoplasmic antibody, Anti-ICA: anti-islet cell antibody, n:number, %:percentage

Table 2. Distribution of ANA positivity according to time intervals [number (%)]

ANA positivity	**Time intervals**								
	Before COVID-19				**COVID-19 pandemic period**				
Six-month rates	April 2018 - September 2018	October 2018 - March 2019	April 2019 - September 2019	October 2019 - March 2020	April 2020 - September 2020	**October 2020 - March 2021**	April 2021 - September 2021	October 2021 - March 2022	*p*
	248/1159 (21,4)	412/1344 **(30,6)**	249/1014 (24,5)	259/1181 (21,9)	163/486 (33,5)	**281/639 (44,0)**	311/815 (38,2)	333/1050 (31,7)	**<0,001**
Annual rates	April 2018-March 2019		April 2019-March 2020		**April 2020-March 2021**		April 2021- March 2022		
	660/2503 (26,4)		508/2195 (23,1)		**444/1125 (39,5)**		644/1865 (34,5)		**<0,001**
Two-yearly rates	April 2018-March 2020				**April 2020-March 2022**				
	1168/4698 (24,9)				**1088/2990 (36,3)**				**<0,001**

ANA: anti-nuclear antibodies

ANA positivity was detected in a total of 2256 patients, of which 2038 had single pattern and 218 had multiple patterns (Fifure 1, Figure 2).

The period with the highest rate of ANA positivity was determined as the second six-month period in the COVID-19 pandemic. The second highest rates were detected in the first and third six months during the COVID-19 pandemic period and there was no difference between them (p=0.094) (Table 2).

When we examined the change in anti-dsDNA positivity rates over time, it was observed that the positivity rate was statistically significantly higher in the first year of the COVID-19 pandemic compared to other years (p=0.038) (Table 3).

When we examined the change in anti-ICA positivity rates over time, it was observed that the positivity rates were statistically significantly higher in the COVID-19 pandemic period with a rate of 7.3% compared to the pre-pandemic period (p=0.034).

There was no difference between anti-endomysium positivity rates before and during the COVID-19 pandemic (p=0.968).

Anti-Gliadin positivity was significantly higher in the second year of the COVID-19 pandemic period with a rate of 6.6% compared to other years (p=0.010). When the six-month rates were analyzed, the highest positivity was found in the third six-month period after COVID-19 (p=0.038).

The rate of ANCA positivity was 0.6% in the fourth six-month period before COVID-19 (April 2018-September 2018), which was lower than the other periods (p=0.023). No significant difference was found

Table 3. Distribution of anti-dsDNA positivity according to time intervals [number (%)]

Anti-dsDNA positivity	Time intervals								
	Before COVID-19				COVID-19 pandemic period				
Six-month rates	April 2018 - Sep. 2018	October 2018 - March 2019	April 2019 - Sep. 2019	October 2019 - March 2020	April 2020 - Sep. 2020	October 2020 - March 2021	April 2021 - Sep. 2021	October 2021 - March 2022	*p*
	1/953 (0,1)	0/954 (0,0)	0/446 (0,0)	1/425 (0,2)	1/288 (0,3)	**3/374 (0,8)**	2/516 (0,4)	0/650 (0,0)	***0,022***
Annual rates	April 2018-March 2019		April 2019-March 2020		April 2020-March 2021		April 2021- March 2022		
	1/1907 (0,1)		1/871 (0,1)		**4/662 (0,6)**		2/1166 (0,2)		***0,038***
Two-yearly rates	April 2018-March 2020				April 2020-March 2022				
	2/1778 (0,1)				**6/1828 (0,3)**				0,289

anti-dsDNA: anti-double-stranded DNA antibody, Sep.: September

between the other periods (p=0.221, p=0.275, respectively).

In addition, during the study period, 41 patients whose COVID-19 test was positive were later found to have a positive ANA test [speckled (74%), dense fine speckled (15%), homogeneous (7%), nuclear membrane (2%) and nuclear with few spots (2%) patterns].

DISCUSSION AND CONCLUSION

Autoimmune disorders are more common in females due to hormonal differences. In a study conducted by Sung et al. in patients with rheumatoid arthritis, the rate of females was reported as 81.9% and the rate of males as 18.1% (6). In a study conducted by Çelikbilek et al. with the sera of patients with ANA positivity, the rate of females was 77% and the rate of males was 23% (7). In our study, 68.8% of the patients with autoantibodies positivity were women and all autoimmune parameters were found more frequently in females. The positivity rates of ANA, AMA, and anti-ICA tests were statistically higher in females than in males. We thought females were more susceptible to autoimmune diseases than males.

Autoimmune diseases can occur at any age, but different diseases have their own characteristic age of onset (8). Barut et al. evaluated 309 patients with positive ANA test by IIFA method and found the mean age to be 42.50±14.66 years (9). In our study, the mean age of patients with autoantibody positivity was found to be 41±19.44 years, which was similar to the studies in our country.

In the study conducted by Yanik et al., in which ANA patterns of 843 samples were evaluated by IIFA, it was found that the most common pattern was speckled (75.0%), the second most common pattern was nucleolar (10.4%), followed by homogenous (6.8%) (10). In a study conducted by Mariz et al. in 918 healthy and 153 individuals with OIH in Brazil, it was shown that the most common ANA pattern in both groups was the dense fine speckled pattern with a rate of 45.8% in healthy individuals and 42% in individuals with ADs. The second most common ANA pattern was shown to be a coarse speckled pattern in individuals with OIH (26.1%) and a dense fine spotted pattern in healthy individuals (33.1%) (11). In our study, 2038 and 218 of 2256 patients with ANA positivity had single and multiple patterns, respectively. When the distribution of single patterns was analyzed, the most common pattern was speckled pattern with 1363, followed by 340 dense fine speckled, 152 homogeneous, 92 nucleolar, 38 nuclear membrane, 32 centromere, 13 few nuclear dots and 8 multiple nuclear dots patterns, respectively. Similar to the single patterns, the most common pattern was specled pattern in the multiple patterns. It has been observed that the most common pattern worldwide is the speckled pattern.

In a study from Izmir, 50 serum samples from acute COVID-19 patients and 50 control serum samples collected before the outbreak were evaluated for ANA positivity by IIFA method. A higher rate of ANA positivity was found in COVID-19 patients (18%)

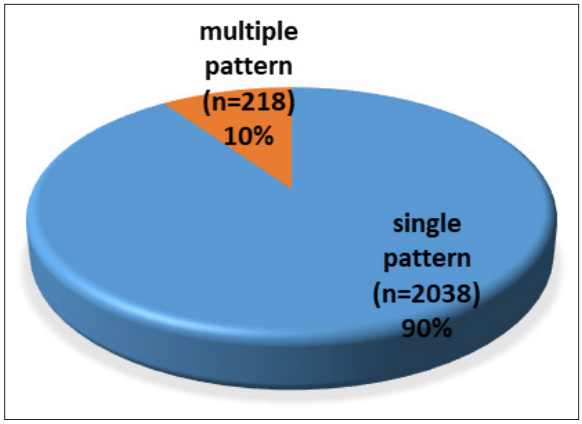

Figure 1. Single and multiple pattern distribution of ANA positivity

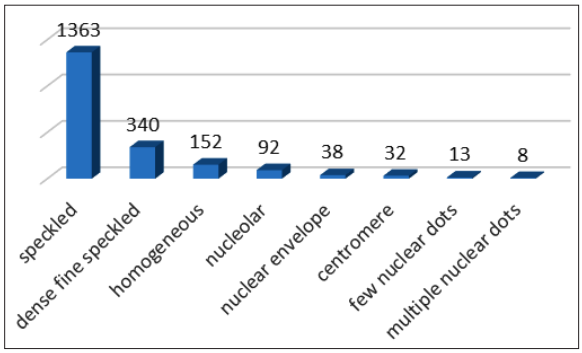

Figure 2. Distribution of single pattern

compared to the control group (2%), but the difference was not statistically significant (12). Pascolini et al. examined the presence of ANA by IIFA method in 31 patients with COVID-19-related pneumonia and 25 patients with pneumonia with etiology other than COVID-19. ANA positivity in patients with COVID-19 (33.3%) was found to be significantly higher than in patients with other non-COVID-19 pneumonia (0.08%) (13). In our study, ANA positivity evaluated by the IIFA method was detected at a higher rate in the post-pandemic period compared to the pre-pandemic period. These results suggested that COVID-19 disease, drugs, or vaccines may activate the autoimmune system.

Chang et al. in a study involving 47 patients hospitalized with COVID-19-induced infection in Korea, ANA positivity rate was found to be 21.3% (10/47). In the same study, the most common patterns were found to be 50% (5/10) nucleolar and 30% (3/10) speckled patterns (14). Peker et al. evaluated ANA by IIFA method in serum samples of 50 patients with acute COVID-19 infection and found that ANA test was positive in 9 patients and nucleolar pattern was the most common pattern (12). In our study, in 41 patients with positive COVID-19 test and positive ANA test, the speckled pattern was the most common pattern in 30 (74%) patients. Dense fine speckled (15%), homogeneous (7%), nuclear membrane (2%), and nuclear with few dots (2%) patterns followed in order of frequency. In our study, the most common pattern in ANA positivity was speckled, which was not found to be consistent with other studies when compared with the literature. In addition, dense fine speckled pattern was not found in patients with COVID-19 infection in other studies and it was the second most common pattern in our study. This suggested that the COVID-19 pandemic may have an effect on systemic autoimmune diseases.

In the study by Peker et al. in which anti-dsDNA antibodies were examined by IIFA method in acute COVID-19 patients and healthy control group, anti-dsDNA antibodies were not detected in both group (12). In our study, when the pre-COVID-19 pandemic period and the COVID-19 pandemic period were compared, a statistically significant increase in the positivity rate of anti-dsDNA antibodies was observed during the COVID-19 pandemic period. These results show that there may be an increase in systemic autoimmune diseases, especially Systemic lupus erythematosus.

In the study by Singh et al., liver enzymes of a COVID-19-positive patient were found to be elevated, and the patient was diagnosed with autoimmune hepatitis-primary biliary cholangitis triggered by COVID-19 infection after AMA, ASMA, anti-ds DNA antibodies were found to be positive in further investigations (15). In our study, although there was no statistically significant difference between the pre-COVID-19 pandemic period and the COVID-19 pandemic period, an increase in the positivity rates of AMA and ASMA antibodies indicating autoimmune liver diseases was observed during the COVID-19 pandemic period.

In a case published by Hollstein et al., a 19-year-old female patient who presented with diabetic ketoacidosis was found to have COVID-19 infection 5-7 weeks prior to admission. In this case, although the relationship between COVID-19 and the development

of diabetes was not fully demonstrated, it was thought that COVID-19 may adversely affect pancreatic function with its direct cytolytic effect on pancreatic β-cells (16). When we examined the change in anti-ICA positivity rates over time in our study, a statistically significant increase was found in the annual rates of the COVID-19 pandemic compared to the annual rates before the pandemic. The findings in our study contribute to the literature by showing the relationship between the COVID-19 pandemic and the incidence of autoantibody-mediated type 1 diabetes.

In the study by Çakır et al. comparing patients diagnosed with celiac disease before and during the COVID-19 pandemic, an increase in the frequency of celiac disease was observed in the paediatric age group during the pandemic period (17). In our study, COVID-19 pandemic had no effect on anti-endomysium antibodies, which is not compatible with the literature.

In the study by Duran et al., vasculitis-associated glomerulonephritis was diagnosed and positive ANCA tests were detected in two patients with recent COVID-19 positivity upon the development of acute kidney injury (18). In a study conducted by Gelzo et al. on 124 COVID-19-positive patients (16 asymptomatic and 108 hospitalised) and 48 control groups to define the frequency of ANCA-related autoimmunity in patients with COVID-19 infection, it was observed that patients with COVID-19 infection had significantly higher serum ANCA levels than the control group (19). In our study, ANCA positivity was found to be higher in the COVID-19 pandemic period (3.3%) compared to the COVID-19 pre-pandemic period (2.4%), although not statistically significant.

There are some limitations in our study due to the retrospective nature of our data. The full spectrum of autoimmune phenomena that may occur in patients during or after COVID-19 is still unclear. However, the findings of our study may help to show the relationship between COVID-19 and new-onset autoimmune diseases.

In our study, it was observed that there was an increase in some autoantibody positivity during the pandemic period. Long-term studies are needed to examine the relationship between COVID-19 disease and new-onset systemic and organ-specific autoimmune diseases.

Conflict-of-Interest And Financial Disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study

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BİYO-TIP ETİĞİ VE HUKUK

SEVTAP METİN

Biyo-tıp etiği, muhtaç olanlara gerektiği şekilde yardım etme biçimindeki genel ahlaki yükümün, doktorun faaliyetinde somutlaştırılması olarak görülür. Bu durumda yardıma gereksinim duyanlar hastalardır ve onlara yapılması gereken yardım esas olarak tıbbidir. Yine de hekimlik etkinliği sadece teknik gerekleri yerine getirmekle yetinemez; öyle ki eğer ahlak boyutu eksikse hekim tıbbı uygulayan bir teknisyen olmaktan öteye geçemeyecektir. Ancak bunun da ötesinde, içinde yaşadığımız 21. yüzyıla dair nitelendirmelerden biri de biyoteknoloji yüzyılı olacağı öngörüsüdür. Bir kısmı şu an için pratiğe geçirilemese de tasavvur ötesi olmayan birçok biyoteknolojik atılım ve bunun insan hayatı ve sağlığına etkisi, görmezden gelinemeyecek aşamaya gelmiştir. İşte bu dönemde tıbbi işlemlerin sadece ahlaki tarafına vakıf olmanın da ötesine geçilerek felsefi bir tartışma ve yaklaşıma her zamankinden daha fazla ihtiyaç vardır.

Türkiye'nin ilk ve tek tıp ve insani bilimler merkezi Beşikçizade Tıp ve İnsani Bilimler Merkezi—BETİM tarafından yayımlanan bu önemli eser tıbbın felsefi yönü ile de ilgilenen okurlar için vazgeçilemez bir başvuru kaynağı olacaktır.

BETİM KİTAPLIĞI

The effects of blood lactate level on mortality in patients developing sepsis in intensive care unit

Yoğun bakım ünitesinde sepsis gelişen hastalarda kan laktat düzeyinin mortalite üzerine etkisi

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Abstract

Aim: Sepsis is a serious condition with high mortality and morbidity in intensive care units (ICUs). Mortality decreases with early and appropriate antimicrobial treatment. We aimed to investigate the relationship between lactate levels and mortality in the ICU of our hospital.

Methods: Patient records > 18, hospitalized in the ICU of Meram State Hospital between January 2022 and January 2024, were retrospectively examined. All patients microbiologically confirmed to have positive blood culture results and diagnosed sepsis were included in the study. Age on admission, gender, diagnoses at hospitalization, Apache II, length of stay, and mortality in ICU were obtained from patients' medical records. In the presence of suspicion of sepsis in a patient hospitalized in intensive care and in the first 72 hours after antibiotic treatment, the lactate level was recorded. Lactate clearance was defined as the percent decrease in lactate from ICU department presentation to hour 72. Mortality rates within the first 28 days were recorded. Lactate levels were compared in patients with and without mortality. The value of lactate in predicting mortality was evaluated statistically.

Results: Of 56 patients included in the study, whose diagnoses of sepsis were microbiologically proven, 38 (67.9%) died. The area under a receiver operating characteristic (ROC) curve Area under curve (AUC) of lactate in predicting mortality was 0.738 [95% confidence interval (CI): 0.590 –0.886, (p=0.004)]. Threshold lactate value for mortality was 1.7 mmol/L (sensitivity: 73.7%, specificity: 61.1%). While lactate levels, lactate clearance, length of hospital stay, Acute Physiologic and Chronic Health Evaluation (APACHE II) score were statistically significant between sepsis patients with and without mortality (p=0,004, p = 0.03 p= 0,00 p=0.003). Baseline lactate was in survivors 2.05±1.37 and in nonsurvivors 1.33±0.98 mmol/L. Survivors compared with nonsurvivors had a lactate clearance of 48.2 ± 24.4 vs. 22.06 ± %, respectively (p = 0.007). It showed lactate clearance to have a significant relationship with mortality (p = 0.03).

Conclusion: Here, we found that lactate level and, lactate clearance may be a significant place in the early treatment and follow-up of sepsis patients in ICUs.

Keywords: Intensive care unit; lactate; mortality; sepsis

Öz

Amaç: Sepsis yoğun bakım ünitesinde (YBÜ), mortalitesi ve morbiditesi yüksek önemli bir durumdur. Mortalite, erken ve uygun antimikrobiyal tedavi ile azalmaktadır. Çalışmamızda hastanemiz 3. basamak yoğun bakım ünitelerinde yatan hastaların kan laktat düzeyleri ile mortalite oranları arasındaki ilişkiyi incelemeyi amaçladık.

Yöntemler: Meram Devlet Hastanesi YBÜ'de yatan Ocak 2022'den Ocak 2024'e kadar olan 2 yıllık süreçte 18 yaş üstü hastaların kayıtları retrospektif olarak incelendi. Sepsis tanısı alan mikrobiyolojik olarak (pozitif kan kültürü sonuçları) doğrulanan tüm hastalar dahil edildi. Hastaların yatış anında yaşları, cinsiyetleri, yatış tanıları, Acute Physiologic and Chronic Health Evaluation (APACHE II), yatış süresi, YBÜ mortalite verileri tıbbi dosya kayıtlarından elde edildi. Yoğun bakıma yatırılan bir hastada sepsis şüphesi varlığında ve antibiyotik tedavisi sonrası ilk 72. saatte laktat düzeyi kaydedildi. Laktat klirensi, yoğun bakıma başvurudan 72. saatte olan laktatta azalma olarak tanımlandı. Hastalarda ilk 28 gün içindeki mortalite kaydedildi. Mortalite gelişen ve gelişmeyen hasta grubunda laktat düzeyleri karşılaştırıldı. Laktatın mortaliteyi öngörmedeki değeri istatistiksel olarak değerlendirildi.

Bulgular: Çalışmaya 56 hasta alınmıştır. Araştırma grubuna dâhil edilen sepsis tanısı mikrobiyolojik olarak kanıtlanan hastaların (%67,9)'i ölüm ile sonuçlanmıştır. Laktatın mortaliteyi öngörmedeki Receiver Operating Characteristic (ROC) eğrisi altında kalan alan (AUC) 0,738 idi [% 95 güven aralığı (GA): 0,590 –0,886] p=0,004). Mortalite için eşik laktat değeri 1,7 mmol/L (duyarlılık: % 73,7, özgüllük: % 61,1 olarak bulundu. Mortalite olan ve olmayanlar sepsis hastaları arasında laktat düzeyi, laktat klirensi, hastanede kalış süresi ve APACHE II istatistiksel olarak anlamlı bulunurken (p=0,004, p = 0.03 p= 0,00 p=0.003), Başlangıç laktat düzeyi hayatta kalanlarda 2,05±1,37, ölen hastalarda 1,33±0,98 mmol/L idi. Hayatta kalanların, hayatta kalmayanlarla karşılaştırıldığında laktat klerensi sırasıyla %48,2 ± 24,4 ve %22,06 ± idi (p = 0,007). Laktat klerensinin mortalite ile anlamlı bir ilişkiye sahip olduğunu gösterdi (p = 0.03).

Sonuç: Çalışmamızda laktat düzeyinin ve laktat klirensinin yoğun bakım ünitelerinde sepsisin erken tedavi ve takibinde önemli bir yeri olabileceği düşünülmüştür.

Anahtar Sözcükler: Laktat; mortalite; sepsis; yoğun bakım ünitesi

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INTRODUCTION

Sepsis is a serious condition with high mortality and morbidity among those staying in the intensive care unit (ICU). Even so, mortality decreases with early and appropriate antimicrobial treatment (1,2). Considering the high mortality of sepsis, it is considered that to make a timely diagnosis, the pre-evaluation of simple and easily accessible biomarkers will support the decision-making process about the clinical status of the patient in the future. Serum lactate levels have been suggested to be a marker of hypoperfusion and tissue hypoxia in sepsis. Even before patients develop significant hypotension, tissue perfusion deteriorates due to myocardial depression, injury-associated hypovolemia, an increase in metabolic activity, and impaired vasoregulatory mechanisms. For this reason, oxygen demand increases, and the production of anaerobic lactate occurs (3). Regardless of the mechanism of lactate production, the mortality rate has been witnessed to increase in patients presenting with the diagnosis of sepsis and with high serum lactate levels (> 4 mmol/L) (4). Measuring the levels of lactate provides beneficial information about the progression of the disease and the effectiveness of the treatment. For those suspected to have sepsis, measuring the levels of lactate provides useful information about the severity of the disease and allows the course of the disease to be monitored (5). Additionally, after a 6-hour-treatment in septic patients, mortality rates have been reported to decrease in those with high lactate clearance (6). In sepsis, elevated lactate levels are associated with increased mortality, independent of shock and organ failure (7). This study aims to investigate the relationship between blood lactate levels and mortality rates of patients hospitalized in the tertiary ICU of our hospital.

MATERIAL AND METHODS

This study was approved by Clinical Research Ethics Committee of the Faculty of Medicine at Karatay University (date: 28.06.2024, decision no: 2024/033). The study was conducted in accordance with the principles stated in the Declaration of Helsinki. Patients' medical records over 18 years of age and hospitalized in the ICU of Konya Meram State Hospital between January 2022 and January 2024 were retrospectively investigated. Diagnosed with sepsis, all patients confirmed microbiologically to have positive blood culture results were included in the study. Blood samples were examined through the BACTEC 9240 fully automatic blood culture device (Becton Dickinson, Diagnostic Device System, Spark, USA). In the presence of suspicion of sepsis in a patient hospitalized in intensive care and in the first 72 hours after antibiotic treatment, the lactate level was recorded. Lactate clearance was defined as the percent decrease in lactate from ICU department presentation to hour 72. Patients' age rates on admission, gender, diagnoses on admission to the hospital, Acute Physiologic and Chronic Health Evaluation (APACHE II) scores, length of stay, and mortality rates in ICU data were obtained from medical file records in the automation system of the hospital. Mortality rates of the patients within the first 28 days were also recorded, and lactate levels were compared in the patient groups with and without mortality. Then, the value of lactate in predicting mortality was evaluated statistically.

Statistical analyses

Statistical analyses of the study findings were evaluated with the Statistical Package for the Social Sciences software for Windows, version 24.0 (SPSS Inc., Chicago, IL, USA). While the nominal data were described as ratios and percentages, mean and standard deviation (±, SD) were used to describe continuous numerical data. Additionally, median and interquartile ranges were used to describe non-normally distributed continuous numerical data. The presence of normal distribution was evaluated using statistical tests and graphical methods. While the Pearson chi-square test was used to compare the categorical data, the Mann-Witney U test was utilized to compare non-normally distributed numerical data in pairs, and the student's *t*-test was used in independent groups to compare normally distributed continuous numerical variables. The receiver-operating characteristic (ROC) analysis was performed to evaluate the ability of laboratory tests to predict whether the sepsis-causing bacterium is a Gram-negative bacterium and to predict mortality. A *p*-value of <0.05 was accepted to be statistically significant.

RESULTS

Fifty-six patients were included in the study, and 29 (51.8%) and 27 (48.2%) of the cases were male and female. The average age was 75.45±11.77. Of 56 patients in the study with the diagnosis of sepsis proven microbiologically, 38 (67.9%) died within 28 days. The ROC analysis was performed to determine the predictive diagnostic value of lactate levels in terms of mortality in patients with sepsis. The area under the ROC curve (AUC) of lactate in predicting mortality was found as 0.738 [95% confidence interval (CI): 0.590 –0.886 (p=0.004)] (Figure.1). The threshold value of lactate for mortality was determined to be 1.7 mmol/L (sensitivity: 73.7%, specificity: 61.1%). Baseline lactate was in survivors 2.05±1.37 and in nonsurvivors 1.33±0.98 mmol/L. Survivors compared with nonsurvivors had a lactate clearance of 48.2 ± 24.4 vs. 22.06 ± %, respectively (p = 0.007). It showed lactate clearance was significantly related to mortality (p = 0.03). Lactate levels, lactate clearance and length of hospital stay were found to be statistically significant between sepsis patients with and without mortality (p=0.004, p = 0.007, p= p=0.00) (Table 1). When the mortality rates of those with lactate levels < 2 mmol and those with lactate levels of ≥ 2 mmol were compared, mortality was found to be significantly higher in those with lactate levels of ≥ 2 mmol. The effects of lactate levels on mortality are given in Table 2.

DISCUSSION AND CONCLUSION

Sepsis is among the leading causes of death in patients staying in ICUs (8). High lactate levels in sepsis have been associated with poor prognosis (9). In our study, while the mortality rates were found as 66% in patients with lactate levels < 4 mmol/L and 83.3% in those with ≥ 4 mmol/L, the mortality rates in ICU were detected to increase 1.5 times. Additionally, the mortality rates in ICU were reported to be 54.8% in patients with lactate levels of < 2 mmol/L and 84% in those with lactate levels between 2-3.99 mmol/L. Mortality rates were seen to be higher in patients with high Apache II scores; Apache II score was 27.87±6.8 in nonsurvivors and 17.21±3.9 in survivors. It showed a significant relationship with mortality

In a study carried out by Shapiro et al. where the relationship between lactate levels and mortality rates was investigated in 1278 patients, the researchers found mortality rates as 4.9% in those with lactate levels of 0-2.4 mmol/L, 9% in those with lactate levels of 2.5-3.9 mmol/L levels, and 28.4% in those with lactate levels of > 4 mmol/L. In the same study, it was also revealed that the evaluation of lactate clearance with serial measurements would help decrease the rates of morbidity and mortality (6). Mortality was found to be high in patients with a lactate level of 4 mmol/L at baseline. These results support our study findings that as lactate levels increase, the mortality rates in ICU also elevate (6). In another

Table 1. Demographic characteristics of patients under mortality rates

	Exitus	**Survival**	***p***
	Median (Q1-Q3)	**Median (Q1-Q3)**	
Age	78±14	76±21	0.97
Gender (F/M)	18/20	9/9	0.85
Lactate (0. day)	2.05±1.37	1.33±0.98	***0.004***
Lactate (3. day)	1.42±1.06	0.82±0.8	***0.007***
Length of hospital stay	22±28 (2-278)	83±87 (28-420)	***0.003***
Apache II score	27.87±6,8	17.21±3,9	***0.003***

Q1-Q3: Quartile 1-3, F/M: Female/Male, Acute Physiologic and Chronic Health Evaluation (APACHE II)

Table 2. Relationship between lactate levels and mortality

Lactate levels	**Mortality rates, % n**
<2 mmol/L	54 (17)
2-3.99 mmol/L	84 (16)
≥ 4 mmol/L	83.3 (5)

n: Number, %: Percentage

study conducted in our country, the mortality rate was found to be 75.6% in patients with a lactate level of < 4 mmol/L and 24.4% in those with a lactate level of > 4 mmol/L (10). In the study evaluating lactate levels among the patients admitted to the emergency department, the researchers demonstrated that a 20% or more decrease in lactate level of > 3 mmmol/L in ICU within the first 8 hours led to a definite decrease of 9.6% in mortality (11). Early Goal-Directed Therapy (EGDT) is a hemodynamic algorithmic approach used for patients with suspected severe sepsis or septic shock, who are admitted to the emergency department in patients. According to EGDT, the early treatment plan and the target of the treatment should be to normalize lactate levels in patients with sepsis-induced tissue hypoperfusion (continuing hypotension despite initial fluid therapy or blood lactate level ≥ 4 mmol/L) and in those with increased tissue blood lactate levels (12). In our study; baseline lactate was in survivors 2.05±1.37 and in nonsurvivors 1.33±0.98 mmol/L. Survivors compared with nonsurvivors had a lactate clearance of 48.2 ± 24.4 vs. 22.06 ± %, respectively. It showed lactate clearance to have a significant relationship with mortality (p = 0.03). Similar to our study, in a study conducted APACHE II score was 20.2 ± 6.8 and lactate 6.9 ± 4.6 mmol/L. Survivors compared with nonsurvivors had a lactate clearance of 38.1 ± 34.6 vs. 12.0 ± 51.6%, respectively (13).

In the 2018 update of the sepsis survival campaign care packages, a significant decrease was demonstrated in mortality through lactate-guided resuscitation. If the lactate level measured first is > 2 mmol/L, the level should be remeasured within 2-4 hours, and the resuscitation should be directed, considering the later measurement. In other words, the normalization of lactate, which is an indicator of tissue hypoperfusion, should be targeted (8). As emphasized in the guidelines of sepsis treatment, lactate level is emphasized as an important indicator of mortality in sepsis. In our study, it was found that lactate level and lactate clearance could be an important biomarker in the early treatment and follow-up of sepsis in ICUs.

Limitations

It was conducted retrospectively and our study included a limited number of sepsis cases.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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Classification of human monkeypox with the Fuzzy C-Means Algorithm using image processing methods and Haralick texture parameters

Görüntü işleme yöntemleri ve Haralick doku parametreleri kullanılarak insandaki maymun çiçeği hastalığının Bulanık C-Ortalamalar Algoritması ile sınıflandırılması

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Abstract

Aim: Human monkeypox can cause skin lesions in the form of blisters of different shapes on various parts of the body. Due to the fact that the skin lesions caused by human monkeypox have a very similar appearance to lesions caused by chickenpox and measles, the study includes images of chickenpox and measles as well as images of human monkeypox. The aim of this study is to distinguish human monkeypox virus skin lesion images from other viral diseases with similar images.

Methods: For this study, the Monkeypox Skin Lesion Dataset, which consists of binary classification data for monkeypox and non-monkeypox (chickenpox, measles) skin lesions, is accessed from the Kaggle.com website. In total, 228 images are processed, with 101 images in the monkeypox group and 127 images in the non-monkeypox group. The images in the Monkeypox Skin Lesion Dataset are processed using image analysis methods and Haralick texture parameters are calculated to create 13 different features for each image. For the classification process in the statistical analysis part of the study, Fuzzy C-Means algorithm is used.

Results: The images used in the study belong to individuals with varying skin tones and from different parts of the body, and the algorithm provides encouraging results in determining the type of skin lesions in the images. The overall classification accuracy rate is 61.8%, and the highest accuracy (76.2%) is achieved in the monkeypox class.

Conclusion: This study demonstrates that images of viral diseases with similar skin lesions can be classified using various image-processing techniques and different statistical methods.

Keywords: Classification; clustering; monkeypox

Öz

Amaç: İnsanlarda görülen maymun çiçeği, vücudun çeşitli yerlerinde farklı şekillerde kabarcıklar şeklinde deri lezyonlarına neden olabilir. İnsan maymun çiçeğinin neden olduğu cilt lezyonları, suçiçeği ve kızamık kaynaklı lezyonlara çok benzer bir görünüme sahiptir. Bu sebeple çalışmada, insan maymun çiçeği görüntülerinin yanı sıra suçiçeği ve kızamık görüntüleri de yer almaktadır. Bu çalışmanın amacı, insan maymun çiçeği virüsü cilt lezyonu görüntülerini, benzer görüntülere sahip diğer viral hastalıklardan ayırmaktır.

Yöntemler: Bu çalışma için maymun çiçeği ve maymun çiçeği olmayan (suçiçeği, kızamık) cilt lezyonlarına yönelik ikili sınıflandırma verilerinden oluşan Maymun Çiçeği Cilt Lezyonu Veri Setine Kaggle.com web sitesinden erişilmektedir. Maymun çiçeği grubunda 101 görüntü ve maymun çiçeği olmayan grupta 127 görüntü olmak üzere toplamda 228 görüntü işlenir. Maymun Çiçeği Cilt Lezyonu Veri Setinde yer alan görüntüler, görüntü analiz yöntemleri kullanılarak işlenmekte ve her görüntü için 13 farklı özellik oluşturacak şekilde Haralick doku parametreleri hesaplanmaktadır. Çalışmanın istatistiksel analiz kısmında sınıflandırma işlemi için Bulanık C-Ortalamalar algoritması kullanılır.

Bulgular: Çalışmada kullanılan görüntüler, farklı cilt tonlarına sahip bireylerden ve vücudun farklı bölgelerinden alınmış olup algoritma, görüntülerdeki cilt lezyonlarının tipinin belirlenmesinde cesaret verici sonuçlar ortaya koymaktadır. Genel sınıflandırma doğruluk oranı %61.8 olarak bulunmakta ve en yüksek doğruluk da (%76.2) maymun çiçeği sınıfında elde edilmektedir.

Sonuç: Bu çalışma, benzer cilt lezyonlarına sahip viral hastalık görüntülerinin, çeşitli görüntü işleme teknikleri ve farklı istatistiksel yöntemler kullanılarak sınıflandırılabileceğini göstermektedir.

Anahtar Sözcükler: Gruplama; maymun poks; sınıflandırma

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INTRODUCTION

As the world continues to grapple with the effects of the ongoing COVID-19 pandemic, the emergence of monkeypox as a rapidly spreading virus has become a new cause for concern. Monkeypox, also known as monkeypox virus disease, has been reported in 75 countries as of July 23, 2022, prompting the World Health Organization (WHO) to declare a global emergency and warn of the potential for the virus to spread to even more countries. So, monkeypox is a viral disease that is similar to smallpox and is primarily found in Central and West Africa. The disease can be transmitted to humans through contact with infected animals, particularly rodents and primates. Symptoms of monkeypox include fever and lesions on the skin. While most cases of monkeypox are mild and self-limiting, severe cases can occur, particularly in individuals with weakened immune systems.

Monkeypox is not a new disease, as it was first identified in 1958 in laboratory monkeys in Copenhagen, Denmark. The disease was named monkeypox virus due to its characteristic skin lesions, but initially, no clinical information about the disease was documented (1). The first recorded case of monkeypox in humans was reported in 1970 when a 9-month-old baby boy in the Democratic Republic of Congo was diagnosed with the disease. Since then, monkeypox cases have been reported in humans in other countries in Central and West Africa, with the majority of cases occurring in the Democratic Republic of the Congo. Monkeypox re-emerged in 2018, with a total of five reported cases in Nigeria, three in the UK, one in Israel, and one in Singapore. Subsequently, in May 2022, numerous cases of monkeypox were identified in regions where the disease is not endemic (2-7).

Monkeypox virus infection produces symptoms that are comparable to smallpox but are usually less severe. The disease is divided into two distinct periods. The first stage is known as the invasion period and is characterized by the onset of fever, severe headache, swollen lymph nodes, backache, muscle aches, and extreme weakness. This stage typically lasts between 0-5 days. Swollen lymph nodes, or lymphadenopathy, are a key clinical feature that distinguishes monkeypox from other diseases that present with similar initial symptoms, such as chickenpox, measles, and smallpox. Typically, a skin lesion appears within 1 to 3 days after the onset of fever, which tends to be most concentrated on the face (in 95% of cases), palms, and soles (in 75% of cases). The number of lesions that appear in monkeypox cases can vary greatly, ranging from only a few to several thousand. In severe cases, the lesions may merge together, causing the affected skin to peel over a large area. Furthermore, severe cases of monkeypox are more frequently observed in children. The Centers for Disease Control and Prevention (CDC) states that there is currently no known cure for monkeypox infection and that treatment involves supportive care. Nevertheless, the CDC website offers detailed information on how to prevent and control the spread of the disease (8, 9).

A review of the literature shows that studies on human monkeypox date back to the 1970s when the first case in humans was reported. In recent years, there has been a significant increase in studies on human monkeypox due to the emergence of the disease in countries where it was previously not observed in 2018, as well as the rapid increase in cases in these countries in 2022. Therefore, there are only a limited number of studies available that focus on the image analysis and statistical classification of the skin lesion symptoms associated with the disease. Ahsan et al. published a preprint article that collected images of monkeypox skin lesions from various sources such as websites, newspapers, and online portals. They obtained a dataset of 43 monkeypox, 47 chickenpox, 17 measles, and 54 normal images, which they augmented to increase the dataset size. The authors aimed to investigate the progression of the monkeypox virus and how its skin lesion findings differ from other similar skin diseases. To achieve this, they performed histogram analysis and analyzed the pixel intensities of the images (10). Haque et al. conducted research on transfer learning-based models using the Monkeypox Skin Lesion Dataset (MSLD) that was also used by Ali et al. in their study. They employed the CBAM attention mechanism and evaluated several models including VGG19, DenseNet121, EfficientNetB3, MobileNetV2, and Xception. The study achieved classification rates of 69.86% for VGG19, 78.27% for DenseNet121, 54.21% for EfficientNetB3, 74.07% for MobileNetV2, and 79.90% for Xception (11). Ali et al. performed a study on the classification of

monkeypox and other similar skin diseases using pre-trained VGG-16, ResNet50 and InceptionV3 models. They used the MSLD developed by them in the study. The results showed that ResNet50 and VGG-16 had correct classification rates of 82.96% and 81.48% respectively. At the end of the study, the authors combined the three models and achieved an accuracy rate of 79.26±1.05 (12). Sahin et al. used the MSLD from Kaggle to classify human monkeypox in their study. The dataset contained binary classification data, with images labeled as either having monkeypox or not (chickenpox or measles). The researchers employed several pre-trained deep learning models on the MSLD dataset and found that the MobileNetV2 and EfficientNetB0 models performed well. Then they converted the entire model into a TensorFlow lite model, allowing it to be adapted for mobile devices. Using this model, they developed a mobile application that could classify images with an accuracy of 91.11% based on test results. The researchers also noted that the application could be used to diagnose other skin diseases, including monkeypox, in a preliminary capacity (13). Sadad et al. developed a new method called FCMRG to identify breast masses in mammograms. Fuzzy C-Means (FCM) and region-growing (RG) algorithms were used in this method. In the feature extraction step of image processing, Local Binary Pattern Gray-Level Co-occurrence Matrix (LBP-GLCM) and Local Phase Quantization (LPQ) were applied to the images. They used machine learning procedures to distinguish between benign and malignant tumors and achieved a high accuracy rate of 98.2% with the proposed method (14). Rohmayani and Rahayu carried out a study to classify lung images into four different categories: normal lung, pneumonia-infected lung, COVID-19-infected lung, and X-ray images of other diseases that involve the lung. They obtained the dataset from Kaggle.com, which consisted of 120 training images and 40 test images. Image processing techniques were applied, and the mean and standard deviation values were used for feature extraction. FCM algorithm was used for classification analysis, and the method achieved an accuracy rate of 65% (15). Zayed and Elnemr tested a dataset containing CT images of 37 patients with lung tumors or pulmonary edema. After performing image processing techniques, they extracted haralick texture features to identify the type of abnormality in the lungs. They found that their proposed method showed potential in detecting lung abnormalities (16).

Our study has three main aims. The first and most important of these is to classify images of virus-induced diseases such as monkeypox, chickenpox and measles. To achieve this, we use the MSLD available on Kaggle website. The second aim is to use the FCM algorithm, a statistical approach that has not been used before in this field, when classifying images of diseases. Finally, using the 13 different statistical features (haralick texture parameters) that we obtained at the end of various pre-processing steps in the image processing section as input variables in FCM analysis. In addition, running the FCM algorithm according to the haralick texture parameters calculated for each image in MSLD is the most innovative aspect of the study.

In this study, we suggest a classification based on a different functioning for MSLD within the framework of our 3 main aims. It can be seen that this study also stands out as a multi-disciplinary study. The use of image processing methods in the study can be explained as the use of computers in health. Classification of haralick texture parameters with the FCM algorithm also includes the science of statistics in the use of computers in health. Thus, this study will make a significant contribution to the literature.

MATERIALS AND METHODS

Early diagnosis is vital for the human monkeypox outbreak, which has become a global health problem in recent years. The disease is diagnosed using Transcription-Polymerase Chain Reaction (TT-PCR) test, like other viral diseases. However, the sensitivity of this test to detect viruses is low and it takes a long time for the test to be completed. These disadvantages of the test require the development of alternative diagnostic systems. Monkeypox skin lesions are considered an important clinical feature in distinguishing the disease from some other viral diseases such as chickenpox and measles. Therefore, computer-aided preliminary evaluation of images of monkeypox skin lesions may be a useful alternative diagnosis. For this reason, the MSLD is created with images collected from relevant news portals, various websites and some publicly available

case reports. It is worth noting that the disease mostly occurs in African countries where access to healthcare is quite difficult. Therefore, a large data set has not been created so far. Of course, more images of chickenpox and measles skin lesions could be collected. However, facing data imbalance is not a desirable situation and may cause other problems because only monkeypox skin lesion images are limited.

For this research, we obtained the MSLD from the Kaggle.com website which consists of binary classification data for monkeypox and non-monkeypox (chickenpox, measles) skin lesions (17). The dataset contains images from the monkeypox class, as well as similar skin lesions caused by chickenpox and measles. Here, there are 228 images in total, 101 images in the monkeypox group and 127 images in the non-monkeypox group. The images in the MSLD are processed using image analysis methods and Haralick texture parameters are calculated to create 13 different features for each image. Additionally, we use the FCM algorithm for the classification process in the statistical analysis part of the study. In this context, we examine the resulting cluster structure and the distribution of images into clusters. Since the disease type of each image is known in advance, we present a detailed evaluation of the classification success of the method.

Prior to starting the coding stage, the algorithm of the study is developed and the procedures to be followed during the implementation phase are defined. The summarized steps are presented as follows.

1. Download the Monkeypox Skin Lesion Dataset (MSLD) from the Kaggle website
2. Transferring image files to the system and reading them as a matrix
3. Histogram equalization
4. Converting to grayscale image format and invert the image
5. Thresholding the image with the appropriate threshold value-converting to binary format
6. Applying morphological operators to the image
7. Calculating Haralick texture parameters
8. Classification using the Fuzzy C-Means algorithm

For all the transactions and analyses in the coding stage, we use the R package program (version 4.1.3), a free and open-source statistical software development environment that includes various original packages added by users. This program is widely accepted for use in academic studies.

Image Processing

Image processing involves various operations on digital images such as segmentation, merging, rotation, adjustment of brightness, contrast or sharpness, removal of defects or unwanted objects, and enhancing the visibility of important objects according to the researcher's requirements. It is a critical technique for obtaining meaningful data from images and gathering diverse information about objects in the image. The process starts with capturing an image, displaying it on a computer, and then digitizing it for further analysis.

When images are digitized, they are represented as a matrix with rows and columns of pixels. Each pixel in the matrix has a color value that corresponds to its color in the original image. The range of numerical values for the color values of the pixels varies depending on the type of image. There are three types of images used in image processing: color images, grayscale images, and binary images. Color images have multiple color channels, usually red, green, and blue (RGB), while grayscale images have a single color channel representing the intensity of the image. Binary images have only two possible color values, usually black and white, and are used for simple image processing tasks such as edge detection and shape recognition. Digital images are represented as a two-dimensional matrix consisting of pixels in rows and columns, with each pixel being assigned a numerical value that represents its color. The range of numerical values assigned to pixels depends on the type of image. There are three main types of images used in image processing: color images, grayscale images, and binary images. Color images have pixel values in the range of 0 to 255, corresponding to the three colors of Red, Green, and Blue. Grayscale images have pixel values ranging from 0 to 1 and consist of black, white, and shades of gray. Binary images have only two colors, black and white, with pixel values of either 1 or 0. Since most image processing algorithms do not work on color images, it is common to convert color images to binary images.

Image thresholding

Thresholding is a fundamental method in image processing that is used to extract information from an image by separating the objects from the background. This process involves converting a grayscale image to a binary image using a threshold value, which is determined by the researcher. Each pixel in the grayscale image is then compared to this threshold value, and if the comparison result is greater than the threshold, it is considered as an object and evaluated as white, otherwise, it is expressed as black and considered part of the background.

Morphological operations

Mathematical morphology is a technique that uses set theory and is based on the shape structure of an image. It involves two fundamental operations: dilation and erosion, and other operations can be obtained through various combinations of these two operations. However, before these operations can be applied, the image must be converted to binary format (18). Expansion is a type of morphological operation which is used to increase the size or thickness of object outlines in a binary image. Its main objective is to fill small gaps and close holes in the image. Erosion is a morphological operation that has the opposite effect of dilation. It reduces the size of objects or thins the boundaries of objects in a binary-converted image. As a result, it separates objects and increases holes in the image. Applying only expansion or erosion operations to an image can cause significant distortions. Therefore, opening and closing operations are often used to eliminate these distortion problems in the image. Opening is performed by applying erosion first, then expansion sequentially to the image. This operation separates objects that are close to each other in the image while causing minimal change. On the other hand, closing is performed by applying expansion first and then erosion to the image. This operation merges objects that are close to each other in the image while causing minimal change.

Haralick Texture Features

Texture features, also known as second-order feature descriptors, are used to capture patterns and provide statistical correlation between pixels in an image. Unlike first-order features, which only consider the distribution of pixel values, texture features incorporate spatial information and analyze the relationships between gray levels in the image. This allows texture features to capture specific patterns that may be missed by first-order features and can help to minimize information loss in image analysis. The concept of using texture features for image classification was first introduced by Haralick and Shanmugam. Second-order statistical features are similar to the features that are important to clinicians, and they provide quantitatively representative data that can yield more information than what is visible to the human eye. Texture features measure the consistency of patterns and colors in an image, and the Haralick texture is a widely used technique for characterizing texture-based images. Texture analysis is a feature extraction method commonly applied to medical images, which involves analyzing the spatial distribution of neighborhoods at the gray color level within the image (19).

Haralick texture is a crucial technique for characterizing texture-based images and is achieved through the computation of the gray level co-occurrence matrix (GLCM). The GLCM is a popular method for extracting texture features due to its simplicity and the ability to compute numerous features. Textural features can be extracted from a grayscale image by using the GLCM matrix for a particular direction and distance of patterns. The fundamental concept behind GLCM is the pixel neighborhood in an image. The GLCM matrix records the frequency of co-occurrences of gray color levels for each neighbor relationship and direction. It shows how frequently different combinations of gray levels occur in an image. The sum of the number of co-occurrences of a pixel with a value of i in a spatial relationship defined by a pixel with a value of j in the input image is the value of each element in the GLCM (20).

In this research, the characteristics of the Gray Level Co-occurrence Matrix (GLCM) are analyzed for gray level images. The formulas used to extract these features are provided below. The equations describe how to compute a set of statistical features for the co-occurrence matrix.

$P_{ij}=P(i,j)$ is the co-occurrence matrix.

$p(i,j)=P(i,j)/R$, normalized co-occurrence matrix.

N_g, number of discrete intensity levels in the image.

R, normalizing constant.

$p_x(i) = \sum_{j=1}^{N_g} p(i,j)$, marginal row probabilities.

$p_y(j) = \sum_{i=1}^{N_g} p(i,j)$, marginal column probabilities.

μ_x and μ_y are the mean gray level intensities of p_x and p_y, respectively. σ_x and σ_y are also the standard deviations of p_x and p_y, respectively.

Haralick presented a set of 13 statistical features that can be extracted from the Gray Level Co-occurrence Matrix (GLCM), which are commonly known as Haralick texture features. The R Bioconductor package EBImage uses these features and assigns them the names h.asm, h.con, h.cor, h.var, h.idm, h.sav, h.sva, h.sen, h.ent, h.dva, h.den, h.f12, and h.f13. The values for these features are calculated using the equations given in Equation (1) through Equation (13) as provided in references (19, 21, 22).

Angular Second Moment (h.asm)

$$f_1 = \sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\left(\frac{P(i,j)}{R}\right)^2 = \sum_i\sum_j p(i,j)^2 \quad (1)$$

Contrast (h.con)

$$f_2 = \sum_{k=0}^{N_g-1} k^2 \left\{\sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\delta_{|i-j|,k}p(i,j)\right\} = \sum_{k=0}^{N_g-1} k^2 p_{x-y}(k) \quad (2)$$

where the Kronecker delta function is defined as;

$$\delta_{m,n} = \begin{cases} 1 & when \quad m = n \\ 0 & when \quad m \neq n \end{cases} \quad (2.1)$$

Haralick and Miyamoto did not use the Kronecker delta function. Instead, they have given the specified summation conditions in the continuation of Equation (9), Equation (12), and Equation (13).

1. Correlation (h.cor)

$$f_3 = \frac{\sum_{i=1}^{N_g}\sum_{j=1}^{N_g}(ij)p(i,j) - \mu_x\mu_y}{\sigma_x\sigma_y} \quad (3)$$

2. Sum of Squares: Variance (h.var)

$$f_4 = \sum_{i=1}^{N_g}\sum_{j=1}^{N_g}(i-\mu)^2 p(i,j) \quad (4)$$

3. Inverse Difference Moment (h.idm)

$$f_5 = \sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\frac{1}{1+(i-j)^2}p(i,j) \quad (5)$$

4. Sum Average (h.sav)

$$f_6 = \sum_{i=2}^{2N_g} i p_{x+y}(i) \quad (6)$$

5. Sum Variance (h.sva)

$$f_7 = \sum_{i=2}^{2N_g}(i-f_8)^2 p_{x+y}(i) \quad (7)$$

6. Sum Entropy (h.sen)

$$f_8 = -\sum_{i=2}^{2N_g} p_{x+y}(i)\log\left(p_{x+y}(i)\right) \quad (8)$$

7. Entropy (h.ent)

$$f_9 = -\sum_{i=1}^{N_g}\sum_{j=1}^{N_g} p(i,j)\log\left(p(i,j)\right) = HXY \quad (9)$$

$$HXY = -\sum_i\sum_j p(i,j)\log(p(i,j)) \quad (9.1)$$

8. Difference Variance (h.dva)

$$f_{10} = variance\ of\ p_{x-y} \quad (10)$$

9. Difference Entropy (h.den)

$$f_{11} = -\sum_{i=0}^{N_g-1} p_{x-y}(i)\log\left(p_{x-y}(i)\right) \quad (11)$$

10. Information Measures of Correlation1 (h.f12)

$$f_{12} = \frac{f_9 - HXY1}{\max(HX, HY)} \quad (12)$$

$$HX = -\sum_i p_x(i)\log\left(p_x(i)\right) = entropy\ of\ p_x \quad (12.1)$$

$$HY = -\sum_j p_y(j)\log\left(p_y(j)\right) = entropy\ of\ p_y \quad (12.2)$$

$$HXY1 = -\sum_i\sum_j p(i,j)\log(p_x(i)p_y(j)) \quad (12.3)$$

11. Information Measures of Correlation2 (h.f13)

$$f_{13} = [1 - \exp(-2(HXY2 - f_9))]^{1/2} \quad (13)$$

$$HXY2 = -\sum_i\sum_j p_x(i)p_y(j)\log(p_x(i)p_y(j)) \quad (13.1)$$

Fuzzy C-Means (FCM) algorithm

FCM, which stands for Fuzzy C-Means, is an unsupervised clustering technique that was introduced by Jim Bezdek. Its purpose is to group data points into different clusters in multi-dimensional spaces. The algorithm determines the appropriate cluster for each data point by measuring the distance between the cluster centers

and the data point. In some cases, a data point may belong to more than one cluster. FCM is particularly useful for overlapping data sets, unlike the k-means clustering algorithm. The FCM algorithm assigns each data point a membership value for each cluster center, indicating the degree of membership to the cluster. However, the number of clusters must be specified in advance. Similarity values are calculated based on the cluster center and membership values, which range from 0 to 1, representing the degree of membership between the data and the cluster centers. Similarity and membership values are positively related. FCM clustering is performed using the function given in Equation (14,23-26).

$$min_{U,H} J_{FCM} = \sum_{i=1}^{n}\sum_{g=1}^{c} u_{ig}^{m} d^2(x_i, h_g), \quad (14)$$

$$s.t. \quad u_{ig} \in [0,1], \sum_{g=1}^{c} u_{ig} = 1, \quad (14.1)$$

$d(x_i,h_g)$ is the Euclidean distance. Euclidean distance is a measure of distance between observations and cluster centers. Also, the cluster center for each cluster is called the prototype (27). is the generic element of the matrix U of order (n × c), which takes values between 0 and 1, called the membership degree. are the prototypes (cluster centers) stored in the matrix H of order (c × p) where and p is the number of variables. Finally, the 'm' in the Equation (14) is the weighting exponent for fuzziness.

RESULTS

Initially, the images are transferred to the R system from files downloaded from the Kaggle.com website. The original images used in this study can be viewed in Figure 1. After the transfer process, the necessary packages are installed to perform image processing methods in R. The required packages are library(EBImage), library(raster), and library(png). Thus, R becomes ready for operations to be performed on the images. First, the images are processed using histogram equalization, which is an image enhancement technique. This technique helps to eliminate color distortion caused by the clustering of color values within a specific range and enhances the visibility of unclear details in the images. Histogram equalization is applied separately to each image to create a fair and uniform structure for all the images. The new images obtained after histogram equalization are presented in Figure 2. Following histogram equalization, the new images are converted to grayscale and inverted. The resulting images after this process can be seen in Figure 3.

Figure 1. Original images: (a) Monkeypox (b) Chickenpox (c) Measles

Figure 2. Images after histogram equalization: (a) Monkeypox (b) Chickenpox (c) Measles

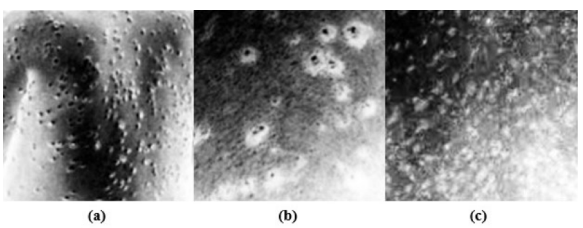

Figure 3. Gray-format inverted images: (a) Monkeypox (b) Chickenpox (c) Measles

The brightness levels of the images are analyzed based on the intensity of light. In order to perform further processing on the images, an appropriate threshold value is determined (0.5) and the images are thresholded accordingly. Thresholding is a critical step in detecting skin lesions in images as it converts the image to binary

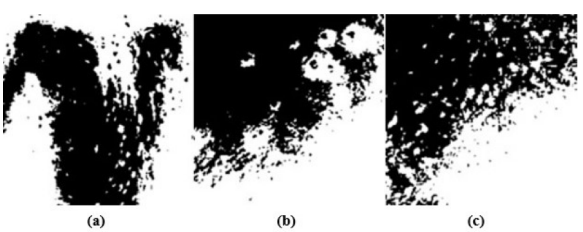

Figure 4. Images after thresholding: (a) Monkeypox (b) Chickenpox (c) Measles

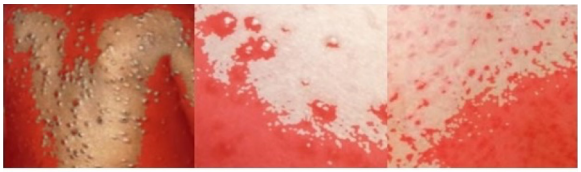

Figure 5. Images after thresholding and after morphological operators: (a) Monkeypox (b) Chickenpox (c) Measles

format. After thresholding, the skin abnormalities and background are completely separated from each other and the images transform into black and white format. The resulting states of the images after thresholding can be viewed in Figure 4. After the mentioned pre-processing steps, we apply some morphological operators to the images to change the pixel sizes of the details for our purpose. We first erode the images and then dilate them which is referred to as the opening process. The application of these morphological operators produces new images, which are shown in Figure 5.

The next step is to calculate the Haralick texture parameters, which are the second-order statistical features of the images and involve 13 of the common

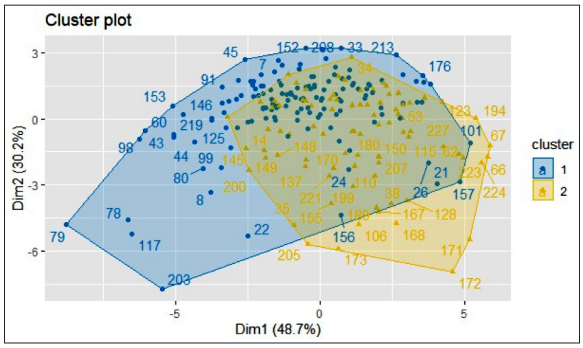

Figure 7. Clusters resulting from analysis with Fuzzy C-Means algorithm

parameters (Details are in the Materials and Methods section). Moreover, a view of the data set created for 13 different Haralick parameters of the images can be seen in Figure 6. These parameters are used as input for the classification process. Based on these parameters, the FCM algorithm analysis results are graphed, which can be presented in Figure 7. It should be noted that the essential packages for fuzzy clustering are used in R. These are: library(cluster), library(fclust), library(dplyr), library(factoextra), library(ppclust).

Filter

	h.asm.s1	h.con.s1	h.cor.s1	h.var.s1	h.idm.s1	h.sav.s1	h.sva.s1	h.sen.s1	h.ent.s1	h.dva.s1	h.den.s1	h.f12.s1	h.f13.s1
1	0.06546286	0.4850268	0.9610611	7.228045	0.8071607	46.177385	2045.81657	1.2175209	1.3749193	0.4850268	0.3354051	0.5507689	0.8051878
2	0.04216555	0.7900239	0.9739247	16.148903	0.7277259	35.548558	1227.48995	1.3771609	1.6248833	0.7900239	0.4094041	0.5100886	0.8193262
3	0.07687494	0.3088386	0.9752187	7.231293	0.8615897	34.088541	1106.05236	1.2033459	1.3051514	0.3088386	0.2742401	0.6457757	0.8437948
4	0.09929914	0.2932062	0.9678593	5.561294	0.8708502	31.979186	970.59693	1.1142386	1.2103192	0.2932062	0.2661223	0.6332227	0.8211103
5	0.06452625	0.3006382	0.9872063	12.749437	0.8609336	43.772231	1851.87886	1.2848010	1.3834896	0.3006382	0.2699369	0.6702297	0.8672199
6	0.04264815	0.5220238	0.9873090	21.566741	0.8495264	37.068795	1351.85149	1.4302407	1.5621060	0.5220238	0.3047595	0.6792942	0.8941500
7	0.04021463	0.5453254	0.9914915	33.046101	0.8378357	28.058333	835.49180	1.4528310	1.5895563	0.5453254	0.3128538	0.6765681	0.8961776
8	0.04243274	2.4724536	0.9010292	13.490819	0.6163937	36.591082	1294.35336	1.2801416	1.6996917	2.4724536	0.5753141	0.3003213	0.6719918
9	0.07740995	0.7826117	0.9900293	40.245537	0.8116642	35.744436	1348.45426	1.2153943	1.3836530	0.7826117	0.3580000	0.5602721	0.8120040
10	0.02762434	0.6840411	0.9853499	24.345883	0.7917980	28.258219	807.44122	1.5235652	1.7214387	0.6840411	0.3678367	0.6197701	0.8870752
11	0.05701780	0.6053939	0.9913648	36.053652	0.7977745	36.616869	1380.42755	1.3916178	1.5750726	0.6053939	0.3641731	0.6064279	0.8637957
12	0.07562758	0.6347055	0.9859701	23.619780	0.7903564	40.362041	1617.62248	1.2752388	1.4633718	0.6347055	0.3743910	0.5607354	0.8247881
13	0.07909278	0.4608732	0.9466634	5.320424	0.8007721	37.223757	1319.91804	1.1253189	1.2850875	0.4608732	0.3295623	0.5050669	0.7618142
14	0.05568135	1.5995519	0.9390187	14.115102	0.7261796	44.442684	1913.97657	1.2788602	1.5843427	1.5995519	0.4817017	0.4243133	0.7576280
15	0.05202921	0.5801109	0.9748538	12.534782	0.7977059	39.465191	1500.62304	1.3198899	1.5129789	0.5801109	0.3625926	0.5634820	0.8336397
16	0.03022385	0.7097171	0.9774588	16.742640	0.7744666	25.844691	656.71602	1.4632393	1.6950983	0.7097171	0.3930724	0.5724025	0.8620705
17	0.03406939	0.7927592	0.9737370	16.092720	0.7640970	27.829431	756.13582	1.4370517	1.6830497	0.7927592	0.4070845	0.5487315	0.8484906
18	0.04058255	0.8401308	0.9707768	15.374362	0.7580272	38.780849	1455.01132	1.3862767	1.6330126	0.8401308	0.4136235	0.5279089	0.8306887
19	0.09266633	0.5158531	0.9491354	6.070843	0.8034517	55.272875	2953.13894	1.1122670	1.2803420	0.5158531	0.3450937	0.5013954	0.7585884
20	0.05437139	0.6241637	0.9791238	15.949181	0.7944027	51.926862	2618.01310	1.3418788	1.5283433	0.6241637	0.3623381	0.5742947	0.8414757
21	0.27261905	0.2944350	0.7143251	1.515332	0.8680110	35.484890	1213.87617	0.6695303	0.7671292	0.2944350	0.2688384	0.3371947	0.5170872

Showing 1 to 22 of 228 entries, 13 total columns

Console

Figure 6. Haralick parameters dataset for the images (h.asm.s1: Angular Second Moment, h.con.s1: Contrast, h.cor.s1: Correlation, h.var.s1: Variance, h.idm.s1: Inverse Difference Moment, h.sav.s1: Sum Average, h.sva.s1: Sum Variance, h.sen.s1: Sum Entropy, h.ent.s1: Entropy, h.dva.s1: Difference Variance, h.den.s1: Difference Entropy, h.f12.s1: Information Measures of Correlation1, h.f13.s1: Information Measures of Correlation2)

Table 1. Accurate classification rates

Fuzzy C-Means Clustering * Original Group Crosstabulation			Original Group		Total
			Group 1	Group 2	
FCM Clustering	Cluster 1	n(%)	77(76.20%)	64(50.40%)	141(61.80%)
	Cluster 2	n(%)	24(23.80%)	63(49.60%)	87(38.20%)
Total		n	101	127	228

FCM: Fuzzy C-Means

Our study aims to classify skin lesion images caused by monkeypox and other virus-induced diseases such as chickenpox and measles using the FCM algorithm. Table 1 presents the results of the classification of skin lesion images. It is worth noting that Table 1 is a crosstable and shows the relationship between the images for which we have preliminary information about the original groups and the new groups created as a result of the FCM algorithm. According to Table 1, the FCM algorithm achieves an accuracy rate of 61.8% in classifying the skin lesion images of monkeypox and other virus-induced diseases (chickenpox and measles). The accuracy rate for the monkeypox class is the highest at 76.2%, while the accuracy rate for the other class is around 50.4%. The accuracy of classification decreases because the other class includes skin lesions caused by both chickenpox and measles viruses, which have similar characteristics to skin lesions caused by monkeypox virus (Table 1). However, empirical findings reveal promising results in detecting the type of skin lesions in the majority of images, with an overall accuracy of 61.8%.

The scarcity of studies using monkeypox image dataset led us to MSLD. The MSLD used in this study is limited and challenging in terms of discriminating monkeypox, chickenpox and measles lesions from each other. Despite this, we reveal the basic clustering structure of MSLD and look at the images from a statistical perspective. Although the classification rates obtained are not very high, our study shows that the FCM algorithm can be used as a method in this field. Moreover, this situation is directly related to the parameters. Because the classification process is performed with Haralick parameters calculated on the images. Therefore, the unique aspect that differentiates our study from other studies using MSLD is that we can present Haralick parameters.

CONCLUSION AND DISCUSSION

Clustering methods are used to discover unknown behavior of data. Thus, valuable information about the data set can be obtained by revealing complex relationships between observations. When our study is looked at in general terms, we aim to make a classification. We propose to use a very different classification algorithm that operates in the same manner as the general clustering algorithm in an unsupervised machine learning task in statistics. The FCM algorithm, we use for classification is also like this. Firstly, it should be noted that no other study using the fuzzy method for the human monkeypox classification has been found in the literature. More specifically, the unique aspect of this study is that it explores not only the features of a single-pixel but also the link of each pixel with neighboring pixels through Haralick parameters. While studies on Haralick texture parameters are already scarce in the literature, texture analysis of human monkeypox images has not been mentioned at all. Therefore, this study can be an inspiration to many scholars conducting research in different fields with its significant contributions to the existing literature.

Ahsan et al. analyze gray-level histograms of images from monkeypox, chickenpox, and measles datasets. This preprint article is MSLD's first study in this field and has inspired us to plan our workflow. It can be seen that some methods such as deep learning are used to distinguish human monkeypox virus skin lesion images from other viral diseases with similar images. For example; the classification performances of deep learning models are examined in the study of Haque et al. and Ali et al. However, a different approach called the FCM algorithm is used to sort out human monkeypox skin lesion images from other viral diseases with similar appearances in our study. The success of

the fuzzy algorithm, in which cluster memberships are based on certain probabilities, in classifying diseases is presented in detail. Sadad et al. use the FCM algorithm to locate tumors on mammograms, opting for various machine-learning procedures for classifying benign and malignant tumors. However, unlike Sadad et al., our study addresses the FCM algorithm in the process of classifying viral diseases with similar skin lesion appearance. Additionally, there are plenty of studies on classifying images using fuzzy algorithms in X-ray images, as in the study of Rohmayani and Rahayu. In these studies, various image processing techniques are applied to the images, but generally, histogram equalization is not applied at first. It can be noted that, unlike other studies, to be fair to the images in our dataset, histogram equalization is done on the images in RGB format first. Moreover, in Rohmayani and Rahayu's paper, the classification process is based on basic statistical criteria such as the gray level mean value of the images. However, we classify the images according to 13 haralick texture parameters, known as second-order feature descriptors. The MSLD, which we used, is similar to the data set used by Sahin et al. However, we design a workflow that differs from Sahin et al. in terms of both the image processing steps applied and the classification model used. In Zayed and Elnemr's study, the haralick parameters calculated after various image processing steps are tested with ANOVA and statistically significant results are found. Our study contains more Haralick texture features (13 parameters) than in the paper by Zayed and Elnemr. Additionally, we classify these features with the FCM algorithm and mention the performance of the algorithm.

The FCM algorithm is an unsupervised machine learning technique that reveals the basic structure of the data set (numerical, categorical, mixed or image data). Applications of this algorithm abound on numerical and categorical or mixed data sets. However, there is no study in the literature that processes image data with this technique and reveals the basic characteristics of images. The literature mostly constructs the analysis of image data (including monkeypox image data) on various CNN architectures, convolutional artificial neural networks and deep learning. The classification performances of such studies are high, but there is always a hidden issue and a question always comes to mind. The question is, what are the parameters used in these studies and this question remains unanswered. Algorithms do not output which parameters are used for classification, the machine runs the process automatically in the background. This is where the importance of our study comes into play. In our study, the images are digitized and the parameters used for classification are presented as output, which are the Haralick parameters. In addition, until this stage, the images are processed in many image pre-processing steps and we do this manually with R program codes in line with our purpose.

This study shows that the proposed approaches can lead to higher accuracy rates in skin lesion classification when applied to more images. Moreover, including images of other similar diseases can improve the study. Choosing different classification algorithms can also affect accuracy levels, and comparing the performance of different algorithms can be a useful approach. Overall, we believe that our research will inspire similar studies using image processing applications and classification algorithms with the help of Haralick texture parameters.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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TIBBİ VE SOSYAL YÖNLERİYLE

SÜNNET CERRAHİSİ

EDİTÖRLER
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BÜLENT ÖZALTAY

İnsanlık tarihi boyunca en çok uygulanan cerrahi işlemlerden olan sünnet (hitan) ile ilgili tıbbi ve sosyal alanda bugüne kadar çokça tartışmalar yürütülmüştür. Bu tartışmaların genellikle bilimsel veriler zemininde ele alınmaması ve farklı önyargıların tesiri altında kalması nedeniyle sünnet cerrahisi ile ilgili net kanaatlere ulaşmak mümkün olmamıştır.

Elinizdeki kitap sünnetin tıbbi, cerrahi ve sosyal yönlerine dair en güncel tartışmaları disiplinler arası işbirliği çerçevesinde sunmayı amaçlamaktadır. Bu çalışmanın sağlık çalışanları, akademisyenler ve sünnete dair rehberlik arayışında olan aileler için kaynak kitap olmasını umuyoruz.

BETİM KİTAPLIĞI

Çocukluk çağı menenjitinde serum ve beyin omurilik sıvısı prokalsitonin düzeyleri ve akut faz göstergeleri ile ilişkisi

The serum and cerebrospinal fluid procalcitonin levels and their relationship with acute phase reactants in childhood meningitis

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Öz

Amaç: Bakteriyel menenjit, yüksek mortalite ve morbiditeye sahip, hızlı tanı ve tedavi gerektiren pediatrik acil bir durumdur. Menenjitte viral-bakteriyel etiyoloji ayrımı yapmak her zaman mümkün değildir ve zaman alır. Bu çalışmada menenjit ön tanısı ile tetkik edilen çocuklarda, serum ve beyin omurilik sıvısı (BOS) prokalsitonin düzeylerinin, bakteriyel ve viral menenjitlerin erken tanısındaki yeri ve akut faz göstergeleri ile ilişkisi araştırılmıştır.

Yöntemler: Çalışmaya menenjit ön tanısıyla lomber ponksiyon (LP) yapılan çocuk hastalar alındı. Bu hastaların serum ve BOS prokalsitonin düzeylerine, eritrosit sedimentasyon hızına (ESH) ve C-reaktif protein (CRP) düzeyine bakıldı.

Bulgular: Çalışma sırasında 75 hastaya menenjit şüphesiyle LP yapıldı. 15 hastaya bakteriyel menenjit ve 6 hastaya viral menenjit tanısı konuldu. 7 hastaya da santral sinir sistemini etkileyen enfeksiyon dışı hastalık tanısı konuldu ve bu grup kontrol grubu olarak kullanıldı. Bakteriyel menenjit grubu ile viral menenjit grubu karşılaştırıldığında ESH ve CRP düzeyi açısından anlamlı bir fark yoktu. Fakat serum ve BOS prokalsitonin düzeyleri bakteriyel grupta istatistiksel olarak anlamlı şekilde yüksekti. Serum ve BOS prokalsitonin düzeyleri hem bakteriyel hem de viral menenjit grubunda BOS protein düzeyi ve CRP düzeyi ile pozitif korelasyon gösteriyordu. BOS prokalsitonin düzeyleri ayrıca BOS hücre sayısı ile pozitif korelasyon gösteriyordu. Bakteriyel menenjit ve kontrol grubu arasında sınır değer serum prokalsitonin için 0,61 ng/mL ve BOS prokalsitonin için 0,5 ng/mL olarak bulundu. Bakteriyel ve viral menenjit grupları arasında ise BOS prokalsitonin için anlamlı bir sınır değer tespit edilemezken serum prokalsitonin için sınır değer 0,2 ng/mL olarak bulundu.

Sonuç: Bakteriyel-viral menenjit ayrımında ESH ve CRP düzeyi sınırlı bilgi verirken serum ve BOS prokalsitonin düzeyleri bakteriyel menenjitte anlamlı olarak daha yüksek olduğu için bu ayrımda yardımcı olabilir.

Anahtar Sözcükler: Akut faz reaktanı; menenjit; prokalsitonin

Abstract

Aim: Bacterial meningitis is a paediatric emergency with high mortality and morbidity requiring prompt diagnosis and treatment. It is not always possible to differentiate between viral and bacterial etiology in childhood meningitis and it takes time. In this study, the value of serum and cerebrospinal fluid (CSF) procalcitonin levels in the early diagnosis of bacterial and viral meningitis and their relationship with acute phase indicators were investigated in children examined with a preliminary diagnosis of meningitis.

Methods: Pediatric patients who underwent lumbar puncture (LP) with the preliminary diagnosis of meningitis were included in the study. Serum and CSF procalcitonin levels, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels of these patients were examined.

Results: During the study, 75 patients underwent LP due to suspicion of meningitis. Fifteen patients were diagnosed with bacterial meningitis and 6 patients with viral meningitis. All 7 patients were diagnosed with non-infectious diseases affecting the central nervous system, and this group was used as the control group. There was no significant difference in terms of ESR and CRP levels when the bacterial meningitis group was compared with the viral meningitis group. However, serum and CSF procalcitonin levels were statistically significantly higher in the bacterial group. Serum and CSF procalcitonin levels showed a positive correlation with CSF protein level and CRP level in both bacterial and viral meningitis groups. CSF procalcitonin levels also positively correlated with CSF cell count. The cut-off value between the bacterial meningitis and control groups was found to be 0.61 ng/mL for serum procalcitonin and 0.5 ng/mL for CSF procalcitonin. While no significant limit value could be determined for CSF procalcitonin between the bacterial and viral meningitis groups, the cut-off value for serum procalcitonin was found to be 0.2 ng/mL.

Conclusion: While ESR and CRP levels provide limited information in the distinction between bacterial and viral meningitis, serum and CSF procalcitonin levels may be helpful in this distinction, as they are significantly higher in bacterial meningitis.

Keywords: Acute phase reactant; meningitis; procalcitonin

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GİRİŞ

Santral sinir sistemi (SSS) enfeksiyonlarının başında gelen ve hayatı tehdit eden enfeksiyonlardan birisi olan menenjit, beyin ve spinal kordu çevreleyen zarların inflamasyonudur (1). Menenjit, özellikle küçük çocuklarda SSS'ye ait yakınma ve bulguların yanı sıra sistemik yakınma ve bulgulara neden olabilir (2). Tanıda etkenin tespit edildiği mikrobiyolojik testler en güvenilir testlerdir. Fakat etkeni tespit etmek her zaman mümkün değildir ve bu testler zaman alır. Oysa erken tanı ve tedavi ile mortalite ve morbiditeyi azaltmak, gereksiz antibiyotik kullanımını önlemek ve hastanede yatış süresini kısaltmak mümkündür.

Menenjit olgularında viral-bakteriyel etiyoloji ayrımı klinik, kan ve beyin omurilik sıvısı (BOS) bulgularına göre yapılır fakat bu ayrım her zaman mümkün değildir. C-reaktif protein (CRP), eritrosit sedimantasyon hızı (ESH) gibi akut faz göstergeleri vücudun enfeksiyona yanıtının bir göstergesidir ancak viral-bakteriyel menenjit ayrımında çoğu zaman yeterli değildirler. Ayrıca enfeksiyon dışı durumlarda da artış gösterebilirler. Prokalsitoninin çocuklarda viral ve bakteriyel menenjitin ayırt edilmesinde tanısal değer taşıyabileceği belirtilmiştir. Bu çalışmada menenjit ön tanısı ile tetkik edilen çocuklarda, serum ve BOS prokalsitonin düzeylerinin, bakteriyel ve viral menenjitlerin ayırıcı tanısındaki değerinin belirlenmesi ve akut faz göstergeleri ile karşılaştırılması amaçlanmıştır.

GEREÇ VE YÖNTEMLER

Çalışmaya menenjit ön tanısıyla lomber ponksiyon (LP) yapılan çocuk hastalar alındı. Bu hastaların BOS ve eş zamanlı olarak serum prokalsitonin düzeylerine bakıldı. BOS'ta >5 lökosit/μL saptanması menenjit olarak kabul edildi. BOS direk ve gram-giemsa boyalı mikroskobik bakısı, BOS biyokimyası (protein değerleri), BOS kültür bulguları ile bakteriyel veya viral menenjit tanısı konuldu (Tablo 1).

Hastaların yaşı, klinik tanısı, kanda lökosit sayısı (polimorfonükleer lökosit, lenfosit ve monosit yüzdeleri), trombosit sayısı, ESH, CRP düzeyleri, kan ve BOS glukoz düzeyleri, BOS/kan glukoz oranı, BOS hücre sayısı, BOS protein düzeyleri, BOS klor düzeyleri, BOS ve serum prokalsitonin düzeyleri kaydedildi.

Prokalsitonin düzeylerine bakılırken VIDAS® BRAHMS PCT kiti ile enzim bağlı floresan değerlendirme (*ELFA, Enzyme-Linked Fluorescent Assay*) tekniği, hsCRP için Dade Behring Marburg CmbH, Almanya® kiti ile immunonefelometri tekniği, ESH için Therma® kiti ile Westergren metodu kullanıldı.

Çalışmaya başlamadan önce Dr Behçet Uz Çocuk Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi Yerel Etik Kurulu'ndan onay alındı (Tarih: 05.11.2008, Karar no: 1).

İstatistiksel analiz

İstatistiksel değerlendirmede çoklu grup karşılaştırması yapıldığı ve hasta sayısı az olduğu için nonparametrik Kruskal-Wallis testi kullanıldı. Post HOC analizde gruplar karşılaştırılırken Mann-Whitney U testi kullanıldı. Korelasyon araştırılırken nonparametrik Spearman testi kullanıldı. Tüm analizlerde p değeri 0,05'ten küçük olduğunda istatistiksel olarak anlamlı kabul edildi. Sınır (*Cut-off*) değerleri hesaplanırken ROC eğrisi analizi yapıldı. Bu analizler için Statistical Package for the Social Sciences package program version 23.0 (SPSS Inc., Chicago, IL, USA) ve Medcalc (version 9, Mariakerke, Belçika) programı kullanıldı.

BULGULAR

Çalışma sırasında 75 hastaya (43 erkek, 32 kız, yaş ortalaması 39±40 ay) akut menenjit şüphesiyle LP yapıldı. İzlemde bu hastaların 15'ine bakteriyel menenjit, 6'sına viral menenjit tanısı konuldu. Hastaların 13'ünde menenjit bulguları olmasına rağmen viral veya bakteriyel menenjit ayrımı yapılamadı. 34 hastaya menenjit dışı ve SSS'yi etkilemeyen enfeksiyon tanısı konuldu. 7 hastaya ise SSS'yi etkileyen enfeksiyon dışı hastalık (3 Guillain-Barre sendromu, 1 epilepsi, 1 hodgkin lenfoma, 1 konvülsiyon, 1 alım eksikliğine bağlı hiponatremi) tanısı konuldu.

Çalışmanın esas amacı bakteriyel ve viral menenjit ayrımında prokalsitoninin değerini belirlemek olduğu için bakteriyel (Grup 1: 15 hasta) ve viral menenjit (Grup 2: 6 hasta) tanısı alan gruplar ve kontrol grubu olarak da enfeksiyon dışı hastalık tanısı alan grup (Grup 3: 7 hasta) değerlendirildi.

Belirlenen üç gruptaki hastaların serum ve BOS prokalsitonin düzeyleri Tablo 2'de verilmiştir.

Tablo 1: Menenjitte beyin omurilik sıvısı (BOS) bulguları (3)

Durum	Normal	Akut bakteriyel menenjit	Kısmen tedavi edilmiş bakteriyel menenjit	Viral menenjit ve meningoensefalit
Basınç (mmH_2O)	50-80	Genellikle yüksek (100-300)	Normal veya yüksek	Normal veya hafifçe yüksek (80-150)
Lökosit (µL)	<5, ≥%75lenfosit	100-10000 veya fazla; genellikle 300-2000; PMNL hakim	5-10000; PMNL sık ama uzun süre tedavi edilmişse mononükleer hücreler hakim olabilir	Nadiren>1000 hücre. Doğu equin ensefaliti ve lenfositik koriyomenenjitte birkaç bin hücre sayılabilir. PMNL nadirdir, ama büyük kısmında mononükleer hücreler hakimdir
Protein (mg/dL)	20-45	Genellikle 100-500	Genellikle 100-500	Genellikle 50-200
Glukoz (mg/dL)	>50 (veya serum glukozunun %75'i)	Düşük,genellikle<40(veya serum glukozunun<%50)	Normal veya düşük	Genellikle normal; bazı viral hastalıklarda özellikle kabakulakta (%15-20 vakada) <40'a düşebilir
Yorum		Organizma Gram boyamada görülür ve kültürde ürer	Organizma Gram boyamada görülebilir. Önceki tedavi BOS'u steril yapabilir. Antijen aglutinasyon testi ile saptanabilir	HSV ensefaliti fokal nöbetler veya BT veya MRG görüntü veya EEG'deki fokal bulgularla tanınır. Enteroviruslar ve HSV BOS'ndan nadiren elde edilir: BOS'nda PCR ile saptanabilir

* BOS: beyin omurilik sıvısı; BT: bilgisayarlı tomografi; EEG: elektroensefalografi; HSV: herpeks simpleks virüsü; MRG: manyetik rezonans görüntüleme; PCR: polimerize zincir reaksiyon; PMNL: polimorfonükleer lökosit

Tablo 2: Hastaların serum ve BOS prokalsitonin düzeyleri (ng/mL)

	Bakteriyel menenjit	Viral menenjit	Enfeksiyon dışı SSS hastalığı	p (Tüm gruplar için)	p (Bakteriyel & Viral)	p (Bakteriyel & Enfeksiyon dışı)	P (Viral & Enfeksiyon dışı)
Serum prokalsitonin							
n	9	4	4				
Ortalama± SS	40,59 ± 65,68	0,10 ± 0,07	0,30 ± 0,30	0,022	0,013	0,022	0,538
Min - maks	0,07-200	0,05-0,20	0,05-0,61				
BOS prokalsitonin							
n	15	6	7				
Ortalama± SS	2,13 ± 4,31	0,05 ± 0,00	0,11 ± 0,17	0,006	0,012	0,064	0,355
Min - maks	0,05-16,67	0,05-0,05	0,05-0,50				

* BOS: beyin omurilik sıvısı; maks: maksimum; min: minimum; n: sayı; SS: standart sapma; SSS: santral sinir sistemi

** İkiden fazla grup karşılaştırmaları için non-parametrik Kruskal-Wallis testi kullanıldı. İki grup karşılaştırmaları için Mann-Whitney U testi kullanıldı.

Gruplar, serum ve BOS prokalsitonin düzeyleri açısından karşılaştırılırken çoklu grup ve hasta sayısı az olduğu için non-parametrik Kruskal-Wallis testi kullanıldı ve gruplar arasında istatistiksel olarak anlamlı fark bulundu; serum prokalsitonin için p=0,022, BOS prokalsitonin için p=0,006. Gruplar arasında farkın nereden geldiğini anlamak için post HOC analiz olarak Mann-Whitney U testi ile gruplar karşılaştırıldı. Grup 1 ve 2 arasında, serum ve BOS prokalsitonin düzeyleri grup 1'de anlamlı yüksekti (p= 0,013 ve 0,012; sırasıyla). Grup 1 ve 3 arasında serum prokalsitonin düzeyleri grup 1'de anlamlı yüksekken (p=0,022), BOS prokalsitonin düzeyleri yine bakteriyel grupta yüksek olma eğilimindeydi fakat bu istatistiksel olarak anlamlı değildi (p=0,064). Grup 2 ve 3 arasında hem serum hem de BOS prokalsitonin düzeyleri arasında istatistiksel fark yoktu; p değerleri sırasıyla 0,538 ve 0,355 idi.

Prokalsitonin düzeylerinin hangi parametrelerle korelasyon gösterdiğini araştırmak için non-parametrik Spearman testi uygulandı. Serum prokal-

Tablo 3: Gruplar arasında anlamlı fark olan parametreler

	Bakteriyel menenjit	Viral menenjit	Enfeksiyon dışı SSS hastalığı	P (Tüm gruplar için)	p (Bakteriyel & Viral)	p (Bakteriyel & Enfeksiyon dışı)	p (Viral & Enfeksiyon dışı)
ESH (mm/saat)	61 ± 39 (10-131)	40 ± 35 (12-106)	24 ± 34 (2-97)	0,011	>0,05	0,007	>0,05
CRP (mg/dL)	9,64 ±8,43 (0,30-30,00)	3,22 ± 3,38 (0,30-8,54)	3,50 ± 6,75 (0,30-18,40)	0,041	>0,05	0,034	>0,05
BOS glukoz (mg/dL)	48 ± 39 (4-168)	66 ± 23 (46-107)	69 ± 114 (50-96)	0,016	>0,05	0,007	>0,05
BOS hücre (sayı/mcL)	831 ± 505 (0-2000)	412 ± 466 (10-1250)	4 ± 5 (0-10)	0,001	>0,05	0,001	0,004
BOS protein (mg/dL)	178 ± 170 (7-673)	47 ± 30 (16-93)	60 ± 58 (15-184)	0,021	0,022	0,029	>0,05

* Değerler ortalama ± standart sapma (minimum – maksimum) olarak verilmiştir

** BOS: beyin omurilik sıvısı; CRP: C- reaktif protein; ESH: eritrosit sedimentasyon hızı; SSS: santral sinir sistemi

*** İkiden fazla grup karşılaştırmaları için non-parametrik Kruskal-Wallis testi kullanıldı. İki grup karşılaştırmaları için Mann-Whitney U testi kullanıldı.

sitonin düzeyleri tüm gruplarda BOS protein düzeyi (r=0,504 p=0,031) ve CRP (r=0,554 p=0,021) ile pozitif korelasyon gösteriyordu. BOS prokalsitonin düzeyleri ise tüm gruplarda BOS protein düzeyi (r=0,400 p=0,035) ve CRP'ye (r=0,392 p=0,039) ek olarak BOS hücre sayısı (r=0,460 p=0,014) ile de pozitif korelasyon gösteriyordu.

Gruplar diğer parametreler açısından karşılaştırıldı ve ESH, CRP, BOS glukoz düzeyi, BOS hücre sayısı ve BOS protein düzeylerinde istatistiksel olarak anlamlı fark bulundu; p değerleri sırasıyla 0,011–0,041–0,016–0,001–0,021 (Tablo 3). Bu beş parametredeki farklılığın nereden kaynaklandığına bakıldı. Bakteriyel menenjit grubu ile enfeksiyon dışı hastalık grubu arasında tüm parametreler açısından istatistiksel olarak anlamlı fark vardı; p değerleri sırasıyla 0,007–0,034–0,007–0,001–0,029. Bakteriyel grup ile viral grup arasında sadece BOS protein düzeyi açısından fark vardı; p=0,022. Viral grup ile enfeksiyon dışı hastalık grubu arasında sadece BOS hücre sayısı açısından fark vardı; p=0,004.

Bakteriyel menenjit ve enfeksiyon dışı hastalık grubu kullanılarak sınır değerleri hesaplandı (ROC eğrisi analizi). Serum prokalsitonin için sınır 0,61 ng/mL bulundu (%66,7 duyarlılık (%95 CI 30,1-92,1), %100 özgüllük (%95 CI 40,2-100)). BOS prokalsitonin için ise sınır 0,5 ng/mL bulundu (%53,3 duyarlılık (%95 CI 26,6-78,7), %100 özgüllük (%95 CI 58,9-100)).

Bakteriyel ve viral menenjit grupları kullanılarak sınır değerleri hesaplandı. BOS prokalsitonin için anlamlı bir değer tespit edilemezken serum prokalsitonin için sınır değer 0,2 ng/mL bulundu (%88,89 duyarlılık (%95 CI 51,7-98,2), %100 özgüllük (%95 CI 40,2-100)).

TARTIŞMA VE SONUÇ

Santral sinir sistemi (SSS) enfeksiyonlarından olan bakteriyel menenjit çocuklarda görülen en ciddi enfeksiyonlardan birisidir, akut komplikasyon ve uzun dönem morbidite riski yüksektir. Mortaliteye neden olabilir. Viral menenjit ise çoğunlukla kendini sınırlayan bir hastalıktır (3). Çalışmamızda bakteriyel menenjitte viral menenjite göre serum ve BOS prokalsitonin düzeylerini daha yüksek bulduk. Fakat ESH ve CRP düzeyleri açısından aralarında bir fark yoktu.

Bakteriyel ve viral menenjitin erken döneminde belirti ve bulgular sıklıkla nonspesifiktir, muayene ve BOS bulguları ile ayırıcı tanı yapmak her zaman mümkün değildir (4,5). Kültür ile etkenin tespit edilmesi en güvenilir yöntemdir. Fakat etkeni tespit etmek her zaman mümkün olmaz ve zaman alır.

Prokalsitonin, son yıllarda şiddetli bakteriyel enfeksiyonların tanısında ve tedaviye yanıtın izlenmesinde kullanılan bir testtir. Yapılan çalışmalarda, pro-

kalsitoninin çocuklarda viral ve bakteriyel menenjitin ayırt edilmesinde de tanısal değer taşıyabileceği belirtilmiştir (6-9). Menenjit tanısının erken konulması olası komplikasyonları ve mortaliteyi önlemek için önemlidir. Akut faz reaktanları kullanılmaktadır fakat sınırlı değeri vardır; zaman gerektirmektedir, enfeksiyon dışı durumlarda da artabilmektedir. Örneğin sık kullanılan CRP düzeyleri enfeksiyon başlangıcından itibaren 12-24 saatte yükselmeye başlarken prokalsitonin 4 saat gibi daha erken sürede tespit edilebilecek düzeylere ulaşır.

Bu çalışmada menenjit ön tanısı ile tetkik edilen çocuklarda, serum ve BOS prokalsitonin düzeylerinin, bakteriyel ve viral menenjitlerin erken ayırıcı tanısındaki değerinin belirlenmesi ve akut faz göstergeleri ile karşılaştırılması amaçlanmıştır.

Bakteriyel menenjit grubu ve viral menenjit grubu arasında ESH ve CRP düzeyleri açısından anlamlı fark yoktu ancak hem serum hem de BOS prokalsitonin düzeyleri anlamlı olarak farklıydı (p değerleri sırasıyla 0,013 ve 0,012). Bakteriyel–viral menenjit ayrımında BOS prokalsitonin için anlamlı bir değer tespit edilemezken serum prokalsitonin için sınır değer 0,2 ng/mL bulundu (%88,89 duyarlılık (%95 CI 51,7-98,2), %100 özgüllük (%95 CI 40,2-100)).

Gendrel ve arkadaşları plazma prokalsitonini bakteriyel grupta anlamlı şekilde yüksek bulurken viral grupta normal ya da hafifçe yüksek bulmuşlardı. BOS prokalsitonini ise her iki grupta anlamlı değildi. CRP'yi bakteriyel grubu viral gruptan ayırmada etkili bulmuşlardı. Prokalsitonin >0,5 ng/mL seviyesinde iken, bakteriyel menenjit için duyarlılığı %94, özgüllüğü %100 saptamışlardı (6).

Schwarz ve ark. da prokalsitonin için sınır değerini 0,5 ng/mL olarak almışlardı (7).

Carrol ve ark. meningokokkal menenjitli çocuklarda prokalsitonini iyi bir belirteç olarak önermiş ve sınır 2 ng/mL iken duyarlılığı %94, özgüllüğü %93 saptanmışlardı (8).

Dubos ve ark. 167 hastanın dahil edildiği çalışmalarında, serum prokalsitonini (0,2 ng/mL) bakteriyel-viral menenjit ayrımında anlamlı bulmuşlardı (%100 sensitivite) (9).

Taşkın ve ark. serum prokalsitonini bakteriyel grupta, kontrol grubuna göre anlamlı yüksek bulurken viral grupta anlamlı bulmamışlardı (10).

Prat ve ark.nın çalışmasında prokalsitonin için sınır 2 ng/mL alındığında spesivite ve sensitivite %100, sınır 0,5 ng/mL alındığında ise spesivite %62 ve sensitivite %100 idi. Pozitif ve negatif prediktif değer %100 idi (11).

Hatherill ve ark. 169 hastalık çalışmalarında, prokalsitonin ve CRP'yi septik şok grubunda, lokalize bakteriyel enfeksiyon, viral enfeksiyon ve nonenfeksiyöz kontrol grubuna göre belirgin yüksek saptamışlardı. Bakteriyel menenjit/ensefalit grubunda ise prokalsitonin ortalama değerlere sahipti. Fakat prokalsitonin bakteriyel menenjit/ensefalit grubunda viral enfeksiyon ve nonenfeksiyöz kontrol grubuna göre belirgin yüksek idi. Prokalsitonin için sınır >2 ng/mL alındığında septik şok ve bakteriyel menenjit için spesivite %62, sensitivite %100, pozitif prediktif değer %69 iken negatif prediktif değer %100 idi (12).

Mills ve ark. çok sayıda (1695) hasta ile yaptıkları çalışmada prokalsitonini meningokokkal hastalıkta anlamlı yüksek saptamışlardı ve 2 ng/mL sınır değerinde spesivite %93, sensitivite %96 idi (13).

Galetto-Lacour ve ark. ateş ile başvuran 124 hastalık bir çalışmada bakteriyel enfeksiyonlu 28 olguda prokalsitonini yüksek ve istatistiksel olarak anlamlı saptamışlardı (prokalsitonin için sınır 0,9 ng/mL, sensitivite %93, spesivite %78, pozitif prediktif değer %55, negatif prediktif değer %97). Prokalsitonin ve CRP birlikte alındığında sensitivite %96, spesivite %67, pozitif prediktif değer %46, negatif prediktif değer %98 idi. Prokalsitonin ve lökositoz birlikte alındığında sensitivite %100, spesivite %62, pozitif prediktif değer %43, negatif prediktif değer %100 idi (14).

Fernandez ve ark.nın yaptığı çok merkezli çalışmada 445 hastanın 122'si viral, 80'i lokalize bakteriyel, 150'si invaziv bakteriyel enfeksiyon tanılıydı. Bakteriyel enfeksiyon için prokalsitonin sınır değeri 0,53 ng/mL iken sensitivite %65,5, spesivite %94,3 idi. İnvaziv bakteriyel enfeksiyon için ise prokalsitonin sınır değeri 0,59 ng/mL iken sensitivite %91,3, spesivite %93,5 idi (15).

Gendrel ve ark.nın yaptığı başka bir 1500 hastalık (ateşli) çalışmada 46 hastada invaziv bakteriyel (septisemi ve menenjit), 78 hastada lokalize bakteriyel, 236 hastada ise viral enfeksiyon saptanmıştı. Gruplar arasında prokalsitonin değeri için belirgin istatistiksel fark saptanmıştı. Ayrıca bakteriyel enfeksiyonlar için

prokalsitonin, CRP'ye göre daha iyi bir belirteç olarak değerlendirilmişti. Bakteriyel enfeksiyonu viral enfeksiyondan ayırmak için optimal prokalsitonin sınır değeri 0,1 ng/mL iken, sensitivite %83, spesivite %93 idi. İnvaziv bakteriyel enfeksiyonu diğer enfeksiyonlardan (viral enfeksiyon ve lokalize bakteriyel enfeksiyon) ayırmak için prokalsitonin sınır değeri 2 ng/mL iken, sensitivite %96, spesivite %87 idi (16).

Somech ve ark.nın 38 hastalık çalışmasında; sebebi bilinmeyen ateş veya sepsis değerlendirmesi yapılmış ve hastalar gruplara ayrılmamıştı, CRP ve prokalsitonin arasında istatistiksel olarak belirgin korelasyon saptanmıştı (17).

Gendrel ve ark. 59 hastalık (18 bakteriyel menenjit, 41 viral menenjit) çalışmalarında prokalsitonin, CRP, BOS lökosit sayısı, BOS protein düzeyi değerlerinde gruplar arasında istatistiksel olarak anlamlı fark saptamışlardı (6).

Dubos ve ark. 28 gün-16 yaş arası 167 hastalık (21 bakteriyel menenjit, 146 aseptik menenjit) çalışmalarında kanda prokalsitonin, CRP, WBC sayısı, nötrofil sayısı, BOS'ta protein, glukoz, WBC sayısı, nötrofil sayısını değerlendirmişlerdi. Bakteriyel menenjit ile aseptik menenjit grubu arasında kan nötrofil sayısı haricinde diğer parametrelerde istatistiksel olarak fark saptamışlardı. Bunlar arasında prokalsitonin ve CRP en yüksek sensitivite ve spesiviteye sahipti. Bakteriyel menenjiti belirlemede prokalsitonin, CRP, BOS proteini istatistiksel olarak en anlamlı parametreler olarak değerlendirilmişti (9).

Jimenez ve ark. BOS ve serum laboratuvar testleri ile bakteriyel menenjitin acil tanısı için, Ocak 2000 ile 2016 arasında yayınlanan 59 makaleyi değerlendirdiler. BOS laktatı, polimorfonükleer lökositlerin oranı, BOS glukozu ve serum prokalsitonini, bakteriyel etiyolojiyi belirlemede en değerli bağımsız faktör olarak buldular. Serum prokalsitonin ve BOS laktatını birleştiren model, %99'u aşan duyarlılık ve özgüllük ile en yüksek tahmin gücüne sahipti. BOS laktatı >33 md/dL ve/veya prokalsitonin >0,25 ng/mL olduğunda bakteriyel menenjiti desteklediğini belirttiler (18).

Konstantinidis ve ark. 58 hastanın BOS örneklerini incelediler. Örnekleri bizim çalışmamıza benzer olarak bakteriyel menenjit, viral menenjit ve bulaşıcı olmayan hastalıkları olan kontrol grubu olarak üç gruba ayırdılar. BOS prokalsitonin değerininin bakteriyel menenjiti, viral menenjit ve diğer enfeksiyon dışı hastalıklardan ayırmada oldukça yardımcı olabileceğini belirttiler (19).

Ahmed ve ark. 2-18 yaşında 48 menenjitli (35'i bakteriyel, 13'ü viral) çocuk hastada çalışma yaptılar. Bakteriyel menenjitli hastalarda viral menenjit ile karşılaştırıldığında daha yüksek serum CRP, serum prokalsitonin ve BOS-CRP ve daha düşük BOS kan şekeri buldular. Multipleks polimeraz zincir reaksiyonu bakteriyel ve viral menenjit tanısında %94 duyarlılığa ve %100 özgüllüğe sahipti (20).

Shokrollahi ve ark. 57 çocukta (30 bakteriyel ve 27 aseptik menenjit) BOS'u incelediler. İki grubu karşılaştırdılar. Bakteriyel menenjitte BOS Ferritin, CRP ve prokalsitonin düzeylerini aseptik menenjite göre anlamlı derecede yüksek buldular (sırasıyla p değerleri= <0,001, 0,001, <0,001) (21).

Zhang ve ark. bakteriyel menenjit tanısında 101 çocuk hastada, serum ve BOS prokalsitonin seviyelerini ve albümin indeksini (Aİ = BOS albümini/serum albümini x 1000) değerlendirdiler. 29 bakteriyel, 25 viral menenjit ve 47 menenjit olmayan hastadan ölçüm yaptılar. Bakteriyel menenjit hastalarında BOS prokalsitonin düzeyi ile Aİ arasında daha güçlü bir pozitif korelasyon gözlediler. Yalnızca BOS prokalsitonini açısından gruplar arasında anlamlı fark buldular ve bakteriyel menenjit için tanısal değeri olduğunu belirttiler (22).

Santotoribio ve ark. 18'i bakteriyel, 12'si viral menenjit olmak üzere 30 hastada serum ve BOS CRP ve prokalsitonini kullanarak bakteriyel menenjiti viral menenjitten ayırmaya yönelik çalışma yaptılar. Serum CRP ve prokalsitoninin BOS'a göre yüksek tanısal doğruluk gösterdiğini testpit ettiler (23).

Kim ve ark. 1462 çocukla yapılan 18 çalışmada meta-analiz yaptılar ve serum prokalsitoninin, çocuklarda bakteriyel menenjitin tanısında iyi bir biyobelirteç olabileceğini belirttiler. Serum prokalsitonininde serum CRP ve lökosit sayısı, BOS lökosit ve nötrofil sayısı ve BOS proteini ve glikoz seviyeleri dahil olmak üzere diğer geleneksel biyobelirteçlerden daha yüksek tanısal doğruluk gösterdiler (24).

Chaudhary ve ark. 3 ay-15 yaş 50 çocuk hastada (22 bakteriyel, 28 bakteriyel olmayan menenjit) serum prokalsitonini, tam kan sayımı ve BOS analizini değerlendirdiler. Serum prokalsitonin düzeylerini bak-

teriyel menenjit grubunda (medyan = 2,04 (1,2-3,18) ng/ml), bakteriyel olmayan menenjit (medyan=0,35 (0,18-0,35) ng/ml) ile karşılaştırdıklarında yüksek buldular; p<0,001. Eşik düzeyi 0,5 ng/ml iken bakteriyel menenjit tanısında serum prokalsitoninin duyarlılığı ve özgüllüğünü sırasıyla %95,45 ve %84,61 buldular ve erken tanı için önerdiler (25).

El Shorbagy ve ark. 4 ay-14 yaş 40 çocuk hasta (24 bakteriyel, 16 aseptik menenjit) ve 25 kontrol grubu sağlıklı prokalsitonin, CRP ve lökosit sayısını başvuru sırasında ve 72 saat sonra tekrar ölçtüler. Bakteriyel menenjit grubunda başlangıçta yüksek prokalsitonin ve 72 saat sonra düşük prokalsitonin buldular (p değeri sırasıyla p<0,001, p<0,05). Başvuruda bakteriyel menenjitin erken tanısı için gerekli olan prokalsitonin değeri >10 ng/ml idi. Ancak prokalsitonin >2 ng/ml değerleri %100 duyarlılığa sahipti. Serum prokalsitoninini tanı ve tedavi izleminde önerdiler (26).

Alkholi ve ark. 4 ay-12 yaş 40 çocuk hastada bakteriyel menenjiti viral menenjitten ayırmada serum prokalsitonini, CRP ve beyaz kan hücresi sayımı ile karşılaştırdılar. Bu değerlere başvuru sırasında ve 3 gün sonra baktılar. Prokalsitonin düzeylerini bakteriyel menenjitli hastalarda (ortalama 24,8 ng/ml), viral menenjitli hastalara (ortalama 0,3 ng/ml) göre anlamlı derecede yüksek buldular (p<0,001). Serum prokalsitonini >2 ng/ml değerinde bakteriyel menenjit tanısı için sırasıyla %100, %66, %68 ve %100 duyarlılık, özgüllük, pozitif öngörü değeri ve %100 negatif öngörü değeri buldular (27).

Mintegi ve ark. bakteriyel menenjiti aseptik menenjitten ayırmak için bir skor (acil durumlar için menenjit skoru) geliştirmeye çalıştılar. Acil servise başvuran 29 gün-14 yaş 1009 hastada (917 aseptik, 92 bakteriyel menenjit) çok değişkenli lojistik regresyon analizi kullanarak, bakteriyel menenjit için: prokalsitonin >1,2 ng/mL, BOS proteini >80 mg/dL, BOS mutlak nötrofil sayısı >1000 hücre/mm3 ve BOS reaktif protein >40 mg/L değerlerini öngörücü olarak belirlediler. Prokalsitonin için 3 puan, BOS proteini için 2 puan ve diğer değişkenlerin her biri için 1 puan atayarak skor geliştirdiler. Skor ≥1, %100 duyarlılık (%95 güven aralığı [CI]: %95,0 - %100), 83,2 özgüllük (%95 GA: 80,6-85,5) ve 100 negatif öngörü değeri ile bakteriyel menenjiti öngördü % (%95 CI 99,4-100) (28).

Umran ve Radhi 45 hastada (29 bakteriyel menenjit, 16 bakteriyel olmayan grup) çalışma yaptılar. Serum prokalsitonin düzeylerini bakteriyel menenjit grubunda, bakteriyel olmayan menenjit grubuna kıyasla anlamlı derecede yüksek (p<0,001), ayrıca CRP ve beyaz kan hücresi sayımına göre de daha duyarlı ve spesifik buldular (29).

Wu ve ark. 29-90 günlük 102 hastada (44 bakteriyel, 58 aseptik menenjit) çalışma yaptılar. Yeni bir puanlama modeli oluşturdular, Bakteriyel Menenjit Skoru ve Acil Durumlar için Menenjit Skoru modelleriyle karşılaştırdılar ve daha tanısal olduğunu belirttiler. Prokalsitonin, BOS glukozu ve BOS proteinini bakteriyel menenjit için bağımsız risk faktörleri olarak tespit ettiler, farkları istatistiksel olarak anlamlı buldular (30).

Sanaei Dashti ve ark. 28 gün-14 yaş çocuk hastalarda bakteriyel ve viral menenjiti ayırmak için çalışma yaptılar. BOS (ferritin, prokalsitonin, mutlak nötrofil sayısı, beyaz kan hücresi sayımı ve laktat) ve serum (prokalsitonin, ferritin, CRP ve ESH) parametrelerinin tanısal değerini araştırdılar. Serum ve BOS prokalsitonini bakteriyel ve viral menenjiti ayırmada anlamlı bulmadılar. Düşük BOS laktatı, mutlak nötrofil sayısı, ESH ve serum CRP kombinasyonunun bakteriyel menenjiti dışlamak için kullanılabileceğini söylediler (31).

Dubos ve ark. 5 Avrupa ülkesinde 29 gün-18 yaş 198 hastada (96'sı bakteriyel menenjit) meta analiz yaptılar. Kan (prokalsitonin, CRP, beyaz kan hücresi sayımı ve nötrofil sayısı) ve BOS (protein düzeyi, glukoz düzeyi, beyaz kan hücresi) parametrelerini karşılaştırdılar. Prokalsitonin seviyesini, diğer belirteçlere göre önemli ölçüde tanısal saptadılar (p=0,001). 0,5 ng/mL eşik değerinde, prokalsitonin düzeyi bakteriyel ve aseptik menenjit arasında ayrım yapmak için %99 duyarlılığa (%95 güven aralığı, %97-100) ve %83 özgüllüğe (%95 güven aralığı, %76-%90) sahipti (32).

İbrahim ve ark. 38 hastada (18 bakteriyel, 20 bakteriyel olmayan menenjit) çalışma yaptılar. Serum prokalsitonini kan lökosit sayısı ve CRP ile karşılaştırdılar. Serum prokalsitonin düzeylerini bakteriyel menenjitte, bakteriyel olmayan menenjit grubuna göre anlamlı derecede yüksek buldular (p<0,001). Tedavi yanıtını değerlendirmede de kullanılabileceğini belirttiler: 3. gün ve 6. gün serum prokalsitonini başvuru seviyelerinden daha düşük buldular (p<0,001) (33).

Çalışmamızın kısıtlılıklarının başında olgu sayısının az olması geliyor. Ayrıca her hastanın eş zamanlı serum ve BOS prokalsitonin düzeylerine bakılamadı.

Sonuç olarak hayatı tehdit edebilen bir enfeksiyon olan menenjitin tanısında zaman oldukça önemlidir. Tanıda etkenin tespit edildiği mikrobiyolojik testler altın standarttır. Fakat etkeni tespit etmek her zaman mümkün olmaz ve zaman alır. Oysa erken tanı ve tedavi ile mortalite ve morbiditeyi azaltmak, gereksiz antibiyotik kullanımını önlemek ve hastanede yatış süresini kısaltmak mümkündür. Bakteriyel menenjit ile viral menenjit ayrımında en sık kullanılan akut faz reaktanları olan ESH ve CRP'nin katkısı sınırlı iken prokalsitonin bu ayrımda katkı sağlayabilir. Bunu doğrulamak için ileri çalışmalara ihtiyaç vardır.

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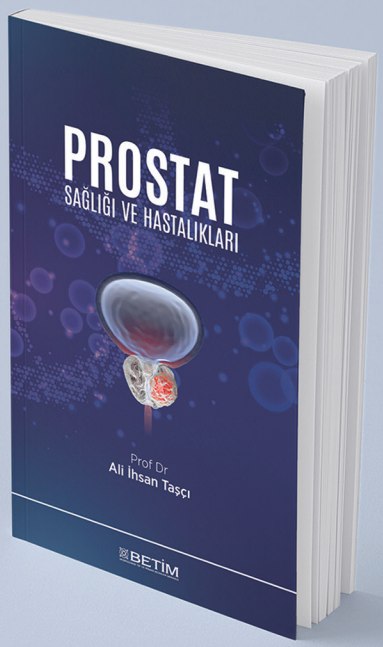

PROSTAT
SAĞLIĞI VE HASTALIKLARI

Prof Dr
Ali İhsan Taşçı

Bazen gençlerde, daha sıklıkla da yaşlanma ile birlikte, erkeklerin birçoğunda prostat ve idrar yolları ile ilgili hastalıklar görülebilmektedir. Prostat konusunda doğru bilgiye ulaşmak isteyenler için hazırlanmış bu kitapta; prostatın yapısı, fonksiyonları, hastalıkları, hastalıklardan korunma, alternatif ve tamamlayıcı tıp uygulamaları sade bir dille anlatılmaya çalışılmıştır.

BETİM KİTAPLIĞI

Do nurses follow the "Right Response"? Mixed methods research

Hemşireler ''Doğru Yanıt'' takip ediyor mu? Karma yöntem araştırması

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Abstract

Aim: Drug administration and management is an important procedure among clinical nursing practices and is one of the significant indicators affecting patient safety and quality of care. It was aimed to determine the nurses' monitoring of drug effects after drug treatment.

Methods: In the study, sequential explanatory design from exploratory and mixed research methods was used. Quantitative data were collected using a data collection form and qualitative data were collected through in-depth and individual interviews using a semi-structured interview form. The interviews were recorded with a voice recorder.

Results: It was determined that the average age, working years, weekly working hours, and daily number of patients cared for by the nurses were respectively 30.46±6.96, 7.1±6.31, 44.92±5.71, 15.42±11.89 years. It was found that 54.2% of the nurses checked the drug package insert before administering the medication, 74.5% of the nurses always considered the history of drug and food allergy to be of vital importance before drug administration, and 97.9% of the nurses reported unexpected side/toxic effects. As a result of in-depth interviews with the nurses participating in the study, three themes were identified: the approach of right drug administration principles, the approach of following the right response, and the follow-up status of nurses after drug administration.

Conclusion: In the study, it was determined that nurses lacked knowledge about the right medication, and could not implement the right response due to high workload, low number of nurses, and lack of time. It was observed that nurses gave the responsibility of right response follow-up to the patient or the patient's relatives. By evaluating the reasons for not implementing the right response, it is recommended that the number of nurses should be increased, the workload should be regulated, and nurses should receive training on the right drug administration and especially on the importance of the right response. It is also recommended that nurses receive training and counseling on their duties, authorities, and responsibilities.

Keywords: Drug monitoring; drug therapy; nurses

Öz

Amaç: İlaç uygulama ve yönetimi, klinik hemşirelik uygulamaları arasında önemli bir prosedür olup, hasta güvenliğini ve bakım kalitesini etkileyen önemli göstergelerden biridir. Hemşirelerin ilaç uygulaması sonrasında ilaç etkilerini takip etme durumlarının belirlenmesi amaçlanmıştır.

Yöntemler: Araştırmada keşfedici ve karma araştırma yöntemlerinden sıralı açıklayıcı tasarım kullanılmıştır. Araştırmanın nicel verileri veri toplama formu, nitel verileri ise yarı yapılandırılmış görüşme formu kullanılarak Temmuz-Eylül 2023 tarihleri arasında derinlemesine ve bireysel görüşme yöntemi ile toplanmıştır. Yapılan görüşmeler ses kayıt cihazı ile kayıt edilmiştir.

Bulgular: Hemşirelerin yaş, çalışma yılı, haftalık çalışma saati ve günlük bakılan hasta sayıları ortalamalarının sırasıyla 30.46±6.96, 7.1±6.31, 44.92±5.71, 15.42±11.89 yıl olduğu belirlendi. Hemşirelerin %54.2'si ilaç uygulamalarını yapmadan önce ilaç prospektüsünü kontrol ettiği, %74.5'inin ilaç uygulama öncesinde ilaç ve besin alerjisi öyküsünü her zaman hayati önemi olan bir durum olduğunu düşündüğü, %97.9'unun beklenmeyen yan/toksik etkileri bildirdiği saptandı. Araştırmaya katılan hemşireler ile yapılan derinlemesine görüşmeler sonucunda ise doğru ilaç uygulama ilkeleri yaklaşımı, doğru yanıt takip etme yaklaşımı ve hemşirelerin ilaç uygulama sonrası takip etme durumları olmak üzere üç tema belirlenmiştir.

Sonuç: Çalışmada, hemşirelerin doğru ilaç uygulama ilkeleri konusunda bilgi eksikliği olduğu, iş yükünün fazla olması, hemşire sayısının az olması ve zaman yetersizliği nedenleriyle doğru yanıt ilkesini uygulayamadıkları belirlenmiştir. Hemşirelerin, doğru yanıt takibinin sorumluluğunu hasta veya hasta yakınına verdiği görülmüştür. Doğru yanıt ilkesinin uygulanmama nedenleri değerlendirilerek, hemşire sayısının artırılması, iş yükünün düzenlenmesi, hemşirelerin doğru ilaç uygulama ilkeleri konusunda ve özellikle doğru yanıtın önemi konusunda eğitimler alması önerilmektedir. Ayrıca hemşirelerin görev, yetki ve sorumlulukları konusunda da eğitim ve danışmanlık alması da önerilerimiz arasında yerini almaktadır.

Anahtar Sözcükler: Hemşireler; ilaç takibi; ilaç tedavisi

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INTRODUCTION

Nurses have a unique role and responsibility in medication management, namely since they are usually the last person to check that the medication is correctly prescribed and administered, prior to administration. Likewise, nurses are the primary health personnel who will follow up on the treatment after the medication is administered (1,2). Medication management is a basic nursing skill and it is the responsibility of nurses to perform it safely and effectively (3).

During nursing education, topics to support clinical medication management and patient safety, known as the 'ten rights' of medication administration, are included in the curriculum content. These 'rights' are the right patient, right drug, right time, right dose, right route, right refusal, right information/understanding, right assessment/response, and right record (4–6). Among these rights, there are various studies in the literature on correct patient, drug, time, dose, route, and registration (4,5,7). However, there is a gap in the literature on the correct response or correct evaluation after medication administration. Medication management is a process and how this process ends is the responsibility of healthcare professionals (8). Nurses in particular, who are in closest communication with patients/healthy individuals, have a great responsibility at this point (9). This study aimed to determine the status of nurses in clinics to follow the right response / right evaluation following drug administration.

When individuals are admitted to the hospital, they expect to be treated for their diseases and to receive quality nursing care. Patient safety and quality of care are essential elements of clinical nursing practices. Medication therapy and management is an important procedure among clinical nursing practices and is one of the significant indicators affecting patient safety and quality of careMetin girmek için buraya tıklayın veya dokunun. and it is one of the main responsibilities of nurses (10). Nurses around the world are educationally prepared, morally responsible and professionally accountable to fulfill their roles safely (9). However, nurses face various challenges in safe medication administration in the delivery of healthcare to patients (7,8). Most nurses are taught safe medication administration using a framework known as the 'ten rights', which is a globally accepted guideline for safe medication management practice (11).

In addition to being included in nursing functions, drug administration is a process that involves a number of disciplines. It is initiated with the order given by the physician after the examination of the patient and ends with the administration of the drug by the nurse, with the doctor, the patient, or his/her relatives, recording and observing the correct response. The nurse should have pharmacologic knowledge about drugs, be able to make decisions about the precautions and interventions to be taken and be able to take responsibility for these. The nurse will minimize the possibility of error by fulfilling her/his roles and responsibilities regarding the administration of medications (12). The World Health Organization (WHO) ranked medication errors as the second most common cause of adverse health events (18.3%). Medication errors are a leading risk to patients, and their annual global cost is estimated at US$42 billion (6,13). Medication error is the most common type of error affecting patient safety and the most common type of error among medical errors (13). In order to minimize medication errors, attention should be paid to the "rights" in medication administration. One of these is "right effect/response" and to the best of our knowledge, no study exists on correct response monitoring in the literature. As only a handful of studies have been published on the rights of correct drug administration/drug rights, this study aimed to determine the nurses' monitoring of drug effects after drug administration.

The following question was sought to be answered in the research.

- Do nurses follow the "right response"?

MATERIAL AND METHODS

Design

In the study, a sequential explanatory design from exploratory and mixed research methods, including qualitative and quantitative methods, was used to determine the nurses' monitoring of drug effects following drug administration (Figure 1).

Study setting and sampling

Sequential explanatory design, one of the mixed research methods, involves collecting quantitative and qualitative data at various times and sequentially, to

examine the same event. This design is a mixed method design in which quantitative data are collected first and then a second phase is used to seek specific results. This type of mixed-method study aims to reach statistical quantitative results from a sample and then to examine these results in more detail with persons selected from the participants in line with the criteria determined (14,15).

The population of the study consisted of 205 nurses working in two state hospitals. Post hoc power analysis was performed and accordingly, when effect size: 0.50, n: 92, and alpha: 0.05 were calculated, the study power was determined as 95%. Five persons on annual leave and eight persons who did not volunteer to participate in the study were excluded from the sample. The quantitative part of the study was conducted with 192 nurses.

The sample of the qualitative part of the study was determined by "criterion sampling" which is one of the subcategories of the purposive sampling method, after analyzing the data obtained from the data collection form results of the participants. The criterion for collecting qualitative data was determined as "performing drug administration" of the nurses participating in the study. In-depth interviews were conducted with the nurses who volunteered to participate in the interview. Consideration was given to ensure that the nurses to be interviewed had the highest number of drug administration procedures, were able to follow the patient after the procedure, and were age-diverse. Since there is no definite rule in qualitative research such as interviewing a certain percentage of the entire sample, a purposive sampling method was used. In qualitative research conducted in the field of health sciences, reaching data saturation is expressed as the "gold standard" in determining the purposeful sample size (16). Based on this criterion, it was thought that a sample size of 5 to 20 persons would be sufficient to reach saturation in the answers given to the questions. According to this purposive sampling method, when there were no new answers to the questions asked, the data collection process was terminated when the answers began to be repeated, that is, when the saturation point was reached, and the research was completed with 12 nurses (16). The characteristics of the nurses interviewed are provided in Table 1.

Data collection

The data was collected through face-to-face interviews between July and September 2023. Quantitative data were collected during July and qualitative data were collected during August and September. Interviews were conducted at the convenience of the participants in the areas of their choice, and the interviews lasted 25 to 30 minutes. During data collection, both instant notes were taken and voice recordings were made to prevent data loss. The tools used in the quantitative and qualitative phases of the study were created by the researchers by reviewing the relevant literature and collecting opinions from six experts in the field of nursing and statistics. A "Data collection form" was used in the quantitative phase and "a semi-structured" interview form was used in the qualitative phase.

Data collection form: The form includes a total of ten questions, including seven questions about the descriptive characteristics of the participants (age, gender, educational status, years of employment, clinic of employment, weekly working hours, number of patients cared daily) and three questions about medication practices.

Semi-structured interview form: Qualitative data were collected through "individual in-depth interviews." The method is a data collection tool that enables individuals to reveal their experiences, opinions, complaints, feelings, and beliefs, and the factors that guide their behavior (16). The reason for using the interview technique in this study was to obtain in-depth information from the participants about monitoring the effects of drug administration. Cohen et al. stated that comparable and reliable qualitative data can be collected through semi-structured interviews (14). In this interview form, there are three open-ended questions about monitoring the effects of drug administration. The questions in the semi-structured interview form were as follows:

- What do you think is the right to administer medicines correctly?
- What do you do to follow up on the positive or negative effects after administering medication to your patients?
- What are your thoughts about nurses' follow-up of the correct response?

Ethical approval

This study was started after the ethical approval of the study was obtained from Kayseri University Ethics Committee (Date: 05.05.2023, Decision No: 31/2023). Informed consent was obtained from all participants and they were informed about the purpose and content of the study. In addition, pre-interview consent was obtained from the interviewed nurses for audio recording. The study was conducted in accordance with the principles of the Declaration of Helsinki from the research design to the publication process.

Statistical analysis

Quantitative data was evaluated using the IBM SPSS 23 Statistics (IBM Corp., Armonk, New York, USA) package program. Quantitative and qualitative methods were used to analyze the data. Number, percentage and mean were used as descriptive statistics in the analysis of quantitative data.

For qualitative interviews, thematic analysis was used to analyze the interview transcripts following the process described by Braun and Clarke (2021) (17). The audio recordings taken during the interviews were transcribed by a researcher. Braun and Clarke's six-stage thematic analysis method was then used. In the first stage, the researchers read and reread each interview to understand its content and get an overall perspective. In the second stage, first impressions and perceived similarities and differences were recorded. In the third stage, the data were systematically broken down into meaningful codes. In the fourth step, these initial codes were noted down and revisited, thus making the codes visible. In the fifth step, the coded data were advanced to thematic map making, where the researchers evaluated the adjustment of themes and sub-themes. In the sixth and final step, each theme was analytically refined and linked to the literature to provide clear definitions for each theme and sub-theme.

RESULTS

The findings obtained from the study conducted to determine the nurses' monitoring of drug effects after drug administration were examined under two headings: quantitative and qualitative sections.

Findings related to the quantitative portion of the study

When the descriptive characteristics of the nurses were examined, it was determined that the mean ages, working year, weekly working hours, and number of patients given daily care, were respectively 30.46±6.96 years, 7.1±6.31 years, 44.92±5.71 hours, 15.42±11.89 years. It was found that 54.2% of the nurses checked the drug package insert before administering medication, 74.5% always took the history of drug and food allergy before drug administration because they thought that it was a vital condition, and 97.9% reported unexpected side/toxic effects (Table 2).

Findings related to the qualitative part of the study

The qualitative data of the study was analyzed independently by the researcher and two instructors from the nursing department, and then divided into themes. After in-depth interviews with twelve nurses, qualitative findings consisting of themes and sub-themes were presented under the following headings under three main themes (Figure 2).

Theme 1: Rights approach to correct medication administration

In response to the question "What do you think are the rights of correct drug administration?" the nurses mainly tried to list the rights. In the interviews, some of the nurses defined the approach to the right to administer medication according to the physician's order (N4, N7), some of them mentioned the right to administer medication (N1, N3, N6, N8) and some mentioned both the physician's order and the right to administer medication (N2, N9, N12).

Subtheme 1.1: Approach according to physician's order

Regarding the right to administer medication correctly, nurses first stated that it should be done according to the physician's order. Examples of nurses' statements "according to the physician's order" are given below.

N4: *"To apply it as it should be applied by following the order written by the physician, to adjust the dose of the drug well and apply it to the patient correctly"*

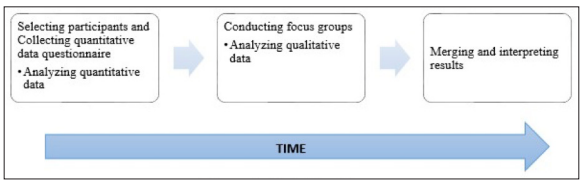

Figure 1. Study flow diagram

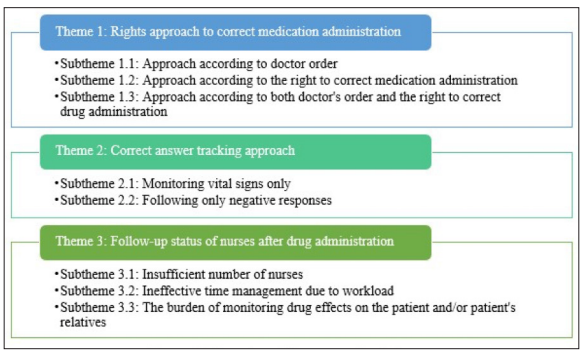

Figure 2. Overview of themes and sub-themes

N7: *"After the examination of the patient, the doctor gives the order, the drug is brought from the pharmacy, the drug is administered to the patient in a controlled manner and then the effects are observed."*

Subtheme 1.2: Approach according to the right to correct medication administration

A number of nurses mentioned the right to administer the correct medication other than the physician's order; some examples of the participants' statements about "the right to administer the correct medication" are given below.

N1: *"I remember the right dose, the right medicine, the right patient, the right time. I think it was eight rights."*

N3: *"To adjust the dose of the drug well and administer it correctly by confirming the patient, the most important thing is to adjust the dose of the drug well."*

N6: *"To administer the right medicine to the right patient at the right time in the right route and dose."*

N8: *"Right drug, right dose, right patient, right time, right route, right form of medication, right record, right response."*

Subtheme 1.3: Approach according to both physician's order and the right to correct drug administration

Among the nurses who participated in the study, there were some who stated that it should be done according to "both the *physician*'s order and the right to administer medication." Sample participant statements are given below.

N2: *"We should administer to the patient as required according to the order given by the physician. The right medicine, the right patient, the right dose."*

N9: *"After the examination of the patient, the physician gives the order, the drug is brought from the pharmacy, the drug is administered to the patient in a controlled manner and then the effects are observed. Right dose, right time, right patient, right route, right effect, right record."*

N12: *"Medicines should be used within the time recommended by the doctor. Medicines should not be interrupted, increased, or decreased without consulting a doctor. They should be used without skipping doses. Right answer, right medicine, right dose, right patient, right way."*

Theme 2: Correct answer tracking approach

After medication administration, nurses assess the patient (e.g., pain level) to monitor whether the medication has had the intended effect and whether any adverse effects have occurred. When nurses were asked about monitoring the correct medication effects, they focused only on vital signs and negative responses. In the interviews conducted on monitoring drug effects, participant nurses stated that they monitored vital signs (N1, N5, N7, N8, N12) and negative responses (N4, N6, N9). Examples of nurses' statements about monitoring vital signs are given below.

Subtheme 1: Monitoring only vital signs

Nurses mentioned that they mainly monitored only vital signs after drug administration. They emphasized that vital signs are important in terms of symptoms in the body. They also stated that they also monitored blood glucose levels.

N1: *"I consult a specialist. I follow vital signs and monitor blood glucose.. I pay attention to skin reactions. I keep the patients under observation for a while against complications and side effects of the drug."*

N5: *"...Attention should be paid to vital signs such as respiration..."*

N7: *"...I check values such as blood pressure and fever with care."*

N8: *"...I constantly check values such as blood pressure and fever."*

Table 1. Characteristics of the nurses interviewed

	Age	Gender	Education status	Working year	Working clinic	Weekly working hours	Number of patients given daily care
N1	38	Female	License	25	Internal medicine	45	14
N2	37	Female	License	12	Internal medicine	45	12
N3	45	Female	License	19	Surgery	40	8
N4	35	Female	License	12	Internal medicine	45	12
N5	48	Female	License	13	Internal medicine	40	9
N6	33	Male	Postgraduate	11	Intensive care	40	16
N7	31	Male	Postgraduate	9	Surgery	40	15
N8	32	Female	Postgraduate	10	Internal medicine	45	15
N9	28	Female	License	7	Intensive care	40	10
N10	32	Male	License	8	Surgery	45	25
N11	32	Male	License	9	Surgery	50	12
N12	29	Female	License	7	Intensive care	50	10

*N: Nickname

Table 2. Distribution of nurses' descriptive characteristics and drug administration behaviors (n=192)

Characteristics	**(Mean±SD)**
Age	30.46±6.96
Working year	7.1±6.31
Weekly working hours	44.92±5.71
Number of patients given daily care	15.42±11.89
Checking the drug package insert before administering medication	**n (%)**
Yes	104 (54.2)
No	10 (5.2)
Sometimes	78 (40.6)
Obtaining drug and food allergy history before the application	
Always; I think it is a vital situation.	143 (74.5)
I only question drug allergies.	44 (22.9)
No; I think the doctor is questioning.	4 (2.1)
No; the patient would have told me if he was allergic.	1 (0.5)
Reporting unexpected side/toxic effects	
Yes	188 (97.9)
No	4 (2.1)

N12: *"...I monitor vital signs and measure blood glucose."*

Examples of statements that nurses monitored drug effects only in terms of negative responses are given below.

N4: *"I go to the patient periodically to check the patient's condition and check whether there are conditions such as blood pressure oxygenation, redness, and swelling."*

N6: *"I stay in contact with the patient and check blood pressure and temperature."*

N9: *"...Allergic reaction and pulse blood pressure spo2 Vascular access, reactions that may occur in the body (swelling, redness, etc.)."*

Theme 3: Follow-up status of nurses after drug administration

Nurses talked about their implementation of the right response principle. The majority of the nurses shared their views on why they did not or could not follow the right response principle. They especially emphasized the low number of nurses per patient, high workload, and lack of time. In addition, they also mentioned that in case the nurses could not follow the right response principle, they put this responsibility on the patient.

Subtheme 3.1: Insufficient number of nurses

The nurses mentioned that they had difficulty in complying with the "rights" in drug administration, especially in following the right response principle. They stated that the main reason for this was the sparse

number of nurses per patient and the fact that all patients were cared for by a single nurse in the inpatient ward during night shifts. They also mentioned that nurses do not have time to realize the right response, especially due to the insufficient number of nurses.

N3: *"I think I did my best in accordance with the rights, but the number of patients per nurse is too high. In this case, it is not possible for me to follow up with each patient after administering medication. Sometimes we only intervene when a complication develops in the patient after administering the medication. Unfortunately..."*

N11: *"I am aware that adverse effects that may develop after administering medication are a great risk for both patients and nurses. However, the clinic where I work is very busy and I have to care for many patients. Which patient can I follow in this situation? Sometimes I just check my patient by asking "Are you okay?" but I don't have time to follow up because I have too many patients waiting. "*

Subtheme 3.2: Ineffective time management due to workload

Nurses mentioned that the workload of nurses is high due to the sparse number of nurses. It was observed that all nurses interviewed agreed on this issue. The nurses mentioned that they have many workloads in the clinic, such as the high number of patients, not only patient care but also documentation procedures, patient records, ensuring the general order of the clinic, cleaning the materials, and not having enough time for medication follow-up. Sample statements are given below (N7, N9).

N7: *"The right response principle needs to be controlled and monitored by all nurses. But I do not only provide patient care in the clinic, I also have many other duties. Since we have very few nurses, the workload of the existing nurses is very high. So when we work in the clinic, our priority is actually to catch up. Therefore, I do not have enough time to monitor the effect of drug administration."*

N9: *"There is an urgent need to regulate the number of patients per person and the number of nurses. I think that many of my colleagues do not have the opportunity due to their busy work schedules. Working conditions must be improved for both the profession and the patient. However, I have so many patients and work to do that I do not have time to evaluate the effects of medication."*

Subtheme 3.3: The burden of monitoring drug effects on the patient and/or patient's relatives

The nurses mentioned that they mostly monitor vital signs for the right response. However, they also stated that they asked both the patient and the patient's relatives to follow the effects of drug applications. Throughout the qualitative interview, the nurses generally mentioned about their heavy workload, not having enough time which prevent them regularly following up with the patients directly. For this reason, it appears that the nurses delegate the responsibility for medication administration follow-up to the patients and/or their relatives.

N1: *"I check whether there is any bad situation by observing and asking questions, and I check values such as blood pressure and fever by paying attention to them. I tell the patient that when he/she feels bad, he/she or his/her relatives should inform us."*

N5: *"I tell patients and their relatives about allergy symptoms and drug complications and ask them to inform me when these symptoms are seen in the patient."*

DISCUSSION AND CONCLUSION

Five rights of medication management have been developed to guide nurses to administer medicines safely and correctly. These are the right patient, right drug, right dose, right route, and right time. However, over time, errors in medication administration have increased. The correct rights in medicines management have been reviewed, and while the basic rights have remained constant, different information on new rights has been put forward. Other proposed rights include the right to refuse, right information, right questions, right challenges, right reason, right advice, right education, right preparation, right assessment data, right documentation, right frequency, right date, right drug approach, right drug-drug interaction, right assessment, and finally, the right response or outcome (4,18).

In the literature, there are studies on five correct rights in the drug method (8,19,20). However, the number of studies including the right to correct response/evaluation, which is among the rights, is relatively low (19,21).

The Joint Commission (2021), an accreditation body in health services, provides implementation standards for the improvement of health organizations. The organization's 2021 patient safety goals for hospitals include the importance of medication management in terms of patient safety practices. These goals comprise recommendations for medication practices, including right-to-know recommendations. Unfortunately, non-compliance with institutional or manufacturer policies and acts of negligence remain a common cause of medication administration errors (22). In addition, important medication administration rights, including right route, right patient, right time procedures, patient-directed preparation of drug doses and monitoring of reactions to the drug, i.e., the correct response steps, are not consistently followed. These situations cause medication administration errors and put both patients and nurses at risk (23,24).

Positive and negative effects of the drug should be monitored in patients depending on drug applications. Improvements in the disease process should be monitored depending on drug applications. However, in some cases, patients may develop unwanted side effects due to drug administration (25). Since nurses administer most medications in health care settings, they have a unique position in the health care team to monitor the patient's response to medication. For this reason, nurses need to monitor their patients to follow the positive and negative effects, to take precautions against adverse effects that may develop, and to apply interventions. They should usually be present when an adverse effect occurs and be involved in taking appropriate measures to improve the problem accordingly (26,27).

In one study, nurses were observed during drug administration over a period of twelve months. According to the results of the study, it was reported that 57.7% of the nurses made at least one error during medication administration and the second most common error was the correct response (27.5%) (28). Castaneda et al. conducted a study on the use of simulation to improve the medication management competence of nursing students. According to the results of their study, it was stated that 54.2% of the students did not perform the correct response step, while the students mostly did the right patient, right dose, right way, right time rights correctly (29). In a study by Mohammed et al. (2022), it was reported that 6.2% of the nurses followed the correct response right incorrectly. In another observational study, it was determined that 88.0% of the nurses practiced the right to the correct answer (30). In our study, it was found that 97.9% of the nurses reported unexpected side/toxic effects and 58.3% attended the patient at certain intervals to check. After the qualitative interviews with the nurses, most of the nurses stated that the right to administer medication should be done according to the physician's order. Very few of the nurses were able to count correct drug administration as five rights. In this case, we can say that nurses lack knowledge about the right to administer medication. At the same time, the fact that the nurses stated that they administered according to the physician's order, suggests that they were not sufficiently informed about their duties, roles and responsibilities. In addition, it is also seen that the correct response follow-up of nurses is not high. Therefore, nurses should first be informed to remind them of their duties, authorities and responsibilities, followed by training on the correct rights for drug administration. When we compare the results of our study with the studies in the literature, it is seen that there are different results regarding the right to correct response. It may be recommended to investigate the reasons for this difference, to review the policies implemented in studies with high right to correct response and to compare them with study regions with low results.

There are multiple reasons for medication administration errors (31). In studies conducted in the literature, some of these reasons are stated as follows: professional factors (such as lack of experience, education, lack of communication skills), organizational factors (high number of patients, insufficient number of nurses, high workload of nurses), work-related factors (such as workload, relationships with other colleagues) and personal factors (such as nurses' health status, fatigue, lack of initiative in resolving drug-related doubts). The high workload of nurses and lack of training in drug administration in particular are stated as the main reasons (30,32). It has been stated in some studies that insufficient time and distractions are the most common factors in errors made in drug administration (24,33). Similarly, in our study, nurses mentioned that they and their colleagues did not have time to realize the right of correct response due to the

sparse and insufficient number of nurses per patient. In addition, all the nurses stated that their workload was too high with the shortage of nurses. At the same time, they revealed that they not only provide patient care in clinical practice but also have many additional duties. As a result of the combination of all these reasons, the nurses stated that they did not have sufficient time for correct response monitoring. According to these results, it is recommended to determine the ideal ratio of the number of nurses per patient and to increase the number of nurses to ensure accurate drug response monitoring (34). At the same time, we can also suggest that the workload of nurses should be regulated by discussing with hospital administrators the factors that make it difficult to follow up the correct response.

While nurses participate in training and skill competency assessments related to safe medication administration, difficulties encountered in a busy working environment can affect their behavior (33). They need support in situations such as insufficient number of nurses and lack of time. Allocating the necessary time to complete each step of the five rights and identifying practice situations that contribute to interruptions or distractions, can reduce errors and prevent adverse effects (35)

One of the striking points in the qualitative interviews was that some nurses stated that they asked both the patient and the patient's relatives, to monitor the effect of drug administration. They stated the reason for this as excessive workload and lack of time. No study on this issue was found in the literature, however, the right response is the responsibility of the nurse. Therefore, it may be recommended to make necessary arrangements by considering the reasons for nurses not practicing the right to a correct answer.

The limitations of the study include the fact that it was conducted in a single center and in the departments (internal medicine, intensive care, and surgery) of health institutions, where most drug administration is performed.

According to the results of our study, while the majority of nurses stated that they reported unexpected/adverse effects, on average, half of the nurses stated that they checked the patients at certain intervals. At the same time, the nurses stated that they could not apply the right to correct response due to a lack of knowledge about the right medication, practicing according to the physician's order, high workload, sparse number of nurses, and lack of time. As a result, some of the nurses stated that they gave the responsibility of correct response follow-up to the patient or the patient's relatives. According to the results of our study, it is recommended that the reasons for not implementing the right response should be evaluated, and the number of nurses should be increased, workload should be regulated, and training should be organized for nurses regarding the right to administer correct medication and in particular, regarding the importance of correct response. It is also recommended that nurses receive training and counselling on their duties, authorities and responsibilities.

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Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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The state of knowledge of nurses and factors influencing it regarding vegetarian/vegan diet

Hemşirelerin vejetaryen/vegan beslenme hakkındaki bilgileri ve etkileyen faktörler

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Abstract

Aim: This descriptive and cross-sectional study aims to investigate the knowledge of nurses and the factors influencing it regarding the vegetarian/vegan diet.

Methods: This study was conducted at a university hospital with the participation of 213 nurses. Data were collected using the "Sociodemographic Data Form," "Vegetarian/Vegan Diet Knowledge Test," and "Vegetarian/Vegan Diet Opinion Form". Data were analyzed by number, percentage, Pearson Correlation, One-Way Analysis of Variance, and Independent Sample T-Test.

Results: The mean age of the nurses was 31.21±7.56 years, 86.4% of which were women, 53.5% were single, and 70.4% had bachelor's degrees. The nurses' knowledge test score was 8.68±3.81 on average (min=0, max=16). Only 27.2% of the nurses correctly answered the following item: "People on a vegetarian/vegan diet could get all the essential amino acids with their diets". The nurses who are married or have completed postgraduate education achieved higher knowledge test scores ($p<0.05$).

Conclusions: Nurses have limited knowledge about vegetarian/vegan diets. Nurses should keep up with up-to-date information about diet types for evidence-based practices.

Keywords: Knowledge; nursing; vegan; vegetarian

Öz

Amaç: Bu çalışma, hemşirelerin vejetaryen/vegan beslenmeye ilişkin bilgilerini ve etkileyen faktörleri ortaya koymak amacıyla tanımlayıcı ve kesitsel tipte yapılmıştır.

Yöntemler: Bu çalışma bir üniversite hastanesinde 213 hemşirenin katılımı ile gerçekleştirilmiştir. Veriler "Sosyodemografik Veri Formu", "Vejetaryen/Vegan Beslenme Bilgi Testi" ve "Vejetaryen/Vegan Beslenme Görüş Formu" kullanılarak toplanmıştır. Veriler sayı, yüzde, Pearson Korelasyon, One-Way Tek Yönlü Varyans Analizi ve Bağımsız Örneklem T-Testi ile analiz edilmiştir.

Bulgular: Hemşirelerin yaş ortalaması 31.21±7.56 yıl olup, %86.4'ü kadın, %53.5'i bekar ve %70.4'ü lisans mezunudur. Hemşirelerin bilgi testi puanı ortalama 8.68±3.81'dir (min=0, max=16). Hemşirelerin sadece %27,2'si "Vejetaryen/vegan beslenen bireylerin diyetleri ile gerekli amino asitlerin tamamını alabilirler" maddesini doğru cevapladı. Evli ve lisansüstü eğitimini tamamlamış hemşirelerin bilgi testi puanları daha yüksek bulundu ($p<0.05$).

Sonuçlar: Hemşireler, beslenme türleri hakkında bireyleri, aileleri ve toplumu doğru bilgilendirmek, bakım vermek, bireyin günlük yaşamına rehberlik etmek ve kanıta dayalı uygulamalara temel oluşturmak için güncel bilgileri takip etmelidir.

Anahtar Sözcükler: Bilgi; hemşirelik; vegan; vejetaryen

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INTRODUCTION

There has been an emphasis in recent years on the need to obtain detailed information about eating habits to better understand the nutritional status and problems of healthy/sick individuals (1-3). Geographical, climatic, and agricultural characteristics of the place where the individual lives and the beliefs, traditions, and socioeconomic status are the main factors that shape people's eating habits (2-3). When assessing the nutritional status of individuals, it is generally considered whether the total food consumed daily meets the energy and nutrient needs (4,5). Research, however, puts into question the understanding that "proper nutrition" is related to longer life and good health as well as what proper nutrition actually is and how we should eat (4). There is an increasing number of people going on diets styled with different purposes and based on different principles, adopting these diets as part of their lifestyles in recent years (6,7). Vegetarian diet, pescatarian diet, paleo diet, ketogenic diet, planetary health diet, diabetic diet, and gluten-free diet are some of these dietary styles (8).

Vegetarianism, the most popular of alternative diets, includes mainly consumption of plant-based foods. The types of vegetarian diets differ according to food limitations (6,9) (Table 1). Although veganism is a subtype of a vegetarian diet, it should be considered separately. It is described as a radical end of vegetarianism (10% of vegetarians are vegans) (10,11). The vegan diet has several benefits for health, both physical and environmental, as foods of animal origin are restricted. Adopting a vegan diet can provide numerous health benefits, including improved heart health, lower diabetes risk, better weight management, and a decreased likelihood of certain cancers (12-15). Additionally, it can contribute to environmental sustainability by reducing greenhouse gas emissions, conserving water, and minimizing land use (16,17). According to the Academy of Nutrition and Dietetics, properly organized vegetarian diets, including vegan diets, are adequate in terms of health and nutrition and may be beneficial for preventing and treating some diseases (12-15). As an example, cross-sectional studies with vegetarians and vegans have shown that these individuals have lower body mass indices and plasma cholesterol concentrations compared to non-vegetarians (omnivores) (18).

Looking at examples from the world, 600.000 people (1.6% of the population) in England are vegan (19), and 3-5% of the USA population are vegetarian and vegan, respectively (20). In Turkey, it is estimated that 5% of the population is vegetarian and 10% of them (80,000) are vegans (11,21). Although more and more people choose alternative diets, health professionals lack knowledge about vegetarian/vegan nutrition. (22,23). This lack of knowledge may impact healthcare and patients' access to evidence-based practices (7).

The number of vegans grows faster than the number of vegetarians (11). Among the major drivers of this are the concerns about the negative effects on the environment, health, and economy arising from diets rich in animal products. The main idea behind a vegan diet is to refuse the use of all kinds of products of animal origin (7,13,14). Vegans describe this as a lifestyle, not a diet, because of their compassion for animals and because they think it has a positive effect on their health. (11).

Nurses as professionals who spend the most time with patients should consider patients' daily living activities holistically (6,22,23). Given the nurses' role as primary care providers, they are in the best position to ensure a patient is well-fed (22). They are responsible for observing the food intake of patients, assessing their nutritional status, and providing dietary education (22,24). The most common cause of wrong diet or diet attempts is the lack of nutritional knowledge (24). One study found that doctors provide dietary advice 2.8 times a day and nurses 2.7 times a day (21). There are some situations when all healthcare professionals, not just dietitians, need to inform patients about their diet. Nurses need knowledge and skills regarding nutrition to prevent patients from deteriorating and to guide them on possible new alternative diets that are becoming increasingly common. Although a vegan diet may seem easy to follow, many nurses may not have the right knowledge about vegan nutrition (6,22-24). It is important to know the reason for the individual's diet choice and possible deficits and to guide them correctly. For example, a vegan individual should be aware of the risk of B12 deficiency and how to supplement it (8). Nurses should possess basic information about the alternatives to the diets preferred by the people they care for.

Vegans in Turkey may have difficulties living according to their beliefs. Most individuals in Turkey are Muslims (25). Islam does not allow for the torture of animals. On the other hand, Muslims offer animal sacrifices (26). According to a study investigating beliefs and vegetarianism/veganism, vegan Muslims want to maintain their religious identity while continuing to live as vegans. Some of them have mentioned that the notion of sacrifice in Islam has changed over time and it is no longer correct to religiously sacrifice animals (27). Vegan individuals in Turkey are also suscept to doubt in terms of their piety (27). Nurses should advocate for the rights of patients, including the choice of diet. They can also guide patients through a healthy and safe way to continue an alternative diet using evidence-based information. From the perspective of this study, which is of special importance for Turkish dietary habits, gains a special importance for our country.

In a study investigating nursing students' knowledge about the vegan diet, 73% of the students consumed animal products daily and 27% weekly, they possessed the basic knowledge of the vegan diet but limited knowledge of the ethical and environmental considerations (22). In a study conducted to determine the knowledge, attitudes, and behaviour of physicians regarding vegetarian/vegan diets, only 1% of the participants were vegetarian/vegan, and 94.8% had not received training on the health effects of the vegetarian/vegan diet before (28). There is limited research on health professionals' knowledge of vegetarian/vegan nutrition. The fact that nurses hold negative and factually wrong opinions about vegetarian/vegan nutrition may cause the patients to underestimate their nutritional expertise and experience stress during care. Thus, it may be a barrier for the individual to receive holistic nursing care. This study aims to determine nurses' knowledge and influencing factors about the vegetarian/vegan diet and thus, to raise awareness.

METHODS

Aim and design

This descriptive and cross-sectional study aimed to investigate nurses' knowledge about vegetarian/vegan diets and the factors affecting it.

Research questions

1. What is the knowledge level of nurses about vegetarian/vegan diets?
2. What are the factors affecting the knowledge level of nurses about vegetarian/vegan diets?

Participants and sample size

We collected the study data in a training and research hospital in the University of Health Sciences, between October 1, 2021, and April 1, 2022. The sample size of the study was calculated using the G*Power 3.1.9.7 program and more precisely, the one-way analysis of variance. The required sample size was calculated at 213 by taking 0.25 effect size (d = 0.25), 5% margin of error ($\alpha = 0.05$) and 80% power ($1-\beta = 0.80$) into account (29,30).

Measurements

The data of the study were collected from nurses working in the hospital during the day shift. The researcher interviewed the nurses in the clinic (intensive care, surgical, internal medicine, outpatient clinic, management, eye/ear-nose-throat, pediatrics, emergency, etc.) where they worked, explained the purpose of the study, and obtained their written informed consent. Then the "*Sociodemographic Data Form*", "*Vegetarian/Vegan Diet Knowledge Test*" and "*Vegetarian/Vegan Diet Opinion Form*" were filled. It took a total of 20 minutes.

Sociodemographic Data Form: The form includes questions prepared by the researchers. It contains 13 questions about participants' sociodemographic characteristics (age, gender, marital status, educational status etc.), their eating habits (diet etc.), and their experiences regarding the vegetarian/vegan diet (trying a vegetarian/vegan diet, any acquaintance on a vegetarian/vegan diet, training on the health effects of vegetarian/vegan diet, etc.) ((2,8-12).

Vegetarian/Vegan Diet Knowledge Test: It includes knowledge-based questions. These questions are answered by the participants as "Right", "Wrong" or "Undecided". Each question given a correct answer scored 1 point whereas incorrect answers or undecided answers scored 0. The lowest score to be obtained from the knowledge test is 0 and the highest is 17. Participants'

answers were evaluated as either correct or incorrect based on the literature published by scientific organizations (2,6,8,11,22,28,31,32). The knowledge test was evaluated by 5 experts (3 academicians from the Department of Nutrition and Dietetics and 2 academicians from the Department of Nursing). Items were rated by experts as "appropriate", "must be changed" or "not appropriate". The items achieved their final form following the feedback of the experts (Item Content Validity Index-I CVI=0.91). The Kuder Richardson (KR-20) score for the Vegetarian/Vegan Diet Knowledge Test was found to be 0.772, indicating acceptable internal consistency for the knowledge test (33).

Vegetarian/Vegan Diet Opinion Form: It includes an open-ended question in which nurses are asked to write any thoughts about the vegetarian/vegan diet.

Ethical approval

This study was approved by Hamidiye Scientific Research Ethics Committee (date: 01.10.2021, decision no: 30/11). We obtained written permission from the hospital and each participant for data collection.

Statistical analysis

We used IBM SPSS Statistics version 21 (IBM Inc., Armonk, NY, USA) for data analysis. The nominal variables were evaluated using frequency and percentage, while the ordinal variables were evaluated using mean and standard deviation. The Kolmogorov-Smirnov Test showed normal data distribution. For this reason, Pearson Correlation, One-Way ANOVA, and Independent Sample T-Test were used to compare the mean test scores.

RESULTS

The mean age of the individuals in the study was 31.21±7.56 years, 86.4% of whom were women, 53.5% were single and 66.2% had no children. As for education and experience, 70.4% had a bachelor's degree, 32.9% had professional experience for 1-5 years and over 10 years, most of them worked in intensive care, internal medicine and surgical clinics, and outpatient clinics. Moreover, 97.2% of them were omnivorous, 88.7% had never tried a vegetarian/vegan diet at any time in their lives, 68.1% did not have any acquaintance following a vegetarian/vegan diet, 73.7% did not have a pet at home, 89.7% had not received any training on vegetarian/vegan diet, and 93.0% had not cared for a patient on a vegetarian/vegan diet (Table 2). The nurses' average Vegetarian/Vegan Diet Knowledge Test score was 8.68±3.81 (Min=0, Max=16) (Table 2).

When the sociodemographic characteristics of the nurses and their vegetarian/vegan diet knowledge levels were compared, married nurses scored higher than singles (p<0,001). The nurses with postgraduate degrees scored higher on the knowledge test than the nurses with bachelor's degrees (p<0.05). The knowledge test scores of the nurses who had acquaintances or relatives on a vegetarian/vegan diet were also higher (p<0.05). There was no difference between nurses' concerning other sociodemographic characteristics and knowledge test scores. (Table 2.).

When we look at each item in the Vegetarian/Vegan Diet Knowledge Test, 15 of them were answered correctly by most nurses, respectively. Item 9 (61.5%), Item 10 (64.8), Item 12 (62.0%), and Item 16. (76.5%) received correct answers from most of the nurses. Very few of the nurses got Item 4 (26.8%) and Item 6 (27.2%) right. One of the most incorrectly answered items (Item 6.) stated that people on a vegetarian/vegan diet could get all the essential amino acids with their diets. For Item 17, half of the nurses gave the correct answer (46.5%), while half were undecided (44.1%). Other answers can be found in Table 3.

In the Vegetarian/Vegan Diet Opinion Form used in this study, some of the nurses provided the following statements about the vegetarian/vegan diets:

– "The vegetarian/vegan diet is healthy but difficult to maintain in social life."

– "I do not approve of the vegetarian/vegan diet."

– "I find it right as a philosophy, but it is difficult to maintain. There should be more vegetarian/vegan options in cafes and restaurants".

– "Animal-based foods should also be consumed for proper nutrition."

– "I would like to try it, but I can't give up the taste of meat."

– "Doing a vegetarian/vegan diet makes you feel restricted, can't we even eat eggs!"

A vegan nurse participating in the study also added:

Table 1. Varieties of vegetarian diet type

Diet	Features
Lacto-vegetarian diet	Aside from plant foods, only milk and dairy products as foods of animal origin can be consumed.
Ovo-vegetarian diet	Aside from plant foods, only eggs as foods of animal origin can be consumed.
Lacto-ovo vegetarian diet	Aside from plant foods, products the animals yield when they are alive such as milk and eggs can be consumed.
Semi-vegetarian diet	Aside from plant foods, poultry and fish can be consumed less than once a week and more than once a month. Eggs, milk and derivatives can be consumed in the semi-vegetarian diet.
Vegan diet	No animal products can be consumed in a vegan diet. Vegans do not eat animal foods and they do not wear clothes made of wool, silk, leather because they are obtained from animals, nor do they use products containing animal fat.

– "People's habits and commitment to comfort prevent them from researching and finding the truth. The rigid prejudices against vegan diets in people working in healthcare are sad and startling. There should be more scientific studies."

DISCUSSION AND CONCLUSION

A plant-based diet is based on foods that come from plants and includes no ingredients from animals. Such diets include vegetables, whole grains, legumes, nuts, seeds, and fruits (34). Individuals may choose a plant-based diet for many different reasons, such as a positive impact on their health, animal protection, environmental concerns, or individual preferences. These diets can support the health of an individual at any age. As with any diet, plant-based eating should be planned to meet the person's nutritional needs (31). Nurses spend more time with patients than all other healthcare professionals and play an important role in planning their daily life activities. They should have basic information about alternatives to the diets preferred by the individuals they care for (7). Nurses who do not have sufficient information about the nutritional preference of the individual may experience stress while giving care. It may even cause them not to respect the preferences of the individual (23). There is no study showing the nurses' perspective on vegetarian/vegan diets in Turkey, and studies around the world are limited (7,22). In the study, 15 items were answered correctly by the majority of the nurses' but the mean score from the knowledge test on vegetarian/vegan diet was only 8.68±3.81 out of 17 points, indicating that nurses possess insufficient knowledge about the vegetarian/vegan diet (Table 2.).

Married individuals are familiar not only with their preferences but also with the needs or preferences of other people and age groups. Likewise, if the nurses live with or have close relationships with people choosing a vegan diet, they are better informed because it has become a part of their lives (22). In this study, the nurses who are married or have vegetarian/vegan-fed relatives scored higher on the knowledge test ($p=0.000$, $p<0,001$ and $p=0.043$, $p<0.05$) (Table 2.).

The nurses who finished postgraduate education, too, scored higher on the knowledge test ($p<0,05$). (Table 2.). This suggests that nursing education should continue after graduation for holistic nursing care.

In the study, only 41.3% of the nurses knew that a vegetarian-vegan diet would not cause folic acid deficiency (Item 1.) (Table 3.). Folate is the natural form of vitamin B9 that is water-soluble and naturally found in many foods. A wide variety of foods (turnip greens, spinach, romaine lettuce, asparagus, Brussels sprouts, broccoli, beans, and peanuts) naturally contain folate (35). A study comparing participant groups on different diets reported that vegans consumed more fiber, folate, vitamin C and E (36).

According to the study, 52.1% of the nurses knew that a vegetarian/vegan diet could cause vitamin B12 deficiency (Item 2.) (Table 3.). The majority of the nurses recognised that individuals on vegan diets were at risk for vitamin B12 deficiency. Vitamin B12 (cobalamin) is an essential nutrient. It is required for nervous system functions, DNA synthesis, and homocysteine metabolism (37). Vitamin B12 requires supplementation for people with a plant-based diet because it is found only in animal products. Vitamin B12 is found in yeast, fortified cereals, and plant milk (soy, almond, oat), but it cannot meet the need because of its low contents. (8).

Table 2. Sociodemographic information's, mean scores and statistically significant differences between groups (n:213)

Characteristic	Mean±SD	Range	Knowledge Score Mean±SD	Test value	p
Age (years)	31.21±7.56	20-52	8.68±3.81	r=0.109	[a]0.113
	n	**%**			
Gender					
Female	184	86.4	8.6±3.9	t=-0.623	[b]0.536
Male	29	13.6	9.0±2.7		
Marital status					
Single	114	53.5	7.8±3.9	t=-3.594	[b]0.000*
Married	99	46.5	9.6±3.5		
With children					
Yes	72	33.8	9.2±3.6	t=1.509	[b]0.133
No	141	66.2	8.4±3.8		
Educational status					
Bachelor's degree	150	70.4	8.2±3.8	t=-2.584	[b]0.010**
Postgraduate	63	29.6	9.7±3.5		
Professional experience					
0-1 years	32	15.0	7.1±4.4	F=1.325	[c]0.185
1-5 years	70	32.9	8.6±3.8		
5-10 years	41	19.2	9.4±3.3		
> 10 years	70	32.9	9.0±3.5		
Working unit					
Intensive care	49	23.0	8.1±3.9	F=1.240	[c]0.240
Surgical	45	21.1	8.8±3.5		
Internal medicine	43	20.2	8.3±4.0		
Outpatient clinic	31	14.6	9.8±2.0		
Management	9	4.2	9.3±5.0		
Eye/Ear-Nose-Throat	9	4.2	7.4±2.9		
Paediatrics	9	4.2	9.5±2.0		
Emergency	11	5.2	7.4±2.2		
Other	7	3.3	9.7±3.6		
Diet					
Omnivore	207	97.2	8.6±3.7		
Vegetarian	1	0.5	15		
Lacto-vegetarian	2	0.9	7.0±1.4		
Pescatarian	2	0.9	10.5±4.9		
Vegan	1	0.5	15		
Triying a vegetarian/vegan diet					
Yes	24	11.3	10.9±3.0		
No	189	88.7	8.3±3.8		
Any acquaintance on a vegetarian/vegan diet					
Yes	68	31.9	9.4±3.5	t=-2.032	[b]0.043**
No	145	68.1	8.3±3.9		
Has pet at home					
Yes	56	26.3	8.6±4.6	t=0.016	[b]0.989
No	157	73.7	8.6±3.4		
Training on the health effects of vegetarian/vegan diet?					
Yes	22	10.3	10.2±3.6		
No	191	89.7	8.5±3.8		
Cared for a patient on a vegetarian/ vegan diet					
Yes	15	7.0	9.1±4.5		
No	198	93.0	8.6±3.7		

SD: Standard Deviation, Knowledge Score: Vegetarian/Vegan Diet Knowledge Test Score, a Pearson Correlation, b Independent sample T-Test, c One Way Anova, * p<0,001, **p<0,05

Table 3. Nurses' knowledge about vegetarian/vegan diet

Items	Questions	Correct Answer	Nurses' Response (n:213)		
		Right/Wrong	Right *n* (%)	Wrong *n* (%)	Undecided *n* (%)
	Vegetarian/vegan diet causes folic acid deficiency.	Wrong	73 (34.3)	**88 (41.3)***	52 (24.4)
	Vegetarian/vegan diet causes vitamin B12 deficiency.	Right	**111 (52.1)***	60 (28.2)	42 (19.7)
	Vegetarian/vegan diet causes vitamin D deficiency.	Wrong	61 (28.6)	**103 (48.4)***	49 (23.0)
	Zinc bioavailability is higher in people not on vegetarian/vegan diets.	Right	57 (26.8)*	49 (23.0)	**107 (50.2)**
	People on a vegetarian/vegan diet get more dietary fibre.	Right	**125 (58.7)***	24 (11.3)	64 (30.0)
	People on a vegetarian/vegan diet cannot get all the essential amino acids from the diet.	Wrong	**98 (46.0)**	58 (27.2)*	57 (26.8)
	People on vegetarian/vegan diet have lower body mass index values.	Right	**78 (36.6)***	75 (35.2)	60 (28.2)
	Vegetarian/vegan diet reduces physical performance.	Wrong	59 (27.7)	**116 (54.5)***	38 (17.8)
	Vegetarian/vegan diet is effective in reducing LDL cholesterol.	Right	**131 (61.5)***	19 (8.9)	63 (29.6)
	Vegetarian/vegan diet reduces the risk of cardiovascular disease.	Right	**138 (64.8)***	29 (13.6)	46 (21.6)
	Vegetarian/vegan diet reduces risk of diabetes.	Right	**120 (56.3)***	46 (21.6)	47 (22.4)
	Vegetarian/vegan diet reduces risk of hypertension.	Right	**132 (62.0)***	32 (15.0)	49 (23.0)
	Vegetarian/vegan diet causes menstrual irregularities in women.	Wrong	27 (12.7)	**110 (51.6)***	76 (35.7)
	A vegetarian/vegan diet reduces sperm count in men.	Wrong	24 (11.2)	**106 (49.8)***	83 (39.0)
	Well-planned vegetarian/vegan diets (with supplements such as vitamin B12 as needed) are suitable for individuals and athletes at all stages of the life cycle.	Right	**118 (55.4)***	37 (17.4)	58 (27.2)
	The reason why individuals prefer a vegetarian/vegan diet may be to be healthier, for ethical reasons, taste preferences, ecological, cultural or religious considerations.	Right	**163 (76.5)***	4 (1.9)	46 (21.6)
	A vegetarian/vegan diet has fewer carbon emissions than diets based on animal sources.	Right	**99 (46.5)***	20 (9.4)	94 (44.1)

* Correct answer option according to the knowledge test. Highest score for each item is in boldface. Abbreviations: n: Sample, LDL: Low-density lipoprotein, %: Percentage

Another finding of the study, 48.4% of the nurses correctly stated that a vegetarian/vegan diet would not cause vitamin D deficiency (Item 3.) (Table 3.). Vitamin D is obtained through the catalysis of ultraviolet (UV) light. Provitamin D accumulates in the skin and transforms into vitamin D form under the influence of sunlight. It is an important vitamin with an active role in bone health and development, cell growth, and nervous system balance. Very few foods in nature contain vitamin D. Although there is vitamin D in animal products (beef livers, cheese, egg yolks), the most important source of vitamin D is sunlight (38,39). Individuals are at risk of low vitamin D if they live in areas with little sunlight, are overly protected from the sun, or have dark skin. These individuals may need to take vitamin D supplements or foods containing vitamin D (40). While there has been some concern that vegetarians/vegans might have inadequate vitamin D levels, studies have shown that this is not the case (39,41).

In the study, only 26.8% of the nurses knew that the bioavailability of zinc was lower in vegetarian/vegan diets (Item 4.) (Table 3.). Zinc is the most abundant

element after iron and is very important for the body's metabolic function. Individuals following plant-based diets have lower plasma zinc levels than omnivores due to phytate intake which reduces absorption. Food preparation techniques, such as soaking and germinating legumes such as beans, chickpeas, nuts, or fermenting bread, can increase the bioavailability of zinc. Phytates reduce the amount of zinc the body absorbs. Vegetarians and vegans might benefit from taking zinc supplements (13,15,42). When all findings are evaluated, it is seen that individuals following a vegan/vegetarian diet should be careful about vitamin B12 and zinc bioavailability, and there is no difference in vitamin D deficiency compared to individuals following other diets.

According to the study, 58.7% of the nurses knew that people on vegetarian/vegan diets consume more fiber (Item 5.), while 27.2% knew that they could get all the necessary amino acids through such diet (Item 6.) (Table 3.). The Academy of Nutrition and Dietetics reported that individuals who use different protein sources and use the energy they receive while on plant-based nutrition can get all the amino acids they need (13,17). In addition, although short-term studies suggest that high protein intake is beneficial (5), its long-term effects on health are a matter of debate (17,43). If nurses think that vegan/vegetarian individuals cannot get the necessary amino acids, it may cause concern that they will be harmed. This may cause conflicts in the nursing care of the individual.

Only 36.6% of the nurses participating in our study knew that the body mass index values were lower in vegetarian/vegan diets (item 7.) (Table 3.). Studies show that people on plant-based diets have lower average body mass (18,36,44).

In the study, 54.5% of the nurses correctly knew that a vegetarian/vegan diet would not decrease physical performance (item 8.) (Table 3.). Like any diet, a vegetarian/vegan diet can be based on processed foods of poor nutritional quality or foods that are high in nutrients and rich in variety. Thus, a well-planned plant-based diet not containing processed foods and including fruits and vegetables would be beneficial whereas a poorly planned plant-based diet may cause insufficient intake of some vitamins and minerals (8,45). With a well-planned herbal diet, athletes gain benefits such as increased carbohydrate and energy intake, fruit and vegetable consumption and regulation of acid-base balance, reduction of oxidative stress, and recovery acceleration thanks to antioxidant fruits (8).

In the study, 61.5% of the nurses correctly answered that the vegetarian/vegan diet reduces LDL cholesterol (item 9.), 64.8% knew that it reduces cardiovascular disease risk (item 10.), 56.3% knew that it reduces diabetes risk (item 11.) and 62.0% knew that it reduces hypertension risk (item 12.) (Table 3.). The plant-based diet has recently increased in popularity due to its positive effects on general health and because it reduces cardiovascular diseases. Plant-based diets, especially vegan diets, are associated with improvement in cardiovascular health and reduce the occurrence of risk factors such as diabetes and hypertension (3). It also reduces the risk of type 2 diabetes and lowers HgA1c levels (46,47). A prospective study in which nurses were followed for 32 years and health workers for 26 years compared animal and vegetable protein intakes and morbidity and mortality and concluded that those who received their energy predominantly from animal proteins experienced more cases of cardiovascular diseases than those who received their energy from plant proteins (46). The same study also found that protein intake from red meat was associated with higher mortality (45). Studies show that a plant-based diet such as a vegetarian/vegan diet has positive effects on cardiovascular health and reduces the level of cholesterol in the blood (16). A healthy diet poses an 11-24% lower risk of death than an unhealthy diet (17,48). Many chronic conditions such as cancer occur due to obesity, insufficient physical activity, and malnutrition (1,2). Studies indicate that a diet that is mostly plant-based, restricts red and processed meats, avoids refined carbohydrates, avoids simple sugars, and restricts alcohol can be healthy and prevent chronic diseases (1,2). It has been reported that consuming non-starchy vegetables such as broccoli, lettuce, and green beans was associated with a lower incidence of stomach, mouth and larynx cancers (49) and consuming foods rich in yellow, green and orange carotene from cruciferous vegetables was associated with less aggressive breast cancers (50). Processed red meats such as salami and sausages are classified as carcinogenic, while red meats such as veal and lamb are classified as potentially carcinogenic (2).

According to the data from our study, 51.6% of the nurses correctly knew that a vegetarian/vegan diet would not cause menstrual irregularities (item 13.), and 49.8% correctly knew that it would not decrease the sperm count in men (item 14.) (Table 3.). Women lose 10-42 mg of iron daily during menstruation compared to 1 mg of iron in non-menstruating women (51). Women are therefore advised to pay more attention to their iron intake during these periods. Plant-based nutrition does not adversely affect the menstrual cycle and is recommended partially for increasing fertility. Studies indicate that the intake of vegetable protein instead of animal protein, and the high consumption of fiber and low consumption of glycaemic carbohydrates increase fertility (51,52). One study highlights the relationship between animal protein intake and increased risk of infertility (53). Women (over 32 years old) who consume protein from plant sources rather than carbohydrates or animal protein have been reported to have a lower risk of infertility (51-53). Mediterranean diet is also recommended as a "pre-pregnancy diet" for individuals receiving infertility treatment (54). According to a prospective study comparing sperm quality between vegan diets and non-vegan diets, people on vegan diets had higher total sperm count and motile sperm percentage than non-vegans (55). According to the literature, not only does plant-based nutrition not reduce sperm count, but it also increases their quality (54,55).

In the study, 55.4% of the nurses stated that well-planned vegetarian/vegan diets (with supplements such as vitamin B12 when necessary) are suitable for individuals and athletes at all stages of their life cycle (item 15.) (Table 3.). Vegetarian/vegan diets can be followed at any age and under any circumstance (31). In studies conducted on athletes of different age groups, it is stated that plant-based nutrition is sustainable (8,32). A study conducted with omnivorous, vegetarian, and vegan pregnant women demonstrated that the babies of vegan mothers had lower birth weights than the babies of omnivorous mothers, but the birth weight decreases were not out of the normal ranges. The same study also concluded that the vegan diet carries less risk than other diet types for excessive maternal weight gain (56). There are also studies suggesting that pregnant women on a vegan diet must take supplements such as vitamin B12 and, if necessary, folic acid and ferritin (56,57).

According to the study, 76.5% of the nurses stated that the reasons why individuals may prefer a vegetarian/vegan diet include the wish to be healthier, ethical reasons, taste preferences, and ecological, cultural, or religious considerations (item 16.) (Table 3.). Studies have reported that individuals choose a vegan diet for different reasons, including religious practices, health effects, animal rights, and environmental awareness (8,58). Only 46.5% of the nurses participating in the study think that the vegetarian/vegan diet leads to less carbon emissions than the diets based on animal sources (item 17.). It is sustainable because less harm is done to the environment (14,18). Nurses need to know that individuals who prefer a vegan/vegetarian diet are not only due to taste, but may have chosen it for different reasons. To provide individualized nursing care, it is necessary to evaluate the individual holistically and respect their wishes and preferences. If the attitudes and behaviors of the individual are not understood by the nurse, it may lead to missed nursing care. In addition, the nurse who does not know the nutritional differences may cause stress while providing care.

The study has some limitations. A valid and reliable scale for the measurement of vegetarian/vegan dietary knowledge has not been found. The study is limited by the cross-sectional survey design.

In conclusion, dietary preferences, adopted by increasingly more people for different reasons, fall under the responsibility of the nurses, who are the closest healthcare professionals to patients. Nurses should keep up with up-to-date information and conduct research to accurately inform people, families, and the public about diet needs, provide care, guide the daily living of the patient, and form a basis for evidence-based practices.

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Evaluation of disaster medicine knowledge levels and e-learning attitudes among prehospital healthcare personnel: A case study of Istanbul

Hastane öncesi sağlık personelinin afet tıbbı bilgi düzeyi ve e-öğrenme tutumlarının değerlendirilmesi: İstanbul örneği

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Abstract

Aim: The aim of this study is to evaluate the disaster medicine knowledge level of prehospital healthcare personnel, identify their educational expectations, and determine their attitudes toward e-learning.

Methods: This cross-sectional study was conducted between February 1 and March 31, 2023. The population of the study consisted of 3817 personnel working in the Istanbul Provincial Ambulance Service, and the sample consisted of 384 personnel. Participants were administered a survey including the Personal Information Form, the Attitude Towards E-learning Scale, and the Disaster Medicine Knowledge questionnaire through face-to-face data collection method.

Results: Of the 384 participants, 119 were Emergency Medical Technicians (EMTs), 241 were paramedics, and 24 were physicians. The average disaster medicine knowledge level was 68.15±14.06, and the average attitude towards e-learning level was 26.69±8.42. Of the participants, 52.1% (n=200) had a low level of disaster medicine knowledge, while 47.9% (n=184) had a high level of knowledge. The majority of participants (n=221, 64.8%) preferred to receive disaster medicine training online. Participants who expressed a desire for disaster medicine training had higher attitudes toward e-learning compared to those who did not (28.43±7.93 vs. 23.74 ± 8.39; p < 0.001).

Conclusion: This study found that the majority of prehospital healthcare personnel had low levels of disaster medicine knowledge, but high attitudes towards e-learning. Developing an online training program tailored to current developments and needs in disaster medicine could systematically prepare prehospital healthcare personnel for their disaster response roles. Making this training a mandatory part of in-service education could enhance the knowledge levels and confidence in personal competence of personnel with lower knowledge levels.

Keywords: Disaster medicine; education; emergency medicine; learning; paramedics

Öz

Amaç: Bu çalışmanın amacı, hastane öncesi sağlık personelinin afet tıbbı bilgi düzeyini değerlendirmek, eğitim beklentilerini belirlemek ve e-öğrenmeye yönelik tutumlarını saptamaktır.

Yöntemler: Bu kesitsel çalışma 1 Şubat ve 31 Mart 2023 tarihleri arasında gerçekleştirilmiştir. Çalışmanın evrenini İstanbul İl Ambulans Servisi'nde çalışan 3817 personel, örneklemini ise 384 personel oluşturmuştur. Katılımcılara yüz yüze veri toplama yöntemi ile Kişisel Bilgi Formu, E-öğrenmeye Yönelik Tutum Ölçeği ve Afet Tıbbı Bilgi Anketi uygulanmıştır.

Bulgular: 384 katılımcının 119'u acil tıp teknisyeni, 241'i paramedik ve 24'ü doktordu. Afet tıbbı bilgi düzeyi ortalaması 68.15±14.06, e-öğrenmeye yönelik tutum düzeyi ortalaması 26.69±8.42 olarak bulundu. Katılımcıların %52,1'i (n=200) düşük düzeyde afet tıbbı bilgisine sahipken, %47,9'u (n=184) yüksek düzeyde bilgiye sahiptir. Katılımcıların çoğunluğu (n=221, %64.8) afet tıbbı eğitimini çevrimiçi olarak almayı tercih etmiştir. Afet tıbbı eğitimi talep eden katılımcılar, talep etmeyenlere kıyasla e-öğrenmeye yönelik daha yüksek tutum sergilemiştir (28.43±7.93 vs. 23.74±8.39; p < 0.001).

Sonuç: Bu çalışma, hastane öncesi sağlık personelinin çoğunluğunun düşük afet tıbbı bilgi düzeyine sahip olduğunu, ancak e-öğrenmeye yönelik yüksek tutum sergilediğini göstermiştir. Afet tıbbındaki güncel gelişmelere ve ihtiyaçlara göre tasarlanmış bir çevrimiçi eğitim programının geliştirilmesi, hastane öncesi sağlık personelini afet müdahale rollerine sistematik bir şekilde hazırlayabilir. Bu eğitimin hizmet içi eğitimin zorunlu bir parçası haline getirilmesi, bilgi düzeyi düşük olan personelin bilgi düzeylerini ve kişisel yeterliliklerine olan güvenlerini artırabilir.

Anahtar Sözcükler: Acil tıp; afet tıbbı; eğitim; öğrenme; sağlık görevlileri

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INTRODUCTION

Disasters are events that can be natural, human-induced, or a combination of both, disrupting the normal functioning of society and causing numerous economic and physical losses that are difficult to manage with local resources (1). To effectively manage these events, a comprehensive understanding of disaster medicine is essential. Disaster medicine is a rapidly evolving field, where prehospital healthcare personnel play a pivotal role (2). These personnel must be adequately prepared to respond and deliver medical care to disaster victims. However, the level of disaster medicine knowledge among prehospital healthcare personnel can vary significantly depending on their education and experience. While some may have received extensive education and participated in numerous disaster drills, others might have limited training and experience in this area (3). This lack of education and experience can lead to challenges that complicate medical interventions, thereby significantly impacting the overall quality of care provided to disaster victims (4). Therefore, it is crucial for prehospital healthcare personnel to possess the necessary knowledge and skills to respond effectively to disasters (5). Although the World Medical Association (WMA) and the World Association for Disaster and Emergency Medicine (WADEM) have advocated for the inclusion of disaster medicine in medical education curricula, current educational programs often lack a comprehensive curriculum and standardization (6,7).

E-learning presents a practical solution for overcoming challenges in disaster medicine education, offering numerous significant advantages (8-10). One major benefit of e-learning is that it allows prehospital healthcare personnel to learn at their own pace and in a convenient location. Additionally, e-learning can result in significant cost savings compared to traditional training programs, as it eliminates the need for physical classrooms and instructors (11). This is particularly crucial for prehospital healthcare personnel working in remote areas who may not have access to conventional educational programs. Moreover, e-learning platforms offer a variety of resources such as videos, simulations, and interactive modules that help prehospital healthcare personnel understand complex concepts and gain practical experience in a safe environment (12). Another advantage of e-learning is its potential to standardize training programs. E-learning platforms can deliver a uniform and comprehensive curriculum that is continuously updated to reflect the latest research findings and best practices. This ensures that prehospital healthcare personnel have access to up-to-date and accurate information, enabling them to acquire the necessary knowledge and skills to respond effectively to disasters.

Improving the knowledge and skills of pre-hospital healthcare personnel and standardizing disaster medicine training programs are vital for effective disaster response. Indeed, insufficient disaster medicine knowledge among these healthcare personnel can complicate the provision of health services during disasters. Therefore, in-service training should be conducted to reduce the vulnerabilities of this personnel to emergencies and disasters and to enhance their personal preparedness (13-15). However, the findings indicate that there are limited studies in the literature assessing the level of disaster medicine knowledge in some provinces, and none that analyze it in conjunction with attitudes toward e-learning. Specifically, there is no research focusing on Istanbul. Therefore, the objective of this study is to assess the disaster medicine knowledge levels of prehospital healthcare personnel in Istanbul and to determine their expectations and attitudes towards e-learning-based training. The findings of this study are hoped to contribute to the development of strategies to enhance the effectiveness of disaster medicine training and represent a significant step towards improving the preparedness of healthcare personnel in Istanbul for disasters.

MATERIAL AND METHODS

Study design and participants

This cross-sectional study was conducted between February 1 and March 31, 2023. The study population comprised 3817 personnel, including emergency medical technicians (EMTs), paramedics, and physicians employed at the Istanbul Provincial Ambulance Service. A simple random sampling method was used to select the study sample. The minimum required sample size was calculated to be 349 using the known population sample calculation formula (16). To ac-

count for potential data loss, the final sample size was increased by 10%, resulting in a total of 384 personnel included in the study. The inclusion criteria were as follows: working in Istanbul, working as a physician, EMT, or paramedic, and volunteering to participate in the study. Individuals who did not meet the inclusion criteria and those who did not agree to participate voluntarily were excluded from the study.

Data collection

A survey consisting of three parts was administered to the participants through a face-to-face survey method. The informed consent form, which included information about the aim of the study, the importance of answering the questions sincerely and honestly, and assurances that their responses would be kept confidential, was provided to the participants in person. Additionally, participants were informed that they had the autonomy to discontinue their participation in the study at any given moment. After reading the informed consent form, the participants were invited to participate in the research verbally and in writing confirming their agreement to partake in the study. Those who agreed to the informed consent form then filled in the survey provided by the researchers in a face-to-face setting. The completion of the survey took approximately 25 minutes, depending on the speed at which the participants answered the questions. Participants were able to ask questions and seek clarification from the researchers during the process, ensuring a thorough understanding of the study's requirements.

Measurement tools

The first section of the survey included questions related to personal information. These questions covered age, gender, education level, unit of employment, length of service, previous disaster medicine education, interest in receiving disaster medicine education, and preferred method for receiving disaster medicine education.

The second section comprised 25 multiple-choice questions designed to assess the knowledge level of disaster medicine. Since there is no valid and reliable measurement tool developed to evaluate disaster medicine knowledge level in the literature, the disaster medicine questions were created by the researchers based on previous studies and the Didactic Course of the European Master Program in Disaster Medicine (17-22). In our study, 25 multiple-choice questions were prepared to assess the level of knowledge in the field of disaster medicine. Each question includes four answer options, and the correct answer is worth 4 points. Using this system, the total score is calculated out of 100 points. The reason for using a 100-point scale is to facilitate calculations and clearly express the results. In the literature, similar studies have established a cut-off point or median value of 70 points (3,18). In this study, a cut-off point of 70 points was also used to classify participants' knowledge levels as sufficient (70 and above) or insufficient (below 70). The purpose of selecting this cut-off point is to ensure consistency with the literature and to facilitate comparative analyses.

The third section contained 9 questions evaluating attitudes toward e-learning. The Attitude Towards E-learning Scale (ATELS) was developed by Zabadi and Al-Alawi (2016) and adapted into Turkish by Aydın, Şahin & Kulakaç in 2022 (23,24). The scale consists of 11 items on a 5-point Likert scale ranging from "strongly agree-5" to "strongly disagree-1". The 9th item is reverse-scored, while the others are scored positively. The scores obtained from the scale range between 9 and 45, with higher scores indicating a more positive attitude towards e-learning. The Turkish validation and reliability study of ATELS determined the Cronbach's alpha reliability coefficient to be 0.913.

Statistical analyses

Statistical analyses was performed using SPSS version 25 (IBM Corp, Armonk, NY). The normality of the variables was assessed using the Kolmogorov-Smirnov test. Categorical data were presented as frequencies and percentages, while continuous data were expressed as means and standard deviations. An independent samples t-test was employed to compare differences between two groups, and Analysis of Variance (ANOVA) was used to compare differences among three or more groups. To identify which groups were responsible for significant differences, the LSD posthoc test was applied. The level of statistical significance was set at $p < 0.05$.

Ethical consideration

The study was approved by the Ethics Committee of the University of Health Sciences (date: 28.12.2022, decision no: 14371). Additionally, permission to conduct the study was obtained from the Istanbul Provincial Directorate of Health with reference number E-15916306-604.01.01.01 on February 15, 2023. Participants were informed about the aim and content of the study, and written informed consent was obtained from all participants prior to their involvement in the study.

RESULTS

Demographic information of prehospital healthcare personnel

Among the participants, the majority were paramedics (62.8%), followed by EMTs (31%) and physicians (6.2%). The age distribution revealed that the largest age group was 26-31 years old (37.8%). Gender distribution was relatively balanced, with a slightly higher percentage of males (57.3%). Most participants were employed in emergency medical service stations, with notable differences in the length of service; 39.5% of EMTs had over 16 years of service, whereas only 9.6% of paramedics and 4.2% of physicians had similar tenure. A significant proportion (44.5%) of the participants had received disaster medicine education previously, with university education being the most common source (42.1%). The majority expressed a preference for receiving disaster medicine education through online courses (68.1%).

Interest in further disaster medicine education is notably high, with 89.9% of EMTs, 88.4% of paramedics, and 87.5% of physicians expressing interest. The preferred method for receiving this education is predominantly online courses, favored by 65.4% of EMTs, 68.1% of paramedics, and 71.4% of physicians (Table 1). Regarding preferred topics for disaster medicine education, "search and rescue" emerged as the most commonly preferred topic (86%), whereas "disaster research and epidemiology" was the least preferred topic (39%), as illustrated in Figure 1.

Disaster medicine knowledge level of prehospital healthcare personnel

Table 2 presents the questions used to evaluate the disaster medicine knowledge level and the details of the answers provided by prehospital healthcare personnel. None of the participants answered all the questions correctly, and no single question was answered correctly by all participants. The question with the highest number of correct answers was Q9, which addressed infectious diseases, correctly answered by 93% (n=337) of the participants. In contrast, Q22, concerning the Simple Triage and Rapid Treatment (START) system, received the lowest number of correct answers, with only 32.3% (n=124) of participants answering correctly. Q9, Q11, Q12, Q13, Q21, Q23, and Q25 were answered correctly by all physicians. The most frequently incorrectly answered question varied by professional role: EMTs struggled most with Q15 (communication and command), paramedics with Q3 (terrorism attack), and physicians with Q17 (legal legislation).

The mean disaster medicine knowledge score was 66.05 ± 13.53 (ranging from 36.00 to 92.00) for EMTs, 71.13 ± 12.61 (ranging from 24.00 to 92.00) for paramedics, and 67.00 ± 8.84 (ranging from 56.00 to 84.00) for physicians. Among all participants, 200 (52.1%) had a low level of disaster medicine knowledge, while 184 (47.9%) had a high level of disaster medicine knowledge. Regarding occupational groups, 37.8% (n=45) of the EMTs, 55.2% (n=133) of the paramedics, and 25% (n=6) of the physicians were found to have a high level of disaster medicine knowledge.

There was a significant relationship between disaster medicine knowledge level and several factors ($p < 0.05$). Firstly, participants aged 31 and over scored higher than those aged 20-25 (71.81 ± 11.36 vs. 67.10 ± 14.87; $p = 0.011$). Secondly, individuals with associate degrees (69.29 ± 12.51), bachelor's degrees (70.41 ± 10.20), and postgraduate degrees (75.65 ± 18.91) scored higher than high school graduates (56.52 ± 15.78; $p < 0.001$). Additionally, those working in Emergency Medical Service Stations (71.82 ± 12.35) scored higher than those in Patient Transport Units (66.66 ± 11.18) and Administrative Units (63.55 ± 15.64; $p < 0.001$). Regarding years of experience, participants with 6-10 years of experience scored higher than those with less than a year of experience (71.09 ± 12.92 vs. 61.76 ± 14.60; $p < 0.001$), and those with 11-15 years of experience scored higher than both those with less than a year and those with 1-5 years of experience (74.61 ± 8.89 vs. 68.00 ± 12.80; $p < 0.001$). Paramedics scored

Table 1. Demographic information of participants

Variables	EMTs (n=119)	Paramedics (n=241)	Physicians (n=24)	p
Age				
20 – 25	29 (24.4)	96 (39.8)	4 (16.7)	
26 – 31	21 (17.6)	110 (45.7)	14 (58.3)	***<0.001*********
> 31	69 (58.0)	35 (14.5)	6 (25.0)	
Gender				
Male	62 (52.1)	140 (58.1)	18 (75.0)	0.108*
Female	57 (47.9)	101 (41.9)	6 (25.0)	
Education level				
High school degree	23 (19.3)	0	0	
Associate degree	53 (44.5)	151 (62.7)	0	***<0.001*********
Bachelor's degree	38 (31.9)	75 (31.1)	21 (87.5)	
Postgraduate degree	5 (4.2)	15 (6.2)	3 (12.5)	
Unit of employment				
Emergency medical service station	57 (47.9)	132 (54.8)	11 (45.8)	
Emergency call center	32 (26.9)	60 (24.9)	11 (45.8)	0.205**
Patient transport unit	15 (12.6)	28 (11.6)	2 (8.3)	
Administrative unit	15 (12.6)	21 (8.7)	0	
Length of service				
< 1 year	7 (5.9)	15 (6.2)	3 (12.4)	
1 – 5 years	27 (22.7)	121 (50.2)	7 (29.2)	
6 – 10 years	18 (15.1)	53 (22.0)	13 (54.2)	***<0.001*********
11 – 15 years	20 (16.8)	29 (12.0)	0	
≥ 16 years	47 (39.5)	23 (9.6)	1 (4.2)	
Have you ever received disaster medicine education before?				
Yes	42 (35.3)	120 (49.8)	9 (37.5)	***0.026****
No	77 (64.7)	121 (50.2)	15 (62.5)	
If so, where did you receive disaster medicine education?				
University education	14 (33.3)	55 (45.8)	3 (33.3)	
NGOs	12 (28.6)	36 (30.0)	2 (22.2)	0.363**
Online course	3 (7.1)	11 (9.2)	1 (11.1)	
In-service training	13 (31.0)	18 (15.0)	3 (33.3)	
Do you want to receive disaster medicine education?				
Yes	107 (89.9)	213 (88.4)	21 (87.5)	0.890*
No	12 (10.1)	28 (11.6)	3 (12.5)	
How would you like to receive disaster medicine education?				
Traditional classroom	37 (34.6)	68 (31.9)	6 (28.6)	0.823*
Online courses	70 (65.4)	145 (68.1)	15 (71.4)	

EMT: Emergency Medical Technician, NGOs: Non-governmental Organizations, n: Number, %: Percentage

* Independent t-test, ** One-way ANOVA.

Table 2. Comparison of disaster medicine knowledge questions by professional role

No	Questions	EMT (n, %)	Paramedic (n, %)	Physician (n, %)	Total (n, %)
1	Crush syndrome	89 (74.8)	208 (86.3)	21 (87.5)	318 (82.8)
2	First aid	95 (79.8)	190 (78.8)	15 (62.5)	300 (78.1)
3	Terrorism attack	39 (32.8)	88 (36.5)	9 (37.5)	136 (35.4)
4	Cardiopulmonary resuscitation	55 (46.2)	157 (65.1)	15 (62.5)	227 (59.1)
5	Chemical disaster response	56 (47.1)	130 (53.9)	15 (62.5)	201 (52.3)
6	Chemical emergency response	103 (86.6)	190 (78.8)	12 (50.0)	305 (79.4)
7	Personal protective equipment	87 (73.1)	188 (78.0)	15 (62.5)	290 (75.5)
8	Radiological disaster response	57 (47.9)	135 (56.0)	9 (37.5)	201 (52.3)
9	Infectious diseases	111 (93.3)	222 (92.1)	24 (100.0)	357 (93.0)
10	Infection management	89 (74.8)	215 (89.2)	18 (75.0)	32 (83.9)
11	Psychological support	104 (87.4)	219 (90.9)	24 (100.0)	347 (90.4)
12	Public health preparedness	102 (85.7)	210 (87.1)	24 (100.0)	336 (87.5)
13	Risk management	108 (90.8)	219 (90.9)	24 (100.0)	351 (91.4)
14	Disaster management	64 (53.8)	158 (65.6)	15 (62.5)	237 (61.7)
15	Communication and command	17 (14.3)	100 (41.5)	9 (37.5)	126 (32.8)
16	Medical aid organizations	66 (55.5)	135 (56.0)	15 (62.5)	216 (56.3)
17	Legal legislation	58 (48.7)	124 (51.5)	6 (25.0)	188 (49.0)
18	Disaster preparedness	100 (84.0)	199 (82.6)	9 (37.5)	308 (80.2)
19	Incident command system	101 (84.9)	158 (65.6)	18 (75.0)	277 (72.1)
20	Incident command management	55 (46.2)	152 (63.1)	15 (62.5)	222 (57.8)
21	Logistic management	96 (80.7)	197 (81.7)	24 (100.0)	317 (82.6)
22	START triage	22 (18.5)	93 (38.6)	9 (37.5)	124 (32.3)
23	Triage coding	110 (92.4)	196 (81.3)	24 (100.0)	330 (85.9)
24	Travma patient management	87 (73.1)	196 (81.3)	9 (37.5)	292 (76.0)
25	Media and public relations	94 (79.0)	207 (85.9)	24 (100.0)	325 (84.6)

EMT: Emergency Medical Technician, START: Simple Triage and Rapid Treatment, n: Number, %: Percentage

higher than EMTs (71.13 ± 12.61 vs. 66.05 ± 13.53; p < 0.001). Lastly, prehospital healthcare personnel who had previously received disaster medicine education scored higher than those who had not received such education (71.39 ± 14.29 vs. 67.62 ± 11.44; p = 0.005).

Attitudes toward E-learning of prehospital healthcare personnel

The Attitude Toward E-learning scores were 28.57 ± 8.05 for EMTs, 27.43 ± 7.96 for paramedics, and 29.41 ± 9.69 for physicians (Table 3). A significant relationship was found between Attitudes Toward E-learning and educational level, length of service, and desire for disaster medicine education. High school graduates had significantly higher scores (35.47 ± 6.08) compared to associate degree holders (27.25 ± 7.93), bachelor's degree holders (27.41 ± 7.79), and postgraduate degree holders (29.08 ± 9.64) (p < 0.001). Those with less than one year of service had higher scores (34.20 ± 5.62) than those with 1-5 years (27.02 ± 8.77), 6-10 years (29.21 ± 8.60), and 11-15 years (26.06 ± 7.14) (p < 0.001). Personnel wishing to receive disaster medicine education scored higher (28.43 ± 7.93) than those who did not (23.74 ± 8.39; p < 0.001). Lastly, those preferring online courses had higher scores (29.27 ± 8.04) compared to those preferring traditional classroom education (26.71 ± 7.44; p < 0.001).

Table 3. Comparison of attitudes toward e-learning and disaster medicine knowledge levels of participants

Variables	DMKL		ATEL	
	Mean ± SD	p	Mean ± SD	p
Age				
20 – 25 years old	67.10 ± 14.87		28.37 ± 8.61	
26 – 31 years old	68.91 ± 11.84	***0.011***[b]	28.85 ± 8.28	0.060[b]
> 31 years old	71.81 ± 11.36		26.58 ± 7.29	
Gender				
Male	68.56 ± 13.46	0.195[a]	27.44 ± 8.15	0.190[a]
Female	70.29 ± 12.09		28.54 ± 8.03	
Education level				
High school degree	56.52 ± 15.78		35.47 ± 6.08	
Associate degree	69.29 ± 12.51	***<0.001***[b]	27.25 ± 7.93	***<0.001***[b]
Bachelor's degree	70.41 ± 10.20		27.41 ± 7.79	
Postgraduate degree	75.65 ± 18.91		29.08 ± 9.64	
Unit of employment				
Emergency medical service station	71.82 ± 12.35		28.36 ± 7.58	
Emergency call center	67.57 ± 12.64	***<0.001***[b]	28.68 ± 8.99	0.070[b]
Patient transport unit	66.66 ± 11.18		26.11 ± 8.39	
Administrative unit	63.55 ± 15.64		25.47 ± 7.44	
Length of service				
< 1 year	61.76 ± 14.60		34.20 ± 5.62	
1 – 5 years	68.00 ± 12.80		27.02 ± 8.77	
6 – 10 years	71.09 ± 12.92	***<0.001***[b]	29.21 ± 8.60	***<0.001***[b]
11 – 15 years	74.61 ± 8.89		26.06 ± 7.14	
≥ 16 years	69.01 ± 13.34		27.38 ± 6.03	
Occupational group				
EMTs	66.05 ± 13.53		28.57 ± 8.05	
Paramedics	71.13 ± 12.61	***<0.001***[b]	27.43 ± 7.96	0.298[b]
Physicians	67.00 ± 8.84		29.41 ± 9.69	
Have you ever received disaster medicine education before?				
Yes	71.39 ± 14.29	***0.005***[a]	28.48 ± 7.57	0.217[a]
No	67.62 ± 11.44		27.45 ± 8.37	
Do you want to receive disaster medicine education?				
Yes	69.10 ± 13.11	0.395[a]	28.43 ± 7.93	***<0.001***[a]
No	70.88 ± 11.18		23.74 ± 8.39	
How would you like to receive disaster medicine education?				
Traditional classroom	67.24 ± 12.48	0.063[a]	26.71 ± 7.44	***0.005***[a]
Online courses	70.00 ± 13.34		29.27 ± 8.04	

ATEL: Attitude Toward E-learning, DMKL: Disaster Medicine Knowledge Level, EMT: Emergency Medical Technician, SD: Standart Deviations.

a Independent t-test, b One-way ANOVA.

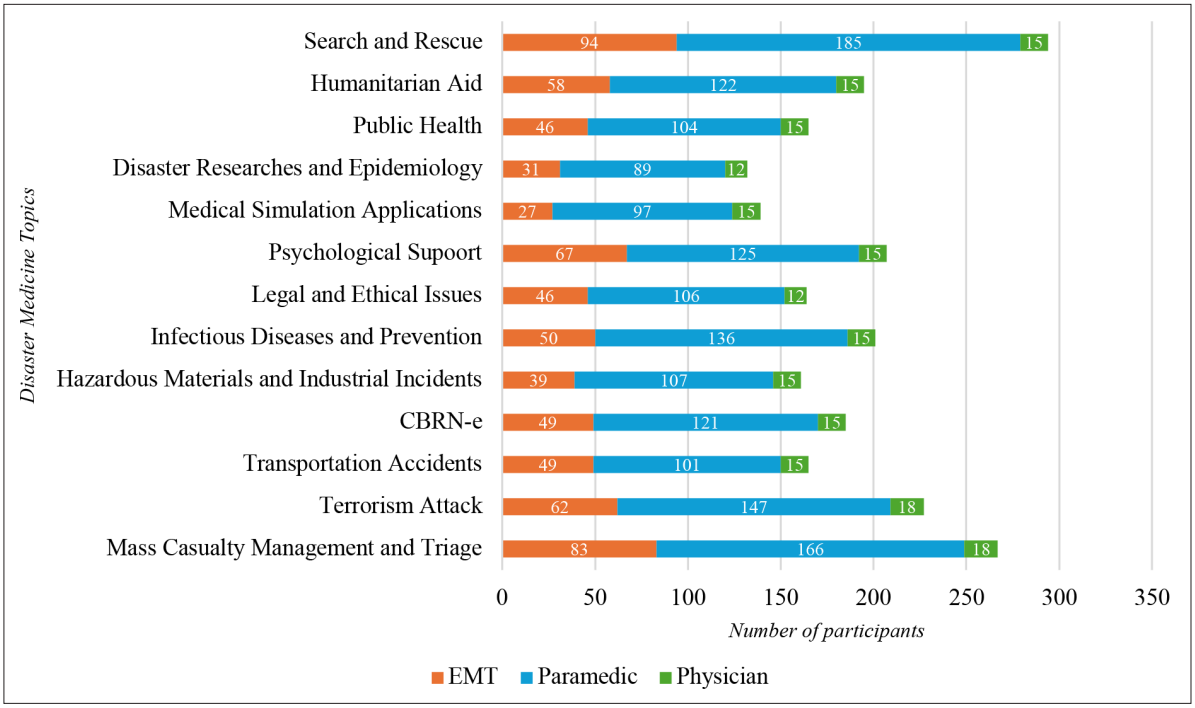

Figure 1. Distribution of participants requesting education in various disaster medicine topics
CBRN-e: Chemical, Biological, Radiological, Nuclear and Explosive

DISCUSSION

This study evaluated the disaster medicine knowledge levels and attitudes toward e-learning among prehospital healthcare personnel. The discussion section has been examined under three headings: Disaster Medicine Knowledge Levels, Attitudes Toward E-learning Levels, and Educational Expectations

Disaster medicine knowledge levels

As a result of the study, the mean disaster medicine scores, from highest to lowest, were observed among paramedics, physicians, and EMTs. Overall, it was found that more than half of the prehospital healthcare personnel possessed low levels of disaster medicine knowledge. A review of similar studies in the literature that evaluate the level of disaster medicine knowledge and educational needs of healthcare professionals reveals findings consistent with our results (20, 25-27). Additionally, a field report published about the devastating Kahramanmaraş earthquake on February 6, 2023, also indicated that healthcare workers were unprepared in terms of disaster-related knowledge and experience (28). The low levels of disaster medicine knowledge among prehospital healthcare personnel are thought to be due to insufficient coverage of disaster medicine topics in their undergraduate education and in-service training programs. Additionally, it was found that the disaster medicine knowledge level of personnel who had previously received disaster medicine education was higher compared to those who had not. This finding suggests that disaster education enhances awareness of disasters and familiarity with basic disaster-related information.

The higher disaster medicine knowledge scores observed among paramedics compared to other groups may be attributable to the fact that a significant number of paramedics have completed their undergraduate education in Emergency Aid and Disaster Management programs (29). In addition, the lower disaster medicine knowledge scores among personnel working in the patient transport unit and administrative unit, compared to those in the emergency medical service station, could be due to their primary focus on formal administrative duties, which may result in a decline in practical skills over time.

The correct responses to the question regarding the Simple Triage and Rapid Treatment (START) method

were low across all three groups. Unlike basic and advanced life support, the START method requires an assessment of the patient's level of consciousness (mental status) after the circulatory step (30). Unfortunately, it was observed that the majority of participants indicated that the assessment of consciousness should be conducted before evaluating respiration and perfusion. This is concerning given the importance of providing rapid care and effectively managing the scene of mass casualties. Additionally, the second most commonly incorrectly answered question was related to command and communication. The lack of standardization in the use of handheld radios and the variations between provinces may have contributed to prehospital healthcare personnel receiving low scores on this question (31).

Attitudes toward e-learning levels

In this study, it was found that the majority of prehospital healthcare personnel who had previously received disaster medicine education did so during their university years. Most prehospital healthcare personnel who had not received disaster medicine education expressed a desire to receive this training. This indicates their awareness of the potential need to work in disaster environments and their desire to be prepared. Furthermore, 67.4% of participants interested in receiving training reported a preference for online education. This preference has resulted in a significant difference in attitudes toward e-learning between those who favor traditional classroom education and those who prefer online education. This inclination towards digital learning platforms suggests that e-learning methods could be effectively utilized to address the current deficiencies in disaster medicine knowledge.

The positive attitude toward e-learning observed in this study aligns with findings from previous research, which highlight the advantages of e-learning in healthcare education. According to Ruiz et al. (2006), e-learning provides flexibility, accessibility, and the ability to update content rapidly, making it an effective tool for medical education (32). Additionally, Cook et al. (2008) found that e-learning is as effective as traditional learning methods in terms of knowledge gain and satisfaction among healthcare professionals (33). Furthermore, studies by Salas et al. (2012) and WHO (2015) emphasize the importance of integrating e-learning into emergency preparedness training, noting that it enhances the readiness and response capabilities of healthcare workers in disaster situations (34,35). These studies suggest that e-learning can bridge the gap in disaster medicine education by providing consistent, standardized, and easily accessible training. Given these findings, the integration of e-learning into disaster medicine education could significantly improve the preparedness of prehospital healthcare personnel. By leveraging the benefits of digital learning platforms, healthcare institutions can ensure that their staff is well-equipped to handle disaster scenarios effectively.

Educational expectations

Participants indicated that they would most like to receive education on search and rescue among the 13 educational options provided. Given that Turkey is a region with a high risk of disasters such as earthquakes and floods, this preference is not surprising (3). Following search and rescue, the most desired training topics were mass casualty management and triage, and terrorism attacks. The interest in these trainings reflects an awareness among prehospital healthcare personnel of their need to be prepared for a range of disaster scenarios, which are highly relevant to their roles. The low interest in disaster research and epidemiology, and medical simulation applications indicates a gap in the perceived relevance or importance of these topics among participants. While search and rescue, mass casualty management, and response to terrorism attacks are directly linked to immediate, hands-on disaster response, disaster research and epidemiology involve more abstract, long-term understanding and planning. The findings suggest a need to better communicate the benefits of medical simulation applications. Increasing awareness and integrating these topics into training programs could lead to more comprehensive preparedness and a more robust disaster response capability among prehospital healthcare personnel (36-38).

LIMITATIONS

This study has some limitations that should be considered when interpreting the results. Firstly, the study

sample is limited to prehospital healthcare personnel working in Istanbul. As a result, the findings may not be generalizable to prehospital healthcare personnel in other regions or countries. Another limitation is the use of a self-developed questionnaire to measure disaster medicine knowledge levels. Since there is no validated and reliable scale available in the literature for assessing disaster medicine knowledge, we had to develop our own instrument. This could affect the validity and reliability of the findings, as the questionnaire has not undergone the extensive testing and validation processes typically required for standardized measurement tools. Despite these limitations, the study also has several strengths. One key strength is the focus on prehospital healthcare personnel who are actively working in the field. Additionally, the use of a questionnaire developed based on literature and researchers' experience ensured that the measurement tool was grounded in practical and theoretical knowledge. This approach helped capture a comprehensive picture of disaster medicine knowledge.

CONCLUSIONS

In this study, the disaster medicine knowledge levels of prehospital healthcare personnel were assessed, and it was found that more than half (n=200) had a low level of disaster medicine knowledge. However, there is a strong interest in receiving disaster medicine education among these personnel. 68% of the personnel who wanted to receive disaster medicine education preferred online courses. Based on the findings of this study, it is evident that there is a need for targeted educational interventions to improve disaster medicine knowledge among prehospital healthcare personnel in Istanbul. Developing an online in-service education program for disaster medicine, tailored to current developments and needs, can systematically prepare these personnel for disaster response roles. Furthermore, making this education a mandatory component of in-service training can motivate those with lower levels of knowledge and enhance participants' confidence in their personal competencies. This will ultimately increase their effectiveness in disaster response, leading to better patient outcomes and more efficient healthcare delivery in disaster situations.

On a broader scale, similar online education programs can be adopted by prehospital care systems in other regions and countries. By addressing both immediate practical skills and broader strategic understanding, such programs can significantly improve preparedness and response capabilities globally. The integration of e-learning methods into disaster medicine education can provide consistent, accessible, and up-to-date training for healthcare personnel worldwide, enhancing their ability to respond effectively to disasters and improving overall public health resilience.

Conflict-of-interest and financial disclosure

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Anesthesia management of a pediatric patient with Wolf-Hirschhorn Syndrome: A case report

Wolf-Hirschhorn Sendromlu pediatrik bir hastanın anestezi yönetimi: Olgu sunumu

Abstract

Wolf-Hirschhorn syndrome (WHS) is a rare chromosomal anomaly caused by the deletion of the short arm of chromosome 4. The leading causes of death are aspiration pneumonia, epilepsy, and infection. In this study, we aimed to present our anesthesia experience in a patient with WHS who was scheduled for cleft palate surgery and in whom we performed total intravenous anesthesia (TIVA).

In the clinical examination of our 8-year-old patient with WHS, weighing 13 kg, who was planned to undergo cleft palate surgery. Growth retardation, cleft palate, micrognathia, epicanthus and hyptonia were present. Anesthesia induction was performed with 1 mg/kg i.v lidocaine, 2 mg/kg i.v propofol and 1 mg/kg i.v fentanyl, 0.5 mg/kg i.v rocuronium bromide. TIVA (0.5 μg/kg/min remifentanil and 75 μg/kg/min propofol i.v) was used for maintenance of anesthesia. In the perioperative period, the pulse rate was 170 beats/min for a short time. Extubation was achieved 13 minutes after the end of surgery.

We think that TIVA (Propofol, remifentanil) and C-MAC videolaryngoscope as intubation device is a reliable method in the anesthetic management of children with WHS syndrome.

Keywords: Airway management; anesthesia; laryngoscope; Wolf-Hirschhorn syndrome

Öz

Wolf-Hirschhorn sendromu (WHS) 4. kromozomun kısa kolunun silinmesiyle ortaya çıkan nadir görülen bir kromozomal anomalidir. Önde gelen ölüm nedenleri aspirasyon pnomonisi, epilepsi ve enfeksiyondur. Bu çalışmamızda WHS' lu yarık damak cerrahisi planlanan Total intravenöz anestezi (TİVA) uyguladığımız bir olguda anestezi deneyimimizi sunmayı amaçladık. WHS tanısıyla takip edilen, yarık damak cerrahisi planlanan 8 yaşında, 13 kg olan olgumuzun klinik muayenesinde, gelişme geriliği, yarık damak, mikrognati, epikantus ve hiptoni mevcuttu. Anestezi indüksiyonunda 1mg/kg i.v lidokain, 2mg/kg i.v propofol ve 1mcg/kg i.v fentanil, 0.5 mg/kg i.v rocuronium bromide uygulandı. Anestezi idamesinde TİVA (0.5 μg/kg/dk remifentanil ve 75 μg/kg/dk propofol i.v) kullanıldı. Perioperatif dönemde nabız kısa süreli 170/atım/dk oldu. Cerrahi bitiminden 13 dk sonra ekstübasyon sağlandı.

WHS sendromlu çocukların anestezi yönetiminde TİVA (Propofol ,remifentanil)' nın ve entübasyon cihazı olarak C-MAC videolaringoskopun güvenilir bir yöntem olduğunu düşünüyoruz.

Anahtar Sözcükler: Anestezi; havayolu yönetimi; laringoskop; Wolf-Hirschhorn sendromu

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INTRODUCTION

Wolf-Hirschhorn syndrome (WHS) is a rare chromosomal abnormality characterized by deletion of the short arm of the 4th chromosome especially in the 4p16.3 region (1).

Clinical findings are usually observed in the early period of life. Short upper lip, wide mouth, craniofacial anomalies (hypertelorism, protruding glabella, depressed nasal root, and micrognathia), severe mental and developmental retardation, cleft palate and lip among midline defects, congenital heart defects (atrial septal defect, patent ductus arteriosus, and pulmonary stenosis), skeletal and ocular anomalies, hypotonia and epilepsy are the most common anomalies (2,3).

The incidence of WHS is 1:50,000-20,000. The female/male ratio is 2:1. The mortality rate in the first two years is 17-30%. The leading causes of death are aspiration pneumonia, epilepsy, and infection (4).

Many surgical interventions are required because of congenital anomalies accompanying WHS cases. Increased incidence of malignant hyperthermia (MH), difficult airway, and difficulty in intubation due to abnormal oral structure and craniofacial anomalies make anesthesia management specific (3).

In this study, we aimed to present our anesthesia experience in a patient with WHS in whom we performed TIVA for cleft palate surgery.

CASE REPORT

Our 8-year-old, 13 kg patient, who was followed up with the diagnosis of WHS and planned for cleft palate surgery, had a normal vaginal birth as the 6th child of a 34-year-old mother, weighing 1600 g delivery. He was operated due to intracranial hemorrhage on the 2nd postpartum day and stayed in the intensive care unit for 40 days. Clinical examination revealed growth retardation, cleft palate, micrognathia, epicanthus, hypertelorism, pesechinovarus, and hyptonia. His history included mental retardation, epilepsy, secundum Atriyal Septal Defekt (ASD) and frequent pneumonia attacks. When the laboratory values of the patient were examined, urine, biochemical and hemogram values were found to be within normal limits.

After explaining the procedure and possible risks to the patient's relatives, written consent was obtained for anesthesia.

The patient was placed on the operating table and standard monitoring was performed with electrocardiography (ECG), heart rate (HR), peripheral oxygen saturation (SpO_2) and noninvasive blood pressure (NIBP). The patient was preoxygenated with 4 L/min 100% O_2 via nasal cannula. Initial vital signs were within normal limits (heart rate 115/min, NIBP: 92/55 mmHg and SpO_2: 95%). Temperature monitoring was also performed. Initial body temperature was 36.7°C.

For induction of anesthesia, 1 mg/kg IV lidocaine, 2 mg/kg IV propofol and 1 mcg/kg IV fentanyl were administered. Upon no difficulty in mask ventilation, IV rocuronium bromide was administered at 0.6 mg/kg as a muscle relaxant. Mallampati score was III in preoperative evaluation. There was no restriction in neck movements. Intubation conditions were optimized by using a shoulder roll. After adequate muscle relaxation was achieved, intubation was achieved on the first attempt with a C-Mac Videolaryngoscope (number 2 bleyd) and an endotracheal tube with a number 5.5 cuff and a spiral stylet. After intubation, ventilation was provided with tidal volume (6-8 ml/kg) and $EtCO_2$ value of 35-40 mmHg in 50% O_2-air mixture.

Surgery lasted a total of 3.5 hours. Vital signs were stable for the first 60 minutes. HR suddenly increased up to 170/min/beat. As a result of volume support and deepening of anesthesia, HR (90-110 min/beat) returned to normal limits. $EtCO_2$ was 35-48 mmHg, SpO_2 was 95-97, and temperature was around 34.7-36.7 Co. At the end of surgery, neostigmine 0.04 mg/kg and atropine 0.02 mg/kg were administered i.v. to reverse neuromuscular blockade. Extubation was achieved 13 minutes after the end of surgery successfully. She was followed up in PACU for 1 hour. Postoperative analgesia was provided with 15 mg/kg i.v paracetamol in patients with (VAS) >5.

When the modified Aldrete score was >9, the patient was transferred to the pediatric intensive care unit (5). The patient was visited in the relevant service at 12-24 hours. In the follow-up, it was observed that vital signs were stable and there was no respiratory distress.

DISCUSSION AND CONCLUSION

WHS is a rare genetic disorder characterized by deletion of the distal portion of the short arm of chromosome 4 (4p-) and is associated with many anomalies. Anesthetic management in WHS patients has many difficulties. Cleft lip/palate, gastroesophageal reflux, muscular hypotonia, skeletal anomalies (scoliosis), malignant hyperthermia, perioperative respiratory complications, micrognathia, oral dental anomalies, congenital heart defects are the main causes (2).

There are some case reports in the anesthesia literature indicating an association between malignant hyperthermia and WHS. Ginsburg R et al. used halothane and succinylcholine as anesthetics in a 21-month-old child who underwent surgery for cleft palate (6). The rectal temperature increased to 38.5 C° at the 7th minute following induction and to 42.2 C° in the following period. This was evaluated as malignant hyperthermia. The temperature rise was taken under control with necessary interventions (6). In a study by Jae Ho Cho et al. in a 33-month-old male pediatric patient scheduled for tympanoplasty and myringotomy, the entry body temperature was measured as 36.2 C°. At the end of the surgical operation, the body temperature was 37.9 C° in the recovery room and 39 C° at the 7th hour postoperatively. Body temperature was controlled with antipyretics and phenobarbital. In the initial evaluation, persistent temperature increase was evaluated as delayed malignant hyperthermia. On detailed examination, it was evaluated as upper respiratory tract infection and the diagnosis of malignant hyperthermia was excluded (7).

Despite the case examples of malignant hyperthermia in the literature. There are also WHS cases in which inhalation anesthetics and succinylcholine were used safely (8). The relationship between WHS and malignant hyperthermia has not been fully proven. In anesthesia practice, propofol, barbiturates, benzodiazepines, narcotics and non-depolarizing muscle relaxants are known as safe anesthetic agents in terms of malignant hyperthermia (9).

In our case, we did not use inhalation anesthetics and succinylcholine to avoid the risk of malignant hyperthermia. In addition, our patient had a history of epilepsy. Therefore, we preferred the use of TIVA (propofol and remifentanil) as an anesthetic because of the safer epileptogenic potential of propofol compared to sevoflurane anesthesia and the antiemetic properties of propofol.

In WHS, cleft palate, cleft lip, micrognathia, defects in oral dentition and skeletal anomalies cause difficult airway management and intubation difficulties (2,10,11).

Therefore, necessary preliminary preparations should be made for difficult airway management in patients with WHS. In our case, the presence of cleft palate was hypothesized to cause intubation difficulties. Care should be taken to administer muscle relaxants in patients who cannot be ventilated after induction of anesthesia (7). In our patient, there was no difficulty in ventilation after induction and we proceeded to the intubation stage. We prepared for difficult airway (flexibil bronchoscopy and C-MAC videolaryngoscope) before induction of anesthesia. We performed intubation on the first attempt with the C-MAC videolaryngoscope without difficulty.

The incidence of hypotonia in WHS cases is >75%. In the presence of hypotonia, care should be taken in the dose of muscle relaxant and the choice of the agent to be used. It is known that the use of succinylcholine is a risk factor for malignant hyperthermia (12). Non-depolarizing muscle relaxants are used more frequently. However, in the presence of hypotonia, the dose of NMBAs should be reduced as it may cause prolonged extubation and recovery time. (13, 7, 14).

In our case, rocuronium from NMBAs was safely used as a neuromuscular agent. Alternatively, there are cases in the literature in which intubation was performed without the use of muscle relaxant (8).

Muscle hypotonia is one of the reasons provoking gastroesophageal reflux in WHS patients. Because of the risk of aspiration during induction and in the postoperative period, it is important to prepare the aspirator and pay attention to the fasting period. In some publications in the literature, rapid sequence intubation is recommended against the risk of aspiration (2).

Congenital heart defects are observed in 50% of WHS cases. The most common form is atrial septal defects (27%) (3). Our patient had a secundum ASD. During the operation, HR: 170 beats/min during operation. Therefore, the patient should be closely moni-

tored to ensure hemodynamic stability and the patient should be prepared for possible deterioration in hemodynamics and intervened in a timely manner.

In conclusion; we think that TIVA (Propofol, remifentanil) and C-MAC videolaryngoscopy as an intubation device is a reliable method in the anesthetic management of children with WHS syndrome.

Conflict-of-interest and financial disclosure

The author declares that he has no conflict of interest to disclose. The author also declares that he did not receive any financial support for the study.

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Artificial systems for the diagnosis of Meniere's disease: A review

Meniere hastalığının teşhisinde Yapay Sistemler: Bir Derleme

Abstract

Meniere's Disease (MD) is a complex, multifactorial inner ear disorder characterized by episodes of spontaneous vertigo, unilateral fluctuating sensorineural hearing loss, aural fullness, and tinnitus. Although endolymphatic hydrops (EH) is often considered a histopathological hallmark of MD, the 2015 diagnostic guidelines emphasize that its presence is not essential for diagnosis. Magnetic Resonance Imaging (MRI) has emerged as a valuable tool for detecting EH, though it remains in a developmental phase.

Recently, artificial intelligence (AI)—a rapidly advancing field that simulates human cognitive processes—has garnered significant attention in the study of MD. This paper reviews the current literature on the application of AI and deep learning in the diagnosis, monitoring, and treatment of Meniere's Disease. Our review encompasses seven relevant studies sourced from PubMed, Scopus, Web of Science, and ScienceDirect. Among these, four articles focus on the use of MRI to detect and quantify endolymphatic hydrops. We present these findings within the context of a development trajectory, discuss the limitations of current methodologies, and outline potential avenues for future advancements.

Keywords: Artificial intelligence; deep learning; endolymphatic hydrops; machine learning; MicroRNA

Öz

Meniere Hastalığı (MH) spontan vertigo atakları, tek taraflı dalgalanan sensörinöral işitme kaybı, işitsel dolgunluk ve tinnitus ile karakterize karmaşık, multifaktöriyel bir iç kulak hastalığıdır. Endolenfatik hidrops (EH) genellikle MH'nin histopatolojik bir özelliği olarak kabul edilse de, 2015 tanı kılavuzları bunun varlığının tanı için gerekli olmadığını vurgulamaktadır. Manyetik Rezonans Görüntüleme (MRG), gelişim aşamasında olmasına rağmen EH'yi tespit etmek için değerli bir araç olarak ortaya çıkmıştır.

Son zamanlarda, insan bilişsel süreçlerini simüle eden ve hızla ilerleyen bir alan olan yapay zeka (YZ), MH çalışmalarında önemli bir ilgi görmüştür. Bu makale, Meniere Hastalığı'nın teşhisi, izlenmesi ve tedavisinde YZ ve derin öğrenmenin uygulanmasına ilişkin mevcut literatürü gözden geçirmektedir. İncelememiz PubMed, Scopus, Web of Science ve Science Direct'ten elde edilen yedi ilgili çalışmayı kapsamaktadır. Bunlar arasında dört makale, endolenfatik hidropsu tespit etmek ve ölçmek için MRG kullanımına odaklanmaktadır. Bu bulguları bir gelişim yörüngesi bağlamında sunuyor, mevcut metodolojilerin sınırlamalarını tartışıyor ve gelecekteki ilerlemeler için potansiyel yolları özetliyoruz.

Anahtar Sözcükler: Derin öğrenme; endolenfatik hidrops; makine öğrenmesi; Meniere hastalığı; MikroRNA; yapay zeka

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INTRODUCTION

Meniere's disease (MD) is a multifactorial inner ear disorder characterized by episodes of spontaneous vertigo attacks, unilateral fluctuating sensorineural hearing loss, aural fullness, and tinnitus. The disease has a prevalence of approximately 34-190 per 100.000 (1). Prevalence shows uncertainty due to the difficulty faced when diagnosing the disease. The disease is hard to diagnose, especially in the early stages since not all the symptoms can be examined, and also it is difficult to distinguish from related disorders such as migraine associated vertigo (2,3).

Pathophysiology of MD is defined by progressive cochlear and vestibular dysfunction, yet the cause of the mechanism is not clearly described (4). Histopathologic findings include distension of scala media and bulging of Reissner's membrane into scala vestibuli, known as endolymphatic hydrops (EH) (5). EH is considered to be a histological marker for MD but is not essential for diagnosis according to 2015 guidelines (1, 6). EH can be detected by inner ear tests and MRI, therefore MD diagnosis can be made with clinical symptoms combined with inner ear tests and MRI. No specific test for MD exists.

The formation of EH in the inner ear and the function of cochlea, saccule, utricle, and semicircular canals (SCC) can be examined with an inner ear test battery. These tests enable the localization of EH and extent of damage it causes on inner ear structures. Test battery includes audiometry, vestibular-evoked myogenic potential (VEMP), and caloric tests. Audiometry is used to measure the hearing level of the patient. VEMP tests consist of cVEMP and oVEMP and are used to determine utricular and saccular function. cVEMP is used to examine saccular hydrops, while oVEMP is used to examine utricular hydrops. A caloric test, in which the ear is irrigated with an airflow, is found to be an effective way to determine the SCC function (7).

MRI is also a useful method to determine the presence of EH, yet it is still in the development stage (3). Visualization of EH with MRI allows physicians to detect EH in living patients, even in asymptomatic ones. This technique was used on patients first when Nakashima and colleagues developed by using intratympanic Gadolinium injection (8). It makes detecting EH in living patients possible but has handicaps. It is an invasive technique and requires a long waiting time. Then Naganawa developed an IV Gadolinium-enhanced MRI technique, which is non-invasive with a shorter waiting time (9). Both methods have been studied since then. Recently, artificial intelligence has been used to evaluate MRI findings.

Artificial intelligence (AI) is a new discipline that uses technology to develop and evaluate theories, methods, and systems in a similar way to human intelligence (10). In recent years, artificial intelligence has become increasingly widespread in the field of healthcare. AI systems work fast and effectively, create more time for physicians, and lower the workload. AI has a wide range of applications including radiology, endoscopy, surgery, and drug production (10). Furthermore, the development of deep learning brought a new insight in AI usage. Deep learning can transform large inputs into various kinds of outputs, evaluates, classifies, and create multiple layered connections between them, without a human direction. The system derives its own rules from the data set itself and shows great performance with large data sets (11). Since the healthcare industry generates vast amounts of data each and every day, using deep learning to evaluate the patients' data could save time, money, and human effort. Consequently, research about the usage of AI and deep learning mechanisms in Meniere's disease gained acceleration over the past few years.

The usage of AI and deep learning in audiology has aimed to enable automated criteria for diagnosis and function as a support system for clinical decisions (12). For instance, in 2021 van der Lubbe et al. developed a machine learning system that used radiomics from MRI scans to distinguish the patients from the control group (13). Also, Gürkov et al. volumetrically quantified endolymph and perilymph spaces and created three-dimensional EH images with AI, to provide a standardized basis for therapeutic monitoring of MD (14). Lastly, but not limited to, in 2023 Bragg et al. applied machine learning algorithms to subjective visual vertical and VEMP tests, in order to establish an algorithm to predict acute versus chronic MD (15). These studies and several more, expressed both the effectiveness and weaknesses of machine learning procedures. This review aims to systematically assess the performance of AI and machine learning processes in the diagnosis of Meniere's Disease.

MATERIAL AND METHODS

A systematic literature search in five databases (PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect) was conducted. All relevant studies related to Meniere disease diagnosis via artificial intelligence methods are reviewed as shown in Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram was used to choose articles. The following terms were used to search the five databases: "Meniere's disease AND artificial intelligence, Meniere's disease and deep learning, Meniere's disease and machine learning, diagnosis of Meniere's disease OR Meniere's disease and artificial intelligence". Ethics committee approval is not required for this study.

Inclusion and exclusion criteria

First, the titles and abstracts of the articles were scanned. Then, the articles were examined in detail and it was determined whether they met the inclusion criteria. Studies using artificial intelligence in the diagnosis of Meniere's disease and those published in English were included. Studies related to Meniere's disease and artificial intelligence, but not on topics other than the diagnosis of Meniere's disease, and those not in English were excluded from the review.

Data extraction

A general search was made from the title and abstract, and only those related to Meniere's disease and artificial intelligence were examined. All potentially relevant studies (n=31) were retrieved. Their titles and abstracts were recorded in an Excel file. Among these articles, there were studies related to artificial intelligence in diseases with sensory loss such as Meniere's disease. In these articles, only articles that included Meniere's disease and did not additionally examine any other diseases with sensory loss were included in the study. Other articles were excluded from the study (n=11). Two of these were related to the classification of imaging in patients with Meniere's disease, meaning it was not used for diagnostic purposes. Two of them were patient support programs developed using artificial intelligence. These four articles were excluded and the other seven were included (n=7). The articles were examined in detail and certain data were extracted. These extracted data were: "Publication year, purpose, method, sample size, artificial intelligence model used, accuracy, specificity, sensitivity".

RESULTS

We reviewed 7 studies that met our search criteria. The distribution of studies by country was as follows: 2 each from South Korea and the USA, and 1 each from the Netherlands, Germany, and Switzerland. Four of the articles are about radiological imaging, one is about the use of Transient-evoked otoacoustic emission (TEOAE) and Pure tone audiometry in the diagnosis of Meniere's disease, one is about the importance of MicroRNA in the diagnosis of Meniere's disease, and another article is about the role of vestibular tests in Meniere's disease as summarized in Table 1.

In the study published by Gurkov, R. et al. in 2014, it was aimed to evaluate the diagnosis, treatment, and disease process of Meniere by measuring the endolymph and perilymph volumes by performing MRI on 16 unilateral Meniere's disease patients (14). They measured the endolymph/total fluid area by applying a machine learning algorithm (Random Forest Classification model was used for total fluid volume segmentation in T2 SPACE sequence, while Niblack local threshold algorithm model was used for endolymph/perilymph segmentation and reduction of contrast heterogeneity) to the combination of MRI T2 SPACE sequence (separates total fluid from surrounding bone) + REAL-IR sequence (separates endolymph from perilymph-bone structure). The endolymph/total fluid area (EL/TFS) ratio, as a measure of the severity of endolymphatic hydrops, was 2–25%, 15% (minimum to maximum; mean) for the cochlea, and 12–40%, 28% (minimum to maximum; mean) for the vestibulum. Therefore, a wide range of endolymphatic hydrops degrees were measured volumetrically. The cochlear EL/TFS ratio was significantly correlated with hearing loss. This correlation was not found between semicircular canal paresis and vestibular EH. The Pearson correlation coefficient for both the ICC (intraclass correlation coefficient) and EL/TFS volume ratio was 0.99 for both the cochlea and the vestibulum. In contrast, the ICC of the manually segmented EL/

TFS area ratios was 0.87 for the cochlea and 0.91 for the vestibulum.

The study published by Cho, Y. S. and colleagues in 2020 aimed to create an automatic analysis system that can accurately and quickly measure the endolymphatic hydrops (EH) rate in real-time in the diagnosis of Meniere's disease (16). For this purpose, 124 patients underwent contrast-enhanced MRI. Then, the sections were evaluated by 1 neuroradiologist and 1 neuro-otologist, and the boundaries of the vestibule and cochlea were manually drawn. In addition, the MR images were read to the Visual Geometry Group (VGG-19)-based INHEARIT (INner ear Hydrops Estimation via ARtificial InTelligence) artificial intelligence model. The artificial intelligence model also determined the boundaries of the vestibule and cochlea. Then, the manually and automatically determined boundaries were compared. The agreement between the EH rates calculated manually by doctors and the rates estimated by the INHEARIT model was also analyzed using ICC (intraclass correlation coefficient) values. The average ICC value was found to be 0.971. These results demonstrate that the AI model is fast and accurate in analyzing IV-Gd inner ear MRI images.

In the study published by Park, C. J. and their colleagues in 2021, the participants were divided into two groups (17). The first group was the,124 patient group in the previous study conducted in 2020 using Machine Learning in the diagnosis of Meniere's by measuring Endolymphatic Hydrops with MRI, and the second group was a new group of 60 people (33 people with possible Meniere's, 17 people with hearing loss and vertigo, and 10 people without symptoms) in addition to this group. The aim of this study was to create a fully automated artificial intelligence model with Deep Learning in the diagnosis of Meniere's. In the MR image segmentation phase, 3into3Inception and 3intoUnet and INHEARIT-v2 artificial intelligence models were used via Python 3.5. Imaging was performed with Gadobutrol 3.0-T MRI. The model was trained with T2-weighted magnetic resonance cisternography annotated images and magnification was performed for segmentation. Segmentation was performed using 3into3Inception and 3intoUnet. The INHEARIT-v2 model selected representative slices for each class according to the size of the segmented area. Positive perilymph images and positive endolymph images were used to evaluate EH. The EH ratio was measured using the HYDROPS-Mi2 image. HYDROPS images were obtained by subtracting positive endolymph images from positive perilymph images. The results of the model are Intraclass correlation coefficient (ICC): 0.968 in vestibule sections, ICC: 0.914 in cochlea sections, and mean ICC: 0.941.

In a multicentric study published by Van der Lubbe, M. F. J. A and colleagues in 2021, MR imaging was performed on 120 Meniere's patients and 140 controls (patients with idiopathic asymmetric hearing loss in whom the labyrinth was natural) from 4 centers (13). There is a study in the literature that aimed to diagnose Meniere's using radiomics, but this study aimed to combine Radiomics with Machine Learning (ML). Manual MR-T2 sequence segmentation was performed from conventional MRI scans and 812 features were determined with radiomics, and the 15 most important variations were detected with Principal Component Analysis. Then, a radiomics model was created using a Multi-layer perceptron classifier. This model was introduced to ML. ML was evaluated with two methods. Train-test split and K-fold cross-validation. The accuracy rate of the training model was 72.9%, the Area Under the Curve (AUC) was 80.6%, sensitivity was 80.2%, and specificity was 65.6%. The test model had an accuracy rate of 82.3%, an Area Under the Curve (AUC) of 86.9%, a sensitivity of 83.4%, and a specificity of 81.8%. The 10-fold cross-validation results showed an accuracy rate of 80.0%, an Area Under the Curve (AUC) of 83.6%, a sensitivity of 78.3%, and a specificity of 77.5%.

In the study published by Liu YW and his colleagues in 2020, it was aimed to create an artificial intelligence model that predicts the prognosis of hearing loss in Meniere patients using Transient-evoked otoacoustic emission (TEOAE) signals. (18) For this purpose, 30 Meniere patients were prospectively followed for 6 months after an acute attack. During this period, TEOAE and pure tone audiometry (PTA) tests were performed at 1, 2, 3, 4 weeks, 2 months, 3 months, and 6 months. TEOAE signal parameters were determined as signal energy at 1 and 2 kHz and group delay. PTA results were divided into two groups: 14 patients with improvement (increase of 15dB or more in any of the

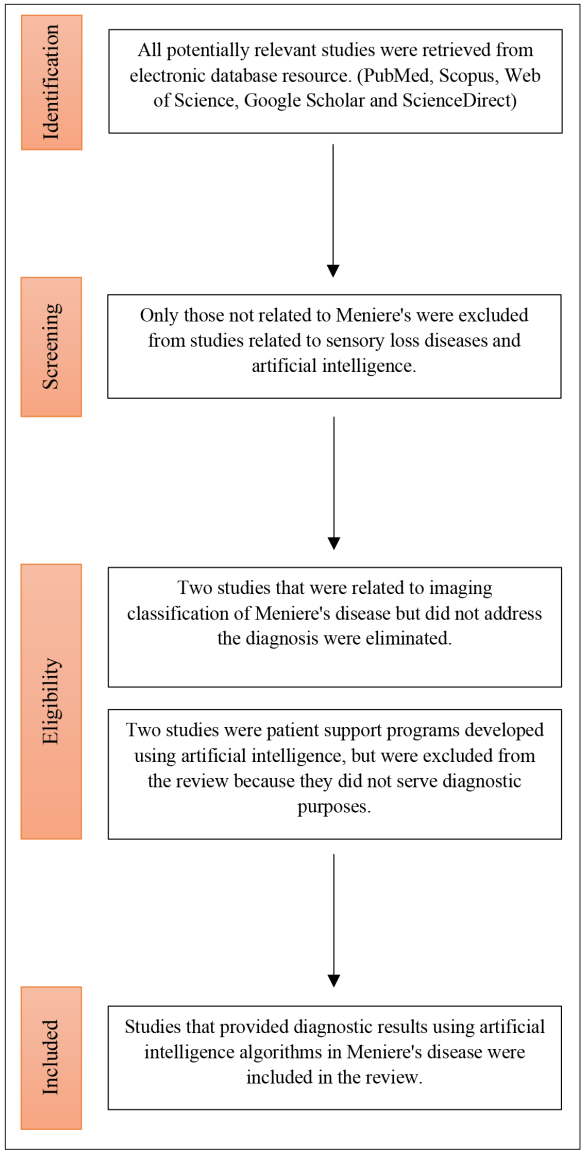

Figure 1. Process for sifting search results and selecting studies for inclusion.

frequencies of 500, 1000, 2000, or 3000 Hz in the last PTA test) and 16 patients with no improvement. Then, the two groups were compared using Welch's t-test. While no significant difference was found between the signal energies of the two groups (p: 0.64), a significant difference was found in the group delay parameter at 1 kHz (p: 0.045). Then, this information was introduced to the Support vector machine (SVM) model for training purposes. SVM model results were evaluated using Fivefold Cross-Validation. When the SVM model evaluated the signal energy and group delay parameters together in the TEOAE test, it predicted the prognosis of the patients with over 80% success, while when it evaluated only the signal energy, the prognosis prediction success remained at the level of 71%.

In the study published by Shew, M. et al. in 2020, the aim was to elucidate the pathophysiology of the disease and develop diagnostic and therapeutic methods by performing MiRNA analysis in Meniere's disease based on the knowledge that miRNAs play an important mechanical role in the development of the inner ear and show different expression patterns in the serum of patients with hearing loss. (19) Since miRNA has a wide expression, it was aimed to develop a Machine Learning model in its analysis to make this process easier. In the study, there were a total of 21 patients, including 5 patients who underwent stapedectomy due to otosclerosis, 11 patients who underwent cochlear implantation due to severe sensorineural hearing loss (SNHL), and 5 patients who underwent labyrinthectomy due to uncontrolled Meniere's. During the surgical procedure, 2-5 µL of perilymph was sampled and MiRNA analysis was performed. Then, these MiRNAs were analyzed by the open-source scikit-learn (v 0.21.3; Python v3.7.1) based Machine Learning (ML) model, which introduced all human MiRNAs, and a comparison was made. The model showed 100% accuracy in distinguishing between conductive hearing loss and Meniere's disease and 66% accuracy in distinguishing between SNHL and Meniere's disease.

In the study published by Bragg, P. G. et al. in 2023, the authors aimed to clarify the role of Subjective Visual Vertical (SVV) and Ocular Vestibular Evoked Myogenic Potentials (o-VEMP) tests in terms of which utricular subsystem each test measure, to characterize the acute and chronic status of MD by identifying differences in the relationship between SVV and o-VEMP results among patients with acute and chronic MD, and to find a machine learning algorithm that can predict acute and chronic MD using SVV and o-VEMP (15). For this purpose, 90 unilateral Meniere's patients were included in the study. c-VEMP, o-VEMP and SVV tests were performed on acute-chronic MD patients. Asymmetry rates in VEMPs and deviation degrees in SVV were determined. Statistical analysis was performed with ANOVA and t-test. Pearson's linear correlation coefficient was calculated (r2). Logistic regression (LR), the Naïve Bayes classifier (NB), ran-

Table 1. Summary of published studies using AI to diagnose MD

Study	Year	AI algorithm	Aim	How the AI algorithm was used	Data set	Validation method	Performance (Accuracy)
Gurkov et al. (14)	2014	RF Classifier, Niblack local threshold algorithm	Correlation of ELH/TF ratio with hearing loss and vestibular paresis	Methodology-Segmentation	16	Accuracy analysis and cross validation	In the AI algorithm, automatic segmentation, ICC score and Pearson correlation scores for both vestibule and cochlea were 0.99. In the manual segmentation ICC and Pearson correlation scores were found to be 0.87 for cochlea and 0.91 for vestibule.
Y. S. Cho et al. (16)	2020	INHEARIT model based on CNN and VGG-19	Diagnosis of Meniere's disease by ELH measurement on MRI	Methodology-Segmentation	124	5-fold cross validation	IoU (concat 3 into 1 VGG) :0.497, 0.533, and 0.528. İoU (3into3VGG): 0.620, 0.716, and 0.711 (low, moderate, high augmentation)
M. Shew et al. (19)	2020	LR, RC, k-NN, Decision tree, RF classifier, Gaussian nai ve bays, SVM, Stochastic gradient classifier, Adaboost, Stochastic gradient boost, Bagging tree classifier	Determination of Meniere-specific miRNA in perilymph	Data analysis-Classification	21	8-fold cross validation	Best performing models: KNN, RF, SGB, BTC: %100 SVM: %96
Y. W. Liu et al. (18)	2020	SVM	Predicting whether SNHL developing during a Meniere attack will regress or not with TE-OAE	Data analysis-Classification	30	5-fold cross validation	Prognosis prediction accuracy for different features: (PC1, PC2, PC3): 0.827 Energy: 0.708 GD-1 kHz: 0.841 GD-2 kHz:0.808
C. J. Park et al. (17)	2021	INHEARIT-v2 (ELH measurement), 3into3Inception and 3intoUNet	Diagnosis of Meniere's disease by ELH measurement	Methodology-Segmentation	128-training set, 60 test set	5-fold cross validation	İoU (3into 3Inception):0.784 İoU (3intoUNet):0.811
M. F. J. A. van der Lubbe et al. (13)	2021	Multi-layer perceptron classification	Meniere's diagnosis via MRI images (not ELH measurement)	Data analysis-Classification	260	Test-training split ,10-fold cross validation	Test accuracy: 0,82. 10-fold cross validation: 0,8. ICC (mean): 0,941
P. G. Bragg et al. (15)	2023	LR, the Naïve Bayes classifier, RF, and SVM	Utricular function assessment with SVV and O-VEMP measurement, predicting acute-chronic Meniere's diagnosis	Data analysis-Classification	90	10-fold cross validation	LR, NB, RF>0,7 SVM<0,5

AI: Artificial Intelligence, RF: Random Forest, ELH: Endolymphatic Hydrops, TF: Total Fluid, ICC: Intraclass Correlation, INHEARIT: INner-ear Hydrops Estimation via ARtificial InTelligence, CNN: Convolutional Neural Network, VGG-19: Visual Geometry Group-19, LR: Logistic regression, RC: Ridge classifier, k-NN: k-nearest neighbors, SVM: Support vector machine

dom forest (RF) and support vector machine (SVM) were used to group (training set, testing set). These classes are right acute (RA) MD, right chronic (RC) MD, left acute (LA) MD, and left chronic (LC) MD. Logistic regression (LR), the Naïve Bayes classifier (NB), and random forest (RF) methods provided over 70% accuracy, while the accuracy rate of support vector machine (SVM) remained below 50% (7).

DISCUSSION AND CONCLUSION

Meniere's disease is an important peripheral vestibular system disorder that causes episodic vertigo, tinnitus, a feeling of fullness in the ear, and hearing loss due to flutter. Although the pathophysiology is mostly focused on endolymphatic hydrops, there are many aspects waiting to be elucidated. Studies on vestibular

system diseases with machine learning and deep learning models have increased recently. When machine learning studies on Meniere's disease were examined, it was seen that the models used had the potential to significantly facilitate the management of the disease by physicians regarding the radiological diagnosis and course of the disease and to illuminate the dark points regarding the pathophysiology of the disease.

Among the studies where machine learning is used for the diagnosis of Meniere's disease, the detection of endolymphatic hydrops (EH) in MR imaging has an important place. The artificial intelligence models used in these studies have gained automatic segmentation and full stack working features over time, and it has been observed that they have gained the ability to calculate EH that is highly correlated with objective and expert physician evaluation. The effectiveness of EH in disease pathophysiology, follow-up during the treatment process, and correlation with disease duration and severity were examined. It should also be noted that the EH ratio measurement time to be used in disease evaluation has been reduced to seconds, which is valuable in terms of preventing physicians from losing time (16).

Studies on the pathogenesis of Meniere's disease are mainly focused on endolymphatic hydrops. In addition, the value of EH progression in showing Meniere's prognosis is being studied. In addition, EH can be shown on MRI in cases such as vestibular migraine that present with a clinical picture similar to Meniere's, and can have diagnostic value. For these reasons, radiological measurement of EH provides valuable information. Until 2014, there have been many studies evaluating Meniere's disease using endolymphatic hydrops measurement. Zou et al. performed segmentation of endolymph and perilymph spaces on MRI images (20). Nakashima et al. conducted a study on endolymphatic hydrops measurement with MRI after intratympanic contrast injection (8). In the study, perilymph and endolymph could be distinguished on the FLAIR sequence, but endolymph-bone could not be distinguished. In a similar study by Liu et al., Endolymph/Total Fluid Space (EL/TFS) measurements were performed on the cochlea and vestibule on the FLAIR sequence (17). The inability to perform endolymph-bone segmentation was stated as a limitation. Naganawa et al. successfully demonstrated the distinction between endolymph-perilymph-bone with Real-IR sequence in MR (21). Since manual segmentation was performed in these measurements, semiquantitative and subjective results were obtained.

In 2014, R. Gürkov and colleagues conducted the first study on endolymphatic hydrops measurement using machine learning. Inner ear total fluid space (TFS) segmentation was performed using Random Forest based machine learning model on T2-SPACE and REAL-IR sequences in MR, and endolymph-perilymph segmentation was performed using Niblack local threshold algorithm (14). EL/TFS ratio was determined by providing objective and volumetric measurements from the obtained images. In previous studies, manual segmentation of inner ear volumes was performed, but the fact that manual segmentation was time-consuming and subjective was considered a limitation. When evaluated in terms of meeting the objective data need, the results obtained here showed that machine learning technology will make a significant contribution to the clinical practice of Meniere's disease. In the study, it was seen that cochlear EL/TFS ratio was blunted with hearing loss, but vestibular EL/TFS ratio did not show the same correlation with semicircular canal paresis.

In the study conducted by Young Sang Cho and his colleagues in 2020, a deep-learning model called INHEARIT (INner ear Hydrops Estimation via ARtificial InTelligence) based on VGG-19 was developed to provide automatic segmentation of the cochlea and vestibule and calculate the objective EH ratio (16). Very good results were obtained with a limited data set. In this study, data augmentation was applied to compensate for the scarcity of data. When the manual measurements made by the neurootologist and neuroradiologist were compared with the EH estimate of the INHEARIT model, the ICC score was obtained as 0.971. In the study conducted by Chae Jung Park and his colleagues in 2021, a full-stack model called INHEARIT-v2 was developed using the 3into3Inception and 3intoUNet network base instead of the CNN base used in the previous model (17). In this model, a high correlation was obtained when the measured EH ratio was compared with the measurements of the specialist physician.

The most important limitation observed in the studies was the lack of a sample size that could determine a specific EH ratio as a cut-off value when diagnosing Meniere's disease. In addition, it was observed that the EH ratio evaluation varied from person to person and did not show a clear correlation between clinical presentations. Since normal people without Meniere's diagnosis were not included in the studies when measuring EH values, normal variant measurement could not be performed. Another disadvantage in determining the cut-off value is that it is difficult to determine a definite value between the upper limit of normal EH in a healthy individual and an early-stage Meniere's patient with a low EH ratio (2014). This may not be necessary to determine the response to treatment in a specific patient, but it is important for future studies on EH cut-off. In the previously mentioned studies, machine learning technology was on segmentation. Apart from these, machine learning has been used successfully in classification-data analysis in studies on Meniere's disease from various aspects.

In 2021, Marly F. J. A. van der Lubbe and his colleagues aimed to reach an artificial intelligence-supported Meniere's diagnosis using features obtained with radiomics from MRIs in two groups of patients with Meniere's diagnosis and healthy patients (13). Multi-layer perceptron classification was used as an artificial intelligence model. Unlike other imaging studies, the artificial intelligence model was used in classification-data analysis. Radiomics technology extracted 812 different features from manually segmented MRI images. Using Principal Component Analysis, these features were subjected to essential-non-essential distinction and the number of features was reduced to two digits by removing non-essential features. These features were introduced to the multi-layer perceptron classification model. Unlike other studies, the model was validated with both train-test split and 10-fold classification. Another important detail of this study was that the diagnosis was made with non-contrast MRI. Integrating automatic segmentation into future studies with radiomics will make radiomics more efficient in terms of objectivity and speed.

In the study published in 2023 by Phillip G. Bragg et al. Subjective Visual Vertical (SVV) and Ocular Vestibular Evoked Myogenic Potential (o-VEMP) tests examining the dynamic and static subsystems of the utricle were used to distinguish between acute and chronic periods of Meniere's disease. (15) In the study where 4 different machine learning models were used, it was observed that SVV and O-VEMP showed linear correlation with acute period Meniere's, but SVV results were normal in chronic period Meniere's. In the study, the classifications made with machine learning models in the distinction of acute and conic period Meniere's were examined. Decision boundary (DB) was taken as the basis for these comparisons. Since DB was observed as linear in the Logistic regression model and nonlinear-flat in the Naïve Bayes classifier (NB) model, these two models were the most sensitive models in classification. Low sensitivity was observed in Random Forest and SVM (Superior Vector Machine) models. While the accuracy rate was >70% in the first 3 models, it was seen that it was <50% in the SVM model. Despite the limited data set with 90 patients, it was seen that a successful classification could be made with the machine learning model especially Logistic regression and NB. The lack of a method to calibrate surface EMG activities in this study may have affected the amplitude values in the o-VEMP results. Future studies may need to perform VEMP and SVV in the same physiological position and include a method to calibrate surface EMG for o-VEMP. These additional measurements may provide more consistent results.

In a study conducted by Matthew Shew et al. in 2020, perilymph samples taken from the preoperative inner ear were examined and MiRNA expression profiles were revealed (19). With the help of machine learning (ML) models, MiRNA profiles associated with Meniere were detected and it was determined that they had a predictive feature in showing the disease diagnosis. It has been revealed in different studies that miRNAs play a role in inner ear development and hearing loss due to various reasons and that there is an increase in MiRNAs showing different expression patterns in inner ear fluids. Since the volume and diversity of these MiRNA patterns are very large, analysis was performed using ML and expression patterns specific to Meniere's disease were determined. It was seen that there was a two-stage ML evaluation in the study. In the first stage, when 11 ML models were subjected to 8-10 cross-validation, the 5 models with the

highest accuracy rate were determined. In the second stage, optimal accuracy rates were achieved with hyperparameter tuning using GridSearchCV. The effects of MiRNAs on model accuracy were determined using a permutation-based approach in each model (permutation feature importance score). The fact that perilymph sampling could not be performed on healthy individuals in the study can be considered as a limitation, but it can also be assumed that the inner ear is not affected in otosclerosis patients. Secondly, the accuracy rate of distinguishing between Meniere's and profound SNHL patients being at 60% is thought to be due to the fact that SNHL is also seen in Meniere's, the selected Meniere's patients are advanced stage patients and the small sample size. More meaningful results can be obtained in future studies with larger samples. In addition, the effect of endolymphatic sac surgery and miRNA expressions in early stage Meniere's patients can be investigated in new studies conducted with this technique. Another limitation of the study is that the perilymph examined contained a small portion of the MiRNA content and other parts of the inner ear could not be evaluated. It should also be noted that the method used in this study was expensive.

It's concluded that Meniere's Disease presents many difficulties in terms of diagnosis, prognosis and treatment. Current studies show that endolymphatic hydrops (EH) plays a significant role in pathophysiology. The effect of current treatments in reducing EH progression is uncertain. Therefore, rapid and most accurate measurement of EH with objective criteria is important in monitoring the response to treatments to be developed for EH progression. It is difficult to determine a cutoff value for EH with the current data we have. This limitation can be overcome by studies with larger data groups or by more advanced artificial intelligence technologies, as better results can be obtained with less data. In addition to EH determination, artificial intelligence algorithms supported by audiological-vestibular tests can be used to follow Meniere's disease with objective data and make objective evaluations of prognosis. Although not yet sufficiently studied, the striking results regarding the MiRNA-Meniere relationship with the support of artificial intelligence algorithms can be a guide to reveal the unknowns about the disease.

Main points

- This review examines the advances provided by AI systems for higher accuracy in the diagnosis of Meniere's disease.
- Machine learning and deep learning methodologies can be employed in the diagnosis of Meniere's disease by analyzing radiological imaging findings, detecting specific microRNAs associated with the condition, and monitoring disease progression through the assessment of transient-evoked otoacoustic emissions and vestibular test results.
- The limitations in predicting the diagnosis and prognosis of Meniere's disease can be overcome through the incorporation of objective assessments facilitated by machine learning and deep learning systems.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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Investigation of neurogenic dysphagia in commonly seen neurological diseases

Sık görülen nörolojik hastalıklarda nörojenik disfajinin araştırılması

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Abstract

Neurological disorders lead to varying degrees of impairment in the functions of vital swallowing structures, such as the cortex, cerebellum, brainstem, cranial nerves, and muscles. Neurogenic dysphagia is observed in approximately 50% of common neurological disorders such as stroke, multiple sclerosis, and Parkinson's disease. Although the pathophysiology and course of the disease vary, dysphagia may occur at any stage of swallowing, including oral preparation, oral, pharyngeal, and esophageal phases. Neurogenic dysphagia ranks among the top symptoms that restrict patients' independence in daily life activities, reduce their quality of life and increase morbidity and mortality rates. Despite being a prevalent and highly impactful symptom among patients, neurogenic dysphagia can go unnoticed among the multiple symptoms experienced by neurological disorders due to their nature. It is important to be aware of disease-specific risk factors for the early detection of neurogenic dysphagia. Overlooked dysphagia can lead to complications such as aspiration pneumonia, dehydration, malnutrition, and weight loss. Among these complications, aspiration pneumonia is the most common, requiring attention due to its recurrent hospitalizations, inpatient treatment, and high healthcare costs. Many patients exhibit common neurogenic dysphagia symptoms such as drinking liquids in small sips, cutting solid foods into small pieces, decreased appetite, and prolonged meal times. The aim of this study is to examine various aspects of neurogenic dysphagia in different neurological disorders, including its etiology, risk factors, symptoms, and prevalence.

Keywords: Demantia; multiple sclerosis; stroke; swallowing disorders

Öz

Nörolojik hastalıklar yutma için hayati öneme sahip korteks, serebellum, beyin sapı, kranial sinirler ve kaslar gibi yapıların fonksiyonlarında çeşitli derecelerde bozulmaya yol açar. Nörojenik disfaji; inme, multiple skleroz, parkinson gibi yaygın görülen nörolojik hastalıkların yaklaşık %50'sinde görülür. Hastalığın patofizyolojisi ve seyrine göre değişmekle birlikte yutmanın oral hazırlık, oral, faringeal ve özefageal fazlarının herhangi birinde disfaji ortaya çıkabilir. Nörojenik disfaji bu hastaların günlük yaşam aktivitelerindeki bağımsızlıklarını kısıtlayan, yaşam kalitelerini azaltan ve morbidite, mortalite oranlarını arttıran semptomlar arasında ilk sıralardadır. Nörojenik disfaji, yaygın görülen ve hastaları oldukça olumsuz etkileyen bir semptom olmasına rağmen nörolojik hastalıkların doğası gereği hastanın yaşadığı çoklu semptomlar arasında gözden kaçabilmektedir. Nörojenik disfajinin erken tespiti için hastalıklara özel risk faktörlerinin iyi bilinmesi önemlidir. Gözden kaçırılan disfaji ilerleyen dönemlerde aspirasyon pnömonisi, dehidrasyon, malnütrisyon, kilo kaybı gibi komplikasyonların oluşmasına neden olur. Bu komplikasyonlar arasında en sık görülen aspirasyon pnömonisi; tekrarlı hastane başvuruları, yatarak tedavi ve yüksek sağlık maliyetleri gerektirmesi nedeniyle dikkat edilmesi gereken bir durumdur. Hastaların birçoğu sıvıları çok yudumda içme, katı gıdaları küçük lokmalara bölme, iştahta azalma, yemek süresinin uzaması gibi ortak nörojenik disfaji belirtilerine sahiptir. Bu çalışmanın amacı farklı nörolojik hastalıklarda görülen nörojenik disfajinin oluşma mekanizması, risk faktörleri, semptomları ve prevelansı gibi yönlerini incelemektir.

Anahtar Sözcükler: Demans; inme; multipl skleroz; yutma bozuklukları

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Neurogenic dysphagia

Swallowing is a neuromotor activity of vital importance. It consists of oral preparation, oral, pharyngeal, and esophageal phases. Swallowing's neuromotor control is carried out by cranial nerves trigeminal, abducens, facial, vagus, and hypoglossal. During swallowing, coordination and control extend to 25 pairs of muscles The term "dysphagia," comes from the Greek roots "dys," meaning "difficulty," and "phagein," meaning "to eat," refers to a swallowing disorder (1). Neurological disorders are the most common cause of dysphagia. Neurogenic dysphagia describes swallowing disorders caused by the central and peripheral nervous system, neuromuscular transmission, or muscle diseases. Neurogenic dysphagia is one of the most common and dangerous symptoms of many neurological diseases. It is estimated that approximately 50% of all patients suffer from neurogenic dysphagia (2). Clinical effects of neurogenic dysphagia include aspiration pneumonia, dehydration, malnutrition, decreased quality of life, and inability to intake food orally. These complications associated with dysphagia can lead to mortality in neurological diseases (3). Understanding the complex patterns of irregular swallowing is crucial in cases of severe dysphagia. This knowledge is necessary for healthcare professionals to accurately diagnose and effectively treat individuals with neurogenic dysphagia. By understanding the neural pathways and mechanisms involved in swallowing, healthcare professionals can develop appropriate therapeutic strategies to address the specific challenges faced by patients with neurogenic dysphagia. This review aims to facilitate the recognition of the differences necessary for the appropriate diagnosis and treatment of swallowing disorders. Additionally, it aims to assist patients, caregivers, and healthcare professionals in acquiring the necessary knowledge to live with the condition.

Stroke

Stroke is a neurological condition that occurs due to occlusion or rupture of arteries supplying the brain, resulting in the sudden loss of brain functions and a neurological presentation lasting longer than 24 hours. Motor function impairments, such as dysphagia, are common in individuals experiencing vascular damage to the central nervous system (4). The incidence of dysphagia in stroke varies between 19% and 81% and is often associated with aspiration pneumonia (5, 6). The prevalence of dysphagia increases from 38% when diagnosed through clinical swallowing examinations to up to 75% when evaluated using instrumental techniques (7). Stroke patients with dysphagia have a threefold increase in the risk of aspiration pneumonia, and those with aspiration have an elevenfold increase in the risk of pneumonia (8). Advanced age, high scores on disease-specific classifications, low quality of life index score, malnutrition, low body mass index, larger lesion volume, subcortical and cortical involvement, brainstem involvement, corticobulbar system involvement, white matter involvement, dysarthria, presence of dysphonia or reduced maximum pitch, cognitive impairment or dementia, male gender, higher Glasgow Coma Scale score at admission, presence of hemorrhagic or ischemic stroke, involvement of the anterior or middle cerebral artery, large or cerebral artery involvement, small vessel occlusion, facial palsy, presence of hyperlipidemia, and thalamic lesions are predictive factors determining the prognosis of dysphagia following stroke (9).

Disruptions in swallowing physiology occur as a result of cerebral, cerebellar, or brainstem strokes, and the severity and pattern of dysphagia vary based on the lesion's localization. Dysphagia resulting from brainstem strokes (40-81%) constitutes the majority of dysphagias observed after stroke (10). Retrospective studies indicate that strokes occurring in the infratentorial region, including the brainstem (midbrain, pons, medulla), and the cerebellum, lead to more severe dysphagia compared to strokes in the supratentorial region, involving deep (thalamus and basal ganglia) or lobar (cortex and subcortical areas) intracerebral regions (11). Infratentorial lesions primarily cause dysphagia due to motor deficits, while supratentorial lesions often result in dysphagia originating from sensory afferent deficits (12). The nucleus tractus solitarius, responsible for initiating swallowing, and the nucleus ambiguus, coordinate the synchronized contraction of lingual, laryngeal, pharyngeal, and muscles. Damage to these neural pathways in the cerebellum diminishes its inhibitory effect on the cerebral cortex, leading to dysphagia (10). Cerebral lesions disrupt the inten-

tional control of chewing and bolus transfer during the oral phase. Cortical lesions involving the precentral gyrus cause impairment in contralateral tongue, lip, and facial motor control, leading to disturbances in contralateral pharyngeal peristalsis. Cerebellar lesions impact cognitive functions, resulting in concentration or selective attention deficits that negatively affect swallowing control. Brainstem lesions affect oral, lingual, and cheek sensation, the timing of pharyngeal swallowing initiation, laryngeal elevation, glottic closure, and cricopharyngeal relaxation (13). The right hemisphere contributes more to the sensory-motor integration of swallowing than the left hemisphere (14). Severe dysphagia and aspiration are more commonly observed with right hemisphere involvement, while oral disorders are more frequent with left hemisphere involvement (Figure 1) (15).

Aspiration, the most severe symptom of dysphagia, is observed in approximately 40% of acute stroke patients. Silent aspiration, primarily caused by reduced sensory input or decreased cough reflex, constitutes the majority of these cases. Stroke-related pneumonia, due to its association with increased mortality, disability rates, and prolonged hospital stays, is a crucial symptom that requires attention (16). Dysphagia leads to malnutrition, dehydration, low-grade fever, loss of appetite, weight loss, wet voice, feeling of blockage in the throat, and airway obstruction. During the oral preparation stage, chewing disorders, prolonged chewing, weak lip seals, drooling while chewing, or solid food pocketing in the cheeks may occur. In the oral propulsion stage, difficulty initiating swallowing is observed, and in the pharyngeal stage, symptoms such as inability to swallow, choking, nasal regurgitation, coughing, shortness of breath, and pain during swallowing are prevalent. In the esophageal phase, symptoms such as belching or indigestion due to reflux, recurrent pneumonia, bad taste in the mouth upon waking, heartburn, chest pain, or discomfort may occur (17).

As a result, one of the common causes of dysphagia is considered to be stroke. Stroke can have significant adverse effects on swallowing physiology, impacting both oral and pharyngeal stages of swallowing. The severity and pattern of dysphagia following cerebral, cerebellar, or brainstem strokes vary depending on the localization of the brain lesion.

Dementia

The prevalence of dementia, and dysphagia associated with dementia increases with aging. Various assessments are conducted in individuals suspected of dementia, but establishing a definitive diagnosis takes time. When dementia is mentioned, cortical changes related to cognitive impairments are typically what come to mind. However, upon examining MRI images from the early stages, damage to the brainstem region involved in swallowing control is observed (18).

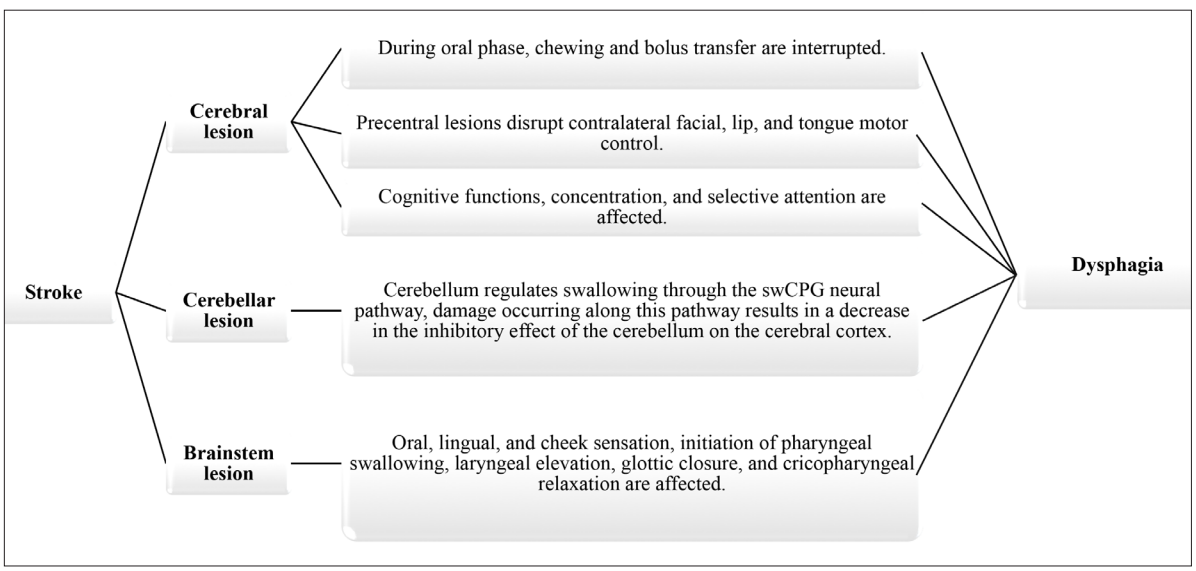

Figure-1. Pathophysiology of Dysphagia in Stroke

Swallowing difficulties observed in the early stages of dementia in patients are attributed to the natural aging process (19). This situation leads to delayed diagnosis of dysphagia in dementia patients and can result in an increase in the complication rate, potentially culminating in mortality in advanced stages (20). Dementia patients experience problems with dysphagia such as increased leakage duration during chewing, prolonged initiation time of swallowing, premature bolus spillage, and decreased bolus clearance (21). Although the prevalence of dysphagia in dementia patients is estimated to be around 45% on average, it varies depending on clinical features such as dementia type, disease stage, and process (22). Apart from those listed below, neurogenic dysphagia is also experienced in frontotemporal and lewy body types of dementia (23).

Alzheimer's disease

Alzheimer's disease, which constitutes 60-70% of all dementia cases, is characterized by progressive cognitive, behavioral, and neuropsychiatric symptoms attributed to hippocampal and bilateral temporal-parietal lobe involvement (24). In Alzheimer's disease, the sensory aspect of swallowing is affected due to neurofibrillary tangles originating from neuritic plaques and olfactory pathway involvement. Dysphagia develops in 84% to 93% of moderate to severe Alzheimer's patients due to impaired cognitive functions, leading to visual recognition inability of bolus and oral-tactile agnosia. Consequently, symptoms such as decreased smell and taste sensations during the oral phase, impaired perception of food in the mouth, inability to initiate voluntary swallowing, and delayed oral transit of liquids are observed (25). The presence of dysphagia in Alzheimer's patients leads to increased hospital admissions, inpatient treatment, and healthcare expenditures (26). Therefore, it is important to be vigilant against risk factors such as difficulty in oral/labial residue clearance and bolus cleaning for early detection of dysphagia (27).

Vascular dementia

In the second most common type of dementia, vascular dementia, the motor aspect of swallowing is affected more than the sensory aspect (28, 29). Disturbances are observed in the chewing of semi-solid food and the formation of the bolus due to the involvement of the trigeminal and hypoglossal cranial nerves responsible for chewing and tongue movements. Patients with vascular dementia experience problems not only in the oral phase but also in the motor components of the pharyngeal phase, including hyolaryngeal movement and epiglottic inversion. Compared to Alzheimer's disease, vascular dementia is associated with a higher incidence of overall aspiration and silent aspiration (29).

Parkinson's disease

Parkinson's disease (PD) is a complex neurodegenerative progressive disorder that affects both motor and non-motor functions. In pathophysiology, dopaminergic neuron loss occurs due to the decrease in dopamine in the basal ganglia and the accumulation of cytoplasmic residues containing the insoluble α-synuclein (αSyn) protein, called Lewy bodies, in more than one cell type (30). Dysphagia, which is difficulty in swallowing, is a common non-motor symptom experienced by people with PD. It can affect any stage of the disease and any of the oral, pharyngeal, esophageal phases It can affect any phase of swallowing, including oral, pharyngeal, and esophageal stages of the disease (31). Swallowing disorders can occur in the early stages or even in the prodromal stage of PD, even if they are typically more noticeable in advanced stages (31, 32). Unlike stroke, dysphagia in PD often worsens with the progression of the disease and appears approximately 10-11 years after the onset of motor symptoms (33, 34). The prevalence of dysphagia in PD varies depending on disease duration, stage, and assessment method (35). There are differences between the prevalence of dysphagia reported subjectively (35%) and that confirmed by instrumental methods (85%) (33). Due to deficiencies in sensorimotor functions and a decreased protective cough reflex, many individuals with PD may not be aware of their swallowing issues. This lack of awareness often leads to asymptomatic dysphagia in the early stages, subsequently resulting in silent aspiration and/or penetration (36, 37, 38). However, several symptoms and signs can contribute to the early diagnosis of dysphagia in PD. These include prolonged meal duration, difficulty swallowing tablets, a sensa-

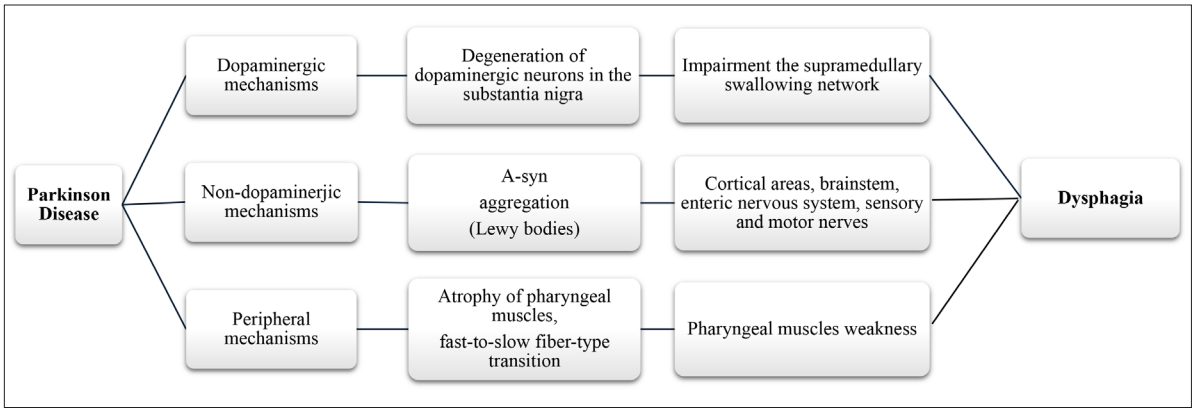

Figure-2. Pathophysiology of Dysphagia in Parkinson Disease

tion of food sticking or persisting in the throat after swallowing, coughing and choking during food and liquid intake, changes in voice (e.g., gurgling voice), and weight loss or low body mass index during recurrent chest infections (39). Even if not exhibiting these symptoms, Parkinson's patients in Hoehn and Yahr stages 4 and 5, with dysphagia-related weight loss or a body mass index <20 kg/m2, drooling or sialorrhea, and clinical predictors such as dementia, should be assessed for screening (40).

In the development of dysphagia in PD, both non-dopaminergic and dopaminergic mechanisms may be involved (41). The extrapyramidal dysfunction arising from the degeneration of dopaminergic neurons in the substantia nigra plays a significant role in the pathophysiology of dysphagia in PD patients by impairing the supramedullary swallowing network crucially involved in swallowing. This hypothesis is also supported by the observation that some PD patients show a significant improvement in swallowing function after L-Dopa and that deep brain stimulation may affect the supramedullary swallowing network by modulating dopaminergic pathways (42). Lewy bodies, which are αSyn aggregates involved in the pathology of PD, have been found to accumulate in various non-dopaminergic cortical areas, including 'central pattern generators' in the medulla, brainstem, enteric nervous system and motor nerves innervating the pharyngeal muscles, which can disrupt the swallowing pattern (43). Peripheral mechanisms, such as atrophy of pharyngeal muscles and fast-to-slow fibre-type transition, also contribute to swallowing dysfunction (Figure 2) (44, 45).

The hallmark features of dysphagia in PD include repetitive or festinated tongue movements, decreased coordination and speed of mastication, significantly prolonged oropharyngeal transit time, pharyngeal spillage, and delayed initiation of swallowing (40, 46). Additionally, studies report increased swallowing frequency for clearing residues in the pharynx, esophageal dysmotility and slowed hyolaryngeal movements. Deficiencies in airway protection may manifest as decreased cough airflow rates, reflex, and airway obstruction due to sensory impairments. (33, 46). Dysphagia can significantly affect the quality of life in patients with PD. Swallowing problems adversely affects well-being, self-confidence, and social integration, leading to frustration and social isolation (39, 46).

In conclusion, dysphagia occurs in PD through dopaminergic, non-dopaminergic, and peripheral mechanisms. Dysphagia can be seen at any stage of the disease, but as the disease progresses, the symptoms worsen and negatively affect the quality of life. Dysphagia in PD causes aspiration pneumonia, leading to severe complications and even death.

Chorea, dystonia, and Wilson disease, which are included under the term movement disorders, are other diseases in which neurogenic dysphagia is observed (23).

Multiple sclerosis

Multiple sclerosis (MS) is the most common neurodegenerative disease of the central nervous system, characterized by chronic inflammation and demyelination (47). The formation of plaques in areas such as the cortex, cerebellum, brainstem, and cranial nerve

regions, which have a functional impact on swallowing, as a result of inflammation, leads to dysphagia in patients with MS (48).

The prevalence of dysphagia in MS patients varies between 21% and 90% (48, 49), with an average estimate suggesting that approximately one out of every three patients has swallowing difficulties (50). Many factors, such as age, affected region, and disease type, influence the prevalence and severity of dysphagia in MS patients (51). It has been reported that MS patients with involvement of the brainstem, forebrain, and central pattern generator regions responsible for controlling swallowing function are more likely to experience dysphagia than other patients (52, 53). Studies investigating the relationship between disease type and prevalence have shown that patients with progressive forms such as primary progressive MS (PPMS) and secondary progressive MS (SPMS) are more affected by dysphagia compared to those with relapsing-remitting MS (RRMS) (48, 54). The clinical course of dysphagia may vary for different MS types. In RRMS, dysphagia can last from 2-3 weeks to 2-4 months during exacerbations and can become chronic during remission periods, whereas for progressive types, there is a continuous increase in the severity of dysphagia (55). Another factor influencing the prevalence of dysphagia is the method of evaluating swallowing function. When evaluated with instrumental techniques, dysphagia prevalence increases to 65.7%, compared to 38.4% diagnosed through clinical swallowing examinations (51).

In the early stages of the disease, dysphagia can go unnoticed among multiple symptoms, and unless serious complications such as aspiration pneumonia develop, dysphagia may be neglected (56), with only 2% of patients diagnosed with dysphagia receiving treatment (57). This delay in intervening in dysphagia may lead to more severe dysphagia and increased disability and mortality rates in the advanced stages of the disease (58, 59). To detect overlooked dysphagia earlier, it is important to be aware of risk factors such as the use of certain medications in MS treatment, the initial symptom being swallowing problems, a high EDSS score (>8), and having motor and cerebellar symptoms, as well as disease duration and progressive disease course (60, 61).

Common signs of dysphagia in MS patients are frequent sips to drink fluids, dividing food into small morsels, and weight loss (60). Dysphagia typically stems from glottal closure issues, weakness in soft palate/laryngeal movements, and penetration during the pharyngeal phase. In rare cases, delayed swallowing reflex or residue transportation during the pharyngeal phase can lead to penetration (58, 62). In some instances, dysphagia is characterized by delayed swallowing reflex and difficulty in bolus manipulation

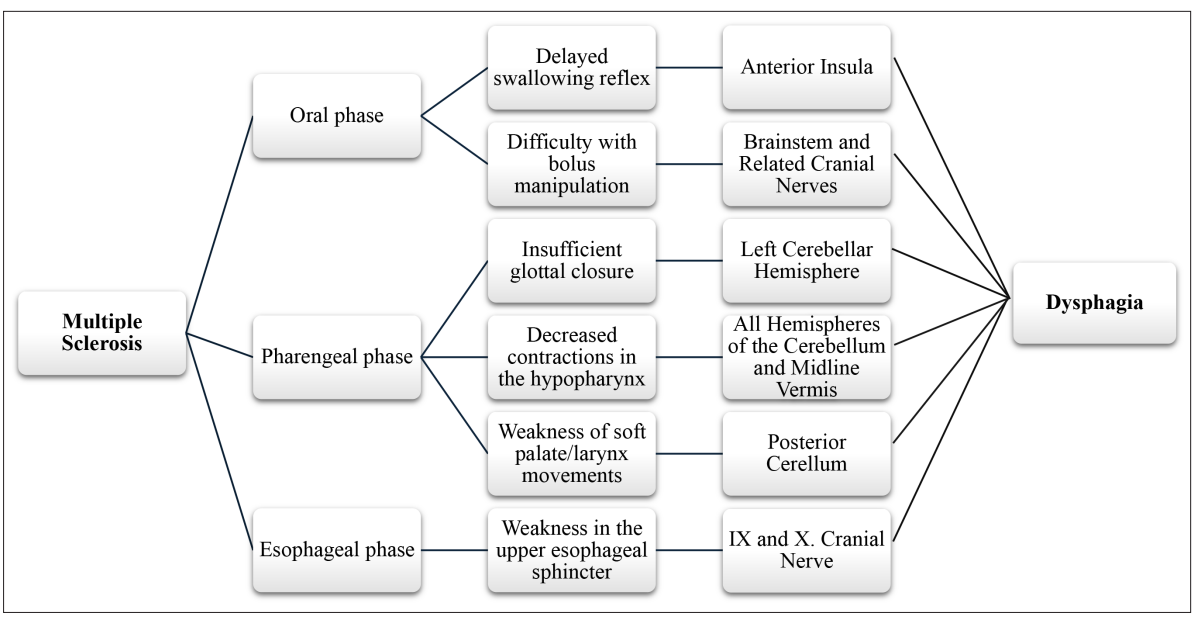

Figure-3. Pathophysiology of Dysphagia in Multiple Sclerosis

during the oral phase. In the advanced stages of MS, dysphagia may be linked to reduced contractions in the hypopharynx or dysfunction of the upper esophageal sphincter (61). Additionally, dysphagia in the oral phase may arise from cerebellar problems, while dysfunction in brainstem function, cognitive functions, and/or cerebellar disorders may contribute to dysphagia in the pharyngeal phase (Figure 3) (63).

In conclusion, dysphagia associated with MS can affect the sensorimotor cortex, cerebellum, brainstem, and cranial nerves depending on the localization of inflammation and demyelination in the central nervous system. Dysfunction in these structures, each vital for swallowing function, can lead to a range of problems such as oropharyngeal sensory deficits, weakness in muscles involved in chewing and swallowing, impaired initiation of voluntary swallowing, disruption of the swallowing reflex, and disturbance in the timing and sequencing of activation of structures involved in swallowing, as well as coordination problems among interacting structures. Complications related to dysphagia can occur in MS patients. Dysphagia should be screened for early using subjective and objective assessment methods regardless of the presence of symptoms in MS patients with various risk factors.

Bacterial and viral meningoencephalitis, tetanus, poliomyelitis and post-polio syndrome, which are included under the term ınflammatory diseases of the central nervous system, are other diseases in which neurogenic dysphagia is observed (23).

Brain tumors

Dysphagia is a prevalent complication of brain tumors, and it is directly associated with the effects of the lesion, tumor resection, and the outcomes of chemotherapy and radiation therapy. Dysphagia observed in brain tumors can lead to complications such as aspiration pneumonia, dehydration, and inadequate nutrition, significantly impacting long-term quality of life and mortality (64). Among all cancer types, dysphagia is most commonly seen in head and neck cancers, with an incidence rate of 89%. Swallowing function activates a complex communication network in the brain, involving bilateral sensorimotor cortex, premotor area, primary motor area, supplementary motor area, insular cortex, inferior frontal gyrus, cingulate gyrus, temporal lobe, inferior parietal lobule, precuneus, cerebellum, basal ganglia, and brainstem. Due to the intricate nature of swallowing, dysphagia can emerge from a tumor-induced lesion in the brain. The nucleus ambiguus, responsible for generating motor responses in muscles, and the nucleus tractus solitarius (NTS), responsible for initiating and maintaining swallowing based on bolus characteristics (size, texture, and temperature), are crucial structures for swallowing (23). In infratentorial brain tumors, compared to supratentorial brain tumors, penetration, aspiration, residue accumulation in the valleculae and piriform sinuses, and weakened swallowing reflex are more common, leading to an increased incidence of dysphagia. When comparing the incidence of dysphagia between benign and malignant tumors, there is no significant difference. Dysphagia arising from brain tumors is known to share similar characteristics with dysphagia resulting from stroke, as both conditions are outcomes of neurological interactions occurring in the same region (64). Tumor-related neurogenic dysphagia is also observed in metastases, neoplastic meningitis, and paraneoplastic syndromes under the umbrella term of brain tumors.

Neuromuscular diseases

Neuromuscular diseases (NMDs) are pathologies involving motor units and sensory nerves, often rooted in genetic factors. The clinical course and manifestations of NMD vary depending on the underlying pathology, with common symptoms including voluntary muscle weakness, muscle cramps, changes in muscle tone, balance problems, and difficulty swallowing (65). Dysphagia in adult NMDs typically affects the oropharyngeal phase, usually due to weakness in vocal cords and pharyngeal muscles. Dysphagia in NMD individuals contributes to decreased quality of life and may lead to increased morbidity and mortality (2, 66). Dysphagia is prevalent across a broad spectrum of NMDs, accompanying the clinical course and manifestations of the disease. Pathologies within this spectrum include Oculopharyngeal Muscular Dystrophy (OPMD), Myotonic Dystrophy (MD), Facioscapulohumeral Muscular Dystrophy (FSHD), Duchenne

Muscular Dystrophy (DMD), Myasthenia Gravis (MG), Amyotrophic Lateral Sclerosis (ALS), , and Spinal Muscular Atrophy (SMA) (67).

OPMD, although a prototypical adult-onset rare hereditary myopathy, presents dysphagia as the initial symptom in 32% of individuals around their fifties (68, 69). Patients often complain of difficulty swallowing solid foods, the sensation of throat blockage, and symptoms like coughing and choking during meals (68, 70, 71). In Myotonic Dystrophy, prolonged contractions and relaxations of swallowing muscles such as the sternocleidomastoid, masticatory muscles, and cricopharyngeal (upper esophageal) sphincter result in dysphagia. The prevalence of dysphagia in MD ranges from 25% to 80%, depending on the duration and severity of the disease (72, 73). FSHD patients develop dysphagia due to weakness in the muscles around the mouth, leading to difficulty in bolus formation. While 25% of patients report symptoms like prolonged meal times and fear of choking, most do not complain of dysphagia (74). In DMD, increased tongue thickness leads to impairment in the oral phase of swallowing. Delayed oral phase problems during swallowing and pharyngeal residues are also believed to reduce tongue strength (75, 76). Approximately 15% of MG patients develop fatigue-related dysphagia, characterized by weakness associated with effort and increased residue with repeated swallowing attempts. In advanced stages of the disease, myasthenic crises occur in 50% of individuals, potentially leading to aspiration due to dysphagia (77). ALS, characterized by progressive degeneration of lower and upper motor neurons, manifests early weakness in head and neck muscles due to corticobulbar pathway involvement. About 30% of patients present with dysphagia at diagnosis, which progresses with the disease (78). Dysphagia in ALS presents as premature spillage and a combination of hypopharyngeal residues in different areas (3). In patients with corticobulbar involvement, swallowing difficulties typically start with decreased tongue mobility, reduced pharyngeal contraction, and difficulty manipulating the bolus. Aspiration due to reduced laryngeal elevation is also common (79, 80).

In conclusion, dysphagia caused by voluntary muscle weaknesses, affecting chewing and swallowing muscles, is one of the clinical symptoms of NMD. Particularly, as the disease progresses and affects esophageal phase muscle activations, dysphagia severity can impact quality of life, morbidity, and mortality rates.

Traumatic brain injuries and spinal cord injuries

Dysphagia is a common complication of traumatic brain injuries (TBIs) and spinal cord injuries. TBIs result in diffuse axonal injury, brain contusion, and/or hematoma-related damage, leading to pathophysiological mechanisms such as edema, increased intracranial pressure, hypoxia, ischemia, and inflammation. Particularly, cervical spine injuries and surgeries, especially at the C3-C5 level, can cause neurogenic dysphagia (81).

Psychogenic dysphagia

Psychogenic dysphagia is observed during adulthood and is more frequent in females. Unlike other types of dysphagia, typical complications such as aspiration pneumonia are not seen in psychogenic dysphagia, and no pathology is usually detected in neurological examinations. It is commonly encountered in individuals with depression, anxiety, and an introverted personality (23). Psychogenic dysphagia encompasses conditions such as globus pharyngis and phagophobia, often confused with eating disorders, arising from psychosocial stress (81).

Conclusion

Dysphagia is a multifaceted and pervasive issue with significant implications for individuals across various neurological conditions. Neurogenic dysphagia, stemming from disorders affecting the central and peripheral nervous systems, neuromuscular transmission, or muscle diseases, presents a range of challenges impacting both quality of life and mortality rates. From strokes to dementia, Parkinson's disease to multiple sclerosis, and various neuromuscular diseases, dysphagia manifests differently in each condition, reflecting the complex interplay of neural pathways and muscular functions involved in swallowing. Understanding the distinct patterns and mechanisms of dysphagia in each neurological disorder is crucial for accurate diagnosis and effective management. Healthcare profes-

sionals must navigate through the intricate neural networks and motor processes implicated in swallowing to develop tailored therapeutic strategies. Moreover, early detection and intervention are paramount to mitigate complications such as aspiration pneumonia, dehydration, malnutrition, and diminished quality of life associated with dysphagia.

Furthermore, dysphagia extends beyond purely neurological origins, encompassing traumatic brain injuries, spinal cord injuries, and even psychogenic factors. Each presents unique challenges that necessitate comprehensive assessment and targeted interventions. In addressing dysphagia, collaboration among healthcare providers, caregivers, and patients themselves is essential. Education and awareness initiatives can empower individuals to recognize symptoms, seek appropriate care, and implement strategies to manage dysphagia effectively. Overall, by deepening our understanding of the complexities surrounding dysphagia in neurological disorders and beyond, we can strive towards improved outcomes, enhanced quality of life, and better support for those affected by this challenging condition.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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ANADOLU KLİNİĞİ TIP BİLİMLERİ DERGİSİ YAZIM KURALLARI

1. GENEL BİLGİLER

- Dergilerin, uluslararası standartları göz önüne alarak, bir makalenin hazırlanması sırasında uyulması gereken ilkeleri belirlemeleri ve değerlendirmeye alacakları makalelerde bu kurallara uygunluğu kontrol etmeleri, bilimsel yayıncılık standartlarımızın yükseltilmesi açısından önem taşımaktadır.
- Bilimsel dergilere gönderilecek bir makalenin hazırlığı sırasında uyulması gereken, uluslararası tıp dergilerinin de kabul ettiği ve uyguladığı en önemli standartlar şu şekildedir:
  - Yayımlanmak için gönderilen çalışmaların daha önce başka bir yerde yayımlanmamış veya başka bir yere yayımlanmak üzere gönderilmemiş olması gerekir.
  - Makale daha önce yayımlanmışsa ve(ya) alıntı yazı, tablo, fotoğraf gibi ögeler içeriyorsa evvelki yayın hakkı sahibinden ve(ya) bu ögelerin telif hakkı sahiplerinden yazılı izin alınması ve bunun makalede belirtilmesi gerekir.
  - Bilimsel toplantılarda sunulan yazılar, bu sunumun dipnot olarak belirtilmesi koşuluyla, değerlendirmeye alınır.
  - Türkçe yazılarda Türk Dil Kurumu'nun güncel ve bilimsel sözlüklerinde geçen yazımlar esas alınmalıdır. İngilizce yazılar Amerikan İngilizcesi ile yazılmalıdır.

2. BİLİMSEL SORUMLULUK

- Gönderilen bilimsel yazıda, tüm yazarların akademik–bilimsel olarak doğrudan katkısı olmalıdır.
- Dergi ile iletişim görevini yapan yazar (yazışma yazarı), tüm yazarlar adına yazının son halinin sorumluluğunu taşır.

3. ETİK SORUMLULUK

- "İnsan" ögesi içeren tüm orijinal araştırmalarda Helsinki Bildirgesi prensiplerine uygunluk şarttır. Bu tip araştırmalarda yazarların, yazılarının GEREÇ VE YÖNTEMLER bölümünde, araştırmaları sırasında bu prensiplere uyduklarını ve ayrıca kurumlarının etik kurullarından ve çalışmaya katılmış insanlardan "bilgilendirilmiş onam" (*informed consent*) aldıklarını belirtmeleri gerekmektedir.
- "Hayvan" ögesi içeren orijinal araştırmalarda ise yazarlar, yazılarının GEREÇ VE YÖNTEMLER bölümünde, araştırmaları sırasında *Guide for the Care and Use of Laboratory Animals* prensipleri doğrultusunda hayvan haklarını koruduklarını ve hayvan etik kurullarından onay aldıklarını belirtmelidirler.
- Vaka sunumlarında sunulan kişi ya da kişilerin kimliğinin açığa çıkıp çıkmadığına bakılmaksızın "bilgilendirilmiş onam" (*informed consent*) alınmalıdır.
- Çalışmaları ile ilgili direkt–endirekt bir ticari bağlantıları veya çalışmalarına maddi destek veren bir destekçileri varsa, yazarlar bunları ve bu ilişkilerinin doğasını (konsültan, diğer anlaşmalar) Editöre Sunum sayfasında belirtmelidirler.
- Makalede "etik kurul onayı" alınması gerekli ise; yazarlar, yazılı etik kurul izni / onayı aldıklarını "Gereç ve Yöntemler" bölümünde "……..etik kurulundan …….tarih ve…… sayı ile etik kurul onayı alınmıştır" şeklinde beyan etmelidir. "Sözlü etik onay alınmıştır" ifadesi kullanılmamalıdır.

4. YAYIN/TELİF HAKKI

- Yayımlanmak üzere kabul edilen yazıların her türlü yayın/telif hakları dergimize aittir. Yazılardaki düşünce ve öneriler tümüyle yazarların sorumluluğundadır.

5. YAZI TÜRLERİNE GÖRE YAZIM KURALLARI

- Derginin yayın dili Türkçe ve İngilizcedir.
- Her tür bilimsel yazı için, *Word* dosyası halinde ayrı ayrı "Editöre Sunum Sayfası" ve "Kapak Sayfası" hazırlanmalı ve dergiye başvuru esnasında ayrı birer dosya halinde gönderilmelidir. Dergimiz İnternet sitesinden "Editore Sunum Sayfası" ve "Kapak Sayfası"na dair örnek şablonlar indirilebilir. Yazım dili Türkçe olan yazılar için sadece Türkçe şablonun, yazım dili İngilizce olan yazılar için ise sadece İngilizce şablonun doldurulup gönderilmesi yeterlidir.
- Her makale için yazarlar "TELİF HAKKI DEVİR FORMU"nu, bilimsel yazılarını dergiye başvuru esnasında doldurup imzalayarak, yazıları ile birlikte dergiye göndermelidirler. Türkçe ve İngilizce form İnternet sayfamızdan indirilebilir. Yazım dili Türkçe olan yazılar için sadece Türkçe formun, yazım dili İngilizce olan yazılar için ise sadece İngilizce formun doldurulup gönderilmesi yeterlidir.
- Bilimsel yazı kabul edildikten sonra baskı öncesi kopyanın her sayfasının ve Telif Hakkı Devir Formu'nun tüm yazarlar tarafından ıslak imza ile imzalanması ve tüm bu evrakın BETİM Hasekisultan Mah., Topçu Emin Bey Çıkmazı, no. 4, 34096 İstanbul adresine posta yoluyla gönderilmesi gerekmektedir (tel. 0212 632 0369; faks 0212 632 0328). İlk başvuruda bunların elektronik olarak yüklenmesi yeterlidir.
- Dergilere yayımlanmak üzere gönderilecek yazıların türlerine göre yazım kuralları aşağıda tanımlanmıştır.

5.1. ORİJİNAL ARAŞTIRMA MAKALESİ

- Yazılar *Microsoft Word*® belgesi olarak hazırlanmalı ve 1,5 aralıklı, 12 punto, iki yana yaslı ve *Times New Roman* karakteri kullanılarak yazılmalıdır. Sayfa kenarlarında 2,5 cm boşluk bırakılmalı ve sayfa numaraları sayfanın sağ üst köşesine yerleştirilmelidir.
- Kör hakemlik ilkesi gereğince, "Editöre Sunum Sayfası" ve "Kapak Sayfası" sisteme ayrı birer dosya halinde yüklenmelidir. Editöre sunum sayfasında olması gereken bilgiler, yazının türü, daha önce başka bir dergiye gönderilmemiş olduğu ve varsa çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve bu özel ve tüzel kişilerin yazarlarla olan ilişkileri belirtilmelidir. Kapak sayfasında ise Türkçe ve İngilizce olarak alt alta olacak şekilde yazının uzun başlığı ve 40 karakteri geçmeyen kısa başlığı, yazar bilgileri ve sorumlu yazar bilgileri ve önerilen hakem bilgileri yer alır. İnternet sitemizdeki örnek şablonlarda bu bilgilerin nerede ve nasıl verileceğine dair yönlendirmeler mevcuttur. Yazarlara, izin alınan etik kurullara ve kurumlara ait bilgiler yazının ana metninde yer almamalıdır. GEREÇ VE YÖNTEMLER bölümünde bu ibareler XXXXXXX şeklinde yazılmalıdır.
- Yazıya ait ana metnin ilk sayfasında çalışmanın uzun başlığı Türkçe ve İngilizce olarak yer almalı, başlık büyük harflerle yazılmalı ve sayfanın geri kalan kısmı boş bırakılmalıdır. Başlıkta kısaltma kullanılmamalıdır.
- Daha sonra önce "ÖZ" (çalışmanın yazım dili İngilizce ise *ABSTRACT*) bölümü yazılmalıdır. Bu bölüm en fazla 300 kelimeden oluşmalıdır. Türkçe ve İngilizce yazılmalıdır. Bu sayfa da ayrı bir sayfa olmalı ve anahtar sözcüklerden başka yazı bölümü içermemelidir.
- Yazının ana metni Türkçe ise önce ilk sayfaya Türkçe ÖZ, ikinci sayfaya İngilizce *ABSTRACT* yazılmalıdır. Yazının ana metni İngilizce ise önce ilk sayfaya İngilizce *ABSTRACT*, ikinci sayfaya Türkçe ÖZ yazılmalıdır.
- ÖZ veya *ABSTRACT* yapılandırılmış olmalıdır. Yapılandırılmış ÖZ (*ABSTRACT*) bölümünde

- "Amaç (*Aim*),"
- "Gereç ve Yöntemler (*Materials and Methods*),"
- "Bulgular (*Results*),"
- "Tartışma ve Sonuç (*Discussion and Conclusion*)"

olmak üzere dört alt başlık yer almalıdır. ÖZ'de paragraflar içeriden başlamamalıdır.

- Türkçe ve İngilizce özetin sonunda yer alacak olan anahtar sözcüklerin sayısı en az iki, en fazla altı olmalıdır. Bunlar birbirinden noktalı virgül (;) ile ayrılmalı ve alfabetik sıraya göre sıralanmalıdır. Örneğin: **Anahtar Sözcükler:** insan denekler; klinik araştırmalar; kontrollü deney; randomize kontrollü deney. İngilizce anahtar sözcükler *Medical Subject Headings* (*MeSH*) doğrultusunda verilmelidir. Anahtar sözcük seçimi için, izleyen bağlantı tıklanarak açılan sayfada, ilgili konuya dair uygun sözcük girilerek anahtar sözcüklere ulaşılabilir: www.nlm.nih.gov/mesh/MBrowser.html. Türkçe anahtar sözcükler Türkiye Bilim Terimleri (TBT) doğrultusunda verilmelidir: www.bilimterimleri.com.
- ÖZ ve *ABSTRACT* bölümlerinden sonra ana metne yeni bir sayfada GİRİŞ bölümü ile başlanmalıdır. Yazıda GİRİŞ, GEREÇ VE YÖNTEMLER, BULGULAR, TARTIŞMA VE SONUÇ, gerekli ise TEŞEKKÜR ve KAYNAKLAR ana bölümleri yer almalıdır. Ana bölümlerin başlığı büyük harflerle ve **kalın** olarak yazılmalıdır. Ana başlıklar sola yaslı olmalıdır.
- GİRİŞ bölümünün son paragrafı çalışmanın amacını açıklamalıdır.
- Kaynaklar, ilgili cümlenin sonunda parantez içinde numaralarla, metin içinde geçtiği sıraya göre verilmelidir. Örneğin; …… (1). veya …… (1,2). veya …… (3–5).
- Ana metinde paragraflar *Word* programında yer alan cetvel yardımıyla 1 cm içeriden başlamalıdır.
- Yazıda yer alan tüm alt başlıkların sadece ilk harfi büyük olmalıdır. Yalnızca alt bölümler içindeki alt bölümlerin (alt-alt bölümlerin) başlıkları *italik* yazılmalıdır.
- GEREÇ VE YÖNTEMLER bölümü ile BULGULAR bölümünde verilmesi düşünülen Tablo ve Görsel yazılarının ilk harfi büyük olmalı ve **kalın** yazılmalıdır. Örneğin **Tablo 1., Görsel 1.** Tablo yazıları ilgili tablonun üzerinde, görsel yazıları ise ilgili görselin altında yer almalıdır.
- Tablo ve şekiller metin içerisinde nerede geçiyor ise o bölümde ilgili cümlenin sonuna parantez içinde **Tablo 1.** veya **Görsel 1.** gibi yazılmalı, ancak ilgili tablo ve görseller başlıklarıyla birlikte kaynaklardan sonra ve her biri bir sayfada olacak şekilde ayrı ayrı verilmelidir. Görsel ve tablo üzerinde kısaltma ve/veya sembol kullanılmış ise tablo/görsel altında 8 punto ile yazılarak açıklanmalıdır.
- Görseller (örneğin fotoğraflar) metne eklenmemeli, ayrı bir dosya olarak (görüntü kalitesi 300 dpi olacak şekilde ve .jpeg, .bmp, .tif vb. formatta) sisteme yüklenmelidir. Görsel alt yazıları, son tablonun olduğu sayfadan hemen sonra, ayrı bir sayfada sırasıyla, ilk harfleri büyük olacak biçimde (**Görsel 1.** Açıklayıcı metin) yazılmalıdır.
- Daha önce basılmış görsel, tablo ve grafik kullanılmış ise yazılı izin alınmalı ve bu izin açıklama olarak görsel, tablo ve grafik açıklamasında parantez içinde belirtilmelidir.
- Çalışmada veri analizi yapılmış ise GEREÇ VE YÖNTEMLER bölümünün son alt başlığı olarak "İstatistiksel analiz" başlığı tanımlanmalı ve bu bölümde hangi amaç için hangi istatistiksel yöntemlerin kullanıldığı ve ilgili paket programlar yazılmalıdır.
- BULGULAR bölümünde yöntem adları verilmemelidir.
- Çalışmada TEŞEKKÜR bölümü gerekli ise bu bölümde, çıkar çatışması, finansal destek, bağış ve diğer bütün editöryal (İngilizce/Türkçe değerlendirme) ve/veya teknik yardım belirtilmelidir.
- KAYNAKLAR bölümü aşağıda belirtilen kurallara uygun olarak yazılmalıdır.

5.2. DERLEME TÜRÜ YAZILAR

Orijinal araştırma yazıları için yukarıda tanımlanan yazım kuralları derleme türü yazılar için de geçerlidir. Sadece aşağıda tanımlanan birkaç maddede değişiklikler söz konusudur:

- Derleme türü yazılarda ana başlıklarda değişiklikler yapılabilir.
- Derleme türü yazılarda ÖZ en fazla 250 kelimeden oluşmalıdır.

5.3. VAKA SUNUMU / VAKA SERİLERİ VE DİĞER TÜRDEN YAZILAR

Orijinal araştırma yazıları için yukarıda tanımlanan yazım kuralları vaka sunumu veya vaka serileri türünde hazırlanan yazılar için de geçerlidir. Sadece aşağıda tanımlanan birkaç maddede değişiklikler söz konusudur:

- Vaka sunumu türündeki yazılarda ana başlıklarda değişiklikler yapılabilir.
- Derleme türü yazılarda ÖZ en fazla 150 kelimeden oluşmalıdır.
- Bu tür yazılarda kaynak sayısı 15'i aşmamalıdır.

Bu üç ana yazı türünden başka;

- Editöryel Yorum/Tartışma türünde (yayımlanan orijinal araştırma makalelerinin, araştırmanın yazarları dışında konunun uzmanı tarafından değerlendirilmesi) veya
- Editöre Mektup türünde (son bir yıl içinde dergide yayımlanan makaleler ile ilgili okuyucuların değişik görüş, tecrübe ve sorularını içeren, en fazla 500 kelimeden oluşan yazı türü) yazılar da gönderilebilir. Bu yazıların hazırlanmasında da genel yazım kuralları geçerlidir. Bu yazı türlerinde,
  - Başlık ve özet bölümleri yoktur.
  - Kaynak sayısı beş ile sınırlıdır.
  - Sayı ve tarih verilerek hangi makaleye atıf yapıldığı belirtilmeli ve sonunda yazarın ismi, kurumu ve adresi bulunmalıdır. Mektuba cevap, editör veya makalenin yazar(lar)ı tarafından, yine dergide yayımlanarak verilir.

KAYNAK YAZIM KURALLARI

- Dergilerin atıf sayılarının sağlıklı olarak tespit edilebilmesi, kaynakların düzgün yazılmasıyla doğrudan ilişkilidir. Dergimizde Vancouver kaynak yazım stilinin bir varyantı kullanılmaktadır.
- Dergiye başvuru sırasında kaynakların ayrıştırılması, atıflar açısından büyük önem taşımaktadır. Bu ayrıştırmanın sağlıklı bir şekilde yapılabilmesi için kaynakların Vancouver kaynak yazım stiline göre yazılması büyük önem arzetmektedir. Dergimiz kaynak yazım kuralları, kaynak yazının türüne göre aşağıda tanımlanmıştır.

Dergi Makaleleri İçin Yazım Kuralları

[Her yazar için] yazarın soyadı, yazarın adının baş harf[ler]i. Makalenin başlığı [yalnızca ilk kelimenin ilk harfi büyük, geri kalanlar özel isim değilse küçük olarak]. Derginin adı [italik, kısaltılmış ve her harf öbeğinin ilk harfi büyük olarak]. Yıl;cilt(sayı):başlangıç sayfa numarası–bitiş sf. no. [mükerrer rakamlar çıkarılmış olarak].

Örnek:
Abaraogu UO, Tabansi-Ochuogu CS. As acupressure decreases pain, acupuncture may improve some aspects of quality of life for women with primary dysmenorrhea: a systematic review with meta-analist. J Acupunct Meridian Stud. 2015;8(5):220–8.

Kitaplar İçin Yazım Kuralları
[Her yazar için] yazarın soyadı, yazarın adının baş harf[ler]i. Kitabın Adı [bağlaç, soru eki vb. hariç, tüm sözcüklerin ilk harfleri büyük olarak], [varsa] ed. [her editör için] editörün soyadı, editörün adının baş harf[ler]i, [ya da varsa] çev. çevirmenin soyadı, çevirmenin adının baş harf[ler]i, X. ed. [ilk edisyon/baskı değilse X. edisyon/baskı olduğu bilgisi]. Yayınevinin kenti: Yayınevinin ismi; yayımlanma tarihi:göstermek istenirse kaynak gösterilen sayfa[lar].

Örnek:
Ankaralı H, Cangür Ş, Sungur MA. Formülsüz Biyoistatistik. İstanbul: BETİM; 2015.

Beauchamp TL, Childress JF. Biyomedikal Etik Prensipleri, çev. Temel MK, 7. ed. İstanbul: BETİM: 2017:263.

Kitaplar Bölümleri İçin Yazım Kuralları
[Her yazar için] yazarın soyadı, yazarın adının baş harf[ler]i. Kitabın bölümünün adı [yalnızca ilk kelimenin ilk harfi büyük, geri kalanlar özel isim değilse küçük olarak]. In: [varsa, her editör için] editörün soyadı, editörün adının baş harf[ler]i, (ed.), [ya da varsa] çevirmenin soyadı, çevirmenin adının baş harf[ler]i (çev.), Kitabın Adı [tüm esas sözcüklerin ilk harfleri büyük olarak], X. ed. [ilk edisyon/baskı değilse X. edisyon/baskı olduğu bilgisi]. Yayınevinin kenti: Yayınevinin ismi; yayımlanma tarihi:bölümün başladığı–bittiği sayfa.

Örnek:
Beauchamp TL, Childress JF. Özerkliğe saygı. In: Temel MK (çev.), Biyomedikal Etik Prensipleri, 7. ed. İstanbul: BETİM: 2017:153–226.

İnternet Kaynakları İçin Yazım Kuralları
İnternet girisini giren kişinin soyadı, adının baş harf[ler]i, ya da, kurumun tam ve açık adı (varsa giri tarihi). Giri başlığı [özel isim olmadığı sürece sadece ilk kelimenin ilk harfi büyük olarak]. Erişim: adresi (erişildi: son erişildiği tarih).

Örnek:
T.C. Resmî Gazete (29.6.2019). Eczacılar ve Eczaneler Hakkında Yönetmelikte Değişiklik Yapılmasına Dair Yönetmelik. Erişim: www.resmigazete.gov.tr/eskiler/2019/06/20190629-8.htm (erişildi: 12.9.2020).

Türk Dil Kurumu. Kesme işareti (’). Erişim: www.tdk.gov.tr/icerik/yazim-kurallari/kesme-isareti (erişildi: 8.8.2020).

Yayımlanmamış Yüksek Lisans/Doktora Tezleri İçin Yazım Kuralları
Yazarın soyadı, yazarın adının baş harf[ler]i. Tezin adı [kitap adı gibi yazılmış şekilde] (yayımlanmamış yüksek lisans/doktora tezi). Yükseköğretim kurumunun kenti: kurumun ismi: yıl [kitapların yayımlandığı yer, yayınevi ve tarih bilgileri gibi].

Örnek:
Barış M. Down Sendromu Bağlamında Seçici Kürtaj Hakkındaki Etik Argümanların Normatif Analizi (yayımlanmamış yüksek lisans tezi). İstanbul: T.C. İstanbul Üniversitesi, İstanbul Tıp Fakültesi, Tıp Tarihi ve Etik Anabilim Dalı; 2017.

6. GENEL AÇIKLAMALAR

Medical Subject Headings (MeSH) nedir?
- Uluslararası başlıca makale tarama dizinleri ve veri tabanlarında, makalelerin sınıflandırılması için kullanılmakta olan, tıbbi–biyolojik terminolojiye standart getirmeyi amaçlayan ve sürekli güncellenen, İngilizce makalelerin anahtar sözcüklerinin seçilebileceği, geniş bir tıbbi–biyolojik terimler dizinidir.

Türkiye Bilim Terimleri (TBT) nedir?
Ulusal düzeyde tıbbi–biyolojik terminolojiye standart getirmeyi amaçlayan, şimdilik 186.000 tıbbi–biyolojik terim içeren ve sürekli güncellenen, Türkçe makalelerin anahtar sözcüklerinin seçilebileceği tıbbi–biyolojik terimler dizinidir.

Anahtar Sözcükler Neden *MeSH* ya da TBT Arasından Seçilmelidir?
- *MeSH* ve TBT terimleri, ana başlıklar ve alt başlıklardan oluşan, birbiri ile ilişkilendirilmiş hiyerarşik bir yapı ile kodlanmışlardır.
- Böylece tek bir terim ile yapılan aramada, ana başlıklar yanında terimin ilişkilendirildiği tüm alt başlıklar da otomatik olarak aramaya dahil edilir.
- Aynı terim, birden çok terminoloji ile tanımlanmış olduğundan, araştırmacının az veriyle, kolay ve hızlı bir şekilde mümkün olduğunca çok makaleye ulaşabilmesini sağlar.

KISALTMA VE AKRONİMLER
Kısaltılacak sözcüğün ya da sözcük öbeğinin ilk geçtiği yerde parantez içinde verilmelidirler. Aynı sözcük(ler) için tüm metin boyunca aynı kısaltma/akronim kullanılmalıdır. Uluslararası kullanılan kısaltmalar için “Bilimsel Yazım Kuralları” (*Scientific Style and Format: the CBE Manual for Authors, Editors, and Publishers)* kaynağına başvurulabilir.

7. YAZININ GÖNDERİM AŞAMASINDA DİKKAT EDİLECEK NOKTALAR
- Sorumlu yazar, “TELİF HAKKI DEVİR FORMU”nu doldurup, çalışma ile birlikte dergiye göndermelidir.
- Yazarlar, makaleyi değerlendirmek üzere potansiyel iki hakemin ismini ve güncel iletişim bilgilerini (e-posta, telefon, faks) Editöre Sunum sayfasında bildirmelidirler. Bununla birlikte editörlerin hakemleri bizzat seçme hakkı mahfuzdur.
- Gönderiler, yazılar TÜBİTAK ULAKBİM DergiPark sistemine (http://dergipark.gov.tr/anadoluklin) yüklenerek gerçekleştirilmelidir.
- Gönderi sırasında Editöre Sunum sayfası, kapak sayfası, yazının ana metni, Telif Hakkı Devir Formu ve varsa görseller ayrı dosyalar halinde yüklenmelidir.
- Yazarlar İnternet sitemizdeki hakem değerlendirme formlarını inceleyerek hakemlerin incelediği konulara özellikle dikkat ederlerse yazımdaki eksikliklerini hakem sürecinden dönmeden gidermiş olurlar. Yine de hakemler her türlü eleştiriyi yapma hakkına sahiptir.

Yıl : 2 Sayı 4. Mart 1935.

Anadolu Kliniği

Üç ayda bir Konyada neşrolunur.

MECMUAYI DAİMİ YARDIM VE HİMAYE ALTINDA BULUNDURAN HEYETİ NAŞİRE :

İSTANBULDAN: Prof. Abdülkadir Lûtfi - Prof. İhsan Hilmi - Prof. Kâzım Nuri - Prof. Kemal Cenap - Prof. Kemal Hüseyin - Prof. Kenan Tevfik - Dr. Mehmet Kâmil - Prof. Neşat Ömer - Prof. Niyazi İsmet - Prof. Server Kâmil - Prof. Süreyya Ali - Prof. Tevfik Salim - Dr. Yakup Hüseyin. Dr. Vefik Vassaf. ANKARADAN : Dr. Emir Necip. - Dr. Mustafa Hilmi - Dr. Ömer Vasfi Dr. Salahi Vehbi - Dr. Şükrü Yusuf. İZMİRDEN : Dr. Hasan Yusuf - Dr. Hüseyin Hulki - Dr. Zühtü Kâmil.

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KLİNİK DERSLERİ.

İGTİDA HASTALIKLARİLE TEDAVİLERİNDE ESASLI NOKTALAR·

Profesör Dr. Server Kâmil Tokgöz.
İstanbul.

İgtida teşevvüşlerinden meydana gelen hastalıklar patolojinin mühim bir kısmını işgal ederler. Bu marazî proçesleri lâyıkile anlayabilmek ve onlara ait tedavileri doğru yapabilmek ancak igtidanın mihanikiyetine nüfuz ile mümkündür. Makale, bu mihanikiyet ile beraber igtida teşevvüşlerini ve teşevvüşlerden mütevellit hastalıkların tedavilerini umumî bir bakımdan hulasa edecektir.

Fisyolojik vazifeler arasında en kompleks bir mevzu olan *İgtida,* hayatta olan uzuvların fisiko-şimik muvazenesini tutan işlerin heyeti mecmuasıdır. *İgtidada* gıdaların imtisası, temessülü, bakayanın ifragı mevzuubahistir.

Gıda, mesiçlerimize lûzumlu olan maddeleri getiren unsurlardır. Bu maddelerin bir kısmı teneffüs ile, diğer mühim bir kısmı da ağız yoluyla alınır. Teneffüş ile alınan oksijendir. bu gazın hem gıdaî hem yakıcı hassası vardır.

Gıdalar hadlizatinde karbonidrat, yağ, albüminden ibaret üç sınıfa mensuptur. Ağızdan alınan bu maddelerin hepsi mide ve mıada mayaların tesirile dahilî uzuviyete girmeğe müsait şekil alırlar. Neticede karbonhydratlar : glikoza; yağlar gliserinle şahmi kamızlara; albüminler: asit aminelere; nükleoproteitler; fosfor ve pürik mürekkebata ayrılırlar. Bu hadiseye istiklabın birinci safhası yani (anabolisme) denir.

Hazım mayaları: amilas, lipas, proteas, grubuna mensup olup bir kısmı midede, diger kısmı mia ve pankreasta bulunur. Bunların sayısı her gün çoğalmaktadır. Netekim amilas yanında maltas; envertin yanında laktas; pepsin ve tripsin yanında erepsin ve enterokinas bulunur. Gıda maddelerinin parçalanmış olanları mia tarafından mas olununca hücrelerin plastik hayatile teneffüsî hayatına lâzım olan karbonidratla yağ ve albümin tekrar teşkil olunur.

Bu teşekkül komplekstir, çünkü teşekkül işi hazırlanan mahsullerin formüllerine göre değil nesiçlerin ihtiyacına göre yapılır. Bu hadiseye de istiklabın ikinci safhası yani (Catabolisme)denir.

Uzvî maddeler haricinde olan emliha ise ya oldukları gibi yahut parçalanarak mas olur ve devrana geçerler. Mas olunan mahsullerin bereketi tegaddinin bolluğu ile alâkadardır. Mamafi alınan gıdaların keyfiyeti arasında vaki olan tercihler uzuviyetin muvazenesini teşviş ederek yeni yeni vaziyetler ihdas eder. Meselâ karbonidratlarla yağlara fazla meclubiyet şişmanlığı; tahditleri, zafiyeti

mucip olduğu gibi safra, kilye taşlarila asidos, alkalos, oksalemi, idropizi de tegaddinin umumunda yahud bir kısmında yapılan ifratın birer neticesidir. Keza hazmî tehammürler barsak bakterilerini artırır, bu artan mikroplar bazı gıdalardan aldeit, asit bütirik, asit oksalik çıkmasına sebep olur. Şu halde igtida işinde önde mia cidarı ile mianın lenfoit nesci gelir Çünkü bunlar moleküler teşekkül vazifesile mükelleftir.

Bundan sonra igtida ile alâkası olan uzuvlar sırasile şunlardır:

1) *Karaciğer;*

Karaciğer; süzmek depo etmek ve ifraz yapmak işlerini üstüne almıştır. Veridi bab ile karaciğere gelen yeni teşekküllerden karbonidratlarla yağlar, demir orada tevkif olunup kükürt fenolla birleşir, aminler desamine olur, setonik cisimler yanar, amonyak çıkar, kolesterin asit kolaliğe ayrılır. Tevkif olunanlardan şeker, asit amine, kükürt, demirin bir kısmı karaciğerde depo halinde muhafaza olunup lüzum ve ihtiyaç zamanında tekrar uzviyete iade olunurlar. Bütün bu çalışma mayalarla karaciğerin oksidan, idratan, litik, desaminan, hassaları sayesinde vukua gelir.

Karaciğerden kurtulmuş yahut kendi tarafından teşkil olunmuş maddelerle mahmul olan kan evvelâ kalbe sonra akciğere gider. Burada hamızı karbonunu verir, yerine oksijen alır, ve yine burada bazı yağlar tahrip edilir, kükürt okside olur. Şu halde vücuda giren gıdaî maddeler bidayeten kısmen karaciğerde, kısmen de akciğerlerde bir muameleye tabi kılınmış olur. Bu iki sahada vukua gelen fisyolojik hadisenin teşevvüsü meydana şu, bu, menşee ait igtida hastalıklarının husulüne vesile olur.

Karaciğer ve akciğerlerde vuku bulan en fisyolojik hadiselerden yakasını kurtarmış olan gıda maddeleri yine kanla uzuviyete yayılarak burada idame ve tamire hizmet etmekle beraber ifraza ait yeni mahsüllerin de meydana gelmesinde amil olurlar. Fevkalâde nazik olan bu son ameliye hücrelerin hariminde vukua gelir.

2) *Hücredeki igtida mihanikiyeti:*

Hücrede vaki olan hadise dörde ayrılır;

A) gıdanın hücreye girmesi,

B) gıdanın temessülü,

C) muzaddı temessül teşekkülât.

D) bakayanın ifragı.

Hücreye girme meselesi kabiliyeti nüfuziye işidir. Bu iş yüksek bir hayvan hücresi için ne ise bir amip bir lökosit için de aynıdır. Şimdiye kadar hayatî bir hadise adedilen kabiliyeti nüfuziye fisiko-şimik bir iştir. Bu hadise her bir unsurun bünyesile değişir. Bazı müellifler hücrede gıdanın geçmeğe mecbur olduğu lipoproteik bir gışadan bahsederler, ve bu gışaya da (L h e r m i t t e - O v e r t a n) gışası denir. Son araştırmalar gışadan ziyade hücrelerin birbirleri üzerinde kümelendiği yerde bir mıntaka mevcudiyetini kabule meylettirmiştir. Bu mıntakaya *systeme lacunaire* dahi diyebiliriz. Bütün fisiko-şimik hadise burada vukua gelir, ve burası şiryanî ve veridî cümleye mütevassıtlık eder. Buraya kadar gelmiş olan gıdaî unsurlar kolloitlerin tansiyonu, osmetik tansiyon gibi muhtelif kuvvetlerin tesirile hücre içine girer ve yerine diğerleri çıkarak mübadele vaki olur. Bu mıntakada şimdiye kadar tetkik edilen muvazeneler şunlardır:

A) acide-base muvazenesi, hamız ve kalevilerin birbiri aleyhine olan ifratı tanzim eder.

B) Lipocytique muvazene, nesiçlerin suyunu tanzimeder;

C) Minero-mineral muvazene: hücrenin içine ve dışına yayılmış olan (K, Na, Ca, Zn)ionlarının keyfiyet ve kemmiyetinde müdahale eder.

Bütün bu muvazenelerin tebeddülünden: dahame, dumur, pletor, idratasyon, kuruma meydana gelir. Mamafih bazı nesiçlerde kabiliyeti nüfuziye elektivité gösterir, yani bazısı albümini, bazısı yagı, bazısı emlihayı diğerlerine nazaran fazla aldığı gibi bazan da şeçim yadar. Bu hal hücrelerin bir kısım maddelere karşi acil ihtiyaçlarını gösterir. Meselâ albüminler adelelerle, karaciğere; karbonidratlar: karaciğer, adelât, kalbe; yağlar: yağlı nesiçlere; kireç, fosfor: kemiklere; kükürt, sürrenal ile kepte; sodyum: hilâli ahlâta; hadit; kırmızı küreyvat ile kept hücrelerine; lesitin: cümlei asabiyeye gider.

Bu vaziyete, nazaran bir nescin igtidasındaki teşevvüş kâh elektif gıdaî bir noksaniyete kâh hücrenin muhtaç olduğu maddeyi kendisine karıştırmak hususunda gösterdiği kifayetsizliğe tabi olmuş olur.

Tesbit, istihâle, ifrag vazifesile mükellef olan hücrenin kimyevi icraatında mûdaliyet vardır. çünki hücre kimyası muhitte başka, merkezde başkadır. Növe hamız, protoplazma kalevidir. Hücre muhiti, tahammuzların mahalli; hücre merkezi, irca mevkiidir. Kolloit miçellerin ve ionların disperse olduğu hücre hariminde elektro şimik mücadele kâh (gel) kâh (sol) gibi mütenavip fiillerle vukua gelir. Burada faaliyete geçen muhtelif cisimler arasında *glutathion* ile eritme, irca, tehammuz muhammirleri bulunur. Hücreye girmiş maddeler bu muhtelif amillerin tesirile birbirlerile kaynaşarak ortaya kolloit ve emlihadan mürekkep yeni cisimler meydana korlar. Bu mürekkebatın teşekkülü için gayri faal bir kolloide cezp ve def filini *(Nevton kanunu)* tanzim eden muayyen elektrik hamulesini hamil bir ion terfik edilmiştir. Esası pek muhtelif maddelerden ibaret olan bu teşekküller her saniye dağılma ve birleşme halinde olduğu gibi hücre faaliyeti de husule gelen yeni cisimleri def etmeğe müntehidir. Haddizatında ifrazda bulun-

mayan göcre izah edilen mihanikıyetle derununa giren maddeleri başka bir şekilde iade etmiş olur. Bu iade edilen maddeler başka nesiçler tarafından kullanılır. Meselâ sürrenal, asit aminelerle adrenalin yapar; pratiroit, guanidini tebdil ederek paratirin yapar: tiroit, iodu triptofanla birleştirerek tiroksin yapar.

3) Endokrin guddelerinin vazifesi:

Gerçi bu guddelerin dahilî ifrazları beslenmede bir rol oynamazsada, lâkin devran işlerinin idamesine, ihtiraklara, tahammuzlara, inkişafa yardım eder Bu ifrazata *Hormon* yahut *Hormozon* derler. En faal gudde tiroit olup ihtirakı körükler. Tiroit; idro - salin, proteik, yağ muvazenesine müessir olduğu gibi kilsin tesbitine, esasî istiklaba, kıl, tırnak dişlerin inkişafına yardım eder. Adrenalin ifrazeden sürrenal kolesterin, kükürt istiklabına hizmetle beraber amilolisi de kolaylaştırır. Pankeras ensülini ise glikozun imtisas ve yanmasını temin eder. Hipofiz: inkişafa, pürik ve yağ metabolismasına; Paratiroitler; kolloit ve kils birleşmesine muavenet eder. Yumurtalıklarla husyelerin tesiri morfojeniktir. Mahaza bu muhtelif guddeler vazifelerinde müstakil değildir, aralarında tam bir sinerji vardır.

Meselâ tiroid'in tenbihi zamanla sürrenal'in hacmini büyütür; hipofiz tenebbühü timüs ve tiroit üzerine tesir eder; husyenin dumuru ekseriya diğer guddelerin küçülmesile terafuk eder. Hülâsa böylece teşekkül eden plüri -glandüler sendrom: şişmanlığı, çok iriliği, ürisemiyi, kolesterinemiyi. glikozüriyi idare eder, neticede endokrin teşevvüşünden geıen igtida hastalıkları ortaya çıkmış olur.

4) Cümlei asabiyenin müdahalesi:

Yukarda yazılan muhtelif guddelerin arasındaki zıddiyet yahut müşareket yalnız hormonlara tabi olmayup hormonların cümlei asabiye üzerindeki tesirlerile guddeler arasındaki asabi münasebetlere de bağlığlıdır. Asabi münasebetleri vejetatif cümle idare eder. Bu cümleyi teşkileden reevi ile sempatik arasında sıkı bir münasebet vardır. Netekim asabı haşevinin tenbihi adrenalin ifrazını artırdığı gibi asabı reevinin tenbihi de mide ve pankreası ifraza sevkeder. Keza adrenalin sempatik cümleye; pepsinle ensülin asabı reeviye; tiroit ifrazı hem reeviye hem sempatiye tesir eder.

Bu tecrübi vakıalar seriiyatta bazı buhranların deklanşe olmasında cümlei asabiyenin tesirini görmekle de teeyyüt eder. Bundan başka sempatik ile reevinin tenbihleri kandaki kalsiyümü birbirine zıt olarak tadil ederler. Netice itibarile endokrin bir guddenin vazife itibarile ifrat yahut kifayetsizliğine cümlei asabiye ıin tenebbüh, nehyi le ınzimam edince: kollesteri iemi dekalsifikasyon, zafiyet, hiperglisemi, ürisemi, obesite, hiperplasi, aplasi, hipertrofi, atrofi, gibi igti la teşevvüşleri meydana çıkar.

5) Kanın müdahalesi:

Kan, gıdaî unsurları nesiçlere veren ve bakayayı nesiçlerden alan bir vasıtadır. Bu alup verme hareketile terkibi daima tebeddül eder. Kanın içine giren ve içinden çıkan maddelerin yekûnu ne olursa olsun kanın kimyevî unsurlarında hayatî bir muvazene vardır. Esasen kanda da hilalî sistemde mevcut olan muhtelif muvazenelerin hepsi vardır, yalnız bu muvazeneler kanda daha fazla proteik hamule ile vazifedardırlar. Çünkü nesiçlere nazaran albüminden zenkin emlihadan fakirdir. Kandaki kolloidal muvazenede istikrar yoktur, ve bu muvazene pepton yahut aşı şırıngası, troma, heycan hafif intan, hazmî toksinler ile bozulabilir. Kollodial bir mahlûl berrak yahut süt rengindedir, bulanırsa calihalaşır. Bu hadiseye flokülasyan derler, ve albüminler üzerine vaki olur.

Flokülasyon bazı şahıslarda diğerlerine nazaran daha kolay olur. Bununda sebebi bu şahısların bir kısmının muhtelif intan ve tesemmüm iln hazırlanmış olmaları, bir kısımlarınında veladî bir istidada malik olmalarındandır. İşte ahlâtta veraset meselesi budur. Bazı ailelerde görülen astm, migren, eksema gibi igtida hastalıklarının da mihanikiyeti budur.

Flokülasyon yanıuda krıstaloitlere isabet eden birde presipitasyon meselesi vardır. Buda hıltın presipitan kuvvetine tabi olup ya kisbi yahut irsi olarak kazanılır. Presipitan temayül neticesinde konkresyonlar teşekkül eder, ve bu teşekküller arasında en çok görülenler fosfat, ürat, oksalat, kolesterin tevazzuatıdır. Teressüp hadisesinde teressüp eden maddelerin fazla alınması bir sebep olarak gösterilmişsede hakikat kemmiyetten ziyade işin keyfiyete tabi olmasıdır.

Bu kısma nihayet vermek için igtidada teşekkülü mecburi olan bakıyanın ittirah tarzında gözden geçirmek gerektir.

6) Bakayanın çıktığı yollar;

İgtidadan meydana çıkan bakayanın bazısı meselâ sürrenal pigmanı azalarda tavazzu ettiği halde mühim bir kısım da ree, deri, barsak, böbrek ile harice atılır. Ree, esnahdaki, dolayısila kandaki tansiyonla muhtelif nisbette hamızı karbon çıkartır, çıkan mikdar tegaddinin tabiatile teneffüsdeki sürate tabidir. Kanda hamızı karbon tansiyonunun fazlalığı gazin fazla nisbette ittirahını intaç ettiği gibi mütekabilen de fazla hamızı karbon basala üzerine tesir ederek teneffüs hareketlerini artırır. Muayyen bir zamanda muttarih olan hamızi karbonla mas olunan oksijen arasındaki nisbete emsali teneffüsi derler. Bu emsal şekerlerle vahide, müsavi olduğu halde, şahimlerle vahidden aşağı, albüminlerle daha aşağıdır, muhtelit bir rejimle vasattır.

Barsaklarla; demir, kireç, hamızı hummaz, ve muhtelif esaslar muttarih olur. Müshiller bu ittirahı çoğaltır; ishal, kanı hamızlaştırır, inkibaz kalevi kılar. Deri ile: su, kükürt, hamızat ve milhler ittirah eder.

Böbreklere gelince: buradan su, asit ürik, asit oksalik, emliha, klorürler, kibritiyetler, asit aminoler, setonik cisimler çıkar. Kilye vazifesindeki kifayetsizlik hamızların, ürenin, pürik müştekatın ihtibasını davet eder.

Bu uzun tetkikten istidlal edilen neticeye göre igtida hastalıklarında başlıca altı sebeb tesbit olunabilir:

A) Tegaddide ifrat, kifayetsizlik,
B) Karaciğerde vazife kifayetsizliği,
C) Endokrin guddlerin vazifelerindeki teşevvüşler,
D) Vejetatif cümlede hiper yahut hipotoni,
E) Bakayanın ittırahındaki kifayetsizlik,
F) Ahlatın fisiko-şimik muvazenesindeki istikrarsızlık,

Bu muhtelif sebeplerin her biri bir patojeniyi, kimyevî bir teşevvüş yahut teşevvüşlerin küllünü hülâsa ettiği gibi bunlarla tebeddül eden bir tedaviyi de idare eder.

Bu muhtelif teşevvüşlerin teşhisi için müteaddit tecrübeler lâzimdır. Evvelâ gıda bilânçosu tetkik olunur. Çünkü hiç bir hastalık yokturki gıda meselesi burada bir mevki almış olmasın. Meselâ pankreas, kept, tiroit vazifesindeki teşevvüşlerin gıdaî hatalar yüzünden vehamete uğradığı görülmektedir. Rejimden sonra hazım mayalariyla, miai transite tabi hazmî imtisas tetkik olunur, bu meyanda aranılacak şeyler şunlardır:

A) Azotun vücuda giren miktarila idrar ve maddei gaita ile harice çıkan miktarları arasındaki nisbet;

B) Karaciğerin vazifesini gösterecek azotürik emsallar: a) *Bouchard emsali* ki üre azotunun mecmu azota nisbetidir; b) *Maillard emsali* ki ürenin amino-asit ve amonyak nisbetidir.

C) Desaminasyonu tetkik için pepton tecrübesi:

D) Kükürtün tahammuzunu anlamak için mutedil kükürtün okside kükürte nisbetini bulmak:

E) Conjugaison'ları anlamak için kâfur tecrübesi yapmak;

F) Pürinlerin tahammuzunu anlamak için adale tecrübesi yapmak:

G) Amilolisi anlamak için adrenalin tecrübesini yapmaktır.

İşte bu muhtelif tecrübeler sayesinde karaciğer ve nesiçler hakkında vuzuhlu malûmat alınır.

Endokrin guddeleri hakkında malûmat almak için yapılacak tecrübeler şunlardır:

Hipotiroidiyenlerde kuvvetli yahut hafif tiroit hülâsasının bir yahut müteaddit defa şırıngası tabiî yahut hipertiroidiyenlerde olduğu gibi ne nabızda ayni betaafi, ne de ayni hipotansiyonu tahrik etmez; tiroidiyen ve sürrenalde adrenalin şırıngası tiroit ve kapsül kifayesizlerinde olduğu gibi ne ayni teserrüü kalbî ne de tevettürü şiryaniyi mucip olmaz.

Paratiroit kifayesizliğinden şüphe ediliyorsa kalsiyum tecrübesi yapılır.

Gidai glisemi ve glikozüri tecrübesinin tefsiri bir az komplekstir, çünkü bu tecrübe bir çok guddelerle alakadardır, meselâ: başta şekeri zabteden kept gelir, ondan sonra vücuda giren şekeri kullanan veya ihmal eden pankreas ifrazı dahilisi gelir, sonra da amilolisi arttıran sürrenal ile şekerin imtisas siasını tadil eden tiroit gelir. İşin içinden çıkmak için bütün bu tecrübelerle beraber teneffüsi hamızı karbonu tetkik etmelidir.

Zira teneffüsi hamızı karbonun mütaleası şekerin hakiki sarfını kanda şekerin çoğalmasile değil ancak ifrag olunan hamızı karbonun miktarile takdir ettirir. Hamızı karbonun tayini metabolismin ameliyesile olur. Esasi istiklap; istirahatte iken uzviyetin çalışmasını temin eden esas sarfiyattır. Hesabı ifra olunan hamızı karbon vasıtasile elde edilen kalori miktarını vücudun metre murabbaına nisbet etmektir. Bu sarfiyatın artması hipertiroitten mütevellit gıda teşevvüşünü gösterir.

Teşhiste tetkike değer bir cümle de vejetatif cümledir. Sempatik ile reevinin tonüsünü anlamak pilokarpin gibi vagotonik, adrenalin gibi sempatikotonik ilaçların şırıngasi ile olur. Dafirei şemsiye üzerine malûmat ise: reflexe oculocardiaque ile alınır.

Bunlardan sonra kilyenin kabiliyeti nufuziyesile ahlatın muvazenesi tetkik olunur. Bunlar için de kanda *p*H, ihtiyat kalevi tayinile beraber hamızı hummaz, kolesterin, hamızı bevil tayin olunur, klorür tecrübesi yapılır, *Mac Clure tes'ti* ile idrofili aranır. En nihayet presipitan temeyülün araştırılması da kolesterin dahili edimme teamülü ile olur.

Bütün bu araştırmalar gıdanın temessülü, ihtirakı, ittirahı, ve hılt muvazenesi hakkında malûmat verir, ve neticede münasip bir rejimle tedavi yapılabilir.

Münasip rejim nedir:

Anlaşıldığı vechile hücre hayatı, mütenasip ve muayyen gıdaların alınmasını istihdaf ediyor. Mecmu kalori sarfiyatını toptan olarak şu, bu gıdadan vermek iyi bir netice vermez. Tetkikat kilo başına bir gram albümin, altı gram maiyetikarbon, bir buçuk gram yağ tesbit etmistir. Bu hesaba göre 60 kilo sikletinde ve vasat iş yapan bir adam için 60 gram albümin, 350 gram maiyeti karbon, 90 gram şahim lâzımdır. Gerçi şişmanlarda bu rejim heyeti umumiyesinde azaltılır, zaiflerde çoğaltılırsada rejime giren bazı gıdaları azaltmak yahut çoğaltmak maksadı daha iyi tatmin eder. Meselâ: şişman adamda yağ ile nişalar azaltılır, zaiflerde çoğaltılır, nükahaya fazla albümin verilir, maden kaybedenlere kireç, kansızlara kan, et üsaresi, kuru sebzeler, yorgunlara lesitinli yağlar verilir. Keza asidozda kaleviden zengin patat, yeşil sebzeler; alkalozde et verildiği gibi ödemlerde tuz kesilir, nikrislilerde sakatat, gelatin ve etli gıdalar verilmez.

Yine bu gün malûmdur ki rejim vücuda yalnız idame ve tâviz maddelerini değil ayni zamanda da hayatdar unsurları getirmelidir. Faaliyet amili olan bu unsurlara *Zymosthenique* maddeler denir. Bunların bazıları asit amine sınıfındandır, triptofan, lösin gibi. Bazıları da hüviyetleri layikile belli olmayan ve aminlerle sterinlere yaklaşan unsurlardır ki bunlara da *vitamin* denir. Vitaminlerin bazıları suda münhal, bazıları yağlarda münhaldir. (B.C) vitaminleri trophisme nerveux ile kan ve via muvazenssine lazım olduğu gibi; (A.B) vitasterinide kseroftalmi ile rahitise mani olarak nümaya hizmet eder; keza (A) vitasterini kirecin yapışmasına (C) vitamini kolesterin metabolismasında; (B) vitamini glüsitlerin yanmasında alâkadardır.

Rejim meselesini hal ettikten sonra tedavide takip edilecek yollar şunlardır :

Keptin vazifesini faal kılmak; bakayanın kilye ve barsaklarla çıkmasını kolaylaştırmak; viaî guddelerin kifayesizliğini tamir edecek opoterapi yapmak (meselâ : obesitede tiroit; spasm ile dekalsifikasyonda paratiroit; diyabette: ensülin ve follikülin kullanıldığı gibi) ; vagosempatik muvazeneyi temin için asabı reeviyi felç eden atropin ile mezkûr asabı faal kılan ezerin ve pilokarpin kullanmak gerektir. Adrenalin sempatiyi tenbih eder, ergotamin felç eder.

Ahlat çok kalevi ise : hamızı fosfor, kalsyum; hamızî ise : bikarbonatlar, asido - setozda ensülin kullanılır. Piperazin ile kaleviler hamızı bevli; magnezi emlihası ile hamızı fosfor da oksalatları eritir. Bazı arızaların da anafilaksiden çıktığını yukarıda söylemiştik, bu nevi müzmin teamüllere karşı aşı, pepton, süt gibi sadme yapacak ilaçlar kullanılır. Netekim bazı artropatilerle migren ve astmada bu nevi tedaviden çok defa faide görülmektedir. Höcre vazifesinin ne kadar mûlak olduğu ve bu vazifede elektro - şimik ve fizik kuvvetlerin mühim nisbette alâkadar oldukları da düşünülürse tesiri oldukça esrarengiz olan fiziko - şimik tedaviden elektrisite, radrasyona müracaat zaruret kesbeder.

Meselâ : haute frequence'in nesiçler üzerindeki tesiri musarrif olduğu gibi tansiyonu da azaltır. Galvano - faradisation, mübadelâtı faal kılar; ionisation, muaddil olan ion ve cation'ları höcrenin içine sokar; ültraviolet, kolesterin inhilaline yardım eder, derideki provitinleri vitamine tebdil eder ve betahsis kirecin tesebbütüne hizmet eder.

Mekanik tedavilerden masaja gelince adelâtı takallüs ettirir; idroterapi, souk sıcak derecesine göre musarrif, müsekkin, münebbih olduğu gibi kan deveranını da faal kılar. Spor, yürüme, teneffüs emsalini arttırdığı gibi teri de intaç ederek bazı teressübatın inhilâline yardım eder.

Krenoterapi, ahlatın kalevileşmesine, höcrenin tenebbühüne , elyafı melsanın tonisitesine, uzuviyetin yıkanmasına, kilyevî, safravî ittiraha hizmet etmekle beraber nesiçlerin içine kabili vezin maddelerden mada radio-actif, nadir gazler, zimostemik gibi maddeleri de sokarak temessülü ve höcre tazelenmesini mucip olur.

Pratik hekimliği alâkadar eden belli başlı meselelere dair:

TIBBÎ İSTİŞARELER.

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Kollaps tedavisi için yapılan pnömotoraks bazı vak'alarda maksadı ifa edemediğinden plevra cevfine hava yerine mayi zerketmek usulü düşünülmüş ve Bernou tarafından zeytin yağı istimali tecrübe edilerek bu usule *Oleothorax* denilmiştir. Zerkedilecek zeytin yağı basit ve muakkam, yahut gomenol, iyodipin gibi azçok antiseptik bir madde ile muayyen bir nisbette karışık olarak kullanılır. Küss tarafından zeytin yağı yerine mayi parafin kullanılmışsada daha az muharriş ve mikropların çoğalmasına daha iyi mani olduğu için zeytin yağı tercih edilmektedir.

Hava yerine zeytin yazı zerkini düşündüren muhtelif sebepler nazarî olarak makul görülmüş ve ilk zamanlarda oleotoraks dahi bir çok müdekkikler tarafından bir çok vak'alarda tatbik edilmiştir. Pnömotoraksta plevra cevfine sevkedilen muhtelif nevi gazler ve hava birer gazdir. Gazlere ait vasıfları haizdir. Gazlerin bilhassa sıkıştırılmakla hacminin küçülmesi, çok seyyal olması, çabuk imtisas olunması bazı vak'alarda kollapsın tahakkuk ettirilmesine, tamamlanmasına mani olur.

Meselâ riede gaz kaçıracak kadar ince bir fistül mevcut ise hava ve yahut herhangi bir gazle kollaps yapılamaz. Yahut riede etrafı sertleşmiş ve kalınlaşmış bir kehif varsa hava ile istenildiği kadar tazyik yapılarak cevf kapatılamaz, plevrada insibab veyahut başka bir sebeble iltisak hasıl olmaya başlar ve terakki istidadı gösterirse hava zerkile bu zararlı hadisenin de önü alınamaz.