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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Clinical, Radiological, and Molecular Findings in Cases with TRAPPopathies

TRAPPopatili Olgularda Klinik, Radyolojik ve Moleküler Bulgular

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ABSTRACT

Objective: Pathologies occurring in Transport Protein Particles (TRAPP) involved in vesicular traffic are rare diseases called TRAPPopathies. The aim of this study was to present a case series of TRAPPopathies, to describe the clinical and molecular findings, and additionally to review our cases together with other cases reported from Turkiye.

Materials and Methods: Patients with neurological findings such as microcephaly, epilepsy, muscular dystrophy, and intellectual disability who were referred to Bezmialem Vakıf University, Faculty of Medicine, Department of Medical Genetics between March 2018 and March 2020 were reviewed for this study. Patients with pathogenic variants in genes with TRAPP complex family with known phenotype or not yet associated any human disease were included in the study. Clinical, radiological, and molecular findings obtained by whole exome sequences of cases were re-evaluated.

Results: Molecular analysis revealed homozygous c.454+3A>G p.(?) variant in *TRAPPC4* (NM_016146.5) gene in Case 1 with neuromotor retardation, intractable seizures, postnatal microcephaly, and cerebral-cerebellar atrophy, homozygous novel c.57C>G p.(Try19Ter) variant in *TRAPPC6B* (NM_001079537.1) in Case 2 with epilepsy, postnatal microcephaly, severe neuromotor retardation, and autism, and homozygous c.2938G>A p.(Gly980Arg) variant in *TRAPPC11* (NM_021942.5) gene in Case 3 with muscular dystrophy, cataract, neuromotor retardation, and microcephaly.

Conclusion: This study showed that newly identified genes in TRAPPopathies are responsible for microcephaly, developmental delay, epilepsy, intellectual disability, cerebral-cerebellar atrophy, and autism. Although the genes in the TRAPP family work independently of each other, the diseases in this group are called TRAPPopathies because their phenotypes overlap. The aim of our study was to discuss the clinical findings and to summarize the mutation profile of the genes in the TRAPP family in Turkiye.

Keywords: Microcephaly, rare diseases, TRAPPopathies

ÖZ

Amaç: Vezikül trafiği ile ilişkili Taşıyıcı Protein Parçacıklarında (TRAPP) meydana gelen patolojiler TRAPPopatiler olarak adlandırılan nadir hastalıklardır. Bu çalışmanın amacı, bir TRAPPopati vaka serisini sunmak, klinik ve moleküler bulguları tanımlamak ve ayrıca vakalarımızı Türkiye'den bildirilen diğer vakalarla birlikte gözden geçirmektir.

Gereç ve Yöntem: Mart 2018-Mart 2020 tarihleri arasında Bezmialem Vakıf Üniversitesi Tıp Fakültesi, Tıbbi Genetik Anabilim Dalı'na sevk edilen mikrosefali, epilepsi, kas distrofisi ve zihinsel yetersizlik gibi nörolojik bulguları olan olgular bu çalışma için gözden geçirildi. Fenotipi bilinen veya henüz herhangi bir insan hastalığı ile ilişkili olmayan TRAPP kompleks familyasına sahip genlerde patojenik varyantları olan hastalar çalışmaya dahil edildi. Klinik, radyolojik ve tüm ekzom dizilerinden elde edilen moleküler bulgular yeniden değerlendirildi.

Bulgular: Nöromotor retardasyon, nöbet, postnatal mikrosefali ve serebral-serebellar atrofili Olgu 1'de *TRAPPC4* geninde (NM_016146.5) homozigot c.454+3A>G p.(?) varyantı, epilepsi, postnatal mikrosefali, nöromotor retardasyon ve otizmi olan Olgu 2'de *TRAPPC6B* geninde (NM_001079537.1) homozigot daha önce bildirilmemiş yeni c.57C>G p.(Try19Ter) varyantı ile musküler distrofi, katarakt, nöromotor retardasyon and mikrosefalili Olgu 3'te *TRAPPC11* geninde (NM_021942.5) homozigot c.2938G>A p.(Gly980Arg) varyantı saptandı.

Sonuç: Bu çalışma, TRAPPopatilerde yeni tanımlanan genlerin mikrosefali, gelişimsel gecikme, epilepsi, zihinsel yetersizlik, serebral-serebellar atrofi ve otizm bulgularından sorumlu olduğunu göstermiştir. TRAPP ailesindeki genler birbirinden bağımsız çalışsa da bu gruptaki hastalıklara fenotipleri örtüştüğü için TRAPPopatiler adı verilir. Çalışmamızda klinik bulguların tartışılması ve Türkiye'deki TRAPP ailesindeki genlerin mutasyon profilinin özetlenmesi amaçlanmıştır.

Anahtar Kelimeler: Mikrosefali, TRAPPopati, nadir hastalıklar

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INTRODUCTION

The correct localization of proteins within the cell is essential for the cell to maintain its biological functions, both spatially and temporally. Recent advances in molecular genetics technologies, such as next-generation sequencing, have facilitated the identification of an increasing number of intracellular trafficking (1).

One of these diseases is a group of rare diseases called TRAPPopathies associated with TRAnsport Protein Particles (TRAPP). TRAPP proteins have been shown to be involved in membrane transport between the endoplasmic reticulum (ER) and the Golgi apparatus (1-3). The TRAPP family was first described as a multi-subunit vesicle-binding complex in yeast. Two subtypes of this protein family, which are subtypes of TRAPP-I, TRAPP-II, and TRAPP-III in yeasts, are similar to TRAPP-II and TRAPP-III identified in humans due to the difference in subunits with a common core structure. The core structure of the TRAPP complex in humans includes C1, C2, C2L, C3, C4, C5, C6, and C6B proteins. In addition to this core structure, there are C9 and C10 proteins in TRAPPII and C8, C11, C12, and C13 proteins in TRAPPIII (1-3). Neurological diseases associated with TRAPPopathies, in the order of elucidation of the disease-related phenotype in the Online Mendelian Inheritance in Man (OMIM), are autosomal recessive mental retardation 13 (MRT13), autosomal recessive limb-girdle muscular dystrophy 18 (LGMDR18), early-onset progressive encephalopathy with brain atrophy and spasticity (PEBAS), early-onset progressive encephalopathy with episodic rhabdomyolysis, neurodevelopmental disorder with microcephaly, epilepsy, and brain atrophy (NEDMEBA), intellectual disability, speech delay, facial dysmorphism, polydactyly, and neurodevelopmental disorder with epilepsy, spasticity, and brain atrophy (NEDESBA), which are caused by the genes *TRAPPC11, TRAPPC12, TRAPPC9, TRAPP6B*, *TRAPPC6A*, and *TRAPPC4*, respectively (4-6). The inheritance pattern of all identified phenotypes associated with TRAPPopathies has been autosomal recessive.

In this study, clinical, radiological, and molecular findings of three cases with pathogenic variants in genes encoding *TRAPPC4, TRAPPC6B,* and *TRAPPC11* proteins are discussed. In addition, we review the findings of our cases by comparing them with the cases of TRAPPopathies previously reported from Turkiye.

MATERIALS AND METHODS

The study included 256 patients with neurological findings (microcephaly, epilepsy, muscular dystrophy, intellectual disability) who were referred to the outpatient clinic of Bezmialem Vakıf University, Faculty of Medicine, Department of Medical Genetics, between March 2018 and March 2020, and who underwent whole exome sequencing (WES) analysis after detailed clinical evaluation. Patients with pathogenic, likely pathogenic, and uncertain significance variants in human disease-associated TRAPPopathies genes according to the American College of Medical Genetics and Genomics (ACMG) criteria were included in the study (7).

For clinical evaluation, detailed three-generation pedigree, clinical and family history, physical and neurological examination, biochemical and metabolic analysis, and radiological findings of the cases were evaluated. DNA was extracted from whole blood using the Puregene® Blood Extraction Kit (Gentra Systems, Qiagen Inc., Mississauga, ON, Canada). WES was performed on Illumina NextSeq 500 (Illumina, San Diego, CA, USA) with the Illumina TruSeq Rapid Capture Exome Library Prep Kit (Illumina, San Diego, CA, USA). Variants were visualized in Alamut Visual Plus version v1.4,

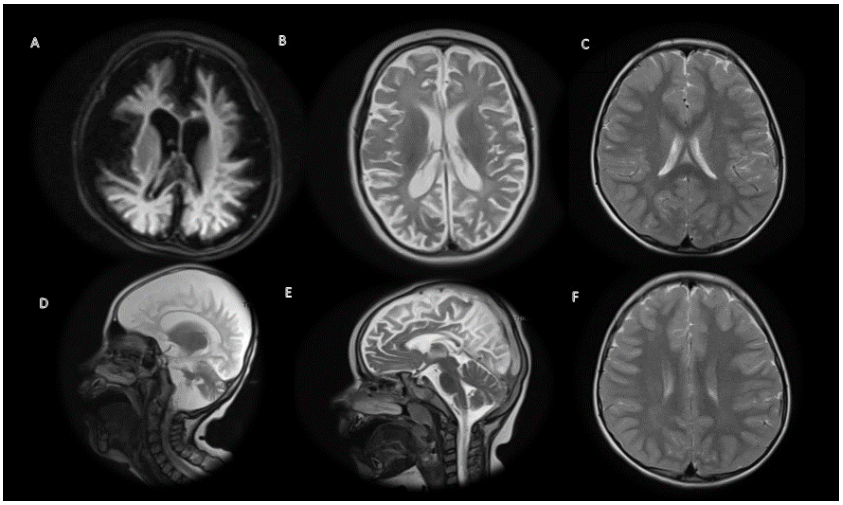

Figure 1: MRI findings of patients with variants in genes encoding for proteins within the TRAPP complex

(A, D) Axial T1-weighted and sagittal T2-weighted images showing severe cerebral and cerebellar atrophy in Case 1 with a pathogenic variant in the *TRAPPC4* gene at 3 years and 3 months of age. **(B, E)** Axial T2-weighted and sagittal T2-weighted images showing cerebral atrophy in Case 2 with a pathogenic variant in the *TRAPPC6B* gene at 2 years and 3 months of age. **(C, F)** Axial T2-weighted images showing hyperintense signal changes in the posterior portions of both lateral ventricles and subcortical regions of the occipital lobe in Case 3 with pathogenic variant in the *TRAPPC11* gene at 3 years and 2 months of age.

2021 (SOPHiA GENETICS, Lausanne, Switzerland). Variants with minor allele frequency (MAF) > 1% in the 1000 Genomes Project, Exome Aggregation Consortium (ExAC v0.3), Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org), and ESP6500 were excluded. Known and common SNPs or non-disease polymorphisms were filtered out. Variants with a frequency of less than 1% in the population were selected. Variants were validated using the Human Gene Mutation Database (HGMD) (http://www.biobase-international.com/product/hgmd), the dbSNP (https://www.ncbi.nlm.nih.gov/snp/), and the ClinVar database (http://www.ncbi.nlm.nih.gov). The study was reviewed and approved by the Ethics Committee of Bezmialem Vakif University Faculty of Medicine (approval number: 2019/2659). Written informed consent was obtained from all parents of the patients included in the study.

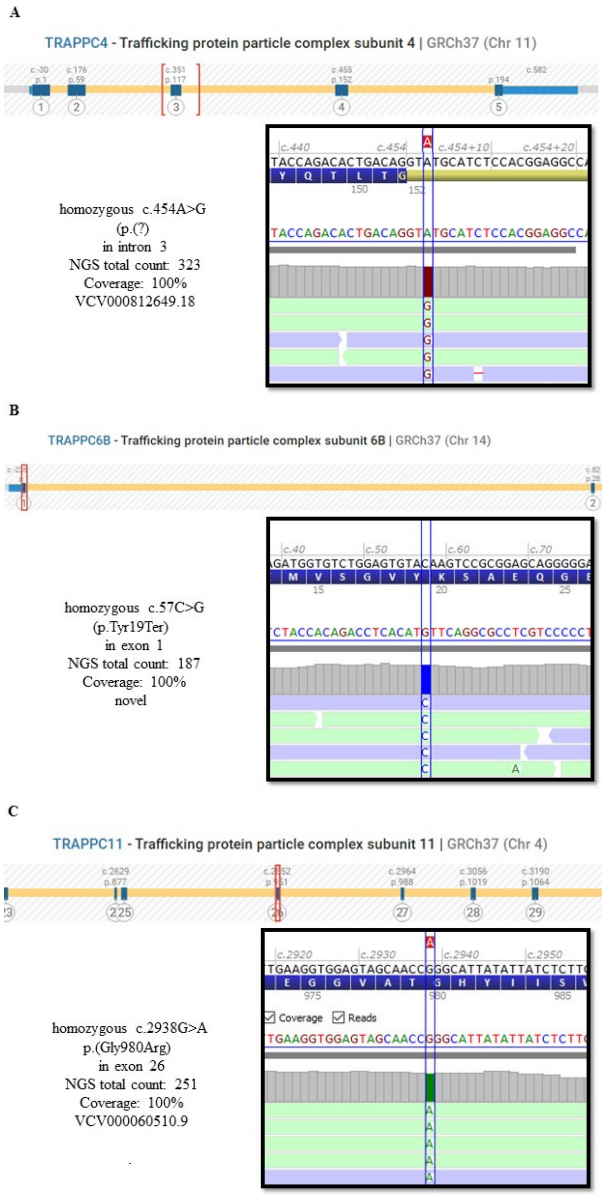

Figure 2: Schematic diagrams and BAM visualization of next generation sequencing using Alamut Visual Plus version v1.4 of *TRAPPC4*, *TRAPPC6B,* and *TRAPPC11* genes

A Case1, homozygous c.454+3A>G p.(?) in the *TRAPPC4* gene

B Case 2, homozygous c.57C>G p.(Try19Ter) in the *TRAPPC6B* gene

C Case 3, homozygous c.2938G>A p.(Gly980Arg) in the *TRAPPC11* gene

RESULTS

Clinical findings

Case 1, a 5 year and 4 month-old female (G3P3), the third child of a first degree cousin marriage) was evaluated for neurodevelopmental disease. The patient, whose family history was unremarkable, had two healthy sisters aged nine and one. After the progression of oligohydramnios, which started at 34th gestational week (GW) in the antenatal period, the pregnancy was terminated by cesarean section at 37th GW with a height of 50 cm (0.87 SD), a weight of 2775 g (0.2 SD), and a head circumference (HC) of 33 cm (-0.45 SD). Her neuromotor development was normal in the first three months and the patient could smile and had eye tracking. ACTH treatment, which was started at the age of 3.5 months with the diagnosis of infantile spasm, was discontinued and valproic acid and clonazepam were started. Generalized chaotic multiple spike wave discharges were observed in EEG examination. Magnetic resonance imaging (MRI) scans showed significant atrophy in the frontotemporal region and severe cerebral-cerebellar atrophy at the age of 3 years (Figure 1 A, D). Poor eye tracking was noted after 9 months of age and the optic disc was pale in the eye examination. At 5 years and 4 months of age, she had severe progressive microcephaly [HC: 41 cm (-6.67 SD)], axial hypotonicity, and spastic tetraparesis. She had a large mouth with bitemporal narrowness, full cheeks, and thin lips.

Case 2, a 4 year and 2-month-old male patient (G2P2), the first child of a first degree cousin marriage) was evaluated for epilepsy, microcephaly, severe neuromotor developmental delay, absent speech, and autism. Family history was unremarkable and his older brother was healthy. The case was delivered at 39th GW by normal spontaneous vaginal delivery with a weight of 3000 g (0.94 SD), a height of 50 cm (-0.95 SD), and a head circumference of 32 cm (-2.32 SD). The patient had global hypotonia from birth. Generalized tonic seizures were noted at the first month. He acquired head control at 2 years of age. At the time of our evaluation at 3 years of age, he had severe microcephaly [HC: 43 cm (-4.50 SD)] axial hypotonia and brisk deep tendon reflexes in four extremities. No obvious facial dysmorphism was noted. Cerebral atrophy was detected on cranial MRI (Figure 1 B, E).

Case 3, a 3 year and 4-month-old male patient (G2P2), the first child of a second degree cousin marriage) was evaluated due to muscular dystrophy. Family history revealed no similar affected patients in the family. He had a healthy 6-year-old brother. Intrauterine growth retardation was detected in the last trimester; the case was born with a weight of 2300 g (-2.61 SD) by cesarean section at 38th GW due to fetal

Table 1: Clinical, radiological and molecular findings of cases with TRAPPopathies from Türkiye

Gene	TRAPPC4	TRAPPC6B	TRAPPC9	TRAPPC11	TRAPPC12
Developmental delay	(+)	(+)	(+)	(+)	(+)
Intellectual disability	(+)	(+)	(+)	(+)	(+)
Microcephaly	(+)	(+)	(+)	(+)/(-)	(+)/(-)
Epilepsy	(+)	(+)	(+)	(+)/(-)	(+)/(-)
Cerebral atrophy	(+)	(+)	(+)	(+)/(-)	(+)
Cerebellar atrophy	(+)	(+)	(+)	(+)/(-)	(+)
Autism	(-)	(-)	(+)	(-)	(-)
Facial dysmorphism	(+)	(-)	(-)	(-)	(-)
Muscular dystrophy	(-)	(-)	(-)	(+)	(-)
Cataract	(-)	(-)	(-)	(+)	(-)
References & Mutations					
Koeher et al. 16				c.1893+3A>G	
Van Bergen et al.5	c.454+3A>G				
Aslanger et al.17					c.1880C>T and c.679T>G
Aslanger et al.18			c.696C>G		
Olmez et al.11	c.454+3A>G				
Bolat et al.19			c.484G>T		
current study	c.454+3A>G	c.57C>G		c.2938G>A	

distress. Birth height and HC were unknown. The patient, who was hospitalized for 3 days due to postnatal hypoglycemia, had a history of neonatal onset hypotonicity. Head control was acquired at the age of 9 months and sitting without support at the age of 2. He had been operated on for bilateral cataract at 2.5 years of age. In his physical examination at 3 years and 4 months, his height was 95 cm (-1.05 SD), his weight was 12 kg (-2.11 SD), HC was 46 cm (-2.96 SD). The patient, who had central hypotonia, could not walk independently yet. The creatine kinase level was found to be 9482 U/L (26-192). MRI showed hyperintense signal changes in the posterior portions of both lateral ventricles and subcortical regions of the occipital lobe (Figure 1 C and F).

Molecular findings

In Case 1, a homozygous c.454+3A>G p.(?) variant in the *TRAPPC4* (NM_016146.5) gene was identified. This variant was previously reported to be associated with a neurodevelopmental genetic disorder, called NEDESBA. It is considered a pathogenic/likely pathogenic variant, as it has been registered in the ClinVar database with the reference number VCV000812649.18. According to the ACMG diagnostic criteria, this variant was classified as pathogenic. Furthermore, the variant is listed as rs375776811 in the dbSNP database and was identified in 0.024% (68/281054) of individuals in the gnomAD.

In Case 2, a homozygous c.57C>G p.(Try19Ter) variant in *TRAPPC6B* (NM_001079537.1) gene was detected. This variant was a novel variant, leading to a null variant, and classified as pathogenic according to ACMG criteria. The variant was found to be extremely rare, with a frequency of 1/251392 in the gnomAD, accounting for 0.0004%. Furthermore, the variant was registered as rs1397140571 in the dbSNP database but was not reported in the ClinVar database.

In case 3, a homozygous c.2938G>A p.(Gly980Arg) in *TRAPPC11* (NM_021942.5) gene was identified. This variant was previously reported in association with autosomal recessive limb-girdle muscular dystrophy subtype 18. The variant was classified as pathogenic according the ACMG diagnostic criteria. Additionally, it has been assigned a pathogenic/likely pathogenic classification, which is supported by its registration in the ClinVar database with the reference number VCV000060510.9. This variant is also identified as rs397509417 in the dbSNP. The radiological and molecular findings of the cases are illustrated in Figures 1 and 2, respectively.

DISCUSSION

Intracellular traffic is a mechanism that allows the exchange of signals and metabolites between organelles. Diseases caused by defects in intracellular trafficking are often associated with vesicular transport, which is the main communication process between membrane traffic and organelles. Vesicular transport allows proteins in membrane-bound vesicles to move between cell compartments, including the plasma membrane. In vesicular transport, proteins are transported from one cell organelle to another via carrier vesicles. TRAPPopathies are diseases associated with pathogenic variants in genes encoding proteins that function in vesicular trafficking (1,8-10). TRAPPopathies with neurological signs associated with

the TRAPP complex are diseases that cause progressive microcephaly, cerebral-cerebellar atrophy, intellectual disability, autism, epilepsy, muscular dystrophy, and severe neuromotor developmental delay (4-6).

In this study, the clinical, radiological, and molecular findings of three cases with pathogenic variants in genes encoding TRAPPC4 and TRAPPC6B proteins in the core complex and TRAPPC11 proteins in the TRAPPCIII complex are discussed.

Case 1 presents with a severe neurodevelopmental disorder including severe microcephaly, cerebral-cerebellar atrophy, intractable epilepsy, spasticity, and facial dysmorphism. Notably, there was no history of perinatal asphyxia, which may be one of the most important causes of this severe condition. The patient's phenotype was attributed to a previously reported homozygous c.454+3A>G variant in intron 3 of the *TRAPPC4* gene, which was predicted to cause a truncating effect by altering a splice site and resulting in the skipping of exon 3, a frameshift, and premature termination (Leu120AspfsTer9), leading to a truncated and likely non-functional TRAPPC4 protein. The *TRAPPC4* gene, initially identified in a 2020 study by Van Bergen et al., was found to harbor a homozygous c.454+3A>G (p.?) variant in eight cases from three unrelated families of Caucasian, Turkish, and French-Canadian origin with a similar syndromic neurodevelopmental disorder, characterized by developmental delay, intellectual disability, microcephaly, and facial dysmorphism (5). In these cases, postnatal onset microcephaly (up to -7 SD), hypotonia, spasticity, failure to gain, psychomotor developmental stages, severe feeding difficulties requiring nasogastric, early onset seizures, cortical visual impairment, and/or poor visual tracking and hearing impairment with dysmorphic features including bitemporal narrowing, full cheeks, prominent nasal tip, long philtrum, wide-open mouth with thinly curved upper lip, and pointed chin were reported. Cranial imaging revealed progressive severe cerebral and cerebellar atrophy. In vitro functional studies confirm that this variant causes splicing error and show a reduction in TRAPP complexes and affecting ER/Golgi trafficking as well as autophagy formation compared to controls. Ghosh et al. reported the same c.454+3A>G (p.?) variant with similar clinical findings in 23 cases from 17 unrelated families in 2021 (6).

The c.454+3A>G variant in the *TRAPPC4* gene, albeit rare according to the gnomAD database, has been calculated to exist in a heterozygous state in at a rate of 2.4 to 5.4 of 10,000 individuals based on research laboratory data on rare diseases. The implications of the carrier frequencies of the recently identified *TRAPPC4* gene are noteworthy. Re-analyses of the exomes performed on patients manifesting the aforementioned phenotype, who had undergone exome sequencing prior to the discovery of the *TRAPPC4* gene, may potentially unveil previously undiagnosed cases affected by TRAPPC4-related disease. In the literature, the same variant was reported in a case from Turkiye in 2022 who was found to have severe cerebral-cerebellar atrophy after infantile spasm (11). So far, two missense (c.191T>C, c.278C>T), one splice (c.454+3A>G), and one gros deletion have been identified. Majethia et al. reported two novel biallelic missense variants, c.191T>C and c.278C>T, in *TRAPPC4* gene in three individuals from two Indian families, with classic clinical presentation in one family and a milder and later onset in the other (12). Case 1 is the fifth case from three different families with this variant reported from Turkiye with the same severe phenotype.

In Case 2, a clinical presentation of epilepsy, microcephaly, severe neuromotor developmental delay, absence of speech, and autism was observed. This study identified a novel c.57C>G (p.Try19Ter) variant detected in the *TRAPPC6B* gene in Case 2. This variant was interpreted as pathogenic with a high probability, as it causes the termination codon. TRAPPC6B-related disease is an autosomal recessive inherited neurodevelopmental disease characterized by autism-like stereotypical movements and absence of speech, accompanying progressive microcephaly. To date, three nonsense, four splicing, and one frameshift variants have been reported in the HGMD. The novel c.57C>G (p.Try19Ter) variant detected in Case 2 also results in a truncating protein, similar to previously reported variants in this gene. Furthermore, the phenotype associated with TRAPPC6B was consistent with the findings observed in Case 2.

Despite being a component of TRAPP complexes, which are binding complexes involved in vesicle transport, the study by Valencia et al. on patient fibroblasts did not reveal any significant endoplasmic reticulum or Golgi morphological changes, nor defects in intracellular trafficking. Functional studies of TRAPPC6B proteins have demonstrated that morpholino knockdown of the trappc6b gene in zebrafish embryos leads to reduced survival and head size, accompanied by increased apoptosis. Additionally, Trappc6b morphants exhibit a decreased seizure threshold, increased spontaneous neuronal firing, and more frequent and prolonged calcium currents, all of which are indicative of neuronal hyperexcitability (13,14).

The clinical signs observed in our case can be plausibly attributed to the newly identified variant in *TRAPPC6B* gene. However, a precise understanding of the functional characterization of its pathogenicity of this variant requires in vivo experiments as opposed to in vitro studies, as stated in previous studies.

In Case 3, which had cataract, muscular dystrophy, microcephaly, and neuromotor developmental delay, a homozygous c.2938G>A (p.Gly980Arg) mutation in *TRAPPC11*gene was identified. The genetic etiopathogenesis of our case was clarified with the known c.2938G>A (p.Gly980Arg) mutation in the *TRAPPC11* gene. So far, 17 missense/nonsense, five splice, two small deletion, and one insertion type variants were identified in HGMD. Our case exhibited similar clinical features as previously reported cases from Syria, where the c.2938G>A (p.Gly980Arg) was identified (15). In the literature, Koehler reported a case from Turkiye with clinical features similar to those observed in our case, which had a homozygous c.1893+3A>G variant in *TRAPPC4* gene (16). The variants

c.1880C>T (p.Ala627Val) and c.679T>G (p.Phe227Val) in *TRAPPC12* gene and c.484G>T in *TRAPPC9* gene were reported in cases with other TRAPPopathies from Turkiye (17-19). The patients with variants in genes encoding for proteins within the TRAPP complex from Turkiye are summarized in Table 1.

Functional studies of TRAPPopathies are invaluable both to elucidate the pathogenicity of previously unreported variants and to understand the role of proteins in the TRAPP complex in vesicular trafficking. To date, function studies of TRAPPopathy genes, immunohistochemical stains in fibroblast cells obtained from cases with pathogenic variants in genes that affect proteins in TRAPP complexes and the effect of vesicular traffic between ER-Golgi organelles, and animal models such as zebrafish studies have been done. One such study, an in vivo functional characterization study on TRAPPopathies in Turkiye conducted by our research group, showed that a missense c.696C>G variant in *TRAPPC9* resulted in decreased mRNA and protein expression. Intracellular findings indicated that TRAPPC9 protein build-up around the nucleus was observed in the mutant type, while there was no specific accumulation in the control cell line. This disrupted protein pattern affected the amount of neutral lipid-carrying vesicles and their homogenous distribution, resulting in decreased levels (18).

Our study has several limitations, one of which is the small sample size in our case series. However, it should be noted that a considerable number of ultra-rare TRAPPopathy diseases have been previously reported in Turkiye. The first case associated with *TRAPPC11* and the novel variant defined in the *TRAPPC6B* gene will contribute valuable information to the mutation profile associated with TRAPPopathy diseases in our country. The discovery of new genes or variants associated with TRAPPopathies has great potential to accelerate functional characterization and therapeutic research, as well as studies of etiopathogenesis. It can also provide a candidate gene approach in cases with similar phenotypes for gene hunting in this area. Very recently, cases with neurodevelopmental disease have been reported in the literature associated with *TRAPPC10* and *TRAPPC6A* genes other than phenotypes reported in the OMIM database (20, 21). To the best of our knowledge, mutations in *TRAPPC1, TRAPPC3, TRAPPC5, TRAPPC8,* and *TRAPPC13* have not been associated with any human disease.

Conclusion: Despite the fact that the genes in the TRAPP family work independently from each other, the diseases in this group are named TRAPPopathies because their phenotypes overlap. The aim of our study is to discuss the clinical findings of TRAPPopathy cases and the etiopathogenesis they cause in vesicular traffic, and to emphasize that other genes of the TRAPP family, which are not yet associated with the disease, may be responsible for possible new phenotypes.

Ethics Committee Approval: This study was approved by the Ethics Committee of Bezmialem Vakif University Faculty of Medicine (approval number: 2019/2659).

Informed Consent: Informed consent was not obtained as it was a retrospective study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study ADA, ES, EY, BG, GY ; Data Acquisition ADA, ES, EY; Data Analysis/Interpretation ADA, ES, EY, BG, Aİ, GY; Drafting Manuscript ADA, ES ; Critical Revision of Manuscript ADA, ES, EY, BG, Aİ, GY; Final Approval and Accountability ADA, ES, EY, BG, Aİ, GY.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Similarities and Differences Between SARS-Cov-2 and Influenza Infection from Symptom to Diagnosis in Childhood

Çocuklarda SARS-Cov-2 ve İnfluenza Enfeksiyonunda Semptomdan Tanıya Benzerlikler ve Farklılıklar

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ABSTRACT

Objective: The COVID-19 pandemic and annual influenza epidemic are responsible for thousands of deaths globally. This study was conducted to identify epidemiological aspects while demonstrating features that distinguish between influenza infection and COVID-19 disease in terms of clinical manifestations, laboratory, and prevention.

Methods: The patients hospitalized with confirmed influenza between October 2009-May 2014 (n=344) and with confirmed COVID-19 between April 2020-June 2021 (n=251) were enrolled in this study.

Results: The age of the patients with influenza infection was statistically significantly younger than the patients with SARS-CoV-2 infection (mean age 6 ± 5.3 years versus 13.0 ± 5.3 years, p <0.001). Fever, cough, and myalgia were the more common symptoms of influenza (p< 0.001; p<0.001, p=0.02). It was found that in cases of COVID-19 (n=55/251, 21.9%), headache complaints were more common at admission. Lymphopenia (n=89/251 35.4%) in COVID-19 and CRP elevation detected in influenza cases (n=201/344 58.4%) were statistically significant (p=0.01/ p<0.001). The mean hospital stay was 6±5 days (1-90 days) in influenza and 1±4 (1-64 days) in COVID-19 (p< 0.001).

The radiological investigations were less necessary in children with COVID-19 because of the lower overall incidence of infected, symptomatic, and severe cases and the lower presence of cough and respiratory symptoms compared to adults.

Conclusions: As the clinical and epidemiological features of COVID-19 have many parallels with influenza, it is important to ensure optimal management of both respiratory diseases as we expect that co-circulation will continue. Clinical findings in children are not sufficient for a definitive diagnosis, so it should be supported by a viral diagnosis test.

Keywords: COVID-19, influenza, children

ÖZ

Amaç: Bu çalışmada, çocuklarda klinik bulgular, laboratuvar tanısı ve hastalığı önleme açısından influenza enfeksiyonu ve COVID-19 hastalığı arasında ayrım yapan özellikleri gösterirken epidemiyolojik verileri de gözden geçirmek ve sentezlemek amaçlanmıştır.

Yöntem: Bu çalışmaya Ekim 2009-Mayıs 2014 yılları arasında hastanede yatan doğrulanmış influenza enfeksiyonu olan (n: 344) ve Nisan 2020-Haziran 2021 tarihleri arasında doğrulanmış COVID-19 (n: 251) nedeniyle yatan hastalar dahil edilmiştir.

Bulgular: İnfluenza enfeksiyonu olanlarda yaş, SARS-CoV-2 enfeksiyonuna göre istatistiksel olarak anlamlı küçük saptandı (ort. yaş 6 ± 5.3/13.0 ± 5.3, p <0.001). Ateş, öksürük ve miyalji influenzada en sık semptomlardı (p<0.001; p<0.001, p=0.02). Baş ağrısı hastaneye başvuruda COVID-19 olgularında daha sık bulundu (n=55/251, 21.9%). COVID-19 da lenfopeni, influenza olgularında ise CRP yüksekliği istatistiksel olarak yüksek bulundu(p=0.01/p<0.001). Ortalama hastanede kalış süresi influenzada 6±5 gün (1-90), COVID-19'da 1±4 gün (1-64) bulundu (p<0.001).

Erişkinlere kıyasla öksürük ve solunum şikayetlerinin daha az olması, semptomatik ve ciddi vakaların da daha az olması sebebiyle radyolojik görüntülemelere COVID-19 hastalarında daha az ihtiyaç duyulmuştur.

Sonuç: COVID-19'un klinik ve epidemiyolojik bulguları influenza ile paralellik göstermekle birlikte, her iki etkenin de dolaşımda devam edeceği düşünülürse her iki hastalığında optimal yönetimini sağlamak önemlidir. Ani başlayan ateş, öksürük, miyalji gibi bulgular influenza açısından uyarıcı olsa da tanı için yeterli olmadığından viral tanı testlerinin kullanımı önemlidir.

Anahtar Kelimeler: COVID-19, İnfluenza, çocuklar

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INTRODUCTION

At the beginning of the 21st century, human public health was marked by the emergence of new viruses and pandemics. The World Health Organization (WHO) declared an influenza A H1N1 pandemic (pH1N1) on 11 June 2009 and a coronavirus pandemic known as COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), on 11 March 2020.

Children and young adults were more susceptible to pH1N1 infection than older persons. Dawood and colleagues reported that a total of 40% of patients were between the ages of 10 and 18 years, and only 5% of patients were 51 years of age or older. Although influenza is common all over the world, the annual attack rate is estimated at 5-10% in adults and 10-20% in children, and the first target in the community is considered to be childhood.

Children younger than 5 years old –especially those younger than 2– are at higher risk of developing serious flu-related complications such as lower respiratory tract infection. In older children and adults, sudden onset of high fever, chills, headache, sore throat and muscle pain, malaise, loss of appetite, and dry cough develop.

Clinical symptoms of children with COVID-19 generally were less severe than adults with COVID-19. Dong et al. reported that 43.1% of the confirmed cases were asymptomatic, and 12.9% had mild disease. In the United States, 22% of the population is made up of infants, children, and adolescents aged <18 years, reported 2,572 (1.7%) of all COVID-19 cases were among children aged <18 years. Among those with available information, 73% of pediatric patients had symptoms of fever, cough, or shortness of breath compared with 93% of adults aged 18-64 years during the same period and nearly one-third of reported pediatric cases (813; 32%) occurred in children aged 15–17 years, followed by those in children aged 10–14 years (682; 27%).

Because of the importance of epidemiological information regarding the last two pandemics, this study aims to synthesize epidemiological aspects that distinguish between influenza infection and COVID-19 disease in terms of clinical manifestations, laboratory diagnosis, and prevention.

METHODS

Pediatric patients under the age of 18 who were hospitalized at the Istanbul University, Pediatric Infectious Disease Department from October 2009–May 2014 with confirmed influenza and patients with confirmed COVID-19 during April 2020-June to 2021 were enrolled in the study. The study was approved by the Public Health Agency, Türkiye Ministry of Health (Number: 2021-09-08T09_20_16), and Istanbul University Ethics Committee (Number: 2021/1642).

On admission, nasopharyngeal swabs were collected using Virocult (Medical Wire & Equipment, UK) and along with tracheal aspirates sent to Istanbul Microbiology and Clinical

Table 1: Symptoms and abnormal laboratory findings of patients

Symptom	İnfluenza n (%)	COVID n (%)	p
Fever	317 (92 .1)	111 (44.2)	**< 0.001**
Cough	300 (87.2)	111 (44.2)	**<0.001**
Vomiting	77 (22.3)	12 (4.7)	0.177
Respiratory distress	66 (19.1)	20 (7.9)	0.108
Myalgia	86 (25)	54 (21.5)	**0.02**
Headache	42 (12.2)	55 (21.9)	**0.032**
Runny nose	48 (13.9)	23 (9.1)	0.147
Diarrhea	27 (7.8)	24 (9.5)	0.276
Throat ache	18 (5.2)	50 (19.9)	0.192
Convulsion	11 (3.2)	2 (0.8)	0.846
Rash	4 (1.2)	3 (1.2)	0.886
Loss of taste	-	22 (8.8)	
Loss of smell	-	24 (9.5)	
Abnormal laboratory findings			
CRP >5 mg/dL	201 (58.4)	66 (26.2)	**<0.001**
Lymphopenia <1000mm^3	61 (17.7)	89 (35.4)	**0.001**
Neutropenia<1500mm^3	28 (8.1)	5 (2)	0.618
Creatinine kinase > 300 IU	17 (4.9)	15 (5.9)	0.501
AST >38 UI	15 (4.3)	22 (8.7)	0.442

Microbiology Department Laboratory within the same day. All samples were transferred to cryo-tubes upon receiving and stored in a -80 °C freezer if not tested on arrival date.

EZ1 Virus mini kit V2.0 (Catalog number: 955134, Qiagen, Germany) was used for total nucleic acid extraction. Real-time PCR-based, multiplex FTDR Respiratory Pathogens 21 kit (fast-track DIAGNOSTICS, Luxemburg) was used for the detection of influenza virus such as on the RotorGene Q platform (Qiagen, Germany).

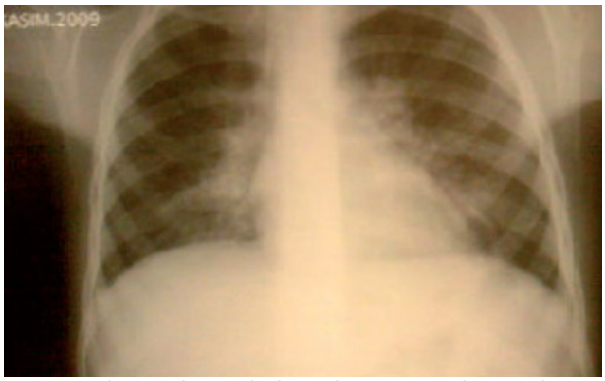

Figure 1: Chest radiograph shows hyperaerated parenchyma, interstitial infiltration in mid and lower zones of both lungs, and symmetric and central distribution.

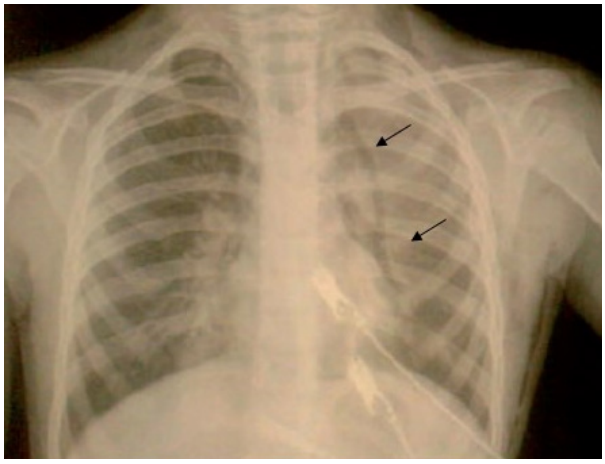

Figure 2: Pnömomediastinum

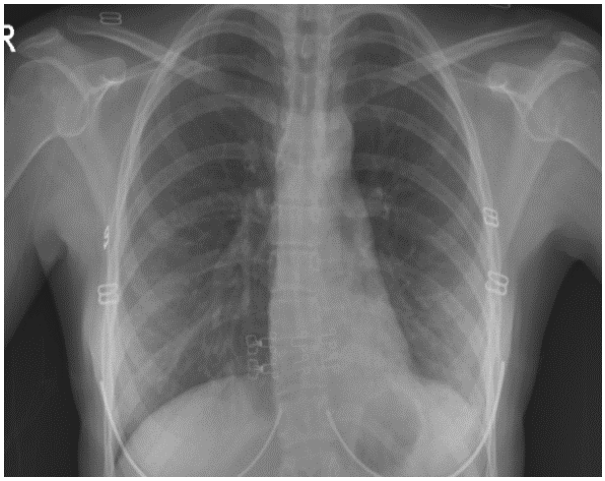

Figure 3: Ground-glass opacities with consolidation on chest radiograph

Extraction of viral RNA from nasopharyngeal swab samples for SARS-CoV-2 PCR testing was done manually with Bio-Speedy® Viral Nucleic Acid Isolation kit (Bioeksen the Co Ltd. R & D Technologies, Turkey). The SARS-CoV-2 PCR process was evaluated as positive by detecting the sample curve of SARS-CoV-2 ORF1ab Nucleocapsid gene regions by Rotor-Gene Q 5 Plex Real Time PCR application (Qiagen, Germany).

Five hundred ninety-five patients with positive SARS-CoV-2 and influenza virus nucleic acid test results were included. Demographic data of patients such as age and gender, admission symptoms, biochemical parameters, and radiological imaging findings were evaluated retrospectively.

Statistical Analysis

Clinical characteristics of patients and frequencies of complications were compared using the Chi-square test for categorical variables, and medians and distributions of continuous variables were compared using the Student T-test. All analyses were performed using IBM SPSS 21 (Statistical Package for Social Sciences, Chicago, IL, ABD) for Windows was used. P value $p < 0.05$ was considered significant.

RESULTS

During the study period, 251 patients with COVID-19 [127 male (50.6%), 124 female (49.4%); the mean age was 13.0 ± 5.3 years and 344 patients with influenza infection [206 male (60%), 137 female (40%) the mean age 6 ± 5.3 years] were enrolled in the study. The age of the patients followed up for influenza was younger than the patients followed up with COVID-19 ($p<0.001$).

Symptoms and abnormal laboratory findings of hospitalized patients are shown in Table 1. The mean hospital stay was 6±5 days (1-90 days) for influenza infection and 1 ±4 days (1-64 days) for COVID-19 ($p< 0.001$).

The 210 of 344 patients with influenza virus infection were evaluated with chest X-rays. Hyperaerated parenchyma (88/210, 41.9%), interstitial infiltration (84/210, 40%), atelectasis (18/210, %8.5), ground-glass opacities (15/210, 7.1%) and pneumothorax/pneumomediastinum (5/210, 2.3%) were imaging findings in these patients (Figure 1-2).

One hundred and five chest radiographs and 52 chest CT examinations of 251 children with COVID were evaluated. Ground-glass opacities with or without consolidation (24/52, 46.1%), feeding vessel sign (20/52, 38.5%), halo sign (12/52, 23,1%), pleural thickening (8/57, 14.0%), interlobular interstitial thickening (6/57, 10,5%) were detected by chest CT examination (Figure 3-6).

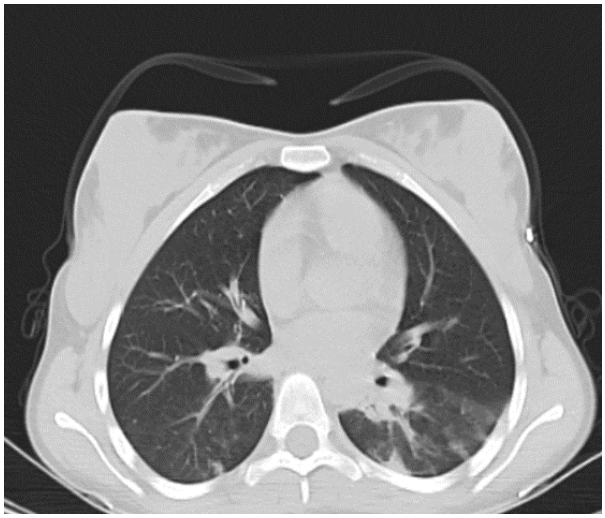

Figure 4: Ground-glass opacities with consolidation on chest CT

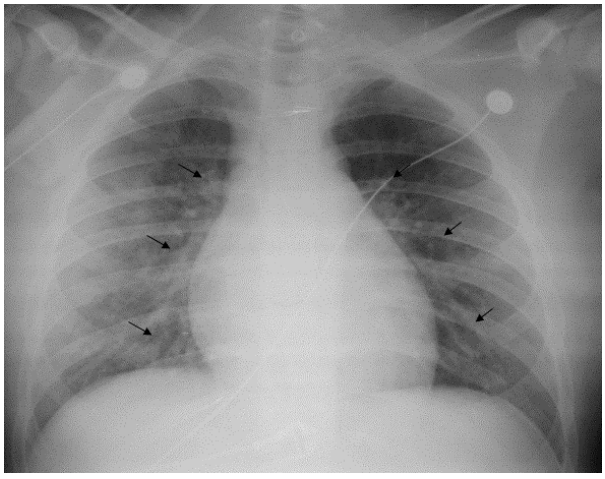

Figure 5: Ground glass density infiltrates in bilateral central and peripheral zones of both lungs on chest radiograph

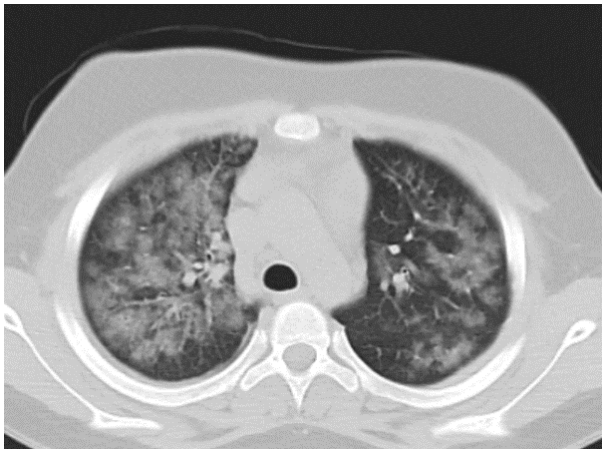

Figure 6: Ground glass density infiltrates in bilateral central and peripheral zones of both lungs on chest CT

DISCUSSION

It was reported that in the first months of the pandemic, children were affected less by 2.2% in China, 1.2% in Italy, and 1.7% in the United States. With the widespread vaccination applied to adults in the second year of the pandemic, it has been determined that 15.5% of all cases (5.292.837/34.198.122) in the pediatric group where vaccination is not yet effective in the USA in September 2021. The reasons for the milder course of SARS-CoV-2 infection in children compared to adults have been investigated, but the reasons have not been clearly determined. Several theories have been discussed involving differences in the immune system, such as thymic function difference, cross-reactive immunity against other coronaviruses, as well as differences in the expression of the angiotensin-converting enzyme 2 (ACE2) receptor that the virus uses to enter the cell. In these studies, it was determined that the mean age of the patients was 7 years (2-13 y).

In our study, the mean age of the patients with COVID-19 was found to be 13.0 ± 5.3 years. This is significantly higher than the patients followed for influenza. It has been thought that this age difference may be caused by the fact that the influenza virus undergoes antigenic changes every year and the attack rate is higher in children, and younger children are more susceptible to this infection.

Although both SARS-CoV-2 and influenza virus are respiratory viruses, fever and cough were detected at high rates (92.1% versus 44.2%) as symptoms at admission to the hospital of patients with influenza infection.

Influenza illness is typically characterized by the abrupt onset of fever 39º to 40ºC and upper respiratory tract signs and symptoms (e.g., fever, chills, myalgia, headache, malaise, nonproductive cough). These symptoms of influenza can be predictive as a distinguishing symptom from other respiratory virus infections.

The major reported risk factors for pediatric COVID-19 cases were close contact with a SARS-COV-2 positive family member as a result of protective measures such as the closure of schools, and children being kept at home. Fever was detected in only 44% of children with COVID at admission to the hospital. Symptoms of pediatric patients with family contact were cough, vomiting-diarrhea, sore throat, convulsion, rash, and inability to taste and smell. In influenza-related upper respiratory tract disease, dry cough is most severe 3-4 days after the onset and continues for several weeks, even if other symptoms improve. In our case series, the cough was found to be a more frequent complaint at admission in influenza infection.

Myositis is classically occurring in children during the convalescent phase from febrile upper respiratory tract infections, most commonly after influenza B and can cause difficulty walking due to severe calf pain. Influenza B virus was detected in 83% of the children diagnosed with myositis in Poland during the influenza outbreaks in 2012/2013 and 2014/2015. In our study, myalgia was found to be a more

common symptom in patients with influenza virus infection than COVID-19, but it was not noticed in the creatinine kinase levels measured in laboratory tests.

There have been many reports of laboratory findings in pediatric COVID-19 patients. In a pediatric review, leukopenia and leukocytosis were present in 7.3% and 10.7% of cases, respectively. In another study, the most frequent abnormal laboratory findings were leukopenia/lymphopenia (28.9%, 95% CI = 19.5-39.2) and increased creatine kinase (20.1%, 95% CI = 1.3-49.9). It seems likely that COVID-19 has an effect in the direction of cytopenia, like other viral infections.

In the pediatric age group, radiological examinations were less necessary in children with COVID-19, due to the lower overall incidence of symptomatic and severe cases and the lower rate of cough-respiratory distress symptoms compared to adults. Foust et al. indicated that abnormal chest radiography findings in children with severe acute respiratory syndrome were unilateral and multifocal in one-third of cases with lower zone predominance. In our pediatric cohort, similar to previous studies, characteristic imaging findings were a peripheral and lower lobe dominant distribution pattern with multiple consolidative opacities.

It was reported that in children with viral pneumonia, 40 (49%) had alveolar changes on chest radiography. Although there are similar imaging features in chest X-rays taken due to both COVID-19 and influenza infection, hyperinflation (88/210, 41.9%) and ground-glass opacity and consolidation (84/210, 40%) were found to be higher in influenza. A different finding, pneumothorax, and pneumomediastinum, has been reported only in the influenza cases. Among all our patients, pneumothorax/pneumomediastinum was detected in 5 cases followed up due to influenza. With the increasing patient burden, the need for rapid diagnosis has made radiological methods, especially thorax computed tomography, frequently used in diagnosis. Chest radiography may be the first study that will be performed on pediatric patients with clinically suspected COVID-19. It makes more sense to consider computerized tomography in moderate or severe patients, to avoid exposure of this sensitive population to radiation.

The reopening of schools may cause an increase in the risk of some respiratory infections (such as influenza) in both children and adults in 2021-2022. In this period while the SARS-CoV-2 pandemic continues, it is essential to identify the infectious groups and to continue the isolation measures. However, COVID-19 has different epidemiologic characteristics from influenza. Influenza tends to be transmitted mainly from children to adults and therefore causes epidemics, and COVID-19 tends to be transmitted from adults to adults, or from adults to children. Although the sudden onset of symptoms such as high fever, cough, and myalgia is primarily a precursor of influenza infection and lymphopenia is primarily predictive of SARS-CoV-2 infection, these findings in children are not sufficient for a definitive diagnosis, so it should be supported by a viral diagnosis test.

Ethics Committee Approval: This study was approved by the Public Health Agency, Türkiye Ministry of Health (Number: 2021-09-08T09_20_16), and Istanbul University Ethics Committee (Number: 2021/1642).

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Eosinophil Count in Infants with Food Protein-Induced Allergic Proctocolitis

Besin Proteinine Bağlı Alerjik Proktokolitli İnfantlarda Eozinofil Sayısının Değerlendirilmesi

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ABSTRACT

Objective: The incidence of allergic proctocolitis due to food protein is increasing. Therefore, studies are needed to elucidate the pathophysiology of the disease as well as to identify simple, non-invasive markers. The aim of this study was to evaluate the relationship between the level of eosinophil in the blood and allergic proctocolitis.

Materials and Methods: The files of patients who were diagnosed with allergic proctocolitis at the Pediatric Allergy Outpatient Clinic of Başkent University's Faculty of Medicine, Ankara Hospital, between 2011 and 2021 were retrospectively reviewed. Three groups were formed according to eosinophil counts. Those with an eosinophil count below 400 10^3/μL were considered as the normal eosinophil group, those whose count was between 400-1499 10^3/μL were considered as the eosinophilia group, and those with 1500 10^3/μL and above were considered as the hypereosinophilia group.

Results: There were 108 patients diagnosed with allergic proctocolitis, of which 49.1% (n:53) were male. Of all the patients, 14.8% (n: 16) were in the hypereosinophilia group and 29.6% (n: 32) were in the eosinophilia group. Eosinophil elevation was more common in boys. There was no statistically significant difference in eosinophil count between those with single and multiple food allergies. It was observed that multiple food allergies were more common in babies older than two months (n:76) than in babies aged two months and younger (n:32) (p=0.031).

Conclusion: In our study, there was no difference between eosinophil levels and symptoms in infants with allergic proctocolitis. However, the importance of investigating multiple food allergies in the presence of eosinophilia in infants older than two months is clear.

Keywords: allergic proctocolitis, food allergy, eosinophil, infant

ÖZ

Amaç: Besin proteinine bağlı alerjik proktokolit görülme sıklığı artmaktadır. Bu nedenle hastalığın patofizyolojisinin aydınlatılmasının yanı sıra basit, invaziv olmayan belirteçlerin belirlenmesine yönelik çalışmalara ihtiyaç duyulmaktadır. Çalışmamızın amacı eozinofil düzeyi ile alerjik proktokolit arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Başkent Üniversitesi Tıp Fakültesi, Ankara Hastanesi Çocuk Alerji polikliniğinde 2011-2021 yılları arasında alerjik proktokolit tanısı almış olan hastaların dosyaları retrospektif olarak incelendi. Eozinofil sayılarına göre üç grup oluşturuldu. Eozinofil düzeyi 400 10^3/μL altında olanlar normal eozinofil grubu, 400-1499 10^3/μL arası olanlar eozinofili grubu, 1500 10^3/μL ve üzeri olanlar hipereozinofili grubu olarak değerlendirildi. Çalışma Başkent Üniversitesi yerel etik kurulu tarafından onaylanan protokole uygun olarak yapıldı.

Bulgular: Alerjik proktokolit tanısı almış 108 hastanın %49,1'i (n:53) erkekti. Median yaş 3,5 (0,5-10) aydı. Tüm hastaların %14,8'i (n:16) hipereozinofili, %29,6'sı (n:32) eozinofili grubundaydı. Eozinofil yüksekliği erkek çocuklarda daha fazla görüldü (eozinofili grubunun %71,9'u, hipereozinofili grubunun %50'si erkekti). Gruplar arasında sadece anne sütü alan ile anne sütü ve formula mama alan infantlar açısından bir farklılık yoktu. Atopik dermatit, eozinofili grubunun %9,4'ünde, hipereozinofili grubunun da %5,9'unda mevcuttu. Sadece 56 hastaya deri prik testi uygulanmıştı. Deri prik testi sonuçlarına göre gruplar arasında anlamlı bir farklılık saptanmadı. Tekli ve çoklu besin alerjisi olanlar arasında eozinofil sayısı açısından istatistiksel olarak anlamlı fark yoktu. İki ay üstü bebeklerde (n:76) çoklu besin alerjisinin iki ay ve altı bebeklere (n:32) göre daha sık olduğu görüldü (p=0,031).

Sonuç: Çalışmamızda, alerjik proktokolitli bebeklerde eozinofil düzeyleri ile semptomlar arasında bir farklılık görülmedi. Ancak iki ay üstü bebeklerde eozinofili varlığında çoklu besin alerjisinin araştırılmasının önemini belirtmektedir.

Anahtar Kelimeler: alerjik proktokolit, besin alerjisi, eozinofil, ınfant

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INTRODUCTION

Food protein-induced allergic proctocolitis (FPAP) is a non-immunoglobulin E (IgE)-mediated food allergy that typically affects the rectosigmoid colon and presents with focal eosinophil infiltration in the lamina propria, increased intraepithelial CD8-positive T lymphocytes, focal mucosal erythema, and aphthous ulcerations (1). It presents with bloody , mucous stools in the first months of life. It mostly develops against cow's milk protein (97.7%), and secondly against egg (22%). More than one food allergy is observed in 34.1% of infants (2). Food allergy is seen in 0.5-1% of infants fed only with breast milk (3). A diagnosis of FPAP is made by taking the history of the patient, by clinical evaluation, and by an improvement in the patient's condition as a result of an exclusion diet. In infants fed with breast milk, foods that are thought to be allergens such as cow's milk and sometimes eggs and soya should be excluded from the mother's diet (1,2). Tolerance develops before the age of one in 40% of the patients, between 1-2 years in 27%, between 2-3 years in 9%, and after the age of 3 in 5% (4).

The incidence of FPAP is increasing (5). Therefore, studies are needed to elucidate the pathophysiology of the disease as well as to identify simple, non-invasive markers. In the literature, studies have been carried out on easy-to-calculate and non-invasive markers. There are studies evaluating the significance of values such as neutrophil/lymphocyte ratio (NLR), mean platelet volume, peripheral eosinophil count, specific IgE (sIgE) values, and positive skin prick test (SPT) in the diagnosis and follow-up of FPAP (1,2,4- 7). Again, higher eosinophil count, higher positive sIgE and positive SPT results were observed in infants with multiple food allergies compared to infants with single food allergies (2).

In light of this information, we wanted to evaluate the severity of clinical findings and the rates of eosinophilia and hypereosinophilia by examining the clinical features, laboratory tests, and especially the eosinophil count in the complete blood count of our patients diagnosed with FPAP. Every patient diagnosed with FPAP has eosinophilic infiltration in the lamina propria, but it is known that the level of eosinophils in the blood increases only in some patients. In particular, we sought to determine in which situations the eosinophil count can be used as a non-invasive marker by evaluating the relationship between the level of eosinophils and the severity of the proctocolitis clinic.

METHOD

The files of patients who were diagnosed with FPAP at the Pediatric Allergy Outpatient Clinic of Başkent University's Faculty of Medicine, Ankara Hospital, between 2011 and 2021 were retrospectively reviewed. Demographic information, age at diagnosis, complaints, presence of single or multiple food allergies, complete blood count, NLR, biochemical values, inflammatory markers, stool analysis, milk, and egg sIgE, and SPT values were examined from the files of the patients. Other causes of rectal bleeding such as infections, intussusception, volvulus, Hirschsprung's disease, and necrotizing enterocolitis were excluded. Three groups were formed according to eosinophil counts. Those with an eosinophil level below 400 10^3/µL were placed in the normal eosinophil group, those between 400-1499 10^3/µL were put in the eosinophilia group, and those with 1500 10^3/µL and above were placed in the hypereosinophilia group (8). The study was performed according to the protocol approved by the local ethics committee of Başkent University (KA 16/166).

Statistical Analysis

In the study, mean ± standard deviation or median (minimum-maximum) depending on assumptions were given for numerical variables as descriptive statistics, and number (n) and percentage (%) were given for categorical data. Analysis of Variance was used if parametric test assumptions were met in examining the difference between eosinophil groups. If not, the Kruskal-Wallis test was used. Pearson Chi-square test, Fisher's Exact test, or Fisher-Freeman-Halton Exact test were used in the evaluation of categorical data, depending on the assumptions. Spearman correlation coefficient and significance test were used to analyse the correlation between the two variables. $P<0.05$ was considered statistically significant in the analyses. The analyses of the study were made using the SPSS IBM v22 software platform.

RESULTS

In our study, 108 patients were evaluated, of which 49.1% (n:53) were male. The median age was 3.5 months (0.5-10 months). The median value of the complaint duration at presentation

Table 1: General characteristics by groups

	Normal eosinophil (n:60)	Eosinophilia (n:32)	Hypereosinophilia (n:16)	p
Boy Girl	36.7% (22) 63.3% (38)	71.9% (23) 28.1% (9)	50% (8) 50% (8)	0.006[a]
Age (month)	4 months (0.5-10)	3.25 months (1-7)	3.5 months (1-6.5)	0.438[b]
Prematüre birth Miad birth	8.3% (5) 91.7% (55)	9.4% (3) 90.6% (29)	6.3% (1) 93.8% (15)	0.999[c]
Time to diagnosis (day)	26.5 (1-150)	30 (1-150)	32.5 (3-130)	0.586[b]

a: Pearson Chi-square test; (n)%
b: Kruskal-Wallis test; Median (min-max)
c: Fisher-Freeman-Halton Exact test; (n)%

Table 2: Admission complaints by groups

Complaint	Normal eosinophil (n:60)	Eosinophilia (n:32)	Hypereosinophilia (n:16)	pa
Mucus poop	16.7% (10)	21.9% (7)	0% (0)	0.155
Bloody poop	76.7% (46)	65.6% (21)	93.8 % (15)	
Skin rash	5% (3)	6.3% (2)	0% (0)	
Unrest	1.7% (1)	0% (0)	0% (0)	
Diarrhea and rash	0% (0)	3.1% (1)	6.2% (1)	
Vomiting	0% (0)	3.1% (1)	0% (0)	

a: Fisher-Freeman-Halton Exact test; (n)%

Table 3: Laboratory results by groups

	Normal eosinophil (n:60)	Eosinophilia (n:32)	Hypereosinophilia (n:16)	p
Hemoglobin (g/dL)	11.9 (9.8-14.6)	11.3 (9.2-13.6)	11.9 (10.2-17.2)	0.213[a]
Mean corpuscular volume (fL)	80.4 (65.5-100.6)	82.25 (56.4-92.1)	79.3 (64.4-104.0)	0.720[a]
Platelets (10^3/µL)	386233±98152	418093±114925	420812±78180	0.249[b]
Neutrophil count (10^3/µL)	1960 (872.0-4950.0)	2010 (720-4370)	2430 (870-7510)	0.066[b]
Lymphocyte count (10^3/µL)	6160 (3380-10270)	6280 (1170-11400)	6810 (1240-10700)	0.250[b]
N/L rate	0.24 (0.21-0.32)	0.1950 (0.12-0.62)	0.94 (0.47-1.42)	0.194[b]
Total IgE (IU/mL)	3.98 (1.00-138.00)	2.75 (1.00-47.50)	2.73 (1.68-6.94)	0.835[b]

a: Analysis of Variance; Mean±Standard Deviation
b: Kruskal-Wallis test; Median(Minimum-Maximum)

was 28 days (1-150 days). Of all patients, 14.8% (n: 16) were in the hypereosinophilia group and 29.6% (n: 32) were in the eosinophilia group. Eosinophil elevation was more common in boys (p=0.006). 71.9% of the eosinophilia group and 50% of the hypereosinophilia group were male. The general characteristics of the patients are presented in Table 1.

The most common presenting complaint in all groups was bloody stool. There was no significant difference between the groups in terms of presentation complaints (p=0.155). The presenting complaints of the hypereosinophilia group were bloody stool (93.8%) and diarrhea with rash (6.2%). Arrival complaints by groups are presented in Table 2.

When the presence of allergy in the baby and/or family was evaluated, there was no significant difference between the groups (p=0.522). While the physical examination was normal in 78.1% of the patients, 18.1% had atopic dermatitis and 3.8% had an anal fissure. In addition, there was no difference in terms of eosinophilia between 'exclusively breastfed' and 'breastmilk and formula formula' infants (p=0.745). Atopic dermatitis was present in 9.4% of the eosinophilia group and 6.2% of the hypereosinophilia group. Those who received the rotavirus vaccine before diagnosis were 15.0% (n:9) in the group with normal eosinophilia, 25.0% (n:8) in the eosinophilia group, and 6.3% (n:1) in the hypereosinophilia group. There was no difference between these three groups in terms of rotavirus vaccination (p=0.227).

Laboratory values were compared. There was no difference between neutrophil count, platelet count, and NLR. Egg sIgE sensitivity was high in 5 patients and milk sIgE sensitivity was high in 4 patients. Only one patient had both milk and egg sIgE sensitivity. Total IgE was found to be high in one patient. There was no difference between the total IgE values measured. There was a weak positive correlation between eosinophil count and platelet levels (p=0.023, rs=0.219). Laboratory results are presented in Table 3.

No difference was found between the groups in stool occult blood (SOB) examination (p=0.651). SOB was positive in 41 patients. Of these patients, 22 (53.7%) were in the normal eosinophil group, 13 (31.7%) in the eosinophilia group, and 6 (14.6%) in the hypereosinophilia group. There were 68 patients for whom fecal-reducing substance (FRS) was tested. Patients with FRS (+) (n:17) had a significantly higher level of eosinophils than those with FRS(-) (n:51) (p=0.011). The number of patients with FRS (+) was 10 (58.8%) in the normal group, 2 (11.7%) in the eosinophilia group, and 5 (29.4%) in the hypereosinophilia group. The number of patients with FRS (-) according to the groups was 28 (54.9%) in the normal group, 20 (39.2%) in the eosinophilia group, and 3 (5.8%) in the hypereosinophilia group.

SPT was applied to 56 patients who did not respond to milk elimination. There was no significant difference between the groups in terms of SPT positivity (p=0.934). Egg positivity was

Table 4: Skin Prick Test results

	Normal eosinophil (n)	Eosinophilia (n)	Hypereosinophilia (n)	pa
Negative	**46.7% (14)**	**41.2% (7)**	**55.6% (5)**	
Milk	**6.7% (2)**	**17.6% (3)**	**0% (0)**	
Egg	**23.3% (7)**	**29.4% (5)**	**33.3% (3)**	
Milk and Egg	**3.3% (1)**	**0% (0)**	**0% (0)**	**0.934**
Nuts	**10.0% (3)**	**5.9% (1)**	**0% (0)**	
Egg and Nuts	**6.7% (2)**	**5.9% (1)**	**0% (0)**	
Egg, Nuts, Milk	**3.3% (1)**	**0% (0)**	**11.1% (1)**	

a: Fisher-Freeman-Halton Exact test; %(n)

the highest in all groups. In the hypereosinophilia group, one patient had positivity for milk and nuts (hazelnut, peanut, walnut, almond) other than eggs. The applied SPT and its results are presented in Table 4.

There was no difference in the frequency of single and multiple food allergies between the groups (p=0.115). Multiple food allergies were 40.0% (n:24) in the normal eosinophil group, 62.5% (n:20) in the eosinophilia group, and 43.8% (n:7) in the hypereosinophilia group.

It was observed that multiple food allergies were more common in infants over two months of age than in infants under two months of age (p=0.031). While 19.6% of infants with multiple food allergies were 2 months and younger, 80.4% were older than 2 months.

DISCUSSION

In our study, the aim of which was to evaluate the relationship between serum eosinophil levels and FPAP , 108 patients with a diagnosis of FPAP were evaluated retrospectively. Eosinophil elevation was evident in male infants. The most common complaint was bloody stool. There was no relationship between eosinophil values and the infant's diet, rotavirus vaccine, single or multiple food allergies, and family history of allergic disease. In addition, there was no difference in eosinophil levels according to the physical examination findings of the patients and the severity of the condition . We found that multiple food allergies were more common, especially in infants older than 2 months.

In FPAP, mucosal edema, focal epithelial erosions, and eosinophilic infiltration in the epithelium and lamina propria occur due to cell-mediated hypersensitivity in the distal region (3). Similar invasive and noninvasive methods are used in the diagnosis of allergic proctocolitis and other eosinophilic esophagitis and gastroenterocolitis with similar pathologies (9). One of the noninvasive tests frequently used by clinicians is blood eosinophil level (10). Every patient diagnosed with FPAP has eosinophilic infiltration in the lamina propria, but it is known that the number of eosinophils in the blood increases only in some patients (3,5,9). In a study conducted by Lozinsky et al., it was shown that 89.3% of 263 infants with FPAP had eosinophilic infiltration in the colonic mucosa and 43.8% had eosinophilia in the blood (11). Recent evidence also indicates dysregulation of specific cytokines in cases of eosinophilic gastroenterocolitis. Compared to normal controls, higher plasma concentrations of IL-5 and IL-15 were observed in these patients, which correlated with the blood eosinophil count (12). Therefore, it can be expected that eosinophil levels will also be increased in FPAP cases. However, since this increase is not observed in every patient, it is considered unnecessary for a definitive diagnosis (3). In our study, 32 (29.6%) of 108 patients had eosinophilia and 16 (14.8%) had hypereosinophilia. The eosinophil count was high in 44.4% of our patients. 71.9% of the eosinophilia group and 50% of the hypereosinophilia group were male. Similar to our study, some studies in the literature also found a higher rate of eosinophilia in males (9,13).

In our study the most common patient complaint was blood in stool in all groups. In fact, FPAP clinic often appears with the complaint of bloody or mucous stool (14). Other complaints were observed in our patients; bloodless mucus stool, skin rash, bloodless diarrhea with skin rash, vomiting, and restlessness. Similar to our patients, the findings in other studies regarding FPAP and other eosinophilic gastrointestinal diseases have features that fall between IgE-mediated food allergy and cell-mediated hypersensitivity (14). The distribution of complaints in our study was independent of eosinophilia levels. This suggests that there is no relationship between the level of eosinophilia and clinical symptoms and the severity of the disease. However, the small number of our patients may be a reason for not detecting this relationship.

In the physical examination findings of our patients, there were skin rash (n:19) and anal fissure (n:4) findings. Seven of the skin rashes were diagnosed as atopic dermatitis. Five of these patients had multiple food allergies, three had eosinophilia and one had hypereosinophilia. The physical examination findings of the patients did not differ according to the eosinophil groups. Consistent with our study, other studies are reporting that the frequency of skin allergies such as atopic dermatitis is significantly higher in FPAP patients than in the healthy population (15,16). None of our patients with anal fissure had constipation on physical examination. They also did not complain of bloody stools. In order to make a differential diagnosis of proctocolitis, both local treatments for anal fissures and elimination diet were performed. The

patients were followed up closely. After the anal fissure findings improved, it was observed that the complaints continued after exposure to cow's milk protein. Thus, the diagnosis of proctocolitis was confirmed.

Similar allergic disease findings were found in the family of 16% of eosinophilic gastrointestinal diseases (14). For this reason, it is thought that genetic and environmental factors interact together in the etiology. In the family history of these patients, 80% have atopic diseases and 62% have specific food sensitivities (14). In our study, 61 (56.4%) of 108 patients had a family history of allergic disease. Eosinophil levels did not differ between the groups in the presence of allergic disease in the family history.

The frequency of FPAP cases is thought to have increased after 1980, especially due to the more frequent use of cow's milk-based infant formulas (5). . In infants who are exclusively breastfed, FPAP occurs due to cow's milk protein and other proteins passed through the mother's diet.'

In our study, FPAP was found to be higher in infants receiving formula with breast milk (n: 61) compared to those receiving only breast milk (n: 47). Eosinophil levels were compared in both. No difference was detected.

FPAP may be misdiagnosed as mucus and occult blood may be seen in the stool after the rotavirus vaccine. In one study, side effects were compared between the oral rotavirus vaccine and the placebo group. The prevalence of fever, vomiting, and diarrhea is similar (17). In another retrospective study, it was observed that the prevalence of food allergy did not increase in children who were vaccinated with rotavirus compared to the general population. Again in this study, the prevalence of food allergy was found to be 1.76% until the 12-month follow-up after the rotavirus vaccine (18). In our study, 18 patients had a history of rotavirus vaccination. In our study, there was no significant difference in eosinophil levels between the groups compared to the rotavirus vaccine.

NLR is used to measure systemic inflammation. The relationship of NLR with some diseases such as heart disease, chronic diseases, and the Mediterranean fever has been shown in the literature (7). In studies investigating NLR values in allergic rhinitis and asthma, higher NLR values were found compared to the control group (19,20). In our study, no difference was found between the groups in neutrophil count and NLR values. There was a positive correlation between eosinophil count and platelet levels. Egg sIgE alone was high in 5 patients, and only milk sIgE was high in 4 patients. Both milk and egg sIgE was elevated in a single patient.

Stool microscopy (SM), SOB, and FRS tests, which are FPAP noninvasive diagnostic tests, rarely give positive results (15). One study evaluated the diagnostic validity of SOB in infants with rectal bleeding secondary to FPAP compared to healthy infants. Although SOB has sufficient sensitivity (84%; negative predictive value 83%), fecal occult blood specificity (66%; positive predictive value 68%) is insufficient because more than one-third of healthy infants are positive (21,22). It is not a reliable result that SM does not contain eosinophilia and occult blood, and there is no reducing substance in the stool. The routine use of these tests is not recommended (3). In our study, FRS was examined in 68 patients with SM, colic-type pain, and diarrhea in 77 patients, and no statistically significant results were found. In 7 patients with high eosinophilia (two in the eosinophilia and five in the hypereosinophilia group), there was a reducing substance in the stool.

In the literature, there are studies emphasising that IgE-mediated food sensitivity may exist in cases of proctocolitis (1). In the study of Çetinkaya et al., 204 patients were evaluated retrospectively. It was observed that 17 patients with IgE sensitivity to irritating foods at the initial evaluation had IgE sensitivity, and 7 patients developed IgE sensitivity in the follow-up. It has been noted that children with BPIAP may become sensitive to irritating foods over time and develop IgE-mediated allergies. In our study, sensitivity to a food was detected in 30 of 56 patients who underwent SPT. Egg sensitivity was the highest in all groups. In addition, there was sensitivity to egg, milk, and nuts (hazelnut, peanut, walnut, almond) in the form of single and multiple associations. These findings can be explained by the feeding habits of our babies and their mothers. Fifteen of 48 patients with an eosinophil level above 400 $10^3/\mu L$ had SPT positivity. When the SPT results were evaluated, no significant difference was found between the groups. Similar to sIgE levels, SPT results are of limited help in diagnosing FPAP, and usually negative or slightly positive test results are obtained (11). In our study, there was no difference between the groups in terms of the frequency of single and multiple food allergies. It was observed that multiple food allergies were more common in infants older than two months compared to infants under two months of age. Babies older than two months may become sensitized to foods over time. According to this result, the diagnosis of multiple food allergies should not be overlooked in patients older than 2 months.

The most important limitation of our study was that it was retrospective. Our laboratory evaluations were not complete for every patient. Having a larger number of cases would have increased the power of the evaluation. Despite all these limitations, we think that our study makes important contributions to the literature for the evaluation and follow-up of allergic proctocolitis cases with increasing incidence.

CONCLUSION

FPAP is one of the earliest signs of food allergies. Rectal bleeding is a benign disease manifested by symptoms such as mucus in the stool, increased frequency, and stool consistency. If there is a delay in the diagnosis when there is no bleeding in the stool, the tolerance may be delayed due to the prolongation of the period and the solution may be difficult with increased sensitivity to other allergens during complementary feeding. Or, with a misdiagnosis, the mother's breastfeeding is stopped, which creates health risks and may adversely affect the attachment process. Therefore, FPAP diagnosis and process management are important. Invasive methods should not be used unless

necessary at the stage of diagnosis. With a detailed anamnesis and physical examination, the process can be managed with the support of non-invasive methods. The results of our study do not support the use of eosinophilia as a predictor of the severity of the FPAP clinic, but they indicate the importance of investigating multiple food allergies in the presence of eosinophilia in infants over two months old. It would be useful to evaluate this issue with more cases and a prospective study.

Ethics Committee Approval: This study was approved by the ethics committee of the local ethics committee of Başkent University (KA 16/166).

Informed Consent: Informed consent was not obtained as it was a retrospective study.

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Author Contributions: Conception/Design of Study- Ö.A., B.T.K., Ö.Y.Ö.; Data Acquisition- Ö.A.; Data Analysis/Interpretation- Ö.A., B.T.K., Ö.Y.Ö., T.Ş.; Drafting Manuscript- Ö.A., B.T.K., Ö.Y.Ö., T.Ş. ; Critical Revision of Manuscript- Ö.A., B.T.K., Ö.Y.Ö.; Final Approval and Accountability- Ö.A., B.T.K., Ö.Y.Ö., T.Ş.

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RESEARCH ARTICLE / *ARAŞTIRMA MAKALESİ*

Management of an Earthquake in a Pediatric Intensive Care Unit

Çocuk Yoğun Bakım'da Deprem Yönetimi

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ABSTRACT

Objective: The 2023 Kahramanmaraş earthquake (7.8 magnitude) devastated Turkey, impacting approximately 14 million people and causing over 50,000 fatalities. This study suggests a pediatric protocol for managing earthquake victims in pediatric intensive care units (PICUs).
Materials and Methods: A retrospective, observational study was conducted. Within a week, 72 patients were followed and initially treated post-stabilization, per the treatment protocol and PICU organization. Of these, 58 were referred to tertiary PICUs in other cities. Thirteen patients treated at our regional PICU were reviewed.
Results: Thirteen patients were studied. Eight had severe crush injuries, including four extremities in one patient and both legs in another. The average time under debris was 14.8±13.8 h. Fasciotomy was performed on 46.1% (n=6) of patients. Debridement was needed in 61.5% (n=8), averaging 3.6±3.8 procedures per patient. Vacuum-assisted closure (VAC) was applied to 53.8% (n=7). Continuous renal replacement therapy (CRRT) was given to two of the three patients with acute kidney injury, while one received intermittent hemodialysis. Four patients underwent an average of 5.2±9.5 therapeutic plasma exchange (TPE) sessions. Hyperbaric oxygen therapy (HBOT) was administered for an average of 15.0±17.5 sessions to eight patients. No patient deaths occurred at our center.
Conclusion: Implementing a treatment protocol was crucial for disaster management. Specialized treatments, including daily TPE, frequent HBOT, anticoagulant and vasodilator therapies, and VAC, contributed to favorable outcomes for patients with severe crush syndrome.

Keywords: disaster, earthquake, pediatric intensive care management, protocol

ÖZ

Amaç: 2023 Kahramanmaraş depremi (7.8 büyüklüğünde) Turkiye'de yaklaşık 14 milyon insanın etkilendiği ve 50,000'den fazla kişinin yaşamını kaybettiği büyük bir felakete yol açmıştır. Bu çalışmada çocuk yoğun bakım ünitelerinde (ÇYBÜ) takip edilen pediatrik depremzede hastaları için bir tedavi protokolü oluşturulması amaçlanmıştır.
Metod: Bu çalışma gözlemsel, retrospektif bir çalışmadır. Deprem sonrası bölgesel yoğun bakıma destek amacıyla gidilmiş bir hafta içerisnde 72 hasta izlenmiş, bu hastaların 58'i başka üçüncü basamak merkezlere sevk edilmiş, 13 hasta hemodinamik ve metabolik stabilizasyonu sağlandıktan sonra kendi merkezimize sevk edilmiştir.
Sonuçlar: Çalışmaya 13 hasta alındı. Sekiz hastada ciddi ezilme hasarı mevcuttu bu hastaların birinin dört ekstremitesi, bir diğer hastanın her iki alt ekstremitesi etkilenmişti. Enkaz altında ortalama kalış süresi 14.8±13.8 saatti. Fasiyotomi hastaların % 46.1 (n=6)'ine uygulandı. Debridman hastaların % 61.5 (n=8)'ine uygulandı, hasta başına ortalama debridman sayısı 3.6±3.8 bulundu. Vakum yardımlı kapama (VAC) hastaların % 53.8 (n=7)'ine uygulandı. Akut böbrek hasarı üç hastada gelişti ve bu hastaların ikisine sürekli renal replasman tedavisi (CRRT) uygulandı, bir hastaya aralıklı hemodiyaliz tedavisi uygulandı. Dört hastaya ortalama 5.2±9.5 seans terapötik plazma değişimi (TPE) yapıldı. Hiperbarik oksijen tedavisi (HBOT) ortalama 15.0±17.5 seans olmak üzere sekiz hastaya uygulandı. Merkezimizde hiçbir hasta kaybedilmedi ve tüm hastalar taburcu edildi.
Sonuç olarak: Afet yönetiminde bir protokol oluşturmak oldukça önemlidir. Günlük TPE, sık aralıklarla uygulanan HBOT, antikoagülasyon ve VAC dahil olmak üzere uygulanan özel tedaviler ile ciddi ezilme sendromu olan hastalarda olumlu sonuçlar elde edilmiştir.

Anahtar Kelimeler: afet, çocuk yoğun bakım yönetimi, deprem, protokol

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INTRODUCTION

The 2023 Pazarcik, Kahramanmaraş earthquake had a magnitude of 7.8, making it one of the largest disasters in Türkiye, affecting 11 provinces with a population of about 14 million people and resulting in more than 50,000 deaths (1,2). More than 500 children lost extremities due to amputation. In this article, we would like to share the invaluable lessons that Turkish healthcare professionals have learned the hard way with those whom we hope will never need it. A medical team from our hospital was sent to the regional PICU to support the treatment of pediatric earthquake victims. They followed many patients there, but some were admitted to our hospital after achieving adequate hemodynamics and metabolic balance for tertiary care.

The aim of this study was twofold. First, to provide healthcare professionals with a pediatric protocol on managing earthquake victims in PICU and sharing its outcomes. Second, to share the valuable knowledge that had been gained regarding how to organize the post-earthquake intensive care organization in the regional PICU and tertiary PICU, how resources will be allocated for different patient needs, and how to determine the appropriate transfer of patients between centers.

MATERIAL AND METHODS

This was an observational retrospective study. Our team arrived at the regional Pediatric Intensive Care Unit (PICU) 36 h after the Kahramanmaraş earthquake, and within a week, we followed up on 72 patients. We initiated their initial therapy and referred 58 patients to tertiary health institutions in other provinces. We performed a retrospective analysis of 13 patients who were referred to our center. This study was approved by the Koc University Committee on Human Research (approval number: 2023.133.IRB1.045). The written informed consent was obtained from the participants of the study or legally authorized parents or representatives. The treatment was provided according to a protocol that included regional PICU and tertiary PICU experiences and treatments.

1. Treatment Protocol

1.1. Hydration and diuresis

We initiated daily IV fluid therapy by administering 3500–4000 mL/m^2 of a 0.45% NaCl solution without potassium and with 50 mEq/L of $NaHCO_3$ added. We requested urine pH at least once daily to monitor urine alkalization and reduced alkalization if urine pH was above 8. During treatment, we monitored urine output and administered 20 ml/kg saline solution followed by 1–2 mg/kg furosemide in case of oliguria (urine output < 2 ml/kg/h). After administering furosemide, we monitored urine output for 1 h (furosemide stress test) and repeated the procedure once more if urine output was insufficient. We limited fluid consumption and prepared for emergency dialysis if urine output remained insufficient. We avoided hypervolemia during fluid therapy.

1.2. Hyperkalemia management

We initiated calcium gluconate treatment at a dose of 1 mEq/kg (maximum = 20 meq) to minimize cardiac side effects. We administered β-adrenergic therapy (inhaled salbutamol) and glucose/insulin solution (1 IU of crystalline insulin for every 4–5 g of glucose) to increase potassium entry into the cell. We used anti-potassium (polystyrene sulfonate calcium) salts in patients with an intact gastrointestinal tract. If the potassium level remained above 7 meq/L despite treatment, we carefully monitored it and initiated dialysis therapy if necessary.

1.3. Hemodialysis versus CRRT

For patients requiring dialysis, we preferred intermittent hemodialysis (HD) if they were hemodynamically stable. However, we preferred continuous renal replacement therapy (CRRT) in patients who were hemodynamically unstable, had a high risk of amputation, or had a serious crush injury.

1.4. Catheter procedure

We used a double-lumen hemodialysis catheter (Able, Covidien, Arrow) ranging from 9–11.5 F, depending on the patient's weight and height. We preferred the right jugular vein for catheterization, and a PICU specialist placed the catheter under ultrasound (US) guidance. We used the same catheter for both therapeutic plasma exchange (TPE) and CRRT in patients who needed it. During CRRT, we connected TPE to the set in tandem and did not insert an extra catheter.

1.5. Prime procedure

For pre-treatment priming of the CRRT and TPE set, we added 2500 U/L heparin to 1000 mL of 0.9% NaCl solution. We used half the dose of heparin in trauma patients. For patients weighing less than 10 kg or with unstable hemodynamics, we prepared the set with cross-matched packed red blood cells after priming with normal saline.

1.6. Hemodialysis method

In children with hemodynamically stable crush injuries and acute kidney injury (AKI), we preferred intermittent hemodialysis (IHD). We performed IHD using a volume-controlled HD machine (Fresenius 4008 S; Fresenius, Bad Homburg, Germany) and polysulfone membranes. The treatment dose for IHD was determined as 3–4 h per day with a blood flow rate of 4–8 mL/kg/min and a dialysate flow rate of 10–15 mL/kg/min (1.5–2 × blood flow rate). We used reverse osmosis distilled water and bicarbonate dialysate with volumetric ultrafiltration control (≤ 0.2 mL/kg/min or ≤ 5% by weight). We adjusted the potassium and sodium concentrations of the bicarbonate-containing dialysate solutions based on individual requirements. We recorded HD duration and total ultrafiltration volume at the end of each session, and we adjusted HD frequency and prescription based on changes in the patient's clinical and laboratory data. If the extracorporeal blood volume estimated by the dialyzer size and tubing exceeded 10% of the blood volume, we prepared circuit blood with 5% albumin or saline to prevent intradialytic hypotension.

1.7. CRRT method

We used CRRT with high-volume hemodiafiltration (CVVHDF) using the PrismaFlex device (Gambro, Lund, Sweden) and AN69 0.6–0.9 m^2 (Prismaflex M60–Prismaflex M100) membrane. We determined the dialysate rate using the 2000 mL/1.73 m^2/h calculation, and we determined replacement volumes using the same formula. We made a 1/3 pre-dilutional and 2/3 post-dilutional replacement capacity adjustment. If the patient weighed between 15 and 30 kg, we modified the blood flow rate to be 4–6 mL/kg/min. If the patient weighed more than 30 kg, we reduced the blood flow rate to 2–4 mL/kg/min.

1.8. Intensive care management in patients considering amputation

We used mangled extremity severity score (MESS) to estimate viability of a crushed extremity (3).

Anti-coagulation: A heparin infusion of 10 U/kg/h (maximum 250 U/h) was initiated in trauma patients who were evaluated and found to have no bleeding on computed tomography or FAST (Focused Assessment with Sonography in Trauma). For patients with fasciotomy or bleeding from the fasciotomy, heparin treatment was stopped for 2 h. If bleeding did not recur, treatment was resumed at a reduced dose of 5 IU/kg/h.

Vasodilator therapy: An IV nitroglycerin infusion was initiated at a dose of 5–10 mcg/kg/min. In severe cases, a nitroglycerin patch or nitroglycerin-soaked sponge was applied topically to the affected extremity. Milrinone (0.2–0.4 mcg/kg/min) and iloprost (0.5–1 ng/kg/min) were also used as vasodilators.

Plasma exchange method: Our protocol recommends considering TPE or referral to a specialized center within the first 24 h after achieving hemodynamic and metabolic stability in patients with severe crush injuries who are being evaluated for amputation. Continuing TPE once a day is necessary to ensure a safe healing process.

During the procedure, the patients were carefully monitored, with close attention paid to their vital signs and ionized calcium levels. Calcium gluconate support was administered when necessary to maintain calcium levels between 1–1.5 mmol/L.

In TPE procedures, the filtration method was preferred using devices such as the Prismaflex (Gambro, Lund Sweden) and MultiFiltrate (Fresenius Medical Care AG&Co KGaA, Germany). Membranes used were TPE 1000 (polypropylene, 0.15 m^2, for infants under 15 kg), TPE 2000 (polypropylene, 0.35 m^2, for children over 15 kg), and Dry Plasma Flux P1/P2 (plasmosulfone, P1 dry, for pediatric patients, 0.3 m^2; P2 dry, for adolescent patients, 0.6 m^2, Fresenius Medical Care AG&Co KGaA, Germany). To determine the volume of plasma to be replaced, the total blood volume (TBV) was calculated first using the equation TBV = 80 mL × BW(kg) for children under 3 years old and 70 mL × BW(kg) for 3 years and older. Total plasma volume was then determined using TBV × (1 - Hct/100). The TPE volume was determined by adjusting 1.5 volumes of plasma in the first session and 1 volume in subsequent sessions.

Hyperbaric oxygen therapy method (HBOT): Patients who were respiratory, hemodynamically, and metabolically stable started hyperbaric oxygen therapy (HBOT) within the first 24 h. Given the potential contraindications and complications of HBOT (such as pneumomediastinum, pneumothorax, high fever, middle ear barotrauma, claustrophobia), sessions were performed every 8 h for the first 2 days and every 12 h for the next 5 days in patients who were being evaluated for amputation. After 1 week, the frequency of HBO treatment was reduced to one session per day based on the patient's condition.

Each treatment involved applying a pressure of 2.4 ata for 90–120 min, with alternating periods of compression and decompression. Hyperbaric oxygen was administered via a mask after the patient was placed in the chamber or tank.

1.9. VAC method

Vacuum-assisted closure (VAC) therapy was utilized in patients who had undergone fasciotomy to expedite the healing of the incisions.

1.10. Tetanus prophylaxis

If the patient's tetanus vaccination history is unclear or they have received less than three doses of the vaccine, both tetanus vaccine and tetanus immunoglobulin (TIG) should be administered for contaminated wounds. Patients who have received at least three tetanus vaccines are exempt from receiving TIG if less than 5 years have passed since their last vaccination. After 5–10 years have passed, patients who have received three doses of the vaccine should only be vaccinated if the wound is dirty; otherwise, there is no need for vaccination. Patients who have received the vaccine at least three times and whose last dose was more than 10 years ago should receive another shot.

1.11. Antibiotic treatment

Sulbactam-ampicillin was administered as a prophylactic antibiotic in patients with crush injuries. For patients with dirty wounds or fasciotomy, meropenem + teicoplanin were initiated, and the antibiotics were adjusted based on culture results. If clinical findings, appearance, or odor suggested an anaerobic infection, clindamycin was added to the treatment regimen.

1.12. Stress ulcer prophylaxis

A stress ulcer prophylaxis treatment consisting of an H2 receptor antagonist or a proton pump inhibitor was administered.

1.13. Analgesics

To alleviate or prevent pain in patients, ketamine (1 mg/kg dose), fentanyl (1–2 mcg/kg/min), dexmedetomidine (0.2–0.6 mcg/kg/h), and paracetamol (4 × 10 mg/kg/dose max 500 mg) were administered. Non-steroidal anti-inflammatory drugs (NSAIDs) were not used due to their potential renal toxicity.

2. Statistic

The collected data was analyzed using the Statistical Package for Social Sciences for Windows version 23.0. Descriptive statistics, including number, percentage, mean, standard deviation, and median, were used to evaluate the data.

RESULTS

Thirteen patients (eight boys and five girls) who were referred to our hospital after the initial intervention in the earthquake area were included in this study. The patients had a mean age of 117.2 ± 46.6 months. On average, the duration of the patients under debris was 14.8 ± 13.8 h (minimum: 1 h; maximum: 42 h). Eight patients had severe crush injuries, including four extremities in one patient and both legs in another. The mean MESS score was 5.30 ± 3.27 and four of the patients had a MESS score above 7 (Table 1). Compartment syndrome developed in six of the patients (46.1%), and as a result, fasciotomy was performed in the regional intensive care unit. Debridement was required in eight patients (61.5%), and an average of 3.6 ± 3.8 debridement procedures were performed. VAC treatment was applied to seven patients (53.8%). Also, four patients had fractures, five had lung injuries, and three developed AKI.

CRRT was applied to two out of the three patients who developed AKI, while intermittent HD was applied to the remaining patient. On average, 5.2 ± 9.5 sessions of TPE treatment were administered to four patients. Eight patients received a mean of 15 ± 17.5 sessions of HBOT. None of the patients developed a systemic infection, while local wound infection developed in three patients. The mean PICU stay and hospital stay was 16.61 ± 11.15 and 32.76 ± 21.58 days respectively. All patients were discharged, and there were no fatalities. The demographic and clinical characteristics of the patients were shown in Table 1 and Figure 1.

DISCUSSION

Once patients rescued from earthquake debris had been stabilized, full intensive care services were only available at the nearest tertiary hospitals that were not affected by the earthquake. It's important to remember that healthcare professionals living in the earthquake zone were also disaster victims.

During a crisis, teamwork and understanding the dynamics of the team, as well as recognizing the limitations of team members, are crucial for effective management. It may be necessary to bring in intensive care support teams from other cities to assist in the region with their own teams.

Establishing a treatment protocol and adapting it to the treatment team is essential for standardizing interventions and quickly reaching each patient. This approach ensures that no time is wasted in providing effective care.

It is crucial to treat every patient rescued from the earthquake zone as a major trauma patient. Although trauma evaluation is typically performed in emergency departments, in the first few days after an earthquake, when the patient flow is high, it may be necessary to skip trauma evaluation and proceed directly to intensive care hospitalizations.

Upon the patient's arrival at the intensive care unit, the primary assessment is made using the ABCDE approach: A for airway patency, B for breathing, C for circulation, D for disability, including the AVPU scale (Awake, respond to Verbal stimulus, respond to Pain stimulus, Unresponsive), blood glucose levels, and light reflex, and E for exposure and head-to-toe examination, as well as a four-quadrant evaluation using FAST (4,5).

Once stabilized, the patient is referred for a computed tomography (CT) scan. Non-contrast CT scans are performed on the cranial, cervical, thoracic, abdominal, spinal, and pelvic regions, and direct radiographs of the long bones are taken. Radiology, neurosurgery, pediatric surgery, and orthopedics consultations should be obtained as needed. If emergency surgical intervention is required, it should be performed before transferring the patient to the intensive care unit, where they will receive ongoing care. Patients with severe crush syndrome require immediate treatment, starting with intravenous alkaline hydration and diuresis to correct electrolyte and acid-base imbalances. Urgent dialysis may be necessary, and maintaining hemodynamic and metabolic balance is critical (6,7).

In crush syndrome, damaged muscles can release myoglobin and intracellular enzymes, such as lactate dehydrogenase, creatine kinase, and uric acid, into the bloodstream, leading to myoglobinuria and potentially causing obstruction and acute tubular necrosis (8). Adequate hydration and diuresis are critical to prevent this accumulation. The furosemide stress test is a useful objective test of tubular function that can be used in patients with crush syndrome (9). If the test is unsuccessful, fluid restriction and dialysis preparation should begin. The patient's hemodynamics, device and circuit availability, and the experience of the nursing staff determine the preferred dialysis method (10). In patients with stable vital signs, intermittent hemodialysis is preferred. Rather than transferring patients to the hemodialysis unit, it may be more practical to dedicate an intensive care room to hemodialysis and include hemodialysis nurses as part of the intensive care team to provide uninterrupted service (11). CRRT should be used for unstable patients requiring dialysis. High-volume continuous venovenous hemodiafiltration (CVVHDF) may be the preferred therapeutic approach for patients undergoing CRRT. This approach may effectively eliminate macromolecules such as myoglobin and large volumes of cytokines generated after trauma (12,13).

Hyperkalemia is another life-threatening condition frequently encountered in patients rescued from earthquake zones, and it is the one of most common causes of death after trauma. As stated in the protocol, if medical treatment of hyperkalemia is unsuccessful, dialysis should not be delayed (14).

The Role of Pediatric Intensive Care in Compartment Syndrome and Amputation Decision

Compartment syndrome is one of the most important problems that can develop in patients due to the crushing

Table 1: Characteristic features and laboratory results of the earthquake victims

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10	Pt 11	Pt 12	Pt 13
Age (month)	198	124	73	165	157	59	52	99	181	118	80	116	102
Sex	Girl	Boy	Boy	Girl	Boy	Girl	Boy	Boy	Boy	Girl	Boy	Boy	Girl
Weight (kg)	59	60	21	40	48	18	14.6	37	43	47	20.1	58	37.5
BMI (kg/m2)	20.4	21.3	12.4	19.8	21.3	10.65	12.07	21.89	15.76	20.89	21	22.97	20.03
Rescue time (hour)	38	24	42	4	1	14	24	12	1	4	2	12	15
Extremities subjected to crushing	Left leg	Left leg	Left leg	Right leg	Right leg	Right ab. flank	Right & left leg	Right foot	Left leg	Four extremities	Left foot	Right leg	Right leg
MESS score	10	10	10	3	2	5	3	2	2	8	2	6	6
Fracture	+	-	-	+	-	-	-	-	-	+	-	-	+
Lung injury	+	-	-	-	-	+	-	-	+	+	-	+	-
Acute kidney injury	+	-	-	-	-	+	-	-	-	-	-	-	-
Local infection	-	+	+	-	-	-	-	-	-	+	-	-	-
Systemic infection	-	-	-	-	-	-	-	-	-	-	-	-	-
DIC	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of surgical operations performed	5	4	7	10	1	0	0	0	0	10	0	6	4
Number of TPE	22	14	27	0	0	4	0	0	0	2	0	0	0
Number of sessions HBOT	40	50	30	2	0	18	20	0	0	0	0	6	29
Laboratory Results on Admission													
Hemogram													
HGB (g/dL)	17.4	9.6	15.6	9.1	12.5	8.6	8.6	13.0	8.4	7.9	14.7	10.4	8.7
PLT (103/uL)	384	260	508	154	350	388	348	361	256	271	283	460	409
WBC (103/uL)	21.29	12.57	23.4	9.49	6.82	10.34	11.2	11.29	8.96	12.7	13.07	25.19	9.55
NEU (103/uL)	17.75	8.60	6.8	6.1	4	7.3	8.6	7.6	5.2	9.5	7.4	17.3	8.5
LYM (103/uL)	1.46	2.9	2	0.7	1.9	0.6	1.7	2.4	2.3	2.2	4.5	5.8	0.9
Biochemistry													
BUN (mg/dL)	22	11	27	11	10	7	6	10	8	6	14	12	5
Urea (mg/dL)	47	224	58	24	21	15	12	21	17	12	31	25	11
Creatinine (mg/dL)	1	0.4	0.4	0.5	0.5	0.3	0.3	0.4	0.5	0.4	0.5	0.5	0.3
Uric Acid (mg/dL)	6.8	5.6	9.1	4.1	3.3	0.9	1.8	2.6	3.4	2.8	5.2	5.4	2.3
Sodium (mmol/L)	133	132	136	139	142	138	137	137	141	140	123	134	139
Potassium (mmol/L)	5.4	4.3	5	3.9	4.2	4.5	4.1	4	4.2	3.5	5	3.5	3.9
Calcium, total (mg/dL)	8.4	9.1	10.2	7.2	10.2	9.7	8.4	9.9	9.4	8.8	8.5	8.9	9.3
Phosphorus (mg/dL)	7.2	2.9	5	3.5	4.2	4.2	3.7	5.2	4.6	3.4	5.3	3.9	4.8
Serum albumin (g/L)	26.8	23.9	45	23.3	47.7	38.1	27.4	40.3	41.4	34.3	24.6	32.2	36.7
AST (u/L)	1910	565	285	100	18	250	1621	73	24	101	22	206	78
ALT (u/L)	695	264	131	29	18	112	405	29	14	93	11	152	67
LDH (u/L)	4500	564	1500	214	205	965	2429	283	281	546	246	659	444
Amylase (u/L)	19	12	24	14	20	30	13	14	15	12	10	18	20
Creatine Kinase (u/L)	134117	6030	120000	3547	2200	9587	52000	1184	1130	2914	620	10085	3264
Urine analysis													
pH	6	7	9	9	6	9	9	8	8	9	7	7	8
Protein (mg/dL)	100	30	0	0	0	15	15	0	15	30	0	0	0
Hemoglobin	3	0	0	0	0	0	2	0	3	1	0	0	0
Density	1037	1037	1010	1010	1008	1013	1007	1012	1015	1016	1003	1009	1004
Myoglobin (µg/L)	5800	65	32	83	8	8	5940	8	8	8	0	8	8

Table 1: Continue

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10	Pt 11	Pt 12	Pt 13
Laboratory Results of the Last Work Up													
Hemogram													
HGB (g/dL)	9.6	11	7.9	10.7	13.0	12.3	10.4	12.8	8.6	7.2	13.2	11.4	9.7
PLT (103/uL)	467	388	497	218	244	282	423	284	389	446	434	122	507
WBC (103/uL)	9.28	9.55	4.68	8.13	4.97	5.54	5.6	9.89	9.95	11.12	11.72	6.76	5.05
NEU (103/uL)	5.5	4.8	2	5.2	3.1	1.8	2.4	7.4	7.5	6.9	7.1	3.4	2.2
LYM (103/uL)	2.3	4.1	2.2	1.9	1.3	3.2	2.1	1.4	1.5	3	3.2	2.6	1.8
Biochemistry													
BUN (mg/dL)	8	8	14	6	11	9	3	10	10	8	7	11	10
Urea (mg/dL)	18	17	29	13	23	20	7	21	21	17	16	24	22
Creatinine (mg/dL)	0.6	0.4	0.2	0.5	0.5	0.2	0.2	0.4	0.4	0.4	0.3	0.4	0.4
Uric Acid (mg/dL)	3.1	4.7	2.5	3	5.3	3.2	2.9	3.4	2.4	2.6	4.7	6.8	3.4
Sodium (mmol/L)	141	135	141	142	140	140	141	141	138	138	127	142	140
Potassium (mmol/L)	3.7	4	4.2	3.9	4.6	4.8	3.1	4.2	4.7	4.4	3.6	4.1	4.7
Calcium (mg/dL), total	8.9	10.4	10.2	9.6	9.7	11.3	10.1	9.8	9.6	9.4	9.1	10.5	10.4
Phosphorus (mg/dL)	3.9	5.2	4.9	4.4	3.9	5.3	5.4	5	4.7	5.8	4.2	5.6	5.8
Serum albumin (g/L)	40.1	43.1	47.2	33.4	46.9	47.4	40.5	45.9	39.6	27.5	30.2	47.9	43.6
AST (u/L)	21	31	26	20	32	32	46	24	21	23	23	54	26
ALT (u/L)	21	27	22	24	63	23	25	21	16	19	9	77	32
LDH (u/L)	209	250	105	183	171	411	437	188	209	354	135	242	213
Amylase (u/L)	15	12	10	13	15	8	10	12	13	10	9	8	12
Creatine Kinase (u/L)	71	105	45	13	40	214	132	121	50	30	71	87	50
Urine analysis													
pH	7	7	8	7	5	7	7	7	8	9	7	6	8
Protein (mg/dL)	0	0	0	15	0	0	0	0	0	0	0	0	0
Hemoglobin	0	0	0	0	0	0	0	0	0	0	0	0	0
Density	1009	1014	1005	1012	1016	1012	1005	1030	1015	1015	1006	1015	1013
Myoglobin µg/L	0	0	0	0	0	0	0	0	0	0	0	0	0

ab.: abdominal, ALT: alanine transaminase , AST: aspartate aminotransferase, BMI: body mass index, BUN: blood urine nitrogen, DIC: disseminated intravascular coagulation, HBOT: hyperbaric oxygen therapy, HGB: hemoglobin, LYM: lymphocyte, LDH: lactate dehydrogenase, MESS: mangled extremity severity score, NEU: neutrophil, PLT: platelet, TPE: therapeutic plasma exchange, WBC: white blood cells

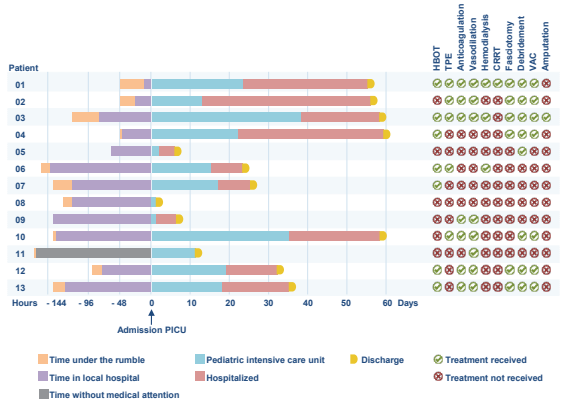

Figure 1: Timeline of the post-earthquake process and the treatments received by the patients

of the extremities (15). To manage this condition, the affected extremities should be elevated above heart level, and pain control measures (such as ketamine, fentanyl, dexmedetomidine, and paracetamol) should be provided. Additionally, patients should be closely monitored for signs of compartment syndrome, with urine output monitored and hypervolemia avoided. A slit catheter that inserted to compartment and connected to an arterial line transducer that can be used to measuring of compartment pressure. An intra-compartmental pressure over 30 mmHg is defined as compartment syndrome. Delta pressure is another way to evaluate compartment pressure that is equal to diastolic pressure minus measured intracompartment pressure. Delta pressure less than or equal to 30 mmHg is an indication of the need for fasciotomy (16). We did not measure the compartment pressure however crushed extremities were carefully evaluated through physical examination to determine the need for fasciotomy and doppler US was used to evaluate blood flow, occlusion, and thrombus formation. Prophylactic fasciotomy in the absence of measured compartment pressure elevation should be avoided (17, 18).

In clinically and hemodynamically stable patients, even if there are signs that may require extremity amputation (such as coldness, ecchymosis, ischemia, absence of pulse, and absence of blood flow on Doppler US), a decision for amputation should

not be made hastily. However, following up with these patients without amputation in hospitals in the earthquake zone, where patient flow is high, can be risky and may lead to overlooking systemic complications and potentially losing patients. Such patients should be referred to tertiary centers with comprehensive facilities, including hyperbaric oxygen therapy, therapeutic plasma exchange, orthopedics, and plastic surgery, where they can be more closely monitored, and the decision for amputation should be left to the referred center. Suppose the clinical condition requires urgent amputation (such as severe systemic inflammatory response syndrome, bleeding, sepsis, or gas gangrene). In that case, a decision should be made based on the patient's needs to prevent systemic and life-threatening complications (19).

Intensive Care Management of a Patient Considering Amputation

In the Kahramanmaraş earthquake of 2023, we observed that four patients with crush injuries and who were considered for amputation (their MESS score =10) and were clinically stable had their extremities revascularized using a protocol that we initiated in the primary earthquake zone and continued in our center (Figure 2).

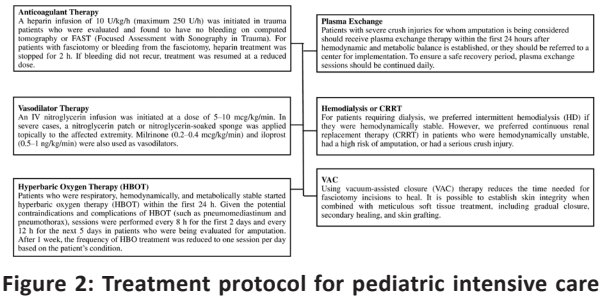

Figure 2: Treatment protocol for pediatric intensive care management of the patients considering amputation

The protocol aims to maintain microcirculation and prevent distal ischemia and necrosis. For patients with severe crush injuries and reduced or no blood flow on Doppler US, heparin infusion was initiated (provided there was no bleeding on FAST and CT imaging) to prevent microthrombus formation in the extremities. We used the doses specified in the protocol and observed no treatment-related bleeding or new thrombus formation in any patient. The main advantage of heparin over low molecular weight heparin is its shorter half-life of 2 h and the availability of an antidote (protamine sulfate) in case of possible bleeding when treatment is discontinued (20,21). Likewise, vasodilator therapies such as intravenous or topical nitroglycerin, milrinone, and iloprost (in patients with reduced or absent arterial phase flows) were employed to maintain microcirculation and enhance perfusion in the extremities. Ilioprost, a synthetic analog of prostaglandin I_2, acting as a potent inhibitor of platelet aggregation and a vasodilator is used in maintaining microvascular circulation of dermal flap in reconstructive surgery and enhance perfusion of ischemic limb in frostbite (22,23).Similarly, nitroglycerin was used in dermal necrosis of soft tissue augmentation surgery and treating vasopressor related digital ischemia in septic shock in previous studies showed to improve flow in dermal vasculature and digital extremities respectively (24,25). When used at the specified doses in our protocol, no treatment-related complications or hypotension were observed in any patient (26).

Ischemic extremities without blood flow can lead to serious systemic and life-threatening events such as thrombocytopenia-related multiple organ failure (TAMOF), systemic inflammatory response syndrome (SIRS), disseminated intravascular coagulation (DIC), sepsis, and gas gangrene. Even transferring a patient with this condition to a tertiary center can pose a significant risk due to potential systemic complications that may develop en route. TPE therapy has proven to provide a safe recovery period, allowing for the safe transfer of patients to tertiary centers and more frequent and longer HBOT for complete recovery or limb-sparing surgery with the establishment of the demarcation line. In previous years, TPE has been used to treat sepsis, TAMOF, and DIC (27). The experience with TPE in crush injury has not yet been reported, however, Klein et al showed the beneficial effect of TPE in severe burn injuries previously (28). Considering the same pathophysiology of the event, crush injury can cause severe endothelial damage, leading to a cytokine storm and SIRS, as well as excessive endothelial exocytosis and the release of large amounts of ultra-large von Willebrand Factor (uLvWF) into circulation, which can lead to microthrombi formation and platelet aggregates. ADAMST-13, an enzyme needed to degrade uLvWF, may be insufficient, leading to the deposition of uLvWF on the endothelium and the formation of microthrombi, impairing organ perfusion and leading to multiple organ failure (29). TPE therapy provides clearance of both pro-inflammatory mediators of the inflammatory pathway and elements of the microthrombotic pathway. The timing of TPE therapy initiation is critical to achieving the benefits of this treatment (30). One of four patients, who had a more severe crush injury and was under the rubble for a similar duration, recovered without the need for amputation due to the early initiation of TPE (on the second day of the earthquake), HBOT and the application of the protocol (Patient 1 in Figure 1). In contrast, the other patient, who had a less severe crush injury and received treatment late (on the sixth day of the earthquake), had to undergo partial amputation distal to the metatarsal joint, although below-knee amputation was ultimately avoided (Patient 3 in Figure 1). This patient was initially followed up in the ward due to their stable clinical condition but was later admitted to the intensive care unit on the sixth day with a plan for above-knee amputation due to impaired leg circulation. This patient highlights the importance of early recognition of extremity changes for pediatricians following up with patients in the ward.

Intensive Hyperbaric Oxygen Therapy (HBOT)

HBOT increases not only the dissolved partial oxygen pressure in the blood but also mitochondrial oxygenation (31). As oxygen cannot be delivered to the necrotic extremities with impaired vascularity through blood, the increase in partial oxygen pressure and the provision of oxygenation at the mitochondrial

level can halt the progression of necrosis in the extremities.

HBOT helps maintain aerobic respiration in all cells and tissues, ensuring survival. Moreover, it has an anti-edema effect by increasing extravascular fluid resorption. By maintaining aerobic metabolism, it can prevent the growth of anaerobic organisms and create a sterile environment (32). One of the most important effects of HBOT is its ability to stimulate collagen synthesis and fibroblast migration, thereby accelerating wound healing. Moreover, it has an anti-edema effect by increasing extravascular fluid resorption. Jirangkul et al suggested that HBOT should be considered in limb salvage procedures to manage extremities of which MESS was over 7. They included 18 patients with severe mangled limbs (MESS ≥ 7). Adjunctive to surgical procedure, the patients received HBOT within 48 hours of injury twice daily for the first three days then following once daily (number of HBOT mean 23.44 ± 6.76). Only one patient (MESS = 12) needed below knee amputation (32). Therefore, in our protocol, patients who were initially considered for amputation (MESS > 7) received intensive HBOT treatment, with hyperbaric therapy administered every 8 h for the first 2 days, every 12 h for the next five days, and finally, daily hyperbaric therapy, resulting in remarkable outcomes.

Vacuum-Assisted Closure (VAC)

Prior research has indicated that VAC treatment can decrease the time needed for fasciotomy incision healing (33). Using the VAC method in treatment has significantly reduced edema in the extremity, which can delay wound healing. Additionally, orthopedic, and plastic surgery procedures performed by a skilled surgical team in the patients' follow-up have made an invaluable contribution to creating a functional limb.

Record-board (Writing whiteboard)

The use of a whiteboard (Figure 3) is crucial for facilitating the follow-up of intensive treatments given to patients by both nurses and doctors, as well as adjusting the timing and coordination of treatment in regional PICUs where there is a high patient flow and in tertiary PICUs where patients are referred. According to Justice et al., using record boards that visually present patients' daily goals enhances communication during multidisciplinary rounds in cardiac critical care units where intensive patient follow-up is conducted (34).

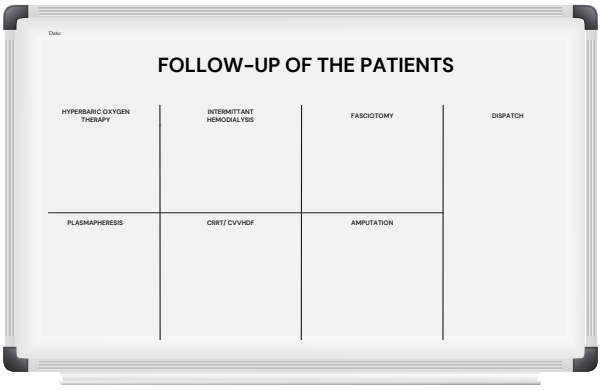

Figure 3: Recording board for adjusting the timing and coordination of treatment in regional PICUs where there is a high patient flow and in tertiary PICUs where patients are referred.

Dispatch

Maintaining the referral network in motion is also crucial (35). Patients at risk of amputation should be referred to tertiary centers in a coordinated manner after metabolic and hemodynamic stabilization has been achieved in primary centers with high patient flow following an earthquake. To avoid communication issues between the center where the patient is being transferred, the emergency coordination center, and the center where the patient will be referred, it was helpful to create a transfer form similar to the one shown in Figure 4.

	Patient Name	Security Number	Age	Diagnosis/Crushed Extremities	Respiration	Vitals	Received treatments	Referral Center	Doctor contact in referral center
First Dispatch									
Second Dispatch									

Figure 4: Transfer form for maintaining the referral network

It is crucial to record the earthquake victim's identity information on the transfer form to ensure that it can be applied again during transport or later if their identity is determined.

CONCLUSION

Disasters cannot be controlled, and this reality highlights the need for rigorous, controlled, and systematic protocols to be prepared in advance and implemented in the event of a disaster that will impact society in many ways. Developing a treatment plan that includes standardized interventions for healthcare teams in major disasters is crucial**.** In this study, we present the treatment plan that we experienced during the 2023 Kahramanmaraş earthquake to be prepared and ready for future disasters.

Patients at risk of amputation should be referred to tertiary centers in a coordinated manner after metabolic and hemodynamic stabilization has been achieved in primary centers with high patient flow following an earthquake. Specialized treatments such as daily TPE therapy with frequent HBOT, anticoagulant and vasodilator treatments, and VAC therapy initiated in regional PICUs and continued in tertiary referral PICUs can produce encouraging results for patients with severe crush syndrome.

Ethics Committee Approval: This study was approved by the ethics committee Koç University (approval number: 2023.133.IRB1.045).

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- M.T., I.B., .Ö.Ö.; Data Acquisition- A..Ç, L.Ö., K.S., M.E.M.; Data Analysis/Interpretation- İ.E., A.Ç.; Drafting Manuscript- M..T, İ.B., K.S., Ö.Ö.; Critical Revision of Manuscript- İ.E., A.Ç., A.Ç., L.Ö., M.E.M.; Final Approval and Accountability- M.T., I.B., Ö.Ö., K.S., A.Ç., L.Ö., İ.E, A.Ç., M.E.M.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Patients Diagnosed with Congenital Glycosylation Defects: A Rainbow of Inherited Metabolic Disorders

Metabolik Bozuklukların Gökkuşağı: Konjenital Glikozilasyon Defekti Tanılı 11 Vakanın Değerlendirilmesi

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ABSTRACT

Introduction: Congenital glycosylation defects (CDGs) manifest with multisystemic symptoms involving the immune, central nervous, endocrine, and musculoskeletal systems. A total of 137 distinct CDG types have been identified to date.
Materials and Methods: Patients diagnosed with CDG in the Division of Pediatric Metabolism and Nutrition, at Çukurova University, between 2013 and 2019 were included in the study. The patients' files were retrospectively reviewed, and demographic, clinical, laboratory and radiological findings and molecular analyses were recorded and evaluated.
Results: The mean age at diagnosis for a total of 11 (6 Female; 5 Male) patients (Four with PMM2-CDG, one with MPI-CDG, one with DOLK-CDG, one with B4GALT1-CDG, three with TMEM165-CDG, and one with PIGN-CDG) was 6.94 years (ranging from 11 months to 22 years). Amongst the patients, 45% (5 individuals) were male. Sixty-three percent of patients exhibited low weight and height (below the 5th percentile). Elevated liver enzymes were observed in 82% of cases, while 82% showed neurodevelopmental delay, 72% had cerebellar atrophy, and 72% experienced growth retardation. Additionally, 73% of patients displayed hepatomegaly and thrombocytopenia, and 63% had renal involvement. An homozygous p.V129M (c.385G>A) mutation in the PMM2 gene confirmed PMM2-CDG diagnosis in four patients. Furthermore, distinct homozygous mutations were detected: p. I399T (c.1193T>C) in the MPI gene, p. Y441S (c.1322A>C) in the DOLK gene, p. Arg126Cys (c.376C>T) in the TMEM165 gene, a novel p. Tyr239* (c.717T>G) mutation in the B4GALT1 gene, and a novel p. Thr266Ala (c.2356A>G) mutation in the PIGN gene.
Conclusion: CDGs exhibit a diverse clinical spectrum, earning them the moniker "the rainbow" of hereditary metabolic disorders. While PMM2-CDG is the most prevalent subtype, only a few instances of other subtypes have been documented. Inverted nipples and abnormal fat pads are primary features of CDGs. The intricate nature of our cases and the rarity of DOLK-CDG, PIGN-CDG, and TMEM-165-CDG diagnoses stand out as notable aspects of this report.

Keywords: glycosylation, congenital glycosylation defects, PMM2, MPI, DOLK, TMEM-165, PIGN, CDG

ÖZ

Giriş: Konjenital glikozilasyon kusurları (CDG), immün, merkezi sinir, endokrin ve kas-iskelet sistemlerini içeren multi sistemik belirtilerle ortaya çıkar. Bugüne kadar toplamda 137 farklı CDG türü tespit edilmiştir.
Materyal ve Metod: Çukurova Üniversitesi Çocuk Metabolizma ve Beslenme Bilim Dalı'nda 2013 ve 2019 yılları arasında takip edilen ve CDG tanısı alan hastalar çalışmaya dahil edildi. Hastaların kayıtları geriye dönük olarak incelendi ve demografik klinik, laboratıvar ve radyolojik bulguları kayıt edilerek değerlendirildi.
Bulgular: Toplam 11 hastanın (Dört PMM2-CDG, bir MPI-CDG, bir DOLK-CDG, bir B4GALT1-CDG, üç TMEM165-CDG ve bir PIGN-CDG) tanı anındaki ortalama yaşları 6.94 yıl (11 ay ile 22 yıl arası) idi. Hastaların %45'i (5 kişi) erkekti. Hastaların %63'ünde ağırlık ve boy, 5. persentilin altında bulunmaktaydı. %82'sinde yüksek karaciğer enzimleri, %82'sinde nörogelişimsel gecikme, %72'sinde serebellar atrofi ve %72'sinde büyüme geriliği gözlendi. Ek olarak, hastaların %73'ünde hepatomegali ve trombositopeni, %63'ünde ise böbrek tutulumu tespit edildi. PMM2 genindeki homozigot p.V129M (c.385G>A) mutasyonu, 4 hastada PMM2-CDG tanısını doğruladı. Ayrıca, MPI geninde p. I399T (c.1193T>C) homozigot mutasyonu, DOLK geninde p. Y441S (c.1322A>C) homozigot mutasyonu, TMEM165 geninde p. Arg126Cys (c.376C>T) homozigot mutasyonu, B4GALT1 geninde novel bir p.Tyr239* (c.717T>G) mutasyonu ve PIGN geninde novel bir p. Thr266Ala (c.2356A>G) mutasyonu tespit edildi.
Sonuç: Konjenital glikozilasyon defektleri çeşitli klinik spektruma sahip olup, onları "genetik metabolik bozuklukların gökkuşağı" olarak adlandırmamıza sebep olmaktadır. Çalışmamızda PMM2-CDG en yaygın görülen tip iken, diğer tiplerden sadece birkaç örnek bulunmaktadır. Konjenital glikozilasyon defektlerinin ana özellikleri arasında ters meme uçları ve anormal yağ yastıkçıkları yer almaktadır. Vakaların karmaşıklığı ve DOLK-CDG, PIGN-CDG ve TMEM-165-CDG tanılarının nadirliği, bu araştırmanın dikkat çeken yönlerini oluşturmaktadır.

Anahtar Kelimeler: glikozilasyon, konjenital glikozilasyon kusurları, PMM2, MPI, DOLK, TMEM-165, PIGN, CDG

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INTRODUCTION

Congenital Glycosylation Defects (CDG), first described by Belgian paediatrician Jaak Jaeken in 1980, exhibit multisystem involvement and are named after the abnormalities observed in the separation of transferrin isoforms (1). Almost all inherited disorders in glycan biosynthesis have been identified in the last 20 years, and approximately 137 types of CDG's have been classified to date. CDGs are a group of rare disorders presenting with clinically and biochemically heterogeneous features affecting numerous organ systems (2). They arise from defects in synthesising glycans of glycoproteins and glycolipids and the attachment of proteins and lipids. Whilst some disorders affect only one glycosylation pathway, others can impact multiple pathways simultaneously. Disorders can arise from defects in sugar activation, presentation, and transport; abnormalities in glycosidase and glycosyltransferase enzymes; disruptions in golgi homeostasis; and regulations of protein glycosylation. CDGs are categorised into groups based on their effects on N-glycosylation (31 types), O-glycosylation (34 types), lipid and GPI glycosylation defects (25 types), and multiple glycosylation pathways (47 types). Additionally, deglycosylation defects like NGLY1-CDG have also been identified. According to the new classification, CDGs are named with mutated genes (e.g., MPI-CDG) (1).

In undefined clinical conditions, when neurological and multiorgan involvement are accompanied by developmental delay, CDG should be considered. Transferrin isoelectric focusing (TIF) can be used as a diagnostic method. However, it should be noted that TIF can diagnose only a limited number of CDG types, especially those associated with sialic acid deficiencies (3). Partial deficiencies in sialic acid result in two types of cathodal shifts: Type 1 and Type 2 patterns. If a Type 1 pattern is detected, based on clinical findings, PMM2-CDG or MPI-CDG should be considered initially. If these diseases are not identified, dolichol-associated glycan analysis, direct mutation analysis targeting known CDG genes, or whole exome sequencing/whole genome sequencing (WES/WGS) analysis should be performed. In cases of Type 2 patterns, a defect in the glycan pathway at an advanced stage may be encountered. Protein-associated glycan analysis, CDG gene panel, or WES/WGS analysis should be considered. Additionally, the level of apolipoprotein C-III is an important laboratory parameter that specifically detects O-glycosylation disorders (4).

N-glycosylation disorders affect multiorgan systems, particularly eyes, hepatic and immune systems, and central and peripheral nervous systems. The general and diverse nature of clinical features complicates the ability of clinicians to diagnose CDG. Developmental delay, hypotonia, coagulation disorders, impaired brain development, and endocrine abnormalities can also accompany the condition (5).

N-glycosylation defects are classified into two types; CDG type 1 (CDG-1) may develop due to disruptions in lipid-linked oligosaccharide or protein transfer or processing in one or both N-glycans. CDG Type 2 (CDG-2) arises from the abnormal processing of incompletely attached glycan to proteins (1). A Total of 133 genes are implicated in CDG, with 177 different clinical phenotypes (5).

MATERIALS AND METHODS

Patients diagnosed with CDG and followed-up in the Division of Pediatric Metabolism and Nutrition, at Çukurova University, between 2013 and 2019 were included in the study. The study was approved by the Ethics in Research Committee of Çukurova University Faculty of Medicine, Adana, Türkiye (approval number: 2019/04-10). Written informed consent was taken from all patients' legal representatives. The patients' files were retrospectively reviewed, and demographic, clinical, laboratory and radiological findings and molecular analyses were recorded and evaluated.

Results: The mean age of diagnosis for the total of 11 patients (four with PMM2-CDG, one with MPI-CDG, one with DOLK-CDG, one with B4-GALT1-CDG, three with TMEM165-CDG, and one with PIGN-CDG) was 6.94 years (11 months to 22 years) (Table 1, Table 2). Forty-five percent of the patients were male, and 91% had consanguineous parents. Sixty-three per cent (63%) of patients exhibited low weight and height (below the 5th percentile). Liver enzyme elevation was observed in 82% of patients, neurodevelopmental delay in 82%, cerebellar atrophy in 72%, and growth retardation in 72%. Additionally, 73% of patients had hepatomegaly, 63% had thrombocytopenia, and 63% had renal involvement. Two siblings and one cousin of our eleven patients had similar complaints and sadly died before a confirmed diagnosis (Figure 2, Table 1). Among the 11 patients, PIGN-CDG and TMEM165-CDG (18%) patients had died: one due to cardiac and respiratory failure and the other due to sepsis and kidney failure, respectively. Individuals with each CDG were described in the case presentation section.

Case presentations:

PMM2-CDG cases (Phosphomannomutase-2 Deficiency)

Case 1: A 7.5-year-old girl was delivered at full term with a birth weight of 2010 g via normal spontaneous vaginal delivery (NSVD). At three months of age, she was referred to a paediatrician due to her inability to control her head and developmental delay. During investigations, a grade 1/6 systolic murmur was detected upon auscultation, and an echocardiogram (ECHO) unveiled pericardial effusion. When she reached six months of age, approximately 80 cc of serohemorrhagic fluid was percutaneously drained from the subxiphoid region—seizures begun at one year old, leading to the initiation of levetiracetam treatment. By age three, hemophagocytic lymphohistiocytosis (HLH) was considered bicytopenia, and bone marrow aspirate results emerged. Treatment with intravenous immunoglobulin and dexamethasone was initiated. At four years old, ureteropelvic dilatation was evident in a urinary ultrasonography (USG). Frequent lower respiratory tract infections necessitated hospitalisation twice a month. The patient's parents were consanguineous, and her cousin displayed similar clinical features.

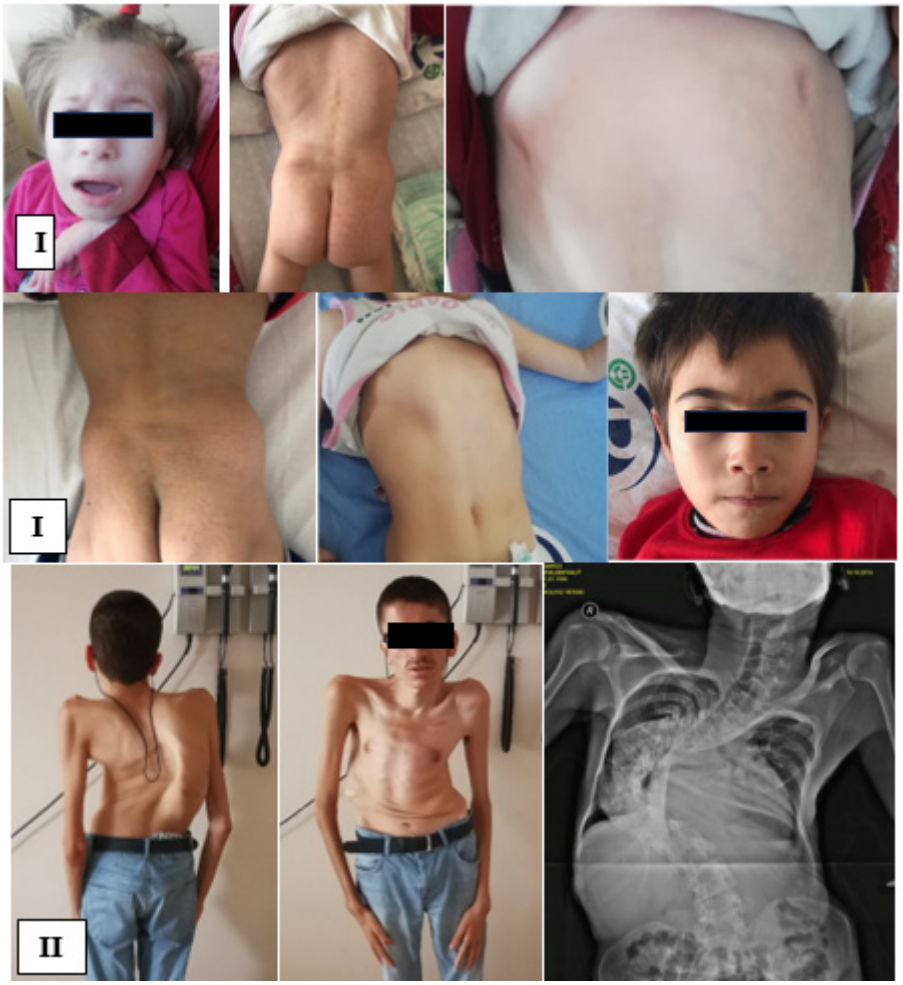

Figure 1: Clinical features of selected CDG cases. I-II. Dysmorphic facial features, abnormal fat pads, inverted nipples of patients with PMM2-CDG [case 1 and 2] III. Dysmorphic facial appearance of Case 8 with PIGN-CDG and his kyphoscoliosis on X-ray.

Upon physical examination, her weight measured 9800 g (<5th percentile), and her height was 82 cm (<5th percentile). She was able to smile and recognise her mother. However, she was confined to a wheelchair, and deep tendon reflexes (DTR) in all four extremities were diminished. Her fingers were slender and elongated, displaying inverted nipples, abnormal fat pads, and pectus carinatum (Figure 1-I). Axial hypotonia and strabismus were notable findings. A fundus examination unveiled retinal atrophy, macular fibrosis, and optic disc pallor in her right eye. Laboratory assessments indicated thrombocytopenia, neutropenia, and low protein S levels, while aspartate transaminase (AST), alanine transaminase (ALT), and prolactin levels were elevated. The coagulation profile appeared normal. Based on the prevailing clinical and laboratory findings, TIF analysis demonstrated a decrease in penta- and tetrasialotransferrin fractions, coupled with an increase in disialo- and asialotransferrin fractions, consistent with the pattern of type 1 CDG. Echocardiography (ECHO) uncovered both pericardial effusion and a significant patent foramen ovale. Further auditory tests exhibited bilateral sensorineural hearing loss.

Case 2: A 5-year-old girl, the cousin of case 1, was admitted to the hospital due to neurodevelopmental delay and recurring lower respiratory tract infections. She was born at full term with a weight of 2900 g via NSVD. Her parents were consanguineous. During the physical examination, her weight was 5200 g (<5th percentile), and her height was 98 cm (<5th percentile). Strabismus, inverted nipples, abnormal fat pads, pectus carinatum, and mongolian spots were evident (Figure 1-II). She was hypotonic but could control her head and sit with support. Abdominal examination indicated hepatomegaly. Laboratory assessments revealed thrombocytopenia, neutropenia, elevated liver enzymes and prolactin levels. Her coagulation profile was normal, but serum protein S levels were notably low. An ECHO displayed left ventricular dilatation alongside mild mitral and aortic valve regurgitation. Abdominal USG supported the hepatomegaly and showed increased parenchymal echogenicity in both kidneys and the liver. Electromyography (EMG) revealed signs of neurogenic involvement, while cranial magnetic resonance imaging (MRI) demonstrated cerebellar atrophy.

Case 3: A 3-year-old male was delivered at term via cesarean section (C/S) with a birth weight of 4000 grams to

consanguineous parents. A Dandy-Walker malformation had been identified during the neonatal period. Family history revealed a previously deceased 13-year-old sister with similar findings. At three months, he was referred to our clinic for neuromotor regression. His height was 10.2 kilograms (<5th percentile), while his height measured 83 centimetres (<5th percentile), with prominent microcephaly. His physical exam findings were inverted nipples and abnormal fat pads. Strabismus was noted, along with axial hypotonia and diminished DTRs. Biochemical tests yielded normal results. Cranial MRI showed severe cerebellar atrophy, an enlarged fourth ventricle, a cystic appearance within the posterior fossa, and a confirmed Dandy-Walker malformation.

Case 4: A 1.5-year-old male was born at full term via C/S, weighing 2800 g at birth. At postnatal ten days, he was admitted to the emergency room (ER) due to feeding difficulties and somnolence, and thrombocytopenia and hypoglycemia were detected in lab tests. Pericardial effusion was detected at age four months after a respiratory infection. On admission, he had growth retardation, developmental delay, microcephaly, hypotonia with diminished DTRs, hepatomegaly, inguinal hernia, inverted nipples, and a large Mongolian spot on physical examination. Laboratory tests showed thrombocytopenia, hypertriglyceridemia, hypercholesterolemia, and a prolonged coagulation profile. Abdominal USG indicated hepatomegaly (103 mm), splenomegaly (82 mm), and grade 2 hyperechogenicity within liver parenchyma and both kidneys. Cranial MRI showed cerebellar hypoplasia, and ECHO demonstrated the presence of pericardial effusion. TIF analyses were abnormal with a Type 1 pattern, suggesting PMM2-CDG. Molecular analysis showed a pathogenic homozygous p.Val129Met (c.385G>A) variant in PMM2, confirming the diagnosis.

Case 5: A 6.5-year-old female was born at term via NSVY with a birth weight of 3500 g. Multicystic dysplastic kidneys were detected at age eight months. She was hospitalised at 9 months of age for fatigue, poor feeding, vomiting, and short myoclonic seizures associated with hypoglycemia, and carbamazepine treatment was initiated for seizures. Hypoglycemia-related tests during the seizure showed high blood ketones and lactate, low cortisol, and abnormal liver function tests. Parents were consanguineous, and a cousin was reported to have similar findings. Physical examination showed a weight of 18 kg (5-10th percentile) and a height of 109 cm (<5th percentile). Her neurological and other system examinations were normal. She could walk independently. Laboratory tests revealed high liver enzymes, low blood sugar levels, a normal coagulation profile, and a normal hemogram. Spot urine protein-to-creatinine ratio was normal. Abdominal USG showed increased liver dimension (117 mm), granular appearance of the liver parenchyma, and multicystic dysplastic kidneys. Voiding cystourethrography revealed vesicoureteral reflux. The left kidney was compensatively hypertrophic in addition to the bladder dysfunction. DMSA scan indicated a non-functioning right kidney. EEG showed generalised slow vawe activities. The molecular analysis detected a pathogenic homozygous p.

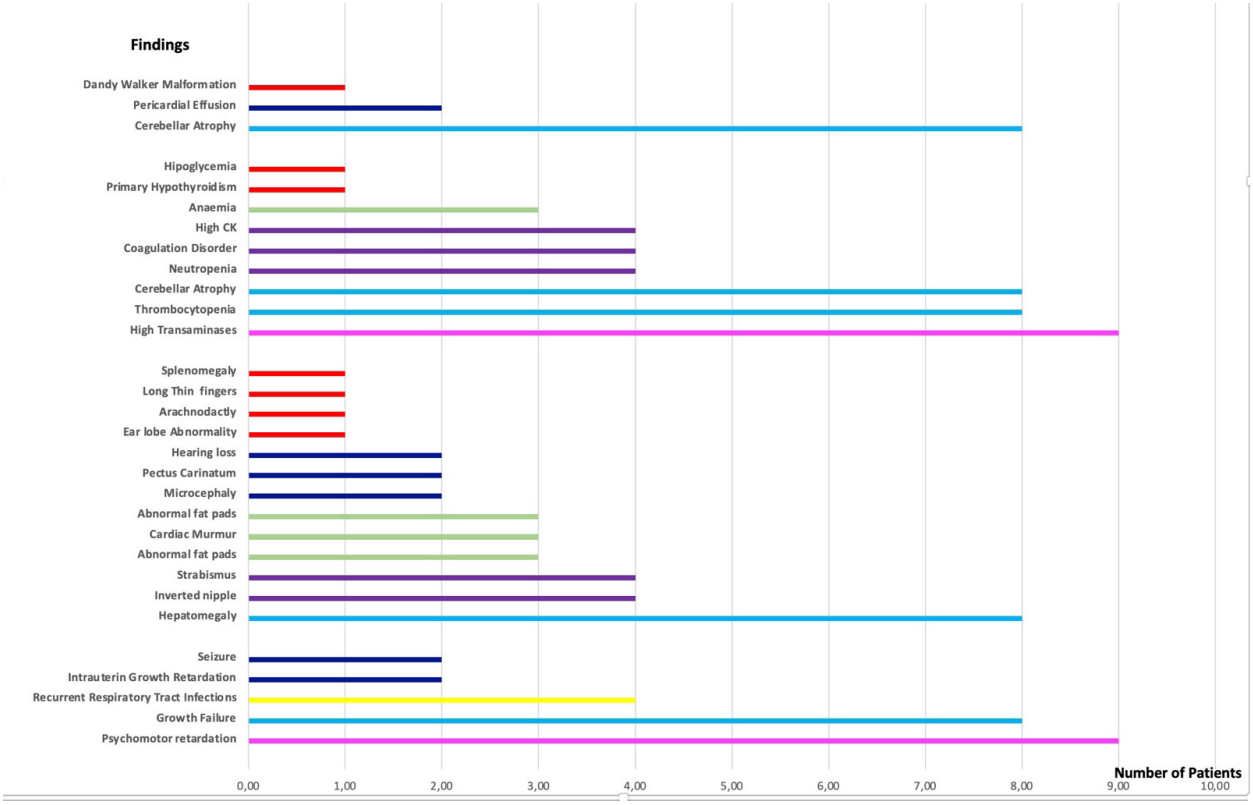

Figure 2: Distribution of Clinical, Physical Examination, Laboratory, and Radiological Findings in 11 Patients Diagnosed with Congenital Glycosylation Defects

Table 1: CDG: Congenital Glycosylation Defect, VUS: Variant of Uncertain Significance p: Percentile.

Cases	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11
Diagnosis	PMM2-CDG	PMM2-CDG	PMM2-CDG	PMM2-CDG	MPI-CDG	DOLK-CDG	B4-GALT1-CDG	PIGN-CDG	TMEM165-CDG	TMEM165-CDG	TMEM165-CDG
Age at diagnosis (Years)	7.5	5	3	1.5	6.5	0.91	17	23	3	8	0.91
Intrauterin Growth Retardation	YES	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO
Recurrent Lower Respiratory Tract Infections	YES	YES	NO	NO	NO	NO	YES	NO	YES	NO	NO
Seizure	YES	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO
Neuromotor Regression	YES	YES	YES	NO	NO	YES	YES	YES	YES	YES	YES
Growth Failure	YES	YES	YES	YES	YES	YES	NO	YES	NO	YES	NO
Weight <5p	YES	YES	YES	YES	YES	YES	NO	YES	NO	YES	NO
Height <5p	YES	YES	YES	YES	YES	YES	NO	YES	NO	YES	NO
Microcephaly	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO
Strabismus	YES	YES	YES	NO	NO	NO	YES	NO	NO	NO	NO
Pectus Carinatum	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
Arachnodactyly	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Inverted nipples	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO
Abnormal fatty pads	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO
Hepatomegaly	YES	YES	NO	YES	YES	NO	NO	YES	YES	YES	YES
Splenomegaly	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO
Cardiovascular System Abnormality	NO	YES	NO	NO	NO	YES	NO	YES	NO	NO	NO
Hearing Loss	Sensorineural	NO	NO	NO	NO	Sensorineural	NO	NA	NO	NO	NO
Anemia	YES	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO
Neutropenia	YES	YES	NO	NO	NO	YES	YES	NO	NO	NO	NO
Thrombocytopenia	YES	YES	NO	YES	NO	YES	YES	NO	YES	YES	YES
Coagulation Disorders	NO	NO	NO	YES	YES	YES	NO	NO	YES	NO	NO
Creatin Kinase Elevation	NO	NO	NO	NO	NO	NO	NO	YES	YES	YES	YES
Elevated Liver Enzymes	YES	YES	NO	NO	YES	YES	YES	YES	YES	YES	YES
Hypothyroidism	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO
Hypoglycemia	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO
Anemia	YES	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO
Neutropenia	YES	YES	NO	NO	NO	YES	YES	NO	NO	NO	NO
Hipothyroidism	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO
Renal Involvement	NO	YES	NO	YES	YES	NO	NO	YES	YES	YES	YES
Pericardial Effusion	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Cerebellar Atrophy	YES	YES	YES	YES	NO	NO	YES	NO	YES	YES	YES
Dandy Walker Malformation	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO
Gene	*PMM2*	*PMM2*	*PMM2*	*PMM2*	*MPI*	*DOLK*	*B4-GALT1*	*PIGN*	*TMEM165*	*TMEM165*	*TMEM165*
Genotype											
Zygosity	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous
Mutation Class	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	VUS	VUS	Pathogenic	Pathogenic	Pathogenic
Known/Novel	Known	Known	Known	Known	Known	Known	Novel	Novel	Known	Known	Known

Evaluation of clinical findings, physical examination, laboratory, radiological findings, and genetic analyses of patients diagnosed with CDG.

Ile399Thr (c.1193T>C) variant in *MPI*, leading to the diagnosis of MPI-CDG.

Case 6: A 6-month-old patient was delivered to non-consanguineous parents at 37 gestational weeks via C/S, weighing 1900 grams at birth. Due to her low birth weight, she was hospitalised. Poor sucking and hypotonia were observed at follow-up. Parents reported watery mucoid stools 8-9 times per day, coupled with failure to thrive since birth. At age one month, she was hospitalised for three months in the intensive care unit (ICU) for intractable fever, septicemia, and dehydration. Following a BCG (Bacille Calmette-Guerin) vaccination, she developed a fever and hypotonia. At five months of age, she was hospitalised again due to diarrhoea, vomiting, and poor weight gain. Her weight measured 3640 grams (<5th percentile), height was 58 cm (<5th percentile), and head

Table 2. CDG (Congenital Glycosylation Defect) Subtypes Observed in Our Patients and their Transferrin Isoelectric Focusing (TIF) Pattern.

Name	Type of Disorder	Clinically Affected Organ and Tissue	Defective Protein	TIF
MPI-CDG	Protein N-Glycosylation Disorder	Intestine, Liver	Mannose 6-phosphate isomerase	**Type 1**
PMM2-CDG	Protein N-Glycosylation Disorder	Nervous system, Adipose tissue, and almost all organs	Phosphomannomutase 2	**Type 1**
DOLK-CDG	Disorders in Multiple and other Glycosylation Pathways (Disorders in Dolichol Synthesis)	Brain, Heart, Skin	Dolikol Kinaz	**Type 1**
B4GALT1-CDG	Disorders in Glycosyltransferase Enzymes	Face (dysmorphic), eyes (myopia)	B-1,4-galactosyltransferaz	**Type 2**
TMEM165-CDG	Others	Brain, Skeleton (especially cartilage), Joints, Heart, Liver, Kidneys	Transmembrane protein 165	**Type 2**
PIGN-CDG	Disorder in Glycosylphosphatidylinositol Synthesis	Brain, Skeleton (palate, fingers), Cardiovascular system, Kidneys	Glycosylphosphatidylinositol ethanolamine phosphate transferaz 1	-

circumference was 38 cm (<5th percentile). A large anterior fontanelle was noticeable, although no facial dysmorphia was identified. Abdominal examination unveiled hepatomegaly. She exhibited axial hypotonia and lacked head control. A grade 2/6 murmur was found during her cardiovascular examination. Her feeding difficulties led her to be brought to the pediatric emergency department (ED). There, elevated transaminases (AST: 1100 U/L, ALT: 800 U/L) and an abnormal coagulation profile (INR: 2.69) were identified, prompting her subsequent hospitalisation.

Over time, her liver enzymes normalised, but neutropenia emerged. Given this neutropenia (25000/mm3), bone marrow aspiration was performed, revealing a lack of mature neutrophils. Considering these findings, Kostmann syndrome was suspected, but no mutation was detected in the HAX1 gene.

At thirteen months, she was readmitted to the hospital due to fever, diarrhoea, vomiting, and lethargy. Laboratory analyses showed a white blood cell count of 4500/mm3 and an absolute neutrophil count of 100/mm3. Her coagulation profile indicated prolonged PT, APTT, INR, and low fibrinogen levels. Echocardiography unveiled an atrial septal defect. Electromyography (EMG) yielded normal results, and cranial MRI displayed bilateral periventricular white matter hyperintensities consistent with hypoxic-ischemic encephalopathy. Hearing tests indicated sensorineural hearing loss. A subsequent bone marrow aspiration depicted a bone marrow rich in medullary cells with a normal megakaryocytic series within age-appropriate limits. The majority of granulocytic cells were in the myelocytic phase, displaying insufficient lobulation in mature forms. The bone marrow aspiration disclosed arrested granulopoiesis.

Metabolic tests returned normal results. However, during her stay in the ICU, the patient's clinical condition continued to deteriorate due to multi-organ failure following septicemia. INR and liver enzyme levels increased, and severe metabolic acidosis ensued. Unfortunately, the patient ultimately passed away due to multi-organ failure.

Postmortem whole exome sequencing (WES) later unveiled a previously known homozygous p. Tyr441Ser (p.Y441S) (c.1322A>C) mutation in the DOLK gene, ultimately confirming the diagnosis of DOLK-CDG after the patient passed away.

Case 7: A nineteen-year-old female was born to consanguineous parents at 37 GW, weighing 2700 gr. At one month of age, she was admitted to the hospital due to failure to thrive and pneumonia. During hospitalisation, elevated liver enzyme levels were detected, sparking suspicion of hepatitis. Additionally, levothyroxine treatment was initiated for primary hypothyroidism. She experienced multiple hospitalisations throughout her childhood due to recurring lower respiratory tract infections. By age five, she was diagnosed with neutropenia during a hospital stay. An eye examination revealed high myopia, restricted outward movement of the left eye, and amblyopia and proptosis. Furthermore, recurrent aphthous lesions were observed in both oral and anal regions.

Laboratory analyses indicated intermittent low absolute neutrophil counts, thrombocytopenia, anaemia, and fluctuating transaminase levels. Brain and orbital MRI results demonstrated mild left cerebellar and vermian hypoplasia, a retro sellar arachnoid cyst, and bilateral frontal subcortical lesions. Whole exome sequencing (WES) analysis brought to light a novel homozygous p.Tyr239* (c.717T>G) mutation

within the B4GALT1 gene. This discovery conclusively led to the diagnosis of B4GALT1-CDG.

Case 8: A twenty-three-year-old male was investigated for fatigue and muscle weakness in his legs at age ten. He was eventually referred to our care at seventeen due to kyphoscoliosis and elevated liver enzymes. The onset of scoliosis was noted at seven years old. He had recurrent episodes of elevated creatine kinase levels, during which he reported passing dark brownish-coloured urine. His parents were consanguineous. Physical examination revealed a weight of 39.7 kg (<5th percentile), and a height of 151.5 cm (<5th percentile). He exhibited facial dysmorphia, a high palate, and severe kyphoscoliosis (Figure 1-III). Intellectual disability was also evident. During cardiovascular assessment, a grade 2/6 murmur was detected. He displayed intermittent elevations in AST, ALT (peaking at 1600-1800 U/L), and CK levels (reaching a maximum of 1000 U/L). Cranial MRI yielded normal results, while cervical, thoracic, and lumbar MRIs displayed severe kyphoscoliosis, intact vertebral bodies, and spinal cord. Abdominal USG indicated hepatomegaly (18 cm), liver and renal parenchymal disease, and mild pelvicaliectasia in the right kidney. A muscle biopsy further revealed vacuolar myopathy. His eyes exhibited macular degeneration, and electromyography (EMG) displayed myogenic involvement. An echocardiography uncovered a left ventricular wall abnormality, global posterior lateral wall hypokinesia, left ventricular hypertrophy, mild aortic and tricuspid valve regurgitation, moderate mitral regurgitation, left ventricular systolic dysfunction, and noncompaction cardiomyopathy. His ejection fraction was measured at 36%. Cardiac MRI findings indicated global and segmental impairments in left ventricular function, high basal left ventricular myocardial mass, dilation, and moderate mitral regurgitation. Consequently, a cardiac pacemaker was implanted. Whole exome sequencing (WES) unveiled a homozygous, previously unknown p.Thr266Ala (c.2356A>G) mutation in the PIGN gene, resulting in the diagnosis of PIGN-CDG. Unfortunately, functional studies were not conducted, as the patient's condition deteriorated and she ultimately died.

Case 9: A three-year-old female patient was born at term, weighing 3200 grams. At one year of age, she was hospitalised two times due to hypotonia, polyuria, polydipsia, electrolyte imbalance, and pneumonia. She was admitted to the intensive care unit due to respiratory failure and stayed on mechanical ventilation for one week. She developed Candida pneumonia. Her motor and mental development was consistently delayed. She gained head control at the age of two. Currently, she is able to sit with support and is unable to speak.

Case 10: An eight-year-old male patient was born at term, weighing 2750 grams, via NSVY. He was hospitalised for three days in the NICU due to meconium aspiration syndrome. Frequent hospital admissions occurred due to growth retardation and neurodevelopmental delay. He underwent surgery for pes equinovarus. She could walk with support and was unable to speak.

Case 11: An eleven-month-old male patient was born at term, weighing 2900 grams, via NSVY. At two months old, he was hospitalised due to vomiting and electrolyte imbalance. Sodium, potassium, and magnesium supplementation were needed for the electrolyte imbalance. Chronic renal failure developed after a pyelonephritis attack (Candida spp.). He passed away at two years of age due to sepsis and kidney failure.

Cases 9, 10, and 11 were siblings and presented facial dysmorphia, a long philtrum, a high palate, and long eyelashes. Hypotonia and hepatomegaly were prominent findings. Their visual, auditory, and cardiological examinations were normal. Unlike the others, case 10 had contractures in both elbows, restricted movement, and short 3rd, 4th, and 5th toes.

Laboratory analyses showed elevated AST, ALT, and CK levels, electrolyte imbalance (hypokalemia, hyponatremia, hypophosphatemia), coagulation disorders, and metabolic alkalosis in the blood gases. Urine protein/creatinine ratios were high. Case 11 also had elevated plasma creatinine levels. Epiphyseal, metaphyseal, and diaphyseal dysplasia were observed in all X-rays. Abdominal USG revealed hepatomegaly, nephrolithiasis, and minimal hydronephrosis.

Case 10 had grade 2 renal parenchymal disease on renal ultrasonography and bilateral diffuse reduced parenchymal activity on the DMSA scan. Cranial MRIs showed cerebellar hypoplasia and a widening of the subarachnoid space. Patients required high doses of sodium, potassium, and magnesium. Muscle biopsy results showed variable muscle size under hematoxylin and eosin (HE) staining. Increased lipid droplets were noted in type 1 muscle fibres with HE staining. TIF results indicated a Type 2 pattern.

WES analysis identified a homozygous pathogenic p.Arg126Cys (c.376C>T) mutation in the TMEM165 gene in Case 9. Both parents were heterozygous carriers for the same mutation. The same mutation was found homozygous in the other two siblings.

DISCUSSION

Congenital disorders of glycosylation generally present with multisystemic involvement (6). Similar to other inherited metabolic disorders, the age of symptom onset and clinical phenotypes vary from mild to severe (6, 7). Most CDG patients may exhibit findings associated with early-onset neurovisceral phenotypes since birth. Detailed clinical evaluation can reveal craniofacial dysmorphisms, growth retardation and a history of non-immune hydrops fetalis during pregnancy, which can guide advanced biochemical and molecular analyses (8). Patients in our study consisted of different CDG types (Table 2), and ages of diagnosis ranged from 11 months to 23 years. In our study, early diagnosis of PMM2-CDG patients were made possible on account of using TIF and single gene analysis due to pericardial effusion, inverted nipples, and abnormal fat pads. The diagnosis age of PMM2-CDG patients ranged from 1.5 to 7.5 years. PMM2-CDG is the most common type of CDG. The severity of

enzyme deficiency and other unidentified factors contribute to a broad clinical spectrum of the disease. While some cases might not exhibit developmental delay, others might exhibit severe developmental delay. Axial hypotonia, hyporeflexia, abnormal eye movements, strabismus, retinitis pigmentosa, stroke-like symptoms, epilepsy, microcephaly, macrocephaly, olivopontocerebellar hypoplasia, peripheral neuropathy, and myopathy might also be observed. Cerebellar involvement is the most consistent finding (9). Cerebellar atrophy was detected in all of our patients. Many patients may exhibit abnormal fat pads, inverted nipples, and arachnodactyly. Abnormal fat distribution may disappear with age. The abnormal fat pads in cases 1 and 2 were very pronounced (Figure 1-I, Figure 1-II). Mild cases may not exhibit dysmorphic features. Endocrine disorders and thrombotic complications might also occur. Many patients can survive into the adulthood period (9).

In our study, PMM2-CDG-diagnosed patients (25%) had epilepsy. While Yılmaz and colleagues observed epilepsy in 36% of their cases (10), this rate was 50% in the French cohort (11). Our patients had psychomotor developmental delay and cerebellar atrophy in cranial MRI. Hepatomegaly was presented in 3/4 of patients, and elevated liver enzymes were presented in 2/4 of PMM2-CDG patients. The frequency of sensorineural hearing loss in PMM2-CDG- patients has been reported to range from 3% to 33% (10, 12, 13). Kasapkara and colleagues reported sensorineural hearing loss in a patient with a similar mutation to our PMM2-CDG-diagnosed patients (14). We also detected sensorineural hearing loss in one of our patients. The most common mutation reported in the literature was c.422G>A (R141H), while the homozygous p.V129M (c.385G>A) mutation was detected in 4 of our patients, possibly due to a regional effect.

In our study, one patient was diagnosed with MPI-CDG (Phosphomannose isomerase deficiency) (CDG-Ib). So far, at least 35 patients have been diagnosed with MPI-CDG. Similar to the literature, our patient did not exhibit any central nervous system involvement, had no dysmorphisms, and was diagnosed while being investigated for intermittent elevated liver enzymes and hypoglycemia. Vomiting, bleeding diathesis, protein-losing enteropathy, recurrent thrombosis, hypoglycemia, liver fibrosis, and symptoms of hypoglycemia (hyperinsulinemic and normoinsulinemic) can lead to expansion of the biliary tract. Treatment can include mannose, liver transplantation, and heparin (15). Our patient's clinical condition remained stable with mannose treatment without hypoglycemic attacks. Cases similar to ours have been described in the literature, and these patients were also diagnosed with polycystic kidney and microcystic changes in the kidney (16, 17).

Regarding DOLK-CDG (CDG-Im), dolichol kinase deficiency catalyses the final step of dolichol phosphate synthesis due to dolichol kinase deficiency (18). Dolichol kinase deficiency is associated with a severe clinical phenotype. Approximately 18 patients have been described to date (19). Patients can exhibit varying cardiac findings, such as dilated cardiomyopathy, neurological findings, especially epilepsy, ichthyosis, hair and eyebrow loss, and dysmorphia. Our patient had died due to severe pulmonary infection at six months of age, similar to other infantile cases in the literature (20). Another research article detailed the cases of two patients of Turkish origin who shared the same homozygous p. Tyr441Ser mutation as in our case. Tragically, these patients succumbed to infections at seven and four months, respectively. Notably, our patient did not exhibit dilated cardiomyopathy, a typical feature often reported in the literature.

Furthermore, an atrial septal defect was identified in our patient's ECHO (21). Cases have been documented in the literature wherein individuals presented with symptoms of heart failure, neutropenia, recurrent infections, and microcytic anaemia. The disease pathogenesis was characterised by a disruption in leukocyte production and differentiation (22). In Case 8, bone marrow aspiration revealed a defect in lymphocyte differentiation, initially prompting consideration of Kostmann syndrome; however, no genetic mutation could be identified. Regrettably, our patient passed away due to liver failure following recurrent infections, ultimately leading to multi-organ failure.

B4GALT1-CDG (also known as CDG-IId), which stands for β-1, 4-galactosyltransferase deficiency 1, is a subtype of CDG known for its pronounced cerebellar atrophy (23). Case 7 exhibited mild cerebellar vermian hypoplasia. Alongside fluctuating neutropenia and liver enzyme levels, a significant clinical feature was short stature. The mutation identified in Case 7 (p.Tyr239* or c.717T>G) was not previously documented in the ClinVar database. B4GALT1-CDG can manifest with developmental delay, hypotonia, thrombosis, stroke, coagulation disorders, elevated creatine kinase levels, and prolonged APTT. Notably, macrocephaly and the coincidental presence of Dandy-Walker Malformation are also possible occurrences. (24, 25).

PIGN-CDG, recognised as Multiple Congenital Anomaly-Hypotonia-Seizure Syndrome 1, is characterised by various manifestations. These include dysmorphism, cardiac anomalies like PDA, PFO, and ASD, respiratory system findings such as lung hypoplasia and diaphragmatic hernia, as well as anal stenosis, imperforate anus, hydronephrosis, hydrocele, dysplastic kidneys, vesicoureteral reflux, bladder trabeculation, gastroesophageal reflux, seizures, hypotonia, intellectual disability, psychomotor retardation, spasticity, tremors, cerebral atrophy, cerebellar atrophy, hyporeflexia, hyperreflexia, and choreoathetosis. Although epilepsy commonly presents in PIGN-CDG patients, its absence in our case was notable. Case 7 displayed intermittent elevation of liver enzymes, episodes of rhabdomyolysis, cardiac involvement, psychomotor retardation, and severe kyphoscoliosis. (26, 27). The literature also reports another patient diagnosed with PIGN-CDG with moderate kyphoscoliosis (28).

TMEM165-CDG (also known as CDG IIk) originates from a genetic disorder involving transmembrane protein 165. Its clinical presentation may encompass short stature, growth retardation, failure to thrive, microcephaly, dysmorphic

features, midfacial hypoplasia, ocular abnormalities, dysplastic ribs, hepatomegaly, feeding difficulties during infancy, psychomotor retardation, seizures, abnormalities in white matter, thrombocytopenia, as well as elevation of AST, ALT, and CK level (29). Patients 9, 10, and 11 were three siblings who prominently exhibited facial dysmorphia, renal parenchymal disease, electrolyte abnormalities, psychomotor retardation, and bone dysplasias. Consistent with the established literature, all three individuals exhibited elevated AST, ALT, and CK levels, which culminated in the diagnosis of TMEM165-CDG. This diagnosis was further substantiated by identifying a confirmed pathogenic mutation as previously documented (30).

CONCLUSION

Timely diagnosis is paramount for several forms of CDG where treatment options are available. The lack of awareness and limitations in diagnostic methods contribute to confusion in roughly half of CDG cases. While the pathophysiology of many types remains partially understood, illuminating the concealed aspects within the intricate problem will advance treatment strategies. Nevertheless, relying solely on molecular methods for CDG diagnosis remains intricate, as exemplified by our patient with an uncertain clinical significance of the PIGN mutation, who regrettably passed away. Collaborative efforts among diagnostic techniques, research endeavours, and referring physicians will bolster the efficacy of molecular testing. The integration of genomic and glycomics approaches will expedite and reinforce diagnostic procedures.

Our study encompassed various CDG types originating from distinct pathogenic mechanisms. Despite variances in clinical presentations from documented cases in the literature, neurodevelopmental delay, heightened vulnerability to infections, elevated liver enzyme levels, thrombocytopenia, and cerebellar atrophy emerged as the most prevalent indicators in our patients, warranting suspicion of CDG diagnosis. Furthermore, Whole Exome Sequencing (WES) proved instrumental in identifying CDG in instances involving immune deficiency or neutropenia. Additionally, it is essential to contemplate the possibility of CDG in cases featuring multicystic kidney disease, acute renal failure, bone involvement, coagulation disorders, and a propensity for thrombosis.

Ethics Committee Approval: This study was approved by the ethics committee of the Ethics in Research Committee of Çukurova University Faculty of Medicine, Adana, Türkiye (approval number: 2019/04-10).

Informed Consent: Legal custodian's assent of the children participated in the research was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- S.K., D.B., D.K., A.B., B.A., N.M., M.Y.; Data Acquisition- S.K., D.B., D.K., B.S.Y., F.D., D.A., M.Y., N.M.; Data Analysis/Interpretation- S.K., M.Y, N.M.; Drafting Manuscript- S.K., N.M.; Critical Revision of Manuscript- S.K., N.M.; Final Approval and Accountability- S.K., D.B., D.K., B.S.Y., A.B., F.D., B.A., D.A., N.M., M.Y.

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RESEARCH ARTICLE / *ARAŞTIRMA MAKALESİ*

The Effect of Parental Vaccine Literacy Level and Attitudes on COVID-19 Vaccination Decisions for Children Aged 5-11 Years: A Cross-sectional Study

Ebeveynlerin Aşı Okuryazarlık Düzeyi ve Tutumlarının 5-11 Yaş Arası Çocuklarda COVID-19 Aşı Kararına Etkisi: Kesitsel Bir Çalışma

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ABSTRACT

Objective: The aim of this study was to determine the decision of parents of children aged 5-11 years to vaccinate their children against COVID-19 and to investigate the relationship between this decision and their vaccine literacy and attitudes.
Materials and Methods: A descriptive and cross-sectional research design was implemented on 635 parents between April 2022 and December 2022. Data were collected using the COVID-19 Vaccine Literacy Scale, the Attitudes Towards the COVID-19 Vaccine Scale, and an Information Form.
Results: A positive and significant relationship was found between the scores of the parents on the COVID-19 Vaccine Literacy Scale and the Attitudes Towards the COVID-19 Vaccine Scale. In the study, it was determined that the total score averages of the Attitudes Towards the COVID-19 Vaccine Scale were significantly higher for the parents who had had all childhood vaccinations for their children, who agreed to have their child vaccinated for the COVID-19 vaccine, who had had the COVID-19 vaccine themselves, and who stated that the vaccine should be mandatory for both adults and children.
Conclusion: It was concluded that parents' willingness to vaccinate their children routinely and their level of vaccine literacy about the COVID-19 vaccine positively influenced their attitude and decisions towards vaccinating their children against COVID-19.

Keywords: vaccine literacy, vaccine attitude, COVID 19 vaccine, children, parents

ÖZ

Amaç: Bu araştırma 5-11 yaş arası çocuğu olan ebeveynlerin çocuklarına COVID-19 aşısını yaptırmaya yönelik kararının ve bu kararın aşı okuryazarlığı ve aşıya yönelik tutum düzeyleri arasındaki ilişkisinin belirlenmesi amacıyla yapılmıştır.
Gereç ve Yöntem: Araştırma, tanımlayıcı ve kesitsel tasarımdadır. Araştırmanın örneklemini 635 ebeveyn oluşturmuştur. Veriler COVID-19 Aşı Okuryazarlığı Ölçeği, COVID-19 Aşısına Yönelik Tutum Ölçeği, Bilgi Formu kullanılarak Nisan 2022-Aralık 2022 tarihlerinde toplanmıştır.
Bulgular: Ebeveynlerin COVID-19 Aşı Okuryazarlığı Ölçeği ile COVID-19 Aşısına Yönelik Tutum Ölçeği puanları arasında pozitif yönde ve anlamlı bir ilişki bulunmuştur. Çalışmada çocukluk çağı aşılarının tamamını yaptıran, çocuğuna COVID 19 aşısı çıkarsa yaptırmayı kabul eden, kendisine COVID 19 aşısı yaptıran, yetişkinler ve çocuklar için aşının zorunlu olması gerektiğini ifade eden ebeveynlerin COVID-19 Aşısına Yönelik Tutumlar Ölçeği toplam puan ortalamalarının anlamlı olarak daha yüksek olduğu belirlenmiştir.
Sonuç: Ebeveynlerin çocuklarını rutin çocukluk çağı aşılamaları konusundaki istekliliği ve COVID-19 aşısı hakkındaki yüksek aşı okuryazarlık düzeylerinin, çocuklarına COVID-19 aşısı yaptırma konusundaki tutum ve kararlarını olumlu yönde etkilediği sonucuna varılmıştır.

Anahtar Kelimeler: aşı okuryazarlığı, aşı tutumu, COVID 19 aşısı, çocuk, ebeveyn

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INTRODUCTION

The first case of the novel coronavirus disease (COVID-19) in December 2019 in Wuhan, China marked the onset of a global health crisis. Rapidly spreading across the world, the disease was eventually declared a pandemic by the World Health Organization (1). Amid the pandemic, numerous countries initiated the vaccination of individuals below 18 years of age, aiming to shield them from newly emerging and highly transmissible variants of COVID-19. Efforts to vaccinate children aged 5 to 11 years increased in Western countries as children are recognized as vulnerable, who are less likely to comply with restrictions and protect themselves (2, 3). Numerous studies had indicated the efficacy of COVID-19 vaccines in reducing transmission rates, hospitalizations, and fatalities, playing a pivotal role in controlling the pandemic (2, 4, 5). In line with these findings, COVID-19 vaccine had been recommended for children over the age of 5 by the health authorities, and supplemental doses have been recommended for those aged 12 and over (6). Vaccination in Türkiye covers children aged 12-17 and people aged 18 and over. The Pfizer-BioNTech® vaccine regimen for the 5-11 age group, which is accepted in European countries, is not yet implemented in Türkiye (7).

Vaccination, recognized as the most effective preventive measure against infectious diseases, is globally embraced as a crucial public health service (8). Furthermore, safeguarding children against infectious diseases through vaccination is deemed a fundamental right (9). Despite the increase in vaccination rates, there are concerns that the continued increase in COVID-19 cases and transmission may increase vaccine hesitancy, rejection or resistance among parents. Systematic reviews and meta-analyses found that the population acceptance rate of the COVID-19 vaccine was approximately 73% (10, 11, 12). It is widely recognized that the success of safe and effective immunization strategies is contingent on widespread vaccine acceptance; hesitancy or resistance among individuals or parents can impede this progress (13). Because parents have the power to make decisions on behalf of their children, they play a critical role in determining whether their child should be vaccinated. Parents' perspectives on COVID-19 preventive measures and their attitudes towards vaccination have a significant impact on their child's immunization status (8, 10).

The concept of vaccine hesitancy is typically analysed by considering three factors: complacency, confidence, and convenience. Essentially, an individual's or parent's choice to accept a vaccine revolves around striking a balance between evaluating the potential advantages and risks associated with it. Vaccine hesitancy arises when there is a diminished recognition of the necessity of vaccination (referred to as complacency) and concerns regarding effectiveness and safety (termed low confidence). Confidence in a vaccine is further eroded by misconceptions about immunization processes, mistrust of government and healthcare authorities, and the novelty of the vaccine. Additionally, the ease of accessing a vaccine (convenience) is also taken into consideration alongside these factors. It is well understood that social dynamics like norms, intentions, and collective responsibility play a significant role in vaccine acceptance (14-16). Furthermore, certain aspects of the ongoing epidemic can impact both complacency (e.g., misrepresenting the severity by comparing it to seasonal flu) and confidence (e.g., rapid vaccine development rate). Various factors influence the willingness to accept a vaccination, including socio-demographic variables, psychological aspects, attitudes regarding vaccination, perceptions of risk and sensitivity to COVID-19, vaccine and health literacy, individual risks, special medical conditions, and others. These factors have been identified as shaping vaccination intentions and uptake (8, 10, 15-17). Studies have demonstrated that enhancing transparency, sharing data openly, and fostering discussions about this data can enhance vaccine acceptance by helping individuals grasp and adjust to the disease (18).

While the existing body of literature extensively examines attitudes towards vaccines within the general population, there is a notable lack of studies that delve into the attitudes and perspectives of parents with children aged 5-11 years regarding the vaccination against COVID-19. Assessing the opinions and emotions of parents within this specific age group concerning the COVID-19 vaccination, particularly considering its non-current status in Türkiye, holds significant importance. This assessment is pivotal in terms of devising necessary strategies for potential COVID-19 vaccination programs and any forthcoming vaccination initiatives. Given the substantial gap in existing research, the main objective of this study is to examine the decision and the attitudes of parents of children aged 5 to 11 years in Türkiye with regard to the COVID-19 vaccine.

Research Questions

1) What is the attitude and decision of parents towards getting their children vaccinated against COVID-19?

2) Is there any correlation between the Attitudes Towards the COVID-19 Vaccine Scale and the COVID-19 Vaccine Literacy Scale score levels of parents regarding their decision to vaccinate their children?

MATERIALS AND METHODS

Design

The aim of the cross-sectional study was to examine the decision and the attitudes of parents of children aged 5 to 11 years in Türkiye with regard to the COVID-19 vaccine.

Participants

The study's participants included parents residing in Türkiye who have children aged 5 to 11 years old. The study consists of parents who met the inclusion criteria and participated in the study between April 2022 and December 2022. The sample size was calculated to be a minimum of 666 individuals, based on a 99% confidence level, a 5% margin of error, and an assumed unknown population proportion of 50%, as determined through power analysis. Ultimately, the study was concluded

with the participation of 635 parents since 31 of the intended participants were excluded from the analysis due to incomplete survey and scale forms.

Inclusion criteria: having a child in the age group of 5-11 years old and being willing to participate in the study.

Exclusion criteria: refusal to participate in the study, having a child younger than 5 years or older than 11 years, and being a healthcare staff.

Data collection process

The data were collected between April 2022 and December 2022 from parents of children living in Türkiye using an online survey created on Google Forms. The survey was disseminated to participants through social media platforms (WhatsApp, Facebook, Instagram). This method was chosen due to the need to adhere to pandemic guidelines, avoiding face-to-face exchanges and maintaining social distancing measures.

The data was gathered through utilization of an Information Form, the COVID-19 Vaccine Literacy Scale, and the Attitudes Towards the COVID-19 Vaccine Scale.

Information form: This questionnaire consists of questions about the socio-demographic characteristics of the participants, their perspectives on vaccine decisions, their understanding and attitudes towards vaccines. The researchers formulated this form after reviewing the available literature in the field (8,19-25).

COVID-19 Vaccine Literacy Scale (COVID-19 VLS): Ishikawa et al. originally developed a scale to assess health literacy in relation to chronic diseases and Biasio et al. adapted this scale for COVID-19 Vaccine Literacy (26,27). The scale consists of 12 items in two different dimensions. The Functional Vaccine Literacy dimension encompasses four items and relies on fundamental reading and writing capabilities for daily tasks. This level of literacy enables individuals to comprehend materials related to vaccines and health education. The Communicative/Critical Vaccine Literacy dimension includes eight items and centres around cognitive aspects such as critical thinking and decision-making. Communicative health literacy encompasses cognitive and social proficiencies, enabling individuals to engage in various health-related activities and employ their existing knowledge to adapt to changing health conditions. Critical health literacy involves advanced cognitive skills that empower individuals to critically assess information and utilize it to exert more control over life circumstances. The scale employs a 4-point Likert-type structure. Items in the Communicative/Critical dimension are rated as (1) Never, (2) Rarely, (3) Sometimes, and (4) Often, whereas items in the Functional dimension are rated reversely as (4) to (1). An average score approaching 4 on the scale indicates a heightened level of vaccine literacy. A study on the Turkish validity and reliability of the COVID-19 vaccine literacy scale was performed by Durmuş et al. (2021), revealing a Cronbach's alpha value of 0.86 (28).

Attitudes Towards the COVID-19 Vaccine Scale (ATV-COVID-19): The scale was originated by Geniş et al. (2020). It comprises 9 items categorized into two sub-dimensions: positive and negative attitudes. Items within the positive attitude sub-dimension are rated using a scale including "Strongly Disagree (1)", "Disagree (2)", "Undecided (3)", "Agree (4)", "Strongly Agree (5)". Conversely, items in the negative attitude sub-dimension are scored in reverse. Calculating the total score for each sub-dimension involves summing the item scores within that sub-dimension and subsequently dividing by the number of items, resulting in a value ranging from 1 to 5. In the negative attitude sub-dimension, higher scores imply a less pessimistic stance toward the vaccine, while elevated scores in the positive attitude sub-dimension denote a favourable attitude regarding the vaccine. The scale exhibited a Cronbach's Alpha value of 0.80 as determined by Geniş et al. (29).

Data analysis

The data analysis was utilized using IBM SPSS Statistics 28.0 software. Descriptive analyses were presented using the mean, standard deviation (SD) and minimum-maximum for the continuous variables with normal distribution. Categorical variables were summarised by frequencies and percentages. For pairwise comparisons of quantitative data, for two groups the Student's t-test was used, and for more than two groups the One-Way ANOVA test was utilized. Pearson's correlation tests were used to reveal relationships between scale scores. The threshold for significance was set at $p < 0.05$.

Ethical consideration

The research adhered to ethical standards and regulations. It received approval from the Koç University's Ethics Committee (Approval Date: 24.03.22, Reference No: 2022.114.IRB3.058) and obtained permission from the Ministry of Health before commencing. The informed consent form highlighted the objectives of the study and the voluntary nature of participation. The investigation was conducted following the principles outlined in the Declaration of Helsinki.

RESULTS

The socio-demographic characteristic of the parents is presented in Table 1. The mean age of the parents was 36.12±5.77, and the average age of their children was 8.19±2.11. Among the parents, 38% of them had less than a high school education and 51.8% of them said that their income was equal to their expenditure. Examining the responses related to their children, it was found that 50.4% of parents had boy children, and 18.9% had a child with a chronic illness (Table 1).

It was determined that 53.1% of the participating parents and 25% of the children had contracted COVID-19. Among the parents, 11.8% stated that their child had not received any of the childhood vaccines, 23.8% stated willingness to have their child vaccinated against COVID-19 if available, 83.9% reported that they themselves had received the COVID-19 vaccine, 47.9% believed that the vaccine should be mandatory for adults, and 10.7% believed that the vaccine should also be mandatory for children (Table 2).

Table 1: Characteristic of the Parents

Characteristic	Mean±SD	Min-Max
Age of parents (year)	36.12±5.77	25-51
Age of children's (year)	8.19±2.11	5-11
Number of children	2.31±0.90	1-5
Characteristic	**n**	**%**
Parent who filled the questionnaire		
Mother	512	80.6
Father	123	19.4
Education level of parents		
Less than high school	241	38.0
High school	227	35.7
University	140	22.0
Master/PhD	27	4.3
Family income level		
Income less than expense	209	32.9
Income and expense equal	329	51.8
Income more than expense	97	15.3
Gender of children		
Female	315	49.6
Male	320	50.4
Presence of Chronic Illness in Children		
(Yes)	120	18.9

Max: Maximum; Min: Minimum; SD: Standard Deviation

Table 2: Parents' answers to the questions related to COVID-19 disease and vaccine

Characteristic	n	%
Parents' COVID-19 positive status		
Yes	337	53.1
No	298	46.9
Children's COVID-19 positive status		
Yes	159	25
No	476	75
Having a relative who died due to COVID-19		
Yes	205	32.3
No	430	67.7
Having children who had not received childhood vaccines		
Yes	75	11.8
No	560	88.2
Willingness to allow their children to receive the COVID-19 vaccine		
Yes	151	23.8
No	239	37.6
I am undecided	245	38.6
Parents' COVID-19 vaccination status		
Yes	533	83.9
No	102	16.1
Vaccination should be mandatory for adults		
Yes	304	47.9
No	186	29.3
I am undecided	145	22.8
Vaccination should be mandatory for children		
Yes	68	10.7
No	289	45.5
I am undecided	278	43.8

The average COVID-19 Vaccine Literacy Scale score of the parents was 2.66±0.56, with a functional vaccine literacy sub-dimension score of 2.63±0.78, and a communicative/critical vaccine literacy sub-dimension score of 2.67±0.73. The average ATV-COVID-19 scale score of parents was 3.34±0.71, with a positive attitude sub-dimension score of 3.30±0.99, and a negative attitude sub-dimension score of 3.37±0.81 (Table 3).

A positive correlation was found between parents' COVID-19 Vaccine Literacy Scale scores and Attitudes Towards the COVID-19 Vaccine Scale scores ($p<0.001$) (Table 4).

Table 3: Average scores of the scales

Scales	Mean ± SD	Min - Max
COVID-19 Vaccine Literacy Scale	2.66± 0.56	1-4
Functional vaccine literacy	2.63±0.78	1-4
Communicative/Critical vaccine literacy	2.67±0.73	1-4
Attitudes Towards the COVID-19 Vaccine Scale	3.34±0.71	1-5
Positive attitudes	3.30±0.99	1-5
Negative attitudes	3.37±0.81	1-5

Max: Maximum; Min: Minimum; SD: Standard Deviation

Table 4: Correlation of the scales

Scales	Attitudes Towards the COVID-19 Vaccine Scale	
	r	**p**
COVID-19 Vaccine Literacy Scale	0.198	<0.001

r: pearson correlation analysis

The comparison of the total scale scores with some characteristics is presented in Table 5. In the study, it was determined that parents who had a postgraduate degree, had lost a relative/close person due to COVID-19, were willing to get their child vaccinated if a COVID-19 vaccine became available, had received a COVID-19 vaccine themselves, and expressed that the COVID-19 vaccine should be mandatory for both adults and children had significantly higher average scores on the COVID-19 Vaccine Literacy Scale. Similarly, parents who had completed all childhood vaccinations, were willing to get their child vaccinated if a COVID-19 vaccine became available, had received a COVID-19 vaccine themselves, and expressed that the COVID-19 vaccine should be mandatory for both adults and children had significantly higher average scores on the ATV-COVID-19 scale (Table 5).

DISCUSSION

The aim of this study was to determine the decision of parents of children aged 5-11 years to vaccinate their children against COVID-19 and to investigate the relationship between this decision and their vaccine literacy and attitudes. Consistent with the existing literature (20, 21, 29, 30), the findings

Table 5: Comparison of scale scores according to some characteristics

Characteristic	COVID-19 VLS Mean±SD	ATV-COVID-19 Mean±SD
Education level		
Elementary education	30.48±6.23	29.52±6.50
High school	31.42±7.03	30.43±5.93
University	34.53±6.03	30.28±6.63
Master/PhD	36.25±6.65	31.66±8.45
	F=15.888	F=1.416
	p<0.001	p=0.237
Having a relative who died due to COVID-19		
Yes	32.86±6.16	30.74±6.44
No	31.52±6.95	29.80±6.41
	t=2.447	t=1.708
	p=0.015	p=0.088
Not having child vaccinated with any of the childhood vaccines		
Yes	31.21±5.14	27.13±7.17
No	32.05±6.91	30.50±6.23
	t=-1.278	t=-3.884
	p=0.204	**p<0.001**
Allowing children to be vaccinated with the COVID-19 vaccine		
Yes	33.83±6.58	33.78±6.48
No	30.69±6.81	26.62±6.19
I am undecided	32.03±6.49	31.24±4.78
	F=10.352	F=78.594
	p<0.001	**p<0.001**
Parents' vaccination status		
Yes	32.47±6.69	31.14±6.11
No	29.24±6.28	24.68±5.28
	t=4.510	t=9.983
	p<0.001	**p<0.001**
Vaccination should be mandatory for adults		
Yes	33.11±6.40	32.57±6.30
No	30.78±7.53	26.70±6.11
I am undecided	31.04±5.90	29.30±4.71
	F=8.820	F=58.483
	p<0.001	**p<0.001**
Vaccination should be mandatory for children		
Yes	34.58±7.25	34.16±6.67
No	31.20±7.20	27.35±6.10
I am undecided	32.10±5.89	31.98±5.47
	F=7.219	F=61.496
	p<0.001	**p<0.001**

F: One Way ANOVA, t:Student t test, p:significance level, COVID-19 VLS: COVID-19 Vaccine Literacy Scale, ATV-COVID-19: Attitudes Towards COVID-19 Vaccine Scale

indicated that only 23.8% of the parents expressed the intention to vaccinate their children against COVID-19. The majority of parents had received the COVID-19 vaccine themselves and believed that it should be mandatory for adults. However, merely 10.7% of parents advocated for mandatory vaccination of children. These findings underscore the lack of parental confidence in administering COVID-19 vaccines to their children. It has been noted that parental hesitancy toward vaccinating children stems from misconceptions such as the swift development of COVID-19 vaccines, potential long-term side effects, and insufficient vaccine research (21, 27, 31-34). Furthermore, it is argued that a diminished perception of the necessity for childhood vaccination (low complacency) and concerns regarding vaccine efficacy and safety in children (low confidence) contributed to a reduced uptake of the COVID-19 vaccine (14).

The current study revealed a significant and positive correlation between parents' COVID-19 vaccine literacy and their attitudes towards the COVID-19 vaccine. As parents' vaccine literacy levels increased, their attitudes towards the COVID-19 vaccine also displayed a corresponding positive enhancement. Previous research has indicated an augmented demand among parents for comprehensive information about vaccine components, a necessity driven by the aim of accurate vaccine perception and the alleviation of hesitations (30, 35, 36). In light of this, the assessment and enhancement of parents' vaccine literacy could potentially serve to facilitate vaccine acceptance and utilization. The active engagement of healthcare professionals in ensuring that parents receive accurate and comprehensive information regarding the COVID-19 pandemic and vaccines is projected to have a favourable impact on their vaccine-related attitudes (7, 27). This, in turn, is expected to amplify vaccine uptake by reinforcing both vaccine complacency and confidence.

A significant difference was found between parents' inclination towards vaccinating their children against COVID-19 and their attitudes towards the COVID-19 vaccine, in addition to their vaccine literacy. The study identified that parents who expressed a desire to vaccinate their children against COVID-19 exhibited positive attitudes towards the COVID-19 vaccine and possessed a higher level of COVID-19 vaccine literacy. Consequently, it emerged as pivotal to assess parents' knowledge and attitudes regarding the COVID-19 vaccine, specifically targeting those who are hesitant or resistant to vaccination, in order to facilitate their consent for vaccinating their children. Addressing families' misconceptions about the vaccine was paramount, necessitating the correction of their misguided beliefs concerning the vaccine's attributes (7, 28, 31, 37). Prior research underscores that when parents are equipped with accurate information sourced from reliable channels, and misinformation is supplanted with accurate facts, their confidence in vaccines tends to surge (38, 39). In this context, healthcare professionals hold the responsibility of guiding parents on obtaining credible information and reliable sources. Employing an empathetic and non-judgmental communication style, healthcare practitioners should consistently engage with families during clinic visits, actively listening to their concerns and addressing misinformation, both during initial consultations and follow-up interactions (7, 31, 40). By doing so, healthcare professionals foster an environment conducive to enhancing vaccine confidence and augmenting vaccine uptake.

It is established that parents who displayed willingness towards childhood vaccines tended to exhibit a more favourable disposition towards the COVID-19 vaccine. Existing research

underscores that when parents diligently adhered to and follow their children's routine vaccination schedules, similar positive attitudes were manifested towards the COVID-19 vaccination (36, 41-43). Furthermore, it can be observed that parents' negative inclinations towards routine vaccines often extended to their attitudes regarding COVID-19 vaccines (36). Notably, Yıldız et al. (2021) discovered that parents who initially declined childhood vaccines maintained their negative stance towards the COVID-19 vaccine as well (44). Consonant with the existing literature, our study's findings align, revealing that parents who had ensured their children received all the recommended routine childhood vaccinations were more likely to harbour positive attitudes towards the COVID-19 vaccine. In light of the understanding that elevated levels of vaccine complacency and confidence in established vaccines contribute to greater acceptance of novel vaccines, it can be inferred that the provision of information and counselling pertaining to all vaccines should be consistently reiterated during each clinic visit involving families.

Attitudes towards the COVID-19 vaccine are shaped by a multitude of factors. Our findings highlight that parents who had experienced the loss of a relative due to COVID-19, those who had personally received the COVID-19 vaccine, and individuals who advocated for mandatory vaccination of both adults and children tended to exhibit higher willingness towards the COVID-19 vaccination and possessed enhanced COVID-19 vaccine literacy. These results resonate with the findings of previous research in the field (29, 36, 45). The congruence between the data from this study and prior literature underscores the importance of identifying the array of factors, whether positive or negative, that exert influence on attitudes towards the COVID-19 vaccine. By delineating these factors comprehensively, it becomes possible to formulate targeted intervention programs aimed at bolstering vaccination rates. In anticipation of averting future vaccine hesitancy or refusal, and in the pursuit of elevating confidence in the vaccine, it is prudent to delve into the determinants that sway vaccine acceptance, operating at both the familial and community levels.

Our study's limitation is the inability to make cause-effect inferences due to the cross-sectional design. Another limitation is that the vaccine was not administered to that age group (5-11 years of age) in our country at the period of the data collection, which can negatively affect complacency and confidence, despite Western countries' ongoing vaccinations. Moreover, a notable limitation arises from the temporal context of data collection. During the study period, the COVID-19 vaccine had not been extended to the targeted age group in our country. This circumstance could potentially exert a detrimental impact on perceptions of complacency and confidence towards the vaccine. It is essential to recognize that this context might differ from Western countries where vaccination efforts were underway. This contextual variation underscores the need to consider the potential bias introduced by this discrepancy when interpreting our results.

CONCLUSION

It is noteworthy that an increase in parents' knowledge and literacy regarding the COVID-19 vaccine had a positive impact on their attitudes towards the vaccine. This correlation also played a significant role in influencing whether or not they chose to vaccinate their children. Given these findings, healthcare professionals hold a pivotal role in evaluating parents' understanding and viewpoints concerning the COVID-19 vaccine. It is imperative to develop strategies to alleviate the anxiety of families in order to increase vaccine uptake and confidence. This can be achieved by eliminating inaccurate or incomplete information and increasing vaccine literacy. In this direction, comprehensive and understandable training programs that encourage open communication, empathy and an unprejudiced stance need to be developed. These programs should serve to alleviate parental anxieties and encourage them to voice any misconceptions they may hold. Healthcare settings such as paediatric outpatient clinics and family health centres, where paediatric doctors and nurses frequently interact with parents, represent opportune platforms for continuous education. It is crucial for parents to receive ongoing education encompassing the safety and potential adverse effects of both the national immunization schedule and the COVID-19 vaccine. Additionally, paediatricians and paediatric nurses should guide parents towards reliable sources of information regarding vaccines. For hesitant parents, vaccination options should be provided after furnishing them with comprehensive information during each visit.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Is Cold Weather Testicle's Friend or Foe?

Soğuk Hava Testisin Dostu mu Düşmanı mı?

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ABSTRACT

Objective: Low air temperature has been shown to predispose testicular torsion (TT). In this study, we aimed to examine the relationship of TT occurrence with monthly average temperature.

Materials and Methods: The files of 75 male patients who were admitted with acute scrotum between 2005 and 2021 and underwent intervention with a preliminary diagnosis of TT after examination were retrospectively analyzed. The mean age, date of admission, torsion side and interventions were recorded. All patients underwent scrotal doppler ultrasonography. Further, monthly average temperature values of the given years for the province were obtained from the General Directorate of Meteorology. Months were ranked in descending order in terms of average monthly temperature and divided into two groups as warmer and colder months.

Results: The mean age of the patients at the time of intervention was 17.02±0.78 years. TT was seen on the right side in 49(67.1%) patients, left side in 23(31.5%) and bilateral in 1(1.4%) patient. Two (2.6%) patients turned out not to have TT and were excluded from the study. The warm months were those from April to September, and the cold months from October to March. It was determined that testicular torsion developed in 41 (56.2%) patients in the warm months and in 32 (43.8%) patients in the cold months. Detorsion and fixation were performed in 50(68.5%) of the patients, orchiectomy in18 (24.6%) and manual detorsion preceded by fixation in another session in 5 (6.9%) patients.

Conclusion: Our results indicated that TT may be observed more frequently in warm months. Thus, TT might not be related to seasonal temperature changes.

Keywords: temperature, seasonal variations, spermatic cord torsion, testis, testicular torsion

ÖZ

Amaç: Testis torsiyonu (TT), testis ve spermatik kordun ekseni etrafında dönüşü ile karakterize akut skrotal ağrıya neden olan acil bir ürolojik patolojidir. Düşük hava sıcaklığının predispozan etkisini gösteren çalışmalar mevcuttur. Bu çalışmada TT'nin soğuk hava ile olan ilişkisinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: 2005-2021 yılları arasında İstanbul Üniversitesi İstanbul Tıp Fakültesi Üroloji AD Çocuk Ürolojisi BD'na skrotal ağrıyla başvurup, muayene ve skrotal doppler ultrasonografi sonrası TT ön tanısıyla cerrahi eksplorasyon yapılan 75 erkek hastanın dosyası geriye dönük incelendi. Hastaların yaş ortalaması, başvuru tarihi, torsiyon tarafı ve yapılan girişimler kaydedildi. Meteoroloji Genel Müdürlüğü'nden İstanbul ili için son 16 yılın aylık ortalama hava sıcaklığı değerleri alındı. Ortalama hava sıcaklığının en yüksek olduğu aydan en düşük olduğu aya doğru sıralama yapıldı. Sıcak ve soğuk aylar olarak iki gruba ayrıldı.

Bulgular: Hastalar cerrahi eksplorasyon esnasında ortalama 17.02 ± 0.78 yaşındaydı. Sağ testis torsiyonu 49 (%67,1), sol testis torsiyonu 23 (%31,5), bilateral torsiyon ise 1 (%1,4) hastada görüldü. Eksplore edilen hastaların 2'sinde ise (%2,6) TT olmadığı saptandı ve bu hastalar çalışma dışı bırakıldı. Tüm olgularda intravaginal torsiyon vardı. Hastaların aylara göre dağılımı ve ayların ortalama sıcaklık değerleri Şekil 1'de gösterilmiştir. Son 16 yılın ortalama hava sıcaklığı Ağustos'ta 26,0°C ile en yüksek, Ocak'ta 6,9°C ile en düşüktü. Nisan - Eylül arası sıcak aylar, Ekim - Mart arası ise soğuk aylar olarak adlandırıldı. Sıcak ayların ortalama sıcaklığı 21,8°C iken, soğuk aylarınki 10,2°C idi. Sıcak aylarda 41 (%56,2), soğuk aylarda 32 (%43,8) hastada testis torsiyonu geliştiği saptandı. Hastaların 50'sine (%68,5) detorsiyon ve fiksasyon, 18'ine (%24,6) orşiektomi, 5'ine (%6,9) manuel detorsiyon yapıldı. Detorsiyon ve fiksasyon yapılan 6 (%8,2) hastada kontralateral orşiektomi geçmişi vardı

Sonuç: Çalışmamızda literatürdeki düşük sıcaklıkta TT insidansının arttığına yönelik bilginin tersi ortaya konmuştur. Sıcaklığın yüksek olduğu 6 ayda TT nedeniyle başvurular daha fazladır. Ayrıca yaz tatilinde çocukların şehir dışına seyahat ettiği varsayılarak, sıcak aylarda hasta sayısının daha fazla olabileceği öngörülmüştür. Farklı bölgelerden çok merkezli çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: sıcaklık, mevsimsel değişimler, spermatik kord torsiyonu, testis, testis torsiyonu

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INTRODUCTION

Testicular torsion (TT) is a urological emergency characterized by the rotation of the testis and spermatic cord around its axis that presents as acute scrotal pain. (1) In TT, delayed intervention may result in organ loss whereas testis can be preserved up to 90% when detorsion is performed within the first 6 hours after the onset of symptoms. However, testicular survival decreases down to 50% and 10%, when the intervention is carried out at the 12th and 24th hours, respectively. (1,2,3)

The etiology of testicular torsion is not understood well, but there are determined risk factors for its occurrence. Age is a very important risk factor as approximately 61% of patients presenting with testicular torsion are under the age of 21. (1,3) Other factors that were reported to be plausible for testicular torsion are a rapid increase in testicular volume with puberty, history of undescended testis, presence of a testicular tumor, large horizontal axis of testis and a long intrascrotal spermatic cord. (4,5) On the other hand, post-traumatic testicular torsion was reported in 4-8% of the patients. (3,6) Another factor that has been expressed in many studies is the hyperactive cremaster reflex in cold weather. (2,7) Some studies conducted in various countries investigated the seasonal prevalence of testicular torsion, its relationship with humidity, and daily temperature changes to prove this hypothesis. (2,7,8) They showed that cold weather played a role in contraction of dartos muscle leading to an increase in the frequency of TT in colder months.

Our observations for a long time were inconsistent with the previously published studies indicating a higher incidence in warmer months. Thus, we hypothesized that TT has no relationship with seasonal temperature changes. Subsequently, this study was carried out to investigate the relationship between testicular torsion and weather temperature in Istanbul, the mostly populated city in Turkey (15,636,405 people as per 2020).

MATERIAL AND METHODS

The files of 75 male patients who applied to our department with scrotal pain and underwent surgical exploration with the preliminary diagnosis of testicular torsion were retrospectively analyzed. All patients were taken into an operating room after examination and scrotal doppler ultrasonography. The mean age, admission date, torsion side and interventions of the patients were recorded.

The monthly average air temperature values of related years for the province of Istanbul were obtained from the General Directorate of Meteorology. Then, months were sorted according to the average temperature from the highest to the lowest. Then, months were divided into two groups as warmer and colder months accordingly.

Briefly, the surgical technique included a 2cm transverse incision on the affected side scrotum skin, then the testis and tunica albuginea were reached by blunt and sharp dissections.

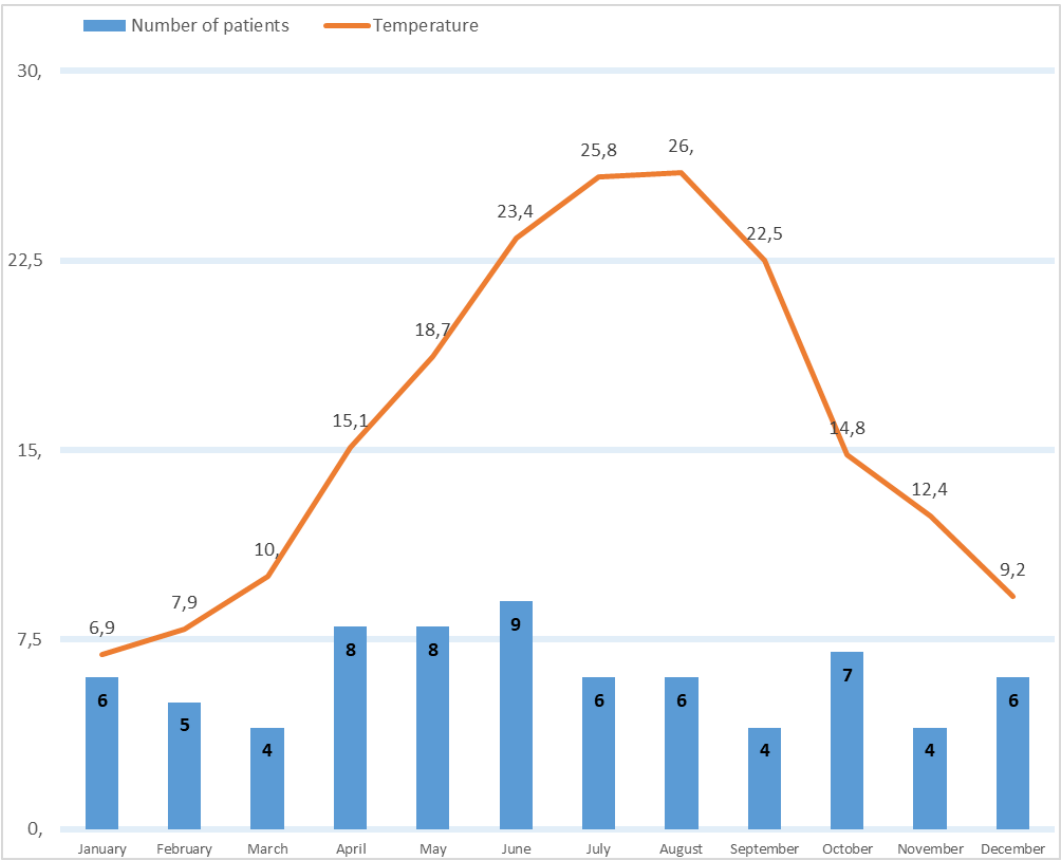

Figure 1. Average air temperature and number of testicular torsion cases by months of the last 16 years

Data on the color of testis, presence of edema, epididymis status, presence of Bell Clapper deformity, and the degree of torsion were recorded. After detorsion of the testis and cord, a warm compress was applied for 8-10 minutes and then left. (9) If no color change to normal was observed and testis was engorged, a 1cm vertical incision was made on the testicular capsule and a tunica vaginalis flap was applied. The testicles, whose blood supply was preserved after detorsion were fixed to the dartos pouch from 3 different points with 4/0 rapid vicryl. Orchiectomy was performed on testes that had no blood flow and lost their vitality after using the previously explained maneuvers. In all cases, contralateral testicular fixation was performed.

RESULTS

The mean age of the patients was 17.02 ± 0.78 years at the time of surgical exploration. Right testicular torsion was seen in 49 (67.1%), left testicular torsion in 23 (31.5%) and bilateral torsion in 1 (1.4%) patient. Two (2.6%) of the explorations did not reveal testicular torsion and these patients were excluded from the study. All cases had intravaginal torsion.

The distribution of the patients according to the months and the average temperature values of the months are shown in Figure 1. The average air temperature of the last 16 years was the highest in August (26.0°C) and the lowest in January (6.9°C). April to September were called the warmer months, and October to March were categorized as the colder months. While the average temperature of the warmer months was 21.8°C, it was 10.2°C in the colder months. We determined that testicular torsion developed in 41 (56.2%) patients in warmer months while in 32 (43.8%) patients in colder months. Furthermore, during the pandemic, testicular torsion was seen in 5 (6.8%) patients. Of these patients, 3 (4.1%) were in May, 1 (1.3%) in June, and 1 (1.3%) in March.

Detorsion was performed in 50 (68.5%) of the patients, orchiectomy in 18 (24.6%) and manual detorsion followed by surgical exploration in 5 (6.9%) patients. In the bilateral case, manual detorsion was performed twice within 5 years in other centers, and then detorsion and fixation was performed in our center. Six (8.2%) patients who underwent detorsion and fixation had a history of contralateral orchiectomy.

DISCUSSION

Testicular torsion can cause testicular loss if not treated urgently, further resulting in low testosterone levels, decreased sperm count and decreased fertility. (10,11) Previous studies hypothesized that cold air triggered testicular hyperactivity by stimulating the capsule of cremasteric muscle and dartos, then the testis was enforced to a reflex movement. (10,11,12) In this way, it was thought that the testis was pulled upwards and rotated around its own axis due to contraction of the cremaster muscle. (12) Our results showed a contrary outcome to previous findings of this information about the occurrence of testicular torsion at low temperatures. (2,7,8,10,12) It was observed that the number of testicular torsion cases was higher in the 6 warmer months when the average temperature was higher.

However, it should be noted that the coldest average air temperature (19.4°C) in the study by Korkes et al. (year?) corresponds to the warmer months in our study. Besides, the factors known to affect TT such as trauma, tumor, previous surgery was not mentioned in the study conducted in New York, USA. In another study that indicated a higher TT rate in winter, exclusion criteria were not mentioned, in addition to a lack of a negative exploration rate and scrotal Doppler USG results. (12) In the study which evaluated national orchiectomy outcomes in the USA including 2876 patients, Cost et al. (year?) stated that testicular torsion did not show any seasonal preponderance whereas orchiectomy was more commonly performed on children aged between 1 and 9. They also found that ethnicity played a role on requirement of orchiectomy whereas it is not certain if this is a racial predisposition or a difficulty in healthcare access. (10) On the contrary, a study from Japan analyzed the data of 39 patients with testicular torsion and determined that the frequency of the disease increased below 15°C, which is the mean air temperature in their study. (13)

Moreover, Preshaw (year?) reviewed 272 TT cases and found no seasonal peak in the incidence for the six coldest months in Canada or any 6-month sequential period. (14) Similarly, a study from Nigeria investigating 131 confirmed TT cases found no statistically significant variance in the incidence of testicular torsion between the warm and cold months. (15) The findings of our study showed seasonal preponderance for testicular torsion is contrary to what is stated in several articles.

On the other hand, during the summer vacation, families of school age children usually travel to their home towns or summer holidays for longer periods. Thus, reducing the number of children in the city. Although there are more children in Istanbul during the colder months, more TT cases were encountered in the warmer months in our study. For this reason, we assume that even more patients might have been observed in the warmer months, especially in the summer. Last but not the least, contralateral testicular fixation is not reported in many of the studies above, we strongly suggest contralateral fixation in testicular torsion due to the increased risk of TT in the future.

There are some limitations to our study. First of all, our study includes all the limitations due to a retrospective design. A relatively small number of patients are included. Also, a study based on the air temperature values at the time of the patient's complaints might give a clearer overview of the effect of temperature rather than average. Further, there are of course, temperature variations during the day both in winter and summer. (16) A study based on the air temperature values at the time of the patient's complaints might give a clearer overview of the effect of temperature rather than average. (17) It would be appropriate to evaluate the application hours of patients who underwent orchiectomy individually.

CONCLUSION

Contrary to what has previously been published, the fact that cold air is a predisposing factor in testicular torsion was not supported in our study. Thus, we conclude that TT has no relationship with seasonal temperature changes. However, multicenter studies from different regions will enhance our knowledge on the relationship between testicular torsion and weather.

Ethics Committee Approval: This study was approved by the ethics committee of İstanbul University, Faculty of Medicine. (17/05/2021 - 5).

Informed Consent: Informed consent was not obtained as it was a retrospective study.

Peer Review: Externally peer-reviewed.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Comparison of Diagnostic Efficacy of Lancet, Multi-Head Applicator, and Specific Immunoglobulin E in Allergy Testing

Alerji Testlerinde Lanset, Çok Başlı Aplikatör ve Spesifik İmmunglobilin E'nin Tanısal Etkinliğinin Karşılaştırılması

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ABSTRACT

Objective: Allergic rhinitis and allergic asthma are common respiratory diseases in children. Skin prick tests (SPT) and allergen-specific immunoglobulin E (SpIgE) measurements play a crucial role in their diagnosis. In recent years, the use of rapid diagnostic kits has increased. This study aimed to investigate the diagnostic performance of multi-headed applicator and allergen SpIgE compared to the gold standard lanset.

Materials and Methods: Skin prick tests were conducted on the same patients using both a multi-headed applicator and lancet with the same allergen solutions. Additionally, allergen SpIgE levels were measured for each patient. The diagnostic performances of multi-headed applicator and allergen SpIgE were statistically compared to those of lancet.

Results: A total of 2100 SPTs were performed on 105 patients, from whom allergen SpIgE levels were also obtained. Allergen sensitivities were detected in order of prevalence as house dust mites, pollens, and molds. Sensitization rates were found to be 73.3% for multi-headed applicators, 82.9% for lanset, and 81% for SpIgE. The diagnostic sensitivity of the multi-headed applicator ranged from 0% to 52%, and its correlations with lanset were weak.

Conclusion: Rapid-result tests aimed at allergen sensitivity assessment showed limited effectiveness. The use of accurate and reliable diagnostic methods such as lancet-based SPT and SpIgE measurements is crucial. This study holds the distinction of being the first to evaluate different SPT methods using allergen solutions, providing important insights for accurate diagnosis and treatment of allergic diseases.

Keywords: skin tests, sensitivity and specificity, equipment and supplies, children, allergy

ÖZ

Amaç: Alerjik rinit ve alerjik astım, çocuklarda sık görülen solunum hastalıklarıdır. Bu hastalıkların tanısında, deri prik testleri (DPT) ve alerjen spesifik immunglobulin E (SpIgE) ölçümleri önemli bir rol oynamaktadır. Son yıllarda hızlı tanı kitlerinin kullanımı artmıştır. Bu çalışmanın amacı çok başlı aplikatör ve alerjen SpIgE'lerin tanısal performanslarını altın standart kabul edilen lanset DPT göre etkinlikleri araştırıldı.

Gereç ve Yöntem: Çok başlı aplikatör, lanset ile aynı alerjen solüsyonları kullanılarak aynı hastalara deri prik testleri yapıldı. Ayrıca, her hastadan alerjen SpIgE düzeyleri ölçüldü. Lanset ile yapılan DPT'lere göre çok başlı aplikatör ve alerjen SpIgE'lerin tanısal performansları istatistiksel olarak incelendi.

Bulgular: Toplamda alerjen SpIgE'leri de alınan 105 hasta üzerinde 2100 DPT yapıldı. Hastalarda sıklık sırasına göre ev tozu akarı, polenler ve küf alerjen duyarlılığı saptandı. Çok başlı aplikatör ile yapılan DPT %73.3, lanset ile yapılan DPT %82.9 ve SpIgE ile yapılan test %81 oranında duyarlanma tespit edildi. Çok başlı aplikatörün tanısal duyarlılık değeri %0-52 arasında ve lanset ile korelasyonları zayıf bulundu.

Sonuç: Hızlı sonuç alma amaçlı testler, alerjen duyarlılığını tespitte yeterince etkin olmamıştır. Lanset ile yapılan DPT ve SpIgE ölçümleri gibi doğru ve güvenilir tanı yöntemlerinin kullanılması önemlidir. Bu çalışma, alerjen duyarlılığı tespitinde alerjen solüsyonları da kullanılarak yapılan farklı DPT yöntemlerinin değerlendirildiği ilk çalışma olma özelliği taşımaktadır ve alerjik hastalıkların tanı ve tedavisinde doğru yönlendirmeler yapmak adına önemli bilgiler sunmaktadır.

Anahtar Kelimeler: deri testleri, duyarlılık ve özgüllük, ekipman ve malzemeler, çocuklar, alerji

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INTRODUCTION

Allergic rhinitis (AR) and asthma are chronic respiratory diseases commonly observed in children, significantly affecting their quality of life.[1] In the diagnosis of these diseases, skin prick tests (SPT) are used to assess allergen-specific immunoglobulin E (spIgE) levels and measurements of allergen-spIgE) play a significant role. [2] Skin prick tests are reliable and sensitive methods commonly used to detect IgE responses to various allergens.[3] In recent years, various techniques and methods have been developed in skin prick tests to obtain rapid results.[4] Especially in developing countries with limited healthcare access like our country, there is a trend towards directing the use of rapid and practical diagnostic techniques instead of the gold standard methods[5] accepted by health authorities, aiming to expedite diagnostic processes and enhance access to public resources. However, this approach can lead to challenges in accurate diagnosis and result in confusing outcomes.

This research article was conducted to assess the reliability of different skin prick test (SPT) methods and allergen-specific IgE measurements in children with allergic rhinitis and asthma. Particularly, for the evaluation of allergenic sensitization, a comparison will be made among the commonly used multi-headed applicator SPTs, lancet-based SPTs, and specific IgE tests, which are widely employed in public hospitals in our country. This comparison aims to assess each testing method's diagnostic accuracy, sensitivity, and specificity. Previous research has demonstrated the effectiveness of SPTs in evaluating specific IgE responses to allergens. [6] However, further research is needed to investigate the outcomes of different methods used in SPTs.

In this study, we aimed to determine which method exhibits better diagnostic performance by comparing skin prick tests and spIgE results conducted through different approaches in children with allergic rhinitis and asthma.

More accurate and reliable diagnostic methods can aid in directing patients toward appropriate treatments promptly and accurately. Furthermore, they can contribute to optimizing treatment options, preventing unnecessary time and financial losses, and adopting a more effective approach to managing allergic diseases. This study will present the details of the investigation focused on comparing the results of skin prick tests in children with allergic rhinitis and asthma, and the findings will be discussed.

MATERIALS AND METHODS

A total of 105 participants voluntarily enrolled in the study, who were diagnosed with allergic rhinitis or asthma. The patients were randomly selected based on their order of presentation at the clinic. Demographic and clinical characteristics including age, gender, allergens causing symptoms according to clinical history, and other relevant factors were recorded for all participants.

Skin Prick Tests

SPTs were conducted on all participants using allergen solutions (ALK-Abello Pharm allergen extracts) known as common triggers for allergic rhinitis and asthma. A multi-headed SPT applicator with 10 distinct chambers (positive control, negative control, *Dermatophagoides Pteronyssinus* (DP), *Dermatophagoides Farinea* (DF), mixture of mold allergens, mixture of weed pollen, mixture of grass pollen, mixture of tree pollen, cockroach, cat, and dog) was employed. Additionally, SPTs were performed using a lancet (ALK®, Horsholm, Denmark) with the same solutions (**Figure 1**). A total of 2100 SPTs (105 patients × 10 tests for each arm × 2 arms) were administered, with 10 SPTs conducted on each arm of the 105 patients. During the tests conducted with a lancet and a multi-headed applicator (Aller-tech rapid allergy test applicator), adherence to the manufacturer's recommended guidelines for application was ensured. The SPTs were conducted on the inner surface of the arm in a standardized area. Each volunteer participant received SPTs on the inner surface of one arm using the multi-headed applicator and on the other arm using the lancet, both with the same allergen solutions. In the multi-headed applicator SPTs, a single allergen was applied to each chamber of the applicator. For the lancet SPTs, a separate lancet was used for each allergen using the same solutions. The SPTs were administered by the same experienced healthcare professional. One minute after the SPTs were performed, the droplets were dried without allowing them to mix. Following the SPTs, independent technicians measured and recorded skin reactions for swelling and wheel size. After 15 minutes, the longest diameter of the wheel was measured, and then the perpendicular diameter was measured and divided by two to determine the wheel diameter. Due to inadequate cockroach solution, enough data related to cockroach allergy could not be collected.

Allergen-specific IgE Measurement

Additionally, blood samples were collected from each participant on the same day. The blood samples were analyzed using the immunoCAP method, commonly employed in laboratory tests, to assess allergen-specific IgE levels.

Data Analysis

The data were analyzed using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, New York, USA) statistical software package. Descriptive statistics were presented as unit count (n), percentage (%), mean ± standard deviation ($\bar{x}$±SD), median values, and minimum-maximum values. SPT results were compared between the multi-headed applicator and lancet-based tests. Furthermore, comparisons were made with allergen SpIgE results. These comparisons were conducted based on performance criteria such as sensitivity, specificity, and positive/negative predictive values.

Correlation analyses were performed between the applicator and SpIgE results compared to lancet-based SPT results. The normality distribution of variables was assessed using the

Kolmogorov-Smirnov test. For variables showing a normal distribution, Pearson correlation analysis was applied, while for non-normally distributed variables, Spearman correlation analysis was utilized to assess correlations.

Ethical Approval:

This research was conducted with the approval of the Istanbul Başakşehir Çam ve Sakura City Hospital Clinical Research Ethics Committee (Date: 22 February 2023 Decision no: 2023-72). Informed consent was obtained from all patients and their parents, and their privacy rights were respected.

RESULTS

Among the 105 patients evaluated for allergen sensitivity, with a total of 2100 SPTs conducted - one arm using a multi-headed applicator and the other arm using a lancet - and allergen-specific IgE levels measured, 67 (63.8%) were male. The median age was 96 months (range: 24-204), of which 63 (60%) had AR, 18 (17.1%) had allergic asthma with comorbid AR, and 24 (22.9%) had isolated allergic asthma. Additionally, 9 (8.5%) patients presented with atopic dermatitis alongside respiratory allergic diseases. Regarding specific allergen sensitivities, 49 (46.7%) cases exhibited reactivity to house dust mites and pollens, 40 (38.1%) to house dust mites, 13 (12.4%) to pollens, and 3 (2.9%) to molds and animal epithelial allergens.

In the SPT administered with a multi-headed applicator, sensitization to at least one allergen was observed in 77 cases (73.3%), whereas in the lancet group, this was noted in 87 cases (82.9%), and through specific IgE testing, 85 cases (81%) showed positive reactions.

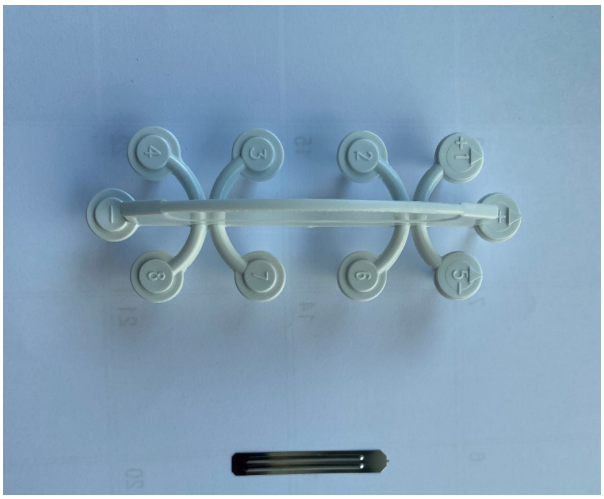

Figure 1: Example of multi-headed applicator and lancet used for tests

Table 1: Diagnostic values for multi-headed applicator and allergen-specific IgE compared to lancet SPT

Lanset (+) N:105		Positivity	Sensitivity	Specificity	NPV	PPV	Accuracy
***D. Pteronyssinus* n:75(71.4%)**	APK	46(43.8%)	39(52%)	23(76.7%)	23(39%)	39(84.8%)	59%
	SpIgE (n:99)	71(71.7%)	65(94.2%)	24(80%)	24(85.7%)	65(91.5%)	90%
***D. Farinea* n:75(71.4%)**	APK	34(32.4%)	29(38.7%)	25(83.3%)	25(35.2%)	25(85.3%)	51.4%
	SpIgE (n:99)	71(71.7%)	65(92.9%)	23(79.3%)	23(82.1%)	65(91.5%)	88.9%
Mix mold n:17(16.2%)	APK	12(11.4%)	3(17.6%)	79(89.8%)	79(84.9%)	3(25%)	78%
	SpIgE (n:95)	5(4.8%)	4(25%)	78(98.7%)	78(86.7%)	4(80%)	86.3%
Grass pollens n:43(41%)	APK	26(24.8)	18(41.9%)	54(58.1%)	54(68.4%)	18(69.2%)	78.1%
	SpIgE (n:101)	26(25.7%)	24(60%)	59(96.7%)	59(78.7%)	24(92.3%)	82.2%
Weeds pollen n:14(13.3%)	APK	8(7.6%)	0(0%)	83(91.2%)	83(85.6%)	0(0%)	79%
	SpIgE (n:97)	11(11.3%)	4(33.3%)	78(91.8%)	78(90.7%)	4(36.4%)	84.5%
Trees pollen n:17(16.22%)	APK	9(8.6%)	2(11.8%)	81(92%)	81(84.4%)	2(22.2%)	79%
	SpIgE (n:21)	4(3.8%)	2(33.3)	13(86.7)	13(76.5%)	2(50%)	71.4%
Cat allergens n:31(29.5%)	APK	16(15.2%)	10(32.3%)	68(91.9%)	68(76.4%)	10(62.5%)	74.3%
	SpIgE (n:65)	22(33.8%)	16(84.2%)	40(87%)	40(93%)	16(72.7%	86.2%
Dog allergens n:9(8.6%)	APK	11(10.5%)	2(22.2%)	87(90.6%)	87(92.6%)	2(18.2%)	84.7%
	SpIgE (n:63)	1(1.6%)	0(0%)	58(98.3%)	58(93.5%)	0(0%)	92%

APK: Skin prick test with multi-headed applicator; SpIgE: allergen-specific immunoglobulin E; NPV: negative predictive value; PPV: positive predictive value

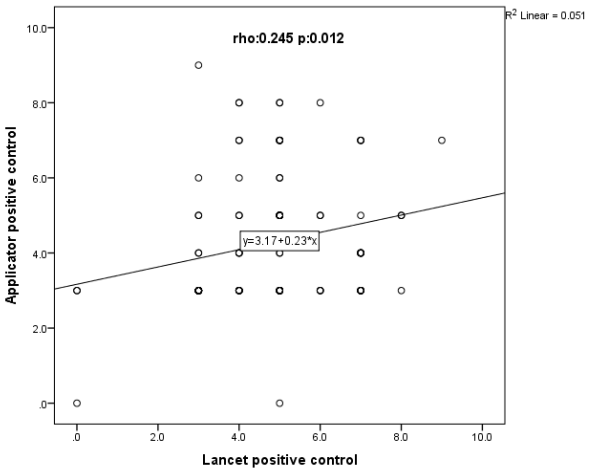

Figure 2: Correlation graph of positive control (histamine) between lancet and multi-headed applicator

In SPTs conducted with the applicator, false negative results for at least one allergen that was clinically compatible (despite positive results in the lancet-based SPTs and/or spIgE) were observed in 80 cases (76.4%). In 23 cases (21.9%), false positive results for at least one allergen, which were clinically incompatible and negative in other tests, were detected in the SPTs conducted with the applicator. False-negative results were observed in 23 cases (20.5%) in SpIgE measurements. Diagnostic values of the multi-headed applicator and inhaled allergen-specific IgE, based on the lancet-based SPT, are presented in Table 1.

In the SPTs conducted with the applicator and lancet, a weak positive correlation was observed between wheal diameters in the positive control test with histamine (rho: 0.245, p: 0.012) (Figure 2).

In the case of *DP* a weak correlation was observed between the wheal diameter of SPTconducted with a lancet and the wheal

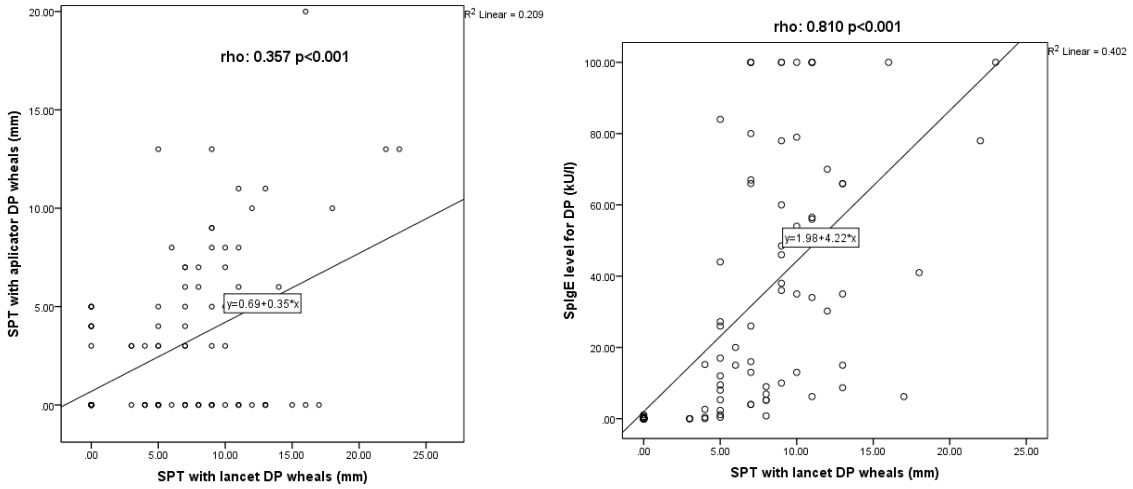

Figure 3: Correlation plots of wheal size from Multi-headed Applicator SPT and spIgE Level for Dermatophagoides pteronyssinus (DP) based on the result of Lancet SPT

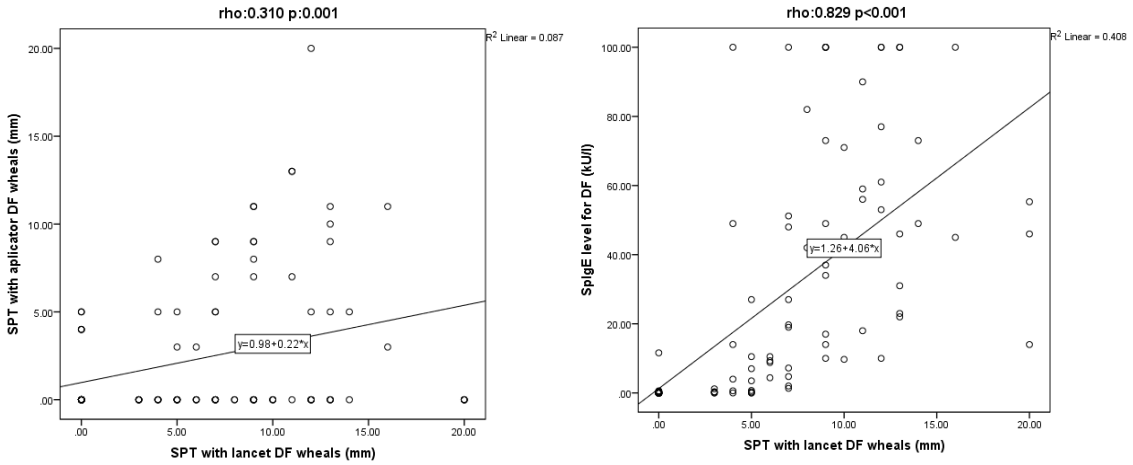

Figure 4: Correlation plots of wheal size from Multi-headed Applicator SPT and spIgE Level for Dermatophagoides farinea (DF) based on the result of Lancet SPT

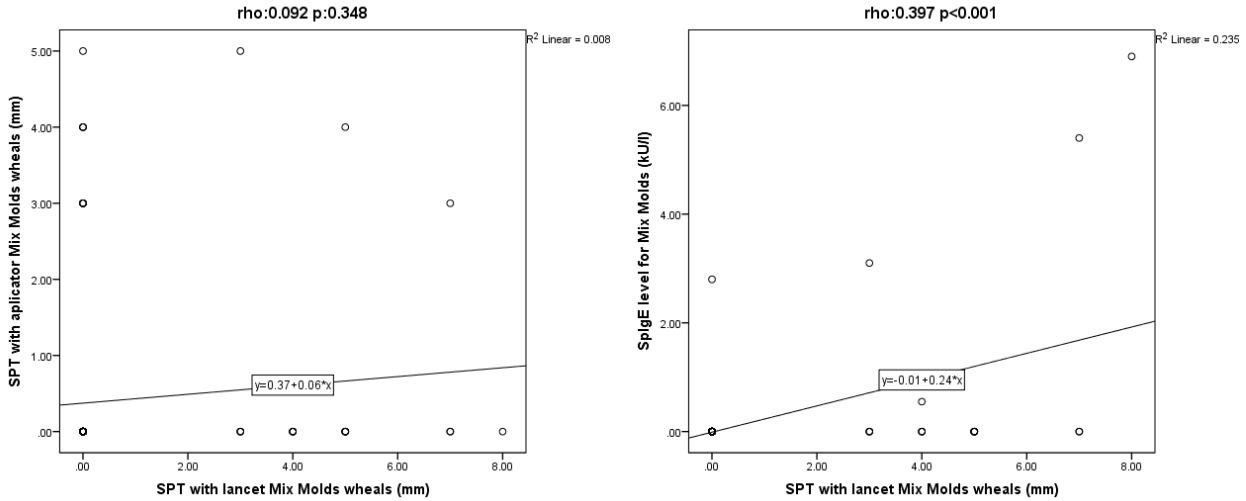

Figure 5: Correlation plots of wheal size from Multi-headed Applicator SPT and spIgE Level for Mix molds based on the result of Lancet SPT

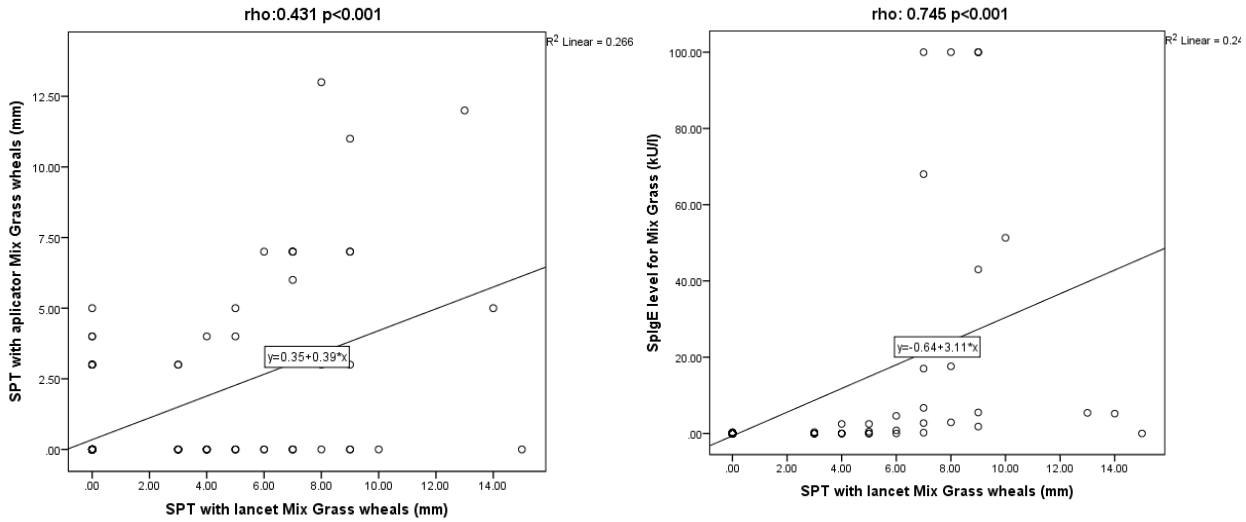

Figure 6: Correlation plots of wheal Size from Multi-headed Applicator SPT and SpIgE Level for Grass pollens based on the result of Lancet SPT

diameter of SPT conducted with an applicator (rho: 0.357, p < 0.001). However, a strong relationship was established between DP-specific IgE levels and the wheal diameter of SPT conducted with a lancet (rho: 0.810, p < 0.001) (Figure 3).

Regarding DF, a weak correlation was found between lancet-based SPT wheal diameter and applicator-based SPT wheal diameter (rho: 0.310, p: 0.001). Conversely, a strong correlation was observed between DF-specific IgE levels and lancet-based DF SPT wheal diameter (rho: 0.839, p < 0.001) (Figure 4).

For the mold mixture, there was no significant correlation between lancet-based SPT wheal diameter and applicator-based SPT wheal diameter (rho: 0.092, p: 0.348). However, a weak correlation was found between mold mixture-specific IgE levels and lancet-based mold mixture SPT wheal diameter (rho: 0.397, p < 0.001) (Figure 5).

There is a moderate correlation between lancet-based and applicator-based SPT wheal diameters for the grass mixture (rho: 0.431, p < 0.001). Additionally, a strong correlation exists between grass mixture-specific IgE levels and lancet-based SPT wheal diameter (rho: 0.745, p < 0.001) (Figure 6).

No correlation between lancet and applicator SPT wheal diameters for weeds mixture (rho: -0.112, p: 0.254), but a weak correlation exists between weeds mixture SpIgE levels and lancet SPT wheal diameter (rho: 0.239, There p: 0.018) (Figure 7).

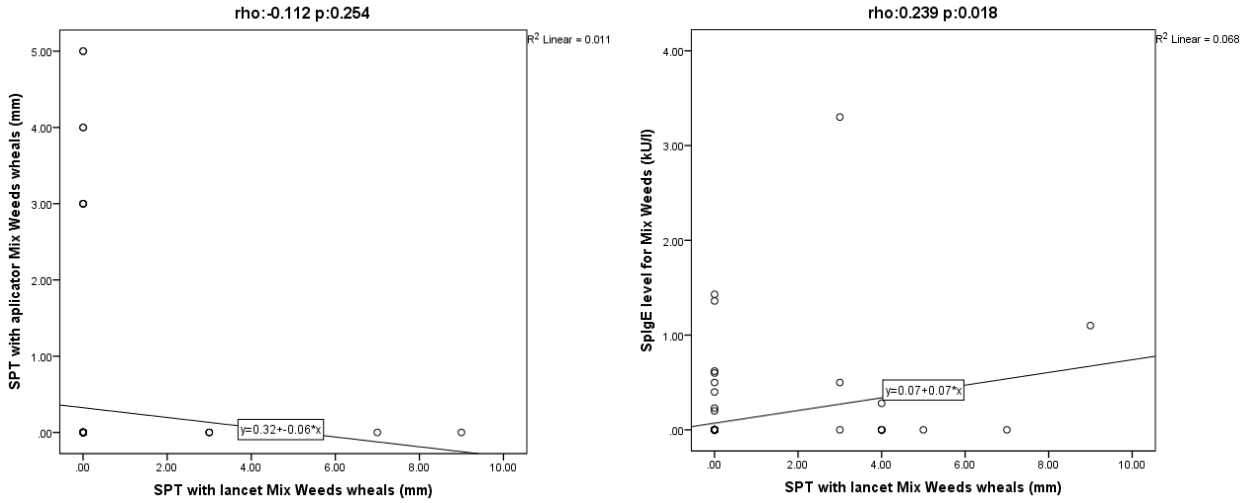

Figure 7: Correlation plots of wheal size from Multi-headed Applicator SPT and spIgE Level for Weeds pollens based on the result of Lancet SPT

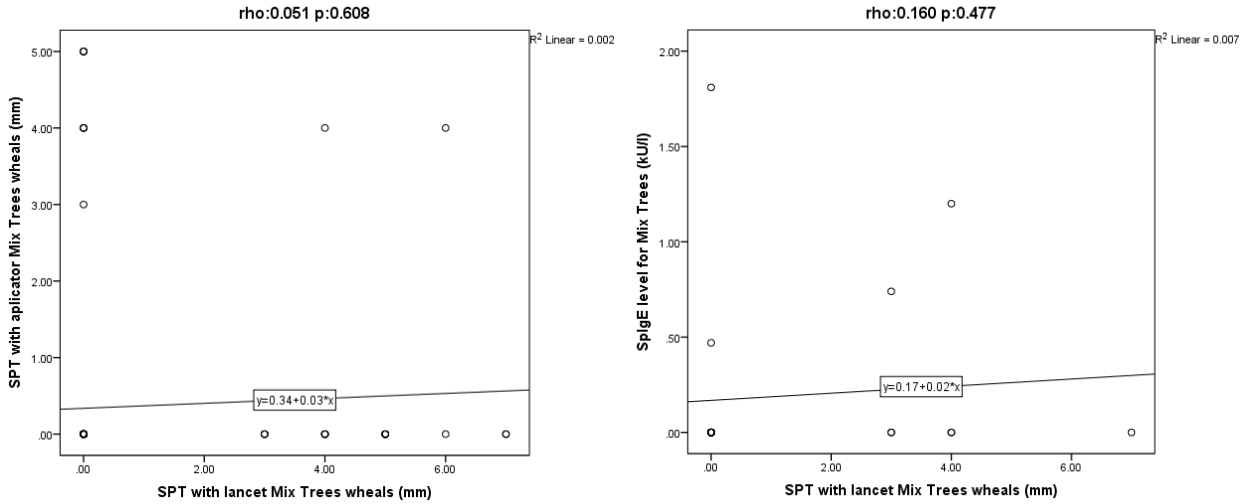

Figure 8: Correlation plots of wheal size from Multi-headed Applicator SPT and spIgE Level for Trees pollens based on the result of Lancet SPT

No correlation between the lancet and applicator SPT wheal diameters for trees mixture (rho: 0.051, p: 0.608) and tree mixture-spIgE levels and lancet SPT wheal diameter (rho: 0.160, p: 0.407) (Figure 8).

Weak correlation between the lancet and applicator SPT wheal diameters for cat allergens (rho: 0.281, p: 0.004) and, a strong correlation between cat allergens lancet SPT wheal diameter and spIgE levels (rho: 0.809, p < 0.001) (Figure 9).

No correlation was found between the lancet and applicator SPT wheal diameters for the dog allergen mixture (rho: 0.149, p: 0.130), no correlation between dog allergen mixture lancet SPT wheal diameter and spIgE levels (rho: -0.46, p: 0.718) (Figure 10).

DISCUSSION

In this study, different SPT methods and allergen spIgE results were evaluated for allergen sensitivity in children with allergic rhinitis and asthma. Sensitization to house dust mites, pollens, and molds was observed in most patients. Through SPTs with the multi-headed applicator, lancet, and SpIgE measurements, sensitization to at least one allergen was observed in 73.3%, 82.9%, and 81% of cases, respectively. The applicator skin prick test yielded 76.4% false negatives and 21.9% false positives, while the spIgE measurement resulted in 20.5% false negatives.

Applicator and lancet SPTs showed weak correlations with histamine-positive control wheel sizes. Strong correlations were observed between lancet SPTs and spIgE levels for DP, DF, and cat allergens. Mold mixture spIgE displayed a weak correlation, while grass mixture exhibited a good correlation, and weeds mixture indicated a weak correlation. No correlations were

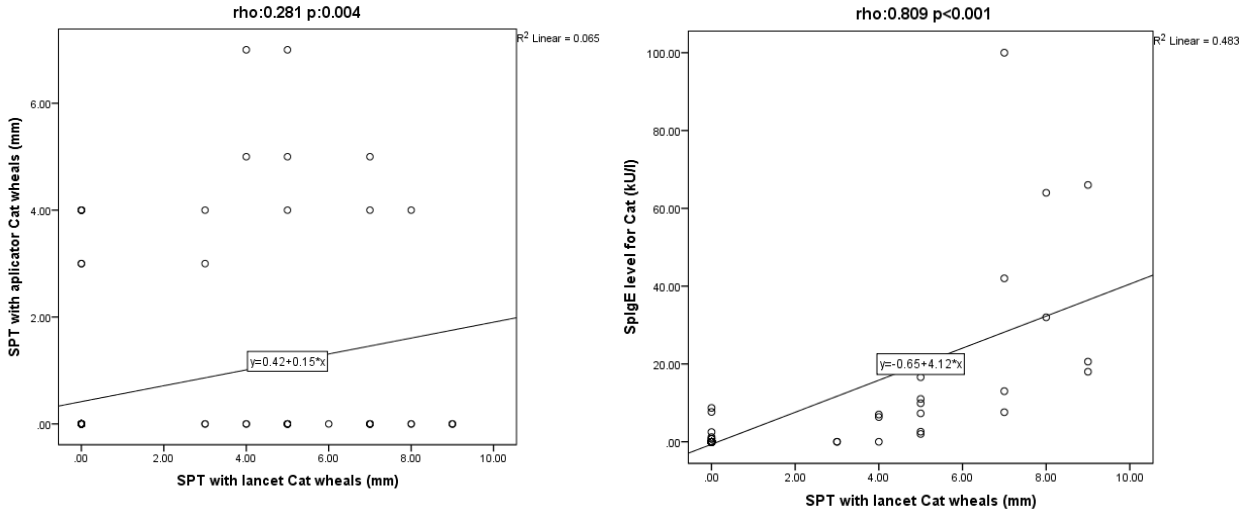

Figure 9: Correlation plots of wheal size from Multi-headed Applicator SPT and spIgE Level for Cat allergens based on the result of Lancet SPT

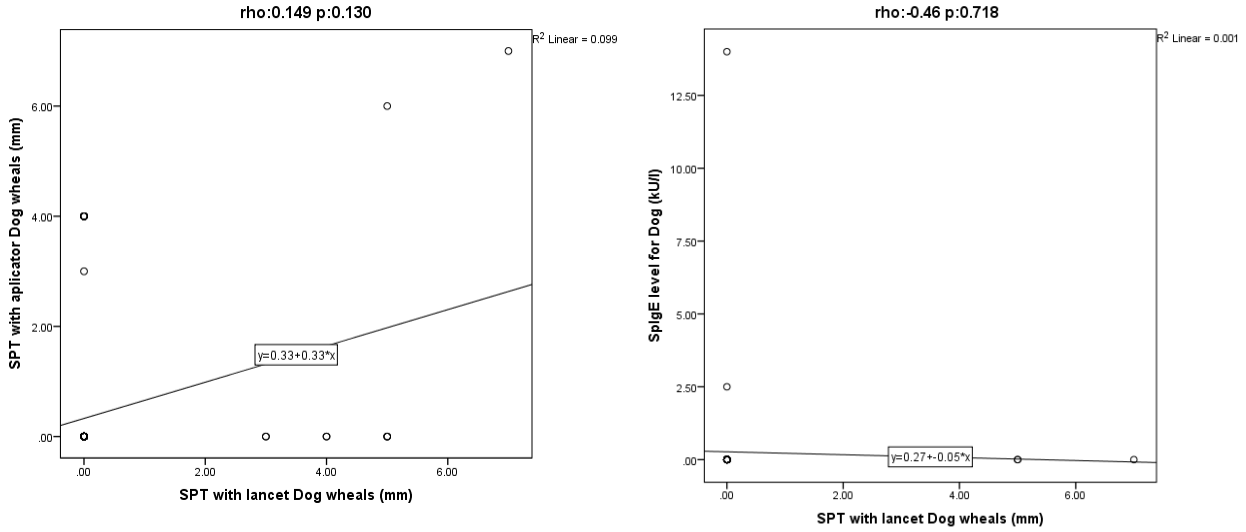

Figure 10: Correlation plots of wheal size from Multi-headed Applicator SPT and spIgE Level for Dog allergens based on the result of Lancet SPT

identified between dog and tree spIgE and lancet SPT wheel sizes. In applicator SPTs, weak correlations were found with house dust mites, grass, and cats, while other allergens showed no significant correlations. Applicator SPTs demonstrated notably low sensitivity, specificity, negative predictive values, positive predictive values, and accuracy.

In the literature, various devices including single-use needles and lancets have been compared, and it has been determined that the best results are obtained with a 23-gauge needle or a metal lancet. The single-use applicator (Stallerpoint®) that we used for testing exhibited a sensitivity of 20% with a single puncture and a sensitivity of 57% after a 90-degree rotation following the puncture. [7] In another study, different puncture and rotation techniques were compared using histamine and saline without using allergen solutions, resulting in a sensitivity of 100%. However, the limited number of cases, the absence of real allergen solutions, and the inclusion of non-atopic patients are noteworthy aspects of this study.[4]

In our hospital's multi-headed applicator, only puncturing is possible. In studies conducted using multi-headed devices, it has been observed that the false negative rate with histamine and saline is higher compared to single lancets or similar devices, and their sensitivities have decreased up to 51%. [8,9] In our study, the sensitivity ranged from 0% to 52% for all allergens with the multi-headed applicator.

Clinicians need to be well-informed about each SPT test device, follow the recommended usage guidelines, and interpret the test results accurately.[10] False negative results in patients with

a history of severe asthma or anaphylaxis can lead to life-threatening consequences.[11]

Similar studies in the literature have evaluated different SPT test devices by assessing their performance with positive controls (histamine) and negative controls (usually saline), as well as pain levels.[4,7–15]

We could not find an English-language published study that utilized actual allergen solutions. To the best of our knowledge, our study appears to be the first one that compares the diagnostic performances of allergen solution-based lancet SPT, multi-headed applicator SPT, and allergen spIgE measurements.

CONCLUSIONS

Skin prick tests conducted with lancets and spIgE measurements are effective methods for evaluating sensitization to allergens. However, newly developed rapid-result testing methods have not shown successful results in accurately detecting allergen sensitivities in patients. Further research is necessary to improve consistency and minimize false results among current skin prick test methods. Additionally, developing more accurate diagnostic and treatment approaches for allergic diseases is vital for effective patient management.

Ethics Committee Approval: This study was approved by the ethics committee of the Istanbul Başakşehir Çam ve Sakura City Hospital Clinical Research Ethics Committee (Date: 22 February 2023 Decision no: 2023-72).

Informed Consent: Written consent was obtained from the participants.

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RESEARCH ARTICLE / *ARAŞTIRMA MAKALESİ*

Adolescent Acute Lymphoblastic Leukemia: A Retrospective Single-Center Experience

Adolesan Akut Lenfoblastik Lösemileri: Geriye Dönük Tek Merkez Deneyimi

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ABSTRACT

Objective: Acute lymphoblastic leukemia (ALL) is one of the most common malignant diseases in children. This study aimed to determine the clinical and prognostic characteristics of adolescent patients with ALL aged 15–18 years who were followed up in our center.
Materials and Methods: The clinical and laboratory characteristics, treatment responses, and survival and relapse rates of adolescent patients with ALL were retrospectively analyzed
Results: The majority of patients were male. The median age of patients was 16 (range 15–17.9) years. About 36% and 74% of patients were diagnosed with T- and B-cell ALLs, respectively. Then, 32% of patients were stratified in the high-risk group. BCR/ABL t (9;22) positivity was detected in one patient. Recurrence was observed in 6 of 31 patients after completing the treatment. The estimated survival rate in the high-risk group at 32 months was 58%.
Conclusion: Ihe prognosis and outcomes of ALL in adolescent and young adult patients are poor compared to younger age groups. Future clinical trials and advance in chemotherapeutic protocols in this age group will help increase the treatment success rates
Keywords: adolescent, leukemia, survival

ÖZ

Amaç: Akut lenfoblastik lösemi (ALL) çocukluk çağında en sık rastlanan habis hastalıklardan biridir. Çalışmamızda merkezimizde ALL tanısı ile takip ve tedavi edilen, 15-18 yaş arası adölesan hastaların klinik ve prognostik özelliklerini belirlemeyi amaçladık.
Gereç ve Yöntem: ALL'li adolesan hastaların klinik ve laboratuvar özellikleri, tedavi yanıtları, sağkalım ve nüks oranları retrospektif olarak analiz edildi.
Bulgular: Hastaların çoğunluğunu erkekler oluşturmaktaydı.Median yaş değeri 16 (15-17,9) yıl idi. Hastaların %32'si yüksek risk grubundaydı ve %26'sı T hücreli ALL %74'ü B hücreli ALL immunfenotipi göstermekteydi. BCRL/ABL t (9;22) pozitifliği bir hastada saptandı. Altı hastamızda tedavi bitimi sonrası nüks görüldü. Yüksek risk grubunda otuz ikinci ayda tahmini sağ kalım oranı %58 idi.
Sonuç: Ergen ve genç yetişkin hastaların prognozu ve sonuçları diğer küçük yaş gruplarından farklı olarak daha kötüdür. Çocukluk çağında kullanılan protokollerin, bu yaş grubuna özel klinik araştırmalarla geliştirilmesi tedavide başarı oranlarının artmasına katkı sağlayacaktır.
Anahtar Kelimeler: adolesan, çocuk, sağkalım

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is one of the most common malignant diseases in children. Despite the increase in the prevalence of childhood malignancies, the 5-year survival rate in children with ALL has reached 90% in recent reports as a result of advances in chemotherapy and supportive care.[1,2] At the intersection between children and adults, caring for adolescent and young adult patients with ALL reveal challenges beyond those faced by other age groups. The National Cancer Institute defined the adolescent and young adult cancer population as generally between the ages of 15 and 39 years.[1,3] Although the event-free survival rates of adolescent and young adult patients were previously reported as 30–45% compared to young children, this group of patients treated with pediatric-based approaches may have better outcomes with disease-free survival rates of up to 60%–70%.[1] This study aimed to determine the clinical and prognostic characteristics of adolescent ALL patients aged 15–18 years who were diagnosed and treated in our clinic.

MATERIALS AND METHODS

A total of 31 adolescent patients with ALL, who were diagnosed and treated between January 2009 and January 2022 at our Pediatric Hematology Oncology Clinic, were retrospectively examined. The demographic, clinical, and genetic characteristics of patients and the results of the ALLIC-2009 and EsPhALL-10 treatment protocols were evaluated.

Table 1: Demographic and clinical characteristics of the patients

Median age, year	**16 (15-17,9)**
Sex, n (%)	
Male	22 (71)
Female	9 (29)
Immunophenotype, n (%)	
B-cell ALL	23 (74)
T-cell ALL	8 (26)
Central nervous system involvement, n (%)	
Positive	3 (10)
Negative	21 (90)
Chemotherapy protocol, n (%)	
ALLIC-2009	30 (97)
EsPhALL 10	1(3)
Risk group, n (%)	
High	10 (32)
Medium	21 (68)
Standard	0 (0)
Stem cell transplant, n (%)	
Haploidentical	3(10)
Match unrelated donor	3(10)

Definitions [4]

Patients with 25% or higher blast percentage in bone marrow aspiration were diagnosed with acute leukemia, and immunophenotyping was used to define the ALL subtype. Bone marrow samples were painted with May Grunwald–Giemsa and was evaluated based on the FAB criteria. The central nervous system (CNS) involvement was defined as the presence of ≥5 lymphoblast/mm^3 in the cerebrospinal fluid (CSF), and traumatic lumbar puncture (LP) was characterized by the presence of >10/mm^3 red blood cells in the CSF. At the beginning of treatment, the patient was divided into risk groups according to age, leukocyte counts, absolute blast count in the peripheral blood on day 8, minimal residual disease (MRD) level in the bone marrow on day 15, and t (4;11) or t (9;22) at the time of diagnosis. Patients aged ≥1 to <6 years at the time of diagnosis, with an initial leukocyte count of <20,000/mm^3, with <1,000/mm^3 blasts of the peripheral blood on day 8, with M1/M2 bone marrow in aspiration on day 15, with MRD level of <0.1% (complete remission) on day 15, without Ph_1 + (BCR/ABL+), or with t (4;11) (MLL/AF4+) were classified as the standard-risk group. Patients with absolute blast count of ≥1,000/mm^3 in the peripheral blood on day 8, M3 bone marrow with ≥25% blasts on day 15, FC MRD level of >10% on day 15, with M2/M3 bone marrow on day 33, and, irrespective of treatment response, with Ph_1 + (BCR/ABL+), with t (4;11) (MLL/AF4+), or with hypodiploidy (<45 chromosomes) were classified as the high-risk group. All patients who were not stratified to standard- or high-risk group were classified into the intermediate-risk group.

Complete remission definitions

1-Bone marrow status: M1 bone marrow: Bone marrow aspirate with <5% lymphoblasts, satisfactory cellularity, and signs of regenerating normal hematopoiesis.

2-The absence of localized leukemic infiltrates/masses based on radiologic or clinical findings.

3-Absence of leukemic cells in the CSF obtained by therapeutic LP on day 33.

Relapse definition

Isolated bone marrow recurrence: More than 25% of blasts in the bone marrow after achieving remission with the initial leukemia treatment

Isolated CNS recurrence: The presence of >5/µL nucleated cells and the presence of blasts on microscopic examination after centrifugation of the CSF sample.

The study was approved by the hospital ethics committee (number: 2022.06.186). Patients signed the informed consent form.

Statistical Analysis: Continuous variables are expressed as medians (ranges), and categorical variables as numbers (percentages). Survival analyses were performed using the Kaplan–Meier method with the IBM SPSS 22.0 (IBM Corporation, Armonk, NY, US) program. Event-free survival

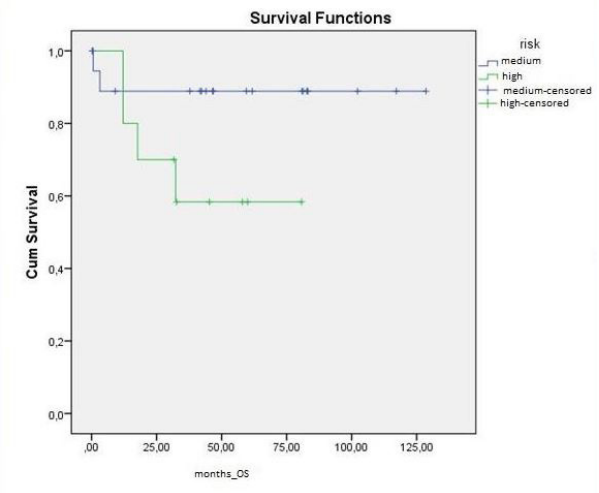

Figure 1: Survival rates by medium (n=21) and high (n=10) risk groups

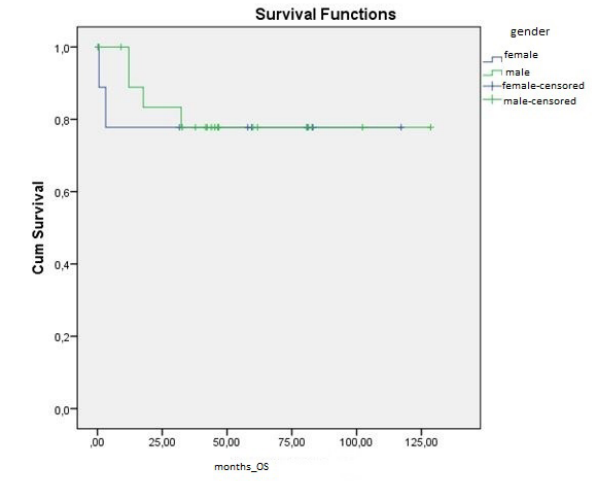

Figure 2: Survival rates by male (n=22) and female (n=9) gender

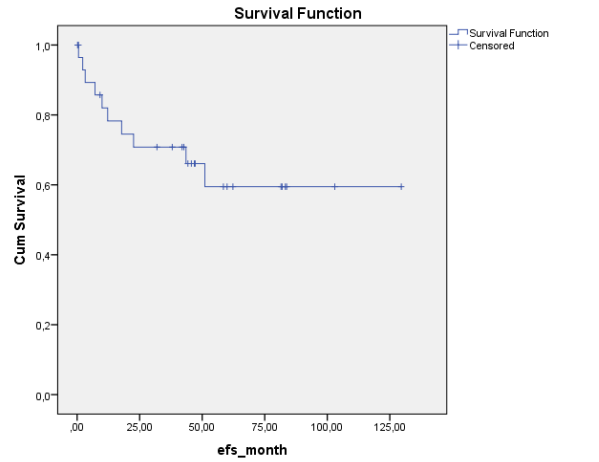

Figure 3: Kaplan-Meier curves of event-free survival (EFS) of all studied patients (n=31)

(EFS) and overall survival (OS) were analyzed using the Kaplan–Meier method and compared with the log-rank (Mantel–Cox) test. OS was defined as the time from the date of diagnosis to death from any cause or last follow-up. EFS were defined as the time from remission until the date of failure (induction failure, relapse or death) or date of the last follow-up.

RESULTS

Of the 31 adolescent patients with ALL, 22 (71%) were males and 9 were females. Their median age was 16 (range, 15–17.9) years. Among them, 10 (32%) were classified in to the high-risk group, and only two (20%) of 10 patients in the high-risk group were females: one due to Philadelphia chromosome positivity and other nine due to the MRD level of >10% and morphologically M3 bone marrow on the 15th day of induction treatment. Demographic and clinical characteristics of the patients are summarized in Table 1. The patient with Philadelphia chromosome positivity was continuously treated with the EsPhALL-10 treatment protocol. A total of 21 of 31 patients were classified into the intermediate-risk group: 8 (26%) with T-cell ALL and 23 with B-cell ALL. Three patients (10%) had CNS involvement at the time of diagnosis. It was observed that the CSF was free of blasts in all of them during treatment. Hematopoietic stem cell transplantation (HSCT) was performed in six patients: from haploidentical donors in three and from a fully matched unrelated donor in the other three. Remission was not achieved in only one patient after the induction therapy. Survival rates were similar between the intermediate- and high-risk groups (p = 0.114) (Figure 1- Survival rates by medium [n = 21] and high [n = 10] risk groups). The estimated survival rate was 58% at the 32-month follow-up in the high-risk group, while it was 89% at the 83-month follow-up in the intermediate-risk group. Survival rates were similar in boys and girls at the 60-month follow-up (p = 0.834) (Figure 2- Survival rates by male [n = 22] and female [n = 9] gender). The 10-month estimated EFS was 82% (Figure 3- Kaplan–Meier curves of event-free survival of all studied patients [n = 31]).

After a median follow-up of 5.2 (range, 0.6–12.2) months, six patients died: three due to sepsis and the others due to acute graft-versus-host disease (GVHD) that developed after HSCT. Of the three patients who died due to acute gastrointestinal GVHD complications, two were transplanted from a haploidentical donor and one from a fully matched unrelated donor. In all six patients, the disease relapsed after the completion of treatment. One of our patients, who was diagnosed at the age of 17 years and 7 months, became pregnant and gave birth to a healthy baby 1 year after the completion of treatment.

DISCUSSION

Adolescents with ALL aged between 15 and 18 years have been historically reported to have inferior survival rates compared to younger children due to an increased rate of induction failure relapses and therapy-related fatalities.[1,3] Thus, adolescent patients with ALL constitute a unique subgroup that still presents specific challenges and needs treatment optimization.[3] Most adolescent patients with ALL have been reported to be

males.[5,6] Compatible with the literature, 71% of patients in the current study were males. Treatment with pediatric protocols in adolescents and young adults with ALL demonstrated a significant survival advantage compared to adult protocols.[1,5,6] In Philadelphia chromosome-positive ALL cases, the outcomes improved after the administration of tyrosine kinase inhibitors together with multiagent chemotherapy.[5,7] The incidence of Philadelphia chromosome-positive ALL is strongly associated with poor outcomes and is found in <3% of ALL patients aged <18 years, although it is one of the most common cytogenetic abnormalities in adult ALLs. The treatment of one patient (3%) with Ph_1 + ALL in our study was continued with the EsPhALL-10 protocol.

ALL in adolescents and young adults accounts for <25% of all ALL cases but causes 80% of ALL-related deaths.[5] Six of our patients (20%) died during treatment: three due to sepsis and three due to acute GVHD after HSCT. Two of the patients who died due to acute gastrointestinal system GVHD were transplanted from a haploidentical and one from a fully matched unrelated donor. While pediatric protocols use higher cumulative doses of drugs, such as asparaginase, vincristine, and steroids, adult protocols more frequently utilize cytarabine and HSCT.[5] Approximately 20% of our patients underwent HSCT, which was more frequent compared to the study by Akhil Rajenda *et al.*[5]

It has been shown that other adverse prognostic features such as intrachromosomal amplification of chromosome 21 and MLL translocation occur more frequently in adolescent and young adult populations.[8] These factors were not encountered in our patient group.

There are a number of biological factors that contribute to low treatment rates in adolescent and young adult patients. T-cell ALL is known to be associated with poor outcomes and occurs in 20–25% of adult ALL cases and 15% in children.[8] Most patients have precursor B (pre-B) ALL, but T-cell ALL is more frequent in the adolescent and young adult groups compared to the pediatric group.[9] In the current study, 8 of 31 patients with ALL (26%) were T-cell ALL and 23 (74%) were B-cell ALL, which was higher as expected than the T-cell ALL ratio compared to younger patients with ALL.

In the analysis results published by the Pediatric Oncology Group, which uses higher-intensity chemotherapy according to the Berlin–Frankfurt–Munster (BFM) protocol, the 5-year OS and EFS rates was reported as 77.5% and 71.5%.[9] Our estimated survival rate at 32 months was 58% in the high-risk group, whereas our survival rate in the medium-risk group was 89% at 83 months. Our estimated EFS rate at 10 months was 82%. Our survival rates at 60-month follow-up were similar in both male and female patients.

In a study by Prasanth Ganesan *et al.*, the presence of BCR-ABL, which was analyzed by reverse transcriptase-polymerase chain reaction or fluorescent in situ hybridization, was detected in 158 of 730 patients.[10] In the current study group, t (9;22) BCRL/ABL positivity was detected only in one patient, and remission was not achieved at the end of induction therapy.

In pediatric patients, the CNS involvement at the time of diagnosis is reported in approximately 3% of cases. It has been reported that this extramedullary leukemia, which manifests itself in the CSF, can be seen in approximately 10% of adolescent and young adult ALL patients.[9] Similarly, in our patient group, three (10%) patients had the CNS involvement at the time of diagnosis, and all patients achieved clearance of blasts from the CSF during the treatment. In the present study, relapse was diagnosed in 6 of 31 patients (19%) after the completion of the treatment, which was lower compared to the literature (40%).[9] All protocols include prophylactic treatment of the CNS to prevent CNS relapse. Some very high-risk cases also require the use of cranial radiation therapy. All studies comparing the cognitive functions in the survivor groups with matched healthy controls report significantly lower scores in the ALL survivor groups.[11] Following cancer treatment, patients often experience late side effects, including the reproductive health problems, which require treatment and follow-up. Male patients who recover from childhood ALL are at a higher risk of long-term infertility, gonadal dysfunction, and poor semen quality due to gonadotoxicity of some treatments, including alkylating agents and testicular irradiation.[12] Many women of reproductive age also desire to have biological children and have cancer. They are concerned that their treatments may affect pregnancy and child health outcomes.[13] While chemotherapy, radiation, and surgical interventions may adversely affect the gametes, they may also affect the uterus and cause comorbidities that affect pregnancy.[13,14] Cyclophosphamide and doxorubicin have the greatest impact on fertility.[15] One of our patient, who was diagnosed at the age of 17 years and 7 months, became pregnant and gave birth to a healthy baby 1 year after the completion of treatment.

The limitation of the current study was the relatively small number of patients.

We think that the development of chemotherapy protocols used in childhood ALL with clinical studies specific to the adolescent age group will contribute to increase the treatment success rates.

Ethics Committee Approval: The study was approved by the Basaksehir Cam and Sakura City Hospital Ethics Committee (Number: 2022.06.186).

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Author Contributions: Conception/Design of Study- E.P.U., C.B.; Data Acquisition- E.P.U., G.N.Ö., S.A.T.; Data Analysis/Interpretation- E.P.U., A.A., G.A.; Drafting Manuscript- E.P.U., C..B, N..Ö, S.A.T., G.A., A.A.; Critical Revision of Manuscript- E.P.U., C.B., N.Ö., S.A.T., G.A., A.A.; Final Approval and Accountability- E.P.U., C.B., N..Ö, S.A.T., G.A., A.A.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Pregnant Women's Attitudes and Practices on Creating a Safe Sleep Environment for Their Babies

Gebelerin, Bebeklerine Uyku Çevresi Oluşturmaya Yönelik Tutum ve Uygulamaları

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ABSTRACT

Objective: Establishing a safe sleeping environment is recommended to protect babies from sudden infant death syndrome (SIDS). The aim of this study is to investigate the safety of the sleeping environment pregnant women will create after their babies are born and to determine their knowledge and attitudes about SIDS. The study also aims to raise awareness on this subject.

Methods: This is a cross-sectional descriptive study. The population of the study consists of 207 pregnant women between the ages of 18-49 who were receiving check-ups at the 30 Ağustos Family Health Center (FHC). The researcher prepared a questionnaire to investigate the knowledge, habits, attitudes and behaviors of pregnant women regarding SIDS risk factors. Pregnant women who applied to the FHC between March 2 and June 1, 2020 were interviewed face-to-face or over the phone.

Results: Of the pregnant women who participated, 23.7% reported planning to put their babies into their cribs in the supine position and 55.5% on their side. Of the women, 50.7% stated having heard of SIDS before, and 32.5% stated having obtained information from elder family members. Multiparous mothers were determined to exhibit correct behaviors such as not using support pillows or putting toys in beds in terms of a safe sleeping environment compared to the nulliparous mothers.

Conclusion: The need exists in Türkiye to increase pregnant women's awareness about safe sleeping environments for babies. Expectant mothers were observed to have adopted the attitudes they'd learned from their family elders and their environment. Attitudes toward safe sleeping were not seen to change over time in multiparous pregnant women. Educating health workers on this subject and adding the principles of safe sleep for babies and information on how to prevent SIDS to the *Antenatal Care Management Guide* used in pregnancy follow-up may be beneficial. Having the Ministry of Health organize a campaign could contribute to rapidly raising awareness in society about safe sleep for infants and how to prevent SIDS.

Keywords: safe sleep environment, sleeping position, sudden infant death syndrome

ÖZ

Amaç: Güvenli uyku çevresinin oluşturulması, bebeklerin Ani Bebek Ölüm Sendromundan (ABÖS) korunması için önerilmektedir. Bu çalışmanın amacı; gebe kadınların bebekleri doğduktan sonra oluşturacakları uyku ortamlarının güvenliğini sorgulamak, ABÖS hakkında bilgi, tutumlarını tespit etmektir. Çalışma ile bu konuda bir farkındalık yaratması da amaçlanmıştır.

Yöntem: Çalışma kesitsel tipte, tanımlayıcı bir araştırmadır. 30 Ağustos Aile Sağlığı Merkezi'ne (ASM) başvuruda bulunan 18-49 yaş aralığındaki 207 gebe, çalışma evrenini oluşturmaktadır. Araştırmacı tarafından gebelerin ABÖS risk faktörleri konusundaki bilgi, alışkanlık, tutum ve davranışları araştırmayı amaçlayan bir anket hazırlanmıştır. Anketler ASM 'ye 2 Mart 2020 – 1 Haziran 2020 tarihleri arasında, ayaktan başvuran gebelere yüz yüze, gelemeyen gebelere de telefonla ulaşılarak doldurulmuştur.

Bulgular: Gebeler bebeklerini sırtüstü (%23,7) ve yan pozisyonda (%55,5) beşiğe yatırmayı planladıklarını bildirdiler. ABÖS'ü %50,7 gebe daha duyduklarını ve %32,5 oranında bu bilgiyi aile büyüklerinden edindiklerini belirtmişlerdir. Multipar gebelerin nullipar gebeler göre güvenli uyku ortamı hakkında bebek yataklarında destek yastığı kullanmama ve içine oyuncak koymama açısından doğru davranışlar sergiledikleri tespit edilmiştir.

Sonuç: Ülkemizde bebekler için güvenli uyku ortamı farkındalığının gebelerde arttırılmasına ihtiyaç bulunmaktadır. Anne adaylarının aile büyüklerinden ve çevrelerinden öğrendikleri tutumları benimsedikleri görülmüştür. Multipar gebelerde de güvenli uyku tutumlarının zaman içinde değişmediği gösterilmiştir. Sağlık çalışanlarının bu konuda eğitilmesi ve gebelik takibinde kullanılan "Doğum Öncesi Bakım Yönetim Rehberi"ne bebeklerde güvenli uyku ve ABÖS'ten korunma ilkelerinin eklenmesi faydalı olabilir. Sağlık Bakanlığı tarafından düzenlenen bir kampanya, bebeklerde güvenli uyku ve ABÖS'den koruma konusunda toplumda hızla farkındalığın oluşmasına katkıda bulunabilir.

Anahtar Kelimeler: güvenli uyku ortamı, uyku pozisyonu, ani bebek ölümü sendromu

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INTRODUCTION

Sudden infant death syndrome (SIDS) is an unexpected infant death that remains unexplained after the case investigation, including the crime scene investigation, autopsy, and clinical history review [1]. Studies have reported the incidence of SIDS to be higher in the first two months of life and to decrease after one year of age [2]. In Türkiye, data about SIDS are obtained from the Institute of Forensic Sciences. When analyzing pediatric deaths in Istanbul, approximately 1.2% of deaths under 5 years of age were reported as SIDS [3]. According to 2021 data, the number of deaths under 12 months of age in Türkiye was 9,938 [4]. The available data suggests the number of reported cases to be lower than the actual number due to the difficulty of diagnosis. Despite extensive studies, the exact cause of this syndrome has not been established, but risk factors and protective measures have been identified (Table 1) [5]. Bed-sharing (sleeping in the same bed or on the same surface as the baby) is considered to be a risk factor for SIDS [6]. Other risk factors include putting the baby to sleep in prone position, preterm birth, use of soft objects and blankets in the bed, parental smoking, and alcohol or drug use by the mother during pregnancy and/or after birth [1].

A safe sleep environment is defined as a sleep environment that minimizes the risk of SIDS [1]. Room sharing is when parents sleep in the same room as their baby but on different surfaces [5]. Parents in Türkiye commonly share a room with their babies when they are at an early age [7]. In addition to a safe sleep environment, this section will also explain the issues of which parents who share a bed with their babies should be aware. Risky situations that have been identified include mothers who smoke, parents sharing a bed when very tired, alcohol use, sedative use, obesity, the presence of other small children who are likely to come to bed, babies with low birth weight, preterm babies, babies under 14 weeks old, sleeping on a surface other than a bed (i.e., sofa, sofa bed), sleeping on a soft surface (i.e., water bed), having a place adjacent to the bed where the baby could fall into and be squeezed, and a baby sleeping face down in a shared bed [8].

The Ministry of Health's General Directorate of Public Health published the *Prenatal Birth Management Guide* to help expectant mothers. The guide provides information to prepare mothers for delivery during pregnancy check-ups and postnatal infant care [9]. Pregnancy also provides an opportunity for expectant mothers to change existing unhealthy behaviors. Education during pregnancy can be effective in improving the mother's and child's health [10].

Sleeping spaces can be related to cultural and socioeconomic structures. Based on studies of mother-infant interactions in different cultures, accurate assessments can be made about the views of families and practices in a country [8]. Türkiye has few studies that have evaluated mothers' safe sleep practices and attitudes toward SIDS and no statistical data as yet about the prevalence of SIDS [7].

The aim of this study is to investigate the safety of the sleeping environments that pregnant women will create for their babies after they are born and to determine their knowledge and attitudes about SIDS. The study also aims to raise awareness among pregnant women about safe sleep practices.

MATERIALS AND METHODS

The study is a cross-sectional descriptive research. The researcher prepared a questionnaire aimed at investigating the level of knowledge, habits, attitudes, and behaviors of pregnant women regarding the risk factors of SIDS. The questionnaire consists of three parts. The first part includes questions about the sociodemographic characteristics of the family and pregnancy check-ups. Families' economic levels were determined by asking about the ratio of total family income to expenses and categorized as low, moderate, or good according to the pregnant women's statements. Questions about the pregnant woman's intention to breastfeed her baby, as well as her attitudes and

Table 1: Recommendations to reduce the risk of SIDS (5)

The supine sleeping position on a hard, flat, non-inclined surface is recommended, even for preterm babies.
Babies who can turn from supine to prone and from prone to supine can be allowed to remain in the sleeping position they are in.
The baby cots and besd must meet standards.
To reduce the risk of strangulation or entrapment the mattress should fit the bed, sheets should be tucked to the edge of the matress.
Pillows, blankets, bedside protectors, toys, pacifier ties, etc. should not be placed in the bed.
It is recommended that babies sleep in the same room as parents, close to the parents' bed but on a separate surface designed for babies, for at least the first 6 months (room sharing).
Breastfeeding should be promoted.
Overheating of the baby should be prevented and the temperature of the room where the baby sleeps should be observed.
Instead of covering the baby with a blanket, it is preferable to dress the baby or to use baby sleeping bag.
Pacifier can be offered when the infant is asleep.
Infants should not be swaddled.
Babies should be fully vaccinated on time.
Ensure that mothers benefit from antenatal care services. Avoid smoking, nicotine and alcohol exposure during pregnancy and after delivery.

Table 2: Distribution of sociodemographic and descriptive characteristics of parents

Question	Answers	n (%)
Mother's working status	No	152 (%73,4)
	Yes	55 (%26,6)
Father's working status	No	8 (%3,8)
	Yes	199 (%96,2)
Family type	Married- nuclear family	179 (%86,5)
	Married -extended family	28 (%13,5)
Level of income	Low	28 (%13,5)
	Moderate	149 (%72,0)
	Good	30 (%14,5)
Smoking status	Does not smoke	181 (%87,4)
	Smoke	14 (%6,8)
	Quit when she got pregnant	12 (%5,8)
Smoking in the house	No	159 (%76,8)
	Yes	48 (%23,2)
Alcohol consumption	No	204 (%98,6)
	Yes	3 (%1,4)
Follow-ups	FHS (Family Health Center)	6 (%2,9)
	State Hospital	14 (%6,8)
	Private Hospital	47 (%22,7)
	FHS + State Hospital	23 (%11,1)
	FHS + Private Hospital	117 (%56,5)

behaviors regarding feeding, were asked in the second part of the questionnaire. The last part asks questions about the sleep environment the pregnant woman planned to create for her baby, the choice of bed, intention to share a room and/or bed, and pacifier use. In addition, the pregnant woman was asked whether she had information and experience about SIDS and whether she had received counseling on this subject.

The population of this study consists of 207 pregnant women between the ages of 18-49 who received check-ups at the 30 Ağustos Family Health Center (FHC) in Istanbul. Consent was obtained from those who chose to volunteer in the study. During the study period between March 2 and June 1, 2020, the researcher filled out the questionnaires by contacting the pregnant women who'd come to the FHC face-to-face and the pregnant women who could not come to the FHC by telephone. The pregnant women were given detailed information about the study, and their written and verbal consent was obtained.

In the FHC where the study was conducted, mothers had at least four check-ups during their pregnancies, in line with the recommendations in the *Prenatal Birth Management Guide* [9]. General health monitoring occurred during each check-up, and the mothers-to-be were also counseled about breastfeeding. During the postnatal check-ups, the mothers used the recommendations from the new *Postpartum Care Management Guide* that had also been republished in 2018 by the General Directorate of Public Health [9].

The program Number Cruncher Statistical System (NCSS) was used for the statistical analyses. Descriptive statistical methods (i.e., mean, standard deviation, median, frequency, percentage, minimum, maximum) were used to evaluate the study data. The Pearson chi-square test was used to compare the qualitative data, with statistical significance being accepted as $p < 0.05$.

Approval for the study was obtained from the Health Sciences University Bakırköy Sadi Konuk Training and Research Hospital Ethics Committee with Decision No. 2020-42 dated February 3, 2020.

Table 3: Distribution of conditions related to the planned sleep environment of infants

Questions	Answers	n (%)
Bed-sharing history with a previous child (n=131)	No	46 (35,1)
	Yes	85 (64,9)
Why did you share bed with your baby? (n=85) *	First pregnancy	76
	There were no other beds	5 (5,6)
	I preferred it	22 (24,4)
	Easy to calm down when she/he cries	63 (70,0)
Buying a mattress for the baby	No	51 (24,6)
	Yes	156 (75,4)
Reason for not buying (n=51)	Got it from someone else	39 (76,5)
	We will sleep in the my bed (bed-sharing)	1 (1,9)
	For financial reasons	11 (21,6)
Where did you get information about baby sleep position and sleep environment? *	Healthcare worker	49 (16,3)
	Family Elders	92 (30,7)
	Neighbors	13 (4,3)
	Previous Experience	82 (27,3)
	Media	51 (17)
	All above	8 (2,7)
	Researched	(1,7)

** More than one option is checked.*

Table 4: Distribution of Responses to Questions on Knowledge of Sudden Infant Death Syndrome (SIDS)

Question	Answers	n (%)
Do you know what is SIDS?	Have not heard	102 (49,3)
	Heard*	105 (50,7)
Where did you hear it?	Healthcare worker	14 (11,2)
	Family Elders	42 (33,6)
	Neighbours	27 (21,6)
	Media	40 (32)
	All above	2 (1,6)
Have you ever encounter SIDS? (n=105)	No	90 (85,7)
	Yes	15 (14,3)
To whom did the SIDS happen? (n=15)	Relative	9 (60,0)
	Neighbor	4 (26,7)
	Other	2 (13,3)
Do you have detailed information about SIDS? (n=105)	No	67 (63,8)
	Yes	38 (36,2)
Where or from whom did you receive detailed information about SIDS? *	Healthcare worker	8 (20,0)
	Family Elders	13 (32,5)
	Neighbor	5 (12,5)
	Media	(35,0)

** More than one option is checked.*

Table 5: Comparison of sleep safety knowledge of mothers according to the number of pregnancies

Question	Answer	Nulliparous n (%)	Multiparous n (%)	P
Sleep position of baby	Supine	22 (28,9)	28 (21,4)	[a]0,220
	Other	54 (71,1)	103 (78,6)	
Mattress firmness	Soft	60 (78,9)	108 (82,4)	[a]0,535
	Hard	16 (21,1)	23 (17,6)	
Pillow use	Yes	38 (50,0)	63 (48,1)	[a]0,791
	No	38 (50,0)	68 (51,9)	
Support pillow in the crib	Yes	64 (84,2)	86 (65,6)	[a]0,004*
	No	12 (15,8)	45 (34,4)	
The way the sheet is laid	Loose	23 (30,3)	31 (23,7)	[a]0,297
	Tense	53 (69,7)	100 (76,3)	
Covering the babies face while sleeping	Yes	17 (22,4)	27 (20,6)	[a]0,766
	No	59 (77,6)	104 (79,4)	
Use of sleeping bag	No	37 (48,7)	75 (57,3)	[a]0,233
	Yes	39 (51,3)	56 (42,7)	
Using pacifier while sleeping	No	42 (55,3)	65 (49,6)	[a]0,433
	Yes	34 (44,7)	66 (50,4)	
Swaddling	Yes	38 (50,0)	62 (47,3)	[a]0,711
	No	38 (50,0)	69 (52,7)	
Toy in the crib/cot	Yes	25 (32,9)	20 (15,3)	[a]0,003*
	No	51 (67,1)	111 (84,7)	
Room temperature	High or Low	9 (11,8)	21 (16,0)	[a]0,409
	Ideal	67 (88,2)	110 (84,0)	

*p<0,05 a Pearson Chi-square Test

RESULTS

This study evaluates the questionnaire data obtained from 207 pregnant women. The mean age of the pregnant women is 29.55 ± 5.35 years (range = 19-46) whose current gestation period was mean = 4.6 months (median = 4 months). The mean age of the expectant fathers was 33.40 ± 5.52 years (range: 20-51). When analyzing the pregnant women's educational status, 7.3% (*n* = 15) were found to be illiterate, 2.9% (*n* = 6) to be literate, 17.4% (*n* = 36) to be primary school graduates, 22.2% (*n* = 46) to be middle school graduates, 25.1% (*n* = 52) to be high school graduates, and 25.1% (*n* = 52) to be university graduates or higher. Detailed demographic information on the families participating in the study is given in Table 2.

Of the pregnant women who participated in the study, 80.7 (% (*n* = 167) reported planning to feed their babies by exclusive breastfeeding for the first 6 months, 25.6% (*n* = 53) to breastfeed their babies until the age of two, and 34.8% (*n* = 72) to breastfeed beyond 2 years. When examining their information source on breastfeeding, 22.4% (*n* = 65) stated obtaining information from healthcare professionals, 28.7% (*n* = 84) from family elders, 5.1% (*n* = 15) from neighbors, 21.2% (*n* = 62) from previous experiences, 17.4% (*n* = 51) from social media, and 4.1% (*n* = 12) from all of the above. Among the pregnant women who participated in the study, only 1.3% (*n* = 4) of expectant women reported having no knowledge about breastfeeding; 80.2 % (*n* = 166) stated planning to start complementary feeding their child at month 6 and 5.3% (*n* = 11) at month 9. The sleep experiences of the pregnant women with previous children and the new sleep environment they planned to set up for their babies are given in Table 3. In the questions inquiring after information about the safe sleep environment, 18.8% (*n* = 39) of the pregnant women stated choosing a firm mattress for their baby, 51.2% (*n* = 106) not putting a pillow in the crib, 27.5% (*n* = 57) not using bumpers in the crib, 73.9% (*n* = 153) using fitted sheets, and 78.7% (*n* = 163) not covering the baby's face while sleeping. Among the pregnant women who participated in the study, 45.9% (*n* = 95) stated they would use a sleeping bag, and 48.3% (*n* = 100) stated they planned to use a pacifier. The percentage of pregnant women who intended to swaddle their babies is 51.7% (*n* = 107). Expectant mothers who intended not to put toys in the crib is 78.3% (*n* = 162). While 4.8% (*n* = 10) plan to keep the baby's room temperature cool, 85.5% (*n* = 177) plan to keep it normal (22-24°C), 6.8% (*n* = 14) planned to keep it warm (>24°), and 2.9% (*n* = 6) didn't

know how to set the room temperature. Among the pregnant women, 49.3% (*n* = 105) reported having heard of SIDS before and 14.3% (*n* = 15) reported knowing someone who'd lost a baby to SIDS. Table 4 shows the distribution of the answers to the questions about SIDS.

Multiparous and nulliparous pregnant women were compared in terms of appropriate answers given with regard to safe sleep recommendations. The rate of multiparous mothers who answered "no" to the statements "Will you put support pillows in your baby's crib?" and "Will you put toys in the crib/cot?" was statistically significantly higher than that of nulliparous pregnant women ($p = 0.004$; $p < 0.05$, $p = 0.003$; $p < 0.05$, respectively). No statistically significant difference was found between the two groups of women regarding their answers to the other questions (Table 5).

DISCUSSION

This study is important in terms of determining expectant mothers' attitudes and information in Türkiye about the safety of the sleep environment they intend to create when their babies are born. The study was conducted among 207 pregnant women, half of whom had graduated at least from high school. The expectant mothers were indicated to lack sufficient information to create a safe sleep environment, with approximately 50% not even having heard of SIDS. Another important finding is that multiparous pregnant women do not behave differently from nulliparous women in terms of safe sleep environment.

Among the pregnant women who participated in the study, 23.7% (*n* = 50) reported planning to place their babies on their backs, and 55.5% (*n* = 117) reported planning to place their babies on their sides. In studies conducted in Türkiye examining the rate of supine sleeping among infants, this rate was found to be 23.5% in Ankara, 41% in Aydın, and 22.1% in Denizli [11-13]. As a result of baby sleep position studies initiated in the United States of America and the United Kingdom in the 1950s, the American Academy of Pediatrics and organizations concerned with child health launched the Back to Sleep Campaign in 1994, which encouraged babies to sleep only on their backs until the age of one. Subsequently in 2012, the content of the campaign was expanded and renamed Safe to Sleep to identify and publicize safe sleeping environments [5]. This campaign used this as an effective method to prevent infant mortality by creating a social perception about SIDS. Conducting evidence-based studies and launch a similar campaign in Türkiye may be beneficial in light of the data.

In the *Prenatal Birth Management Guidelines* of the General Directorate of Public Health, expectant mothers are counseled on breastfeeding during the third and fourth pregnancy check-ups. After delivery, breastfeeding education and information are provided in accordance with the *Postnatal Care Management Guide* from the General Directorate of Public Health starting from the first postnatal check-up. In the second postnatal check-up breastfeeding is monitored and information about infant care is provided. The third postnatal check-up monitors the mother-infant relationship and provides counseling on how to maintain breastfeeding [9]. According to the Türkiye Population and Health Survey's (TPHS) 2018 data, 41% of mothers stated exclusively having breastfed their babies for the first 6 months, and 66% stated that they had continued to use breast milk until 12 months of age [13]. 99% of pregnant women in this study stated knowing how much breast milk they would feed their babies. Prenatal and postnatal counseling about breastmilk and breastfeeding is provided. However, no recommendations are found for safe sleep regarding infants or counseling on how to prevent SIDS in the pregnancy check-ups. When analyzing knowledge about SIDS in this study, 49.3% of the pregnant women had never heard of it. Studies conducted in Türkiye on this subject have reported 50%-61% of mothers to have not heard of SIDS [15]. Providing safe sleep principles and counseling families about SIDS in pregnancy and postpartum check-ups can be effective. One study examining the knowledge and attitudes of health professionals about the positions in which infants are put to sleep, only 17% of health professionals were found to recommend the supine position [16]. Another finding from this study is that the pregnant women had mostly (30.7%) obtained information on infant sleep position and sleep environment from family elders. The *Basic Newborn Care Guide* published by the Ministry of Health's Public Health Institution of Türkiye's Department of Adolescents and Children provides information about the sleep position of the newborn baby and SIDS as a guide for healthcare professionals to reduce infant mortality in our country [17]. We believe that revising and increasing the frequency of training given to health personnels working in the field of maternal and infant health based on this book may contribute to increasing the strengths of the counseling personnel and their ability to inform families and society.

We found no statistical difference between multiparous and nulliparous pregnant women in terms of their infants' sleep positions, choice of mattress for their babies, pillows used in their beds, covering their child's faces, the way the sheets are laid, swaddling, or room temperature adjustments. This suggests that the sleep environment habits mothers acquire in their first pregnancies are maintained after their other pregnancies. Only multiparous pregnant women were found to exhibit the correct behaviors in terms of not using support pillows and not placing toys in the baby's bed.

Turkish families commonly share a room with the baby up to the first 24 months. However, this study's results suggest that bed sharing may be more common than reported [7]. In Türkiye, the rate of parents who share beds with their infants varies between 16%-24% [13, 16]. In this study, of the multiparous pregnant women (*n* = 131) who were asked if they had slept with their previous children, 64.9% (*n* = 85) reported having slept alongside their children. Thus, bed sharing can be said to be a common parenting practice in Türkiye.

According to TPHS data, the rate of cigarette consumption among women of childbearing age was 28% in 2018 [13]. The rate of expectant mothers in this study who smoke was

found to be 6.8%, and 5.8% stated they would quit smoking during pregnancy. Pregnancy is a chance to change unhealthy behaviors [2]. Studies conducted in Türkiye have shown 10-13% of mothers to smoke during pregnancy [14, 15]. Parental smoking in mother-infant dyads who share a bed is associated with an increased risk of SIDS [18]. Providing information about this issue may form a reason for expectant mothers to give up this habit before their babies are born.

This study has some limitations. Not all pregnant women receiving check-ups in the FHC where the study was conducted could be reached. The economic levels of the pregnant women participating in the study were classified according to their own statements. As a result, all socioeconomic strata may not have been covered.

In conclusion, this study believes this issue should be emphasized more during pregnancy check-ups in order to create a safe sleep environment for infants. Increasing training for healthcare professionals who guide pregnant women may be necessary, and adding the principles of safe sleep and how to prevent SIDS to the *Prenatal Birth Management Guide* established by the General Directorate of Public Health may be useful for guiding expectant mothers. Because the expectant mothers were observed to mostly get the information from their family elders and these habits to continue in multiparous mothers, the principles of safe sleep for infants can be spread through a nationwide campaign in order to raise family awareness. Infant deaths could be prevented by increasing awareness about the risk factors for SIDS.

Ethics Committee Approval: This study was approved by the ethics committee of the Health Sciences University Bakırköy Sadi Konuk Training and Research Hospital Ethics Committee with Decision No. 2020-42 dated February 3, 2020.

Informed Consent: Written consent was obtained from the participants.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Prevalence of Asthma and Allergic Diseases Among Children in Adıyaman, Türkiye: a Cross-sectional Study

Adıyaman İlindeki Çocuklarda Astım ve Allerjik Hastalıkların Prevalansı: Kesitsel Bir Çalışma

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ABSTRACT

Objective: To determine the prevalence and associated risk factors of asthma and allergic diseases in school children and adolescents in Adıyaman, Turkey.
Material and Methods: The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was completed online by parents of 280 children aged 6–7 years and 163 adolescents aged 13–14 years living in Adıyaman. Additional questions were added to the online survey to determine the prevalence of food and drug allergies.
Results: The prevalence of allergic diseases in the 6–7 and 13–14 age groups were as follows: 23.2% and 18.4% for asthma, 21.4% and 18.4% for allergic rhinitis, 11.4% and 11% for eczema, 10.4% and 8.6% for food allergy, and 8.6% and 3.7% for drug allergy. In the 6–7-year age group, male sex was associated with asthma and allergic rhinitis; cesarean delivery with drug allergy; and fewer siblings with atopic eczema and drug allergy. In the 13–14-year age group, having pets and more siblings were associated with eczema and food allergy, respectively.
Conclusion: This is the first study that demonstrated the prevalence of allergic diseases in Adıyaman province and showed that the overall prevalence of allergic diseases is high in the region.

Keywords: asthma, allergic rhinitis, children, drug allergy, eczema, food allergy

ÖZ

Amaç: Adıyaman'da okul çağındaki çocuk ve ergenlerde astım ve alerjik hastalıkların prevalansını ve ilişkili risk faktörlerini belirlemeyi amaçladık.
Gereç ve Yöntemler: Uluslararası Çocukluk Çağı Astım ve Alerji Çalışması (ISAAC) anketi Adıyaman'da yaşayan 6-7 yaş arası 280 çocuğun ebeveynleri ve 13-14 yaş arası 163 adölesanların kendileri tarafından online olarak cevaplandı. Bu online ankete besin alerjisi ve ilaç alerjisi prevelanslarını belirlemeye yönelik ek sorular eklendi.
Bulgular: Altı-yedi ve 13-14 yaş gruplarında alerjik hastalık prevalansı sırası ile şu şekilde bulundu: Astım için %23,2 ve %18,4, alerjik rinit için %21,4 ve %18,4, egzama için %11,4 ve %11, besin alerjisi için %10,4 ve %8,6 ve ilaç alerjisi için %8,6 ve %3,7. Altı-yedi yaş grubunda, erkek cinsiyet astım ve alerjik rinit ile; sezaryen doğum ilaç alerjisi ile; daha az kardeş ise atopik egzama ve ilaç alerjisi ile ilişkiliydi. On üç –on dört yaş grubunda evcil hayvan sahibi olmak egzama ile; daha fazla kardeşe sahip olmak besin alerjisi ile ilişkiliydi.
Sonuçlar: Adıyaman ilinde alerjik hastalıkların prevalansını gösteren bu ilk çalışmada, bölgede alerjik hastalıkların genel prevalansının yüksek olduğunu gösterdik.

Anahtar Kelimeler: alerjik rinit, astım, besin alerjisi, çocuk, egzama, ilaç alerjisi

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INTRODUCTION

Asthma, allergic rhinitis, and atopic eczema are the most prevalent chronic inflammatory conditions in childhood. These conditions impose a significant global burden in terms of healthcare expenses and morbidity, frequently starting in childhood (1-3). The prevalence of allergic disorders has significantly increased in recent decades, particularly in low- and middle-income countries, where up to 10%–30% of the population suffers from at least one allergic disease (4-6). However, the reasons behind this growth are not entirely established yet, and the global distribution of allergic diseases has a substantial variability (4).

The International Study of Asthma and Allergies in Childhood (ISAAC) was founded to promote epidemiological research on asthma and allergic disease in children by establishing a standardized methodology and by facilitating international collaboration (7). Its aims were to describe the prevalence and severity of asthma, rhinitis, and eczema in children, compare them between centers, obtain baseline measures, and provide a framework for etiological research. The design comprised three phases: Phase 1, assessing the prevalence; Phase 2, investigating possible factors; and Phase 3, assessing trends in the prevalence. More than any other epidemiologic study of asthma, allergic rhinitis, and eczema, the simplicity of the ISAAC methodology and its relatively low cost allowed it to be conducted in most settings worldwide (5).

The studies demonstrated significant variations in the prevalence of allergic diseases, which are apparent not only between different regions and countries but also among different centers within the same country and even within the same city (6). Understanding the prevalence of allergic diseases in a region is crucial for planning health services, implementing preventive measures, and assessing the burden on society and the economy (8). Studies conducted in different regions in Türkiye have determined the prevalence of allergic diseases (8-10). To the best of our knowledge, no previous study has been conducted to determine the prevalence of allergic diseases in children in Adıyaman province.

Adıyaman is situated at the point where the Southeastern Anatolia Region meets the Mediterranean Region to the west. It ranks 32nd in terms of population density among the 82 provinces in Türkiye. Before the Kahramanmaraş earthquake on February 6, 2023, it had a population of approximately 636,580 inhabitants. The climate in Adıyaman is characterized by hot and dry summers and relatively mild winters. In the socioeconomic development ranking across Türkiye, Adıyaman is positioned at the 66th place (11). Before the year 2021, no allergist was practicing in Adıyaman province, and thus, the prevalence of allergic diseases has not been previously investigated. Due to the potential variation of allergic disease prevalence in region to region even within the same province, regional allergic diseases should be investigated.

Therefore, this study aimed to determine the prevalence of asthma, allergic rhinitis, atopic eczema, food allergy, and drug allergy and the associated risk factors in children aged 6–7 years and adolescents aged 13–14 years in Adıyaman province.

METHODS

Study design and participants

This cross-sectional study was conducted in adolescents aged 13–14 years and children aged 6–7 years in Adıyaman province, Türkiye, between November 15, 2022, and January 21, 2023. The study involved schoolchildren within the specified age brackets, attending both government and private schools in the Adıyaman province, with authorization granted by the Adıyaman Directorate of National Education. The core ISAAC questionnaires, along with queries concerning physician-diagnosed food and drug allergies, were devised using online Google surveys. The school children were divided into two age groups: 13–14-year-olds (adolescents) who self-completed the questionnaires and 6–7-year-olds (children) whose questionnaires were filled out by their parents.(5) A questionnaire link was distributed to the parents of the 6–7-year-old group and directly to the 13–14-year-olds, who filled out the online queries with the guidance of their respective schoolteachers acting as intermediaries.

In Adıyaman province, a total of 12,822 students were aged 6–7 years (1st grade of the primary school) and 11,620 students were aged 13–14 years (8th grade of the middle school). In a previous study by Ones *et al.*(9), the prevalence of ever wheezing was reported to be 25.3%. A study conducted in Diyarbakır, a province adjacent to Adıyaman, reported that the prevalence of ever wheezing was 22.4% (12). Using these data, the sample size was calculated as 479 with a significance level of 0.05 and a power of 80%using the ClinCalc LLC online sample size calculator (13). Schools in Adıyaman were randomly selected, and teachers were given information about the study and the link to the online survey. However, due to the Kahramanmaraş Earthquake on February 6, 2023, that occurred during data collection, the study had to be terminated early without reaching the intended sample size. The online survey link was provided to approximately 1,250 students or parents. A total of 534 adolescents or parents of children responded to the online survey.

The adapted and validated Turkish version of the ISAAC questionnaire was used to determine the prevalence of asthma, allergic rhinitis, and eczema (7,9,14). Since there is no internationally accepted and validated questionnaire to assess the prevalence of food and drug allergies, the follow additional questions prepared by the authors were included in the questionnaire: “Does your child have physician-diagnosed food allergies?,” “Which foods trigger allergic reactions in your child?,” “Does your child have physician-diagnosed drug allergies?,” and “Which medications induce allergic reactions in your child?.” To identify the potential risk factors, including sex, mode of delivery, timing of birth (preterm or full-term/post-term), number of siblings, passive smoking at home, presence of pets (cats, dogs, birds, fish), and presence of ornamental plants, another questionnaire was prepared to be completed by parents or adolescents.

Statistical analysis

The IBM SPSS Statistics for Windows V.25.0 (IBM, Armonk, New York, USA) was used for statistical analysis. Continuous variables were presented as median [interquartile range (IQR)], whereas categorical variables were expressed as numbers and percentages. Categorical variables were compared using the appropriate chi-square test (Pearson's, Yates', or Fisher's exact test). The association between physician-diagnosed allergic diseases and the number of siblings was assessed using the Mann–Whitney U test. *P*-values of <0.05 (two-tailed) were considered statistically significant.

Ethics committee approval was received for this study from the local ethics committee of the Adıyaman University (protocol number: 2022/3-7) according to the Helsinki Declaration. Online informed consent was obtained from all participants and their parents. In the online surveys, a concise overview of the study was initially provided. Those willing to provide consent for participation were prompted to select the "I consent" option, and only participants who granted consent were directed to the subsequent questions. In this way, online consent was obtained from all participants. The principles of the Declaration of Helsinki were followed in this study.

RESULTS

Study participation

A total of 534 individuals responded to the survey questions. Among them, 17 children were aged <6, 61 children were within the 8–12 age group, and 5 children were older than 15 years, who were consequently being excluded from the study. Data collected from 280 children aged 6–7 years and 163 children aged 13–14 years were included in our study. Among the 6–7 age group, 142 (50.7%) were girls, while among the 13–14 age group, 94 (57.7%) were girls.

Prevalence of allergic diseases

Table 1 shows the prevalence of allergic diseases among the participants. The prevalence of asthma was 23.2% and 18.4% in 6–7- and 13–14-year-old children, respectively. Approximately 48.6% and 33.1% of 6–7- and 13–14-year-olds, respectively, had ever experienced wheezing. The prevalence of allergic rhinitis was 21.4% and 18.4%, and that of eczema was 11.4% and 11% in 6–7- and 13–14-year-olds, respectively. The prevalence of food allergy was 10.4% and 8.6%, and that of drug allergy was 8.6% and 3.7% in 6–7- and 13–14-year-olds, respectively. Parents of children aged 6–7 years were more likely to report all symptoms of allergic diseases compared to adolescents. (Table 1).

Associated factors

Factors associated with allergic diseases are presented in Table 2 for the 6–7 age group and in Table 3 for the 13–14 age group. In the 6–7 age group, children with physician-diagnosed asthma and allergic rhinitis exhibited a statistically higher male ratio. Furthermore, within this age group, children with physician-diagnosed drug allergies had a higher rate of cesarean section (CS) births. In the 6–7-year age group, children with physician-diagnosed atopic eczema and drug allergy had a higher number of siblings compared to the groups without atopic eczema and drug allergy (Table 2). In the 13–14 age group, adolescents with physician-diagnosed atopic eczema had a higher presence of pets in their homes, and the number of siblings was higher among adolescents with a physician-diagnosed food allergy than those without food allergy (Table 3). No statistically significant differences in terms of other risk factors were observed among the groups.

DISCUSSION

Our study, which was conducted in Adıyaman province and aimed at determining the prevalence of asthma and allergic diseases in children and adolescents for the first time, as well as the risk factors associated with the prevalence, yielded important results. The study revealed high prevalence rates of asthma, allergic rhinitis, atopic eczema, food allergy, and drug allergy in Adıyaman province. Among children and adolescents included in our study, asthma was the most frequently reported allergic disease. In the 6–7-year age group, male sex was found to be associated with physician-diagnosed asthma and allergic rhinitis; cesarean delivery with drug allergy; and having fewer siblings with atopic eczema and drug allergy. In the 13–14 age group, the presence of pets at home was associated with atopic eczema and having more siblings was associated with food allergy.

Mallol *et al.* (6) conducted a global synthesis of ISAAC studies conducted worldwide. They reported that the global prevalence of asthma, allergic rhinitis, and eczema in the 13–14-year age group was 14.1% (5.4%–23.3%), 14.6% (7.7%–20.6%), and 7.3% (3.2%–13.7%), respectively. In the 6–7-year age group, the prevalence of asthma, allergic rhinitis, and eczema was 11.7% (6.1%–24.3%), 8.5% (3.8%–13.1%), and 7.9% (3%–17%), respectively (6). Studies conducted in Türkiye reported that the prevalence of asthma, allergic rhinitis, and eczema in children aged 6–7 years ranged from 3.6% to 17.3%, 3.4% to 9.5%, and 2.3% to 7.3%, respectively (8,15-17). Among adolescents aged 13–14 years in Türkiye, the prevalence rates of asthma, allergic rhinitis, and eczema ranged from 1% to 12.9%, 2.9% to 8.7%, and 2.7% to 2.8%, respectively.(16,18,19) Some prevalence studies of allergic diseases in Türkiye also used the ISAAC questionnaire in children between the ages of 6 and 18 years, without specifically distinguishing between the 6–7 and 13–14 age groups. In these studies, the prevalence of asthma, allergic rhinitis, and eczema was found to be 1.8%–17.8%, 7.9%–43.2%, and 2.1%–10.7%, respectively (9,10,12,20-24). The prevalence of allergic diseases tended to be higher in more recent studies. In our study, the prevalence rates of asthma, allergic rhinitis, and eczema was higher than that of these previous studies. Several previous studies were conducted more than a decade ago, and the continued increase in allergic diseases over time may explain the increased prevalence found in our results. Studies clearly demonstrate that the prevalence of allergic diseases can be very high in populations with low

socioeconomic status (6). The relatively lower socioeconomic status of Adıyaman province compared to other provinces in Türkiye could be one of the contributing factors to the observed high prevalence of allergic diseases. In addition, several environmental factors, including geography, climate, diet, and exposure to environmental allergens, have been shown to be associated with the prevalence of allergic diseases and may contribute to the observed differences (4,21).

Food allergy is commonly observed in children under the age of 4 years, and therefore they are often excluded from prevalence studies in school-aged children (20). The prevalence of self-reported food allergy varies from 3% to 35% in the general population. However, the prevalence of confirmed FA determined by oral food challenge tests is observed between 1% and 4% (25). Orhan *et al.* (26) conducted a study on 2,739 school children aged 6–9 years in the Eastern Black Sea Region of Türkiye. They reported that the prevalence of parent-reported food allergy was 5.7%. To confirm food allergy, oral food challenge tests were performed, and they found that the prevalence of IgE-mediated food allergy was actually 0.80%. This study showed that the confirmed prevalence of food allergy was significantly lower than the self-reported prevalence of food allergy. A survey study in Türkiye showed a physician-diagnosed prevalence of food allergy of 6.5% in children aged 11–12 years (20). In our study, we found a higher prevalence of self-reported physician-diagnosed food allergy. However, as shown in previous studies, a much lower prevalence can be found when detailed tests such as the oral provocation test are used (27).

In epidemiological cross-sectional studies conducted on children using the questionnaire-based method, the prevalence of drug allergies has been reported between 2.8% and 11.8% (28,29). However, when these patients were further evaluated with detailed tests, evidence of drug allergy was found in 1% to 5% of cases (29). Limited information is available on the prevalence of drug allergy and drug reactions in Turkish children. A survey of 10,096 parents was conducted to assess the prevalence of drug allergy in Turkish children. The rate of immediate-type drug hypersensitivity reported by parents was 7.87%. However, a telephone survey revealed a clinical history suggestive of drug allergy in only 1.16% of the children. Subsequent comprehensive diagnostic evaluation revealed that the true incidence of immediate-type drug hypersensitivity was 0.11% (28). Parents often exaggerate their children's drug allergies, leading doctors to prescribe alternative medications to prevent severe reactions. However, these medications are often more expensive, are less effective, and have more side effects. The high prevalence rates demonstrated in our study support the need for a comprehensive diagnostic evaluation to confirm a suspected drug allergy in a child (28).

Epidemiologic studies have shown that the male sex is a risk factor for asthma and allergic rhinitis in children, with the prevalence of asthma being twice as high in males than in females (9,30,31). In our study, we found an association between asthma and allergic rhinitis and male sex in the 6–7-year age group, but this association was not observed in adolescents aged 13–14 years. With increasing age, however, the gender difference decreases. Before the age of 14 years, males have been shown to have narrower airways relative to the lung size and the higher airway resistance than females. This anatomical variance in the airway structure and hormonal factors may contribute to increased wheezing and lower respiratory rates in males (9,32). In our study, a lower number of siblings was associated with atopic eczema and drug allergy in the 6–7-year age group. This finding could be explained by the hygiene hypothesis, which suggests that having older siblings increases microbial exposure and consequently leads to a lower prevalence of allergic diseases (33, 34). In the 13–14-year age group, a higher number of siblings was associated with food allergy in adolescents. However, we were unable to provide an explanation for this finding. In the 13–14-year age group, the presence of pets was found to be associated with atopic eczema in adolescents. These children are possibly sensitive to pet dander, which may contribute to the persistence of eczema in this group. An association between drug allergy and cesarean delivery in the 6–7-year old group of children. The literature does not provide information on the relationship between CS delivery and the development of drug allergy in children. Cesarean delivery may result in the maternal use of antibiotics, which could lead to early exposure and sensitization of the infant to antibiotics through intrauterine exposure or breastfeeding. This sensitization could potentially contribute to the development of drug allergies later in life.

The main strength of the study is that it first attempts to determine the prevalence of allergic diseases in children and adolescent population in Adıyaman province. Another noteworthy aspect of our study is its timing, as it was completed just before the February 6, 2023, earthquake in Kahramanmaraş. Following the earthquake, an increase in the prevalence of atopic dermatitis and asthma and a worsening of asthma control were observed (35,36). Since our data corresponds to a period before the earthquake, it can serve as preliminary data for future studies investigating the impact of earthquakes on allergic diseases in Türkiye.

The diagnosis of allergic diseases is a global research challenge due to the lack of a universally accepted gold standard. However, the ISAAC diagnostic approach is limited because it relies on self-reported symptom definitions for allergic diseases. In addition, the ISAAC questionnaire may be influenced by a recall bias. Another limitation is that nonstandardized questions were used to determine the prevalence of food and drug allergies. Moreover, objective data, such as results from physical examinations or allergy screening tests, were not available. Furthermore, due to the earthquake in Kahramanmaraş on February 6, 2023, the intended sample size was not reached.

CONCLUSIONS

We have shown that allergic diseases have a high prevalence in Adıyaman province. However, challenges remain in the accurate

diagnosis and treatment of allergic diseases, which represent a significant public health burden. Thus, it is essential for health policymakers and practitioners to adapt health services to meet the specific needs in this area.

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Ethics Committee Approval: This study was approved by the ethics committee of the local ethics committee of the Adıyaman University (protocol number: 2022/3-7) according to the Helsinki Declaration.

Informed Consent: Legal custodian's assent of the children participated in the research was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- V.Ç., H.T.; Data Acquisition- V.Ç., H.T., F.E.K., T.T.; Data Analysis/Interpretation- V.Ç.; Drafting Manuscript- V.Ç., F.E.K.; Critical Revision of Manuscript- V.Ç., H.T., T.T.; Final Approval and Accountability- V.Ç., H.T., F.E.K., T.T.

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RESEARCH ARTICLE / *ARAŞTIRMA MAKALESİ*

The Effect of the Use of Black and White Flashcards on Acute Pain Levels in Infants*

Siyah Beyaz Dikkati Başka Yöne Çekme Kartlarının Bebeklerin Hissedilen Akut Ağrı Düzeyine Etkisi

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ABSTRACT

Objective: Vaccination practices are one of the most painful procedures in infancy, creating anxiety and distress for both infants and their parents. This study was planned to determine the effect of black and white flashcards on the level of acute pain infants feel during vaccination applications.
Materials and Methods: The sample of this prospective randomized controlled trial comprised 119 infants who were brought to the family health center for the 2nd and 3rd dose of the combined 5-vaccine and who met the inclusion criteria. The data were obtained using the information form, which included descriptive characteristics of the baby and family, and the FLACC pain assessment tool.
Results: The mean pain scores of the infants (2.76 ± 2.06) in the black and white flashcard group were significantly lower than those of the control group (4.61 ± 2.00) ($p < 0.01$). Additionally, there was statistically no significant difference between the total durations of crying and the periods of the infants between initial crying and calming down in both the experimental and control groups ($p>0.05$).
Conclusion: We concluded that the use of black and white flashcards during the vaccination practices was efficient. In line with these results, we recommend that nurses use black and white flashcards, an easily applicable method, to decrease the pain sensitivity of infants during vaccine applications.

Keywords: pain, vaccination, distraction

ÖZ

Amaç: Aşı uygulamaları, bebeklik dönemindeki ağrı ve en acı verici prosedürlerden biri olup hem bebekler hem de ebeveynleri için endişe ve sıkıntı yaratıcı durumdur. Araştırma; aşı uygulamaları sırasında kullanılan siyah beyaz dikkati başka yöne çekme kartlarının bebeklerde hissedilen akut ağrı düzeyine etkisini belirlemek amacı ile planlandı.
Gereç ve Yöntem: Randomize kontrollü araştırmanın örneklemini aile sağlığı merkezine 5'li karma aşının 2. veya 3. dozu için başvuran vaka seçim kriterlerine uyan toplam 119 (dikkati başka yöne çekme grubu (n=60), kontrol grubu (n=59)) bebek oluşturdu. Veriler bebek ve ailenin tanıtıcı özelliklerini içeren bilgi formu ve FLACC ağrı değerlendirme ölçeği kullanılarak elde edildi.
Bulgular: Dikkati başka yöne çekme yönteminin uygulandığı grupta yer alan yenidoğanların (2.76 ± 2.06) işlemsel ağrı puan ortalamaları kontrol grubuna (4.61 ± 2.00) göre anlamlı derecede düşüktü ($p < 0.01$). Hem deney hem de kontrol grubunda yer alan yenidoğanların toplam ağlama süreleri ile ilk sakinleşme süreleri arasında istatiksel yönden anlamlılık bulunmadı ($p>0.05$).
Sonuç: Sonuç olarak, aşı uygulamaları sırasında hissedilen ağrıyı azaltmada dikkati başka yöne çekme kartlarının etkili olduğu belirlendi. Bu sonuçlar doğrultusunda; bebeklerin aşı uygulamaları sırasında ağrıya hassasiyetini azaltmak için kolay uygulanabilir bir yöntem olarak dikkati başka yöne çekme kartlarının hemşireler tarafından kullanımı önerilmektedir.

Anahtar Kelimeler: ağrı, aşılama, dikkati başka yöne çekme

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INTRODUCTION

The vaccine is one of the most effective inventions concerning its positive impact on human health, and immunization is considered an effective method of protection in the fight against infectious diseases (1,2). Vaccines are the most common source of iatrogenic pain in early childhood, which is also an important pain source for the children, who are being exposed to this procedure, their parents, and people responsible for the vaccination process (3). Vaccination practice is one of the most painful procedures in infancy, and it creates anxiety not only for the infants but also for their parents (4,5). Pain is a complex and multidimensional situation, which is personally perceived at different levels. Pain, according to the Taxonomy Committee of the International Association for the Study of Pain, is a biochemical or sensational situation or behavior that originates from a particular region of the body. It results from actual or potential tissue damage, is affected by the experience of the person, and is displayed in an attempt to avoid an unpleasant and unwanted situation (3,6,7).

Two-thirds of children experience a fear of vaccination in childhood due to painful experiences that even continue in adulthood (4). The fear of injection experienced due to vaccination practices in early childhood may lead to refusal of treatment, and refusal or detention of certain necessary examinations (4,8,9). In the literature, it is reported that, according to the Centers for Disease Control and Prevention (CDC), syncope cases in adolescents emerge in response to the anxiety and fear of pain associated with immunization (4). It has also been noted that relieving pain during vaccination is an important strategy against vaccine hesitancy today (WHO, 2016) (10). Additionally, it was reported that some factors during vaccination practices affect the behavioral and vocal responses of infants to painful stimuli, therefore, it is necessary to control the factors to minimize pain (11). Infants depend on their parents for consolation and reassurance. Similarly, parents are uncomfortable with the thought of causing their children to suffer while they are administered vaccines. Consequently, if parents are anxious, frightened, or reluctant, babies' ability to regulate their emotions is compromised and eventually the pain becomes more severe.

Treating pain during vaccination is part of pediatric primary care services around the world and is stated to be a fundamental human right (4). Therefore, up until today, various pain relief methods have been applied to prevent/reduce vaccination pain from the infancy period onwards. Pain management in the newborn is usually based on the "3-P" approach, which involves pharmacological, physical, and psychological strategies (12). In many studies, non-pharmacological methods are effective in coping with pain (3,4,5,13-15). Non-pharmacological methods can be used in pain control alone or together with pharmacological methods. Non-pharmacological methods are among the preferred methods in recent years as they are non-invasive, inexpensive, reliable, have no side effects, and constitute the independent practice of nurses (7).

Non-pharmacological methods used in pain control in infants and children are collected in the following three main groups: supportive methods, cognitive/behavioral methods, and physical methods. While supportive methods comprise techniques such as watching videos, reading books, and ensuring that the family stays with the child during the painful procedure, physical methods consist of techniques such as touching, positioning, massage, skin stimulation, and heat and cold application (8,16,17,18). On the other hand, cognitive/behavioral methods which consist of methods such as relaxation and distraction are based on the argument that pain has a perceptual, sensory, and behavioral dimension (9,17). As stated in Sıktaş and Uysal (17), the use of distraction cards reduces injection-related pain.

It has been reported that distraction cards used during interventions such as phlebotomy, intramuscular injection, and skin prick tests in children are effective in reducing the pain and anxiety levels of children in different age groups. In the literature, there are studies, although limited in number, in which the effectiveness of the use of musical mobile, a method of distraction which is one of the cognitive/behavioral methods used to reduce pain in infants during vaccination applications is indicated (19). In recent years, black and white cards have been used as a popular example of neuroscience and neuro-parenting. In the literature, it is stated that black and white are the first colors that attract babies' attention due to their strong contrasts and that they are effective in stimulating babies (20). Our search for randomized controlled studies conducted on the use of black and white flashcards during vaccination applications revealed a gap in the literature. Thus, we thought that there was a need for studies to be conducted on this topic.

The present study is significant in that it can be a response to whether the use of black and white flashcards for infants, one of the distraction methods to be applied during vaccination practices, is an accurate and effective method. We expect that it will reveal the best distraction method to be used during vaccination through an evidence-based approach.

In light of this information, the study was planned to determine the effect of the use of black and white flashcards on the acute pain level and crying status of infants during vaccine administration.

MATERIALS AND METHODS

Design

The present study conducted to assess the effect of the use of black and white flashcards on the level of acute pain felt by infants was planned as a randomized controlled experimental study. The study was approved by the non-interventional clinical research ethics committee (IRB number 04–14, March 28, 2018), and from the relevant institution where the study would be conducted. Before the study, verbal and written consent was obtained from the parents of all the infants with the Informed Consent Form after they were informed about what the purpose of the study was, how it would be performed,

and how the data would be used. They were also told that they could withdraw from the study at any time without having to explain their excuses.

Setting and Participants

The population of the present study comprised infants aged 1-12 months who were registered with a family health center in Bandırma, a city in northwestern Türkiye, for medical follow-up between July 2018 and July 2019. The sample of the study comprised infants aged 4-6 months who were brought to the center for the 2nd and 3rd doses of the combined 5-vaccine as specified in the Ministry of Health's vaccine calendar, who met the research inclusion criteria, and who were selected through the randomized controlled method. The inclusion criteria of the study for the infants and their families were as follows: volunteering to participate in the study, being a 4-6-month-old, term, and healthy infant, having no health problems after birth, and having taken no analgesic medication in the last 3 hours before the vaccination process.

Randomization

In Power analysis based on the literature (13,21), the sample size was determined as 120 (reliability level: 90%; α: 0.05. The infants in the sample were randomly assigned to the control group and distraction cards group. To determine which case would be included in which group, numbers were randomly distributed to the two groups through a computer program without repetition of numbers. Because one of the parents wanted to withdraw from the study, her baby was not included in the study. Therefore, the number of participants included in the study was 60 in the experimental group with the black and white flashcards and 59 in the control group (Fig. 1).

Procedures

The vaccine application and data collection processes were carried out in the Family Health Center vaccination room. Before the procedure, it was ensured that the vaccination room was calm, warm, and well-lit, and all the infants were awake, fed and their diapers were changed. To ensure the reliability of the study results, the vaccine injection was administered by the same nurse who had 10 years of professional experience. The pain behaviors and crying status/durations of all the infants were observed by the same researcher. In both groups, the infants were laid in a supine position on the examination couch, and their parents were allowed to stay with the infants during the vaccination (To eliminate the parental factor, parents didn't hold their babies)

At the onset of the study, the infants' parents who were satisfied with the experimental and control group selection criteria were informed about the purpose, method, and implementation of the study and were asked whether they wanted to participate in the study. Using the Child Information Form, the following data on what the socio-demographic characteristics of the infants and parents were, whether the child had an intramuscular injection before, and whether the infant had previously been subjected to a painful intervention, etc. were obtained from the parents who agreed to participate in the study. Before the vaccine administration, weights, heights, and head circumferences of all the infants in the experimental and control groups were measured. Before the vaccination, a video camera was placed in the vaccination room to videotape the infants. Each infant was recorded by the researcher for 1 min before the procedure, 2 min during the vaccination, and 2 min after the procedure. Using the FLACC Scale, the researcher assessed pain scores before and after the vaccination as well as the total duration of crying, and the total time which elapsed between the start of crying and calming down. The researcher started the stopwatch as soon as the baby started crying during the vaccine administration and stopped it as soon as the baby stopped crying. Then, she recorded the time which elapsed.

Black and White Flashcard Group: The cards used during the vaccination were designed in a simple way to stimulate the baby and support its visual development. Black and white flashcards were shown in front of the faces of infants in the experimental group by the researcher during and one minute after the procedure. During vaccination, parents are allowed to be together in the examination chair without touching their baby. If a baby cried more than a minute after the procedure, the baby's parent was allowed to comfort the baby owing to the ethical principles.

Control group: The infants in this group underwent no intervention to reduce their pain during vaccination. During vaccination, parents are allowed to be together in the examination chair without touching their baby.

Measures

The study data were obtained using the Child Information Form, Pain Assessment Tool – FLACC, black and white flashcards, and a video camera.

Child Information Form: This data collection form consisted of 18 items questioning what the socio-demographic characteristics of the child and the parents were, whether the child was previously subjected to an intramuscular injection, whether the child was previously exposed to a painful intervention, how long the duration of crying during the vaccination was, and how much time elapsed between the start of crying and calming down.

Pain Assessment Tool (Face, Legs, Activity, Cry, Consolability - FLACC): The FLACC scale, which was developed by Merkel et al. (22), in 1997, is used to assess five behavioral parameters. Each of the five parameters (the baby's facial expression, leg movements, activity, crying, and Consolability) is scored as 0, 1, or 2 and the total score is between 0 and 10. While "0" points indicate that the baby has no pain, "1-3" points indicate mild pain, "4-6" points indicate moderate pain, and "7-10" points indicate severe pain. This scale is used in the postoperative period in children between 2 months and 7 years of age who cannot express their pain and cannot communicate. It was determined that, in later years, the FLACC scale could be used

for pain assessment in all age groups of children and adults after necessary reliability and validity tests were conducted (22).

Black and white flashcards: These flashcards are created for babies aged between 0 and 1 year and include contrasting colors (black, and white). The size of each card is 15*15 cm (23) (Fig. 2). The retina of a baby is not fully developed at birth; therefore, a newborn's retina can only distinguish between light and dark, or the contrast between black and white. In the literature, it was reported that high-contrast, black-and-white images with sharp outlines make it much easier for the baby to see in the first few months of its life while its vision is still developing. Therefore, it is reported that everything with a clear contrast such as black-white edges and lines is the most appropriate stimulus, supporting the development of the baby in the first months. The flashcards used during the application were designed in a simple way to stimulate the infant and support its visual development.

Video camera: To videotape the vaccine administration process, a rechargeable battery-powered video camera with 30x optical zoom (SONY-HDR-PJ410) was used. Each infant was recorded by the researcher for 1 min before the procedure, 2 min during the vaccination, and 2 min after the procedure. The videotaped footage was recorded on an external hard drive.

Data analysis

The IBM SPSS Statistics 22 package program was utilized in the statistical analyses of the data obtained in the study. Whether the parameters were suitable for normal distribution was evaluated through the Shapiro-Wilks test. In addition to the descriptive statistical methods (arithmetic mean, standard deviation, frequency), the Student-t test was used for the comparison of the quantitative data between two groups demonstrating normal distribution. The Chi-Square test was used to compare qualitative data. The significance level was accepted as $p<0.05$.

RESULTS

Comparison of the groups in terms of some variables

In the study, 59 baby girls and 60 baby boys were included. The mean age of the children was 4.78 ±.98 (min: 4, max:6) months. The children included in the study were randomly divided into the following two groups: the black and white flashcards group (n=60) and the control group (59). Characteristics of the children are given in Table 1. Accordingly, some variables such as age (month), sex, and total duration of the process were similar in both groups.

Comparison of the groups in terms of the pain levels, durations of crying, and time which elapsed between the start of crying and calming down.

Comparisons of the two groups in terms of the pain levels, duration of crying, and time that elapsed between the start of crying and calming down are presented in Table 2. As is seen in Table 2, the pain levels of children in the control group were higher than those of the children in the black and white flashcards group, and the difference was statistically significant (p= .003).

The duration of the crying and the time that elapsed between the start of crying and calming down were similar in both groups, and the difference was not statistically significant (p>.05).

DISCUSSION

Considering that the first pain experience of healthy infants is vaccination, pain management in vaccine applications is of vital importance (9). Many pharmacological and non-pharmacological methods are applied to control pain while children are vaccinated (3,9). The method to be used in vaccine applications to reduce pain should be effective easy, fast, unprepared, and tolerable by infants/children (9,10).

Cognitive-behavioral non-pharmacological methods involving distraction have been experimentally supported in acute pediatric pain management (9,24). Distraction is a method to increase pain tolerance by diverting attention away from the painful stimulus. This method is used as a powerful anxiety and pain management tool in children's pain. It is a suitable method for infants as it does not require advanced cognitive skills. Moreover, in the literature, it is stated that distraction is the most effective method among non-pharmacological pain relief methods in pediatric vaccine applications in the first 7 years of life (9,17,20,25).

Table 1: Group Comparison of the Demographic Characteristics of the Infants

		Total	Group		*Test Value*
			Black and White Flashcard Group (n=60)	Control Group (n=59)	
Sex n (%)	Girls	59 (49.6)	30 (50.0)	29 (49.2)	0.009
	Boys	60 (50.4)	30 (50.0)	30 (50.8)	†0.926*
			Black and White Flashcard Group (n=60)	**Control Group (n=59)**	
Age (Month)	*Min-Max (Median)*	4-6 (4)	4-6 (4)	4-6 (4)	-0.859
	Mean ± SD		4.86±0.99	4.71±0.96	††0.392*
Duration of Procedure			3.26±0.82	3.50±1.16	1.311 ††0.193*

†*Pearson Chi-Square Test;* †† *t Test; *p>0.01*

Table 2: Comparison of the groups in terms of the mean FLACC Pain Scores of the infants

		Total	Black and White Flashcard Group (n= 60)	Control Group (n= 59)	t / p
Mean FLACC score during the procedure	*Min-Max (Median)*	0-8 (5)	0-8 (4)	1-7 (6)	2.989
	Mean ± SD	4.54±1.75	4.08±1.81	5.01±1.58	**.003***

*Data are represented as mean ± standard deviation. FLACC, a pain assessment tool; **t**=t Test; *p<0.01*

Table 3: Group Comparison of the Infants Concerning the Total Durations of Crying and Time Periods Between the Start of Crying and Calming Down

		Total	Black and White Flashcard Group (n= 60)	Control Group (n= 59)	t / p
Total duration of crying (sec)	*Min-Max (Median)*	0-45 (6)	0-45 (5)	0-22 (8)	1.016
	Mean ± SD	7.52±6.00	6.96±7,24	8.08±4.39	.312*
Time which elapsed between the start of crying and calming down (sec)	*Min-Max (Median)*	0-60 (5)	0-60 (5)	0-24 (7)	1.329
	Mean ± SD	7.23±6.93	6.40±8.42	8.08±4.92	.186*

*t=t Test; *p>0.05*

The distraction method is used to reduce pain during many invasive interventions in childhood. In this regard, in the literature, there are numerous previous studies in which the distraction methods such as watching cartoons, inflating balloons, creating foam bubbles, speaking things irrelevant to the intervention, virtual reality glasses, listening to music, using kaleidoscope, etc. are investigated during vaccine applications in various age groups (9,26-28). It was determined that there were no previous studies in which distraction methods with black and white flashcards were used during vaccine applications in infants.

Bekar and Efe (28) reported that lullabies sung by the mother while their 2-month-old babies are vaccinated were effective in reducing vaccine-induced pain. Şıktaş, and Uysal (17), stated that the pain levels of the 12-month-old babies who were administered the measles, mumps, and rubella vaccine were lower in the Buzzy group than in the control group. Vaziri et al. (29) reported that inhaling low-concentration lavender oil during vaccine applications has a pain-relieving and sedative effect on infants. In a study conducted by Gedam et al. (30), it was reported that luminous toys, sound-producing toys, and cartoons are effective in reducing pain during vaccine applications. In their study, Shahid et al. (15) noted that the distraction technique of using an iPad during vaccination practices in children aged 2-6 years was effective in reducing pain levels and increasing satisfaction. In our study, the mean FLACC pain score of the infants in the experimental group, in which black and white flashcards were used, was significantly lower than that of the infants in the control group (p= .000). The results of the present study in which black and white flashcards were used in infants were consistent with the results of several studies in the literature in terms of reducing pain with a distraction method (17,28,29).

Crying behavior is described as the most obvious and traceable behavioral reaction displayed by infants against pain (5,30). In our study, the total duration of crying, and time that elapsed between the start of the crying and calming down were similar in both groups, and the difference between the groups was not statistically significant (p>0.05). In the literature, there are various studies in which the effect of different methods applied during vaccine applications on durations of crying was investigated. Vaziri et al. (29), determined that the duration of crying was shorter in the infants in the lavender-oil-inhaling group than it was in the infants in the control group. In their study conducted with 4-6-month-old infants who were administered DTaP-IPV/Hib vaccine, a 5-in-1 combination vaccine Göl and Altuğ Özsoy (31), investigated the effect of 10-second manual pressure on the vaccination point before the procedure and non-aspirated rapid injection technique on crying time determined that the duration of crying (in seconds) of the infants in the experimental group during and after the procedure was shorter than was that of the infants in the control group (p=0.001). Koç and Gözen (20) determined that there was a significant difference between the control and experimental groups of infants who were administered the reflexology method before the vaccination process in terms of the mean durations of crying (p< 0.05). Karakuş Türker (32) who investigated the effect of breastfeeding and kangaroo methods during vaccination practices determined that the infants in the breastfeeding group cried for a shorter time than did those in the kangaroo group, though the difference was not statistically significant. The results of our study, which were consistent with the results in the literature, indicated that the total crying period of the infants in the experimental group was shorter than that of the infants in the control group, though the difference was not statistically significant. Our study results are consistent with the result of Karakuş Türker's (32) study in that there is statistically no significant difference between the durations of crying. It is thought that the difference between the studies in terms of the duration of crying of infants is due to the use of non-pharmacological methods through different

distraction practices and in different age groups.

Study Limitations

Flashcard study is a new method. This study determined the effect of only one method in relieving pain caused by vaccine administration.

Clinical Implications

One of the most important purposes of nursing care is reducing or eliminating pain. Since one of the first pain experiences of healthy babies is the vaccine application, the significance of pain management becomes apparent. It is thought that this method to be used in reducing pain during vaccine applications may be preferred by nurses in a greater number of clinics because they are practical, cheap, and easy to use. In addition, it is thought that it will contribute to nursing practices because it is a new and alternative method that can be used in infants to reduce pain during vaccination practices. Using black and white flashcards can help reduce pain during vaccine injections and increase the comfort of both infants and parents.

CONCLUSIONS

In conclusion, we determined that the black and white flashcards shown during vaccine applications were effective in reducing the pain level of infants, that the use of black and white flashcards did not create a significant difference between the infants concerning the duration of crying, but that we observed a decrease in the duration of crying in infants.

In line with these results, black-and-white information cards, which are an easy-to-apply method to reduce infants' pain sensitivity during vaccine administration, can be used by nurses. However, most other relevant studies were conducted with children aged 2 to 18 years. In the present study, the applicability and effectiveness of black and white flashcards in the treatment of pain in 4-6-month-old babies without any complications were demonstrated. Therefore, we expect that our study might contribute to the literature on the use of black and white flashcards in pain management in infants. According to the results obtained in the present study, we recommend that further studies should be conducted in which larger sample groups are compared by using different distraction methods.

Ethics Committee Approval: This study was approved by the Karamanoğlu Mehmetbey University non-interventional clinical research ethics committee (IRB number 04–14, March 28, 2018)

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- D.Y., N.C.S., Z.E.E.; Data Acquisition- D.Y., Z.E.E.; Data Analysis/Interpretation- N.C.S.; Drafting Manuscript- D.Y., N.C.S., Z.E.E. ; Critical Revision of Manuscript- D.Y., N.C.S., Z.E.E.; Final Approval and Accountability- D.Y., N.C.S., Z.E.E.

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RESEARCH ARTICLE / *ARAŞTIRMA MAKALESİ*

The Effect of Sociodemographic and Obstetric Characteristics of Pregnant Women on The Health of Newborn Babies: A Retrospective Study

Gebelerin Sosyodemografik ve Obstetrik Özelliklerinin Yenidoğan Sonuçlarına Etkisi: Retrospektif Bir Çalışma

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ABSTRACT

Objective: Birth history and obstetric characteristics of pregnant women are important factors which can determine the health of newborn babies. The aim of this study was to retrospectively examine the sociodemographic and obstetric characteristics of pregnant women and the health outcomes of newborns in deliveries performed in a hospital within a one year period.
Materials and Methods: This study is retrospective, descriptive and correlational . The target population consisted of pregnant women who were both followed up and delivered in a private hospital in a city center between 1st January and 31st December , 2022. Sample selection was not made in the study, which included 440 pregnant women who were followed up between the specified dates. The data were collected using the patient information form prepared by the researchers, patient files, and patient registration forms in the hospital. The data were then analyzed using a computer.
Results: The mean age was 29.47±4.64 years. All the pregnant women included in the study gave birth to live babies, and 53.9% of the babies were male. The mean birth weight was 3275.12±491.66 grams, and the mean height was 48.12±2.52 cm. The median Apgar score was 9 for the first minute of life. Age, pre-pregnancy weight, maternal weight at birth, reason for admission to hospital, delivery indications, number of abortions, number of multiple births and number of days in hospital were found to affect birth weight, height, head circumference and Apgar score in the first minute ($p<0.05$).
Conclusion: As the weight of the pregnant women increases, the weight, height and head circumference of the babies increase, and the Apgar score is lower in pregnant women with repeated cesarean section indications. It is recommended that women's health studies be planned both before and during pregnancy to improve neonatal growth and development indicators.

Keywords: newborn health, pregnancy, child health

ÖZ

Amaç: Gebelerin doğum öyküsü ve obstetrik özellikleri, yenidoğan sağlığını belirleyen önemli bir unsurdur. Bu araştırmanın amacı, bir hastanede son bir yıl içinde gerçekleştirilen doğumlarda gebelerin sosyodemografik ve obstetrik özellikleri ile yenidoğanların sağlık sonuçlarının retrospektif olarak incelenmesidir.
Gereç ve Yöntem: Araştırma, retrospektif tanımlayıcı ve ilişki arayıcı tiptedir. Araştırmanın evrenini, 01 Ocak-31 Aralık 2022 tarihleri arasında Ordu Özel Umut Hastanesi'nde hem izlemi hem de doğumu gerçekleşmiş gebeler oluşturmaktadır. Araştırmada örneklem seçimi yapılmamış olup belirtilen tarihler arasında takip edilmiş 440 gebe araştırmaya dahil edilmiştir. Araştırmanın verileri araştırmacılar tarafından hasta dosyalarından yararlanılarak hazırlanan hasta bilgi formu ile toplanmıştır. Veriler, hastanedeki hasta kayıt formları incelenerek toplanmıştır. Verilerin analizi bilgisayar ortamında analiz edilmiştir.
Bulgular: Araştırmaya katılan gebelerin yaş ortalaması 29.47±4.64'tür. Araştırmada gebelerin her biri birer tane bebek dünyaya getirmiş olup bebeklerin %53.9'u erkektir. Bebeklerin doğum ağırlığı ortalama 3275.12±491.66 gram, ortalama boy uzunluğu 48.12±2.52 cm'dir. Bebeklerin baş çevresi ortalaması 35.27±1.39 ve %99.1'inin 1. dakikada APGAR skoru 9'dur. Gebelerin yaşı, gebelik öncesi kilosu, doğumda kilosu, şikayeti, hikayesi, kürtaj sayısı, çoğul doğum sayısı ve hastanede yattığı gün sayısı ile doğum ağırlığı, boyu, baş çevresi ve APGAR skoru arasında istatistiksel olarak anlamlı fark vardır ($p<0.05$).
Sonuç: Araştırma sonuçlarına göre gebelerin kilosu arttıkça bebeklerin kilosu, boyu ve baş çevresi artmakta olup eski sezaryen olan gebelerde APGAR skoru daha düşüktür. Bu sonuçlar doğrultusunda; yenidoğan büyüme ve gelişme göstergelerini iyileştirmek için hem gebelik öncesi hem de gebelik sırasında kadın sağlığı çalışmalarının planlanması önerilir.

Anahtar Kelimeler: yenidoğan sağlığı, gebelik, çocuk sağlığı

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INTRODUCTION

Maternal health encompasses the well-being of women during pregnancy, labor, and after childbirth. Despite significant advances over the last two decades, maternal mortality still remains high, with 287,000 women developed pregnancy or childbirth complications in 2020. The primary causes of maternal mortality are hemorrhage, infection, high blood pressure, unsafe abortions, and deliveries. Maternal anemia, malaria infection, and heart disease also contribute indirectly to maternal mortality (1). The health status of women during pregnancy and after delivery, known as maternal health, significantly impacts neonatal health and overall outcomes. According to the World Health Organization, neonatal deaths account for nearly half of all under-five deaths, with one-third of newborns dying on the day of birth and almost three-fourths within the first week post-birth (2).

Maternal sociodemographic characteristics, diseases, and obstetric factors have a profound influence on neonatal health. Several studies conducted in different regions have revealed higher preeclampsia frequencies and lower Apgar scores in adolescent pregnant women compared to their adult counterparts (3). Additionally, younger pregnant women have shown higher rates of complications than their normal-aged counterparts in another study conducted in Düzce (4). A study in Hatay found that the risk of complications was higher in adolescent pregnancies due to anatomical and physiological immaturity (5). Moreover, adolescent pregnant women face risks of preterm delivery, intrauterine growth retardation, preeclampsia, anemia, fetal distress, low Apgar scores, and low birth weight, as reported in another study (6). A Central African study highlighted common poor perinatal outcomes, including fetal distress and the need for neonatal resuscitation, among adolescent pregnancies, with Apgar scores lower than 7 and frequent non-progressive deliveries (7). Additionally, maternal obesity has been emphasized as an important factor in increasing pregnancy complications and fetal-neonatal morbidity. Studies have shown that obese pregnant women experience gestational diabetes, hypertension, a higher frequency of cesarean sections due to cephalopelvic incompatibility or non-progressive labor, prolonged hospital stays, large babies, and an increased occurrence of maternal-fetal-neonatal adverse outcomes when compared to normal-weight pregnant women (8). In another study, preeclampsia emerged as one of the leading causes of maternal and perinatal morbidity and mortality, with approximately one in five pregnancies followed by eclampsia resulting in fetal loss, and a maternal mortality rate of 2.6% (9).

Health problems during or after delivery can stem from factors related to the mother or the baby. A retrospective hospital study found that the most common birth traumas included soft tissue damage, bone tissue damage, nerve tissue damage, intracranial hemorrhage, and intraabdominal organ damage. Maternal multiparity, diabetes, mode of delivery, gestational week, and birth weight were identified as factors related to birth trauma (10). Another study conducted in Bangladesh revealed the most common types of morbidity to be birth asphyxia, low birth weight, prematurity, and neonatal sepsis (11).

Evaluating the birth history, obstetric characteristics, and neonatal health outcomes of pregnant women plays a pivotal role in planning nursing interventions for women's health and designing public health studies for the protection and development of both maternal health during pregnancy and neonatal health. Accordingly, this study was designed to retrospectively examine the sociodemographic and obstetric profiles of pregnant women and the health outcomes of newborns from deliveries performed in a hospital during 2022 .

MATERIALS AND METHODS

Type of Research

The design of this study was retrospective, descriptive, and correlational in nature.

Study Population and Sample

The study's population comprised of pregnant women who received both follow-up care and delivery services at a private hospital in a city center from 1st January to 31st December 2022. The study did not involve sample selection, as all pregnant women (n=440) who underwent follow-up care within the specified timeframe were included in the research.

Data Collection Tools

The data for this study were gathered using a patient information form, meticulously prepared by the researchers, and by extracting relevant details from patient files. The questionnaire form included various aspects of sociodemographic characteristics pertaining to the pregnant women, including age, educational status, family type, employment status, spouse's occupation, and kinship status. Additionally, obstetric characteristics were probed, such as gravida, number of living children, number of miscarriages, abortions, stillbirths, and multiple births. Furthermore, essential information about the newborns was collected, including birth week, blood group, weight, height, head circumference, gender, and APGAR score.

Data Collection

The principal investigator undertook the data collection process by thoroughly examining patient record forms in the hospital's archive room. Several days a week, the investigator diligently reviewed patient files and completed a patient information form for each individual as part of the data collection procedure.

Data Evaluation

The data were analyzed using various statistical tests such as number, percentage, mean, median, and standard deviation, within a computerized environment. To assess statistical differences between variables, the study employed Mann-Whitney U, Wilcoxon t-test, Kruskal-Wallis, and Spearman correlation analysis, in addition to independent groups t-test, ANOVA analysis, Bonferroni correction, and Pearson correlation analysis. The adopted statistical significance level for the study was set at $p<0.05$.

Ethical Dimension

Before commencing the study, institutional permission was acquired from the hospital where the research took place, and ethical approval was obtained from Ordu University's ethics committee (Date: 28.04.2023, Number: 2023/122). As the analyzed data were extracted from patient records, and patient consent was obtained during hospitalization, no additional verbal or written consent was sought from the individuals included in the study sample.

FINDINGS

The study included pregnant women with a mean age of 29.47±4.64 years, and 53.9% of them were between 19-29 years old. Among the pregnant women, 34.1% had blood group 0 RH+. Additionally, 35.9% of the pregnant women held a bachelor's degree, while 33.4% were housewives. Notably, none of the pregnant women had a direct family relationship with their husbands, as indicated in Table 1.

Regarding pregnancy-related factors, the mean gravida was 1.82±0.97, and 44.6% of the pregnant women had been pregnant only once. Moreover, 58.2% of the pregnant women had no living children, 79.5% had never experienced a miscarriage, and 97% had never undergone an abortion. Furthermore, 1.8% of the pregnant women had a history of stillbirth, while 0.9% had a history of multiple births. The mean pre-pregnancy weight of the pregnant women was 66.5±14.1 kg, and 56.1% had a pre-pregnancy weight of between 37-65 kg. Concerning birth weight, the mean value for pregnant women was 81.0±14.1 kg, and 51.8% had a birth weight of between 51-79 kg. Regarding medical history, 14.5% of the pregnant women's mothers had type II diabetes mellitus, and 87% reported using medication during pregnancy. However, only 8.6% of the pregnant women reported smoking during pregnancy, with 78.9% of them smoking more than one cigarette daily. Notably, none of the pregnant women reported consuming alcohol. However, 98.4% reported consuming tea or coffee during pregnancy. The majority (99.5%) of pregnant women had received monthly examinations during pregnancy, and 83.4% had received two doses of the tetanus vaccine. The primary reason for hospital admission was pain for 93.9% of the pregnant women, and 33.7% underwent repeated caesarean section with the use of spinal anesthesia. The average duration of hospitalization was 1.15±0.40 days, and all pregnant women were discharged after receiving treatment, as indicated in Table 2.

In this study, each pregnant woman gave birth to one live baby, and 53.9% of the babies were male. The mean birth weight of the babies was 3275.12±491.66 grams, with 88.6% having a birth weight of between 2500-4000 grams. The mean height of

Table 1: Sociodemographic characteristics of pregnant women who participated in the study (n=440)

Characteristics	n	%
Age ($\bar{X}\pm ss$=29.47±4.64)		
Between 19-29	237	53.9
Between 30-44	203	46.1
Blood type		
A RH+	143	32.5
B RH+	62	14.1
O RH+	150	34.1
AB RH+	21	4.8
A RH-	30	6.8
B RH-	9	2.0
O RH-	19	4.3
AB RH-	6	1.4
Education level		
Primary school graduate	14	3.2
Secondary school graduate	39	8.9
High school graduate	155	35.2
Associate degree	68	15.5
Bachelor's degree	158	35.9
Graduate degree	6	1.4
Occupation		
Housewife	147	33.4
Worker	126	28.6
Civil servant	91	20.7
Shopkeeper	41	9.3
Unemployed	35	8.0
Kinship with spouse		
None	440	100.0

Table 2: Obstetric characteristics of pregnant women who participated in the study (n=440)

Characteristics	n	%
Gravida ($\bar{X}\pm ss$=1.82±0.97)		
1	196	44.6
2	158	35.9
3	63	14.3
4	16	3.6
5	3	0.7
6	3	0.7
7	1	0.2
Number of children alive ($\bar{X}\pm ss$=0.51±0.67)		
0	256	58.2
1	143	32.5
2	39	8.9
3	2	0.5
Number of miscarriages ($\bar{X}\pm ss$=0.26±0.61)		
0	350	79.5
1	72	16.4
2	13	3.0
3	4	0.9
6	1	0.2
Number of abortions ($\bar{X}\pm ss$=0.03±0.20)		
0	427	97.0
1	11	2.5
2	2	0.5
Number of stillbirths ($\bar{X}\pm ss$=0.01±0.13)		
0	432	98.2
1	8	1.8
Number of multiple births ($\bar{X}\pm ss$=0.009±0.09)		
0	436	99.1
1	4	0.9

Table 2: Continue

Characteristics	n	%
Pre-pregnancy weight ($\bar{X}\pm ss$=66.5±14.1)		
Between 37-65 kg	247	56.1
Between 66-121 kg	193	43.9
Weight at birth ($\bar{X}\pm ss$=81.0±14.1)		
Between 51-79 kg	228	51.8
Between 80-130 kg	212	48.2
Family history		
Maternal type II diabetes	64	14.5
No disease	376	85.5
Medications taken during pregnancy		
Yes	383	87.0
No.	57	13.0
Smoking during pregnancy		
Yes	38	8.6
No	402	91.4
Number of cigarettes smoked (n=38)		
One a day	5	13.1
More than once a day	30	78.9
One packet a day	3	8.0
Alcohol use during pregnancy		
Yes	0	0.0
No	440	100.0
Tea and coffee consumption during pregnancy		
Yes	433	98.4
No	7	1.6
Frequency of examination during pregnancy		
Once a week	2	0.5
Once a month	438	99.5
Administered tetanus vaccine dose		
1 dose	65	14.8
2 doses	367	83.4
3 doses	8	1.8
Reason for hospital admission		
Water breaking	27	6.1
Labor pain	413	93.9
Type of intervention		
C-section	440	100.0
Type of anaesthesia		
Spinal anaesthesia	440	100.0
Indication		
Head pelvis mismatch	126	28.6
Repeat caesarean section	148	33.7
Unspecified	166	37.7
Number of days in hospital ($\bar{X}\pm ss$=1.15±0.40)		
1	377	85.7
2	56	12.7
3	7	1.6
Result		
Discharged with treatment	440	100.0

the babies was 48.12±2.52 cm, and 40.9% of them measured 49-50 cm in length. Additionally, the mean head circumference of the babies was 35.27±1.39 cm, and 86.4% had a head circumference of 34-37 cm. The APGAR score of 99.1% of the babies in the first minute was 9, as presented in Table 3.

Table 3: Distribution of infant characteristics (n=440)

Characteristics	n	%
Sex		
Girl	203	46.1
Boy	237	53.9
Birth weight ($\bar{X}\pm ss$=3275.12±491.66)		
1400-2499 grams	22	5.0
2500-4000 grams	390	88.6
4001-4700 grams	28	6.4
Infant length ($\bar{X}\pm ss$=48.12±2.52)		
Between 38-48 cm	213	48.4
Between 49-50 cm	180	40.9
Between 51-53 cm	47	10.7
Infant head circumference		
($\bar{X}\pm ss$=35.27±1.39)	253	57.5
33 cm and below	32	7.3
between 34-37 cm	380	86.4
between 38-40 cm	28	6.4
APGAR score in the first minute		
6	1	0.2
7	1	0.2
8	2	0.5
9	436	99.1

The study found a statistically significant difference between the age of the pregnant women and the head circumference of the babies ($p<0.05$). Babies born to pregnant women aged between 30-44 years had larger head circumferences. Additionally, there was a significant association between the pre-pregnancy weight of pregnant women and birth weight, height, and head circumference ($p<0.05$). Babies born to heavier pregnant women tended to have higher birth weights, and wider head circumferences, and they tended to be longer in length. Similarly, a significant relationship existed between birth weight, height, and head circumference ($p<0.05$). Babies with higher birth weights also had greater head circumference and were longer in length.

Moreover, the study found a statistically significant difference between the reason for hospital admission and birth weight, head circumference, and APGAR score in the first minute ($p<0.05$). Babies of pregnant women admitted due to labor pain had higher birth weights, larger head circumferences, and higher APGAR scores in the first minute compared to pregnant women whose water had broken. Additionally, a statistically significant difference was observed between the indication for pregnant women and birth weight, height, head circumference, and APGAR score at the first minute ($p<0.05$). Babies of pregnant women with head-pelvis incompatibility had higher birth weights and lengths and wider head circumferences, while those with repeated caesarean section indication had lower APGAR scores in the first minute compared to those without any indication or with head and pelvis discrepancy, as shown in

Table 4. Also, the study did not find any statistically significant difference between educational level, occupation, family history, drug use during pregnancy, smoking during pregnancy, number of cigarettes smoked, tea/coffee consumption during pregnancy, frequency of examination during pregnancy, tetanus vaccination dose administered, and newborn birth weight, length, head circumference, and APGAR score in the first minute (p>0.05).

The correlation analysis of the obstetric characteristics of pregnant women in relation to the characteristics of infants is presented in Table 5. The results reveal a statistically significant correlation between the number of abortions and birth weight, head circumference, and the APGAR score in the first minute (p<0.05). There is a very weak negative correlation between the number of abortions and birth weight and head circumference, along with a weak negative correlation with the APGAR score in the first minute. This suggests that as the number of abortions increases, there is a slight decrease in birth weight, head circumference, and the APGAR score in the first minute. Similarly, the study found a statistically significant relationship between the number of multiple births and birth weight, height, and head circumference (p<0.05). The correlations in this case are very weak and positive, indicating that as the number of multiple births among pregnant women increases, there is a slight increase in birth weight, height, and head circumference of the infants. Furthermore, there was a statistically significant relationship between the number of days that pregnant women were hospitalized and birth weight, height, and head circumference (p<0.05). The correlations are very weak and negative, suggesting that as the number of days of hospitalization increases, there is a slight decrease in birth weight, length, and head circumference of the infants.

DISCUSSION

This study retrospectively analyzed the sociodemographic and obstetric characteristics of pregnant women who gave birth in a hospital during the year 2022, along with the health outcomes of newborns.

Birth weight, which is the first weight measurement taken immediately after birth, is a crucial parameter for assessing

Table 4: The distribution of infant characteristics according to certain sociodemographic and obstetric characteristics of pregnant women (n=440)

Characteristics	Birth weight	Length	Head circumference	APGAR in the first minute
Age				
Between 19-29	t=-0.178	z=-0.571	z=-2.212	z=-0.153
Between 30-44*	p=0.859	p=0.568	**p=0.027**	p=0.878
Pre-pregnancy weight				
Between 37-65 kg	t=-4.946	z=-3.397	z=-5.168	z=-1.774
Between 66-121 kg*	**p=0.000**	**p=0.001**	**p=0.000**	p=0.076
Weight at birth				
Between 51-79 kg	t=-5.176	z=-2.318	z=-4.874	z=-0.929
Between 80-130 kg*	**p=0.000**	**p=0.020**	**p=0.000**	p=0.353
Reason for hospital admission				
Water breaking	t=-3.356	z=-1.866	z=-1.968	z=-5.754
Labor pain*	**p=0.001**	p=0.062	**p=0.049**	**p=0.000**
Indication				
Head pelvis mismatch[a]	F=26.814	KW=33.117	KW=32.487	KW=7.946
Repeat caesarean section[b]	**p=0.000**	**p=0.000**	**p=0.000**	**p=0.019**
Unspecified[c]	a>b,c	a>b,c	a>b,c	a,c>b

* The group from which the significance originates.
t: Independent groups t test, F=OneWay Anova, z=Mann Whitney U, KW=Kruskal Wallis

Table 5: Correlation analysis of obstetric characteristics of pregnant women and infant characteristics (n=440)

Characteristics	Birth weight	Length	Head circumference	APGAR in the first minute
Gravida	r=-0.042	ρ=-0.052	ρ=0.024	ρ=-0.089
Number of children alive	r=0.018	ρ=-0.035	ρ=0.106	ρ=-0.007
Number of miscarriages	r=-0.018	ρ=-0.003	ρ=-0.068	ρ=0.048
Number of abortions	r=-0.197*	ρ=-0.077	ρ=-0.116**	ρ=-0.273*
Number of stillbirths	r=0.031	ρ=0.034	ρ=0.019	ρ=0.013
Number of multiple births	r=0.140*	ρ=0.142*	ρ=0.099**	ρ=0.009
Number of days in hospital	r=-0.110**	ρ=-0.118**	ρ=-0.102**	ρ=-0.028

r: Pearson correlation analysis, ρ: Spearman correlation analysis, *p<0.01, **p<0.05

neonatal health. According to the World Health Organization, a birth weight of between 2500-4000 grams is considered normal for healthy newborns, while a birth weight below 2500 grams is classified as a low birth weight, and a birth weight above 4000 grams is categorized as a high birth weight (12). Existing literature highlights that both low and high birth weight can have significant implications for the neonatal health and future well-being of the infant (13,14). In this study, the majority of newborns fell within the normal birth weight range, but there were also cases of low and high birth weight. Notably, there was a statistically significant difference in birth weight relating to various factors, including the pre-pregnancy weight, weight at birth, reason for admission to the hospital, indication for birth, number of abortions, number of multiple births, and the duration of hospitalization ($p<0.05$). Newborns of pregnant women who were overweight before pregnancy and at birth, pregnant women admitted due to pain, pregnant women with head and pelvis incompatibility, those with multiple births, and women with fewer abortions and shorter hospitalization durations had higher birth weights. A retrospective study conducted in the United States of America revealed that low weight gain during pregnancy was associated with increased maternal and perinatal mortality rates, as well as unfavorable birth outcomes (15). The process of intrauterine growth and development is critical and vulnerable in the human life cycle, and birth weight serves as a reliable indicator of this process. It is an essential factor for assessing the newborn's potential for survival, growth, and long-term physical and psychosocial development (16). Another study in Poland found a significant relationship between neonatal birth weight and maternal body mass index before pregnancy and weight gain during pregnancy. It was reported that women who gained less weight during pregnancy had a higher likelihood of giving birth to a newborn with low birth weight compared to those who gained more weight (17).

The length of newborns is another critical parameter to consider for neonatal health, as it directly correlates with height throughout infancy and into adulthood (18). A normal length at birth is typically regarded as 49-50 centimeters (19). In our study, the mean length of the infants was measured to be 48.12±2.52 cm, with 40.9% of them falling within the range of 49-50 cm. Neonatal length can be influenced by various factors, including genetic, maternal nutrition, and environmental factors (18,20). In our study, we observed a statistically significant difference in length based on several factors, such as pre-pregnancy weight, weight at delivery, indication for birth, number of multiple births, and duration of hospitalization ($p<0.05$). Infants of pregnant women who had higher pre-pregnancy weight and birth weight, those with head and pelvis incompatibility, and those with a higher number of multiple births tended to be longer in length. Conversely, infants of women with more days of hospitalization were shorter. A retrospective study in Pakistan indicated that a higher mid-arm circumference of the mother, additional meal consumption during pregnancy, and a high hemoglobin level in the mother were predictors of infant length (21).

Neonatal head circumference measurement is another crucial parameter that warrants close monitoring for neonatal health, growth, and development. According to the International Centre for Disease Control, normal values for mean head circumference at birth typically fall within the range of approximately 34-37 cm (22). In our study, the mean head circumference of the infants was 35.27±1.39 cm, with 86.4% falling within the range of 34-37 cm. We identified a statistically significant difference in head circumference based on various factors, including maternal age, pre-pregnancy weight, weight at birth, indication for hospital admission, number of abortions, number of multiple births, and duration of hospitalization ($p<0.05$). Pregnant women between the ages of 30-44 years, those with higher pre-pregnancy and birth weights, those with complaints of pain, those with head and pelvis incompatibility, and those with a higher number of multiple births tended to have infants with larger head circumferences. Conversely, infants of women with a higher number of abortions and longer hospitalization durations had smaller head circumferences. Studies have shown that parental head circumference and birth weight can impact infant head circumference (23). Additionally, in a cohort study encompassing South Asian and African countries, factors affecting infant head circumference were identified as body weight, socioeconomic status, and maternal height (24). Our study aligns with the existing literature, emphasizing the significance of certain sociodemographic, obstetric characteristics, and genetic factors of the pregnant women in head circumference measurement.

Neonates can undergo a clinical evaluation using the Apgar score test immediately after birth, allowing for a quick and practical assessment of their physical status. This evaluation helps in determining the need for any additional medical or emergency care (25). In our study, 99.1% of the babies received an Apgar score of 9 in the first minute. However, we observed that the Apgar score was lower in pregnant women whose water had broken, those with indications for repeated caesarean section, and those with a history of more abortions ($p<0.05$). Consistent with previous research, advanced-age pregnant women and those with threatened miscarriage in the first trimester have been associated with lower Apgar scores (26,27). Other studies have identified factors such as gravidity, parity, haemoglobin level during pregnancy, prenatal haemorrhage, membrane status, delivery time, mode of delivery, type and indication of caesarean section to be linked with sudden low Apgar scores (28). In Ethiopia, fetal birth weight less than 2500 grams, time from skin incision to delivery, pregnancy-induced hypertension, antenatal haemorrhage, general anaesthesia, amniotic fluid with meconium, and emergency caesarean section were found to be associated with Apgar scores (29). Likewise, indications for cesarean section, type of anaesthesia, type of surgery, preterm delivery, preeclampsia, and anaemia were also found to be associated with low Apgar scores in another study (30). Our study aligns with the existing literature, as we also found that a higher Apgar score is expected in cases of healthy pregnancies and non-risk labors.

CONCLUSION AND RECOMMENDATIONS

Based on an analysis of patient files, the study revealed that the average age of pregnant women was below 30 years. The newborns had a mean birth weight exceeding 3000 grams, an average length of approximately 50 cm, and a head circumference of around 35 cm. Furthermore, the APGAR score in the first minute was high. Various factors related to pregnant women, such as their weight before pregnancy and at birth, reason for hospital admission, indications for birth, history of previous miscarriage, number of abortions, number of multiple births, and duration of hospitalization, had a notable impact on the growth and development of newborns. Notably, an increase in the weight of pregnant women correlated with higher birth weight, length , and head circumference of the babies. Additionally, pregnant women with indications for repeated caesarean sections tended to have lower APGAR scores in the first minute. Based on these study findings, it is advisable to plan women's health activities both before and during pregnancy in order to enhance neonatal growth and development indicators.

Ethics Committee Approval: This study was approved by the ethics committee of the Ordu University's ethics committee (Date: 28.04.2023, Number: 2023/122).

Informed Consent: Informed consent was not obtained as it was a retrospective study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- E.Ş.; Data Acquisition- E.Ş.; Data Analysis/Interpretation- G.D.B.; Drafting Manuscript- E.Ş., G.D.B.; Critical Revision of Manuscript- E.Ş., G.D.B.; Final Approval and Accountability- E.Ş., G.D.B.

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RESEARCH ARTICLE / *ARAŞTIRMA MAKALESİ*

The Effect of Sleep Hygiene Education on Sleep Quality of Children with Intellectual Disabilities and Their Mothers According to The Health Promotion Model

Zihinsel Engelli Çocuk ve Annelerine Sağlığı Geliştirme Modeline Göre Verilen Uyku Hijyeni Eğitiminin Uyku Kalitesine Etkisi

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ABSTRACT

Objective: This study was conducted to investigate the effect of sleep hygiene education on sleep quality of children with intellectual disabilities and their mothers according to the health promotion model.
Materials and Methods: The study enrolled 80 children with intellectual disabilities ranging in age from 2 to 18 years and their mothers (intervention and control groups). The socio-demographic data form of the mother and child, Child Sleep Habits Questionnaire (CSHQ), Pittsburgh Sleep Quality Index (PSQI), and sleep sensor device were used for data collection. The SPSS 25.0 data analysis program was used in the statistical analysis of the data obtained in the study, and the chi-square test, t-test, Mann U Whitney test and Pearson correlation were used for data analysis.
Results: The children and mothers in the intervention and control groups were found to be homogeneous within their respective groups, and there was a statistically significant difference between the sleep data and the mean scores of children with intellectual disabilities in the intervention and control groups before and after sleep hygiene education ($p<0.05$). It was determined that there was a statistically significant difference between the sleep data and the mean scores of the mothers in the intervention group before and after the education ($p<0.05$).
Conclusion: Sleep hygiene education has been shown to enhance the development of regular sleep behaviours in children with intellectual disabilities and their mothers.

Keywords: child with intellectual disabilities, health promotion model, mother, sleep hygiene education

ÖZ

Amaç: Bu araştırma, sağlığı geliştirme modeline göre zihinsel engelli çocuklar ve annelerinin uyku hijyeni eğitiminin uyku kalitesine etkisini araştırmak amacıyla yapılmıştır.
Gereç ve Yöntem: Çalışmaya yaşları 2 ile 18 arasında olan zihinsel engelli 80 çocuk ve anneleri (deney ve kontrol grupları) dahil edilmiştir. Veri toplama aracı olarak anne ve çocuğun sosyo-demografik veri formu, Çocuk Uyku Alışkanlıkları Anketi (CSHQ), Pittsburg Uyku Kalitesi İndeksi (PSQI) ve uyku sensörü cihazı kullanılmıştır. Araştırmada elde edilen verilerin istatistiksel analizinde SPSS 25.0 veri analiz programı kullanılmıştır. Verilerin analizinde ki-kare testi, t-testi, Mann U Whitney testi ve Pearson korelasyonu kullanılmıştır.
Bulgular: Deney ve kontrol grubundaki çocuk ve annelerin kendi grupları içinde homojen olduğu, deney ve kontrol grubundaki zihinsel engelli çocukların uyku hijyeni eğitimi öncesi ve sonrası uyku verileri ile puan ortalamaları arasında istatistiksel olarak anlamlı bir fark olduğu görülmüştür ($p<0,05$). Deney grubundaki annelerin eğitim öncesi ve sonrası uyku verileri ile ortalama puanları arasında istatistiksel olarak anlamlı bir fark olduğu belirlenmiştir ($p<0,05$).
Sonuç: Uyku hijyeni eğitiminin zihinsel engelli çocuklarda ve annelerinde düzenli uyku davranışlarının gelişimini arttırdığı saptanmıştır.

Anahtar Kelimeler: zihinsel engelli çocuk, sağlığı geliştirme modeli, anne, uyku hijyeni eğitimi

*This study was conducted in the doctoral thesis (It is a quantitative work).

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INTRODUCTION

Children with intellectual disabilities are individuals who have deficiencies or limitations in social and daily life skills in terms of mental functions and need special education and supports (1). It has been stated that children with intellectual disabilities experience physical, psychological and social problems in addition to their own disabilities (2,3). The most common of these problems is sleep problems that occur as a result of disruption of sleep patterns that affect the quality of life of both the child and the family (4).

It has been determined that children with intellectual disabilities have sleep problems such as difficulty falling asleep, drowsiness, waking up frequently, having nightmares/ bad dreams, talking during sleep, teeth grinding, somnolence, snoring, temporary cessation of breathing during sleep apnea and involuntary awakening (4,5,6,7).

Sleep hygiene is a critical aspect of sleep health maintenance. Sleep hygiene is described as engaging in activities that promote sleep (maintaining regular sleep patterns) and abstaining from behaviors that disrupt sleep (watching movies, interesting conversations or consuming caffeine-containing products) (8). Therefore, it is essential for children with intellectual disabilities and their mothers to develop healthy sleep habits, routines, and behaviors (9). Providing sleep hygiene education to children and their parents who have such problems will improve their sleep quality (10).

Sleep hygiene education is a method for enhancing the quality of sleep (11). It is critical for preventing sleep problems and defects associated with sleep disorders (12). It has been established that research and programs focusing on sleep hygiene education are beneficial for treating sleep problems. Austin et al. (13) conducted a study in which six parents of children with developmental disabilities between the ages of 3-7 participated in sleep education. After 15 weeks of sleep education, it was discovered that children's sleep problems decreased. In another study conducted with parents of children with ASD (autism spectrum disorder) between the ages of 2-10 revealed that sleep education had a positive impact on sleep duration (14). The effectiveness of a sleep education program provided in a small group arrangement was examined in the study by Reed et al. (15). While the focus groups consisted of families of 3-5 individuals, the study enrolled a total of 20 families with ASD. The ages of the children ranged from 3 to 10. The research indicates that the sleep education program positively impacts children's sleep behaviors and daytime behavior and their families' stress levels.

Implementing health promotion practices for both children and mothers will help minimize the negative effects of sleep deprivation (5). Health promotion is a term that refers to the activities aimed at optimizing the health potential of individuals, families, society, community groups and enhancing the level of well-being, and also maximizing the individual's current health behavior (16). Nola J. Pender first developed the health promotion model was first in 1987 and was revised in 1996. The model's purpose is to describe the components of lifestyle-related health promotion behaviors, evaluate the factors that may influence an individual's experiences and perceptions of health behavior and aid health professionals in comprehending the determinants of healthy lifestyle behaviors (17). In addition, the model is capable of guiding health promotion practices (18). To minimize sleep problems, it is critical to provide sleep hygiene education to children with intellectual disabilities and their mothers according to a health promotion model.

This study was conducted to investigate the effect of sleep hygiene education on sleep quality of children with intellectual disabilities and their mothers according to the health promotion model.

MATERIALS AND METHODS

Design

This research is a quasi-inversion study with a pretest-post-test control group design.

Participants

Children with intellectual disabilities between the ages of 2-18 and their mothers who had sleep problems, were included in the study. It was calculated based on previous studies with the G. Power-3.1.9.2 program to determine the sample size (13,19,20). As a result of the analysis, the sample size of the intervention and control groups was calculated as 80, 40 in the intervention group and 40 in the control group, with a level of α= 0.05 and a theoretical power of 0.80, an effect size of 0.70. Children were randomly divided into 2 groups according to the calculated groups from the group they belonged to.

Inclusion and exclusion criteria for research

Sampling inclusion criteria mother's.

- Having a child with intellectual disability aged 2-18,
- Voluntary and willing to participate in the study
- Not using regular sleeping pills
- Mother's sleep routines irregularity *children.*
- 2-18 age group children with intellectual disability
- Consent from the family

Mother's sampling exclusion criteria

- Mother's refusal to voluntarily participate in the study.
- Mothers who use sleeping pills regularly
- Mothers with no sleep problems *children.*
- Children without intellectual disability
- Aged other than 2-18 years
- Without sleep problems.

Research questions

- Is there a relationship between the effect of sleep hygiene training given to mentally retarded children and their mothers according to the health promotion model on sleep quality?

Data collection

In data collection, Sociodemographic Data Form of mother and child, which includes questions about the sociodemographic characteristics of children with intellectual disabilities and their mothers, prepared by the researchers using the literature; Child Sleep Habits Questionnaire (CSHQ), Pittsburgh Sleep Quality Index (PSQI) and Sleep Sensor Device were used.

Sociodemographic data form for mother and child: It consists of 8 questions to determine the sociodemographic characteristics of mothers and children.

Child sleeping habits questionnaire (CSHQ): The Children's Sleep Habits Questionnaire (CSHQ) - Abbreviated Form, developed by Owens et al. in 2000 to investigate children's sleep habits and related problems, consists of 33 items in total (21). The Turkish validity and reliability study (22) of the scale was conducted by colleagues including bedtime resistance (1,3,4,5,6,8 items), delay in falling asleep (item 2), sleep duration (items 9,10,11).), sleep anxiety (items 5,7,8,21), night awakenings (items 16,24,25), para-somnias (12,13,14,15,17,22,23), sleep Eight subscales were defined, which can be listed as respiratory impairment (18,19,20 items), and waking up in the morning/daytime sleepiness (items 26,27,28,29,30,31,32,33). Internal consistency of the scale and subscales was calculated using the Cronbach's alpha coefficient. The Cronbach's alpha coefficient was found to be 0.78.

The Pittsburgh Sleep Quality Index (PSQI): PSQI was developed by Buysse et al. in 1989 and has been shown to have adequate internal consistency, Cronbach alpha = 0.80), test-retest reliability and validity (23). The validity and reliability study of PSQI (Pittsburgh *Sleep* Quality Index) in our country was performed by (24). In this study, the Cronbach's alpha value of the scale was found to be 0.79 (Cronbach's alpha = 0.79). PSQI is a self-report scale that assesses sleep quality and disturbance over a one-month period. In the scale consisting of 24 questions, 19 questions are answered by the person, while the last 5 questions are filled by the person's roommate or bed partner. With 19 questions answered by the individual, 7 sub-dimensions are evaluated, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping pills, and daytime dysfunction.

Sleep sensor device (Beurer): The sleep device (Beurer) was used to evaluate the pulse and breathing frequency, apnea status, sleep-wake process of the individual during sleep. Sleep Score recording. Here the application creates an index from the saved values (between 0 and 100). This index provides information on daily sleep quality. The higher the sleep score, the higher the sleep quality (25).

Intervention

Pre-test: In the pre-test of children with intellectual disabilities aged 2-18 and their mothers in the intervention and control groups, the data were obtained from the mothers by using the "Sociodemographic Data Form of the Mother and Child", the Child Sleep Habits Questionnaire (CSHQ), the Pittsburgh Sleep Quality Index (PSQI), and the Sleep Sensor Device. The data were collected through face-to-face interviews with mothers. As data collection tools, questionnaires and scales were applied to the mothers in the school environment in the form of 10 minutes, and the sleep sensor device was given to the mothers by teaching them to use the sleep sensor device for 1 week in such a way that they would put their children in their beds, at the time of going to bed in the evening and waking up in the morning.

Sleep hygiene education: In the first stage of the research, the content/module of sleep hygiene education to children with intellectual disabilities and their mothers according to the health promotion model was prepared according to the data obtained from in-depth data interviews. The content of the training was prepared by using the interviews with the mothers and the literature. The education was given to mothers (intervention groups, n=40) of children with intellectual disabilities ranging in age from 2 to 18 years. The researcher conducted the education for eight weeks, two hours each day and two days a week. Each session lasted approximately 60 minutes. The education was intended to be conducted in groups of five participants, but mothers were trained individually in the research due to the pandemic. The education process began with the establishment of regulations for the opening, introduction, and meeting (10 minutes). In addition, the presentation on sleep hygiene education for children with intellectual disabilities and their mothers (40 minutes) was given according to the health promotion model and included the distribution and explanation of written education material (general information about sleep, factors that hinder and facilitate sleep, and information to increase sleep hygiene) (10 minutes).

Post-test: In the post-tests, the Child Sleep Habits Questionnaire, the Pittsburgh Sleep Quality Index (PSQI), and the Sleep Sensor Device were re-administered to the children in the intervention and control groups. The data collection tools used before the training were applied to the mothers again in the form of questionnaires and scales after the training, in the form of 10 minutes in the school environment, and the sleep sensor device was given to the mothers to use the sleep sensor device for 1 week, in the form of putting them in their children's beds, for the timing of going to bed in the evening and waking up in the morning.

Variables of the study

Independent Variable: Mother's age, marital status, educational status, number of children, child's age, gender, diagnosis, mental disability, sleep hygiene education.

Dependent Variable: The Pittsburgh Sleep quality index mean score, child sleep habits questionnaire mean score (sleeping problem, sleep behavior, departure time, bedtime, wakefulness), sleep sensor device indicators (night sleep time, daytime sleep time, total sleep time, nighttime sleep time, morning wake-up time, number of sleep interruptions, time to fall asleep, time to wake up in the morning).

Ethics Committee Approval

Approval from Kıbrıs İlim University Ethics Committee (decision no: 09, Date: 26.12.2019) and the official permission of the schools where the research was conducted. Verbal and written consent was obtained from the mothers.

Statistical analysis

SPSS 25.0 data analysis software was used in the statistical analysis of the data obtained during the study. Parametric tests were used for statistical evaluations for data with normal distribution (t-test) and non-parametric tests (Mann Whitney U and Kruskal Wallis test, Wilcoxon test) were used when it was not suitable for normal distribution. Chi-square analysis was used to test the homogeneity between categorical variables. Pearson correlation was used to test the relationship between continuous variables.

RESULTS

Findings related to socio-demographic characteristics

Socio-demographic characteristics of the mothers are shown in Table 1. There was no statistically significant difference between sociodemographic characteristics (p>0.05), and the groups were homogeneous. Socio-demographic characteristics of Children are shown in Table 2. There was no statistically significant difference between the socio-demographic characteristics of the children (p>0.05), and the groups were homogenous.

Table 1: Distribution of mothers by sociodemographic characteristics

		Experiment		Control		
		n	%	n	%	p
Age	20-24	4	10.0	3	7.5	1.494 0.738
	25-29	6	15.0	7	17.5	
	30-34	8	20.0	12	30.0	
	35 and over	22	55.0	18	45.0	
Marital status	Maried	33	82.5	36	90.0	0.949 0.518
	Single	7	17.5	4	10.0	
Edcation status	No education	1	2.5	0	0.0	4.047 0.542
	Primary school	11	27.5	8	20.0	
	Middle school	8	20.0	10	25.0	
	High school	14	35.0	18	45.0	
	University	6	15.0	4	10	
Number of children	1	11	27.5	10	25.0	4.145 0.245
	2	20	50.0	19	47.5	
	3	6	15.0	11	27.5	
	4 and over	3	7.5	0	0.0	
Total		**40**	**100.0**	**40**	**100.0**	

*p<0.05

Table 2: Distribution of children according to their sociodemographic characteristics

		Experiment		Control		
		n	%	n	%	p
Age	2-6	9	22.5	7	17.5	0.587 0.941
	7-10	10	25.0	11	27.5	
	11-15	11	27.5	13	32.5	
	16-18	10	25.0	9	22.5	
Gender	Girl	24	60.0	20	50.0	0.808 0.500
	Boy	16	40.0	20	50.0	
Diagnosis	Autism	16	40.0	24	60.0	7.063 0.070
	Down syndrome	9	22.5	11	27.5	
	Asperger syndrome	1	2.5	0	0.0	
	Other	14	35.0	5	12.5	
Disability level	Very light	2	5.0	1	2.5	1.780 0.931
	Light	20	50.0	19	47.5	
	Middle	15	37.5	17	42.5	
	Severe	2	5.0	3	7.5	
	Very severe	1	2.5	0	0.0	
Total		**40**	**100.0**	**40**	**100.0**	

*p<0.05

Table 3: Comparison of PSQI score averages of mothers in the experimental and control groups

	Pre-Training					
Group	**Min**	**Max**	**$\bar{X}$**	**SS**	**Test Value**	**p**
Experiment	5.00	17.00	11.70	2.43	1.000**	0.321
Control	7.00	16.00	11.17	2.26		
	Post-Training					
	Min	**Max**	**$\bar{X}$**	**SS**	**Test Value**	**p**
Experiment	7.00	12.00	9.32	1.24	774.500***	0.801
Control	5.00	15.00	9.47	1.78		

*p<0.05, ** t test, ***Mann Whitney U test

Comparison of psqi score averages of mothers in the experimental and control groups

The data on the comparison of the mean PSQI scores of the mothers in the intervention group who received sleep hygiene education and the mothers in the control group are shown in Table 3. There was no statistically significant difference between the mean PSQI scores of the mothers in the intervention and control groups before education (p=0.321). And there was no statistically significant difference between the mean PSQI scores of mothers in the study and control groups (p=0.801).

Comparison of the sleep habits questionnaire mean scores of the children in the experimental and control groups

Table 4: Comparison of the sleep habits questionnaire mean scores of the children in the experimental and control groups

	Pre-Training						
	Group	**Min**	**Max**		**SS**	**Test Value**	**p**
Bedtime resistance	**Experiment**	7.00	15.00	10.82	2.29	-3.241**	**0.002***
	Control	10.00	14.00	12.10	0.95		
Delay in falling asleep	**Experiment**	1.00	3.00	1.95	0.78	-0.594**	0.556
	Control	2.00	3.00	2.02	0.15		
Sleep time	**Experiment**	3.00	9.00	6.17	1.17	-1.659**	0.101
	Control	4.00	8.00	6.55	0.81		
Sleep anxiety	**Experiment**	4.00	12.00	7.30	2.16	-1.535**	0.131
	Control	4.00	9.00	7.87	0.96		
Night awakenings	**Experiment**	3.00	9.00	5.17	1.75	-2.632**	**0.011***
	Control	3.00	7.00	6.02	1.04		
Parasomnias	**Experiment**	7.00	17.00	10.85	2.66	-6.571**	**0.000***
	Control	11.00	19.00	14.20	1.81		
Sleep disturbance	**Experiment**	3.00	9.00	4.70	1.78	-2.477**	**0.015***
	Control	3.00	9.00	5.65	1.64		
Daytime sleepiness	**Experiment**	6.00	20.00	12.97	3.73	-4.596**	**0.000***
	Control	12.00	18.00	15.80	1.09		
Total	**Experiment**	44.00	81.00	59.95	9.24	-6.288**	**0.000***
	Control	57.00	81.00	70.22	4.61		
	Post-Training						
	Group	**Min**	**Max**		**SS**	**Test Value**	**p**
Bedtime resistance	**Experiment**	6.00	10.00	7.40	1.29	-12.672**	**0.000***
	Control	6.00	14.00	11.42	1.53		
Delay in falling asleep	**Experiment**	1.00	2.00	1.30	0.46	-6.789**	**0.000***
	Control	1.00	3.00	1.95	0.38		
Sleep time	**Experiment**	3.00	6.00	3.87	0.93	-8.798**	**0.000***
	Control	3.00	8.00	5.60	0.81		
Sleep anxiety	**Experiment**	4.00	7.00	4.85	1.02	-13.842**	**0.000***
	Control	4.00	10.00	8.02	1.02		
Night awakenings	**Experiment**	3.00	5.00	3.50	0.67	-11.320**	**0.000***
	Control	3.00	7.00	5.80	1.09		
Parasomnias	**Experiment**	7.00	11.00	8.10	1.05	-17.462**	**0.000***
	Control	11.00	19.00	13.97	1.84		
Sleep disturbance	**Experiment**	3.00	6.00	3.67	0.82	297.500***	**0.000***
	Control	3.00	9.00	5.50	1.72		
Daytime sleepiness	**Experiment**	6.00	13.00	8.57	1.79	-18.311**	**0.000***
	Control	11.00	18.00	15.37	1.51		
Total	**Experiment**	33.00	50.00	41.27	3.43	1.000**	**0.000***
	Control	49.00	77.00	67.65	5.25		

*p<0.001, ** t test, ***Mann Whitney U test

The data regarding the comparison of the children's sleep habits questionnaire mean scores of children in the intervention and control groups are shown in Table 4. There was a statistically significant difference between the resistance to bedtime, waking at night, parasomnias, respiratory disturbances during sleep, and daytime drowsiness, and the total scores of the questionnaire compared to the groups before education ($p<0.01$). As a result, it negatively affects sleep quality. In addition, there was a statistically significant difference between the resistance to bedtime, waking at night, parasomnias, respiratory disturbances during sleep, and daytime drowsiness, and the total scores of the questionnaire compared to the groups after education ($p<0.01$). After the education, the study group has better scores (lower) more items than before treatment. This is an important result because it shows the effectiveness of the treatment.

Comparison of the sleep device data used by the children in the experimental and control groups before and after

The data on the comparison of the sleep tracker indicators of the children in the intervention and control groups before and after the education is shown in Table 5. Compared to the groups before the education, there was a statistically significant difference between the duration of daytime sleep, waking time

Table 5: Comparison of the sleep device data used by the children in the experimental and control groups before and after education

Pre-Training							
	Group	**Min**	**Max**		**SS**	**Test Value**	**p**
Sleep score	**Experiment**	20.00	89.00	65.12	16.61	697.500***	0.323
	Control	46.00	89.00	66.57	8.58		
Night sleep time	**Experiment**	2.00	8.00	4.70	1.36	-1.568**	0.121
	Control	2.00	8.00	5.25	1.75		
Daytime sleep time	**Experiment**	0.00	6.00	2.35	1.57	574.500***	**0.024***
	Control	0.00	3.00	1.55	0.90		
Total sleep time	**Experiment**	0.13	9.16	5.98	2.21	697.500***	0.324
	Control	3.21	8.54	6.16	1.15		
Night wake up time	**Experiment**	0.00	5.00	2.42	1.59	2.472**	**0.016***
	Control	1.00	4.00	1.70	0.93		
Morning wake up time	**Experiment**	0.30	10.08	6.38	2.43	731.000***	0.507
	Control	2.30	23.56	7.64	2.90		
Number of sleep splits	**Experiment**	0.00	5.00	3.00	1.24	298.000***	**0.000***
	Control	1.00	8.00	1.65	1.29		
Time to fall asleep	**Experiment**	2.00	25.00	8.97	5.80	746.000***	0.600
	Control	3.00	15.00	7.17	2.39		
Morning wake up time	**Experiment**	3.00	20.00	8.95	4.15	505.500***	**0.004***
	Control	1.00	10.00	6.42	2.28		
Post-Training							
	Group	**Min**	**Max**		**SS**	**Test Value**	**p**
Sleep score	**Experiment**	20.00	93.00	56.02	18.90	535.500***	**0.011***
	Control	47.00	84.00	66.72	10.22		
Night sleep time	**Experiment**	2.00	5.00	3.35	0.85	0.861**	0.392
	Control	1.20	6.50	3.17	1.00		
Daytime sleep time	**Experiment**	0.00	3.00	0.87	0.99	1.047**	0.298
	Control	0.00	3.00	0.65	0.86		
Total sleep time	**Experiment**	1.41	8.18	5.29	1.99	-3.305**	**0.001***
	Control	3.09	11.31	6.67	1.71		
Night wake up time	**Experiment**	0.30	23.46	3.07	3.41	753.000***	0.651
	Control	0.50	6.26	2.65	0.96		
Morning wake up time	**Experiment**	6.07	10.34	7.70	1.35	1.895**	0.062
	Control	3.58	10.50	7.14	1.30		
Number of sleep splits	**Experiment**	1.00	12.00	4.00	2.50	466.000***	**0.001***
	Control	0.00	4.00	2.22	1.07		
Time to fall asleep	**Experiment**	0.00	15.00	5.47	2.96	1.815**	0.073
	Control	0.00	10.00	4.27	2.95		
Morning wake up time	**Experiment**	1.00	10.00	4.30	2.58	-0.358**	0.721
	Control	0.00	12.00	4.52	3.02		

*p<0.05, ** t test, ***Mann Whitney U test

at night, the number of sleep interruptions, and the waking time in the morning (p<0.05). According to the scoring results, it was determined that sleep quality increased after sleep hygiene training.

Examination of the relationship between the sleep quality mean scores of mothers and children in the experimental group

The data on the examination of the relationship between the sleep quality mean scores of the mothers and children in the intervention group are shown in Table 6. There was a statistically significant difference between the sleep quality scores of the children (CSHQ) and mothers (PSQI) in the intervention group, and there was a strong positive correlation between the sleep quality scores after sleep hygiene education (p=.086, p=.072 p<0.05).

DISCUSSION

Table 6: Examination of the relationship between the sleep quality mean scores of mothers and children in the experimental group

	Child Sleeping Habit Questionnaire (CSHQ)	PSQI
Child Sleeping Habit Questionnaire	1.000	0.323
p	-	**0.042***
PSQI Scale		1.000
p		-
Sleep Hygiene Training		
p	**0.086***	**0.072***

*p<0.05 Pearson correlation

Age is a significant sociodemographic characteristic. In the study conducted (14) on the sleep of children with intellectual disabilities and mothers, 62% of the mothers were 30 years and older, 10% were 20-30 years old in the intervention group, and 21% of the mothers were 35 years and older, and 7% were 20-30 years old in the control group. The marital statuses of the mothers were discovered to be 82.5% married and 17.5% single in the intervention group, whereas 90% of the mothers were married and 10% were single in the control group. In a randomized parallel study evaluating the sleep problems of children with special needs, it was concluded that 81.4% of the mothers were married and 18.6% were single in the intervention group, whereas 72% of the mothers were married and 28% were single in the control group (26). In the data regarding the education status of the mothers, it was determined that 35% of the mothers were high school graduates, and 27.5% were primary school graduates in the intervention group, whereas 45% of the mothers were high school graduates and 25% were secondary school graduates in the control group.

In the study conducted on the sleep problems of preschool children with cerebral palsy and intellectual disability, it was stated that 65% of the children were 13 years old, 30% were 6 years old, and 5% were 1 year old (27). According to the gender data from the sociodemographic characteristics of the children, 60% of the children were girls, and 40% were boys in the intervention group included in our study, whereas 50% of the children were girls and 50% were boys in the control group. In the study conducted on children with intellectual disabilities studying at a primary special education school in Izmir and their families, 42.4% of the children were girls, and 57.6% were boys (28). According to the diagnosis status of the children included in the study, 40% of the children had ASD, and 2.5% had Asperger's syndrome in the intervention group, whereas the children in the control group had 60% ASD and 12.5% had other intellectual disabilities. When data on disability levels from the sociodemographic characteristics of the children with intellectual disabilities included in the study were analyzed, it was revealed that 50% of the children had mild, and 2.5% had very severe disability levels in the intervention group. In comparison, 47.5% of the control group had mild, and 2.5% had a very mild disability level.

Children with intellectual disabilities between the ages of 2-10 and their mothers were included in the study. Children's sleep was monitored with a child sleep habits questionnaire, sleep diaries, and actigraphy (14). Parents were provided with individualized sleep hygiene education for their children for 1 month. It was concluded that the children's sleep problems decreased after the education. In another study, children with intellectual disabilities between the ages of 5-15 and their mothers participated. They have stated that they experience sleep problems such as bedtime resistance, waking up at night, and spontaneous awakening at night. In addition, the child sleep habits questionnaire and the parent efficacy scale were used for evaluating the sleep quality of children and parents. The factors that prevent sleep were determined, and a 3-month sleep hygiene education was provided to the intervention group in a behavioral sleep program regarding these factors. After the education, measurements regarding the sleep of children were repeated, and the result indicated that the intervention group had greater sleep quality than the control group, which is consistent with the findings of the study (29). According to the results of the child sleep habits questionnaire and actigraphy after the education on sleep hygiene, it was established that the children's sleep problems decreased.

The findings indicated that there were differences in the mean sleep quality scores of mothers and children in the intervention group before and after the sleep hygiene education given in line with the health promotion model. Behavioral treatment for sleep problems in children with severe intellectual disability had similar results with the study regarding the treatment's effect on mothers and fathers (30). Discovered that children with ASD and learning difficulties and their mothers had sleep problems such as resistance to sleep and waking up at night (31). Children's sleep was recorded using a child sleep habits questionnaire, and mothers were handed a picture booklet. It was determined that they followed the instructions in the

sleep booklets and the methods for resolving sleep problems, and that sleep problems in children and mothers decreased, and there was a relationship between the mean sleep quality scores. Study on the sleep problems of children and families with ASD (32), according to the feedback received from the parents after the education, it was stated that there were positive effects on sleep levels by 32%, the sleep quality of children increased, and accordingly, there was a relationship between the average sleep quality scores of mothers.

Limitations of the study

The results of the research can be generalized to the children with intellectual disabilities in the age group of 2-18 and their mothers who have participated in the study.

CONCLUSION

Sleep hygiene education has been shown to aid in the development of regular sleep behaviors in children with intellectual disabilities and their mothers. Based on Pender's Health Promotion Model, a nurse education concept was created to improve sleep patterns through sleep hygiene education. In conclusion, the health promotion model developed to improve sleep patterns was found to be a viable guide for enhancing the sleep patterns and habits of children with intellectual disabilities and their mothers. In addition, it is recommended to evaluate the sleep quality of children with intellectual disabilities and their mothers on a regular basis, to provide education on sleep hygiene (physiological, psychological, and environmental factors), and to conduct studies examining the effectiveness of education and counseling programs applied by pediatric nurses to children with intellectual disabilities and their mothers in improving sleep quality.

Ethics Committee Approval: This study was approved by the ethics committee of Cyprus Science University Ethics Committee (decision no: 09, Date: 26.12.2019).

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- Ç.M.H., A.A.; Data Acquisition- Ç.M.H.; Data Analysis/Interpretation- Ç.M.H., A.A.; Drafting Manuscript- Ç.M.H.; Critical Revision of Manuscript- A.A.; Final Approval and Accountability- Ç.M.H., A.A.

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DERLEME / *REVIEW*

Çocukluk Çağı Kanserlerinde VEGF Sinyal Yolağının Etiyopatogeneze Etkisi ve Anti-VEGF Tedaviler

The Effects of VEGF Signal Pathway on Etiopathogenesis and Anti-VEGF Treatments in Childhood Cancers

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ÖZ

Vasküler endotelyal büyüme faktörü (Vascular Endothelial Growth Factor, VEGF) endotel hücrelerine direkt olarak etkiyen fizyolojik ve patolojik olarak en güçlü anjiyogenik moleküldür. İnsanlarda VEGF ailesi adı altında 5 adet VEGF tipi bulunmaktadır; VEGF-A, VEGF-B, VEGF-C, VEGF-D ve plasental büyüme faktörü (Placental Growth Factor, PlGF). VEGF'nin bağlanabileceği üç reseptör vardır; VEGFR-1 (VEGF reseptörü), VEGFR-2, VEGFR-3. VEGF reseptörüne bağlanınca; endotel hücre proliferasyonu, endotel hücre migrasyonu, apopitozisin inhibisyonu, kapiller dilatasyon ve geçirgenliğin artışı sağlanmış olur. Temel olarak VEGFR-1 hematopoezi, VEGFR-2 anjiyogenezi ve VEGFR-3 de lenfanjiyogenezi destekler. VEGFR-1 endotel hücrelerinin migrasyonunda önemli bir rol oynar. Özellikle de embriyonik gelişimde anjiyogenezde rol oynamaktadır. VEGFR-2'nin aktivasyonuyla; endotel hücre proliferasyonu, migrasyonu gerçekleşir ve aynı zamanda anti-apopitotik etkisiyle endotel hücrelerinin ömrü uzar. VEGF-A'nın VEGFR-2'ye bağlanması sonucu tümör neovaskülarizasyonu sağlanır ve tümörün metastaz yapması kolaylaşır. VEGF tümör progresyonunda ve sağkalımda rol oynayan temel moleküllerden biridir. VEGF'nin patofizyolojisinde rol oynadığı tümörler genellikle kötü prognozludur ve eğer tedavi edilmezlerse maalesef ölüm kaçınılmazdır. Bunu engellemek için tümörün progresyonunda önemli bir molekül olan VEGF'nin reseptörüne bağlanmasını engellemek tedavi yöntemlerinden biri olabilir. Bu yüzden de anti-VEGF tedaviler bu tümörlerin tedavi protokollerinde önemli bir yer tutmaktadır. Bevacizumab, 2004'te Amerika Birleşik Devletleri Gıda ve İlaç Dairesi (Food and Drug Administration, FDA) tarafından onaylanan ilk monoklonal antikordur. Bevacizumab; VEGF-A'nın tüm izoformlarını bağlayan ve inaktive eden bir ajandır, bu bağlanma sonucunda da VEGF-A'nın VEGFR-1 ve VEGFR-2 ile etkileşimini önler ve böylece neovaskülarizasyonu sağlayan VEGF sinyal yollarını inhibe eder. Bu inhibisyon, tümör kan damarlarının neovaskülarizasyonunda azalmaya yol açar ve böylece tümör dokularına kan akışını sınırlar. Bu etkiler ayrıca doku interstisyel basıncını düşürür, kan damarlarının geçirgenliği arttırır ve bu yolla kemoterapötik ajanların dağılımını arttırır ve tümör endotel hücrelerinin apopitozunu destekler. Bevacizumab günümüzde birçok kanser tedavisinde kemoterapötiklerle kombine olarak parenteral yolla kullanılmaktadır. Bevacizumabın kombine tedavilerde kullanımı 2-3 haftada bir intravenöz 10-15mg/kg'dır. Bu derleme; VEGF'in tümör patofizyolojisindeki yerini ve önemini son gelişmeler doğrultusunda irdelemeyi ve yeni tedavi alternatifleri hakkındaki bilgileri sunmayı amaçlamaktadır.

Anahtar Kelimeler: anjiyogenesis, vasküler endoteliyal büyüme faktörü, VEGF, bevacizumab

ABSTRACT

Vascular endothelial growth factor (VEGF) is the most physiologically and pathologically potent angiogenic factor that acts directly on endothelial cells. Its five isoforms, namely, VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF) are present in humans. They bind to three receptors VEGFR-1, VEGFR-2, and VEGFR-3. When they bind to a VEGF receptor, endothelial cell proliferation, migration, apoptosis inhibition, capillary dilatation, and increased capillary permeability occur. VEGFR-1, VEGFR-2, and VEGFR-3 promotes hematopoiesis, angiogenesis, and lymphangiogenesis respectively. Further, VEGFR-1 plays an important role in the migration of endothelial cells; especially in angiogenesis during embryonic development. With VEGFR-2 activation, endothelial cell proliferation and migration occur, and the lifespan of endothelial cells is simultaneously prolonged owing to its antiapoptotic effect. Binding of VEGF-A to VEGFR-2 results in neovascularization of tumor, facilitating tumor metastasis. Thus, VEGF is an essential molecule required for tumor progression and survival. Tumors wherein VEGF plays a role in their pathophysiology generally have a poor prognosis. Such tumors, if untreated can eventually cause the death of patients. Inhibiting VEGF from binding to its receptor is one of the treatment methods: to prevent thşs situation. Therefore, anti-VEGF therapy is important in the treatment protocols of such tumors. The Food and Drug Administration in 2004 approved the first monoclonal antibody, bevacizumab, which binds to and inactivates all isoforms of VEGF-A. Binding to VEGF-A prevents its interaction with VEGFR-1 and VEGFR-2, thereby inhibiting the VEGF signaling pathways that facilitate neovascularization. This inhibition leads to decreased neovascularization of tumor blood vessels and limits blood flow to tumor tissues. Furthermore, it reduces the tissue interstitial pressure and increases blood vessels permeability, thereby increasing the distribution of chemotherapeutic agents and promoting apoptosis of tumor endothelial cells. Bevacizumab is currently used parenterally in combination with chemotherapeutics in many cancer treatments. The dosage of bevacizumab in combined treatments is 10-15 mg/kg intravenously every 2-3 weeks. This review not only investigates the role and importance of VEGF in tumor pathophysiology in childhood cancers but also compiles information regarding new treatment alternatives.

Keywords: angiogenesis, vascular endothelial growth factor, VEGF, bevacizumab

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GİRİŞ

İnsan vasküler endotelyal büyüme faktörü (Vascular Endothelial Growth Factor, VEGF) heterodimerik ve 40 kDa boyutunda glikoprotein yapısındaki bir gen tarafından kodlanır. VEGF, endotel hücrelerine fizyolojik ve patolojik olarak etkiyen en güçlü anjiyogenik maddedir.

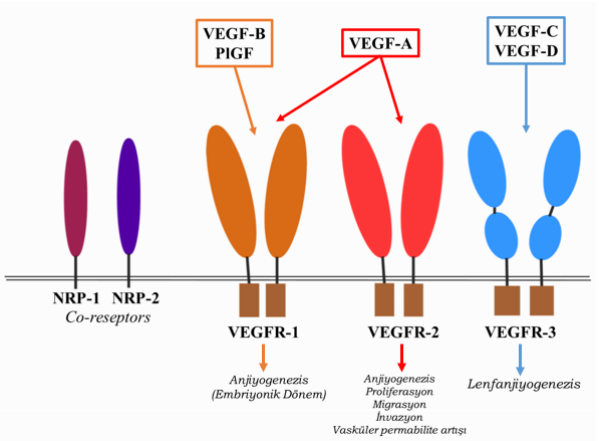
İnsanlarda VEGF ailesi adı altında birden fazla VEGF tipi bulunmaktadır. Bunlar; VEGF-A, VEGF-B, VEGF-C, VEGF-D ve plasental büyüme faktörü (Placental Growth Factor, PlGF)'dür. Yakın zamanda bu aileye eklenen bir diğer VEGF tipi ise endotelyal gland VEGF (EG-VEGF)'tir. 1983'te Senger ve arkadaşları hayvanlardaki tümör hücrelerinde damar geçirgenliğini arttıran bir molekül keşfederler ve ona vasküler permeabilite faktörü (VPF) adını koyarlar. 1989'da ise Ferrara ve arkadaşları VEGF proteinini izole edip tanımlamış ve direkt olarak anjiyogenezle ilişkisini ortaya koymuştur. Daha sonra VEGF'nin VPF ile çok benzer bir yapıya sahip olduğu kanıtlanmış ve aslında aynı molekül oldukları anlaşılmıştır[1,2,3,4,5,6].

Anjiyogenez, pro ve anti anjiyogenik faktörlerle denetlenmektedir. Proanjiyogenik moleküller; fibroblast büyüme faktörü (fibroblast growth factor, FGF), platelet türevli büyüme faktörü (platelet-derived growth factor, PDGF), transforme edici büyüme faktör beta 1 (transforming growth factor beta-1, TGFß1), transforme edici büyüme faktör alfa (transforming growth factor alpha, TGF-α), epidermal büyüme faktörü (epidermal growth factor, EGF) ve VEGF'tir. Bunlardan en potent olan VEGF; endotel hücrelerine özgü mitojen ve anjiogenik bir madde olmasının yanında vasküler geçirgenliği de arttırır[6].

VEGF reseptörlerinin (VEGFR) tirozin kinaz aktivitesi vardır ve anjiyogenezin endotel hücreleri üzerinden direkt uyarılmasını sağlar. Bu özellik tümör neovaskülarizasyonunda kilit aşamadır. Tümör hücrelerinin artmış besin ihtiyacı ve beraberinde hücre yükünün getirmiş olduğu hipoksik ortam VEGF sentezi için tetikleyicidir. Fazla miktarda VEGF sentezleyen tümörler daha hızlı vaskülarize olur, bu da tümörün metastaz yapmasını kolaylaştırır.

Hem tümör hücrelerinde hem de normal hücrelerde VEGF sentezinin temel uyaranı hipoksidir. Hipoksiye maruz kalan hücrelerde sentezlenen hipoksiyle indüklenen faktör (HIF)-1; VEGF geninin transkripsiyon hızını ve aynı zamanda VEGF mRNA'sının sağlamlığını arttırır. Sentezlenen VEGF'nin bağlanabileceği üç reseptör vardır; VEGFR-1, VEGFR-2, VEGFR-3. Her bir reseptörün kendine özgün görevleri vardır. Bu üç reseptör dışında VEGF'nin bağlanabildiği bir diğer reseptör tipi de nöropilin reseptörleridir (NRP-1 ve NRP-2). VEGFR'nin üç tane alt birimi vardır; VEGF'yi bağlayan ekstraselüler alt birim, transmembran alt birim ve tirozin kinaz aktivitesine sahip olan intraselüler alt birim. VEGF, reseptörüne bağlanınca otofosforilasyon sonucunda hücre içi sinyal yolakları aktive olur. Bu sayede de endotel hücre proliferasyonu, endotel hücre migrasyonu, apopitozisin inhibisyonu, kapiller dilatasyon ve geçirgenliğin artışı sağlanmış olur. Temel olarak VEGFR-1 hematopoezi, VEGFR-2 anjiyogenezi ve VEGFR-3 de lenfanjiyogenezi destekler[6].

VEGFR-1 ve VEGFR-2 temel olarak endotel hücrelerinde eksprese edilseler de monositler/makrofajlar, hematopoetik progenitör hücreler, trofoblastik hücreler ve tümör hücreleri gibi hücrelerde de bulunabilir. VEGFR-3 ise sadece lenfoid sistemin endotel hücrelerinde eksprese edilir. VEGFR-1 yüksek affiniteyle VEGF-A'yı bağlamakla birlikte VEGF-B ve PlGF'yi de bağlayabilir. VEGFR-1 endotel hücrelerinin migrasyonunda önemli bir rol oynar. Özellikle de embriyonik gelişimde anjiyogenezde rol oynamaktadır. VEGFR-2'nin VEGF-A'ya karşı yüksek affinitesi vardır. VEGFR-2'nin aktivasyonuyla; endotel hücre proliferasyonu ve migrasyonu gerçekleşir, aynı zamanda anti-apopitotik etkisiyle endotel hücrelerinin ömrü uzar. Yani VEGF-A'nın VEGFR-2'ye bağlanması sonucu tümör neovaskülarizasyonu sağlanır ve tümörün metastaz yapması kolaylaşır. VEGFR-3 özellikle VEGF-C ve VEGF-D'yi bağlar. VEGFR-3'ün temel görevi gerek embriyonik dönemde gerekse de yetişkin dönemde lenfoid sistemin oluşumunu sağlamaktır[6].

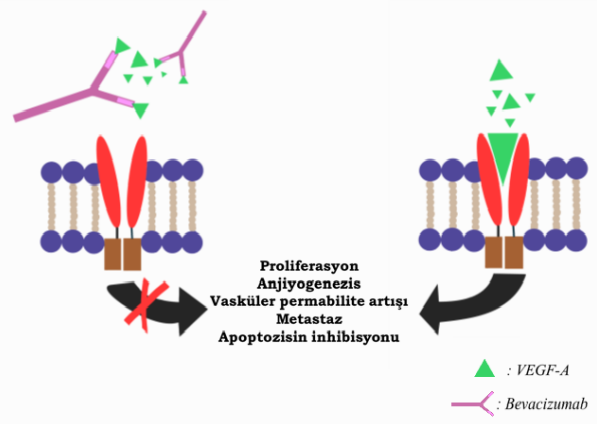


Figür 1: VEGF ve VEGF reseptörleri

Bevacizumab (Avastin®)

VEGF'yi hedefleyen anjiyogenez inhibitörü olan bevacizumab, 2004'te Amerika Birleşik Devletleri Gıda ve İlaç Dairesi (Food and Drug Administration, FDA) tarafından onaylanan ilk monoklonal antikordur. Bu antikor; anjiyogenezi, tümör büyümesini ve proliferasyonunu inhibe etmek için VEGF-A'nın tüm izoformlarını bağlayan ve inaktive eden bir ajandır[7]. Bevacizumab, VEGF-A'ya bağlanarak VEGF-A'nın VEGFR-1 ve VEGFR-2 ile etkileşimini önler ve böylece neovaskülarizasyonu sağlayan VEGF sinyal yollarını inhibe eder. Bu inhibisyon, tümör kan damarlarının neovaskülarizasyonunda azalmaya yol açar ve böylece tümör dokularına kan akışını sınırlar[8,9]. Bu etkiler ayrıca doku interstisyel basıncını düşürür, kan damarlarının geçirgenliği arttırır. Bu sayede kemoterapötik ajanların dağılımını arttırır ve beraberinde tümör endotel hücrelerinin apopitozunu destekler.

İlk kullanım alanı metastatik kolorektal karsinom olan bevacizumab, artık günümüzde birçok kanser tedavisinde kemoterapötiklerle kombine olarak parenteral yolla kullanılmaktadır[8,9]. Bevacizumabın kombine tedavilerde kullanımı 2-3 haftada bir intravenöz 10-15mg/kg'dır[10,11,12].



Figür 2: Bevacizumabın etki mekanizması

Tablo 1. Bevacizumabın endikasyonları

Bevacizumab Endikasyonları	
ΦMetastatik Kolorektal Karsinom	жΦPilositik Astrositom
ΦKüçük Hücreli Olmayan Akciğer Karsinomu	жΦOsteosarkom
ΦMetastatik Meme Karsinomu	жNöroblastom
ΦGlioblastoma Multiforme	жRetinoblastom
ΦOver Karsinomu	жHepatoblastom
ΦServiks Karsinomu	жWilms' Tümörü
ΦRenal Hücreli Karsinom	жRabdomyosarkom
жΦMedulloblastom	жEwing Sarkom

ж: Çocukluk Çağı Kanseri Φ: Yetişkinlerde Görülen Kanser

Bevacizumab ile tedavi sırasında en sık görülen yan etkiler; hipertansiyon, yorgunluk, diyare ve abdominal ağrıdır. Bu gibi yan etkilerde hastanın izlemine göre tedavi devamlılığına karar verilir. Bevacizumab tedavisi sırasında doza bağımlı gelişen hipertansiyon ise; yakın kan basıncı takibi gerektirir ve genellikle standart antihipertansiflerle kontrol altına alınabilir. Bevacizumabın en ciddi yan etkileriyse; gastrointestinal perforasyon, hemoraji ve tromboembolizm olarak karşımıza çıkmaktadır. Bevacizumab; hamilelik sırasında embriyogenezis için gerekli olan anjiyogenezi inhibe ettiği için kullanımı kontrendikedir[12].

KLİNİK ve ARAŞTIRMA ETKİLERİ

VEGF'nin çocukluk çağındaki birçok tümörde anjiyogenezde önemli bir rol oynadığını biliyoruz. Bu tümörlerin birçoğu kötü prognozludur ve bunlar tedavi edilmedikleri takdirde hastanın ölümüne yol açabilmektedirler. Bunu engellemek için tümörün progresyonunda önemli bir molekül olan VEGF'nin reseptörüne bağlanmasını engellemek, tedavi yöntemlerinden biridir. Bu yüzden Anti-VEGF tedavi bu tümörlerin tedavi protokollerinde önemli bir yer tutmaktadır.

Retinoblastom genellikle lökokori, strabismus ve orbital kitleyle gelebilen bir çocukluk çağı kanseridir. Areân ve ark.'nın [13] retrospektif çalışmasında VEGF'nin artmış ekspresyonunun progresyonu hızlandırdığı ve mitotik-apoptotik indeksle pozitif korelasyon gösterdiği saptanmıştır. Bu çalışmaya üniversite hastanesi oftalmoloji kliniğinde, 2000-2007 yılları arasında tedavi edilen ortalama tanı yaşları 29 ay olan 129 hastadan 47'si dahil edilmiştir. Patolojik piyeslerde VEGF ekspresyonu, tümör büyümesi ve invazyonu değerlendirilmiş, kontrol grubu olarak da renal doku kullanılmıştır. Çalışmaya dahil edilen 47 kişiden 43'ünde VEGF yüksek oranda pozitif eksprese olurken, 4 örnek nekroz nedeni ile incelenememiştir. Sonuç olarak VEGF'nin yüksek seviyede ekspresyonunun; progresyonu arttırarak enükleasyona olan gidişi hızlandırdığı kanıtlanmıştır.

Hepatoblastom, çocukluk çağında karında kitleyle gelen ve nadir görülen bir kanserdir. Wen ve ark. [14] VEGF'nin artmış ekspresyonunun hepatoblastomun prognozuna olan etkisini retrospektif kohort çalışma ile araştırmışlardır. Çalışmaya 2013-2016 yılları arasında Capital Medical Üniversitesinde (Pekin) tedavi edilmiş ve ortalama tanı yaşları 34 aylık olan 31 çocuk dahil edilmiştir. Çocuklarda yapılan karaciğer biyopsilerinde immünohistokimyasal boyama ile VEGF ekspresyonu araştırılmış ve 31 çocuktan 14'ünde yüksek, 17'sinde ise düşük oranda ekspresyon saptanmıştır. Bu iki grubu karşılaştırdıklarında ise; VEGF'yi düşük eksprese edenlerin 2 yıllık remisyon oranları ve sağkalımlarının daha iyi olduğu bulunmuştur.

Wilms' tümörü çocukluk çağında görülen en sık böbrek tümörüdür. Rowe ve ark.[15] Wilms' tümöründe VEGF'nin tümör boyutu üzerine olan etkisini araştırmak üzere 28 fare üzerinde bir kohort çalışması gerçekleştirmişlerdir. Farelere önce tümör enjekte edilmiş, inkübasyon sonrasında da fareler kontrol ve anti-VEGF tedavi grubu olarak ikiye ayrılmıştır. Kontrol grubunda tümör boyutu ile birlikte anjiyogenezin ve nekroz oranının da arttığı gözlemlenmiştir. Üç hafta anti-VEGF tedavi alan grupta ise tümör boyutunun %95 oranda küçüldüğü, neoanjiyogenezin ve uzak metastazların olmadığı görülmüştür. Sonuç olarak Wilms' tümöründe VEGF'nin anjiyogenezde ve uzak metastazda önemli rol oynadığı saptanmıştır.

Nöroblastom; çocukluk çağında görülen en sık ekstrakraniyal solid tümördür. 2014 yılında nöroblastomda VEGF'nin prognoza olan etkisini araştırmak için Gheytanchi ve ark. [16] Ali-Asghar Çocuk Hastanesinde (Tahran) 2001-2010 yılları arasında opere olmuş nöroblastom tanılı, ortalama yaşları 34 ay olan 20 çocukta retrospektif bir çalışma gerçekleştirmişlerdir. Yirmi çocuğun her birinin patolojik piyesinde Ki67 ve VEGF immünohistokimyasal olarak incelenmiştir. Yirmi çocuğun 14'ünde VEGF yüksek düzeyde eksprese edilmiştir. Sonuç olarak VEGF'nin, nöroblastomun prognozunda ve progresyonunda önemli rol oynadığı ve tıpkı Ki67 gibi nöroblastomda prognostik bir belirteç olabileceği kanıtlanmıştır.

Medulloblastom en sık görülen çocukluk çağı malign beyin tümörüdür, çocukluk çağı beyin tümörlerinin %20'sini oluşturur. Medulloblastomlar hastanın tanı yaşı, tanıda metastaz durumu ve rezidüel tümör volümüne göre klinik risk gruplarına ayrılmaktadır. Medulloblastomun 4 grubu arasından en agresif olanı grup 3'tür. Tümör gelişiminde anjiyogenezin rolü ve önemi ise hala bilinmemektedir. 2017 yılında Thompson ve ark.[17]medulloblastomlarda angiogenezin önemini araştırdığı

prospektif kohort çalışmada; Grup 3 medulloblastom ksenogreftleri, sıçanlara intrakraniyal olarak implante edilip belirli aralıklarla vasküler yoğunlukları ve VEGF-A ekspresyonları takip edilmiştir. Sonuç olarak VEGF-A seviyeleri yüksek olan, özellikle de Grup 3 medulloblastom vakalarında sağkalımın daha düşük olduğu gösterilmiştir.

Malign gliomalar; özellikle glioblastoma multiforme (GBM), vaskülarize tümörlerdir ve yüksek oranlarda VEGF eksprese ederler. GBM'lerde anti-VEGF tedavinin yararı kanıtlanmış olsa da tedavideki uygun doz aralığı hala tartışmalıdır. 2020 yılında Yulei Chen ve ark. [18] PubMed, EMBASE ve Cochrane Library kaynaklarından taradıkları 2020 öncesi makalelerden derledikleri meta-analizde, nüks GBM'li hastalarda standart dozda bevacizumab (5 mg/kg/hafta) kullanımının vasküler geçirgenlikte bir azalmaya neden olduğu ve bunun da eşzamanlı kemoterapi verilmesini sınırlandırdığı gösterilmiştir. Bu nedenle daha düşük doz bevacizumab kullanımı, hipoksiyi geciktirerek oksijenizasyonun ve ilaç dağılımının daha iyi olmasını sağlar. Bu meta-analizde, iki doz grubu arasında genel sağkalım (overall survival, OS) ve hastalıksız sağkalım (progression-free survival, PFS) açısından anlamlı bir fark olmadığı, bu nedenle nüks yüksek dereceli gliomalı hastalarda düşük doz bevacizumab protokolünün standart doz bevacizumab kadar etkili olduğu gösterilmiştir.

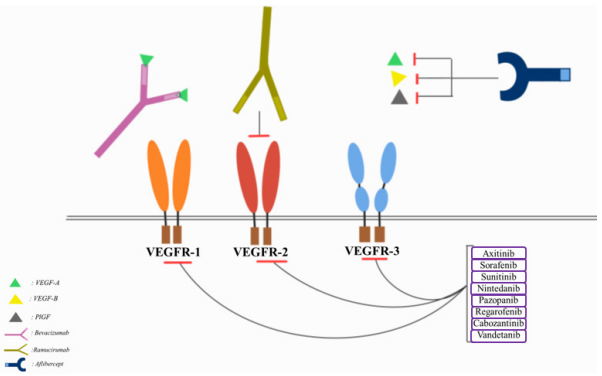
Pilositik astrositomlar çocuklarda en sık görülen beyin tümörleridir. Anti-VEGF tedavinin glioblastom üzerindeki etkisi daha önce yapılan araştırmalarda kanıtlanmıştır. M. Sie ve ark. [19] tarafından 2010 yılında yapılan retrospektif kohort çalışmasında 59 pilositik astrositomlu pediyatrik hasta, 62 glioblastom tanılı erişkin hasta ile karşılaştırılmıştır. Tümör dokularındaki vaskülarizasyon ve ayrıca VEGF ekspresyon derecesi immünhistokimyasal boyama yöntemiyle incelenmiştir. Sonuç olarak VEGF-A'nın yüksek ekspresyonunun anjiyogenezi arttırdığı gösterilmiştir.

Rabdomyosarkom (RMS), çocuklarda tüm solid tümörlerin %10-15'ini ve tüm yumuşak doku sarkomlarının %50'sini oluşturur. Çocuklarda rastlanan kanserlerin ise %6'sı rabdomyosarkomdur. Myers ve ark.'nın [20] prospektif kohort çalışması, alveolar rabdomyosarkom (ARMS) tedavisinde bevacizumab ile iyonize radyasyon tedavisinin birlikte kullanıldığı ilk çalışmadır. Bu çalışmada farelere insan alveolar tip rabdomyosarkom hücreleri enjekte edilmiş, iyonize radyasyon (IR) ve bevacizumab kombine tedavisinin ARB üzerine etkisini değerlendirmek için fareler altı farklı gruba ayrılmıştır. Tedavi grupları; kontrol, tekli bevacizumab, tekli IR, IR'den 2 gün önce verilen bevacizumab, IR'den 5 gün önce verilen bevacizumab ve IR'den 10 gün önce verilen bevacizumab tedavi grupları şeklindedir. Tümörler daha sonra vaskülarizasyonun yoğunluğu, matürasyonu, geçirgenliği, tümör içi oksijenizasyon ve büyümedeki değişiklikler açısından değerlendirilmiştir. Bevacizumab tedavisinden 2 veya 5 gün sonra IR ile tedavi seçeneği en iyi yanıt gösteren antitümör aktiviteye sahipti. Bevacizumab hem RMS ksenogreftlerinde tümörün oksijenizasyonu üzerinden hem de adjuvan IR'ye olan tümör duyarlılığını arttırarak önemli bir etki göstermektedir. Bu çalışma kombinasyon tedavisinin etkinliğini optimize etmek için IR'ye adjuvan olarak bevacizumab eklenmesinin zamanlamasının önemini vurgulamakta ve dikkatli bir şekilde yapılması gerektiğini belirtmektedir.

Primer malign kemik tümörü olan osteosarkom, en sık çocuklarda ve adolesanlarda (<20 yaş) görülür. [21] Osteosarkomun özellikle akciğerlere uzak metastaz yapma eğilimi yüksektir. Sisteinden zengin Anjiyojenik İndükleyici 61 (Cyr61) ve VEGF, tümör anjiyogenezinin ve ilerlemesinin düzenlenmesinde yer alan sinyal proteinleridir. Yanming Liu ve ark. [22] osteosarkomda Cyr61 ve VEGF ekspresyonlarının klinikopatolojik ve prognostik önemini göstermek için 84 osteosarkom hastasından alınan doku örnekleri üzerinde çalışmıştır. Cyr61 ve VEGF, osteokondrom dokularına kıyasla osteosarkom dokularında daha yüksek oranda eksprese edilmiştir. Her iki proteinin artmış ekspresyonu; hastalarda azalmış genel sağkalım ile ilişkili bulunmuştur.

Geçmişten Günümüze Yeni Tedaviler

Bazen tümör anjiyogenezi sadece VEGF üzerinden olmamaktadır. Böyle durumlarda anti-VEGF tedaviye dirençle karşılaşılabilir ve alternatif tedavilere başvurmak gerekebilir. Alternatif tedavi olarak; tirozin kinaz inhibitörleri (sorafenib, pazopanib, cabozantinib vs.), ramucirumab, aflibersept, immünoterapiler vs. kullanılabilir. [23]



Figür 3: Alternatif tedaviler

**Tirozin Kinaz İnhibitörleri*

Normal bir hücrede tirozin kinaz reseptörleri büyüme sinyalinin hücre nükleusuna iletilmesinden sorumludur. Eğer bu reseptörler herhangi bir nedenle mutasyona uğrarsa; tümör gelişimine, tümörün progresyonuna ve hatta metastaz yapmasına yol açabilmektedir. Tirozin kinaz inhibitörleri (TKI); reseptörün fosforilasyonunu önleyerek reseptörü bloke eder.

İlk onay alan TKI, 2001 yılında kronik miyeloid lösemide kullanılmak için geliştirilen imatinibdir. Diğerleri BRAF, Epidermal Büyüme Faktörü Reseptörü (Epidermal Growth Factor Receptor, EGFR), Vasküler Endotelyal Büyüme Faktörü Reseptörü (Vascular Endothelial Growth Factor Receptor,VEGFR), İnsan Epidermal Büyüme Faktörü Reseptörü 2 (Human Epidermal Growth Factor Receptor 2, HER2), Kit, Platelet Kaynaklı Büyüme Faktörü Reseptörü (Platelet-derived Growth Factor Receptor, PDGFR), Rapamisin Protein Kompleksinin Memeli Hedefi

(Mammalian Target of Rapamycin, mTOR), Hepatosit Büyüme Faktörü (Hepatocyte Growth Factor, HGF)/c-mesenchymal epithelial transition factor (c-Met), Fibroblast Büyüme Faktörü Reseptörü, (Fibroblast Growth Factor Receptor, FGFR) şeklinde sıralanabilir. TKI'lerin yan etkileri; diyare, deri reaksiyonları, yorgunluk, bulantı, kusma, hipertansiyondur. [24,25]

→Sorafenib

Sorafenib, anjiyogenezi VEGFR-1, VEGFR-2 ve VEGFR-3 üzerinden inhibe eden ilk oral bir multipl kinaz inhibitörüdür. İleri evre renal hücreli karsinom, hepatosellüler karsinom, akut miyeloid lösemi ve tiroid karsinomunun tedavisinde kullanımı FDA tarafından onaylanmıştır. Ymera ve ark.'nın preklinik çalışmasında[26] sorafenibin osteosarkom hücrelerinde proliferasyonu doza bağımlı olarak inhibe ettiği gösterilmiştir. Ayrıca apoptozu indükleyerek yeni damar oluşumunu da engellediği kanıtlanmıştır. Mei ve ark. [27] sorafenibin VEGFR-2, transfeksiyon sırasında yeniden düzenlenen kinaz (Rearranged During Transfection, RET) ve mitojenle aktive edilen kinaz/hücre dışı sinyalle düzenlenen kinaz (Mitogen-Activated ERK Kinase / Extracellular Signal-Regulated Kinase, MEK/ERK) sinyal yolları üzerinden osteosarkom hücrelerinin proliferasyonunu inhibe ettiğini bildirmiştir. Sorafenib yeni bir ilaç olmasına rağmen, günümüzde artık ileri evre hepatoselüler karsinom ve renal hücreli karsinom için birinci basamak tedavi olarak kabul edilmektedir. Ancak son çalışmalarda tedavide sorafenibin tek başına kullanılmasının, osteosarkomda geçici bir tümör stabilizasyonu yaptığı, bu nedenle kalıcı remisyon elde etmek için daha etkili kombinasyon tedavi rejimlerine ihtiyaç olduğu bir gerçektir. Özellikle metastatik ve refrakter osteosarkom hastalarında sorafenibin etkinliğini değerlendirmek için daha fazla klinik veriye ihtiyaç vardır.

→Pazopanib

Pazopanib; VEGFR, PDGFR, KIT ve FGFR'ye karşı yüksek afinitesi olan oral olarak kullanılan çok hedefli tirozin kinaz inhibitörüdür. Pazopanibin metastatik renal hücreli karsinom (mRCC) tedavisinde onay almasının ardından yumuşak doku sarkomları üzerine olan etkisi de araştırılmıştır. Pazopanib ile plasebonun karşılaştırıldığı randomize bir çalışmada ise progresyonsuz sağkalımı önemli ölçüde iyileştirdiği gösterilmiştir[28].

Metastatik kemik sarkomlarında kemoterapinin etkisi zayıftır ve hastalık çoğu zaman ölümle sonuçlanmaktadır. Bu nedenle yeni tedavilere ihtiyaç duyulmaktadır. Pazopanibin anti-kanser etkisini osteosarkom fare modellerinde hem anjiyojenik hem de onkojenik sinyal yollarını inhibe ederek gösterdiği bildirilmiştir. Pazopanibin antianjiyogenik etkileri, topotekan ile kombine edildiğinde önemli ölçüde artmaktadır. Danimarkalı araştırmacılar tarafından yapılan bir araştırmada, pazopanib tedavisini takiben ileri osteojenik sarkomlu 3 hastada parsiyel remisyon (PR) bildirilmiştir. Umeda ve arkadaşları, pazopanib tedavisinden sonra 21 aydan uzun süre hayatta kalan, refrakter seyirli 3 olgu tanımladılar. Bu raporlar, pazopanibin güçlü anti-tümör aktivitesine sahip olduğunu, diğer TKI'lere kıyasla daha olumlu sonuçlar alındığını ve toksisite profilinin de tedavi için kabul edilebilir olduğunu göstermiştir[29].

→Cabozantinib

2019 yıllarının başında, öncesinde sorafenib kullanmış hepatoselüler karsinom hastalarında kullanılması için onaylanan cabozantinib; VEGFR1-3'ün yanı sıra MET (Mitogen-Activated ERK Kinase) ve TAM (Tyro3, Axl, MerTK) tirozin kinaz reseptörlerinin de inhibitörüdür. Bu reseptörlerin fosforilasyonunu önleyerek aktivitelerini engeller. Cabozantinibin tirozin kinaz inhibitör aktivitesinin yanında immün modülatör etkisi de bulunmaktadır. Bu özelliği cabozantinibin immün kontrol noktası inhibitörleriyle birlikte kombine kullanımına yol açmıştır. Antianjiyogeniklere direnç geliştiğinde cabozantinibin çoklu yolak inhibitör özelliği bu noktada faydalı olmaktadır[30].

2018'de yapılan çift-kör randomize çalışmaya, hepatoselüler karsinomu (HCC) olan ve daha öncesinde sorafenib ile tedavi edilen 707 hasta dahil edilmiş, 707 hastanın 470'i cabozantinib grubuna 237'si ise plasebo grubuna alınmıştır[31]. Cabozantinib alan grubun genel sağkalım ve PFS'si plasebo grubuna göre daha iyi bulunmuştur. Yine cabozantinibin etkisinin tümör yüküyle ve alfa-fetoprotein (AFP) yüksekliğiyle doğru orantılı olarak arttığı bulunmuştur. Yan etki oranları cabozantinib alan grupta daha yüksek oranda görülmüştür. Bu yan etkiler; palmar-plantar eritrodizestezi, hipertansiyon, AST düzeyinde artış, yorgunluk, diyare şeklindedir.

**Aflibersept*

Afliberseptin mekanizması, VEGFR yapısını taklit ederek gerçek VEGFR'den önce VEGF molekülüne bağlanıp esas reseptörün bağlanmasını önlemektir. Farmakokinetik ve farmakodinamik açıdan bevacizumabdan sonra en umut vaat eden ilaçlar arasındadır. 2015 yılına kadar yapılan in vivo deneylerde; rabdomyosarkom, gliom ve melanomlarda hücre bölünmesini kayda değer biçimde inhibe ettiği kanıtlanmıştır. Yan etkiler olarak; disfoni, hipertansiyon ve proteinüri görülebilmektedir[32].

**Ramucirumab*

Ramucirumab, VEGFR-2'nin ekstraselüler subünitini hedefleyen IgG1 tipinde bir monoklonal antikordur. Ramucirumabin kullanımı 2014 yılında Amerika Birleşik Devletleri'nde refrakter, ileri evre mide ve metastatik küçük hücreli olmayan akciğer kanserinde onaylanmıştır. İleri evre kolorektal, mide ve akciğer kanserlerinde anti-VEGF tedaviye alternatif olarak kullanılan bir antianjiyogenik ajandır. Çeşitli ileri evre karsinomlarda, özellikle ileri evre kolorektal karsinomda ikinci basamak tedavi olarak bevacizumaba eklenen ramucirumabın plasebo kullanan gruba göre progresyonsuz ve genel sağkalımı uzattığı gösterilmiştir. Ramucirumabın sık görülen yan etkileri; ishal, yorgunluk, anoreksi, hipertansiyon, nötropeni ve stomatittir[33,34,35].

**PD-1/PD-L1 İnhibitörleri*

Son yıllarda kanser tedavisinde çığır açan bir gelişme olan PD-1/PD-L1(Programlanmış Ölüm Proteini-1/Programlanmış Ölüm Protein Ligandı-1) inhibitörleri, düşük toksisite ve uzun vadeli etkileriyle birçok kanser tedavisinde umut verici başarı göstermiştir.

İmmünoterapilerin mekanizması kısaca şöyledir: Tümör hücrelerinin yüzeyinde eksprese edilen PD-L1'in; aktive olmuş T hücreleri, B hücreleri ve makrofajlar üzerinde bulunan PD-1'e bağlanmasıyla immün sisteminin anti-tümör yanıtı baskılanır ve bu sayede tümör hücreleri immün sistemden kaçabilir. PD-1 veya PD-L1 blokajı, tümör antijenine özgü T hücrelerinin anti-tümör aktivite yeteneklerini geri kazanabilmeyi sağlar[36].

Bir grup kanser hastasında yapılan klinik çalışmada, tümör dokularında TIL' lerin (Tümör Mikroçevresini İnfiltre Eden Lenfositler) bulunmadığı ve bunun PD-1/PD-L1 inhibitörlerinin aktivitesini azalttığı gösterilmiştir. Bu nedenle, lenfositlerin tümör dokularına infiltrasyonunun artması, PD-1/PD-L1 inhibitörlerinin etkinliğinin artmasına yardımcı olacaktır[37].

Anti-VEGF/VEGFR antikorlarından; bevacizumab ve ramucirumabın lenfositlerin tümör dokularına infiltrasyonunu arttırma yeteneğine sahip olduğunu gösteren çok sayıda kanıt bulunmaktadır. Bu nedenle PD-1/PD-L1 inhibitörlerinin etkinliğini arttırabilmek için anti-VEGF tedaviler kanser tedavisinde immünoterapi ile kombine olarak kullanılmaya başlanmıştır.

SONUÇ

Tümörlerin progresyonunu azaltmak hatta durdurmak için, anjiyogenezde kullanılan sinyal yolakları keşfedilmekte ve bu yolakları inhibe etmek için çeşitli moleküler yapıda ajanlar üretilmektedir. Bu çalışmanın ana konusu olan bevacizumab, 2004'te FDA tarafından onaylanan ilk monoklonal antikordur. Antianjiyojenik tedavi, yukarıda incelediğimiz birçok tümör türünde sağkalımı arttırarak fayda sağlamaktadır. Doz aralığını, yan etkileri ve diğer tedavilerle kombinasyonlarının olası sonuçlarını saptamak açısından önümüzde daha uzun bir yol olduğu kesin. Gerçek başarıya ulaşmak, tümörü eradike etmek için bevacizumab ve benzeri tedavilerin tek başına yeterli olmadığı, günümüze kadar yapılan çalışmalarda kanıtlanmıştır. Bu yolda anti-VEGF ile birlikte anti-VEGFR, VEGF-Trap, ve Tirozin kinaz inhibitörleri gibi diğer yolakların da etki mekanizmaları keşfedildikçe çok daha geniş çapta hasta popülasyonuna uygun tedaviler ulaştırmış olacağız.

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DERLEME MAKALESİ / *REVIEW ARTICLE*

Homeopathy in Pediatric Dentistry

Çocuk Diş Hekimliğinde Homeopati

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ABSTRACT

Homeopathy is an alternative treatment approach that has been widely used for over 200 years. It is popularized as a safe and cost-effective alternative to allopathy. For a holistic approach, homeopathic remedies are used to improve not only patients' physical condition but also psychological or emotional condition. In dentistry, homeopathy has been used as an adjunct to conventional treatment since 18th century. Many studies indicate that the effect of homeopathic remedies is not different or superior to that of placebo. Institutions such as the World Health Organization and the Food and Drug Administration have not yet approved the ethics and safety of homeopathy as a treatment form. In recent years, regulations on homeopathy by many institutions have been increased, and its prevalence has been limited. Further clinical research is needed to elucidate whether homeopathic remedies can effectively treat conditions that appear to be linked to patients' spiritual, emotional, mental, and physical conditions, and whether this has a placebo effect. This review aimed to introduce the basics of homeopathy, which has been accepted as part of the Traditional and Complementary Medicine by the Turkish Ministry of Health as of 2016, and to discuss its possible applications in pediatric dental practice.

Keywords: pediatric dentistry, dentistry, homeopathy

ÖZ

Homeopati, 200 yıldan daha uzun süredir yaygın olarak kullanılan alternatif bir tedavi yaklaşımıdır. Allopatiye karşı güvenli ve uygun maliyetli bir alternatif olarak popülerleşmiştir. Homeopatik ilaçlar, bütünsel bir yaklaşım benimseyerek hastaların fiziksel durumları ile birlikte psikolojik veya duygusal durumlarını iyileştirmek için de kullanılmaktadır. Diş hekimliğinde 18. yüzyıldan beri geleneksel tedaviye ek olarak kullanıldığı bildirilmektedir. Yapılan çalışmaların birçoğu homeopatik ilaçların etkisinin plasebodan farklı ya da üstün olmadığını belirtmektedir. Homeopatinin bir tedavi biçimi olarak kullanımının etik ve güvenliği Dünya Sağlık Örgütü (DSÖ) ve Amerikan Gıda ve İlaç Dairesi (FDA) gibi kurumlar tarafından halen kabul görmemiştir. Son yıllarda birçok kurum tarafından homeopati ile ilgili olarak yapılan düzenlemeler arttırılmış ve yaygınlığı sınırlandırılmıştır. Homeopatik ilaçların, hastaların ruhsal, duygusal, zihinsel ve fiziksel koşullarına bağlı görünen durumları tedavi edip etmediğini ve bunun plasebo etkisi olup olmadığını anlamak için daha fazla klinik araştırma yapılması gerekmektedir. Bu makalenin amacı, ülkemizde 2016 yılı itibariyle Sağlık Bakanlığı tarafından Geleneksel ve Tamamlayıcı Tıp kapsamında kabul edilmiş olan homeopatinin temellerini tanıtmak ve çocuk diş hekimliğinde olası homeopatik uygulamaları gözden geçirmektedir.

Anahtar Kelimeler: çocuk diş hekimliği, diş hekimliği, homeopati

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INTRODUCTION

Homeopathy is an alternative treatment approach existing for over 200 years. It originated from the combination of the German words *homoios*, which means "similar" or "alike," and *pathos*, which signifies "sensation" and "illness," and their origins were derived from the Greek words *homoios* and *patheia* (1, 2, 3). The origins of homeopathy trace back to Hippocrates; however, owing to its unknown mechanism of action, it continues to be a subject of debate among scientists, regarding it as a controversial topic. It is often labeled as pseudoscientific (2, 4, 5). However, it has become a cultural component of many countries and has rapidly gained popularity worldwide since the mid-1990s (3, 6). It has a broad range of applications, encompassing not only for humans and animals but also in agriculture and reproductive fields (7). The main reason for the widespread adoption of homeopathy, which emerged in the 19th century and has become increasingly popular, is rooted in the medical practices of the past. These practices often involved procedures such as bloodletting, instrument use such as cupping, incision in various parts of the patient's body, and ineffective and potentially harmful treatment options (8).

Homeopathy is primarily based on the notion that the presence of disease-associated symptoms does not indicate a faulty state within the organism. Instead, these symptoms are manifestations of an individual's protective and healing behaviors in response to stress and infection. It underscores that illness is not a result of succumbing to stress and infection factors within the body's system but a response of the body's struggle against these factors (9).

Principles of Homeopathy

Homeopathy is grounded on three fundamental principles: the law of similars, minimum dose, and individualization. The law of similars adopts the principle of "like cures like." Thus, in homeopathy, a specific disease can be treated with a substance that, when taken in high doses, produces symptoms similar to those caused by the disease. For example, bee venom, which causes itching, is used for treating pruritus, and coffee is used to treat insomnia (10). In the principle of minimum dose, the substance associated with the disease is transformed into a solution to reduce side effects and determine an effective dose; this solution is then serially diluted. These dilutions are referred to as potencies, and after these stages, the substance can become a homeopathic remedy (3, 11, 12). Moreover, the principle of individualization asserts that no single remedy is sufficient to treat every illness; this principle recognizes that each person's illness can follow a unique course (9).

In homeopathy, all symptoms of a patient are matched with different homeopathic remedies. These symptoms encompass not only physical aspects but also emotional and mental ones. The homeopath not only addresses the primary afflictions but also inquires about minor discomforts, preferred and disliked foods, favored room temperatures, moments of happiness or unhappiness during the day, specific hours of the day when the patient experiences certain feelings, and where the patient feels better or worse. By asking such questions, the homeopath could understand patient's psychology, emotional state, and character. Through this acquired information, homeopaths may be able to treat the illness using a prepared medicinal solution (9, 13).

Substances Utilized in Drug Production and Prescription Process in Homeopathy

In homeopathy, solutions are prepared from substances such as minerals, viruses, plants, and animal sources (e.g., snake venom, protozoa, and microfungi), as well as from materials obtained from diseased but noninfected tissues. For instance, the "Psorinum" solution developed for treating pancreatic cancer is an alcoholic extract containing the surface of scabies-infested skin, crusts, and pus cells (14). In the homeopathy production process, homeopathic substances are combined with lactose sugar crystals and then pulverized, allowing to be dissolved in water multiple times. This procedure is called trituration. The next step is potentization to reduce the chemical toxicity of the substance and enhance, improve, or increase its medicinal effect. Potentization involves a series of dilutions through vigorous shaking between each solution. Currently, this process uses three different scales. Hahnemann introduced the C scale wherein each step involves diluting the product by a factor of 100. According to this scale, 1 unit of the substance is diluted with 99 units of the solvent (1C potency). In homeopathy, the potency of a solution is directly proportional to the number of dilution steps. Therefore, a solution made at 1C potency is assumed to have low potency. Higher potency levels may increase the duration of the effect (9, 11, 15). For localized symptoms, low potencies (below 12C) are prescribed, whereas for systemic treatment, higher potencies (30C–200C) are used. Evaluating whether symptoms are more emotional or physical should be taken into consideration. Homeopaths tend to give more importance to the patient's emotional and mental states, as well as their physical condition. The more emotional and mental symptoms are present, the higher the potency of the solution is typically used (3). Figure 1 shows the adopted dilution–potency relationship in the prepared homeopathic solutions (11).

Figure 1: Dilution–potency relationship adopted in homeopathic solutions (11).

Critiques and Insufficiency of Scientific Foundations

Most scientists outside of the growing number of alternative medicine proponents reject homeopathy; these scientists

Table 1: Explanations regarding the potential efficacy of homeopathic preparations (31, 32).

Placebo Effect	Having high expectations toward homeopathic remedies can lead to this situation.
Therapeutic Effect of Consultation	While describing oneself to a homeopathic practitioner, the positive emotions a patient has can arise.
Spontaneous Remission without External Factors	The spontaneous recovery of numerous diseases without any external intervention is possible.
Unknown Therapeutic Factors	An unrelated food, exercise, environmental factors, or a procedure applied for the treatment of a different disease might show an effect.
Regression to the Mean	Considering the cyclical nature of many conditions or illnesses, symptoms evolve over time, and patients often seek the most assistance when their condition is at its worst. Nevertheless, the timing of patients' visit to the homeopath can align with the period of their improvement.
Nonhomeopathic Treatment	Patients can receive standard medical treatment and homeopathic treatment simultaneously, and in some cases, the initial medical treatment may contribute to the improvement of the condition.
Discontinuation of Unwanted Treatment	Homeopaths recommend that patients decline medical treatments, such as surgeries or drug applications, which could result in various side effects. Although discontinuing the initially administered medical treatment might seem to be the cause of improvement, this correlation is often linked to homeopathy. However, this scenario can pose a potential risk to the patient because the underlying disease remains untreated.

consider such practice as fraudulent and quackery (16, 17, 18). Currently, reliable statistical evidence for therapeutic effects remains to have no consensus, consistent with the absence of any biologically plausible pharmacological agent; nevertheless, the body of supporters of alternative medicine continues to grow (19). Additionally, proponents of homeopathy claim that homeopathic remedies possess as-yet-unidentified mechanisms of action (20). The notion that any homeopathic remedy has a distinction from the placebo effect remains inconclusive (19).

Homeopathic solutions have been prepared in extremely low concentrations since the 1800s, and some of them contain virtually none of the original substance because of repeated dilutions; this concept is at the core of the issues regarding the mechanisms of action of homeopathic remedies. The Avogadro constant, which is used to determine the number of particles in a mole, is stated to be $6.02214076 \times 10^{23}$ (23, 24, 25). Therefore, a homeopathic substance at 12C ($1/10^{24}$) potency possibly has molecules of the homeopathic substance in the final solution after roughly diluting 1 mole. If further dilution is applied, such molecules may no longer be present in the solution (22, 26). Hence, the minimum amount of substance present in the solution would be one molecule; therefore, a 30C potency solution would need to contain at least one molecule of the original substance dissolved in 1×10^{57} molecules of water. This method would require a container that is approximately 30 billion times the size of the Earth (27). Supporters of modern homeopathy have developed a concept known as "water memory," suggesting that water can remember substances dissolved within it and transmit the effects when ingested. However, this concept contradicts the current understanding of matter, with no evidence to support the idea that water memory has biological or other detectable effects (28, 29). Pharmacological effects do not occur without any actual active component; this inconsistency is attributed to the law of mass action and the observed dose–response relationship of therapeutic drugs not aligning with homeopathy (30). Table 1 explains the potential efficacy of homeopathic preparations (31, 32).

Homeopaths assert that their procedures yield active solutions exclusively containing the specific homeopathic substances they determine, and these substances possess therapeutic properties. Nevertheless, critics focused on the potential that the water employed in the process might have interacted with a myriad of distinct materials over time. Homeopathic practitioners cannot present specific evidence as to why a particular homeopathic substance is selected (17).

Randomized Controlled Trials and Meta-analyses

In 1997, Linde et al. reviewed 186 placebo-controlled trials, utilizing 89 of them for meta-analysis assessment. They investigated whether the clinical effects of homeopathy are influenced by placebo, and found that such clinical effects cannot be solely attributed to placebo. Nevertheless, they underscored the absence of comprehensive and well-designed studies that could be independently replicated, particularly for specific diseases. The studies also highlighted the lack of substantial evidence demonstrating the specific clinical conditions for which a particular homeopathic treatment is clearly effective. In their own research, they identified two shortcomings in terms of providing scientific evidence for experiments. First, the credibility of the presented evidence often diminishes because of the involvement of low-budget studies conducted by homeopathy proponents. Second, the potential for publication bias within research related to homeopathy is highlighted (33).

In 2005, Shang et al. compared and assessed allopathy and homeopathy under placebo-controlled conditions. The outcomes could not confirm that homeopathy outperforms placebo, and they demonstrated that modern medicine holds significant advantages. They pointed out the cumulative impact of various sources of bias and the asymmetry in the funnel plot within the findings (34). Figure 2 depicts the funnel plot. However, they substantiated that the clinical effects of homeopathy arise from nonspecific placebo or context effects. Examples of context effects include the patient–practitioner

relationship in homeopathy, the patient's robust convictions regarding treatment efficacy, and the impact of cultural influences (35).

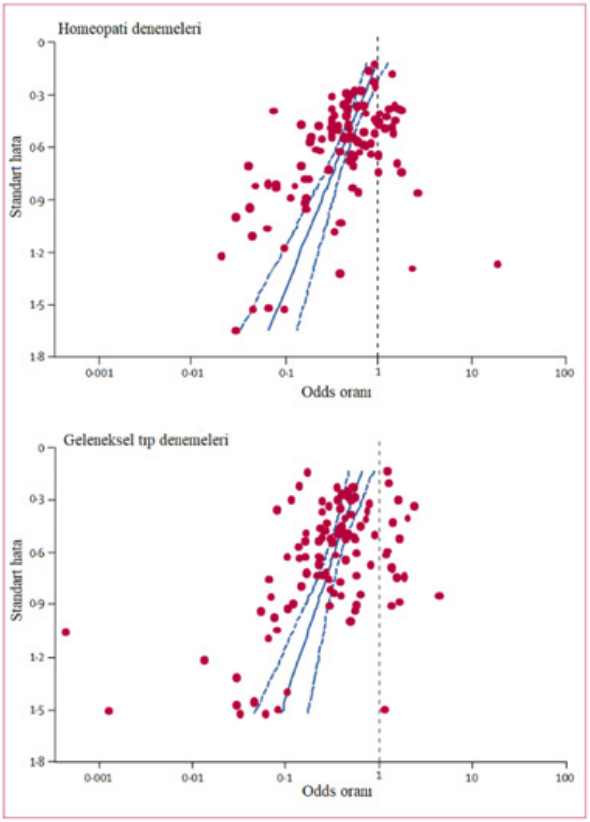

Figure 2: Funnel plot depicting the comparison between homeopathy and conventional medicine (35).

Ernst et al. examined the effects of a homeopathic arnica solution in eight patients with tissue trauma and observed that the effects were not superior to placebo (36). They also reviewed all systematic reviews up to that year and found that certain solutions still did not exhibit significant benefits or superiority over placebo (19).

Various studies are also being conducted in the field of psychology to investigate the effects of homeopathy. One study reviewed 168 cases of attention deficit hyperactivity disorder treated with ritalin as a homeopathic agent, and found that ritalin did not provide specific benefits (37). In a meta-analysis conducted by Rotella et al., homeopathy showed to be more effective than placebo, but no difference was observed between homeopathy and placebo for attention deficit hyperactivity disorder. Considering the available data, the clinical use of homeopathy remains to have insufficient evidence (38).

Organizations Associated with Homeopathy

In the field of homeopathy, three independent organizations have been recognized worldwide. The British Homeopathic Association began its activities in 1902 to promote homeopathic practices among physicians and other healthcare professionals. In May 2019, its name was changed to Homeopathy UK (39). The Faculty of Homeopathy, located in the UK, was established in 1944, and it operates in the academic field (40). The Society of Homeopaths, established in 1978, operates as a private British company in the field of homeopathy (41).

Moreover, the British Homeopathic Dental Association was established in 1991 and is the only organization specifically active in the field of dentistry. This organization aimed to promote the use of homeopathy in dentistry and facilitate a professional understanding of this subject (42). Homeopathy Association in Türkiye was established in Istanbul in 2008 with the purpose of promoting homeopathy, training homeopathy experts, providing homeopathy consulting services, and conducting projects and research (43).

Ethics and Safety

A study conducted by homeopaths in 2000 observed that homeopathic agents were less likely to cause serious side effects (44). However, in 2012, a study systematically examining the potential side effects of homeopathy reported that homeopathy could potentially harm patients and consumers both directly and indirectly (45). Another systematic review and meta-analysis conducted in 2016 reported that the frequency of side effects observed in individuals using homeopathic treatments was similar to that in individuals using placebos and traditional medicines (46).

Some homeopathic agents contain active substances such as arsenic, belladonna, and poison ivy. In rare cases, these agents can be present in formulations in detectable amounts because of incorrect preparation or inadequate dilution (45). Serious symptoms such as seizures and even death can develop as side effects in some individuals, and cases of arsenic poisoning have been reported (47).

In 2016, the Food and Drug Administration (FDA) issued a safety alert warning on the use of homeopathic teething gels and tablets (48). These products are reportedly not properly diluted, containing dangerous amounts of belladonna. Reports of serious side effects in children who use them are consistent with belladonna toxicity (49).

Opting for homeopathic practices instead of evidence-based medicine in patients may increase the risk of missing timely diagnosis and appropriate treatment, thereby worsening the course of diseases, especially those requiring early diagnosis and treatment such as cancer (50, 51). The Pseudoscience Commission does not find homeopathy reliable because it leads to excessive spending on drugs that truly do not work and neglects known effective treatments, causing patients to waste money (52).

Regulations and Prevalence of Homeopathy Worldwide

Homeopathy has been practiced globally, and professional qualifications and licenses are required for practitioners in

many countries (53). According to a report published by the World Health Organization (WHO) in 2019, 100 out of the 133 countries surveyed in 2012 used homeopathy. Among these 100 countries, 22 had established guidelines for regulated homeopathic practices, and in 13 of them, health insurance coverage was provided for homeopathic practitioners (54). Furthermore, homeopathy has been integrated into the existing national healthcare systems in several countries, including India, Mexico, Pakistan, Sri Lanka, and the United Kingdom, since the year 2001 (53). In 2021, France removed all these medical integrations (54). In the USA, the FDA guideline allowing the sale of unapproved homeopathic drugs was also revoked in 2019, stating that no homeopathic products have been approved by the FDA anymore (55, 56)

Homeopathy is one of the most popular approaches in alternative medicine, showing a significant market worldwide. Although exact figures are unknown, available information on the sales of homeopathic remedies suggests a substantial share in the pharmaceutical market. According to the WHO, expenditures on homeopathic remedies were reported as $2.9 billion in the USA in 2007, $408 million in France in 2008, $26 billion in China, $62 million in the United Kingdom, $346 million in Germany, and $7.3 million in Australia (6).

Türkiye was introduced to homeopathy approximately 175 years ago through John Martin Honigberger. Honigberger was a student of Hahnemann; he lived in Istanbul for 2 years, and during the plague outbreak, he administered treatments using homeopathic agents. Until 1998, no research had been conducted on homeopathy in Türkiye. However, since 2016, the Ministry of Health has declared that it is recognized as part of Traditional and Complementary Medicine (43).

Application Areas of Homeopathy in Dentistry

The use of homeopathic remedies by homeopaths in dentistry can be recommended for various conditions, such as stomatitis, xerostomia, neuralgia, temporomandibular joint disorders, sialorrhea, lichen planus, and bruxism (9). A study conducted in 2008 on rats indicated that the homeopathic plant *Symphytum* (comfrey) increased the peripheral bone density around titanium implants (57).

In 2009, Mousavi et al. conducted two single-blind clinical studies. The first study identified the effect of a homeopathic solution obtained from the *Strychnos ignia* plant on erosive oral lichen planus. In the examination where, average lesion size and pain measurements were evaluated at the end of a 4-month period, *Ignatia* was found to be successful (58). In the second study, 100 patients with minor aphthous ulcers were treated with individualized homeopathic remedies or placebo and then followed up for 6 days. Statistically significant results were obtained between the groups in terms of pain intensity and ulcer sizes on the 4th and 6th days (59).

Homeopathic Dana Ullman's book, which was published in 2002, provides suggestions and formulations for toothache. He recommends using a solution at 6C, 12C, or 30C potency administered every 30 minutes for severe pain and every 2–4 hours for mild pain. In case of no improvement after three doses, he suggests applying a different prescription (9). Below are some of the recommended compounds for homeopathic solutions applied for certain dental conditions.

Hepar Sulphuris Calcareum is a compound obtained by mixing the sulfur-rich inner layer of oyster shells with sulfur and heating it. It is commonly used for treating sharp, needle-like pains caused by tooth abscess or extreme sensitivity to dental touch and cold sensation. Patients with this condition often exhibit halitosis. Figure 3 provides a visual representation of Hepar Sulphuris Calcareum (60).

Figure 3: Image of *Hepar Sulphuris Calcareum* belonging to the Homeopathy Plus! pharmaceutical company (60).

Ruta graveolens, also known as rue, is commonly used by individuals experiencing pain after dental interventions. It is also reported to be effective against alveolitis (9). Figure 4 presents a botanical illustration of the *Ruta* plant (61).

Figure 4: Botanical illustration of Ruta graveolens by Otto Wilhelm Thomé (61).

Mercurius solubilis, also known as black oxide of mercury, is preferred for use in individuals with excessive salivation and severe toothache. It is used during night pains and when pain increases with extremely cold or hot conditions. These patients are also prone to halitosis (9).

Atropa belladonna is also known as deadly nightshade. Its leaves produce the hallucinogenic substance "atropine." It can be used for treating sudden throbbing toothaches that can appear and disappear abruptly. Patients with this condition have excessively red gum tissues and dry mouth (9). Figure 5 shows a botanical illustration of *A. belladonna* (62).

Figure 5: Illustration of Atropa belladonna found in Köhler's Medicinal Plants book. (62).

Matricaria chamomilla, also known as wild chamomile, is recommended for patients with severe toothache that lessens when drinking cold beverages but worsens when consuming hot foods and drinks (9). Figure 6 shows a botanical illustration of wild chamomile (63).

Figure 6: Jacob Sturm's illustration of Matricaria chamomilla (63).

Coffee: Drinking coffee is suggested as a treatment option for toothache, especially if it is relieved when drinking a cold beverage and worsens when drinking a warm water. Given that toothache burdens the patient both physically and mentally, consuming coffee with similar effects might be beneficial (9).

Homeopathic Practices in Pediatric Dentistry

The primary goal of pediatric dentistry is to instill positive attitudes and behaviors in children through treatment while maintaining their physical and mental well-being. In pursuit of this goal, similar to all other aspects of health, methods such as Ayurveda, acupuncture, naturopathy, and homeopathy can be employed in the field of oral and dental health (64, 65). Pediatric homeopathy is often valued by its proponents for its low cost, quick recovery time, minimal side effects, and noninvasive nature (64, 66). Considered as part of holistic dentistry, homeopathy is used to address issues such as dental phobia, tooth decay, and toothache (67, 68, 69). Table 2 presents symptoms related to various diseases and the homeopathic remedies that can be used for these symptoms (2). In addition to these agents, toothpastes and lip balms are suitable for homeopathic approaches and treatments. However, their effectiveness has not yet been proven, owing to insufficient evidence (67, 68, 69).

CONCLUSION

Homeopathy is a considerably popular yet controversial field of science that has been used by various societies for decades. Considering all the studies reviewed, homeopathy having statistically significant benefits compared with placebo remains unevident. Its effectiveness still has no clear and sufficient evidence; thus, patients undergoing this treatment procedure should be informed accordingly. Particularly when used for child health and pediatric oral and dental health, its validity is unconfirmed because of the scarcity of standardized studies. Hence, further clinical studies are required to verify whether homeopathic remedies have positive effects on symptoms seemingly related to a patient's emotional, mental, or physical state, and whether these effects are independent of the placebo effect.

Today, the longest lifespans in recorded human history have been achieved. Through modern medicine, millions of people are saved from serious epidemic diseases every year. This accomplishment is made possible through modern diagnostic methods, double-blind studies, and scientifically conducted reliable research. In light of all these observations, modern medical science can potentially gain value from homeopathy, which has long been debated and defined as pseudoscientific. By doing so, a patient-centered, personalized approach can be established. This way, modern medicine can acquire new insights and can be taken a step further.

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TANIM

Çocuk Dergisi, İstanbul Üniversitesi, İstanbul Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı'nın ve İstanbul Üniversitesi Çocuk Sağlığı Enstitüsü'nün; çocuk sağlığı ve hastalıkları alanındaki uluslararası, hakemli, açık erişimli, bilimsel yayın organıdır. Dergi yılda dört sayı olarak Mart, Haziran, Eylül ve Aralık aylarında yayınlanmaktadır. Ocak 2023 tarihi itibariyle süreçteki makaleler hariç, dergi değerlendirmek üzere sadece İngilizce makaleleri dikkate almaktadır ve derginin yayın dili İngilizce'dir.

AMAÇ VE KAPSAM

Çocuk Dergisi, çocuk sağlığı ve hastalıkları alanında nitelikli özgün araştırma, temel konular ile ilgili güncel değişimleri ele alan derleme ve olgu sunumları yayınlayarak literatüre katkıda bulunmayı hedefler.

Temel alınan çocuk sağlığı ve hastalıkları alanının yanında; bu alanla ilgili olmak kaydı ile diğer dahili ve cerrahi bilimlerin hazırlamış olduğu yazılar da kabul edilmektedir. Derginin hedef kitlesini akademisyenler, araştırmacılar, profesyoneller, öğrenciler ve ilgili mesleki, akademik kurum ve kuruluşlar oluşturur.

POLİTİKALAR

Yayın Politikası

Dergi yayın etiğinde en yüksek standartlara bağlıdır ve Committee on Publication Ethics (COPE), Directory of Open Access Journals (DOAJ), Open Access Scholarly Publishers Association (OASPA) ve World Association of Medical Editors (WAME) tarafından yayınlanan etik yayıncılık ilkelerini benimser; Principles of Transparency and Best Practice in Scholarly Publishing başlığı altında ifade edilen ilkeler için: https://publicationethics.org/resources/guidelines-new/principles-transparency-and-best-practice-scholarly-publishing

Gönderilen makaleler derginin amaç ve kapsamına uygun olmalıdır. Orijinal, yayınlanmamış ve başka bir dergide değerlendirme sürecinde olmayan, her bir yazar tarafından içeriği ve gönderimi onaylanmış yazılar değerlendirmeye kabul edilir.

Makale yayınlanmak üzere dergiye gönderildikten sonra yazarlardan hiçbirinin ismi, tüm yazarların yazılı izni olmadan yazar listesinden silinemez ve yeni bir isim yazar olarak eklenemez ve yazar sırası değiştirilemez.

İntihal, duplikasyon, sahte yazarlık/inkar edilen yazarlık, araştrma/veri fabrikasyonu, makale dilimleme, dilimleyerek yayın, telif hakları ihlali ve çıkar çatışmasının gizlenmesi, etik dışı davranışlar olarak kabul edilir. Kabul edilen etik standartlara uygun olmayan tüm makaleler yayından çıkarılır. Buna yayından sonra tespit edilen olası kuraldışı, uygunsuzluklar içeren makaleler de dahildir.

İntihal

Ön kontrolden geçirilen makaleler, iThenticate yazılımı kullanılarak intihal için taranır. İntihal/kendi kendine intihal tespit edilirse yazarlar bilgilendirilir. Editörler, gerekli olması halinde makaleyi değerlendirme ya da üretim sürecinin çeşitli aşamalarında intihal kontrolüne tabi tutabilirler. Yüksek benzerlik oranları, bir makalenin kabul edilmeden önce ve hatta kabul edildikten sonra reddedilmesine neden olabilir. Makalenin türüne bağlı olarak, bunun oranın %15 veya %20'den az olması beklenir.

Çift Kör Hakemlik

İntihal kontrolünden sonra, uygun olan makaleler baş editör tarafından orijinallik, metodoloji, işlenen konunun önemi ve dergi kapsamı ile uyumluluğu açısından değerlendirilir. Editör, makalelerin adil bir şekilde çift taraflı kör hakemlikten geçmesini sağlar ve makale biçimsel esaslara uygun ise, gelen yazıyı yurtiçinden ve /veya yurtdışından en az iki hakemin değerlendirmesine sunar, hakemler gerek gördüğü takdirde yazıda istenen değişiklikler yazarlar tarafından yapıldıktan sonra yayınlanmasına onay verir.

Açık Erişim İlkesi

Dergi açık erişimlidir ve derginin tüm içeriği okura ya da okurun dahil olduğu kuruma ücretsiz olarak sunulur. Okurlar, ticari amaç haricinde, yayıncı ya da yazardan izin almadan dergi makalelerinin tam metnini okuyabilir, indirebilir, kopyalayabilir, arayabilir ve link sağlayabilir. Bu BOAI açık erişim tanımıyla uyumludur.

İşlemleme Ücreti

Derginin tüm giderleri İstanbul Üniversitesi tarafından karşılanmaktadır. Dergide makale yayını ve makale süreçlerinin yürütülmesi ücrete tabi değildir. Dergiye gönderilen ya da yayın için kabul edilen makaleler için işlemleme ücreti ya da gönderim ücreti alınmaz.

Telif Hakkında

ETİK

Yayın Etiği Beyanı

Çocuk Dergisi, yayın etiğinde en yüksek standartlara bağlıdır ve Committee on Publication Ethics (COPE), Directory of Open Access Journals (DOAJ), Open Access Scholarly Publishers Association (OASPA) ve World Association of Medical Editors (WAME) tarafından yayınlanan etik yayıncılık ilkelerini benimser; Principles of Transparency and Best Practice in Scholarly Publishing başlığı altında ifade edilen ilkeler için adres: https://publicationethics.org/resources/guidelines-new/principles-transparency-and-best-practice-scholarly-publishing

Yayın sürecindeki tüm tarafların (Editör, Hakem, Yazar ve Yayıncı) belirtilen etik ilkelere uymaları beklenir.

Gönderilen tüm makaleler orijinal, yayınlanmamış ve başka bir dergide değerlendirme sürecinde olmamalıdır. Yazar makalenin orijinal olduğu, daha önce başka bir yerde yayınlanmadığı ve başka bir yerde, başka bir dilde yayınlanmak üzere değerlendirmede olmadığını beyan etmelidir. Uygulamadaki telif kanunları ve anlaşmaları gözetilmelidir. Telife bağlı materyaller (örneğin tablolar, şekiller veya büyük alıntılar) gerekli izin ve teşekkürle kullanılmalıdır. Başka yazarların, katkıda bulunanların çalışmaları ya da yararlanılan kaynaklar uygun biçimde kullanılmalı ve referanslarda belirtilmelidir. Her bir makale en az iki hakem tarafından çift kör değerlendirmeden geçirilir. İntihal, duplikasyon, sahte yazarlık/inkar edilen yazarlık, araştırma/veri fabrikasyonu, makale dilimleme, dilimleyerek yayın, telif hakları ihlali ve çıkar çatışmasının gizlenmesi, etik dışı davranışlar olarak kabul edilir.

Kabul edilen etik standartlara uygun olmayan tüm makaleler yayından çıkarılır. Buna yayından sonra tespit edilen olası kuraldışı, uygunsuzluklar içeren makaleler de dahildir.

Araştırma Etiği

Çocuk Dergisi araştırma etiğinde en yüksek standartları gözetir ve aşağıda tanımlanan uluslararası araştırma etiği ilkelerini benimser. Makalelerin etik kurallara uygunluğu yazarların sorumluluğundadır.

- Araştırmanın tasarlanması, tasarımın gözden geçirilmesi ve araştırmanın yürütülmesinde, bütünlük, kalite ve şeffaflık ilkeleri sağlanmalıdır.
- Araştırma ekibi ve katılımcılar, araştırmanın amacı, yöntemleri ve öngörülen olası kullanımları; araştırmaya katılımın gerektirdikleri ve varsa riskleri hakkında tam olarak bilgilendirilmelidir.
- Araştırma katılımcılarının sağladığı bilgilerin gizliliği ve yanıt verenlerin gizliliği sağlanmalıdır. Araştırma katılımcıların özerkliğini ve saygınlığını koruyacak şekilde tasarlanmalıdır.
- Araştırma katılımcıları gönüllü olarak araştırmada yer almalı, herhangi bir zorlama altında olmamalıdırlar.
- Katılımcıların zarar görmesinden kaçınılmalıdır. Araştırma, katılımcıları riske sokmayacak şekilde planlanmalıdır.
- Araştırma bağımsızlığıyla ilgili açık ve net olunmalı; çıkar çatışması varsa belirtilmelidir.
- İnsan denekler ile yapılan deneysel çalışmalarda, araştırmaya katılmaya karar veren katılımcıların yazılı bilgilendirilmiş onayı alınmalıdır. Çocukların ve vesayet altındakilerin veya tasdiklenmiş akıl hastalığı bulunanların yasal vasisinin onayı alınmalıdır.
- Çalışma herhangi bir kurum ya da kuruluşta gerçekleştirilecekse bu kurum ya da kuruluştan çalışma yapılacağına dair onay alınmalıdır.
- İnsan öğesi bulunan çalışmalarda, "yöntem" bölümünde katılımcılardan "bilgilendirilmiş onam" alındığının ve çalışmanın yapıldığı kurumdan etik kurul onayı alındığı belirtilmesi gerekir.

Etik Kurul Onayı ve Bilgilendirilmiş Onam

Çocuk Dergisi, World Medical Association (WMA) Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (2013) ve WMA Statement on Animal Use in Biomedical Research (2016) standartlarını kabul eder ve etik standartları ilke olarak benimser.

Klinik ve deneysel çalışmalar, ilaç araştırmaları ve bazı olgu sunumları için yukarıda belirtilen uluslararası standartlara uygun Etik Komisyon raporu gerekmektedir. Gerekli görülmesi halinde Etik Komisyon raporu veya eşdeğeri olan resmi bir yazı yazarlardan talep edilebilir. İnsanlar üzerinde yapılmış deneysel çalışmaların sonuçlarını bildiren yazılarda, çalışmanın yapıldığı kişilere uygulanan

prosedürlerin niteliği tümüyle açıklandıktan sonra, onaylarının alındığına ilişkin bir açıklamaya metin içinde yer verilmelidir. Hayvanlar üzerinde yapılan çalışmalarda ise ağrı, acı ve rahatsızlık verilmemesi için yapılmış olanlar açık olarak makalede belirtilmelidir. Hasta onamları, Etik Kurul raporunun alındığı kurumun adı, onay belgesinin numarası ve tarihi ana metin dosyasında yer alan Gereç ve Yöntem başlığı altında yazılmalıdır. Hastaların kimliklerinin gizliliğini korumak yazarların sorumluluğundadır. Hastaların kimliğini açığa çıkarabilecek fotoğraflar için hastadan ya da yasal temsilcilerinden alınan imzalı izinlerin de gönderilmesi gereklidir.

Yazarların Sorumluluğu

Makalelerin bilimsel ve etik kurallara uygunluğu yazarların sorumluluğundadır. Yazar makalenin orijinal olduğu, daha önce başka bir yerde yayınlanmadığı ve başka bir yerde, başka bir dilde yayınlanmak üzere değerlendirmede olmadığı konusunda teminat sağlamalıdır. Uygulamadaki telif kanunları ve anlaşmaları gözetilmelidir. Telife bağlı materyaller (örneğin tablolar, şekiller veya büyük alıntılar) gerekli izin ve teşekkürle kullanılmalıdır. Başka yazarların, katkıda bulunanların çalışmaları ya da yararlanılan kaynaklar uygun biçimde kullanılmalı ve referanslarda belirtilmelidir.

Gönderilen makalede tüm yazarların akademik ve bilimsel olarak doğrudan katkısı olmalıdır, bu bağlamda "yazar" yayınlanan bir araştırmanın kavramsallaştırılmasına ve dizaynına, verilerin elde edilmesine, analizine ya da yorumlanmasına belirgin katkı yapan, yazının yazılması ya da bunun içerik açısından eleştirel biçimde gözden geçirilmesinde görev yapan birisi olarak görülür. Yazar olabilmenin diğer koşulları ise, makaledeki çalışmayı planlamak veya icra etmek ve / veya revize etmektir. Fon sağlanması, veri toplanması ya da araştırma grubunun genel süpervizyonu tek başına yazarlık hakkı kazandırmaz. Yazar olarak gösterilen tüm bireyler sayılan tüm ölçütleri karşılamalıdır ve yukarıdaki ölçütleri karşılayan her birey yazar olarak gösterilebilir. Yazarların isim sıralaması ortak verilen bir karar olmalıdır. Tüm yazarlar yazar sıralamasını Telif Hakkı Anlaşması Formunda imzalı olarak belirtmek zorundadırlar.

Yazarlık için yeterli ölçütleri karşılamayan ancak çalışmaya katkısı olan tüm bireyler "teşekkür / bilgiler" kısmında sıralanmalıdır. Bunlara örnek olarak ise sadece teknik destek sağlayan, yazıma yardımcı olan ya da sadece genel bir destek sağlayan, finansal ve materyal desteği sunan kişiler verilebilir.

Bütün yazarlar, araştırmanın sonuçlarını ya da bilimsel değerlendirmeyi etkileyebilme potansiyeli olan finansal ilişkiler, çıkar çatışması ve çıkar rekabetini beyan etmelidirler. Bir yazar kendi yayınlanmış yazısında belirgin bir hata ya da yanlışlık tespit ederse, bu yanlışlıklara ilişkin düzeltme ya da geri çekme için editör ile hemen temasa geçme ve işbirliği yapma sorumluluğunu taşır.

Editör ve Hakem Sorumlulukları

Baş editör, makaleleri, yazarların etnik kökeninden, cinsiyetinden, uyruğundan, dini inancından ve siyasi felsefesinden bağımsız olarak değerlendirirler. Yayına gönderilen makalelerin adil bir şekilde çift taraflı kör hakem değerlendirmesinden geçmelerini sağlar. Gönderilen makalelere ilişkin tüm bilginin, makale yayınlanana kadar gizli kalacağını garanti eder.

Baş editör içerik ve yayının toplam kalitesinden sorumludur. Gereğinde hata sayfası yayınlamalı ya da düzeltme yapmalıdır.

Baş editör; yazarlar, editörler ve hakemler arasında çıkar çatışmasına izin vermez. Hakem atama konusunda tam yetkiye sahiptir ve dergide yayınlanacak makalelerle ilgili nihai kararı vermekle yükümlüdür.

Hakemler, araştırma, yazarlar ve/veya araştırmaya fon sağlayanlarla çıkar çatışması içinde olmamalıdır. Hakemler değerlendirmelerinin sonucunda tarafsız bir yargıya varmalıdırlar. Gönderilmiş yazılara ilişkin tüm bilginin gizli tutulmasını sağlamalı ve yazar tarafında herhangi bir telif hakkı ihlali ve intihal fark ederlerse editöre raporlamalıdırlar.

Hakem, makale konusu hakkında kendini vasıflı hissetmiyor ya da zamanında geri dönüş sağlaması mümkün görünmüyorsa, editöre bu durumu bildirmeli ve hakem sürecine kendisini dahil etmemesini istemelidir.

Değerlendirme sürecinde editör hakemlere gözden geçirme için gönderilen makalelerin, yazarların özel mülkü olduğunu ve bunun imtiyazlı bir iletişim olduğunu açıkça belirtir. Hakemler ve yayın kurulu üyeleri başka kişilerle makaleleri tartışamazlar. Hakemlerin kimliğinin gizli kalmasına özen gösterilmelidir. Bazı durumlarda editörün kararıyla, ilgili hakemlerin makaleye ait yorumları aynı makaleyi yorumlayan diğer hakemlere gönderilerek hakemlerin bu süreçte aydınlatılması sağlanabilir.

HAKEM DEĞERLENDİRME POLİTİKALARI

Daha önce yayınlanmamış ya da yayınlanmak üzere başka bir dergide halen değerlendirmede olmayan ve her bir yazar tarafından onaylanan makaleler değerlendirilmek üzere kabul edilir. Gönderilen ve ön kontrolü geçen makaleler iThenticate yazılımı kullanılarak intihal için taranır. İntihal kontrolünden sonra, uygun olan makaleler baş editör tarafından orijinallik, metodoloji, işlenen konunun önemi ve dergi kapsamı ile uyumluluğu açısından değerlendirilir.

Seçilen makaleler en az iki ulusal/uluslararası hakeme çift taraflı kör hakemlik ile değerlendirmeye gönderilir; yayın kararı, hakemlerin talepleri doğrultusunda yazarların gerçekleştirdiği düzenlemelerin ve hakem sürecinin sonrasında baş editör tarafından verilir.

Editör ve Hakem Sorumlulukları
Baş editör, makaleleri, yazarların etnik kökeninden, cinsiyetinden, uyruğundan, dini inancından ve siyasi felsefesinden bağımsız olarak değerlendirirler. Yayına gönderilen makalelerin adil bir şekilde çift taraflı kör hakem değerlendirmesinden geçmelerini sağlar. Gönderilen makalelere ilişkin tüm bilginin, makale yayınlanana kadar gizli kalacağını garanti eder.

Baş editör içerik ve yayının toplam kalitesinden sorumludur. Gereğinde hata sayfası yayınlamalı ya da düzeltme yapmalıdır.

Baş editör; yazarlar, editörler ve hakemler arasında çıkar çatışmasına izin vermez. Hakem atama konusunda tam yetkiye sahiptir ve dergide yayınlanacak makalelerle ilgili nihai kararı vermekle yükümlüdür.

Hakemler, araştırma, yazarlar ve/veya araştırmaya fon sağlayanlarla çıkar çatışması içinde olmamalıdır. Hakemler değerlendirmelerinin sonucunda tarafsız bir yargıya varmalıdırlar. Gönderilmiş yazılara ilişkin tüm bilginin gizli tutulmasını sağlamalı ve yazar tarafında herhangi bir telif hakkı ihlali ve intihal fark ederlerse editöre raporlamalıdırlar.

Hakem, makale konusu hakkında kendini vasıflı hissetmiyor ya da zamanında geri dönüş sağlaması mümkün görünmüyorsa, editöre bu durumu bildirmeli ve hakem sürecine kendisini dahil etmemesini istemelidir.

Değerlendirme sürecinde editör hakemlere gözden geçirme için gönderilen makalelerin, yazarların özel mülkü olduğunu ve bunun imtiyazlı bir iletişim olduğunu açıkça belirtir. Hakemler ve yayın kurulu üyeleri başka kişilerle makaleleri tartışamazlar. Hakemlerin kimliğinin gizli kalmasına özen gösterilmelidir. Bazı durumlarda editörün kararıyla, ilgili hakemlerin makaleye ait yorumları aynı makaleyi yorumlayan diğer hakemlere gönderilerek hakemlerin bu süreçte aydınlatılması sağlanabilir.

Hakem Süreci
Daha önce yayınlanmamış ya da yayınlanmak üzere başka bir dergide halen değerlendirmede olmayan ve her bir yazar tarafından onaylanan makaleler değerlendirilmek üzere kabul edilir. Gönderilen ve ön kontrolü geçen makaleler iThenticate yazılımı kullanılarak intihal için taranır. İntihal kontrolünden sonra, uygun olan makaleler baş editör tarafından orijinallik, metodoloji, işlenen konunun önemi ve dergi kapsamı ile uyumluluğu açısından değerlendirilir.

Baş Editör, makaleleri, yazarların etnik kökeninden, cinsiyetinden, uyruğundan, dini inancından ve siyasi felsefesinden bağımsız olarak değerlendirir. Yayına gönderilen makalelerin adil bir şekilde çift taraflı kör hakem değerlendirmesinden geçmelerini sağlar.

Seçilen makaleler en az iki ulusal/uluslararası hakeme değerlendirmeye gönderilir; yayın kararı, hakemlerin talepleri doğrultusunda yazarların gerçekleştirdiği düzenlemelerin ve hakem sürecinin sonrasında baş editör tarafından verilir.

Baş editör; yazarlar, editörler ve hakemler arasında çıkar çatışmasına izin vermez. Hakem atama konusunda tam yetkiye sahiptir ve dergide yayınlanacak makalelerle ilgili nihai kararı vermekle yükümlüdür.

Hakemlerin değerlendirmeleri objektif olmalıdır. Hakem süreci sırasında hakemlerin aşağıdaki hususları dikkate alarak değerlendirmelerini yapmaları beklenir.

- Makale yeni ve önemli bir bilgi içeriyor mu?
- Öz, makalenin içeriğini net ve düzgün bir şekilde tanımlıyor mu?
- Yöntem bütünlüklü ve anlaşılır şekilde tanımlanmış mı?
- Yapılan yorum ve varılan sonuçlar bulgularla kanıtlanıyor mu?
- Alandaki diğer çalışmalara yeterli referans verilmiş mi?
- Dil kalitesi yeterli mi?

Hakemler, gönderilen makalelere ilişkin tüm bilginin, makale yayınlanana kadar gizli kalmasını sağlamalı ve yazar tarafında herhangi bir telif hakkı ihlali ve intihal fark ederlerse editöre raporlamalıdırlar.

Hakem, makale konusu hakkında kendini vasıflı hissetmiyor ya da zamanında geri dönüş sağlaması mümkün görünmüyorsa, editöre bu durumu bildirmeli ve hakem sürecine kendisini dahil etmemesini istemelidir.

Değerlendirme sürecinde editör hakemlere gözden geçirme için gönderilen makalelerin, yazarların özel mülkü olduğunu ve bunun imtiyazlı bir iletişim olduğunu açıkça belirtir. Hakemler ve yayın kurulu üyeleri başka kişilerle makaleleri tartışamazlar. Hakemlerin kimliğinin gizli kalmasına özen gösterilmelidir.

YAZIM KURALLARI

Makale Hazırlama ve Gönderim

Makaleler, ICMJE-Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (updated in December 2015 - http://www.icmje.org/icmje-recommendations.pdf) ile uyumlu olarak hazırlanmalıdır. Randomize çalışmalar CONSORT, gözlemsel çalışmalar STROBE, tanısal değerli çalışmalar STARD, sistematik derleme ve meta-analizler PRISMA, hayvan deneyli çalışmalar ARRIVE ve randomize olmayan davranış ve halk sağlığıyla ilgili çalışmalar TREND kılavuzlarına uyumlu olmalıdır.

Makaleler sadece https://dergipark.org.tr/en/pub/jchild adresinde yer alan derginin online makale yükleme ve değerlendirme sistemi üzerinden gönderilebilir. Diğer mecralardan gönderilen makaleler değerlendirilmeye alınmayacaktır.

Gönderilen makalelerin dergi yazım kurallarına uygunluğu ilk olarak editöryal ofis tarafından kontrol edilecek, dergi yazım kurallarına uygun hazırlanmamış makaleler teknik düzeltme talepleri ile birlikte yazarlarına geri gönderilecektir.

Yazarların makale ile birlikte aşağıdaki form ve belgeleri göndermeleri ve özet ve anahtar kelime konusundaki standartlara uymaları gerekmektedir.

- **Telif Hakkı Anlaşması Formu**
- **Yazar Formu ve ICJME Potansiyel Çıkar Çatışması Beyan Formu**
- **Etik Komite Onayı**
- **Editöre Ön Yazı**
- **Kapak Sayfası:** Gönderilen tüm makalelerle birlikte ayrı bir kapak sayfası da gönderilmelidir. Bu sayfa;

Makalenin Türkçe ve İngilizce başlığını ve 50 karakteri geçmeyen Türkçe ve İngilizce kısa başlığını,

- Yazarların isimlerini, kurumlarını, akademik derecelerini ve ORCID numaralarını
- Finansal destek bilgisi ve diğer destek kaynakları hakkında detaylı bilgiyi,
- Sorumlu yazarın ismi, adresi, telefonu (cep telefonu dahil), faks numarası ve e-posta adresini,
- Makale hazırlama sürecine katkıda bulunan ama yazarlık kriterlerini karşılamayan bireylerle ilgili bilgileri içermelidir.

Özet: Editöre Mektup türündeki yazılar dışında kalan tüm makalelerin Türkçe ve İngilizce özetleri olmalıdır. Özgün Araştırma makalelerinin özetleri "Amaç", "Gereç ve Yöntem", "Bulgular" ve "Sonuç" alt başlıklarını içerecek biçimde hazırlanmalıdır. Olgu sunumu ve derleme türündeki yazıların Özet bölümleri alt başlık içermemelidir. Türkçe ve İngilizce özetlerin her biri 250 kelime olmalıdır.

Anahtar Kelime: Tüm makaleler en az 3 en fazla 6 anahtar kelimeyle birlikte gönderilmeli, anahtar kelimeler Türkçe ve İngilizce özetlerin hemen altına Türkçe ve İngilizce olarak yazılmalıdır. Kısaltmalar anahtar sözcük olarak kullanılmamalıdır. Anahtar sözcükler National Library of Medicine (NLM) tarafından hazırlanan Medical Subject Headings (MeSH) veritabanından seçilmelidir http://www.nlm.nih.gov/mesh/MBrowser.html

Makale Türleri

Özgün Araştırma: Ana metin "Giriş", "Gereç ve Yöntem", "Bulgular" ve "Tartışma" alt başlıklarını içermelidir. Sonucu desteklemek için istatistiksel analiz genellikle gereklidir. İstatistiksel analiz, tıbbi dergilerdeki istatistik verilerini bildirme kurallarına göre yapılmalıdır (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). İstatiksel analiz ile ilgili bilgi, Yöntemler bölümü içinde ayrı bir alt başlık olarak yazılmalı ve kullanılan yazılım kesinlikle tanımlanmalıdır.

Birimler, uluslararası birim sistemi olan International System of Units (SI)'a uygun olarak hazırlanmadır.

Derleme: Yazının konusunda birikimi olan ve bu birikimleri uluslararası literatüre yayın ve atıf sayısı olarak yansımış uzmanlar tarafından hazırlanmış ve Çocuk Dergisi tarafından davet mektubu almış olan yazılar değerlendirmeye alınır. Bir bilgi ya da konunun klinikte kullanılması için vardığı son düzeyi anlatan, tartışan, değerlendiren ve gelecekte yapılacak olan çalışmalara yön veren bir formatta hazırlanmalıdır. Ana metin "Giriş", "Klinik ve Araştırma Etkileri" ve "Sonuç" bölümlerini içermelidir.

Olgu Sunumu: Olgu sunumları için sınırlı sayıda yer ayrılmakta ve sadece ender görülen, tanı ve tedavisi güç olan hastalıklarla ilgili, yeni bir yöntem öneren, kitaplarda yer verilmeyen bilgileri yansıtan, ilgi çekici ve öğretici özelliği olan olgular yayına kabul edilmektedir. Ana metin; "Giriş", "Olgu Sunumu", "Tartışma" ve Sonuç" alt başlıklarını içermelidir.

Editöre Mektup: Dergide daha önce yayınlanan bir yazının önemini, gözden kaçan bir ayrıntısını ya da eksik kısımlarını tartışabilir. Ayrıca derginin kapsamına giren alanlarda okurların ilgisini çekebilecek konular ve özellikle eğitici olgular hakkında da Editöre Mektup formatında yazılar yayınlanabilir. Okuyucular da yayınlanan yazılar hakkında yorum içeren Editöre Mektup formatında yazılarını sunabilirler. Özet, anahtar sözcük, tablo, şekil, resim ve diğer görseller kullanılmaz. Ana metin alt başlıksız olmalıdır. Hakkında mektup yazılan yayına ait cilt, yıl, sayı, sayfa numaraları, yazı başlığı ve yazarların adları açık bir şekilde belirtilmeli, kaynak listesinde yazılmalı ve metin içinde atıfta bulunulmalıdır.

Tablolar

Tablolar ana dosyaya eklenmeli, kaynak listesi sonrasında sunulmalı, ana metin içerisindeki geçiş sıralarına uygun olarak numaralandırılmadır. Tabloların üzerinde tanımlayıcı bir başlık yer almalı ve tablo içerisinde geçen kısaltmaların açılımları tablo altına tanımlanmalıdır. Tablolar Microsoft Office Word dosyası içinde "Tablo Ekle" komutu kullanılarak hazırlanmalı ve kolay okunabilir şekilde düzenlenmelidir. Tablolarda sunulan veriler ana metinde sunulan verilerin tekrarı olmamalı; ana metindeki verileri destekleyici nitelikte olmalıdır.

Resim ve Resim Altyazıları

Resimler, grafikler ve fotoğraflar (TIFF ya da JPEG formatında) ayrı dosyalar halinde sisteme yüklenmelidir. Görseller bir Word dosyası dokümanı ya da ana doküman içerisinde sunulmamalıdır. Alt birimlere ayrılan görseller olduğunda, alt birimler tek bir görsel içerisinde verilmemelidir. Her bir alt birim sisteme ayrı bir dosya olarak yüklenmelidir. Resimler alt birimleri belli etme amacıyla etiketlenmemelidir (a, b, c vb.). Resimlerde altyazıları desteklemek için kalın ve ince oklar, ok başları, yıldızlar, asteriksler ve benzer işaretler kullanılabilir. Makalenin geri kalanında olduğu gibi resimler de kör olmalıdır. Bu sebeple, resimlerde yer alan kişi ve kurum bilgileri de körleştirilmelidir. Görsellerin minimum çözünürlüğü 300 DPI olmalıdır. Değerlendirme sürecindeki aksaklıkları önlemek için gönderilen bütün görsellerin çözünürlüğü net ve boyutu büyük (minimum boyutlar 100x100 mm) olmalıdır. Resim altyazıları ana metnin sonunda yer almalıdır.

Makale içerisinde geçen tüm kısaltmalar, ana metin ve özette ayrı ayrı olmak üzere ilk kez kullanıldıkları yerde tanımlanarak kısaltma tanımın ardından parantez içerisinde verilmelidir.

Ana metin içerisinde cihaz, yazılım, ilaç vb. ürünlerden bahsedildiğinde ürünün ismi, üreticisi, üretildiği şehir ve ülke bilgisini içeren ürün bilgisi parantez içinde verilmelidir; "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)".

Tüm kaynaklar, tablolar ve resimlere ana metin içinde uygun olan yerlerde sırayla numara verilerek atıf yapılmalıdır.

Özgün araştırmaların kısıtlamaları, engelleri ve yetersizliklerinden Sonuç paragrafı öncesi "Tartışma" bölümünde bahsedilmelidir.

Revizyonlar

Yazarlar makalelerinin revizyon dosyalarını gönderirken, ana metin üzerinde yaptıkları değişiklikleri işaretlemeli, ek olarak, hakemler tarafından öne sürülen önerilerle ilgili notlarını "Hakemlere Cevap" dosyasında göndermelidir. Hakemlere Cevap dosyasında her hakemin yorumunun ardından yazarın cevabı gelmelidir. Revize makaleler karar mektubunu takip eden 20 gün içerisinde dergiye gönderilmelidir. Yazarların revizyon için ek süreye ihtiyaç duymaları durumunda uzatma taleplerini ilk 20 gün sona ermeden dergiye iletmeleri gerekmektedir.

Yayına kabul edilen makaleler dil bilgisi, noktalama ve biçim açısından kontrol edilir. Yayın süreci tamamlanan makaleler, yayın planına dahil edildikleri sayıyla birlikte yayınlanmadan önce erken çevrimiçi formatında dergi web sitesinde yayına alınır. Kabul edilen makalelerin baskıya hazır PDF dosyaları sorumlu yazarlara iletilir ve yayın onaylarının 2 gün içerisinde dergiye iletilmesi istenir.

Kaynaklar

Atıf yapılırken en son ve en güncel yayınlar tercih edilmelidir. Atıf yapılan erken çevrimiçi makalelerin DOI numaraları mutlaka sağlanmalıdır. Kaynakların doğruluğundan yazarlar sorumludur. Dergi isimleri Index Medicus/Medline/PubMed'de yer alan dergi kısaltmaları ile uyumlu olarak kısaltılmalıdır. Altı ya da daha az yazar olduğunda tüm yazar isimleri listelenmelidir. Eğer 7 ya da daha fazla yazar varsa ilk 6 yazar yazıldıktan sonra "et al." konulmalıdır. Ana metinde kaynaklara atıf yapılırken parantez içinde Arap rakamları kullanılmalıdır. Farklı yayın türleri için kaynak stilleri aşağıdaki örneklerde sunulmuştur:

Dergi makalesi: Blasco V, Colavolpe JC, Antonini F, Zieleskiewicz L, Nafati C, Albanèse J, et al. Long-term outcome in kidney recipients from donors treated with hydroxyethylstarch 130/0.4 and hydroxyethylstarch 200/0.6. Br J Anaesth 2015;115(5):797-8.

Kitap bölümü: Sherry S. Detection of thrombi. In: Strauss HE, Pitt B, James AE, editors. Cardiovascular Medicine. St Louis: Mosby; 1974.p.273-85.

Tek yazarlı kitap: Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Marcel Dekker; 1993.

Yazar olarak editör(ler): Norman IJ, Redfern SJ, editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

Toplantıda sunulan yazı: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992.p.1561-5.

Bilimsel veya teknik rapor: Smith P. Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX) Dept. of Health and Human Services (US). Office of Evaluation and Inspections: 1994 Oct. Report No: HHSIGOE 169200860.

Tez: Kaplan SI. Post-hospital home health care: the elderly access and utilization (dissertation). St. Louis (MO): Washington Univ. 1995.

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SON KONTROL LİSTESİ

- **Editöre Ön Yazı**
  - Makalenin türü
  - Başka bir dergiye gönderilmemiş olduğu bilgisi
  - Sponsor veya ticari bir firma ile ilişkisi (varsa belirtiniz)
  - İstatistik kontrolünün yapıldığı (araştırma makaleleri için)
  - İngilizce yönünden kontrolünün yapıldığı
  - Yazarlara Bilgide detaylı olarak anlatılan dergi politikalarının gözden geçirildiği
  - Kaynakların NLM referans sistemine göre belirtildiği
- Telif Hakkı Anlaşması Formu
- Yazar Formu
- Daha önce basılmış materyal (yazı-resim-tablo) kullanılmış ise izin belgesi
- İnsan öğesi bulunan çalışmalarda "gereç ve yöntem" bölümünde Helsinki Deklarasyonu prensiplerine uygunluk, kendi kurumlarından alınan etik kurul onayının ve hastalardan "bilgilendirilmiş olur (rıza)" alındığının belirtilmesi
- Hayvan öğesi kullanılmış ise "gereç ve yöntem" bölümünde "Guide for the Care and Use of Laboratory Animals" prensiplerine uygunluğunun belirtilmesi
- Kapak Sayfası
  - Makalenin kategorisi
  - Makalenin Türkçe ve İngilizce başlığı
  - Makalenin Türkçe ve İngilizce kısa başlığı
  - Yazarların ismi soyadı, unvanları ve bağlı oldukları kurumlar (üniversite ve fakülte bilgisinden sonra şehir ve ülke bilgisi de yer almalıdır), e-posta adresleri
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  - Varsa teşekkür bilgisi
- Makale ana metni dosyasında olması gerekenler
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  - Özetler 250 kelime Türkçe ve 250 kelime İngilizce
  - Anahtar Kelimeler: 3 -6 Türkçe ve 3 -6 İngilizce
  - Makale ana metin bölümleri
  - Kaynaklar
  - Teşekkür (varsa belirtiniz)
  - Tablolar-Resimler, Şekiller (başlık, tanım ve alt yazılarıyla)

DESCRIPTION

Journal of Child is an international, scientific, open acces, peer-reviewed official publication of Istanbul University, Faculty of Medicine, Department of Child Health and Diseases and Istanbul University, Institute of Child Health. It is a quarterly journal published in March, June, September and December. Starting from January 2023, except for the articles in process, the journal has started to consider manuscripts in English for evaluation and publication language has become English.

AIMS AND SCOPE

Journal of Child aims to contribute to the literature by publishing high quality original articles, reviews focusing on key subjects and contemporary developments, and case reports in the field of child health and diseases.

The journal welcomes articles about internal and surgical medicine as well, provided that these are related to child health and diseases. The target group of the journal consists of academicians, researchers, professionals, students, related professional and academic bodies and institutions.

POLICIES

Publication Policy

The journal is committed to upholding the highest standards of publication ethics and pays regard to Principles of Transparency and Best Practice in Scholarly Publishing published by the Committee on Publication Ethics (COPE), the Directory of Open Access Journals (DOAJ), the Open Access Scholarly Publishers Association (OASPA), and the World Association of Medical Editors (WAME) on https://publicationethics.org/resources/guidelines-new/principles-transparency-and-best-practice-scholarly-publishing

The subjects covered in the manuscripts submitted to the Journal for publication must be in accordance with the aim and scope of the Journal. Only those manuscripts approved by every individual author and that were not published before in or sent to another journal, are accepted for evaluation.

Changing the name of an author (omission, addition or order) in papers submitted to the Journal requires written permission of all declared authors.

Plagiarism, duplication, fraud authorship/denied authorship, research/data fabrication, salami slicing/salami publication, breaching of copyrights, prevailing conflict of interest are unethical behaviors. All manuscripts not in accordance with the accepted ethical standards will be removed from the publication. This also contains any possible malpractice discovered after the publication.

Plagiarism

Submitted manuscripts that pass preliminary control are scanned for plagiarism using iThenticate software. If plagiarism/self-plagiarism will be found authors will be informed. Editors may resubmit manuscript for similarity check at any peer-review or production stage if required. High similarity scores may lead to rejection of a manuscript before and even after acceptance. Depending on the type of article and the percentage of similarity score taken from each article, the overall similarity score is generally expected to be less than 15 or 20%.

Double Blind Peer-Review

After plagiarism check, the eligible ones are evaluated by the editors-in-chief for their originality, methodology, the importance of the subject covered and compliance with the journal scope. The editor provides a fair double-blind peer review of the submitted articles and hands over the papers matching the formal rules to at least two national/international referees for evaluation and gives green light for publication upon modification by the authors in accordance with the referees' claims.

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The journal is an open access journal and all content is freely available without charge to the user or his/her institution. Except for commercial purposes, users are allowed to read, download, copy, print, search, or link to the full texts of the articles in this journal without asking prior permission from the publisher or the author. This is in accordance with the BOAI definition of open access.

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All expenses of the journal are covered by the Istanbul University. Processing and publication are free of charge with the journal. There is no article processing charges or submission fees for any submitted or accepted articles.

ETHICS

Statement of Publication Ethics
Journal of Child is committed to upholding the highest standards of publication ethics and pays regard to Principles of Transparency and Best Practice in Scholarly Publishing published by the Committee on Publication Ethics (COPE), the Directory of Open Access Journals (DOAJ), the Open Access Scholarly Publishers Association (OASPA), and the World Association of Medical Editors (WAME) on https://publicationethics.org/resources/guidelines-new/principles-transparency-and-best-practice-scholarly-publishing

All parties involved in the publishing process (Editors, Reviewers, Authors and Publishers) are expected to agree on the following ethical principles.

All submissions must be original, unpublished (including as full text in conference proceedings), and not under the review of any other publication synchronously. Authors must ensure that submitted work is original. They must certify that the manuscript has not previously been published elsewhere or is not currently being considered for publication elsewhere, in any language. Applicable copyright laws and conventions must be followed. Copyright material (e.g. tables, figures or extensive quotations) must be reproduced only with appropriate permission and acknowledgement. Any work or words of other authors, contributors, or sources must be appropriately credited and referenced.

Each manuscript is reviewed by at least two referees under double-blind peer review process. Plagiarism, duplication, fraud authorship/denied authorship, research/data fabrication, salami slicing/salami publication, breaching of copyrights, prevailing conflict of interest are unethical behaviors.

All manuscripts not in accordance with the accepted ethical standards will be removed from the publication. This also contains any possible malpractice discovered after the publication.

Research Ethics
Journal of Child adheres to the highest standards in research ethics and follows the principles of international research ethics as defined below. The authors are responsible for the compliance of the manuscripts with the ethical rules.

- Principles of integrity, quality and transparency should be sustained in designing the research, reviewing the design and conducting the research.
- The research team and participants should be fully informed about the aim, methods, possible uses and requirements of the research and risks of participation in research.
- The confidentiality of the information provided by the research participants and the confidentiality of the respondents should be ensured. The research should be designed to protect the autonomy and dignity of the participants.
- Research participants should participate in the research voluntarily, not under any coercion.
- Any possible harm to participants must be avoided. The research should be planned in such a way that the participants are not at risk.
- The independence of research must be clear; and any conflict of interest or must be disclosed.
- In experimental studies with human subjects, written informed consent of the participants who decide to participate in the research must be obtained. In the case of children and those under wardship or with confirmed insanity, legal custodian's assent must be obtained.
- If the study is to be carried out in any institution or organization, approval must be obtained from this institution or organization.
- In studies with human subject, it must be noted in the method's section of the manuscript that the informed consent of the participants and ethics committee approval from the institution where the study has been conducted have been obtained.

Ethics Committee Approval and Informed Consent
Journal of Child takes as principle to comply with the ethical standards of World Medical Association (WMA) Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects revised in 2003 and WMA Statement on Animal Use in Biomedical Research revised in 2016.

An approval of research protocols by the Ethics Committee in accordance with international standards mentioned above is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, signed releases of the patient or of their legal representative should be enclosed.

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It is authors' responsibility to ensure that the article is in accordance with scientific and ethical standards and rules. And authors must ensure that submitted work is original. They must certify that the manuscript has not previously been published elsewhere or is not currently being considered for publication elsewhere, in any language. Applicable copyright laws and conventions must be followed. Copyright material (e.g. tables, figures or extensive quotations) must be reproduced only with appropriate permission and acknowledgement. Any work or words of other authors, contributors, or sources must be appropriately credited and referenced.

All the authors of a submitted manuscript must have direct scientific and academic contribution to the manuscript. The author(s) of the original research articles is defined as a person who is significantly involved in "conceptualization and design of the study", "collecting the data", "analyzing the data", "writing the manuscript", "reviewing the manuscript with a critical perspective" and "planning/conducting the study of the manuscript and/or revising it". Fund raising, data collection or supervision of the research group are not sufficient roles to be accepted as an author. The author(s) must meet all these criteria described above. The order of names in the author list of an article must be a co-decision and it must be indicated in the Copyright Agreement Form. The individuals who do not meet the authorship criteria but contributed to the study must take place in the acknowledgement section. Individuals providing technical support, assisting writing, providing a general support, providing material or financial support are examples to be indicated in acknowledgement section.

All authors must disclose all issues concerning financial relationship, conflict of interest, and competing interest that may potentially influence the results of the research or scientific judgment.

When an author discovers a significant error or inaccuracy in his/her own published paper, it is the author's obligation to promptly cooperate with the Editor to provide retractions or corrections of mistakes.

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Editor-in-Chief evaluates manuscripts for their scientific content without regard to ethnic origin, gender, citizenship, religious belief or political philosophy of the authors. Editor-in-Chief provides a fair double-blind peer review of the submitted articles for publication and ensures that all the information related to submitted manuscripts is kept as confidential before publishing.

Editor-in-Chief is responsible for the contents and overall quality of the publication and must publish errata pages or make corrections when needed.

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A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The anonymity of the referees must be ensured. In particular situations, the editor may share the review of one reviewer with other reviewers to clarify a particular point.

PEER REVIEW POLICIES

Only those manuscripts approved by its every individual author and that were not published before in or sent to another journal, are accepted for evaluation.

Submitted manuscripts that pass preliminary control are scanned for plagiarism using iThenticate software. After plagiarism check, the eligible ones are evaluated by editor-in-chief for their originality, methodology, the importance of the subject covered and compliance with the journal scope.

The editor hands over the papers matching the formal rules to at least two national/international referees for double-blind peer review evaluation and gives green light for publication upon modification by the authors in accordance with the referees' claims.

Responsibility for the Editor and Reviewers
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Editor-in-Chief evaluates manuscripts for their scientific content without regard to ethnic origin, gender, citizenship, religious belief or political philosophy of the authors and ensures a fair double-blind peer review of the selected manuscripts.

The selected manuscripts are sent to at least two national/international referees for evaluation and publication decision is given by Editor-in-Chief upon modification by the authors in accordance with the referees' claims.

Editor-in-Chief does not allow any conflicts of interest between the authors, editors and reviewers and is responsible for final decision for publication of the manuscripts in the Journal.

Reviewers' judgments must be objective. Reviewers' comments on the following aspects are expected while conducting the review.

- Does the manuscript contain new and significant information?
- Does the abstract clearly and accurately describe the content of the manuscript?
- Is the problem significant and concisely stated?
- Are the methods described comprehensively?

- Are the interpretations and consclusions justified by the results?
- Is adequate references made to other Works in the field?
- Is the language acceptable?

Reviewers must ensure that all the information related to submitted manuscripts is kept as confidential and must report to the editor if they are aware of copyright infringement and plagiarism on the author's side.

A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The anonymity of the referees is important.

AUTHOR GUIDELINES

Manuscript Organization and Submission

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2015 - http://www.icmje.org/icmje-recommendations.pdf). Author(s) are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at https://dergipark.org.tr/en/pub/jchild Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Author(s) are required to submit the following documents together with the manuscript and must ensure that the abstract and keywords are in line with the standards explained in below.

- **Copyright Agreement Form**
- **Author Form and ICMJE Potential Conflict of Interest Disclosure Form**
- **Ethics Committee Approval**
- **Cover Letter to the Editor**
- **Title Page:** A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, academic degree(s) and ORCID ID(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfil the authorship criteria.

Abstract: A Turkish and an English abstract should be submitted with all submissions except for Letters to the Editor. Submitting a Turkish abstract is not compulsory for international authors. The abstract of Original Articles should be structured with subheadings (Objective, Materials and Methods, Results, and Conclusion). Abstracts of Case Reports and Reviews should be unstructured. Abstracts should be 250 words.

Keywords: Each submission must be accompanied by a minimum of 3 to a maximum of 6 keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (http://www.nlm.nih.gov/mesh/MBrowser.html) .

Manuscript Types

Original Articles: The main text of original articles should be structured with Introduction, Material and Method, Results, Discussion, and Conclusion subheadings. Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in

accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Review Articles: Manuscripts prepared by experts who have received an invitation letter from the Journal of Child have knowledge on the subject of the article and whose knowledge is reflected in the number of publications and citations in the international literature are welcomed. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

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Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

Revisions

When submitting a revised version of a paper, the author(s) must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed

by the author's reply) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 20 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 20-day period is over.

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Reference Style and Examples

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study KidneyInt: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktivitelerive Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. SağlıkBilimleriEnstitüsü, DoktoraTezi. 2007.

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodIElD/cid.htm.

CHECKLIST

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  - The category of the manuscript
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  - Including disclosure of any commercial or financial involvement.
  - Confirming that the statistical design of the research article is reviewed.
  - Confirming that last control for fluent English was done.
  - Confirming that journal policies detailed in Information for Authors have been reviewed.
  - Confirming that the references cited in the text and listed in the references section are in line with NLM.
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- Statement that informed consent was obtained after the procedure(s) had been fully explained. Indicating whether the institutional and national guide for the care and use of laboratory animals was followed as in "Guide for the Care and Use of Laboratory Animals".
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  - The category of the manuscript
  - The title of the manuscript both in Turkish and in English
  - Short title (running head) both in Turkish and in English
  - All authors' names and affiliations (institution, faculty/department, city, country), e-mail addresses
  - Corresponding author's email address, full postal address, telephone and fax number
  - ORCIDs of all authors.
  - Acknowledgement (if exists)
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  - Abstracts both in Turkish and in English (250 words)
  - Key words: 3 - 6 words both in Turkish and in English
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  - References
  - All tables, illustrations (figures) (including title, description, footnotes)