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Review

Neuroblastoma and Hippo Signaling Pathway

Nöroblastom ve Hippo Sinyal Yolağı

Selen Kum Özşengezer
Zekiye Altun
Nur Olgun

ABSTRACT

Neuroblastoma (NB) is a malignant tumor often seen in early childhood and originating from the sympathetic nervous system.Hippo signal pathway is a mechanism involved in organ growth, differentiation and plays an important role in stem cells, cancer stem cells and tumorigenesis.YAP,which is the transcription co-activator, is an important part of this mechanism and the inhibition effect of YAP inhibition on cell proliferation highlights the effect of this pathway on cancer. In the diagnosis and prognosis of pediatric tumors, more beneficial clinical applications of YAP and other routes can be considered and further research can be expected.Hippo pathway members, especially YAP, are potential new treatment targets for tumors that show overexpression. Along with the clinical features that affect the progression of the NB, chromosomal abnormalities and both oncogenes and tumor suppressor genes need to be evaluated together to develop new treatment strategies, especially in aggressive NB's. In recent studies, YAP inhibition has been shown to impair tumor growth and NB's cisplatin resistance.This defines YAP as a potential therapeutic target, especially for cisplatin-resistant NB.Hippo is a new glimmer of hope for NB in the signal pathway and open to study and development since all steps cannot be actively determined.

Keywords: *Neuroblastoma, hippo signaling pathway, pediatric oncology*

ÖZ

Nöroblastom (NB) sıklıkla erken çocukluk döneminde görülen ve sempatik sinir sisteminden kaynaklanan malign bir tümördür. Hippo sinyal yolağı, organ büyümesi, farklılaşması ile ilgili bir mekanizmadır ve kök hücreler, kanser kök hücreleri ve tümör oluşumunda önemli bir rol oynar. Transkripsiyon aktivatör olan YAP, bu mekanizmanın önemli bir parçasıdır ve YAP inhibisyonunun hücre çoğalması üzerindeki inhibisyon etkisi, bu yolun kanser üzerindeki etkisini vurgular.Pediatrik tümörlerin tanı ve prognozunda YAP'ın ve diğer yolların daha faydalı klinik uygulamaları düşünülebilir ve daha fazla araştırma beklenebilir. Hippo yolu üyeleri, özellikle YAP, aşırı ekspresyon gösteren tümörler için potansiyel yeni tedavi hedefleridir. NB'nin ilerlemesini etkileyen klinik özelliklerin yanı sıra, özellikle agresif NB'lerde yeni tedavi stratejileri geliştirmek için kromozomal anormalliklerin ve hem onkogenlerin hem de tümör baskılayıcı genlerin birlikte değerlendirilmesi gerekir. Son çalışmalarda YAP inhibisyonunun tümör büyümesini ve NB'nin sisplatin direncini bozduğu gösterilmiştir. YAP'ın özellikle sisplatine dirençli NB için potansiyel bir terapötik hedef olarak tanımlar. Hippo, sinyal yolunda NB için yeni bir umut ışığıdır ve tüm adımlar aktif olarak belirlenemediği için çalışmaya ve gelişmeye açıktır.

Anahtar kelimeler: *Nöroblastom, hippo sinyal yolağı, pediatrik onkoloji*

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Neuroblastoma

Neuroblastoma (NB) is a childhood solid cancer that accounts for about 15% of patient deaths in pediatric oncology. Neuroblastoma originates from the primitive sympathetic neural precursor cells in the peripheral nervous system [1,2]. Although tumors can occur anywhere in the body along the sympathetic nervous system, many of the primary neuroblastoma types can originate in the abdomen, even from the adrenal gland. One of the most common embryonal cancers is neuroblastoma, especially in patients under 5 years of age [3,4]. It is the second most common tumor of solid origin among children under 15 years of age. Prognosis is better in babies less than 18 months old and diagnosed with neuroblastoma not amplified with MYCN. However, children with neuroblastoma may have different clinical, biological, and prognostic features in adrenal, abdominal / retroperitoneal, neck, thoracic, or pelvic regions, depending on the location of their primary tumors in another region [5]. Neuroblastomas can be seen as

different clinical representations ranging from spontaneous regression, metastatic and treatment-resistant disease. Patients are classified by risk groups before treatment as having very low, low, intermediate and high risk. Various stages have been identified using the International Neuroblastoma Staging System (INSS). These stages are classified as 1, 2A, 2B, 3, 4 and 4S. The classification criteria include many factors such as the degree of surgical excision of the primary tumor, lymph node involvement, spread to distant organs, the level of bone marrow involvement, and age [6]. In addition, the International Neuroblastoma Risk Group (INRG), a new classification system, has also been developed [7]. MYCN amplification or 11q heterozygous loss are often found in high-risk neuroblastoma patients which is related to poor prognosis and recurrence of disease. MYCN amplification has been identified as an important poor prognostic factor for survival and remains one of the most important validated biomarkers in neuroblastoma. Inhibition of Aurora A kinase (AURKA) in the treatment of neuroblastoma has been extensively investigated. Aurora A and Aurora kinase B (AURKB) are two important regulators of the cell cycle. AURKA plays an important role in MYCN amplification. AURKA or AURKB expressions are associated with poor prognosis in neuroblastoma and might be targeted with specialized inhibitors. Inhibition of both AURKA and AURKB can be targeted using pan-Aurora kinase (AurK) inhibitors. Tozasertib (a pan-Aurora inhibitor) has been shown to be active in drug-resistant neuroblastomas [8]. High-dose chemotherapy, surgery, radiotherapy and anti-GD2 immunotherapy are used in the treatment of high-risk diseases [9]. NB tumors consist of two types of cells: neuroblastic ganglionic cells and reactive schwannian stromal cells which are divided into four basic morphologic types. These morphologic types include ganglioneuroma, mixed ganglioneuroblastoma, nodular ganglioneuroblastoma and neuroblastoma. These morphological characterizations demonstrate the levels of tumor differentiation in neuroblasts. Neuroblasts die during differentiation and maturation period before they reach the required maturity levels and leave a dominant schwannian stroma. After that, ganglioneuromas express a fully matured and differentiated NB. Although the reason for the assortment and differentiation of Schwann cells is not fully known, retinoic acid treatments are applied to differentiate residual disease with an increase in event - free survival [10].

Neuroblastoma and Development of Neural Crest

The neural crest (NC) forms during the gastrulation and neurulation processes and migrates throughout the embryonal development. Then it harbors a temporary embryonal cell population and differentiates to many various tissues. NC is a temporary embryological tissue originating from neuroectoderm. Development of neural creast involves various stages. During the neural tube formation, a complex and remarkable maturation process occurs. Thus, NC precursors gain the potential for differentiation and form a self-regenerating phenotype reminiscent of embryonic stem cells [11]. With the formation of tissues involved in neural tube development throughout gastrulation, development of neural crest is induced. The primitive neural tube consists of non-neural ectoderm and neural plate (NP) and neural plate border (NPB) tissues. Expression of the NC determining genes is triggered by the induction of genes in NPB. Interconnected signaling pathways of bone morphogenic protein (BMP), Wingless / Int (WNT), Fibroblast growth factor (FGF), and to a lesser extent Notch / Delta signal mediate this induction. This induction chain activates key transcription factors. Cascading signal gradients of BMP, Wnt, Notch and alternative ligands permit differentiation of assorted endothelial elements [12].

Oncogenic and Transcriptional Agents in Neuroblastoma

Although tumorigenesis in neuroblastoma is initiated by the deteriorating development of the neural crest precursors, no single genetic or epigenetic mutation is initiated after DNA and RNA sequencing [13]. There is no common specific-genomic variation

or genetic translocation attributed to all high-risk neuroblastoma tumors, but 1p deletion, MYCN amplification, or 17q gain, neuroblastoma and survival effect can identify subtypes. There are many oncogenic and transcriptional agents effective in neuroblastoma formation. Genes such as MYCN, ALK, and PHOX2B play roles in the pathogenesis of neuroblastoma.

MYCN; oncogene plays an important role in the development of neuroblastoma. The MYCN amplifier is identified by poor prognosis and is found in approximately 20% of cases. In transgenic mouse models, irregular MYCN expression is sufficient for high penetration tumor formation. It activates and suppresses genetic targets (eg mRNA, miRNAs, lncRNAs) by binding directly to DNA. In addition, it activates indirect protein-protein interaction mechanisms. It also has MYCN, anti-p53, proliferative, and pro-epithelial mesenchymal transition (EMT) functions. Throughout the development of embryogenesis and neural crest, MYCN is temporarily expressed in migrating crest cells to become sympathetic ganglion. Therefore, while high levels of MYCN can be found in some aggressive neuroblastomas, in many high-risk cases, minimum MYCN expressions are observed that independently suggest involvement of additional mechanisms in tumorigenesis [14,15].

ALK; Activating mutations of anaplastic lymphoma kinase (ALK) play important roles in the development of neuroblastoma. in all cases of familial neuroblastoma (<1% of total NB cases) and between 6-10% of spontaneous cases. This receptor tyrosine kinase (RTK) is also noted as an oncogene in different types of cancer, where it is typically present as a translocated fusion gene (ALK-NPM). Recent studies have been associated with the necessity of neural crest cells migrating in zebrafish models of ALK for sympathetic neuron development and neurogenesis [16]. This gene is an important regulator of STAT3-dependent stem cell functions. With the latest data from neuroblastoma mouse models, it has been observed that ALK and MYCN cooperate in tumor formation. This kinase suitable for drug targeting, is used in clinical trials for ALK- mutant neuroblastoma [17].

PHOX2B; In a subgroup of familial neuroblastoma and in approximately 4% of sporadic cases, there are mutations of Paired-like Homeobox 2B (PHOX2B). PHOX2B and PHOX2A enables differentiation of neural crest precursors towards sympathetic neurons (18). Recent studies have shown that neuroblastoma differentiation prevents PHOX2B from impairing calcium regulation with resultant loss of function. PHOX2B can also inhibit ALK expression in neuroblastoma [19].

Non-coding RNAs; Non-coding RNAs (microRNA, lncRNAs, piRNAs) are transcriptional regulators in stem cell biology, development, and neural crest differentiation. Many of these microRNAs are released in aggressive neuroblastomas, block p53 activity, activate EMT and metastases. It is reported that the MYCN oncogene can assume tumorigenic effects by regulating miRNAs that are effective for neural cell differentiation and apoptosis. Recent studies have shown that it triggers tumorignesis in neural crest and microRNA by inhibiting Let7a microRNA-mediated tumor suppression of LIN28 regulator expression. In addition, there are many other microRNAs that are directly related to the regulation of metastasis or tumor differentiation [20-22].

Epigenetically, specific structures that differentiate neuroectoderm, neural crest and more mature neural conditions have been demonstrated by different sequencing studies. Especially histone modifications in the crest indicate the presence of t enhancers of various genes. DNA demethylation dependent on DNA-methyltransferase-3-beta (DNMT3B) participates in neural crest maturation, and changes in this process promotes the tumor formation. It activates the differentiation of the neuroblastoma along the programmed neural crest maturation pathway. Alpha-thalassemia mental retardation X-linked (ATRX) factor is an epigenetic factor in NB seen in older children and adolescents. It plays a role in the regulation of telomere length. These mutations occur in 44% of cases of stage IV neuroblastoma in children 12 years of age or older, and only 9% of cases in children under 12 years of age. This gene critically regulates neural crest maturation [23-25].

Neural Crest Induction

Induction of genes within the junction neural plate boundary (NPB) leads to expression of neural crest determining genes. Different signaling mechanisms are involved in neural crest induction [10]. We can evaluate these mechanisms as follows:

Bone morphogenic protein (BMP)

BMP is a protein from the growth factor beta (TGFβ) family and activates the transcription factors of the Smad family which leads to the transcription of genes involved in growth and differentiation. Using an ESC model, there was a reduction in induction with early inhibition (0-2 days) and delayed (3-4 days) inhibition with noggin (BMP antagonist), which led to a decrease in neural crest induction. These studies have shown that BMP expression is required for neural crest induction. In neuroblastoma, BMP has been associated with neuroblastoma differentiation [26].

Wingless / Int (WNT) Signal Pathway

The signaling of WNT / β-catenin has been shown to be effective in neuroblastoma and its developmental pathway. However, WNT / β-catenin signal components have been shown to play a role in neuroblastoma proliferation. Specifically, initiation of the WNT / β-catenin signal pathway in MYCN non-amplified cell lines has been shown to increase MYCN levels. Thus, the 'canonical' ligands (WNT1, WNT6 etc.) support an important role for neuroblastomas. In the SH-SY5Y neuroblastoma cell line, RNAi suppression of WNT1 expression has been shown to significantly reduce cell viability [27].

Fibroblast growth factor (FGF) Pathway

Fibroblast growth factor (FGF) is a cell signaling protein that is secreted by binding to the receptor tyrosine kinase, also known as a fibroblast growth factor receptor (FGRR). Signal activation via FGFR activates many downstream pathways related to proliferation and survival. During induction of neural crest, FGF is released by paraxial mesoderm. In multiple cancer stem cell (CSC) models, including neural tumors such as glioblastoma, it has been indicated that STAT3 induces different transcription factors and contributes to the protection of CSCs [28].

Notch Pathway

Notch proteins are transmembrane signaling molecules that function as intracellular receptors (with Delta / Jagged protein ligands). With the binding of delta ligands, Notch's intracellular space is split, transported to the nucleus and bound to transcription factors. In mice and zebrafish models, Notch pathway has been found to be important in neural crest differentiation and induction. In neural systems, Notch1 is reliable for the regulation of the cell cycle and the protection of neural stem cells. With inhibition of Notch signal components (RBPjs), it can lead to a premature termination of neurogenesis. In neuroblastoma, inhibition of Notchl in the SH-SY5Y human NB cell line has been shown to induce neuronal differentiation via a JNK-CRT (Notch signal blockade) mediated pathway. Treatment of NB xenograft mice with Notch inhibitors (γ -secretase inhibitors, GSI) leads to suppression of tumor progression [29,30].

Hippo Signaling Pathway

The Hippo pathway is a signal pathway that modifies key target genes to control a large number of biological processes including cellular proliferation, survival, differentiation, determination of cell fate, organ size, and tissue homeostasis. The main components of the pathway is serine / threonine kinases, sterile 20-like kinase 1/2 (MST1 / 2) and large tumor suppressor 1/2 (LATS1 / 2). Latest studies have shown that MAP4K and TAOK kinases directly phosphorylate LATS1 / 2, so they demonstrate similar activities with MST1 / 2. These kinases, together with adapter proteins, Salvador homolog 1(SAV1) and MOB kinase activator 1A / B (MOB1A / B), down effector proteins, Yes-associated protein 1 (YAP1) and PDZ, phosphorylate, and inhibit paralo-

gous transcriptional coactivator. The binding motif (TAZ) (also known as WWTR1) sequences them in the cytoplasm by binding to 14-3-3 proteins. Tumour suppressor neurofibromin 2 (also called Merlin) joins these kinases to inhibit YAP and TAZ activity by triggering activation of the pathway. Additional phosphorylation of YAP / TAZ results in facilitation of proteasomal degradation, expedited by attachment to β-TrCP. This regulatory process prevents the build-up of YAP / TAZ within the nucleus and binding to a family of transcription factors known as TEA DNA-binding proteins (TEAD1-4), mediates functions of proliferative and pro-survival genes [31]. The nuclear / cytoplasmic distribution of YAP and TAZ is important in regulating cell polarity. Nuclear localization of YAP and TAZ facilitates tissue regeneration and increases the proliferation of undifferentiated progenitor cells in different organs. Abnormal activation of nuclear TAZ and YAP causes stem cell proliferation. The transition of YAP to cytoplasm ends in cellular differentiation and maturation. Signals activated by YAP and TAZ are also important in determining cell fate. The elements of the Hippo pathway affect mesenchymal stem cells and regulate their differentiation. Hippo pathway involving in embryogenesis and organogenesis is effective in the development of many pediatric cancers. As a diagnostic and prognostic biomarker in oncology, the Hippo pathway plays a role in pediatric malignancies with suggestion to the clinical uses of YAP (Fig.1) [32].

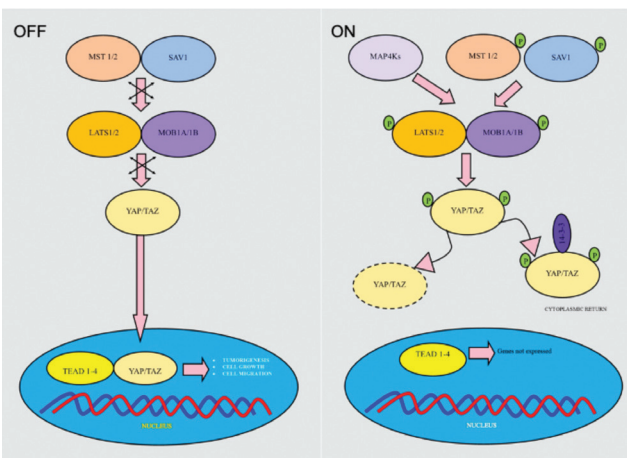

Figure 1. Core components of the Hippo signal path.

Hippo Signaling Pathway and Cancer

The Hippo signaling pathway plays a significant role in the development of stem cells, cancer stem cells and tumorigenesis. The defects in Hippo pathway elements evoke tumor formation in various adult cancers. Hippo core kinases, MST1 / 2 and LATS1 / 2 are often used as tumor suppressors. Other members of the Hippo pathway, for example KIBRA, may also play a role in the improvement of cancers [32,33]. YAP and TAZ principally relate with the TEAD family of transcription factors in cancer pathogenesis. The effective mechanism of YAP in tumorigenesis has not been determined exactly. Previous studies have shoıwn increases in the levels of YAP protein in various types of cancer. That is why YAP is defined as an oncogene. Overexpression of YAP in cancers has been associated with poor prognosis [33]. YAP acts as a tumor suppressor by activating cell apoptosis. In addition, YAP induces apoptosis in various hematological malignancies. Phosphorylation may be related to nuclear and cytoplasmic localization of YAP as an oncogene and tumor suppressor gene. The effective impact of the Hippo pathway in embryonic organogenesis indicates its important role in the development of pediatric cancers. Stopping cellular separation at embryonal level is seen in many pediatric cancers. This is thought that childhood cancers are associated with oncogenesis due to impaired normal embryological development which is associated with development of congenital malformations [34].

Hippo Signaling Pathway and Neuroblastoma

The element of the Hippo signal pathway is expressed in neural crest and regulates phenotype and cell migration. The expression of YAP begins to decrease with the maturation and differentiation of neural crest cells. It is estimated that members of the Hippo pathway originating from neural crest are overexpressed in neuroblastoma. Activation of YAP / TAZ has been demonstrated in neuroblastoma. It has been stated that this activation positively correlates with negative prognostic features. PTPN14

mutations encoding a negative regulator of YAP in recurrence of neuroblastoma have been acknowledged. Neuroblastoma cells being particularly immigrant and invasive have been associated with overexpression of TAZ. TAZ has been proven to support epithelial development to mesenchymal transition and neuroblastoma metastasis. Although studies have shown that YAP and TAZ are therapeutic targets, no experiment has ever been accomplished related to expression levels of these proteins in different subtypes of clinical neuroblastoma cases [35].

The Role of Hippo Signal Pathway and Tumor Immunogenicity

There are several reports related to tumor immunity in the Hippo pathway. Loss of Lats1 / 2 has been shown to inhibit tumor growth in syngeneic mouse tumor models. Lats 1/2 secrete extracellular vesicles rich in nucleic acid that increase tumor immunogenicity and impair activation of T cells in depleted tumor cells [36]. It has also been found that MST1 / 2 mutate in a rare human combined form of immune deficiency (CID), where proliferating T cells increase apoptosis [37]. Further studies are needed in the future to clarify the effects of these findings on cancer. Contrary to the studies, it has been stated that YAP is highly expressed and involves in the formation of directing T cells (Tregs). YAP induces activin expression by regulating TGFβ / SMAD signals. The Hippo pathway has also been shown to regulate the immune checkpoint molecule PD-L1. Reduction of MST1 / 2 or LATS1 / 2 increases the expression of PD-L1 in breast and lung cancer cells. TAZ also plays an important role in increasing PD-L1 expression in cancer cells. Thus, it directs the immune cells to escape which has been shown to be specific to species [38]. PD-L1 expression is also induced by the BRAF inhibitor in resistant melanoma. In a different study, it has been shown that TAZ plays a very important role in the regulation of differentiation of T helper and Treg cells [39].

Conclusion and Suggestions

Alternative treatments that target the Hippo pathway in cancer or immune system cells can cause some confusion.

Further studies are needed to clarify whether the members of the core Hippo pathway have an active role in different immune cells before any clinical or translational relationships are identified. In the diagnosis and prognosis of pediatric tumors, greater number of beneficial clinical applications of YAP and other pathways can be considered and conduction of further research can be expected. Hippo pathway members including especially YAP, are potential new therapeutic targets for tumors showing overexpression. Since YAP and TAZ are exposed to nucleocytoplasmic transport, the identification of small molecules that stop nuclear transport can give another approach to the negative regulation of YAP and TAZ. In addition to the clinical options that have an effect on the progression of the neuroblastoma, chromosomal abnormalities and both oncogenes and tumour suppressor genes should be evaluated so as to develop new treatment strategies, particularly in aggressive neuroblastomas.

In recent studies, inhibition of YAP has been shown to impair tumor growth and NB's resistance to cisplatin treatment which defines YAP as a potential therapeutic target, especially for cisplatin-resistant neuroblastoma. Activation of the Hiippo pathway is rare in human cancers. Therefore, whether inhibition of LATS1 / 2 can increase tumor immunity in many types of cancer should be investigated in future studies. The main goals are to improve the treatment outcomes in cases with advanced stage neuroblastoma and to reduce related side effects. In addition, alternative effective ways are sought in treatment protocols like risk-based national neuroblastoma treatment protocol (TPOG - NBL2009) [2, 40-43]. Hippo signaling pathway is a new glimmer of hope for treatment strategies of neuroblastoma.

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Research Article

Our Clinical Experiences in Patients with Nutcracker Syndrome

Nutcracker Sendromlu Hastalarda Klinik Deneyimlerimiz

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ABSTRACT

Objective: *Nutcracker syndrome (NCS) is a rare condition caused by the compression of the left renal vein between the abdominal aorta and superior mesenteric artery. The purpose of the study was to evaluate our management of NCS.*
Methods: *Patients were retrospectively reviewed and sex, age, main symptoms at application, physical examination, radiological findings, laboratory examinations, and treatment were recorded.*
Results: *23 patients (16 girls, 7 boys; age range, 5 to 16) diagnosed with NCS. Microhematuria was detected with 14 (60.8%) patients before diagnosis. And four of 9 (39.1%) were determined after diagnosis. Microhematuria was not detected in 5 (21.7%) of the patients. All patients (100%) had orthostatic proteinuria. 17 (73.9%) patients had mild, 3 (13.0%) patients had moderate and 3 (13.0%) had severe proteinuria. The mean diameter of the left renal vein (LRV) at the aortomesenteric (AM) portions and the hilar were 1.69mm±0.70 and 8.01mm±2.27. The mean angle between the superior mesenteric artery and LRV was 25.26º±7.98.*
Conclusion: *In the case of especially colic flank pain, hematuria, and proteinuria NCS should keep in mind in the differential diagnosis. Surgical management may supply more enough clinic improvement when the patient has a response to medical therapy.*

Keywords: *Nutcracker syndrome, renal colic, hematuria, proteinuria*

ÖZ

Amaç: *Nutcracker sendromu (NCS), abdominal aorto ve superiar mezenterik arter arasındaki sol renal venin sıkışmasından kaynaklanan nadir bir durumdur. Çalışmanın amacı, NCS tanısı konulan hastalara genel yaklaşımımızı değerlendirmektir.*
Yöntem: *Hastalar retrospektif olarak incelendi ve cinsiyet, yaş, uygulamadaki ana semptomlar, fizik muayene, radyolojik bulgular, laboratuvar muayeneleri ve tedavi kaydedildi.*
Bulgular: *23 hasta (16 kız, 7 erkek; yaş aralığı, 5-16) NKS tanısı aldı. Tanıdan önce 14 hastada (%60,8) mikrohematüri saptandı. Teşhisten 9 taneden dördünde (%39,1) tanı aldıktan sonra belirlendi. Hastaların 5'inde (%21,7) mikrohematüri saptanmadı. Tüm hastalarda (%100) ortostatik proteinüri vardı. 17 (%73,9) hastada hafif, 3 (%13,0) hastada orta, 3 (%13,0) hastada ciddi proteinüri vardı. Aortmezenterik (AM) ve hilerde sol renal venin (LRV) ortalama çapı 1.69mm±0,70 ve 8,01mm±2,27 idi. Üst mezenterik arter ve LRV arasındaki ortalama açı 25,26±7,98 idi.*
Sonuç: *Özellikle kolik yan ağrısı, hematüri ve proteinüri olması durumunda NCS ayırıcı tanıda akılda tutulmalıdır. Cerrahi tedavi, hasta tıbbi tedaviye yanıt verdiğinde daha fazla klinik iyileşme sağlayabilir.*

Anahtar kelimeler: *Nutcracker sendromu, renal kolik, hematüri, proteinüri*

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INTRODUCTION

Nutcracker syndrome (NCS) is a rare condition caused by the compression of the left renal vein (LRV) between the abdominal aorta and superior mesenteric artery (SMA). Nutcracker Phenomenon (NP) is an asymptomatic finding of LRV squeeze, however, NCS is a complex of clinical signs and symptoms differently from NP [(1)]. The syndrome was first defined anatomically by Grant in 1937 as: "the left renal vein, as it lies between the aorta and superior mesenteric artery, resembles a nut between the jaws of a nutcracker" [(2)]. In the etiology of the disease, rapid growth in the puberty period is accused of maturation of vertebral body and angle between SMA and aorta narrows [(2)]. NCS typically presents with left flank pain, hematuria, orthostatic proteinuria, orthostatic intolerance, and gonadal varices (varicocele or ovarian vein syndrome) [(1,3,4)]. Diagnosis is made by ultrasonography, color Doppler ultrasonography, computed tomography angiography, or magnetic resonance angiography [(5-9)]. The treatment ranges from a conservative approach to open surgery according to the patients' clinic and severity of the disease.

We performed a retrospective review of patients diagnosed with NCS in our institution and aimed to evaluate the clinical characteristics and management of 23 patients with this condition.

MATERIAL and METHOD

We retrospectively reviewed 23 cases of NCS (16 girls, 7 boys; age range, 5 to 16) from 2013 to 2018 at our Pediatric Nephrology and Pediatric Surgery Department in Karadeniz Technical University, Faculty of Medicine. The clinical characteristics of the patients, main symptoms at application, physical examination, radiological findings (renal Doppler ultrasonography, magnetic resonance angiography, computed tomography angiography), laboratory examinations, and clinical management were analyzed retrospectively.

The diagnosis was based on the clinical (colic flank pain), laboratory findings (microhematuria, proteinuria -spot and 24-hour protein excretion- and orthostatic proteinuria), and the findings of renal Doppler ultrasonography, magnetic resonance (MR), and computed tomography (CT) angiographies. All patients have done renal Doppler ultrasonography before and after exercise and measured the diameter of the LRV at the aortomesenteric (AM) portions and the hilar region and the mean angle between the superior mesenteric artery and the LRV. Some patients need also MRI or CT angiographies. Patients with an angle between the superior mesenteric artery and the left renal vein less than 35°-40° were diagnosed with NCS.

Microhematuria was defined as while urine color was normal, the presence of 5/HPF erythrocyte in urine microscopy, and blood reaction positivity in dipstick test. Proteinuria in spot urine was defined as protein/creatinine ratio (mg/mg) is 0.2-1: mild, 1-3,5: moderate, >3,5 heavy proteinuria. Daily urinary protein excretion in 24-h urine ($mg/m^2/h$) was defined as 4-10 mild, 10-40 moderate, and > 40 as severe. Proteinuric patients are evaluated for the presence of orthostatic proteinuria. The patients woke up 2 hours or more at night and discharged their bladder. Urine analysis and spot urine protein and creatinine ratio were examined as soon as they got out of bed in the morning. Proteinuria is negative in the dipstick test and the spot urine protein/creatinine ratio in mg/mg <0.2 was defined as orthostatic proteinuria.

All patients' urine analysis, renal function tests, electrolytes, complete blood count, and blood pressures were normal. The patients who have other urological disorders were excluded from the study.

Statistical Analysis

Analyses were performed using the Statistical Package for the Social Sciences 18.0 (SPSS). The characteristics of the patients were determined using descriptive statistics. Parameters compatible with normal distribution were defined as mean ± standard deviations.

RESULTS

We retrospectively investigated 23 children who were diagnosed as having NCS from 2013 to 2018 of which 16 (65.6%) were female and 7 (34.4%) were male. The mean age of our patients was 12.04±2.96 years (range 5 to 16). All patients complained of colic left flank pain to the hospital. They all resorted to the emergency and needed a painkiller again and again.

14 (60.8%) patients had microhematuria before diagnosis. Four of 9 (39.1%) patients without microhematuria were determined microhematuria after diagnosis. Microhematuria was not detected in 5 (21.7%) of the patients.

All patients (100%) had orthostatic proteinuria. 17 (73.9%) patients had mild, 3 (13.0%) patients had moderate and 3 (13.0%) had severe proteinuria.

We successfully obtained renal Doppler ultrasonography before and after exercise and MRI angiographies from LRV at the AM and hilar portion in 22 patients. Only one patient underwent CT angiography after renal Doppler ultrasonography. All patients in our study were diagnosed with anterior NCS. The mean diameter of the LRV at the AM portions and the hilar were 1.69mm±0.70 and 8.01mm±2.27. The mean angle between the superior mesenteric artery and the LRV was 25.26º±7.98; all patients' values were under 40° (Table 1). Radiological images of one of the patients who underwent surgery were shown in figures. The length between the abdominal aorta and superior mesenteric artery was 44 mm (Figure 1a) and the length between the abdominal aorta and superior mesenteric artery was 17 mm (Figure 1b) before exercise. The aorta mesenteric angle was 28 degrees (Figure 2a) before exercise; 22 degrees (Figure 2b) after exercise.

Table 1. Baseline clinical characteristics and left renal vein findings of the study.

Variables	Study population (n=23)
Age (years)	12.04±2.96 (5-16)
Gender, n (%)	female, 16 (65.6%) male, 7 (34.4%)
Clinical findings, n (%)	Colic flank pain, 23 (100%)
Microscopic hematuria, n (%)	
Before diagnosis	14 (60.8%)
After diagnosis	4 (17.3%)
Undetected	5 (21.7%)
Ortostatic proteinuria n (%)	23 (100%)
Proteinuria	17 (73.9%)
Mild	3 (13.0%)
Moderate	3 (13.0%)
Severe	
LRV findings	
Diameter at the AM portion (mm)	1.69 mm±0.70
Diameter at the hilar portion (mm)	8.01 mm±2.27
Angle between SMA and LRV	25.26º±7.98
Treatment, n(%)	
Conservative	20 (86.9%)
Surgery	3 (13.0%)

Parameters compatible with normal distrubution were defined as mean±standard deviations. LRV=Left renal vein, AM=Aortomesenteric, SMA=Superior mesenteric artery.

A total of our twenty (82%) patients responded to medical treatment. Medical treatment includes painkillers, exercise restriction, and posture correction.

Surgical Procedures

A total of three patients had refractory colic pain and proteinuria. There was no clinical or laboratory improvement despite exercise limitation and painkillers applied to other patients. Surgical treatment was applied to these three patients whose quality of life deteriorated and did not respond to medical treatment. The aim of the surgery should be to remove the pressure on the renal vein, protective vessel graft placement or venous transposition surgery was preferred.

Our 3 patients (18%) who underwent surgery have serious recurrent colic flank pain and resistant proteinuria (especially 2 of them in 24-hour protein excretion). Left renal vein transposition has been done on two patients. We preferred the abdominal laparotomy approach for these patients. We have found and changed the position of the LRV relative to the SMA and aorta. The left renal vein, which was trapped between the aorta and SMA, was released by carefully sharp and blunt dissections and fixed more inferiorly. We did not need excision and anastomosis to the LRV. We checked the current in the LRV and ended the process.

A protective vessel graft was placed around the left renal vein of one of the patients and her CT angiography images were shown in Figure 1a,b,c, and Figure 2a,b. At the hilus level, the left renal vein diameter was measured as 70 mm at rest and 83 mm after exercise. The length between the abdominal aorta and superior mesenteric artery was 44 mm at rest and 17 mm after exercise. The aorta mesenteric angle was 28 degrees at rest and 22 degrees after exercise. The angle was too narrow and there was no clinical improvement with medical treatment.

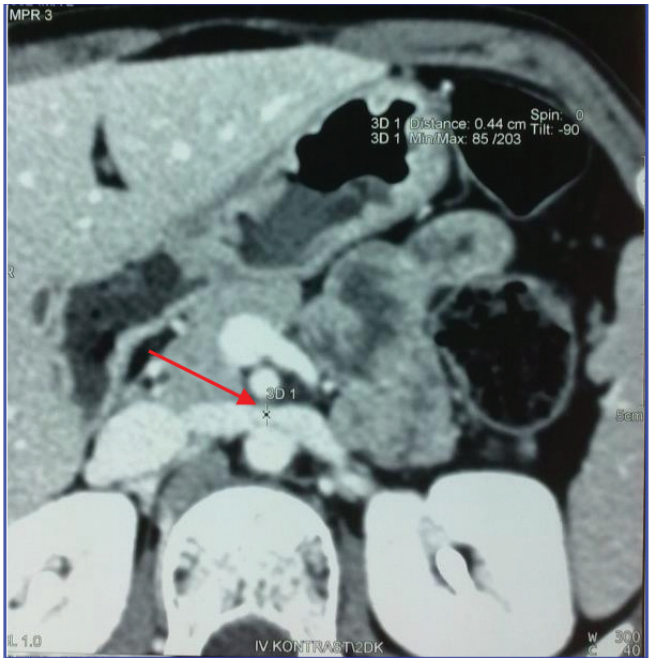


Figure 1a. Renal ven computed tomography angiography images before exercise, The length between abdominal aorta and superior mesenteric artery (44mm) marked with a red arrow.

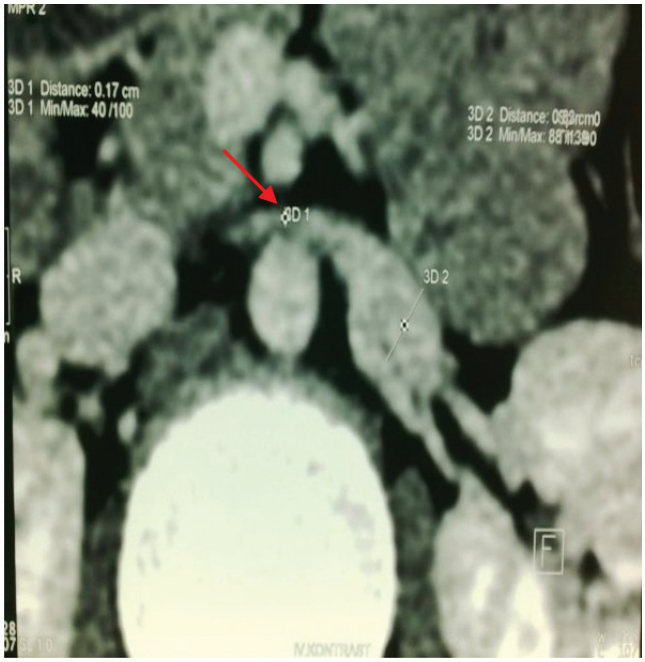


Figure 1b. Renal ven computed tomography angiography images after exercise, The length between abdominal aorta and superior mesenteric artery (17mm) marked with a red arrow.

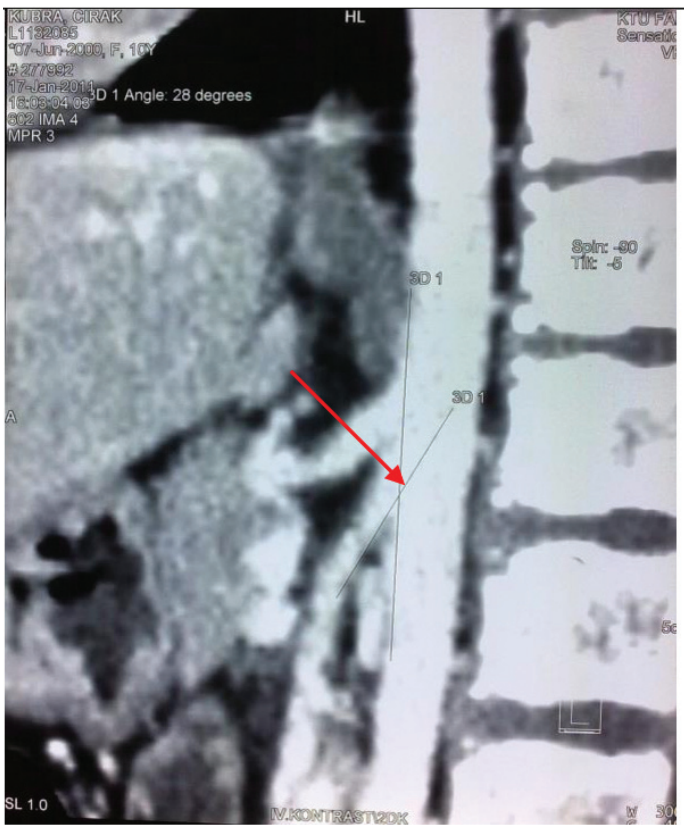
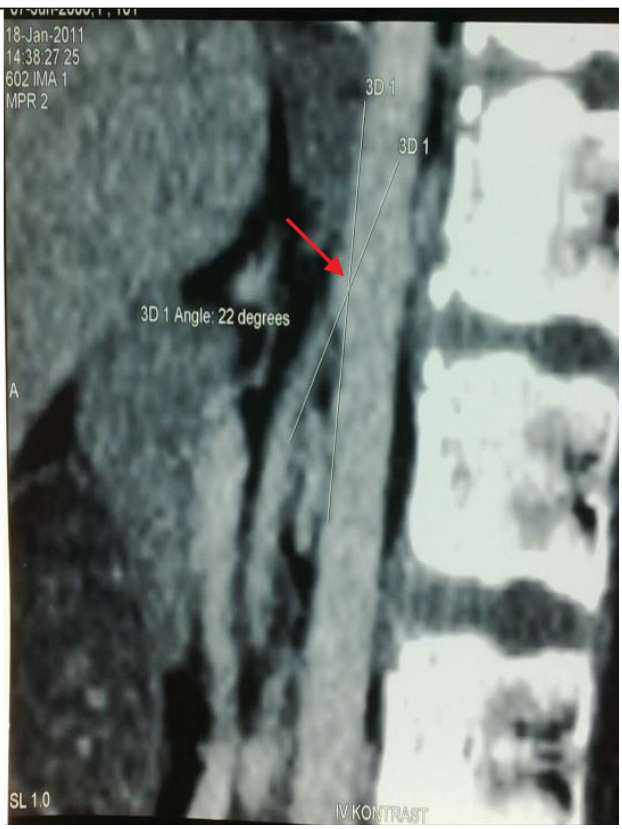


Figure 2a. Renal ven computed tomography angiography images before exercise, the aorta mesenteric angle was 28 degrees marked with a red arrow.



Renal ven computed tomography angiography images after exercise, the aorta mesenteric angle (22 degrees) marked with a red arrow.

The patients, who did not repeat the complaints during the follow-up, was discharged following the urine microscopy. On the control examination, it was learned that the pain attacks and the microscopic hematurias did not recur.

DISCUSSION

Nutcracker syndrome (NCS) is a rare anatomicopathological condition defined as the compression of LRV between the abdominal aorta and the superior mesenteric artery [5,10]. Also, NCS is defining as anterior and posterior versions. Most variants of developmental LRV are the circumaortic and the retrocaval LRV. When the LRV is entrapping between the aorta and SMA called anterior NCS; whereas occurs between the vertebral column and the aorta called posterior NCS [1]. All patients in our study were anterior NCS. Physiologically, the angle between the superior mesenteric artery and the left renal vein is mostly between 35°-40°. Nutcracker syndrome should be diagnosed when this angle decreases. All patients' angles were narrow. Diagnosis is made by ultrasonography, color flow Doppler ultrasonography, computed tomography angiography, or magnetic resonance angiography [5-8]. We first performed Doppler ultrasonography on our all patients and then were diagnosed with MRI and CT angiographies.

NCS is mostly seen in young and middle-aged ladies and usually presents ranging from asymptomatic to variable clinical symptoms like recurrent renal colic pain, micro or macroscopic hematuria, orthostatic proteinuria, and proteinuria attacks similar to our patients [2,6]. Her colic pains occurred after exercise. The pathology of hematuria is secondary to the rupture of septum separating veins because of increased left renal vein pressure and venous hypertension [6,11-13]. Our only 5 patients had no hematuria for any time. We showed orthostatic proteinuria in all our patients. 17 of our patients had mild, 3 had moderate and three others had severe proteinuria.

The management of NCS is based on the evaluation of the pathologic anatomy and physiology; and the treatment varies from a conservative approach to nephrectomy (progressive hematuria, proteinuria, and pain affecting daily life) depending on the patient's clinic and the severity of the disease [14]. Medical treatment(exercise restriction, painkillers, and posture correction), surgical, intravascular, or extravascular stent implantation, or intrapelvic chemical cautery are used in the treatment. In cases with NCS, major surgery is frequently performed in the form of renal retransposition, renal vein direct or graft reimplantation, medial nephropexy, left renal vein bypass, superior mesenteric artery (SMA) transposition, renal-to-inferior vena cava shunt, and nephrectomy [7,11].

Barnes et al. [15] first described extravascular stent in 1988. It is also an open surgery and some the complication may occur like in-stent stenosis, fracture, migration, or erosions. In the literature, some series preferred surgery as the first choice; however, conservative-medical treatment must be preferred at the first choice in childhood, as in our series [16]. Surgical treatment should be preferred in resistant cases because there is a risk of thrombosis and hypertension for these patients [17]. Surgical treatment was performed in our three patients who did not respond to the painkillers, exercise restriction, and posture correction. Patients had resistant proteinuria and the aorta mesenteric angles were too narrow especially after exercises. Specifically, the narrowed aortomesenteric angle was so important and it was a guide for surgery for us. The application of protective graft around the left renal vein has been done successfully in our one patient and clinical success was achieved. Left renal vein transposition was done on our other two patients. We think that surgery should not be avoided in patients with recurrent flank pain and laboratory findings who do not respond to medical therapy.

CONCLUSION

We recommend that in case of especially colic flank pain, proteinuria and hematuria NCS should keep in mind in the differential diagnosis. We finally suggest that surgical management may supply more enough clinic improvement when the patient has a response of medical therapy to prevent the risk of LRV thrombosis and hypertension.

Ethics Committee Approval: Karadeniz Teknik University Faculty of Medicine Scientific Research Ethics Committee approval was obtained (2019/359).

Conflict of Interest: The authors declared that there were no conflicts of interest.

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Informed Consent: Since our study was retrospective, consent was not obtained from the patients.

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Research Article

Cranial MRI Findings in Predicting the Severity of Hypoxic-Ischemic Encephalopathy in Term Neonates

Term Yenidoğanlarda Hipoksik-İskemik Ensefalopati Şiddetini Öngörmede Kraniyal MRG Bulguları

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ABSTRACT

Objective: *The aim of this study is to compare magnetic resonance imaging (MRI) findings with severity of hypoxic-ischemic encephalopathy (HIE) in term neonates.*
Methods: *Sixty-three newborns with HIE in whom cranial MRIs were performed within the first 3 weeks of life between 2016 and 2020 were included in the study. Severity of HIE was graded using Sarnat & Sarnat staging. In statistical analysis, Stage 1 was considered as mild, Stage 2 or 3 as severe HIE. The signal intensities of perirolandic cortex, posterior limb of internal capsule (PLIC), globus pallidus, and cerebrospinal tract on T1- weighted imaging (T1WI), and of perirolandic cortex, PLIC, ventrolateral thalamus, lateral edge of putamen and tegmentum on T2WI, and brain diffusion weighted imaging (DWI) findings were evaluated with consensus by two radiologists blinded to clinical findings. Gestational age, birth weight and MRI signal intensities were compared with HIE groups using t test, and Fisher-Exact test.*
Results: *There were 31 and 32 infants with mild and severe HIE, respectively. Gestational age and birth weight were not different between mild and severe HIE groups. The number of cases with abnormal signals in PLIC and globus pallidus on T1WI, and PLIC on T2WI were significantly higher in severe HIE (p=0.022, p=0.008, and p=0.032, respectively). The presence of signal abnormality in other regions and DWI were not significantly different between HIE groups.*
Conclusion: *Cranial MRI may play a remarkable role in determining pattern and severity of HIE. Signal abnormality in PLIC and globus pallidus may suggest severe HIE in term neonates.*

Keywords: *Neuroimaging, magnetic resonance imaging, diffusion magnetic resonance imaging, hypoxic-Ischemic encephalopathy, neonate*

ÖZ

Amaç: *Bu çalışmanın amacı, term yenidoğanlarda manyetik rezonans görüntüleme (MRG) bulgularıyla hipoksik-iskemik ensefalopati (HİE) şiddetinin karşılaştırılmasıdır.*
Yöntem: *2016 ile 2020 arasında HİE tanılı ve doğumdan sonraki 3 hafta içerisinde kraniyal MRG yapılan 63 term yenidoğanı kapsamaktadır. HİE, Sarnat & Sarnat sınıflaması ile evrelenmiştir. Evre 1 hafif HİE, evre 2 veya 3 şiddetli HİE olarak kabul edildi. T1 ağırlıklı görüntülemede (AG) perirolandik korteks, internal kapsül arka bacağı (İKAB), globus pallidus, serebrospinal tractus sinyali, T2AG'de perirolandik korteks, İKAB, ventrolateral talamus, putamen lateral kenarı ve tegmentum sinyali ve difüzyon kısıtlaması klinik bilgiden yoksun 2 radyolog tarafından konsensüs ile değerlendirildi. Hafif ve şiddetli HİE hasta grubu, gebelik haftası ve doğum ağırlığı açısından t testi, MRG sinyali Fisher-Exact testi kullanılarak karşılaştırıldı.*
Bulgular: *Otuz-bir yenidoğanda hafif, 32 yenidoğanda şiddetli HİE vardı. Hafif ile şiddetli HİE hasta grubu karşılaştırıldığında, gebelik haftası ve doğum ağırlığı açısından fark yoktu. T1A'da İKAB ve globus pallidusta, T2A'da İKAB'da anormal sinyal, şiddetli HİE'de daha fazlaydı (sırasıyla p=0,022, p=0,008 ve p=0,032). Diğer bölgelerin T1 ve T2A sinyali ve difüzyon kısıtlılığı farklı değildi.*
Sonuç: *MRG, HİE şiddetini ve paternini tespit etmede önemli bir rol oynar. Term yenidoğanda kraniyal MRG'de, İKAB'da T1 ve T2A'da ve globus pallidusta T1A'da anormal sinyal, şiddetli HİE'yi akla getirmelidir.*

Anahtar kelimeler: *Nörogörüntüleme, manyetik rezonans görüntüleme, difüzyon ağırlıklı görüntüleme, hipoksik-iskemik ensefalopati, yenidoğan*

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INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE), in other words perinatal asphyxia, is one of leading causes of neonatal mortality and morbidity worldwide [1]. Hypoxic or ischemic processes may result in brain injury which can be reversible or irreversible. Approximately 40% of survivors have neurological disorders such as cerebral palsy, mental retardation, epilepsy despite hypothermia treatment [2,3].

In hypoxic-ischemic neonates, the first 6 hours of life is critical to start therapeutic hypothermia. Hypothermia, as a neuroprotective treatment, reduces neonatal mortality and morbidity, and improves long-term outcomes [2,4,5]. Despite hypothermia treatment, neonates with severe and prolonged HIE still develop adverse outcomes [3,6]. Severity of HIE can be determined by Sarnat & Sarnat clinical staging in early period [7]. The Bayley Scales of Infant and Toddler Development-III (Bayley-III) is used in infants between 18 and 24 months to determine long- term results. However, MRI is the ideal technique to detect perinatally acquired cerebral lesions and evaluate therapeutic efficacy of hypothermia [4].

In a healthy term infant, perirolandic cortex, posterior limb of internal capsule (PLIC), cerebrospinal tractus, and globus pallidus demonstrate high signal intensities on T1-weighed images (T1WI). Perirolandic cortex, PLIC, ventrolateral thalamus, tegmentum and lateral edge of putamen have low signal intensities on T2WI [5]. Absence of increased T1 signal intensity of PLIC may predict severe outcome [8]. Widespread signal abnormalities were also significantly associated with poor neurological outcome [9]. We evaluated MRI signal intensities of these specific regions one by one.

The main goal of this study is to compare MRI findings with severity of HIE in term neonates.

MATERIAL and METHOD

Study population

This was a retrospective study approved by the ethics committee. It included hospitalized term (≥35 weeks of gestational age) neonates, who were clinically diagnosed with HIE, and had cranial MRI within the first 3 weeks after birth between 2016 and 2020. The cases who had any contraindication for MRI, could not undergo MRI due to unstable clinical conditions or death, underwent MRI when older than 3 weeks of age (n:3), had non-diagnostic MRIs due to prominent artifacts (n:2) and preterm infants were excluded from the study.

Categorization of HIE

Severity of HIE was graded using Sarnat & Sarnat scale [7]. Accordingly, stages of HIE were divided into 3 levels using characteristic features as alertness, muscle tone, posture, reflexes, pupils, seizures, electroencephalography (EEG) findings, and duration of HIE. Stage 1 infants are hyperalert, have normal or increased muscle tone, normal posture, hyperactive tendon reflexes, mydriatic pupils without seizures and normal EEG with HIE lasting less than 24 hours. Stage 2 infants are lethargic, hypotonic, miotic, and had weak reflexes. Conversely, Stage 3 infants are in coma, and characterized with flaccid muscle tone, decerebrate posture, absence of tendon reflexes, anisocoric pupils, decerebrate seizures, and burst suppression or isoelectric activity in EEG persisting for weeks. Stage 1 was considered as mild, Stages 2 and 3 as severe HIE in statistical analysis.

Acquisition and evaluation of the MRIs

All patients were scanned with a 1.5 Tesla (T) scanner (Toshiba, Japan). Cranial MRIs included axial and sagittal T1W fast spin echo (FSE), axial T2W FSE, axial and coronal T2W fluid attenuated inversion recovery (FLAIR), axial flow-sensitive black blood imaging susceptible to hemorrhage, and axial diffusion weighted imaging with b:0 and b:1000 sec/mm2 and apparent diffusion coefficient map. The acquisition parameters are given in Table 1.

In the first session, the images were evaluated independently by two radiologists blind to any clinical information. Interreader agreement was determined. In the second session, discrepancies were resolved, and definitive results were achieved by consensus.

Table 1. Acquisition parameters of cranial MRI.

	Field-of-view (mm)	Matrix (frequency x phase)	Slice thickness (mm)	TR (msn)	TE (msn)
Axial T1WI FSE	190x190	304x160	2.5	773	12
Axial T2WI FSE	190x152	352x160	2.5	6206	105
Axial T2WI FLAIR	190x152	256x160	2.5	7900	105
Coronal T2WI FLAIR	170x170	320x160	3	6898	105
Sagittal T1WI FSE	210x168	256x160	3	432	8
Axial GRE*	180x144	256x160	1	29	20
DWI**	280x124	192x128	4	5600	120

TR: repetition time; TE: echo time; T1WI: T1 weighted imaging; T2WI: T2 weighted imaging; FSE: fast spin echo; FLAIR: Fluid attenuated inversion recovery; GRE: gradient echo; DWI: diffusion weighted imaging.
**Flow-sensitive black blood imaging susceptible to hemorrhage.*
***Diffusion weighted imaging with b:0 and b:1000 sec/mm^2 in axial plane.*

The signal intensities of perirolandic cortex, PLIC, globus pallidus, and cerebrospinal tract on T1WI, and of perirolandic cortex, PLIC, ventrolateral thalamus, lateral edge of putamen and tegmentum on T2WI were evaluated. The signal intensities of these regions were recorded as normal or pathologic based on the predefined criteria [5]. DWI and ADC images were evaluated for the presence or absence of diffusion restriction.

Statistical analysis

Data were analyzed with SPSS version 20 (IBM®, Armonk, NY, USA). Interreader agreement was determined using Kappa statistics, and classified as follows: 0.01-0.20, slight; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, substantial; and 0.81-0.99, almost perfect interreader agreement.

In patient groups with mild and severe HIE, gestational ages and birth weights were compared using t test, and MRI signals using Fisher Exact test. P<0.05 was considered statistically significant.

RESULTS

The median age of 63 cases (33 girls and 30 boys) included in this study was 7 days (±3.2). Median gestational age and birth weight were 39 weeks and 3340 grams, respectively (Table 2). Twenty-eight infants were born by normal vaginal delivery, and 35 infants by cesarean section.

Table 2. Demographic results of the cohort .

	Mean±SD	Minimum-maximum
Age (days)	6.8±3.2	1-21
Gestational age (weeks)	38.8±1.8	35-42
Birth weight (grams)	3268±506	1300-4230
	#Girl	#Boy
Gender	33	30
	#Normal	#C/S
Type of birth	28	35

SD: standard deviation; C/S: cesarean section.

According to Sarnat & Sarnat classification, the neonates had Stage 1 (n=31), 2 (n=21), and 3 (n=11) HIE. Consequently, 31 newborns had mild, and 32 had severe HIE.

Interreader agreement was almost perfect (Kappa=0.867). Thirty-three (52.4%) infants had totally normal MRI findings (Figure 1). Twenty-one of 33 (63.6%) infants had mild, while 12 (36.4%) infants had severe HIE. On the other hand, 30 (47.6%) infants had at least a pathology in their MRIs. On T1WI, the signal was abnormal in perirolandic cortex in 10, internal capsule in 17, globus pallidus in 16, and cerebrospinal tract in 12 infants. On T2WI, the signal was abnormal in perirolandic cortex in 7, internal capsule in 14, thalamus in 12, putamen in 7, and tegmentum in 9 infants (Figure 2). On DWI, diffusion restriction was not seen in 38 out of 63 patients (Figure 3).

There was no significant difference between mild and severe HIE groups in terms of gestational age and birth weight (p=0.183 and p=0.625, respectively). PLIC signal on T1WI was abnormal in 12.9% of infants with mild HIE, and in 40.7% of infants with severe HIE with a statistically significant intergroup difference (p=0.022). Globus pallidus signals detected on T1WI was abnormal in 9.7% of infants with mild , and 40.7% of infants with severe HIE with a statistically significant intergroup difference (p=0.008). PLIC signal on T2WI was more frequently abnormal in infants with severe HIE (p=0.032). The signal intensities of other regions were not statistically different between mild and severe HIE groups (Table 3). Diffusion restriction was noted in 29% of infants with mild, and 50% of infants with severe HIE without any statistically significant intergroup difference (p=0.123).

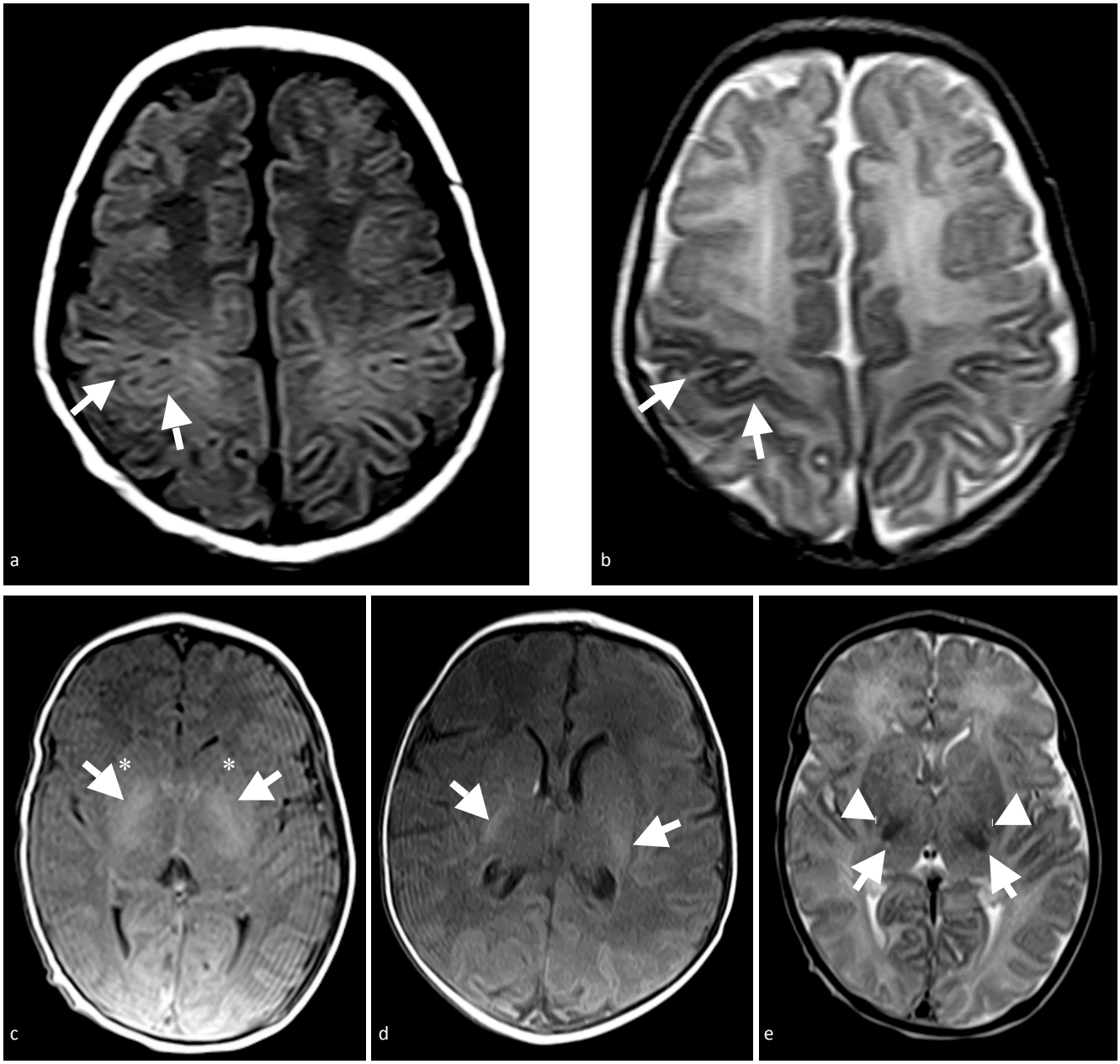

Figure 1. Normal signals of the specific regions in different term neonates with mild HIE. Perirolandic cortex is a) hyperintense in T1, and b) hypointense in T2 weighed imaging (WI) (arrows). c) Globus pallidus (arrows) is brighter than putamen (asterisks), and d) posterior limb of internal capsule (PLIC) is hyperintense (arrows) in T1WI. e) PLIC (arrowheads) is shown as a thin dark bant, and ventrolateral thalamus (arrows) was hypointense in T2WI.

DISCUSSION

In this study, we found that signals of PLIC on T1WI and T2WI and globus pallidus on T1WI were more frequently abnormal in term infants with severe HIE than in term infants with mild HIE. All infants included in the study were in their first 3 weeks of life.

Two basic MRI patterns are defined in term infants with HIE: 1. Peripheral/watershed pattern, 2. Central/basal ganglion-thalamic pattern [5,6,10,11]. Mild to moderate HIE causes peripheral injury which

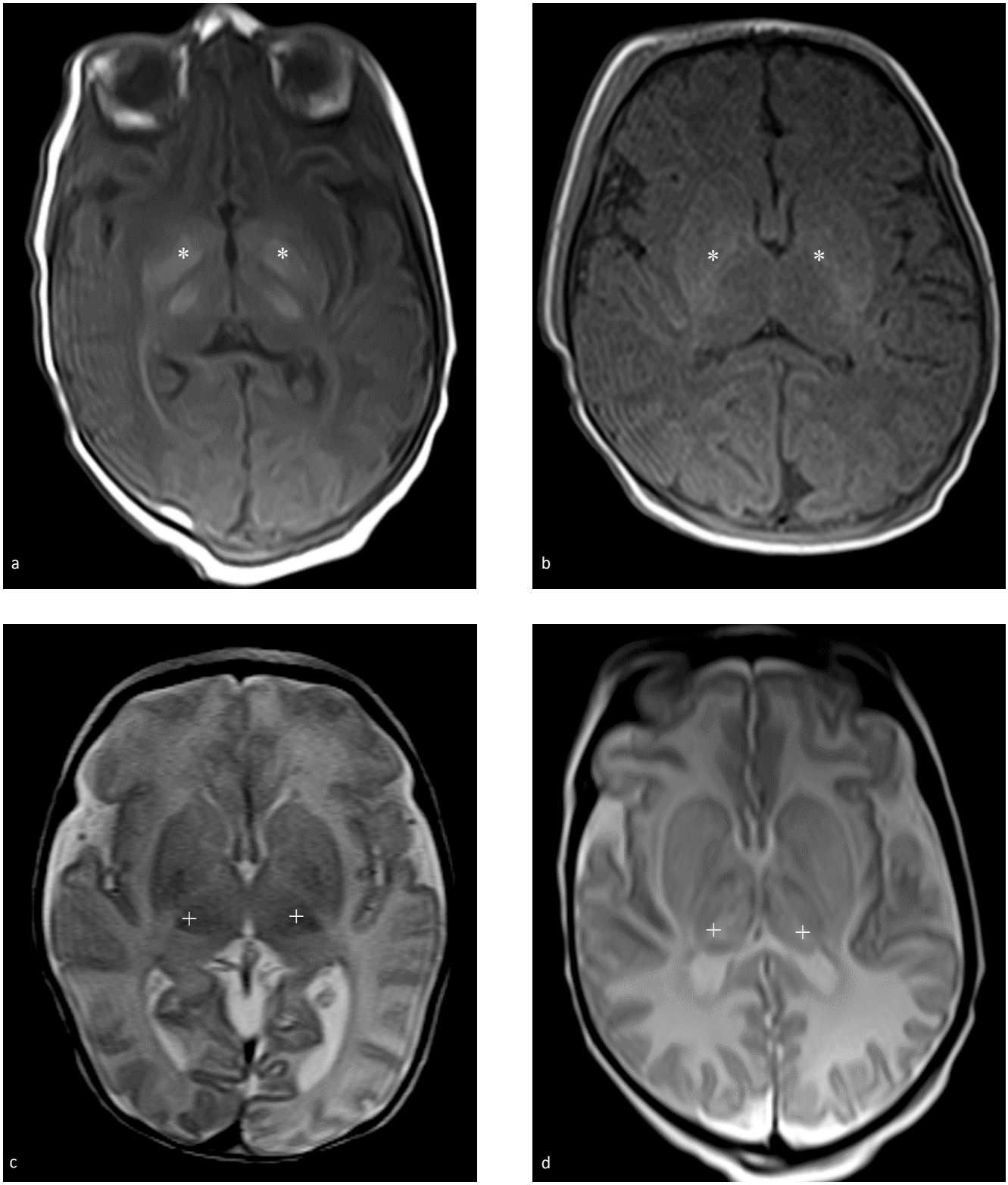

Figure 2. Abnormal signals of the specific regions in different term neonates with severe HIE. a) Case 1 is presented with absent hyperintense posterior limb of internal capsule (PLIC) despite having hyperintense globus pallidus (asterisks) in T1 weighted imaging (WI). b) Case 2 has abnormal globus pallidus without hyperintensity in T1WI. c) Case 3 has absent hypointense PLIC sign despite having hypointense ventrolateral thalamus (plus signs) in T2WI. d) Case 4 has neither hypointense PLIC nor hypointense thalamus in T2WI.

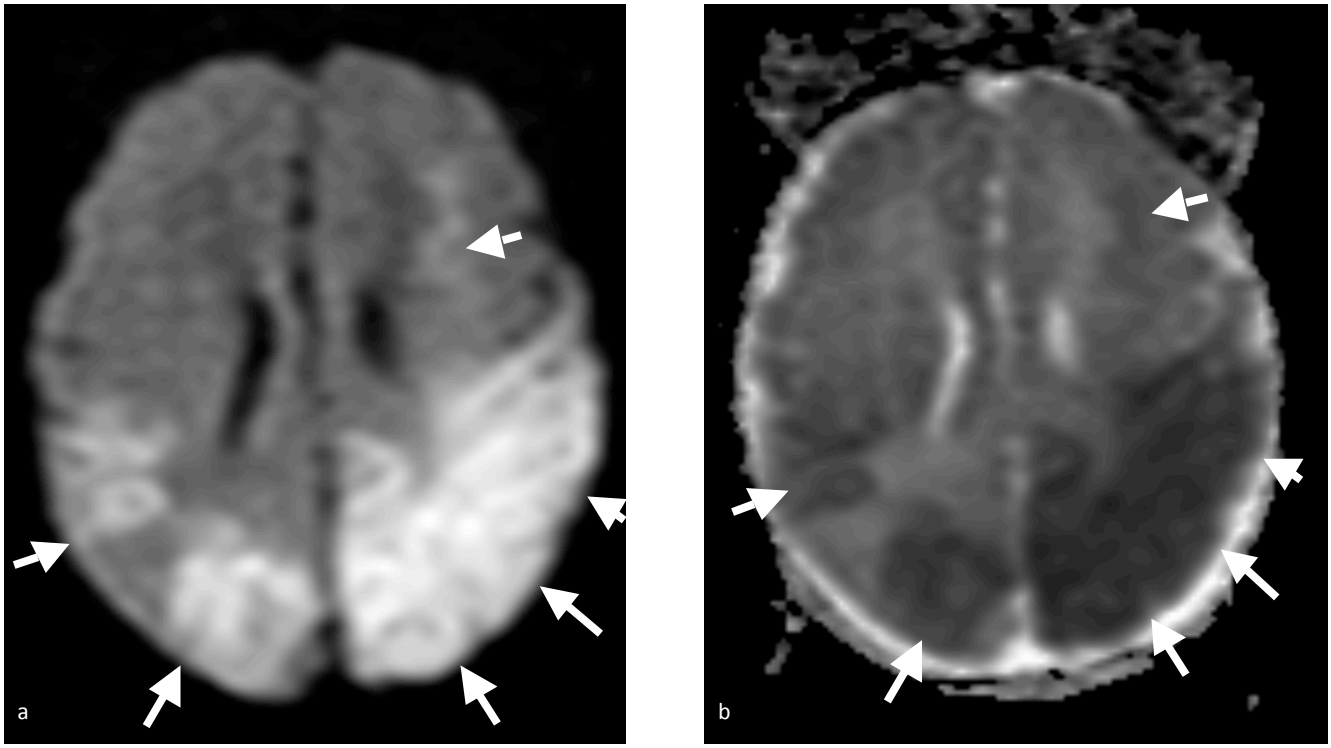

Figure 3. Diffusion weighted imaging with a) b:1000 sec/mm² and b) apparent diffusion coefficient map (ADC) is showing extensive acute diffusion restriction affecting left frontal deep white matter and almost diffuse bilateral parietal lobe (arrows).

Table 3. Comparison of MRI findings of the infants with mild and severe HIE.

	#Mild HIE n:31 (%)	#Severe HIE n:32 (%)	P value
Gestational age (weeks) (mean±SD)	39±1.7	38.5±1.8	0.183
Birth weight (grams) (mean±SD)	3297±569	3239±444	0.625
Number of cases with normal MRIs	21	12	
Number of cases with abnormal MRIs	10	20	
Abnormal signals			
Perirolandic cortex on T1WI	4 (12.9)	6 (18.8)	0.732
PLIC on T1WI	4 (12.9)	13 (40.7)	0.022
Globus pallidus on T1WI	3 (9.7)	13 (40.7)	0.008
Corticospinal tractus on T1WI	3 (9.7)	9 (28.1)	0.107
Perirolandic cortex on T2WI	3 (9.7)	4 (12.5)	1
PLIC on T2WI	3 (9.7)	11 (34.4)	0.032
Thalamus on T2WI	3 (9.7)	9 (28.1)	0.107
Putamen on T2WI	2 (6.5)	5 (15.6)	0.426
Tegmentum on T2WI	3 (9.7)	6 (18.8)	0.474
Diffusion restriction on DWI	9 (29)	16 (50)	0.123

HIE: hypoxic ischemic encephalopathy; SD: standard deviation; T1WI: T1 weighted imaging; PLIC: posterior limb of internal capsule; T2WI: T2 weighted imaging; DWI: diffusion weighted imaging.

involves peripheral cortex and adjacent subcortical white matter in the parasagittal border zones. Severe HIE results in central injury affecting basal ganglia, thalamus, hippocampus, and brain stem [6]. Miller et al reported that the central pattern was associated with more intensive resuscitation at birth, more severe encephalopathy, and seizure. It was related with impaired cognitive and motor sequelae at 30 months, as well [12]. In our study, abnormal globus pallidus signal on T1WI was associated with severe HIE. This result supports the assumption that central pattern may have a poor prognosis.

Internal capsule carries critically important fibers including corticospinal tractus with major motor fibers and corticothalamic connections [13]. These fibers are myelinated in term infants and easily visible with high signal intensity on T1WI and low signal intensity on T2WI [5,6,13]. Abnormal signal in PLIC is a strong predictor of abnormal motor outcome [8,9,14]. Okereafor et al. [14] reported that 86% of term infants who died or developed cerebral palsy had abnormal signals in PLIC. Liauw et al. [15] investigated signals of 19 different

brain regions on T1WI and found that lower signal ratio of PLIC/posterolateral putamen was correlated with adverse outcome. Positive predictivity of PLIC/putamen ratio was higher than that of Sarnat & Sarnat staging (69% vs 52%, respectively). In our study, abnormal PLIC signals on T1 and T2WI were more frequently associated with severe HIE when compared with mild HIE.

American College of Obstetricians and Gynecologists (ACOG) suggested that early imaging can be obtained within the first 24-96 hours, optimally at 10 days but with an acceptable window between 7-21 days of life [3]. DWI is useful in detection of cytotoxic edema even at 24th hour. It is more sensitive than T1W1 or T2WI in the first week. Signal abnormality on DWI usually peaks at 3-5 days of life while early imaging before 5 days may underestimate the injury on T1WI and T2WI. On the other hand, T1WI and T2WI present details about anatomy and myelinization process. These sequences are valuable between 7-14 days of life when signal abnormality begins to normalize on DWI (pseudo-normalization on 10th-12nd day) [6,11]. Additionally, neonatal brain MRI should be optimized with a higher repetition time, compared to adults, for both T1WI (800 msec vs 400 msec) and T2WI (6500 msec vs 4000 msec) [16]. In our study, MRIs were optimized for neonatal imaging and obtained within 3 weeks complying with ACOG's proposal. Although the purpose of the study was not to make comparisons between DWI and conventional MRI sequences, we realized that abnormal signals were more often seen on DWI than on T1WI or T2WI. In our study, DWI findings were not significantly different between mild and severe HIE groups which may be due to the timing of our DWI acquisitions. DWI evaluation within the first 5 days of life would improve the value of this technique. We evaluated DWI data only for the presence or absence of diffusion restriction; however, detailed evaluation including the location of diffusion abnormality would further improve the benefits of DWI.

Cranial ultrasonography is an option in suspected cases with HIE. It is useful in detection of hydrocephalus, cystic periventricular leukomalacia, and germinal matrix hemorrhage which is a predominant pattern in HIE of premature infants. It has a limited value in the detection of cortical lesions and highly operator dependent [6]. CT may be useful in screening for bleeding without need for sedation [17]. However, it has several disadvantages including limited contrast resolution, inability to discriminate between gray, and white matter abnormalities, and radiation exposure. Magnetic resonance spectroscopy (MRS) has a potential in early detection of HIE even within first 24 hours after birth in term neonates [5]. Elevated lactate-choline ratio was related with poor neurological outcome [18]. However, MRS is prone to artifact formation, may require sedation, and has limited availability [6,19]. We did not use these methods due to the limitations described above.

This study had several limitations. Firstly, it was a retrospective study with a small sample size. These types of studies have the potential of bias. We evaluated the MRIs by two radiologists blinded to clinical findings to minimize bias. Secondly, some infants were too small that resulted in low signal-to-noise ratio. Motion-free acquisition is also difficult in infants. Although non-diagnostic MRIs were excluded (n:2) and MRIs were optimized for infants, the image quality was still poor in 1.5 T for some neonates. The 3 T scanners might provide a better image quality. Thirdly, the findings of MRIs were compared with Sarnat & Sarnat clinical staging. Further clinical outcomes could not be estimated based on these results due to lack of long-term neurological assessment.

In conclusion, cranial MRI demonstrates involvement and spread of brain injury in HIE. Abnormal signals detected in PLIC and globus pallidus in conventional MRI may suggest severe HIE. These retrospective findings should be supported with prospective studies.

Ethics Committee Approval: S.B.Ü. Izmir Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Ethics Committee approval was obtained (19.11.2020/209).
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Research Article

Are Number of Passes Related with Complications in Pediatric Native Kidney Biopsies?

Pediatrik Nativ Böbrek Biyopsisinde Geçiş Sayısı Komplikasyonla İlişkili midir?

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Şeyma Akkuş
Şükran Keskin Gözmen
Malik Ergin
Erkin Serdaroğlu
Nida Dinçel

ABSTRACT

Objective: *The aim of this study was to determine the relationship between number of passes and complications in pediatric native kidney biopsies performed under ultrasonography guidance.*
Methods: *Forty-nine children who underwent native kidney biopsies using a 16 Gauge semi-automatic needle between 03/2019-03/2020 were included in the study. All patients were evaluated with ultrasonography before and after biopsy procedure to detect complication(s). Two or more passes were performed in most cases where electron microscopy was required. Requirement for transfusion or intervention was considered as a major complication. The technical success was calculated considering number of glomeruli harvested. Number of passes were compared with complication rates and number of glomeruli sampled. In statistical analysis, chi-square, t-test, and ANOVA tests were used.*
Results: *Minor, major complications and technical success rates were 36.7%, 0% and 100%, respectively. Number of passes were 1 in 4, 2 in 30, 3 in 11 and 4 in 4 cases. Increasing number of passes were related with higher complication rates (p=0.002). The complication rates were 23.5%, and 66.7% when ≤2, and ≥3 passes were used. Complication rate was higher when ≥3 passes were used (p=0.009), without any increase in the number of glomeruli sampled (p=0.839).*
Conclusion: *Pediatric native kidney biopsy was a safe procedure using 16 Gauge needle under ultrasonography guidance. Three of more passes caused an increase in minor complication rates without any increase in the number of glomeruli sampled.*

Keywords: *Pediatric renal biopsy, needle biopsy, bleeding, hematoma*

ÖZ

Amaç: *Bu çalışmanın amacı çocuk hasta grubunda ultrasonografi rehberliğinde gerçekleştirilen nativ böbrek biyopsilerinde geçiş sayısı ile komplikasyon ilişkisini saptamaktır.*
Yöntem: *03/2019-03/2020 arasında US eşliğinde 16 Gauge yarı otomatik iğne ile nativ böbrek biyopsisi yapılan 49 çocuğu kapsamaktadır. Tüm olgular biyopsi öncesi ve sonrası ultrasonografi ile komplikasyon varlığı açısından tarandı. Elektron mikroskopisi gereken durumlarda veya ilk örneklemin yetersiz görüldüğü olgularda 2 veya daha fazla geçiş yapıldı. Transfüzyon veya girişim gerekliliği majör komplikasyon olarak belirlendi. Glomerül sayısına göre işlemin teknik başarısı hesaplandı. Geçiş sayısı ile komplikasyon gelişimi ve glomerül sayısı birbiriyle karşılaştırıldı. İstatistiksel analizde, Ki-kare, t ve ANOVA testlerinden faydalanıldı.*
Bulgular: *Minör, majör komplikasyon ve teknik başarı oranı sırasıyla %36,7, %0 ve %100'dü. 4 olguda 1 kez, 30 olguda 2 kez, 11 olguda 3 kez ve 4 olguda 4 kez geçiş yapıldı; artan geçiş sayısı ile komplikasyon varlığı arasında anlamlı ilişki bulundu (p=0,002). Geçiş sayısı ≤2 ile ≥3 karşılaştırıldığında: İlk grupta komplikasyon oranı %23,5, diğerinde %66,7 idi. Geçiş sayısı ≥3 olanlarda ≤2'ye kıyasla daha sık komplikasyon izlenirken (p=0,009), glomerül sayısı açısından fark yoktu (p=0,839).*
Sonuç: *Çocuklarda, ultrasonografi altında 16 Gauge iğne ile nativ böbrek biyopsisi güvenlidir. Üç ve üzeri geçiş, glomerül sayısını artırmazken minör komplikasyonda artışa neden olur.*

Anahtar kelimeler: *Pediatrik renal biyopsi, iğne biyopsisi, kanama, hematom*

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INTRODUCTION

Kidney biopsy is the gold standard in the diagnosis of parenchymal renal disease. Since it is an invasive procedure and carries the risk of complications, it is performed in a limited number of patients. Native kidney biopsy is indicated under following conditions: nephrotic syndrome, nephritic syndrome, proteinuria, suspicion of rapidly progressing glomerulonephritis, renal involvement of systemic diseases (such as systemic lupus erythematosus, Henoch-Schonlein purpura etc.), and treatment follow-up [1-3].

The blood flow to kidneys is one liter per minute [4]. Since kidney has high tissue blood supply per unit mass, kidney biopsy is prone to complications mostly hemorrhage. Therefore, renal biopsy is performed mostly under real-time ultrasound (US) guidance [5]. Complications can be minimized by preserving critical structures (such as ureter, renal artery and vein, renal pelvis etc.) and adequate sampling can be achieved with orienting the needle to the parenchyma under real-time US guidance [1].

The British Pediatric Nephrology Association (BAPN) proposed standards for the kidney biopsy procedures in children. Accordingly, all patients should receive written information, ≤3 passes should be achieved in 80% of cases, adequate tissue material for diagnosis should be obtained in 95% of cases, and rates of major complications defined as requirement for further investigation, intervention or monitoring should be less than five percent [6,7].

In this study, the relationship between the number of passes and complications was investigated in pediatric US-guided native kidney biopsies using 16 Gauge (G) semi-automatic needles.

MATERIAL and METHODS

This retrospective study was approved by the institutional board and included 49 children who underwent native kidney biopsies using 16 G semi-automatic needle under real-time US guidance between March 2019 and March 2020. The patients who did not give written consent, biopsies performed under non-US guidance or not using 16G biopsy needle (n:1) were excluded from the study. In all patients International Normalization Ratio (INR) <1.5 and platelet counts > 100.000/µL were ensured before the procedure.

All patients were hospitalized for at least 1 day after biopsy. Hematocrit values were recorded before and 4 hours after the procedure and differences in hematocrit values were calculated. The patients who had hematoma thicker than 10 mm or whose hematocrit levels decreased 10 units were observed for at least 48 hours.

The procedure was performed with the patient in prone position and inferolateral poles of the left, and right kidneys were targeted in 39, and 10 cases, respectively. Sedation was achieved with intravenous midazolam (0.1 ml/kg) and lidocaine (2-4 ml) was used as a local anesthetic. Native kidney biopsies were performed by an interventional radiologist and pediatric nephrologist in collaboration using a semi-automatic 16 G biopsy needle (Geotek®, Ankara, Turkey) under real time US-guidance. The first sampling was done by a pediatric nephrologist, the following procedures by an interventional radiologist. US guidance was provided by an interventional radiologist. Multiple entries were performed in most cases requiring electron microscopy examination or inadequately sampled at the first pass.

Ultrasonographic examination was performed using a 6-9 mHz high-frequency linear probe (Aplio 500, Toshiba/Canon®, Japan) by an interventional radiologist who sought for the presence of a complication 24 hours after the procedure. Hematoma requiring transfusion or intervention, injury to ureter, renal artery or vein, and death were considered as major complications.

Total number of glomeruli in the samples was noted by the pathologist. The adequacy of the sample for histopathological examination was determined based on the number of glomeruli sampled. Accordingly, sampling was suboptimal and nondiagnostic if <10 and <5 glomeruli were collected, respectively [8]. The cases were divided histopathologically into 7 subgroups: normal, nonspecific (minimal change disease or nephronophthisis), glomerulonephritis (GN), acute tubular necrosis (ATN), tubulointerstitial nephritis (TIN), IgA nephropathy, and focal segmental glomerulosclerosis (FSGS).

Statistical analysis

Statistical analysis was performed using SPSS version 20 (IBM® Corp., Armonk, NY, USA). The relationship

between gender, age, and complication was tested using Fisher exact and t test, respectively. Differences in hematocrit values were compared with the presence of complication using t-test. Correlations between the number of passes and complication rates were evaluated using the chi-square test. Correlation between the number of passes and glomeruli sampled was evaluated using ANOVA test. The number of passes were grouped as ≤2 and ≥3. The groups were compared with complication rates using Fisher exact test and with number of glomeruli sampled using t-test. P<0.05 was considered statistically significant.

RESULTS

The median age of 49 cases included in the study was 9 (standard deviation: ± 4.6, range: 0.5-17) years. Our study population consisted of 29 boys and 20 girls . Histopathology results were as follows: 15 normal, 7 nonspecific, 12 GN, 3 ATN, 3 TIN, 8 IgA nephropathy, and 1 FSGS.

Minor complications were seen in 18 (36.7%) cases. No major complication was observed. The thickest hematoma was 22 mm in diameter. Four cases with hematoma thicker than 10 mm were followed and no additional treatment was needed (Figure 1). The longest hospitalization was 3 days. There was no complication other than hematoma.

Any significant relation was not observed between age, gender, and complication rates (p=0.621 and p=0.417, respectively). Average decreases in hematocrit levels were 1.5% (±6.7), and 1% (±4.7) in cases with and without hematoma, respectively without any statistically significant intergroup difference (p=0.903) (Table 1).

Table 1. Comparison of age, gender, hematocrit decrease and the number of pass with complication.

Characteristic	No complication (n:31)	Complication (n:18)	P value
Mean age (year)	9.6 (±4.6)	8.8 (±4.7)	0.621
Number of gender (male, female)	17, 14	12, 6	0.417
Mean hematocrit decrease (%)	1.0±4.7	1.5 (±6.7)	0.903
Number of pass			
1 (n:4)	4	0	0.002
2 (n:30)	22	8	
3 (n:11)	2	9	
4 (n:4)	3	1	
≤ 2 (n: 34)	26	8	0.009
≥ 3 (n: 15)	5	10	

A total of 113 passes were performed: One (n=4), two (n=30), three (n=11), and four (n=4) passes were performed in respective number of cases. Increasing number of passes was correlated with complication rates (p=0.002).

Adequate sampling was achieved in all cases with 100

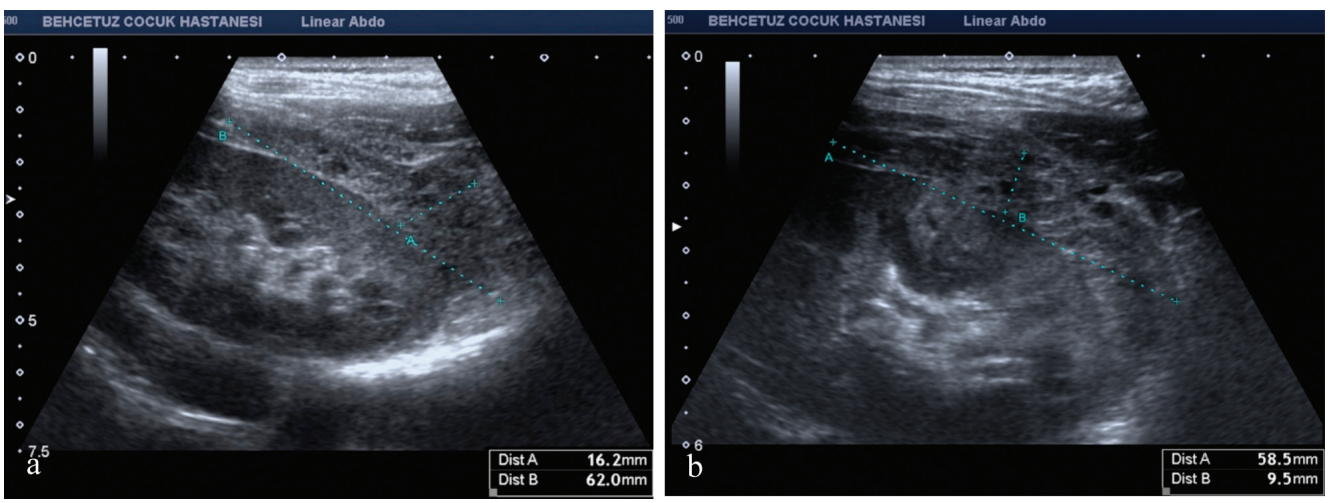

Figure 1. A 13-year-old boy who underwent renal biopsy with three passes. a) A 16x62 mm subcapsular hematoma was observed at the 24th hour US examination. b) The hematoma size was reduced to 10x59 mm and he was discharged at the third day. Hematocrit was 41.2%, 40.2%, and 38.9% before, four hours, and three days after the procedure, respectively.

% technical success rate. Median number of 32 (± 20, 8-100) glomeruli were harvested. Sampling was optimal in all except one case where only 8 glomeruli were collected. Median number of 40, 37, 38, and 30 glomeruli were sampled with one, two, three, and four passes, respectively. There was no relation between the number of passes and the number of glomeruli sampled (p=0.913).

The complication rates were 23.5% , and 66.7% when ≤2, and ≥3 passes were performed. Complications were more frequently encountered when ≥ 3 passes were used (p=0.009). Number of glomeruli sampled were not different between these groups (p=0.839).

DISCUSSION

This study examined pediatric native kidney biopsies performed with 16G semi-automatic needle. Minor hematoma was seen in 36.7% of the cases without any major complication. Adequate sampling was achieved in all. Using 3 or more passes raised minor complication rates without increasing the number of glomeruli collected. These results supported the proposal of BAPN standard as, "The number of passes should be ≤3 in 80% of cases" [7].

Usage of automatic needle under real-time US guidance has facilitated the procedure [9]. In a study including 533 children, minor hematoma was less common, and the hospital stay was shorter when biopsies were performed under real-time US guidance [10]. In a meta-analysis, it was reported that real-time US guidance did not change the rates of minor or major complications in children [11]. However, in plenty of studies opposing outcomes have been reported [10,12,13]. Using automatic needles greater number of glomeruli have been harvested with lower complication rates relative to former hand-driven system [14,15]. In this study, semi-automatic needles under US guidance were used in all cases. We argued that under real-time US guidance adequate tissue sampling can be achieved, and semi-automatic needles with traceable distal needle tip are safer and reduce complication rates.

Hematoma was the most common complication seen after biopsy [2]. Post-biopsy bleeding rates ranged between 4% and 44% in the literature [12,13,16-19]. In a study by Ding et al. [18] including 183 children, minor, major complications, and technical success rates were 12.9%, 3% and 98%, respectively. Printza et al. [12] reported that, the corresponding rates were 11%, 0%, and 97.7%, respectively. In the meta-analysis of Varnel et al. [11] minor complication was seen in 18% whereas transfusion and intervention were required in 0.9%, and 0.7% of the cases , respectively. Major hemorrhage requiring transfusion or intervention were seen in 3% of the adults, and 1.9% of the children in the Norwegian Kidney Registry data including 9288 cases. Besides, it was emphasized that major hemorrhage was more common in the centers performing less than 30 biopsies per year [19]. In our study, minor, major complications, and technical success rates were 36.7%, 0%, and 100%, respectively. Our minor bleeding rate was relatively higher compared to the literature which may be related to the use of high frequency linear probe . Linear probe provides higher resolution with increased detectability of small hematomas, such that the thickness of the subcapsular hematoma was less than 10 mm in 14 of 18 attempts (77.8%).

The caliber of the biopsy needle was correlated with complication and technical success rates. In renal biopsy usually 14, 16, and 18 G needles have been used [2]. The diameters of these biopsy needles are 1000, 700, and 350 µm, respectively. An 18 G needle may cause glomerular fragmentation or undersampling since the glomeruli can be as small as 250 µm in diameter [1]. In a study comparing 14 and 16 G automatic needles, the number of glomeruli sampled did not differ, while perirenal hematoma was more frequently seen when 14 G biopsy needles were used [20]. In the study of Roth et al. [21] comparing 16 and 18 G needles, complication rates were similar while greater number of glomeruli were harvested using 16 G needles. Sinha et al. [9] reported that the median number of 25, and 13 glomeruli were sampled when 16, and 18 G biopsy needles were used, respectively. It was emphasized that using 16 G biopsy needles was advantageous in sampling greater number of glomeruli without any increase in complication rates. In our study, all cases were sampled using standard 16G semi-automatic needles and adequate sampling was achieved in all with a median of 32 glomeruli collected.

In a study by Korbet et al. [14] any significant relation between the number of passes and the presence of hematoma could not be found. Minor hematoma was

seen in 13.5% of the cases when ≤2 passes and in 18.5% of them when ≥3 passes were used. However, this study was performed with adult patients. Nevertheless, the National Kidney Foundation recommended less than 5 passes due to the increased risk of bleeding [1]. British Pediatric Nephrology Association proposed that ≤3 passes should be achieved in 80% of occasions [6,7]. In this study, minor hematoma was more frequent in the pediatric native kidney biopsies performed with ≥3 passes without any increase in the number of glomeruli harvested.

The factors such as surgeon's experience, systolic high blood pressure, low hemoglobin level, and renal failure were also associated with development of complications [2,14,18,19,22].

This study had several limitations. First, possible risk of selection bias exists due to its retrospective design. Second, the patient population was small. Third, the procedure was performed by two different surgeons. The experience of surgeons was different and had a potential of affecting the complications albeit increased generalizability of the results. Fourth, the biopsy procedure and US examination to detect presence of any complication were performed by the same interventional radiologist which carried risk of bias. US images were recorded in archives to prevent this limitation.

In conclusion, pediatric native kidney biopsy is safe under real-time US guidance using a 16 G semi-automatic needle, and ≥ 3 passes increase the risk of minor hematoma without any increase in the number of glomeruli sampled. Two passes may be convenient for adequate sampling.

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Research Article

Do Fetal Isolated Mild Venticulomegaly Make Any Difference in Regional ADC Values at Magnetic Resonans Imaging?

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Deniz Öztekin

Fetal İzole Ilımlı Ventrikülomegali Manyetik Rezonans Görüntülemede Bölgesel ADC Değerlerinde Farklılık Yaratır mı?

ABSTRACT

Objective: *Ventriculomegaly may not only develop secondary to a process,but it may also be in the form of isolated ventriculomegaly with no specific reason. MRI is performed to show the presence of accompanying pathologies.In this study, we measured ADC values in mild ventriculomegaly cases and aimed to investigate the role of ADC value measurements in predicting neurological prognosis in isolated mild ventriculomegaly during MRI.*
Methods: *In our study, ADC values were measured of 37 patients detected to be present with mild ventriculomegaly and 17 fetuses in the control group who had no additional central nervous system patology. For the measurement, ROI was placed in differtent brain regions (frontal lobe white matter,occipital lobe white matter, basal ganglia, thalamus, cerebellum and pons). The analysis of the data obtained was performed using the SPSS (20th version) program. MannWhitney U test was applied. Statistical significance level was set as p<0.05.*
Results: *There was no statistically significant difference between the isolated mild ventriculomegaly and the control group in terms of the mean maternal age (p=0.160). Also, no statistically significant difference was observed between the mean gestational age in the ventriculomegaly group and the control group (p=0.890). There was also no statistically significant difference between ADC measurements in different brain regions in the isolated mild ventriculomegaly and the control group (p=0.807).*
Conclusion: *In order to determine the prognosis in isolated mild ventriculomegaly, other quantitative parameters such as ADC measurement, beyond morphological evaluation and diameter measurement should be determined, and also we need more studies comprising more cases in this field.*

Keywords: *Isolated ventriculomegaly, ADC measurments, fetal brain*

ÖZ

Amaç: *Ventrikülomegali gelişimsel, destrüktif ya da obstruktif bir sürece sekonder gelişebileceği gibi hiçbir nedenin bulunamadığı izole ventrikülomegali şeklinde de olabilir. Ventrikülomegali tespit edilen olgularda eşlikçi patolojilerin varlığını göstermek amacıyla Manyetik Rezonans Görüntüleme tetkiki yapılır. Bu çalışmada manyetik rezonans görüntülemede ADC değeri ölçümlerinin izole Ilımlı ventrikülomegali olgularında nörolojik prognozu öngörmedeki rolünü araştırmayı amaçladık.*
Yöntem: *Çalışmamızda fetal MRG tetkiki bulunan ılımlı ventrikülomegali tespit edilen 37 hastanın ve santral sinir sistemi patolojisi bulunmayan 17 fetusun diffüzyon ağırlıklı görüntülemede iş istasyonunda manuel olarak frontal ve oksipital loblarda beyaz cevherden, bazal ganglionlar, talamus, pons ve cerebellumdan bilateral simetrik olarak Region of Interest yerleştirerek ADC değerleri ölçüldü. Elde edilen verilerin analizi bilgisayarda SPSS (20. versiyon) programında yapıldı. MannWhitney U testi uygulandı. İstatistiksel anlamlılık düzeyi p<0.05 alındı.*
Bulgular: *İzole ılımlı ventrikülomegali grubu ve kontrol grubunda maternal yaş ortalaması arasında istatistiksel olarak anlamlı fark saptanmadı (p= 0.160). Ventrikülomegali grubu ve kontrol grubunda gestasyonel yaş ortalaması arasında istatistiksel olarak anlamlı fark saptanmadı (p= 0.890). İzole ılımlı ventrikülomegali grubu ve kontrol grubunda frontal, oksipital, bazal gangliyon, talamus, pons ve serebellumda ADC ölçümleri arasında istatistiksel olarak anlamlı fark saptanmadı (p=0.807).*
Sonuç: *İzole ılımlı ventrikülomegalide prognozu belirlemek amacıyla morfolojik değerlendirme ve çap ölçümünün ötesinde, ADC ölçümü gibi mikrostriktüel değişiklikleri yansıtabilecek başka kantitatif parametreler belirlenmesi gerekmekte olup bu alanda daha fazla sayıda olgu içeren daha çok çalışmaya ihtiyaç vardır.*

Anahtar kelimeler: *İzole ventrikülomegali, ADC ölçümleri, fetal beyin*

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INTRODUCTION

Ventriculomegaly (VM) is defined as the diameter of the atrium of the lateral ventricles just above the thalamus over 10 mm in the measurements performed in axial plane on the posterior end of the choroid plexus. Atrium diameters in the normal population range between 5.4 mm-7.6 mm on average [1].

Ventriculomegaly is observed regardless of the gestational week in the event that the ventricle diameter exceeds 10 mm at atrium level. While a ventricular diameter measuring in a range of 10-15 mm is defined as mild, and severe ventriculomegaly when measured above 15 mm.

It is called asymmetric ventriculomegaly if the difference between the two ventricles is found as > 2 mm in the measurements performed at the atrium level of the lateral ventricles, and if found lower than this, it is called symmetric ventriculomegaly [2,3].

Mild ventriculomegaly is divided into two subgroups as combined and isolated forms. While there are various neurological diseases accompanying ventriculomegaly in its combined form, there is no etiological cause accompanying ventriculomegaly in its isolated form [4,5]. The question of how and how often this pathology should be followed-up is hard to be clarified for perinatologists in isolated mild ventriculomegaly cases. Growth retardation was found in 0-36% of the cases diagnosed with isolated ventriculomegaly by ultrasonography [6-9].

In studies conducted to determine the prognosis in cases with ventriculomegaly, the underlying cause mostly remains unknown, making it difficult to provide information about the course of the disease and problems arise in patient management. Fetal cranial Magnetic Resonance Imaging (MRI), which also includes ADC sequences, is performed to detect the presence of accompanying pathologies in isolated mild VM cases. In cases such as hydrocephalus and ischemic lesions, interpretation can be made about the prognosis of the disease by making use of the variability in ADC values in cranial MRI. With the same principle, we aimed to provide quantitative data to the clinicians in predicting prognosis by performing ADC measurements in different parts of the brain in fetal MRI examination in isolated mild VM cases.

MATERIAL and METHOD

In this study, 58 pregnant women with a gestational weeks of 17 to 39, who were sonographically detected to be present with ventriculomegaly between the dates of January 2014 and January 2016, and who underwent fetal Magnetic Resonance Imaging (MRI) examination were enrolled, while 17 fetuses referred for different reasons between the same dates with no Central Nervous System (CNS) pathology were enrolled in our control group. Diffusion examination was not performed on MRI imaging in 8 of 58 ventriculomegaly cases, and again the ventricle width of 8 of them was measured over 15 mm (severe ventriculomegaly). ADC measurements could not be performed in 5 of them due to non-diagnostic images related to patient motion artifact. A total of 21 patients were not included in our study group. In our study, while 37 patients were included in mild VM group, 17 patients detected to have no pathology in the CNS were included as a control group. In our study, lateral ventricle diameters of 37 patients with isolated mild VM and 17 patients in the control group were measured. Measurements were carried out just above the thalamus at the level of the atrium in the axial plane, from the posterior end of the choroid plexus and from the middle part of the ventricle height in the coronal plane in an axis perpendicular to the 3rd ventricle (Figure 1). Patients with a diagnosis of mild ventriculomegaly were examined in three subgroups as asymmetric (both ventricle width difference being ≥ 2-2.4 mm), symmetric (both ventricle width difference being <2-2.4 mm) and unilateral asymmetric (one-sided ventricular width is normal) ventriclomegaly.

The gestational ages of our cases at the time when they were diagnosed with ventriculomegaly were determined through Ultrasonography (USG) criteria (gestational sac diameter, crown-rump length, biparietal diameter, femur length) and last

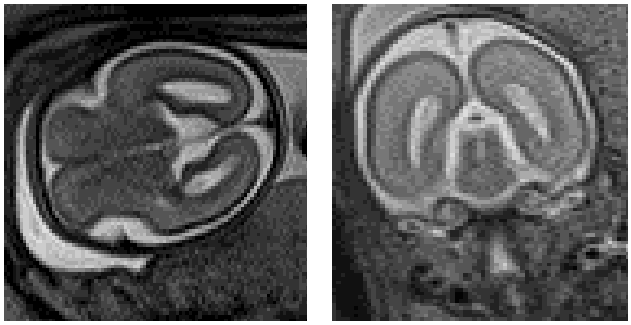


Figure 1. Measurement of ventricle diameter in axial and coronal planes.

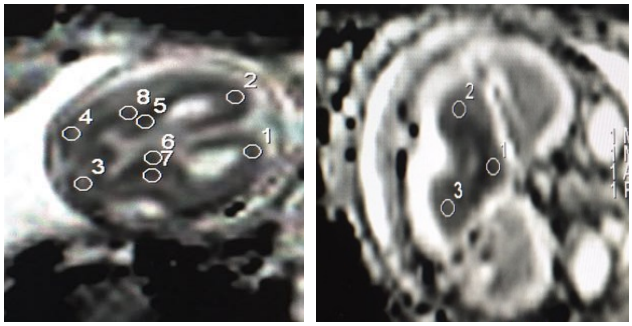


Figure 2. Example of ROI placement during ADC measurement from different parts of the brain (1-2 frontal white matter on the left, 5-6 thalamus, 7-8 basal ganglia, 3-4 occipital white matter), (1 pons on the right, 2-3 cerebellum).

menstrual period. Fetal MRI examinations were retrospectively evaluated in our study. MR imaging was performed using a body coil on a 1.5 T MR device (Siemens magnetom aera).

Fetus was monitored applying T2 weighted Single-Shot Fast Spin Echo (SSFSE) sequence, with slice thickness of 3 mm, with no gap, Field of View (FOV): 385, matrix: 256 × 256, Echo Time (TE): 200 ms, Repetition Time (TR): 5000 ms, and Fourier Acquired Single-shot Turbo Spin-Echo (FASTE) sequence slice thickness: 3 mm, no gap, FOV: 375, matrix: 256 × 512, TE: 100 ms, TR: 1298 ms, in sagittal, coronal and axial planes. MR images obtained for ADC measurements were analyzed in DICOM format on the workstation. Manual ADC measurements were made from axial, sagittal or coronal sections by selecting the most immobile section containing the whole brain. For the measurement, The Region of Interest (ROI) was placed symmetrically and bilaterally on the frontal lobe white matter, occipital lobe white matter, basal ganglia, thalamus and cerebellum, and when it comes to the pons level, it was placed on a single area in the center (Figure 2). During the placement of the ROI, the ROI volume was tried to be kept small during the measurements, taking into account the partial volume artifacts, especially in areas containing different tissue components. Although the shape and size of the ROI varied depending on the brain area measured, it was in the range of 32-69 mm^2.

The analysis of the obtained data was performed with the SPSS program. The MannWhitney U test, a nonparemetric evaluation based on statistical probability, was used. Statistical significance level was set as $p < 0.05$.

RESULTS

Ventriculomegaly was encountered on MRI in 58 patients included in our study. Diffusion examination was not carried out on MRI imaging in 8 of 58 ventriculomegaly cases, while the ventricle width of 8 of them was measured over 15mm. ADC measurements could not be performed in 5 of them due to non-diagnostic images caused by patient motion artifact. A total of 21 patients were not included in our study group, while the remaining 37 were evaluated as isolated mild ventriculomegaly. 17 fetuses without any CNS pathology were included in our control group.

Mean lateral ventricle diameter measured on MRI was found to be 10.24 mm in the isolated mild ventriculomegaly group, while the same was 6.40 mm in the control group. Also, the mean right lateral ventricle diameter of isolated mild ventriculomegaly cases measured on MRI was 10.54 mm, while the mean left lateral ventricle diameter was measured to be 9.94 mm. Of the isolated mild ventriculomegaly cases, 13 were seen to be present with symmetrical bilateral ventriculomegaly and 24 with unilateral asymmetric ventriculomegaly.

While the maternal age distribution of the cases was calculated between 18-44 years, the mean maternal age of 37 cases with isolated mild

ventriculomegaly was 28.62 SD (± 5.60) and the mean maternal age of 17 cases in the control group was 31.05 SD (± 6.12). No statistically significant difference was found between the mean maternal age in the isolated mild ventriculomegaly group and the control group. (p= 0.160) (Table 1).

The gestational age distribution of the cases was between 17th and 37th weeks, and the mean gestational age of 37 cases with isolated mild ventriculomegaly was found to be 25.64 SD (±5.74), while the mean gestational age of 17 cases in the control group was found to be 25.21 SD (±4.97) (Graphic 1). No statistically significant difference was detected between the mean gestational age in the isolated mild ventriculomegaly group and the control (p= 0.890) (Table 1).

The mean frontal ADC measurement for 37 cases with isolated mild ventriculomegaly were found to be 1.60 SD (± 0.24), while the same measurement performed for 17 cases in the control group was 1.61 SD (±0.18) (Graphic 2). No statistically significant difference was found between the frontal ADC measurement in the isolated mild ventriculomegaly group and the control (p= 0.807) (Table 2).

Table 1. Demographic characteristics.

	Ventriculomegaly (+) n=37	Ventriculomegaly (-) n=17	P
Maternal age	28.62 SD(±5.60)	31.05 SD(±6.12)	0.160
Gestational age (weeks)	25.64 SD(±5.74)	25.21 SD(±4.97)	0.890

The mean occipital ADC measurement value of 37 cases with isolated mild ventriculomegaly was detected to be 1.63 SD (±0.27), while the mean occipital ADC measurement value of 17 cases in the control group was 1.68 SD (±0.21) (Graphic 2). No statistically significant difference was found between occipital ADC measurements in the isolated mild ventriculomegaly group and the control group (p= 0.649) (Table 2).

The mean basal ganglia ADC measurement value of 37 cases detected to be present with isolated mild ventriculomegaly was 1.40 SD (±0.24), and the mean basal ganglia ADC measurements of 17 cases in the control group was 1.34 SD (±0.18) (Graphic 2). No statistically significant difference was found between basal ganglia ADC measurements in the isolated mild ventriculomegaly group and the control group (p= 0.408) (Table 2).

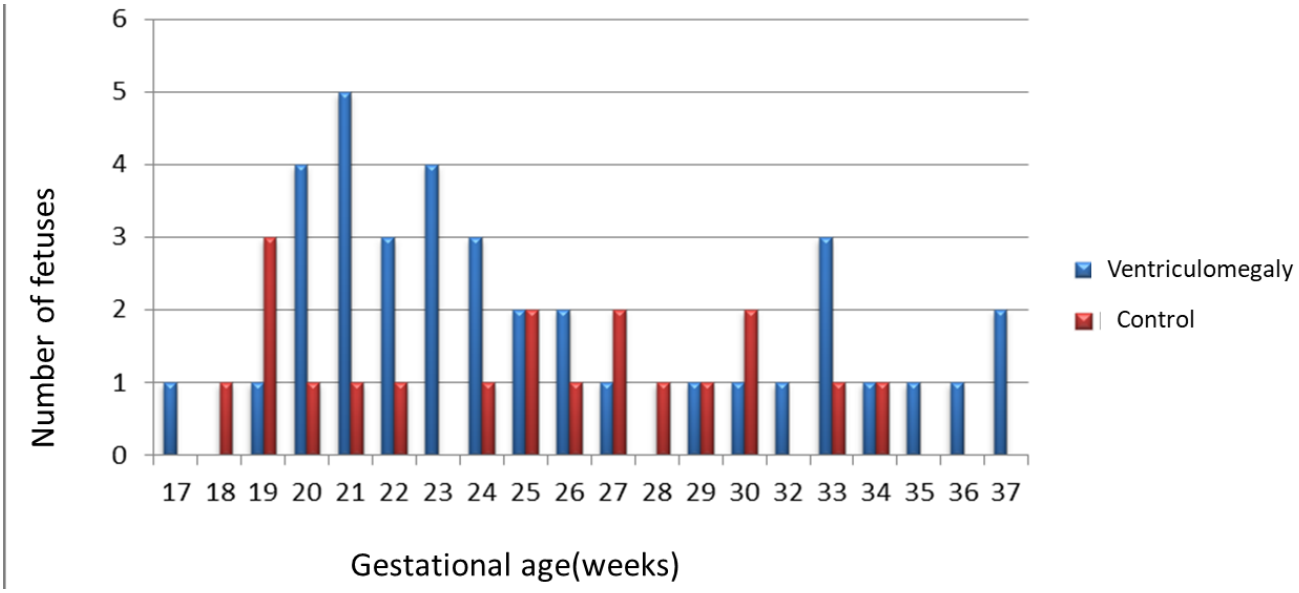
Table 2. Comparison of ADC values in patients with isolated mild ventriculomegaly and control group (ADC (× 10^{-9} mm^2 / sec)).

ADC Value measurement	Ventriculomegaly (+) n=37	Ventriculomegaly (-) n=17	P
Frontal white matter	1.60 SD (±0.24)	1.61 SD (±0.18)	0.807
Occipital white matter	1.63 SD (±0.27)	1.68 SD (±0.21)	0.649
Basal ganglia	1.40 SD (±0.24)	1.34 SD (±0.18)	0.408
Thalamus	1.42 SD (±0.26)	1.34 SD (±0.19)	0.340
Pons	1.32 SD (±0.19)	1.34 SD (±0.31)	0.498
Cerebellum	1.55 SD (±0.22)	1.51 SD (±0.27)	0.436

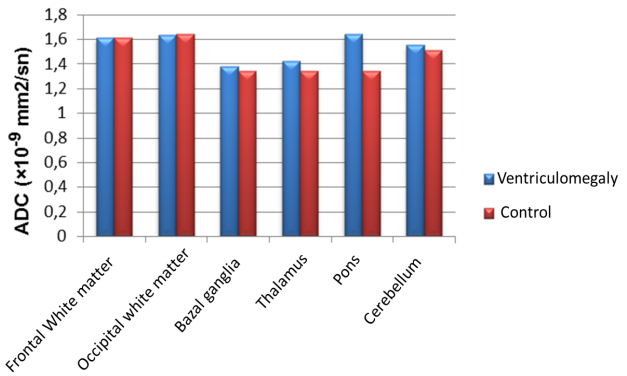
The mean thalamus ADC measurement value of 37 cases with isolated mild ventriculomegaly was 1.42 SD (±0.26), while the mean of thalamus ADC measurements of 17 cases in the control group was 1.34 SD (± 0.19) (Graphic 2). No statistically significant difference was found between thalamus ADC measurements in the isolated moderate ventriculomegaly group and the control (p= 0.340) (Table 2).

On the other hand, the mean pons ADC measurements of 37 cases with isolated mild ventriculomegaly was 1.32 SD (± 0.19), while the mean pons ADC measurements of 17 cases in the control group was 1.34 SD (± 0.31) (Graphic 2). No statistically significant difference was found between the pons ADC measurements in the isolated mild ventriculomegaly group and the control group (p= 0.498) (Table 2).

Also, the mean cerebellar ADC measurements of 37 cases with isolated mild ventriculomegaly was 1.55 SD (±0.22), while the mean of cerebellar ADC measurements of 17 cases in the control group was 1.51 SD (±0.27) (Graphic 2) and again, no statistically significant difference was found between the cerebral ADC measurements in the isolated mild ventriculomegaly group and the control (p=0.436) (Table 2).



Graphic 1. Gestational age (weeks) distribution graph of the control and ventriculomegaly groups.



Graphic 2. Mean values of ADC measurements in different regions of the brain in patients with isolated mild ventriculomegaly and in the control group.

In our study, ADC values decreased as the gestational age progressed in occipital white matter, basal ganglia, thalamus, pons and cerebellum, except frontal white matter (Graphic 3).

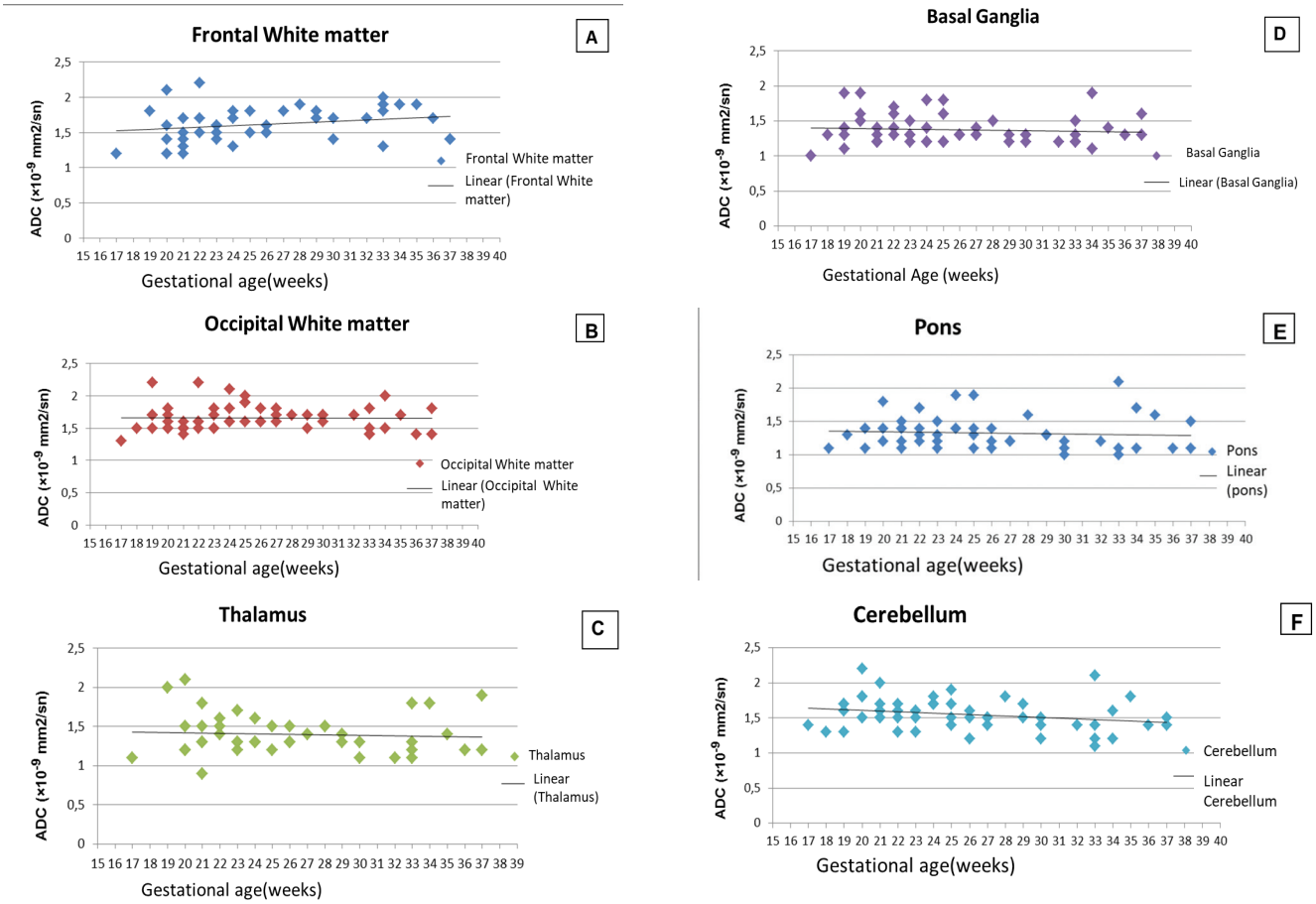
DISCUSSION

Different ADC values in different parts of the brain;

In our study, different values were obtained from different parts of the brain in the ADC value measurements performed between 17th and 39th weeks. ADC values in white matter and pons were found to be similar to each other, which were higher than the basal ganglia, thalamus and cerebellum. Similarly, Chen hoffman et al. [10] found higher ADC values in white matter than in the basal ganglia, thalamus, pons and cerebellum. Gal Yaniv et al. found higher ADC values in white matter in the frontal region than in the basal ganglia, thalamus, pons and cerebellum [11]. It has been revealed in previous studies that the reason for the higher ADC values in white matter could be related to the fact that the white matter has not completed its maturation yet, or that the cellularity could be higher in the basal ganglia and thalamus, or that the myelinization is insufficient [12,13]. In the studies conducted by Boyer and Vasung, it was revealed that maturation in cerebellum occured earlier than in the occipital and maturation in the occipital was earlier than the frontal white matter, as myelinization progressed from the back to the front, from the bottom up and from the inside out. There was no significant difference in the basal ganglia and thalamus [14,15].

ADC values decrease as gestational age progresses;

In our study, as the gestational age increased, ADC values, except for frontal white matter, decreased (Graphic 1). Previous studies showed that ADC values decreased over time towards the end of pregnancy, except for frontal white matter, as gestational age increased [14]. In another study, as gestational age



Graphic 3. Scatter plot of ADC values by gestational age in different brain regions (A, B, C, D, E, F). In our study, ADC values decreased in occipital white matter, basal ganglia, thalamus, pons and cerebellum as gestational age progressed.

increased, a decrease in ADC values was only observed in the cerebellum, pons and thalamus, whereas no decrease was observed in other regions [12,13], which was thought to be due to the fact that the gestational age range of the fetuses included in the study was not kept in a wide spectrum. The gestational age range should include all trimesters for significant results. The main reason for the decrease in ADC values as gestational age progresses is that the water molecule content of the fetal brain decreases as the pregnancy progresses, which continues after birth until the age of 2. At the same time, an increase in the lipid content of the brain is observed with myelination in this process, which contributes to the decrease in ADC values [16,17].

The region with the fastest decrease in ADC values;

In our study, the fastest decrease in ADC values as pregnancy progresses was observed in the cerebellum, which was followed by occipital white matter, thalamus, basal ganglia and thalamus, while the minimal increase was observed in ADC values in frontal white matter;this speed was highest in the occipital white matter in a study by Riu Han et al. [18].

While a consensus on patient management and treatment planning has been reached in the combined mild VM and severe VM group there is no consensus on the main topics discussed in the discussion part of the study for patients diagnosed with isolated mild VM [19-21]. Although the slight increase in ventricular atrium width is not a prognostic factor in direct relation with fetal neurological development, an answer should be sought for whether the detected VM status is really an isolated one or a component of an additional pathology that cannot be detected in the early period which can be presented late at the

stage of neurological development.

Limitations

One of our limitations during the course of the study was that the tissue sampled due to partial volume artefacts could contain structures other than white matter, especially at the level of the frontal lobe, occipital lobe, and basal ganglia while placing the ROI to determine ADC values. Basal ganglia is the first place where the effects of edema caused by increased pressure in the brain parenchyma because of ventriculomegaly due to its location right next to the ventricle. Therefore, the measurements performed may not be precise due to the presence of different tissue compositions in the basal ganglions.

Another limitation of our study is that the number of patients including the control group and subgroups of isolated mild ventriculomegaly was not large enough.

CONCLUSION

In parallel with the literature, it was revealed in our study that isolated mild ventriculomegaly did not create a significant difference in ADC values in comparison with normal cases in the control group.

More studies with involving more cases are needed to determine quantitative parameters that will be a concrete indicator of prognosis reflecting microstricular changes, beyond morphological evaluation and diameter measurement in isolated mild VM cases.

ABBREVIATIONS

VM	Ventriculomegaly
MRG	Magnetic Resonance Imaging
CNS	Central Nervous System
USG	Ultrasonography
SSFSE	Single-Shot Fast Spin Echo
FOV	Field of View
TE	Echo Time
TR	Repetition Time
FASTE	Fourier Acquired Single-Shot Turbo Spin-Eko
ROİ	Region Of Interest

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Research Article

Dynamic Renal Scintigraphy Results of Pediatric Patients Operated Due to Unilateral Ureteropelvic Junction Obstruction: A Novel Approach to Overestimated Ipsilateral Differentiated Renal Function

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Unilateral Üreteropelvik Bileşke Obstrüksiyonu Nedeniyle Opere Edilen Pediatrik Hastaların Dinamik Renal Sintigrafi Sonuçları: İpsilateral Diferansiye Renal Fonksiyonun Yüksek Ölçümüne Yeni Yaklaşım

ABSTRACT

Objective: *The aim of this study was to scintigraphically investigate the preoperative and postoperative renal functions of patients operated due to ureteropelvic junction obstruction, discuss the factors affecting the indication of surgery and emphasize the important points to consider during scintigraphic examination.*
Method: *We retrospectively analyzed pediatric cases who underwent pyeloplasty due to ureteropelvic junction obstruction. Patients operated for primary ureteropelvic junction obstruction whose preoperative and postoperative dynamic scintigraphy results could be obtained were included in the study. The patients were divided into two groups as those with <50% and ≥50% ipsilateral differentiated renal function. The difference between the groups was considered statistically significant when p<0.05.*
Results: *The median ages of 36 cases in <50% DRF group and 24 cases in ≥50% DRF group were 7.7 months and 8.5 months, respectively. The mean ipsilateral differentiated renal function values of the main groups were significantly different from each other both in the preoperative and postoperative periods. The changes within the two main groups were also analyzed, yielding significant differences. Ipsilateral differentiated renal function changes on a general, group and subgroup basis, and preoperative ultrasound findings of the ipsilateral kidney in subgroups were revealed.*
Conclusion: *Increased hydronephrosis degree and renal pelvis anterior-posterior diameter are closely related to overestimated ipsilateral kidney function. For deciding on surgery in patients with ureteral obstruction, scintigraphic examinations make sense with the help of US and the clinical condition of the patient.*

Keywords: *Dynamic renal scintigraphy, ureteropelvic junction obstruction, pyeloplasty, supranormal function, differentiated renal function, pediatric*

ÖZ

Amaç: *Bu çalışmanın amacı, üreteropelvik bileşke obstrüksiyonu nedeniyle opere edilen hastaların preoperatif ve postoperatif renal fonksiyonlarını sintigrafik olarak incelemek, ameliyat endikasyonunu etkileyen faktörleri tartışmak ve sintigrafik inceleme sırasında dikkat edilmesi gereken önemli noktaları vurgulamaktır.*
Yöntem: *Üreteropelvik bileşke obstrüksiyonu nedeniyle piyeloplasti yapılan pediatrik olgular retrospektif olarak incelendi. Primer üreteropelvik bileşke tıkanıklığı nedeniyle ameliyat edilen ve hem preoperatif hem de postoperatif dinamik sintigrafi sonuçlarına ulaşılabilen hastalar çalışmaya dahil edildi. Hastalar <%50 ve ≥%50 ipsilateral diferansiye renal fonksiyonu olanlar olarak iki gruba ayrıldı. Gruplar arasındaki fark p<0,05 olduğunda istatistiksel olarak anlamlı kabul edildi.*
Bulgular: *<%50 DRF grubundaki 36 olgunun medyan yaşı 7,7 ay ve ≥%50 DRF grubundaki 24 olgunun medyan yaşı 8,5 aydı. Ana gruplar arasında yapılan karşılaştırmada, ortalama ipsilateral diferansiye renal fonksiyonun hem preoperatif hem de postoperatif dönemde birbirinden anlamlı derecede farklı olduğu görüldü. İki ana grup içindeki değişiklikler de analiz edildi ve anlamlı farklılıklar görüldü. Genel, grup ve alt grup bazında ipsilateral diferansiye renal fonksiyon değişiklikleri, ayrıca alt gruplarda ipsilateral böbreğin preoperatif ultrason bulguları ortaya konuldu.*
Sonuç: *Artmış hidronefroz derecesi ve renal pelvis ön-arka çapı, fazla ölçülen ipsilateral renal fonksiyon ile yakından ilişkilidir. Üreter obstrüksiyonlu hastaların cerrahi endikasyonu için kullanılan sintigrafik incelemeler US bulguları ve hastanın klinik durumu ile beraber anlam kazanır.*

Anahtar kelimeler: *Dinamik renal sintigrafi, üreteropelvik bileşke obstrüksiyonu, piyeloplasti, supranormal fonksiyon, diferansiye renal fonksiyon, pediatrik*

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INTRODUCTION

Scintigraphic diuretic renogram is a highly effective method for visualizing the ureteropelvic junction obstruction (UPJO) and revealing the loss or recovery of renal function. Renal scintigraphy, which can provide information about the degree and level of obstruction, thus contributes to determining surgical indication. Many researchers have shown that most cases of severe hydronephrosis exhibit obstruction in diuretic renogram [1,2]. Today, since it is easily applicable from the third week of life and has imaging advantages compared to others, the most preferred agent is Technetium-99m-Mercaptoacetyltriglycine (Tc-99m MAG_3). Technetium-99m-Diethylenetriaminepentaacetic acid (Tc-99m DTPA) also shows MAG_3-like behavior, but it cannot be secreted from tubules like MAG_3 [3].

Dynamic renal scintigraphy, which provides quantitative data on differentiated renal function (DRF) and obstruction even in hydronephrotic renal units, can be used to diagnose both UPJO and other ureteral obstructions. It is a useful method for long-term monitoring of renal functions.

In this study, it was aimed to scintigraphically investigate the preoperative and postoperative renal functions of patients operated due to UPJO, discuss factors affecting the indication of surgery and emphasize the important points to consider during scintigraphic examination.

MATERIALS and METHODS

Patient population

From 2004 to 2017, we retrospectively analyzed pediatric cases who underwent pyeloplasty due to UPJO in a tertiary center. Approval for the study was obtained from the clinical research ethics committee of our hospital. During hospitalization, consent for further clinical studies was obtained from parents. Collected data included patient demographics and scintigraphic/ultrasonographic imaging results.

Surgical intervention is performed for the following indications:

- Symptoms including pain, infection, etc.
- Increase in hydronephrosis grade and decrease in the function of the affected kidney so that it is less than the threshold of 40 percent of split renal function, or there is a serial loss greater than 10 percent.
- Massive hydronephrosis with a renal pelvis anterior-posterior (PAP) diameter >50 mm or palpable flank mass (especially in neonates).

Inclusion and exclusion criteria

Patients operated for primary UPJO whose preoperative and postoperative dynamic scintigraphy results could be obtained were included in the study. The prominent reason for not being able to reach the scintigraphy results of the patients was that the examinations were performed in another center. Cases with UPJO secondary to posterior urethral valve or vesicoureteral reflux, those with solitary kidney or non-functional contralateral kidney (multicystic dysplastic kidney, etc.), bilateral UPJO, recurrent cases and other cases with additional urinary anomalies on the ipsilateral or contralateral sides were excluded from the study. Non-operative follow-up patients were also not included.

Imaging studies

In our clinic, dynamic renal scintigraphies are routinely performed in UPJO patients during the preoperative and postoperative (6-12 months after surgical repair) periods. While preoperative and postoperative MAG3 dynamic renal scintigraphy results were compared, the patients were divided into two groups as those with <50% and ≥50% ipsilateral DRF. The radionuclide excretion patterns in the renogram curve of ipsilateral kidney were evaluated. Arithmetic means of DRF and interval values were calculated in two main groups and four subgroups of age (0-3 weeks, >3-6 weeks, >6-12 weeks and >12 weeks). Although dynamic scintigraphic examinations are not considered to yield optimal results under the age of three weeks, we chose to perform them due to patients' rapidly progressing hydronephroses.

Ultrasound (US) is the most used diagnostic tool

in the diagnosis/follow-up process of UPJO patients. The US findings of the patients just before the operation were analyzed. Arithmetic means and interval values of ipsilateral renal pelvis anterior-posterior (PAP) diameters were calculated. The reported hydronephrosis (HN) degrees were evaluated according to Society of Fetal Ultrasound grading system. Subgroup calculations for US findings were performed as previously described.

Evaluation and outcome measures

Successful outcome was defined as resolution of symptoms, regression of hydronephrosis with parenchymal thickening, reduction of renal PAP diameter and kidney length on US evaluation (at least by 1 grade) and stable US findings with resolution of symptoms or improvement of excretion curve on diuretic renogram (radiological improvement in half-life of the maximum activity [$T_{1/2}$] to less than 10 minutes). The patients were called for a follow-up visit every 3 months in the first postoperative year. The follow-up visits were performed every 6 months in the second postoperative year, and then yearly.

Statistical analysis

Clinical data were recorded in Microsoft Office-Excel (2016). Mean and interval values were calculated with the same program. Statistical analysis between groups was performed using Fisher's exact test and Student's t-test. The difference between groups was considered statistically significant when $p<0.05$.

RESULTS

During the study period of thirteen years, 114 patients underwent pyeloplasty for UPJO. Among these, 60 cases met the inclusion criteria. The median ages of 36 cases in <50% DRF group and 24 cases in ≥50% DRF group were 7.7 months (8 days-11.6 years) and 8.5 months (11 days-9.5 years), respectively. It was remarkable that right sided UPJO was not seen in ≥50% DRF group. Patient demographics are summarized in the Table 1. Clinical presentation consisted of prenatal diagnosis (41), pain (9), incidental (4), urinary incontinence (2), abdominal distension (1), recurrent urinary tract infection (1), cyclical vomiting (1) and fever (1).

In the comparison for the main groups of <50% and ≥50% DRF, the mean ipsilateral DRFs significantly differed both in the preoperative and postoperative periods. Mean DRF distribution of the groups is also summarized in Table 1. Ipsilateral DRF was below 10% in two cases. Postoperative ipsilateral DRF in one of these patients was 30%, while the other's DRF increased, but remained below 10%.

Table 1. Comparison between <50% and ≥50% DRF groups. Patient demographics, mean DRFs, interval and p values.

Variables	<50% group	≥50% group	p
Number of patients:			
Male	26	21	0.21
Female	10	3	
Number of laterality:			
Left	23	24	0.0008
Right	13	-	
Median age at surgery (range)	7.7 months (8 days-11.6 years)	8.5 months (11 days-9.5 years)	0.47
Preoperative mean ipsilateral DRF, % (range)	36 (4-49)	56 (50-66)	0.00001
Postoperative mean ipsilateral DRF, % (range)	41 (5-67)	52 (43-59)	0.0002

DRF: Differentiated renal function.

The overall preoperative mean ipsilateral DRF was 44%, which increased to 45% in the postoperative period (p=0.33). However, mean ipsilateral DRF changed significantly in both main groups. Ipsilateral DRF changes on a general, group and subgroup basis, and preoperative US findings (HN grade, PAP diameter) of the ipsilateral kidney in subgroups are summarized in Table 2.

In all cases, the renogram curve showed a dilated obstructive pattern (plateau form) and $T_{1/2}$ was over 20 minutes. However, in the postoperative period, the renogram curves either returned to normal in most cases or showed a non-obstructive dilated pattern in a small number of the cases. US was routinely used to monitor postoperative change of hydronephrosis. The mean postoperative follow-up

Table 2. Preoperative/postoperative scintigraphic changes in general, main groups, subgroups, and preoperative US findings in subgroups. Mean DRFs, mean HN grade, mean PAP diameter, interval values, number of cases and p values.

Groups	Preoperative mean ipsilateral DRF, %	Postoperative mean ipsilateral DRF, %	p
General	44	45	0.33
<50% DRF	36	41	0.0035
≥50% DRF	56	52	0.0003

	<50% DRF group			≥50% DRF group				
Subgroups of age, weeks	Preoperative mean ipsilateral DRF, % (range)	Postoperative mean ipsilateral DRF, % (range)	p	Preoperative mean ipsilateral DRF, % (range)	Postoperative mean ipsilateral DRF, % (range)	p	Preoperative mean ipsilateral HN grade (range)	Preoperative mean ipsilateral PAP diameter, mm (range)
0-3 [n=6]	39 [n=1]	33	-	57 (54-62) [n=5]	56 (53-59)	0.36	4	34 (28-38)
>3-6 [n=8]	35 (4-48) [n=7]	37 (5-67)	0.53	66 [n=1]	54	-	3.7 (3-4)	32 (13-47)
>6-12 [n=6]	31 (10-48) [n=4]	31 (10-53)	0.75	59 (53-64) [n=2]	50 (47-52)	0.2	3.2 (3-4)	27 (13-43)
>12 [n=40]	37 (4-49) [n=24]	44 (23-54)	0.002	55 (50-64) [n=16]	51 (43-57)	0.0045	3.2 (2-4)	28 (12-56)

DRF: Differentiated renal function, HN: Hydronephrosis, PAP: Pelvis anterior-posterior.

period was 4.7 years (7 months-9.8 years). All patients are followed-up eventlessly, as described in the methodology section.

DISCUSSION

The scintigraphic diuretic renogram is one of the important tests used to demonstrate renal function. There are studies showing that diuretic renography with MAG3 is the most suitable method for patients with UPJO after therapeutic interventions [4].

Although scintigraphic examination is an especially useful method in demonstrating obstruction and renal function monitoring, it has various disadvantages, including slight radiation exposure, performance in qualified centers only, and the need for an experienced nuclear medicine specialist for interpretation and evaluation of supranormal function.

Patients with UPJO have lower DRFs on the affected side [5]. Supranormal function, seen in 9-22% of all cases with congenital unilateral hydronephrosis, is defined by DRF≥55% in a hydronephrotic kidney [6,7]. Today, supranormal function is still controversial. Some authors regard supranormal function as an artifact associated with several factors, such as the use of different radiotracers, the time chosen to accurately predict DRF after radionuclide administration, the identification of relevant areas, the method of calculation or the subtraction of background activity [8-11]. Pippi Salle et al. [12] experimentally showed that supranormal function is not an artifact, but a condition based on parenchymal thinning caused by significant hydronephrosis and radioisotope distribution according to the γ-camera.

DRF measurement is an important parameter in patient management. It is calculated by dividing the values of each kidney by the total value. DRF is

considered normal between 45-55% and its low rate at the time of diagnosis or decrease in the follow-up process are effective in deciding on surgical treatment [13]. In our study, it is noteworthy that 40% of patients had 50% or more ipsilateral renal function. An operation decision should not be based on DRF only. In fact, it reflects the accumulation of radionuclide in the pelvic region and may create a false perception as if the function of the ipsilateral kidney exceeds the other. If the contralateral kidney is healthy, it is theoretically not possible to have ≥50% DRF in an ipsilateral kidney showing an obstruction pattern despite diuretic administration. Therefore, based on this hypothesis, we divided our patients into two groups preoperatively as those who showed <50% and ≥50% DRF on the ipsilateral side in scintigraphy. Our main goal was to answer this question: Will we be able to find a different result from the studies conducted about the supranormal function to date?

The overall mean ipsilateral DRF increased from 44% in the preoperative period to 45% in the postoperative period. A statistically significant increase was observed in mean ipsilateral function in the <50% DRF group and a significant decrease was seen in the ≥50% DRF group (Table 2). All these results can be interpreted as indicators of a kidney that tends to normalize after treatment. In particular, the results in the ≥50% DRF group support our hypothesis that the diseased kidney cannot have more function than the healthy kidney in any way.

In subgroup examinations, high ≥50% ipsilateral DRF ratio (83%) in the 0-3 weeks group is remarkable. Also, with decreasing age, increases in both the mean hydronephrosis degree and mean PAP diameter indicate that these two parameters may be associated with the overestimated ipsilateral DRF (Table 2). A calculation error most likely occurs in patients (especially in neonates) whose kidney size increases due to high grade hydronephrosis. Some authors argued that this was due to reservoir effect of a dilated excretory system and increased renal mass [8,14,15].

This study has some limitations, first one being our small sample of patients. This was caused by the inability to obtain the scintigraphy results of numerous patients. We think that this may have affected our subgroup results. The fact that non-operated patients were not included in the study may also be a limitation. Even though the sample was small, significant conclusions could be drawn. Further studies may be helpful with patients who are both surgically treated and followed up for hydronephrosis.

Dynamic renal scintigraphy is a useful imaging method that can be used actively in the diagnosis and follow-up of patients with ureteral obstruction. Increased hydronephrosis degree and renal PAP diameter (hence increased kidney size) are closely related to overestimated ipsilateral kidney function. Increased ipsilateral kidney function after surgery indicates the success of the operative treatment. Similarly, postoperative loss of function in cases with preoperative ≥50% ipsilateral DRF is not a failure but an indication that the kidney is normalizing. Therefore, instead of focusing only on DRF, the excretion curve must also be evaluated correctly. In patients with ureteral obstruction, dynamic renal scintigraphy is not used alone for surgical indication; scintigraphic examinations make sense with the help of US and the clinical condition of the patient. It may be useful to re-evaluate scintigraphy reports with incorrect interpretations such as ≥50% ipsilateral DRF together with the nuclear medicine specialist. Otherwise, medicolegal problems may be encountered because a kidney with reported ≥50% DRF is operated. In addition, developing a different measurement method, in which the amount retained in the pelvis is measured, for the interpretation of the dynamic scintigraphy may facilitate the work of both nuclear medicine specialists and surgeons in UPJO cases.

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Research Article

Relationship Between Intraoperative Cerebral Desaturation and Postoperative Complications In Pediatric Patients Undergoing Congenital Heart Surgery: Prospective Cohort Study

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Konjenital Kalp Cerrahisi Geçiren Pediatrik Hastalarda Serebral Desatürasyon ile Komplikasyonlar Arasındaki İlişki: Prospektif Kohort Çalışması

ABSTRACT

Objective: *In this study, we aimed to investigate the incidence of cerebral desaturation and the possible relationship between intraoperative cerebral desaturation and postoperative complications.*
Methods: *A prospective, observational study was performed 115 patients under 18 years of age who required open heart surgery in a university hospital. Cerebral desaturation was defined as a 25% decrease in cerebral saturation (low alarm limit) when compared with the basal value. Duration (second) was referred to the amount of time the patient stays below low alarm limit. Depth (%) was referred to gap between the patient's cerebral regional oxygen saturation (rSO_2) level and the rSO_2 low alarm limit. The cerebral desaturation score was calculated using the %*seconds. The patients were divided into two groups: group 1 (desaturation score >3000 %sec) and group 2 (desaturation score ≤ 3000 %sec). The groups were compared in terms of demographic data, intraoperative and postoperative variables, postoperative complications, and duration of intensive care and hospital stays.*
Results: *In the study, 59 patients (51.3%) were male and 28 patients (24.3%) had cyanotic heart disease. A total of 55 patients (47.8%) experienced over 3000 %sec desaturation. Postoperative complications were found to be increased in group 1 (71% vs 3.3%; χ^2=57.119, p<0.001). In the multiple logistic regression analysis, desaturation score>3000 %sec (p<0.001), low body surface area (p=0.001) and prolonged cardiopulmonary bypass (p=0.006) were found to be associated with postoperative complications.*
Conclusion: *In patients undergoing congenital heart surgery, cerebral desaturation score >3000 %sec is associated with a negative effect on patient prognosis.*

Keywords: *Cardiac surgical procedures, congenital heart defects, cerebral hypoxia, complications, spectroscopy, near-infrared*

ÖZ

Amaç: *Biz bu çalışma ile bir yıl içinde konjenital kalp cerrahisi geçiren pediatrik hastalarda serebral desatürasyon oranlarını ve serebral desatürasyon ile komplikasyonlar arasındaki ilişkiyi araştırmayı amaçladık.*
Yöntem: *Çalışma prospektif gözlemsel olarak bir üniversite hastanesinde gerçekleştirildi. Çalışmaya konjenital kalp cerrahisi geçirecek 18 yaş altındaki 115 hasta dahil edildi. Serebral desatürasyon bazal değere göre %25'lik doku oksijen satürasyonunda azalma (alt alarm limiti) olarak tanımlandı. Süre (sn), hastanın düşük alarm limitinin altında kaldığı saniye olarak, derinlik (%) hastanın serebral doku satürasyonu (rSO_2) ile düşük alarm limiti altındaki rSO_2 farkı arasındaki yüzdeyi ifade etmekteydi. Serebral desatürasyon skoru (eğri altında kalan alan) %*sn kullanılarak hesaplandı. Hastalar iki gruba ayrıldı: grup 1 (desatürasyon skoru >3000 %sn) ve grup 2 (desatürasyon skoru ≤% 3000 %sn). Gruplar demografik veriler, intraoperatif ve postoperatif değişkenler, postoperatif komplikasyonlar, yoğun bakım ve hastanede kalış süreleri açısından karşılaştırıldı.*
Bulgular: *Çalışmada 59 hastayı (%51.3) erkekler oluşturmakta iken, 28 hastanın (%24.3) siyanotik kalp hastalığı mevcuttu. Ellibeş hastada (%47.8) desatürasyon skoru 3000 %sn üzerinde idi. Postoperatif komplikasyonlar Grup 1'de anlamlı olarak fazla idi (% 71 vs % 3.3; χ^2=57.119, p<0.001). Logistik regresyon analizinde desaturasyon skorunun >3000 %sn (p<0.001) olmasının, düşük vücüt yüzey alanının (p=0.001) ve uzamış kardiyopulmoner baypas süresinin (p=0.006) postoperatif komplikasyonlarla ilişkili olduğu saptandı.*
Sonuç: *Konjenital kalp cerrahisi geçiren hastalarda serebral desatürasyon skorunun 3000 %sn üzerinde olması hasta prognozunda negatif sonuçlara neden olmaktadır.*

Anahtar kelimeler: *Kardiyak cerrahi işlemler, doğumsal kalp kusurları, serebral hipoksi, komplikasyonlar, spektroskopi, yakın kızıl ötesi*

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INTRODUCTION

Rates of mortality and morbidity associated with heart surgery have recently fallen as a result of gaining experience and advanced technology in surgery and anesthesia; thus success rates have increased considerably. In addition, studies have been conducted with a goal of reducing complications caused by cardiopulmonary bypass (CPB). Thanks to the prediction and early diagnosis of these potential complications, their prevention and successful treatment is possible. Considering that one of the most significant factors in the pathogenesis of cardiopulmonary bypass-related complications are the changes in tissue oxygenation, the importance of monitoring tissue oxygenation during CPB is obvious. However, we know that parameters such as heart rate (HR), mean arterial pressure (MAP) and arterial oxygen saturation (SaO_2) are not always sufficient indicators of tissue oxygenation [1-3]. Studies to overcome this shortcoming in monitoring have assessed tissue oxygenation using near-infrared spectroscopy (NIRS) and cerebral regional oxygen saturation (rSO_2), among others. Although cerebral rSO_2 measured with the NIRS method has been criticized, itís usage as a trend monitoring method has been approved by the US Food and Drug Administration. Studies that monitored cerebral rSO_2 using NIRS in cardiac surgery have shown its positive effects on postoperative cognitive functional disorders, neurological complications, and length of hospitalization [4-6]. NIRS has also been shown to be efficacious in cerebral oxygenation and somatic (hepatic, renal, mesenteric) monitoring [7,8].

The primary aim of this study was to determine the rates of cerebral tissue desaturation in congenital open heart surgery. The secondary aim was to find the relationship between the desaturation scores and the complications. We hypothesized that lower cerebral NIRS values would be associated with a greater incidence of early complications in patients undergoing congenital heart surgery.

MATERIALS and METHODS

Upon receiving the approval of the Clinical Research Ethics Committee of Our Faculty (Decision Number: 12-11.1/2), the informed consent form was read to the patientsí relatives, who signed it in writing. A total of 115 patients' under 18 years of age who required open-heart surgery were included in our study. Adult patients undergoing congenital heart surgery, patients who did not require cardiopulmonary bypass, patients with missing data, patients who lost their lives during the intraoperative period and patients required emergency surgery were excluded from the study.

Nonadult patients were taken to the operating room following premedication [5 mg kg^{-1} ketamine and 10 µg kg^{-1} atropine administered intramuscularly, while adult children were given oral midazolam (0.5 mg kg^{-1}) as a premedication. All patients were monitored with electrocardiography, pulse oximetry, noninvasive pressure measurements, and NIRS (EQUANOXô, Nonin Medical Inc., Plymouth, MN, USA) under sedation. The probes of near-infrared spectroscope (pediatric sensors for patients weighing less than 40 kg and adult sensors for patients weighing ≥ 40 kg) were placed on both frontal areas after the patient's skin surface was cleaned with alcohol. Initial mean values were recorded (baseline NIRS values were obtained prior to preoxygenation) and peripheral vascular access was established. Anesthesia induction was achieved with inhaled sevoflurane [1.5-2 minimal alveolar concentration (MAC)], rocuronium 1 mg kg^{-1} and fentanyl 2 µg kg^{-1} intravenously. After the patients were intubated, a central venous catheter (through right or left internal jugular vein), an arterial catheter (through femoral or radial artery), a nasogastric heat probe were inserted and transesophageal echocardiography (it was performed in patients weighing less than 6 kg because we had not the suitable echocardiography probe) was performed. Anesthesia was maintained with a volatile anesthetic (sevoflurane 0.5-1 MAC) and fentanyl (total 5 µg kg^{-1}) titrated based on blood pressure and pulse rate of the patient; while rocuronium (0.15 mg kg^{-1}) was added for muscle

relaxation. The patients were ventilated by adjusting FiO_2, tidal volume (6-8 ml kg^{-1}) and respiratory rate according to age, and pathology detected. At the beginning of CPB, ketamine (1 mg kg^{-1}) and midazolam (20 µg kg^{-1}) were given intravenously to all patients. As the starting solution for CPB, erythrocyte, fresh frozen plasma and supplementary electrolyte solution were perfused so as to achieve an average hematocrit value of 30% after CPB in all patients. According to their cardiac pathologies, the body temperatures of the patients were dropped down to 26-32°C. After aortic cross-clamping, cardiac arrest was achieved with antegrade hypothermic blood cardioplegia. Perfusion pressure was determined by centrifugal pump flow (nonpulsatile) with pressures in the range of 50-60 mm Hg. Hemofiltration was applied to hypervolemic patients during CPB. Blood gas analysis was performed with α-stat management. The patients were evaluated by transesophageal echocardiography intraoperatively and during separation from CPB. Inotropic or vasoconstrictor agents were started to *achieve target HR* and MAP values after separation from CPB. After surgery, the patients were transferred to the intensive care unit, and intubated. The patients were extubated after they become hemodynamically stable. NIRS was only performed during the intraoperative period. Cerebral desaturation was defined as a 25% decrease in cerebral oxygen saturation (low alarm limit) when compared with the baseline value. Duration in seconds was referred to the amount of time the patient stays below the low alarm limit. Depth (%) was referred to the gap between the rSO_2 low alarm limit and rSO_2 under low alarm limit (depth (%)= [rSO_2 low alarm value - rSO_2 under low alarm value] /rSO_2 low alarm value). The cerebral desaturation score (area under curve) was calculated using the duration of depth (%*seconds) and increased only when the rSO_2 level dropped below the selected low alarm limit. A value of 3000 %sec is actually the area under the curve of cerebral desaturation and automatically calculated by the NIRS monitor. The values were recorded by NIRS monitor every four seconds before induction of anesthesia until the end of surgery (Figure 1). A cut-off value of 3000 %sec was used [7]. In addition, mean NIRS data were collected and analyzed at the following time points: baseline (before anesthesia induction), after intubation, sternotomy, cannulation, initiation of CPB, separation from CPB, closure of thorax, and end of surgery.

The following maneuvers were applied when

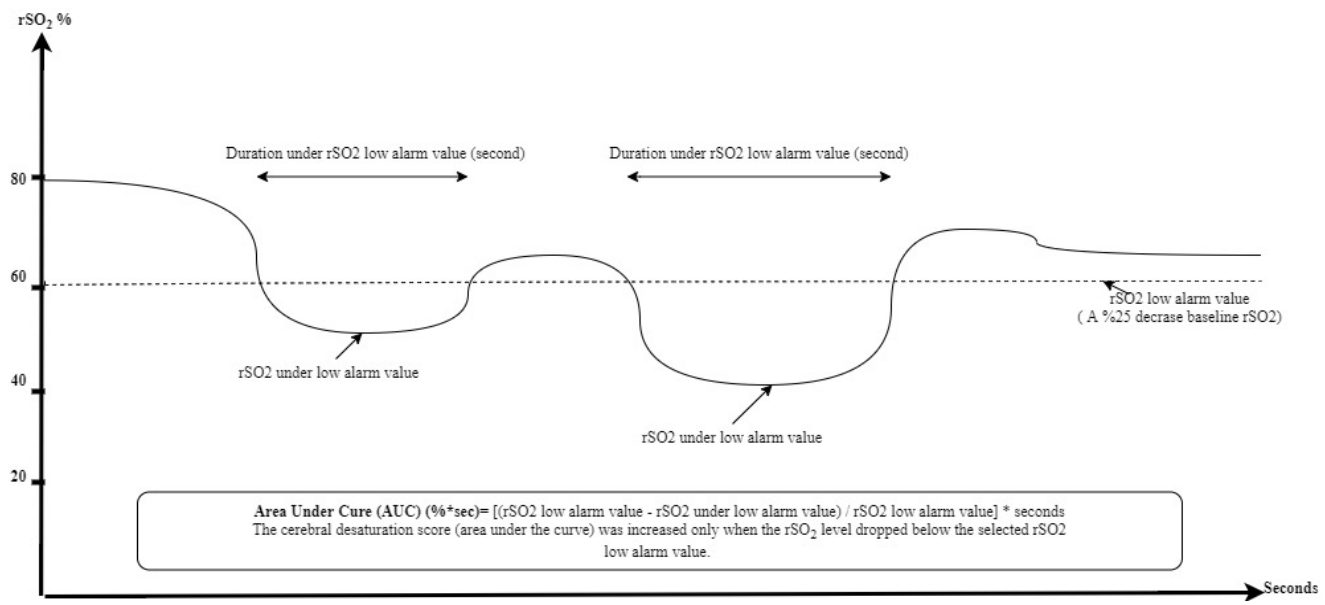

Figure 1. Calculation of the desaturation score (Area Under Cure)
Abbreviations: rSO_2; cerebral regional oxygen saturation
Desaturation score was calculated and accumulated by NIRS monitor every four seconds.

cerebral desaturation was detected: venous cannula and head position were checked, FiO_2 was increased, mean arterial pressure >50 mmHg was maintained, iincreased depth of anesthesia was maintained, $PaCO_2$ was optimized at 30-40 mmHg, hematocrit was established at <20% and then erythrocyte suspension was transfused. The patients were divided into two groups: desaturation score >3000 %sec (Group 1) and desaturation score ≤3000 %sec (Group 2). The groups were compared in terms of demographic data, intraoperative and postoperative variables, complications, and duration of intensive care and hospital stays. Complications were defined as follows:

Cardiac complications: postoperative myocardial infarction, right or left heart failure, atrial or ventricular arrhythmias requiring treatment, requirement for mechanical circulatory support (intra-aortic balloon pump, ventricular assist device, and extracorporeal membrane oxygenation [ECMO]).

Respiratory complications: pneumonia, re-intubation, tracheotomy, acute respiratory distress syndrome and prolonged mechanical ventilation (>48 hours).

Cerebrovascular complications: convulsion, stroke, transient ischemic attack, cerebral hemorrhage, and cerebral infarct.

Renal dysfunction: 50% decrease in the estimated creatinine clearance rate, urine output <0.5 mL kg^{-1} h^{-1} for 16 hours, and the need for renal replacement treatment/hemodialysis (the pediatric RIFLE criteria).

Gastrointestinal complications: ileus, and mesenteric ischemia.

Hematologic complications: massive transfusion (transfusion of >40 mL kg^{-1}), hemolysis, and disseminated intravascular coagulation.

Multiple organ dysfunction (MODS): dysfunction of two or more organs.

Need for reoperation: need for revision due to bleeding or for any other indication.

Statistical Analysis

Statistical procedures were carried out on SPSS 21.0 (SPSS for Windows Inc., IL, USA). The data were presented as mean±standard deviation (SD), median (range) and percentage (%). The distribution of demographic data, intraoperative and postoperative variables, and duration of intensive care and hospital stays were first evaluated using the Kolmogorov-Smirnov test. In the statistical analyses of the comparisons between groups, chi-square and Fisherís exact tests were used for categorical variables; independent samples t-test (parametric data) and the Mann-Whitney U test (nonparametric data) were utilized for quantitative data. Any complication was considered as one of the outcome measures. Binary logistic regression analysis was used to determine the risk factors associated with complications. When choosing for the independent variables in the regression analysis, absence of collinearity among predictors was taken into account (If tolerance <0.2 or variance inflation factors (VIF) was >10, the variable was removable from the model). A value of p≤0.05 was considered significant.

RESULTS

Among 115 patients enrolled in the study (Figure 2), 59 patients (51.3%) were male and 28 patients (24.3%) had cyanotic heart disease. The most common diagnoses were atrial septal defect (23.5%), ventricular septal defect (14.8%) and tetralogy of Fallot (9.6%). Details on the diagnoses and patientsí preoperative and intraoperative variables are presented in Tables 1 and 2. There were 55 patients in Group 1 (desaturation score >3000 %sec) and 60 patients in Group 2 (desaturation score ≤3000 %sec). Baseline mean MAP values (76±18 mm Hg vs. 81±16 mm Hg, p=0.105) were similar in both groups, while Group 2 had lower baseline HR [117 bpm (73-160) vs 142 bpm (74-192), p=0.006] values when compared with Group 1. Group 1 had lower baseline SaO_2 [98% (73-100) vs. 99% (84-100), p=0.013], lower mean baseline hemoglobin (12.4±1.9 mg dL-1 vs. 13.2±1.6 mg dL-1, p=0.022) and rSO_2 [75.1%±9.6 (44-93) vs 80.8%±8.6 (50-91), p=0.001] values when compared with Group 2. Baseline mean rSO_2 value in cyanotic patients was 74%±9.5 (44-89), while baseline mean rSO_2 value in noncyanotic patients was 79.4%±9.2 (50-93) (p=0.010).

Fifty-five patients (47.8%) had desaturation over

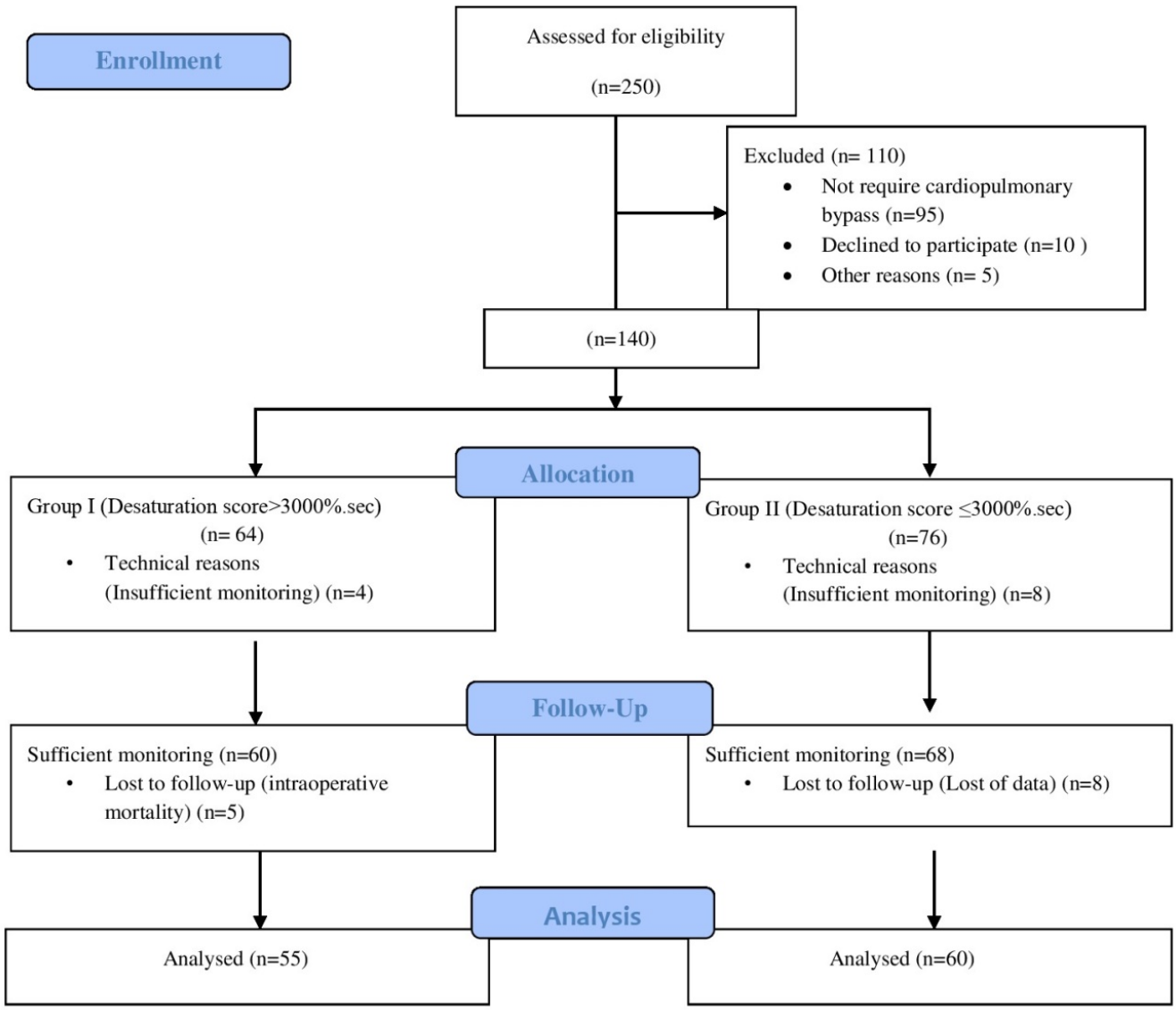

Figure 2. Patients' flow diagram.

3000 %sec. Postoperative complications were found to be increased in Group 1 (71% vs 3.3%). Forty-one (35.7%) patients developed at least one complication. Patients had cardiac (n=26:22.6%), respiratory (n=27:23.5%), neurologic (n=8: 7%), renal (n=11: 9.6%), gastrointestinal (n=7: 6.1%), hematologic (n=14:12.2%) complications, sepsis (n=13:11.3%), MODS (n= 15:13%), and 7 patients (6.1%) required revision surgery (Table 3). In the multiple logistic regression analysis; desaturation score >3000 %sec (OR=50.016; 95% CI= 6.2– 401; p<0.001), decreased body surface area (OR=0.003; 95% CI= 00.001 – 0.105; p=0.001) and prolonged cardiopulmonary bypass (OR= 1.037; 95% CI= 1.01 – 1.065; p=0.006) were found to be independent risk factors associated with postoperative complications (Table 4). In Group 1, rSO_2 values were lower than those in Group 2 in all time points (Figure 3). Two patients had their surgery under total circular arrest (TSA). A patient who underwent Jatene operation required venoarterial ECMO support as a result of respiratory and cardiac insufficiency at the end of surgery. Seven (6.1%)

Table 1. Diagnosis and baseline rSO_2 values of patients (baseline NIRS values were obtained prior to preoxygenation before induction of anesthesia).

Noncyanotic patients	Frequency (%)	rSO_2 values Mean ±SD (range)
Atrial Septal Defect (ASD)	27 (23.5)	80.8±10.3 (50-91)
Ventricular Septal Defect (VSD)	17 (14.8)	80.2±9 (61-91)
ASD+VSD	5 (4.3)	75.6±3.3 (72-79)
Atrioventricular canal defect (AVCD)	9 (7.8)	76.9±10.2 (57-93)
Pulmonary stenosis	6 (5,2)	81.74±7.2 (70-88)
Pulmonary regurgitation	8 (7)	77.4±10.3 (64-89)
Other valve disease	11 (9.6)	80±8 (63-91)
Ebstein Anomaly	2 (1.7)	73±1.4 (72-74)
Coronary Anomalies (ALPACA)	2 (1.7)	82±2 (79-85)
Cyanotic patients		
Tetralogy of Fallot (TOF)	11 (9.6)	78.5±5.4 (70-89)
Single Ventricle	3 (2.6)	77.7±3.2 (73-81)
Anomalous Pulmonary Venous Return	4 (3.5)	68.8±11.9 (61-82)
Truncus Arteriosus	1 (0.9)	63
Transposition of the Great Arteries (TGA)	6 (5.2)	68.4±7.7 (61-79)
Double Outlet Right Ventricle (DORV)	3 (2.6)	68±21.2 (44.82)
Total	**115 (100)**	**78.1±9.5 (44-93)**

Abbreviations: rSO_2; cerebral oxygen saturation, SD; standard deviation.

Table 2. Demographic and intraoperative data of patients (Independent-Samples T Test and Mann-Whitney U Test).

	Group 1 (n=55)	Group 2 (n=60)	p
Age (month)	13 (0.07-192)	69 (0.67-204)	<0.001
Gender (Female) (%)	26 (47.3)	30 (50)	0.852
Weight (kg)	8 (2.2-66)	18.5 (3.4-68)	<0.001
Height (cm)	76 (50-164)	112.5 (52-162)	<0.001
BSA (m2)	0.4 (0.2-1.72)	0.78 (0.21-1.7)	<0.001
Cyanotic (%)	16 (29.1)	12 (20)	0.257
RACHS-1			
I-III	48	57	0.030
IV-VI	7	3	
CPB time (minutes)	84.4±34.1	69.5± 32.8	0.019
Aortic cross-clamp time (minutes)	65.3±30.5	55±25.4	0.057
Operation time (minute)	220 (150-360)	222 (105-390)	0.739
Duration of anesthesia (minutes)	284± 54.5	278.3±57.6	0.619
Mechanical ventilation time (hours)	8 (2-600)	4 (2-192)	<0.001
ICU stay (hours)	46 (20-600)	22 (16-576)	<0.001
Hospital stay	7 (1-90)	7 (5-53)	0.052

Abbreviations: rSO_2; cerebral oxygen saturation, SD; standard deviation.

patients died because of postoperative MODS and all of them had >3000 %sec desaturation.

DISCUSSION

The main finding of this study is that cerebral desaturation of 47.8% of the patients undergoing pediatric open-heart surgery were over 3000%.sec. Therefore, all of the observed postoperative complications were found to be related to cerebral desaturation (71% vs 3.3%).

Cerebral desaturation may occur as a result of a decrease in oxygen supply due to insufficient blood flow to brain (ischemia), low arterial oxygen intake (hypoxia), low hemoglobin concentration (anemia), or increased brain metabolism. The exposure of

Table 3. Intraoperative cerebral desaturation and postoperative complications.

Complications (n, %)	Group 1 (n=55)	Group 2 (n=60)	p
Cardiac	25 (45.5)	1 (1.7)	<0.001
Respiratory	25 (45.5)	2 (3.3)	<0.001
Neurological	7 (12.7)	1 (1.7)	0.027
Renal	11 (20)	0 (0)	<0.001
GI	7 (12.7)	0 (0)	0.005
Hematologic	14 (25.4)	0 (0)	<0.001
MODS	14 (25.4)	1 (1.7)	<0.001
Sepsis	11 (20)	2 (3.3)	0.007
Revision	6 (10.9)	1 (1.7)	0.053

Abbreviations: GI; gastrointestinal, MODS; multiple organ dysfunction syndrome.

Table 4. Logistic regression analysis of risk factors associated with complications.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	0.954 (0.934-0.975)	**<0.001**		
Weight	0.766 (0.684-0.858)	**<0.001**		
Heigh	0.929 (0.904-0.956)	**<0.001**		
BSA	0.001 (0.001-0.0011)	**<0.001**	0.003 (0.001-0.105)	**0.001**
Cyanotic	3.307 (1.370-7.980)	**0.008**		
RACHS-1	2.452 (1.497-4.018)	**<0.001**		
Baseline MAP	0.951 (0.927-0.977)	**<0.001**		
Baseline HR	1.053 (1.030-1.080)	**<0.001**		
Baseline O_2 saturation	0.884 (0.806-0.969)	**0,008**		
Baseline rSO_2	0.926 (0.885-970)	**0.001**		
CPB time	1.024 (1.01-1.04)	**<0.001**	1.037 (1.01-1.065)	**0.006**
Aortic cross-clamp time	1.023 (1.01-1.04)	**0,003**		
Duration of anesthesia	1.008 (1.001-1.015)	**0,003**		
Desat. score ≥3000%.sec	70.69 (15-38-324.8)	**<0.001**	50.016 (6.2-401)	**<0.001**

Abbreviations: BSA; Body surface area, MAP; Mean arterial pressure, HR; Heart rate, CPB; Cardiopulmanary bypass, Desat. score; Cerebral desaturation score, RACHS-1; Risk-adjusted Classification for Congenital Heart Surgery, OR; Odds ratio, rSO_2; cerebral regional oxygen saturation, 95% CI; 95% confidence interval.

brain to insufficient oxygenation directly affects its activity and function. Therefore, the time spent during desaturation is critically important and real-time method is needed to identify its occurrence and provide timely intervention. Computed tomography and magnetic resonance imaging are late-term diagnostic methods to identify brain damage. Unfortunately, there is no bioanalytical method that can detect the onset of brain damage. Near-infrared spectroscopy is a continuous and noninvasive method that allows for early detection of cerebral desaturation and helps to reduce postoperative complications. Cerebral oximetry can assess the brainís supply-demand oxygen balance and the results are comparable to other invasive techniques such as jugular venous blood saturation measurement methods [1-3].

Postoperative complications associated with pediatric cardiac surgery were observed more frequently in younger age, underweight patients, patients undergoing complex congenital heart surgery, and prolonged bypass [9,10]. Vida VL et al. [10] stated that the patients who developed complications were underweight, at younger age and with higher desaturation scores. They found that the development of complications (51% vs 22%, p=0.007) and mortality (15% vs 4.3%, p=0.05) rates were higher in the neonatal group than in the infant group. Flechet M

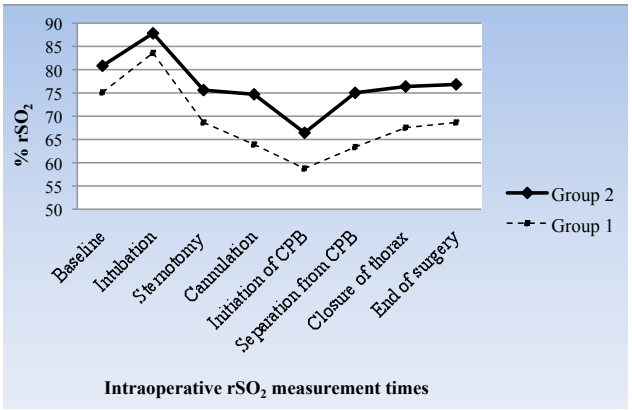

Figure 3. Intraoperative rSO_2 trends in Groups
Abbreviations: rSO_2; cerebral regional oxygen saturation, CPB; cardiopulmanary bypass (At all measurement time points, rSO_2 values in Group 1 were lower than Group 2, p<0,001).

et al. [11] stated that the rSO_2 values were lower in patients with cyanotic heart disease compared to the noncyanotic patient group, whereas baseline hemoglobin values were higher.

Similarly, in our study, patients in the higher desaturation score group (Group 1) were relatively younger, underweight, and had lower BSA. At the same time, hemoglobin and arterial oxygen saturation were lower in Group 1. For this reason, baseline rSO_2 values were significantly lower in the this group. Moreover, the baseline rSO_2 values of the cyanotic group were lower than the noncyanotic group. The BSA, baseline values for hemoglobin, arterial oxygen saturation, rSO_2, being cyanotic, RACHS-1 score, desaturation score (over 3000% sec), and CPB time were included in the Binary Logistic Regression Analysis; while age, weight and height were excluded from the regression model due to multicollinearity. However, only three parameters (BSA, CPB time and desaturation score) were found to be independent predictive markers for complications.

Lassnigg et al. [8] reported that the decrease in hemoglobin level (from 11.7 mg dL^{-1} to 8.5 mg dL^{-1}) during CPB caused a decrease in NIRS values. There is an increase in cerebral blood flow and oxygen extraction to compensate for the reduced oxygen transport due to hemodilution.

Tortoriello et al. [12] compared cerebral oxygen saturation measurements in 20 patients undergoing congenital heart surgery (15 single ventricle and 5 biventricular repairs) using noninvasive (rSO_2 with NIRS) and invasive (mixed venous oxygen saturation (SvO_2) in blood samples obtained via a pulmonary artery catheter or central venous oxygen saturation ($ScvO_2$) in blood samples obtained through a central venous catheter) methods and found significant correlations between noninvasive and invasive measurements at all time points. Tanidir et al. [9] studied cerebral tissue oxygenation during cardiac catheterization in 123 patients. The procedures were carried out for treatment purpose in 73 patients (59%). Thirty-nine of these patients developed 41 complications. İncluding desaturation (n=18: 9.5%), arrhythmia (n=10: 8.1%), respiratory failure (n=3: 2.4%), cardiac arrest (n=6: 4.8%), anemia requiring transfusion (n=3: 2.4%) and one patient (0.8%) developed a hypoxic episode. The decreases of 9% in the cranial NIRS values were associated with 2.3% of the complications. However, decreases of over 32% in the cranial NIRS values increased complication rates up to 13.5%. The authors reported that NIRS monitoring could detect development of cyanotic spell 10-15 second earlier than its manifestation on the pulse oximetry in Tetralogy of Fallot.

In their study of 104 infants undergoing biventricular repair, Kussman et al. [13] reported a desaturation rate of 22% (23 patients). The investigators considered a rSO_2 value of ≤ 45% as desaturation; the NIRS values used in CABG operations were used as a reference. Their study was conducted with a relatively homogeneous cardiac surgery population and they reported early postoperative outcomes. Thus, a critical threshold value was not possible to determine in that study. Norwood procedures or complex surgical procedures like interrupted aortic arch repair could show different postoperative outcomes.

In their retrospective study, Zulueta et al. [7] examined 22 congenital heart surgery patients and found desaturation in 13 patients (desaturation score >3000 %sec). The investigators found that central venous oxygen saturation (SvO_2, p=0.002), cardiac index (CI, p=0.004) and oxygen delivery index (DO_2I, p=0.0004) were lower, while the oxygen

extraction rate was higher (ERO_2, p=0.0005) in all desaturated patients. Nine patients had prolonged postoperative hospital stays, and all of these patients had received high inotropic and ECMO support. One patient died because of cardiac failure and an inability to come off ECMO.

In our study, 47.8% of the patients experienced over 3000 %sec desaturations. While, 25% of instant drop in the baseline NIRS values over 3000 %sec were found to be related to postoperative complications, the duration of mechanical ventilation, and intensive care unit stay. The complex surgical procedures and the prolonged CPB period are the most important risk factors for the complications which manifested themselves by the decrease in NIRS values. Nearly one-third of the patients developed at least one complication. Cardiac and respiratory complications were observed in nearly one-fourth of the patients, whereas the incidence of neurological complications was approximately 7%. All of these findings were consistent with the literature. Seven patients died because of MODS; all of these patients developed desaturations over 3000 %sec and underwent complex surgical procedures.

This study has some limitations: First, the study was designed as a prospective observational study and it needs to be supported by prospective randomized controlled trials. Second, this study was designed to include all pediatric patients undergoing congenital open heart surgery; thus it did not include patients belonging to a particular disease group. Further studies in homogeneous patient groups may be required.

In conclusion, complications following pediatric heart surgery continue to be a serious problem. Effective monitoring of tissue oxygenation would be expected to lead to a decrease in these complications. In this respect, NIRS seems to be the best monitor currently available. In the multiple logistic regression analysis, desaturation score >3000 %sec, low body surface area and prolonged cardiopulmonary bypass were found to be independent risk factors associated with complications. This finding shows that NIRS can be used to predict postoperative complications in pediatric patients undergoing congenital heart surgery. This technique may also be used in different areas of the body, but that seems to be an area requiring further investigations.

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Research Article

War, Migration and Health: The Importance of Social Work for Refugees' Children

Savaş, Göç ve Sağlık: Mülteci Çocukları İçin Sosyal Hizmetin Önemi

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ABSTRACT

Objective: *The conflicts in the Middle East during the last decade displaced millions of people and led to a serious population movement. Many Syrians have had to leave their country and became a refugee in Turkey. Over the last decade, migration has become one of the most important social, political and public health issues in Turkey. In this study, we aimed to review pediatric refugee cases who were consulted to the Social Service at a Tertiary Hospital.*
Methods: *A retrospective study was performed with refugees admitted to our hospital between January 2012 and December 2018. The socio-demographic data (age, sex, birthplace), medical diagnosis, the reason for the social work consultation and the classification of the social problems were recorded.*
Results: *The number of refugee children that were detected from the medical records was 88; the median age was 10 months (IQR 60.5), and nearly half of them were female. The most frequent diagnosis of the cases obtained from the medical charts was acute respiratory system disorders. The main reason for a social work consultation was poverty.*
Conclusion: *We concluded that professionals working with immigrant children and families should be able to access social and psychological support services. Pediatricians and pediatric societies should work to improve the sensitivity of their respective populations towards migrants and refugees.*

Keywords: *Child health, migration, refugee, social service, war*

ÖZ

Amaç: *Son on yılda devam eden Asya ve Orta Doğu'daki gruplar arasındaki savaş milyonlarca insanı göçe zorladı ve ciddi bir nüfus hareketine yol açtı. Birçok Suriyeli ülkelerinden uzaklaşarak Türkiye'ye geçiş yaptı. Bu nedenle göç Türkiye'nin en önemli sosyal, politik ve halk sağlığı sorunlarından biri haline geldi. Bu çalışmada bir üniversiteye bağlı devlet eğitim ve araştırma hastanesinde sosyal hizmet uzmanlarına refere edilen sığınmacı ailelerin çocuklarını ve yapılan sosyal çalışmaları incelemek amaçlandı.*
Yöntem: *Ocak 2012-Aralık 2018 tarihleri arasında hastanemize başvuran sığınmacı ailelerin çocuklarına ait veriler retrospektif olarak gözden geçirildi. Çalışmaya alınan olguların sosyodemografik verileri (yaş, cinsiyet, doğum yeri), tıbbi tanıları, sosyal servis konsültasyon nedenleri ve saptanan sosyal sorunlar kaydedildi ve değerlendirildi.*
Bulgular: *Tıbbi kayıtlarda tespit edilen sığınmacı çocuk sayısı 88, ortanca yaş 10 aydı (çeyrekler arası aralık 60,5) ve yaklaşık yarısını kız çocukları oluşturmaktaydı. Olguların en sık tıbbi tanısı solunum sistemi hastalıklarıydı. Sosyal Hizmet Birimi'ne yapılan konsultasyonların başlıca nedenleri sosyal ve ekonomik sorunlar idi.*
Sonuç: *Göçmen çocuklarla ve ailelerle çalışan profesyonel çalışanların sosyal çalışma ve duygusal destek hizmetlerine erişimi olması gerektiği sonucuna vardık. Çocuk doktorları ve pediatri toplulukları, göçmenlere, sığınmacılara ve mültecilere karşı duyarlılığını artırmak için çalışmalıdır.*

Anahtar kelimeler: *Çocuk sağlığı, göç, mülteci, sosyal hizmet, savaş*

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INTRODUCTION

In the last decade, the armed conflicts in the countries around us have forced many people to leave their countries, and become refugees. Since February 2019, there were nearly 3.6 million Syrian refugees and, since September 2018; 370.400 non-Syrian refugees including 172.000 Afghans, 142.000 Iraqis, 39.000 Iranians, 5.700 Somalis, and 11.700 "others" amounting to a total of slightly more than four million refugees had immigrated to Turkey. In addition, the number of nonregistered refugees in Turkey is estimated to be several hundred thousand including Syrian and non-Syrian citizens. The arrival of Syrian refugees is changing Turkish population demographics, and now constitute almost five percent of Turkey's population [(1)].

Displacement as a result of armed conflict is beyond doubt is the worst form of migration. The "health" of people whose lives have been completely upset, had to leave all their valuables back, and suffered from poor treatment and losses during their long trip. Unfortunately better-health-related quality of life cannot be expected where minimum standards of living conditions are not fulfilled.

These prevailing unfavorable conditions affected the oriented approach through first-level health facilities. As a result, existing health system failed to meet the requirements in the face of an unexpected influx of refugees. Most of the social services for Syrians are provided by national and international non-governmental organizations [(2-4)].

Over the last ten years, migration has been one of the most important socioeconomic and public health issues in our country. Here, we aimed to review the pediatric refugee cases that were consulted to the Social Service at a University affiliated Tertiary Government Teaching Hospital. We hope that this study would give an additional data to bring solutions to the problems of refugees who live under poor conditions.

MATERIAL and METHOD

A retrospective study was designed with refugees who admitted to our pediatric emergency room between January 2012 and December 2018. The design of the study was approved by the Local Ethics Committee (2019/18-13). Medical records of the hospital were used.

The sociodemographic data (age, sex, birthplace), medical diagnosis, the reason for the social work consultation and the classification of the social problems were recorded and evaluated. The staff included 65 pediatricians- 50% of them had an academic degree-75 pediatric residents and 80 pediatric nurses. A total of 160.000 patients were admitted to our pediatric emergency service per year, and about 25% of annual admissions consist of immigrants.

RESULTS

Eighty-eight refugee children (43 male, and 45 female infants) with a median age of 10 months (IQR 60.5) were admitted to our hospital, Most of the cases were born in Turkey; the other birthplaces were Syria (n=37;42%), Iraq (2;2,3%) and Afghanistan (1;1.1%), respectively. One child who had lost parents, during the migration through the Aegean Sea around Lesbos Island in 2015, and two children who had lost one of their parents in road traffic accident while going to the Aegean Coast were also admitted to our hospital.

Table 1. Diagnostic classification of diseases.

	N=88	% (100)
Pneumonia/bronchiolitis	29	32
Prematurity and low birth weight	23	26
Neurometabolic diseases	10	12
Injuries	8	9
Surgical emergencies (acute abdomen, etc.)	6	7
Gastrointestinal problems	5	6
Congenital heart defects	5	6
Urinary system disorders (UTIs, etc)	2	2

UTI: Urinary Tract Infection

The diagnoses of the cases obtained from the medical charts based on ICD-10 codes were listed in Table 2. The main reason for a social service consultation was poverty (Table 3). Interventions made by social workers were listed in Table 4.

Table 2. Problems that required the social work.

	N	%
Poverty, lack of a social insurance (unregistered) and homelessness	52	59.1
Language and compliance problems with medication(s) and/or with the hospital	17	19.3
Peer or family related problems	8	9.1
Other legal problems	8	9.1
Child neglect	3	3.4

Table 3. Tasks performed by social workers.

	N	%
Provision of personal needs (child care, hygiene)	30	35
Psychosocial interview	21	24
Referral to the Refugee Association (MUSAM)	20	23
Counseling and guidance	10	11
Notification to the provincial social services	3	3
Provision of interpretation service	3	3
Referral to the child protection agency	1	1

Table 4. Implementations by social workers.

	N	%
Supply for personal needs (child care, hygiene)	30	35
Psychosocial interview	21	24
Referral to the Refugee Association (MUSAM)	20	23
Counseling and guidance	10	11
Notification to the provincial social services	3	3
Provide interpretation service	3	3
Referral to the child protection agency	1	1

DISCUSSION

Most of the refugees have a social insurance in our health system. The main reasons for referral for social service consultation were social and economic problems. In addition, a few cases needed child protection for child neglect. Total number of 146.112 (3.3% of the population in Izmir) Syrian refugees were registered in Civil Registry of İzmir Metropolitan City. Syrian children have the same rights as their local peers in the health system. Since 2014, 17.500 refugees officially listed as deceased [1-3]. In particular, child neglect and death during migration through the sea must be prevented which requires joint work by security, social services, and health services.

The majority of the refugee children were born in Turkey. The Syrian population in our country is growing naturally in percentage of the Turkish population. While the number of number of refugees has tapered off, the population of the Syrians is growing through unchecked birth rates. In 2018, Interior Minister of Turkey announced that 385.431 Syrian babies registered in Turkey since 2011 [5]. Moreover, the birth rate seems to be increasing, based on the reports of the well-regarded experts. In November 2017, academician Murat Erdoğan reported that 306 Syrian babies were born per day [6]. Nearly a year later, in October 2018, academician Şebnem Köşer Akcapar has estimated an average of 350 Syrian births per day in our country [7]. Given the Syrian community's disproportionately younger population, it seems that the birth rate remain to increase. Meanwhile, Turkish population's fertility rate has been decreasing for years and is nowadays at a rate of 2.1 children per woman (its lowest level since World War I) [8].

In our study, the main reason for a social work consultation was poverty, and the social workers provided medical supplies when needed. Some patients need interpretation for particular conditions such as consent for a major surgery or in some forensic problems. Lacking of health information and cultural differences are the major barriers to receivie appropriate health care [2]. Unlike the high prevalence in Turkish adolescents, no immigrant was admitted to medical services with a suicide attempt.

The social workers made several interventions in order to solve problems encountered by the refugees. The main topic was the personal needs, such as provision of infant formula following discharge or personal hygiene materials. Particularly the mother and some adolescents needed psychosocial and motivational support for different reasons, such as issues of social isolation. Social isolation is the major determinant for refugees that compounds other health problems even after settlement in their new country. Despite the challenges they face, refugee children demonstrate resilience that can be nurtured to promote good psychosocial health. The general health of refugee children is related to their general health before they leave their homeland, the conditions during their long journey and at their new

home, and also the psychosocial health of their primary caregivers. Migrant children may have experienced several forms of trauma including armed conflict, violence, and exploitation. They may suffer from malnutrition and physical diseases including vaccine- preventable ones [9].

There were some limitations in our study. First, forced child marriages are associated with an increased rate of early pregnancy, maternal mortality and other obstetric complications. There is no obstetric department at our hospital for the investigation of these issues. This might be another target for our further studies. Second, due to retrospective methodology of the survey, limited data could be obtained from medical records. On the other hand, this is one of the few studies that examine the problems of refugee children in our region.

We concluded that professionals working with migrant children and families should have access to social and psychological support services. Pediatricians and pediatric societies should work hard to improve the social sensitivity of their respective populations towards migrants, asylum seekers, and refugees. Ultimately, we might have been born in different countries, but we must fight to foster humanitarian conditions for all.

Ethics Committee Approval: Ethical approval was obtained from the Non-Invasive Ethics Committee of İzmir Tepecik Health Application-Research Center (approval number: 2019/18-13, approval date: 26.12.2019)

Conflict of Interest: The authors have no conflicts of interest to declare.

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Research Article

Medical Faculty Students' Attitudes, Behaviors and Beliefs About Covid-19 Pandemic

Tıp Fakültesi Öğrencilerinin Kovid-19 Pandemisine İlişkin Tutum, Davranış ve İnançları

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ABSTRACT

Objective: *The aim of this study is to evaluate the attitudes, behaviors, and beliefs of medical faculty students about the covid-19 pandemic.*
Methods: *Between 29/03/2020 and 04/13/2020 a total of 1,332 students had been questioned in three Turkish speaking countries (Turkey, Azerbaijan, Turkish Republic of Northern Cyprus).*
Results: *The average age of the students were 20.1 ± 1.6. Among all 895 (67.7%) of them were female and 427 (32.3%) were male. 1020 (77.2%) of the studens were in Turkey, 195 (14.8%) were in Azerbaijan and 107 (8.1%) were in the TRNC. 104 of the students (7.9%) had a chronic disease. It was found that number of alcohol and cigarette users decreased significantly during the pandemic. (p <0.001, p <0.001). Anxiety levels of those who quit or reduced smoking were found to be higher than those who increased or did not change their amount of smoking (p=0.034). It was found that the most benefited sources were "their faculty lecturers" (n=453, 34.3%), "Worldometer ® website" (n= 449, 34%) and "Youtube videos" (n=396, 30%).*
Conclusion: *Longitudinal studies are needed on the effects of pandemic on alcohol and tobacco use. It is important to educate future physicians in social media literacy, interpretation and responsibilities for social media posts. In this way, perhaps we can contribute to minimize the public's erroneous beliefs and maladaptive behaviors regarding the pandemic and reduce stigmatizing attitudes towards physicians, elders and Asians.*

Keywords: *COVID-19, pandemic, medical student, MSIC, social media*

ÖZ

Amaç: *Bu çalışmanın amacı, tıp fakültesi öğrencilerinin covid-19 pandemisi hakkında tutum, davranış ve inanışlarını değerlendirmektir.*
Yöntem: *29.03.2020 ve 13.04.2020 tarihleri arasında Türkçe konuşulan üç ülkede (Türkiye, Azerbaycan, Kuzey Kıbrıs Türk Cumhuriyeti) toplam 1.332 Tıp Fakültesi öğrencisine çevrimiçi anket uygulandı.*
Bulgular: *Çalışmaya katılan öğrencilerin yaş ortalaması 20.1 ± 1.6 idi. 895'i (% 67,7) kadın, 427'si (% 32,3) erkekti. Öğrencilerin 1020'si (% 77,2) Türkiye' de, 195'i (% 14,8) Azerbaycan'da ve 107'si (% 8,1) KKTC'de eğitim görmekte idi. Öğrencilerin 104'ü (% 7,9) sürekli ilaç kullanımı gerektiren kronik bir hastalığa sahipti. Pandemi döneminde alkol tüketen ve sigara kullanan öğrenci sayısının azaldığı saptandı(p<0.001, p<0.001). Sigarayı kullanmayı bırakan veya azaltanların anksiyete düzeyleri kullanmaya devam eden veya arttıranlara göre yüksek saptandı (p=0.034). Öğrencilerin pandemi hakkındaki bilgilerini en sık olarak kendi fakültelerindeki öğretim üyelerinden (n=453, 34.3%), Worldometer internet sitesinden (n= 449, 34%) ve Youtube videolarından aldığı saptandı (n=396, 30%).*
Sonuç: *Pandeminin alkol ve tütün kullanımına etkilerini inceleyecek uzun süreli çalışmalara ihtiyaç vardır. Geleceğin hekimlerini sosyal medya okuryazarlığı, yorumlaması ve paylaşım sorumlulukları konusunda eğitmek önemlidir. Bu şekilde, belki de toplumun pandemiye ilişkin hatalı inançlarının ve uyumsuz davranışlarının, hekimlere, yaşlılara ve Asyalılara yönelik damgalayıcı tutumlarının azaltılmasına katkıda bulunabiliriz.*

Anahtar kelimeler: *COVID-19, pandemi, tıp fakültesi öğrencisi, MSIC, sosyal medya*

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INTRODUCTION

A new type of coronavirus-related pneumonia cases were reported for the first time in December 2019 in Wuhan Province of People's Republic of China. The epidemic spread rapidly all over the world. The World Health Organization (WHO) defined the newly identified virus as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) and its disease as COVID-19 (Coronavirus Disease 2019) in February 2020. WHO, then, declared that this epidemic is a pandemic on March 11th, 2020. According to WHO, COVID-19 has been detected in 3,090,045 people in 213 countries and 217,769 people were lost by April 30th, 2020 [(1)].

The COVID-19 outbreak continues to pose a threat to people's lives and health in almost every country in the world. The rapid progress of this pandemic caused crises in health systems in Italy and Iran. It has led to early graduations of medical students in the USA, Italy and the UK to ensure that senior medical school students are at the forefront to combat the pandemic [(2)]. Waiting for students to take an active role in pandemic by interrupting their medical education or continuing only online education constitutes a contradiction [(3)]. In the past, there were examples where medical school students have been actively involved in outbreaks. Medical students took their place in the fight against the epidemics of 1918 Spanish influenza in the USA and 1952 polio epidemic in Denmark [(2)].

The future health professionals are not directly involved in our country in the fight against the pandemic. However, we think that their attitudes, perceptions, the sources of information they refer to and their beliefs about the pandemic may affect the society.

Although there are many studies investigating the level of anxiety and knowledge of healthcare workers and the general community in pandemics, only a few publications have investigated the level of anxiety of medical students or their attitudes, behaviours and beliefs about the current pandemic [(4-6)].

We think that it is important to comprehend medical students' attitudes and beliefs in order to prepare for the bad scenarios and plan the future appropriately in this pandemic, where we still cannot predict its end and consequences. For this purpose, we planned a survey study evaluating the anxiety levels of the medical students, their protective measures for the epidemic, their sources of information and their general beliefs in this pandemic.

MATERIALS and METHODS

A total of 1,332 students had been questioned via an online survey in three Turkish speaking countries (Turkey, Republic of Azerbaijan, Turkish Republic of Northern Cyprus (TRNC)). The survey was open between 03.29. 2020 and 04.13. 2020. At the time of the study, 23 days had passed since the first case of COVID-19 was seen in Turkey and 95 days since the first case was seen in the World.

A questionnaire was used as a data collection tool which includes 32 questions about sociodemographic and educational data, alcohol consumption and tobacco use, anxiety levels, used sources of information about pandemic, activities during isolation and quarantine period, personal protection measures, their care when using stigmatic expressions associated with the pandemic, and beliefs about vaccine and conspiracy theories.

The survey was created through the online survey portal SurveyMonkey® (www.tr.surveymonkey.com). The link of the survey was sent to the WhatsApp® accounts of TurkMSIC, Azerbaijan Physicians and Medical Students Association (AzerMDS) and members of the Medical Students Association of Northern Cyprus (MSANC).

TurkMSIC is an independent, non-profit, non-political organization formed in 1952 by medical students in Turkey. There are local representatives of the organization in 82 medical faculties across the country with a gross network encompassing more than 30,000 medical students. It represents Turkey at an international level within the International Medical Students' Associations Federation (IFMS).

The ethics committee approval for the study was obtained from the Non-Interventional Clinical Research Ethics Committee of Izmir Democracy University (dated March 20th 2020 and numbered 2020 / 08-4). Approval of the Ministry of Health was obtained on May 5th 2020.

Statistical Analysis

Survey results were analyzed with IBM SPSS 20.0 Statistics (IBM Corporation, New York, USA) package program. Categorical data were indicated by numbers (n) and percentages (%). The numerical data that met the parametric assumptions are shown with arithmetic mean ± standard deviation (mean ± SD) and minimum-maximum (min-max) values; those that did not meet the parametric assumption were expressed with median and interquartile range (IQR). Chi-square test was used to compare categorical data. Post-hoc Bonferroni test was used to compare more than two groups. Mann-Whitney U test was used to compare two independent variables that did not meet the parametric assumptions , and Kruskall Wallis test was used to compare more than two nonparametric variables. The relationship between the two groups was examined with Spearman correlation analysis. $p<0.05$ value was considered statistically significant.

RESULTS

A total of 1,322 medical school students took the survey. The mean age of the students was 20.1 ± 1.6 years. The study population consisted of 895 (67.7%) female and 427 (32.3%) male students. The students were living in Turkey (1020 :77.2%), Republic of Azerbaijan (n= 195 :14.8%) and TRNC (n=107 :8.1%). The students were in their first (n=595 :45 %), second (n=309 : 23.3%), third (n=, 219: 16.5 %), fourth (n=83 :6.2%) , fifth (n= 93 (7%) , and sixth (n=23 :1.7%) year of their medical education A total of 104 (7.9%) students had a chronic disease that required continuous use of medication.

Before WHO announced COVID-19 as a pandemic, 284 (21.5%) participants stated that they were smokers. After the announcement, 108 (8.2%) participants stated that they quit smoking and 127 (9.6%) participants stated that they reduced the pack-years of cigarettes smoked. The number of smokers (n=284, 21.5%) were significantly reduced (n=176 13.3%) after the announcement of pandemic ($p<0.001$).

A total of 498 (37.7%) students stated that they consumed alcohol regularly before pandemic. After the announcement of the outbreak 113 (8.5%) students stated that they quit drinking alcoholic beverages and 202 (15.3%) students indicated that they reduced their weekly alcohol consumption. The number of alcohol users (n=385, 29.1%) decreased significantly after the announcement of the pandemic (n=498, 29.1%) ($p<0.001$).

Students were asked to score, and rate their "anxiety levels about pandemic" between 1 to 10 points (1 point is "I am not anxious" and 10 points is "The most severe anxiety I have ever experienced"). The median score of anxiety levels about pandemic was 6 (IQR=5-7) points (Figure 3). Anxiety scores of females were significantly higher ($p<0.001$). There was no significant correlation between students' age and their anxiety scores ($p=0.598$; $r=0.015$). The median anxiety scores of participants from Turkey, Azerbaijan and TRNC were 6 (IQR=5-7), 6 (IQR=5-7) and 6 (IQR=4-7) points , respectively without any significant difference among them ($p=0.680$).

Anxiety scores of smokers were found to be significantly lower ($p=0.013$). The median anxiety scores of students whose daily amount of cigaterres smoked increased, decreased, did not change, and of quitters were 4 (IQR=2-6), 6 (IQR=4-7), 5 (IQR=3-7) and 6 (IQR=4-7) points respectively. When these four goups were compared, the anxiety levels of those who quitted or reduced smoking were found to be higher than those who increased or did not change their amount of smoking ($p=0.034$).

Students' behavior towards personal protection was also investigated during the pandemic. Most (n=1197 :90.5%) participants stated that they applied standard hand washing methods every time they washed their hands and 1059 (80.1%) participants purchased or obtained hand disinfectants. Besides, 868 (65.7%) participants stated that they always

wore medical masks when they were outside and 1132 (85.7%) of them indicated that they did not get out of home except for obligatory situations.

Those who wore medical gloves (p<0.001), medical masks (p<0.001), and carried with them bottles of hand disinfectants (p<0.001), and/or eau de cologne which contains a mixture of citrus oils including oils of lemon, orange, tangerine, clementine, bergamot, lime, grapefruit and orange in a base of dilute ethanol (70–90%),] (p<0.001), and complied with hand washing methods (p=0.001) reported higher anxiety levels (Table 1).

Information sources of the participants were their faculty lecturers" (n=453, 34.3%), "Worldometer ® website" (n= 449, 34%) and "Youtube videos" (n=396, 30%) (Figure 1).

When three countries were compared in terms of age,gender alcohol/tobacco use, anxiety scores, and medical mask use; any significant difference was not found between age and anxiety scores of the students (p>0.05 and p>0.05). The number of female participants were slightly higher in Azerbaijan than other two countries (p=0.046). Highest rates of smoking and alcohol use were found among TRNC students both before and during pandemic. In Turkey, Azerbaijan and TRNC, respective rates of smoking before (22.5%, 9.7%, 33.6%, p=0.001) and during pandemic (14.1%, 5.6%, and 19.6%, p=0.001) were as indicated. In Turkey, Azerbaijan and TRNC respective rates of alcohol consumption before (40.9%, 15.4%, and 47.7%, p=0.001) and during (31.8%, 10.3%, and 38.3%, p=0.001) pandemic were as indicated. Highest rates of mask use were observed in Azerbaijan (p=0.001). Comparison of three countries in terms of demographic variables, alcohol/ tobacco use, anxiety scores, and medical mask use is shown in Table 2.

When in-house activities practiced by medical school students during isolation or quarantine period were evaluated, it was found that the biggest share was taken by household activities as watching movies or TV series (n=1235, 93.4%), spending time with social media (Facebook, Instagram, Twitter etc.) (n=1206, 91.2%) and chatting with their friends via

Table 1. Factors affecting medical students' anxiety scores.

Variable	25	Median	75	p
Sex				
Male (n=427, 32.3%)	4	5	7	<0,001*
Female (n=895, 67.7%)	5	6	7	
Smoking rates during pandemic				
Increased (n=6, 0.5%)	2	4	6	0,0341**
Decreased (n=127, 9.6%)	4	6	7	
Didn't change (n=43, 3.3%)	3	5	7	
Quittted smoking (n=108, 8.2%)	4	6	7	
I don't smoke (n=1038, 78.5%)	5	6	7	
I always practice the standard hand washing method				
Yes (n=1197, 90.5%)	5	6	7	0,001*
No (n=120, 9.1%)	4	5	7	
I carry hand sanitizer with me				
Yes (n=620, 46.9%)	5	6	8	<0,001*
No (n=681, 51.5%)	4	6	7	
I carry hand cologne with me				
Yes (n=731, 55.3%)	5	6	8	<0,001*
No (n=579, 43.8%)	4	6	7	
I wear a medical mask outside				
Yes (n=675, 51.1%)	5	6	8	<0,001*
No (n=627, 47.4%)	4	6	7	
I wear medical gloves outside				
Yes (n=526, 39.8%)	5	7	8	<0,001*
No (n=778, 58.9%)	4	6	7	

**: Mann Whitney U Test; **: Kruskal Wallis Test; 1: the median values of the "increased" and "didn't change" groups were statistically lower than the other two groups.*

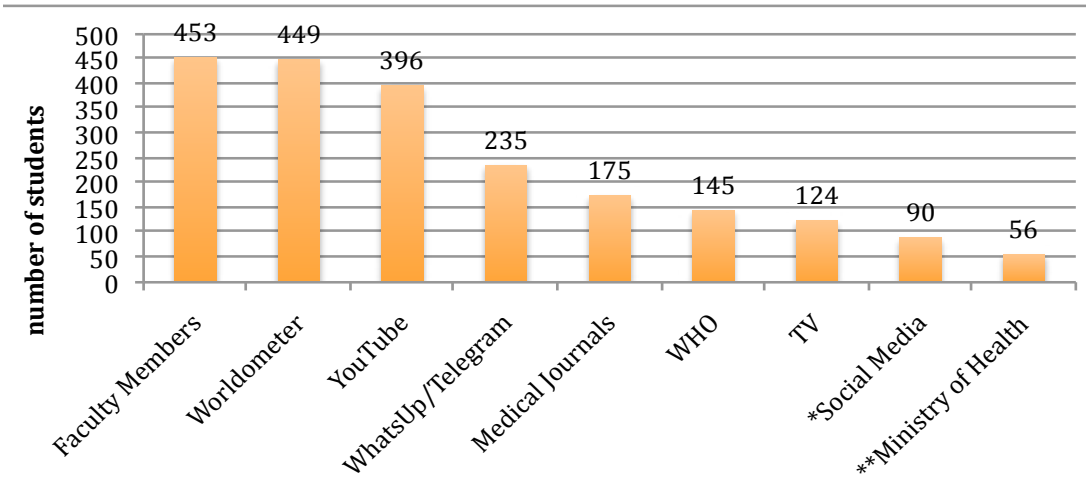

Figure 1. Sources used for getting information about pandemic.
**Facebook/Instagram/Twitter;*
***Official websites of their country's health ministries*

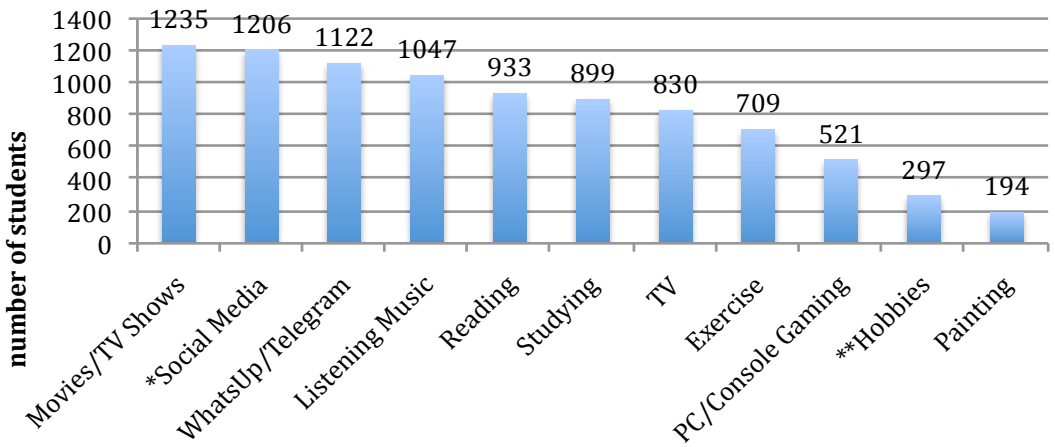

Figure 2. In-house activities of medical students during isolation/quarantine periods.
**Facebook/Instagram/Twitter;*
***Handicrafts, culinary arts, etc., except music and painting*

WhatsApp or Telegram (n=1122, 84.9%) (Figure 2).

When students were asked about their beliefs on a probable vaccine, 814 (81.6%) of them stated that they believed a vaccine would be developed within a year." While 774 (58.5%) of them stated that "the probable COVID-19 vaccine would reduce anti-vaccine movement in the world" Three hundred and forty (25.7%) participants indicated that the perception about vaccine would not change and 184 (13.9%) of them stated that anti-vaccine movement would grow.

When asked how this pandemic would affect the attitudes of the society towards healthcare professionals, most of the students (n=966 73.1%) stated that the society would have a more positive perspective. While others (n=329: 24.9%) indicated that it would not change their viewpoints , and a few of them (n=23 :1.7%) asserted that the people would more frequently develop negative attitude towards health professionals

When students asked about their wievs about conspiracy theories about SARS CoV-2 virus; 163 (12.3%) students stated that SARS CoV-2 was definitely a biological weapon, while 333 (25.2%) of them indicated that SARS CoV-2 might be a biological weapon. The rest of the students (n=529 :40%)

Table 2. Comparison of three countries in terms of demographic variables, alcohol/tobacco use, anxiety scores, and medical mask use.

	Turkey (n=1020, 77.2%)	Azerbaijan (n=195, 14.8%)	TRNC* (n=107, 8.1%)	p-value
Age (mean ± SD) (20.1 ± 1.6 years)	19.9±1.4	21.0±1.7	20.9±2.7	p>0.05
Gender				
Female (n=895, 67.1%)	632 (66.9%)	146(74.9%)	67 (62.6%)	
Male (n=437, 32.8%)	338 (33.1%)	49(25.1%)	40 (37.4%)	[1]p=0.046
Anxiety scores (6, **IQR=5-7)	6 (IQR=5-7)	6 (IQR=5-7)	6 (IQR=4-7)	p>0.05
Having a chronic disease (n=104, 7.9%)	67 (6.6%)	18 (9.2%)	19 (17.8%)	[2]p=0.001
Tobacco use before pandemic (n=284, 21.5%)	229 (22.5%)	19 (9.7%)	36 (33.6%)	[3]p=0.001
Tobacco use during pandemic (n=176, 13.3%)	144 (14.1%)	11 (5.6%)	21 (19.6%)	[4]p=0.001
Alcohol use before pandemic (n=498, 37.3%)	417 (40.9%)	30 (15.4%)	51 (47.7%)	[5]p=0.001
Alcohol use during pandemic (n=386, 28.9%)	324 (31.8%)	20 (10.3%)	42 (38.3%)	[6]p=0.001
Mask use (n=868, 65.7%)	628 (61.6%)	161 (82.6%)	79 (73.8%)	[7]p=0.001

[1]The significance was between Azerbaijan and the other two countries.
[2]The significance was between TRNC and the other two countries.
[3]The significance was between all three countries.
[4]The significance was between Azerbaijan and the other two countries.
[5]The significance was between Azerbaijan and the other two countries.
[6]The significance was between Azerbaijan and the other two countries.
[7]The significance was between all three countries.

asserted that SARS CoV-2 was not a biological weapon" and 290 (21.9%) participants answered the question as "I have no idea"

The students were asked the question: "How much do you take care to avoid using stigmatizing expressions such as "Chinese virus" or "old people virus" in daily use?", and the responses were rated on a scale of 10 points (0: I do not care at all; 10: I pay attention to every statement). The average of the scores they obtained was 0 (IQR=0-5).

DISCUSSION

In this study, it was determined that number of alcohol and cigarette users decreased significantly during the pandemic. Anxiety levels were higher in those who quit or reduced smoking and those who comply with personal protection measures. Most of them get their information about the pandemic from their faculty lecturers or from Worldometer website or Youtube videos. One of three students believed that SARS CoV-2 is a biological weapon and a vaccine will be found in a year.

In a study conducted in Chinese medical school students, it was reported that one in four of them had anxiety symptoms and some sociodemographic factors such as living in the city, stable income in their families, and living with parents were protective against anxiety [(5)]. In our study, we did not find any significant relationship between socio-demografical factors (age, gender, country of residence, having a chronic disease) and anxiety levels, except gender. Anxiety levels in female students were higher. Concordant with our findings, exhaustion and anxiety levels were found to be higher in women healthcare workers and it has been reported that younger and female healthcare workers are more adversely affected during the current pandemic [(7-9)].

In previous outbreaks, it has been reported that those with low levels of anxiety complied less with social distancing practices and hygiene measures [(11)]. Parallel to these data we found higher anxiety levels in those who applied protective measures (wearing a medical mask, providing hand disinfectant or eau de cologne and following hand washing methods). Our results show that people with very low anxiety levels may have maladaptive behaviors regarding compliance with preventive and hygiene measures. Feeling anxious to a real external threat like a pandemic is a natural and healthy response but people with very low anxiety levels may have maladaptive behaviors regarding compliance with preventive and hygiene measures.

In a recent study, it has been reported that Iranian

medical students applied personal protection measures at a high rate during pandemic [6]. In our study, it was determined that the students applied personal protection measures at a high rate, except for the use of medical masks outside. At the time of this study, there was no clear suggestion about the use of masks outside. We think that the low rate of mask use is associated with this situation.

Increased alcohol and tobacco use after disasters has been shown in the majority of the publications investigating this relationship [6]. Contrary to previous data we found reduced amount of alcohol and tobacco use among medical school students. Findings from researches have shown that alcohol and smoking may worsen the course of SARS CoV-2 related diseases [10]. From this point of view, the decrease in smoking and alcohol use should be evaluated as a protective behavior which we found to be highly pursued in medical school students. Furthermore we can speculate that reduced smoking and alcohol consuption may be related to reduced socialization.

Although anxiety scores and ages of students didn't differ between three countries, tobacco and alcohol use were found to be at a highest level in students from TRNC and masks were most frequently used by students from Azerbaijan. This may be due to sociocultural differences between countries.

Center for Disease Control and Prevention (CDC) suggests avoiding overexposure to COVID-19 media broadcasts, eating a healthy, balanced diet, exercising regularly, sleeping regularly and adequately, avoiding alcohol and drugs, practicing one's favourite activities, connecting with others and maintaining healthy relationships in order to cope with stress and increase endurance against anxiety [13]. When the in-house activities performed by medical school students during isolation/quarantine period evaluated, it was determined that most frequently watching movies or TV series, spending time on social media and communicating with online applications, at least playing sports, and/or computer games, painting and other hobbies have been practiced.

The main method of relieving the anxiety felt by individuals in pandemics is to provide clear and reliable information. Frequent updates on data and developments will minimize panic and rumors [14]. In the online survey study that investigated the sources of university students' knowledge about the Ebola epidemic in the USA, it has been reported that official websites such as WHO and NIH were the least used sources, while conventional media and social media were most frequently referred sources [15]. In the study evaluating the knowledge, behavior and risk perceptions of the medical students in Iran regarding the COVID-19 pandemic, it was reported that the students benefited from WHO, CDC and UptoDate more frequently than the local guidelines [6]. However, when evaluating these results, it should be remembered that the use of internet and social media in Iran is subject to restrictions. In our study, it was determined that the students benefited the least from the announcements of ministry of health and the most from their faculty members about the pandemic. They also benefited less from the WHO data compared to the social media sources. Our results point to the importance of social media among medical students in getting news and information about pandemic.

Outbreaks have been the subject of conspiracy theories throughout history [12]. Conspiracy theories have emerged about the Spanish flu, the Zika virus outbreak, the Swine flu outbreak, and even the Bubonic plague outbreak in Italy in 1576. HIV has been claimed to be a bioengineered weapon intended to eliminate homosexuality or Afro-Americans [16,17]. In a study conducted in Nigeria, almost half of the participants stated that they believed that SARS CoV-2 was a biological weapon produced by China [18]. In our study, one in three of the participants stated that they believed that SARS CoV-2 might be a biological weapon. Accurate information is essential in preventing conspiracy theories. While compliance with protection methods is strictly obeyed, strong belief in conspiracy theories suggests that the information these people have gotten is not convincing enough.

Increases in stigmatization can be expected in periods of pandemic, when public anxiety increases. Stigmatization involves negative, disparaging, hostile,

devaluating, and discriminatory attitudes towards a person , group, and the geographic region affected by a particular disease, and issues related to the disease [20]. In the SARS epidemic, very similar to today's events, the British media linked the epidemic to the dirty market environment in China, their close living with animals, and to the improper hygienic and cultural behaviors of Chinese people [21]. In Turkey, during the outbreak of the pandemic, stigmatization for the Asian people, then the elderly and ultimately the healthcare workers attracted attention in the media and social media. The way we express our thoughts about COVID-19 is critical in reducing stigmatization. In our study, unfortunately, it was determined that students did not take care not to use stigmatizing expressions in this way. Our results indicate that we should inform and educate students about the psychological effects and stigmatization of the pandemic.

In our study, the most important restrictive factor was failure to use a standard anxiety scale. However, the main purpose of this study is to determine the attitudes and behaviors of the students during the pandemic. Therefore, the students were asked to rate their anxiety levels. Reaching 1332 students in 3 different countries is one of the strongest aspects of our study.

CONCLUSION

The reduction in alcohol use and smoking rates is one of the most striking results of our study. Since the primary aim of our study was not to determine the rates of alcohol and tobacco use, screening tests for these subjects were not used. Longitudinal studies should be conducted in this regard.

In Turkey, medical faculties have started online education due to the current epidemic. Online tools are getting more and more effective in data collection and communication in the education of the students. For this reason, official institutions and universities should use social media more actively in informing the public. We also think it is important to educate future health professionals on social media literacy and sharing responsibilities. Thus, we can minimize the misinformation that spreads as fast as viruses, infects our minds, feeds our anxiety, conspiracy theories, stigmatization, erroneous beliefs and maladaptive behaviors.

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Conflict of Interest: None.

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Research Article

Evaluation of Approaches and Knowledge Levels of Pediatric Infectious Diseases Physicians about the Diagnosis and Treatment of Tuberculosis

Çocuk Enfeksiyon Hastalıkları Hekimlerinin Tüberküloz Tanı ve Tedavisinde Yaklaşımlarının ve Bilgi Düzeylerinin Değerlendirilmesi

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ABSTRACT

Objective: *In this study, we aimed to evaluate the approaches and knowledge levels of pediatric infectious diseases research workers and pediatricians in the diagnosis and treatment of tuberculosis under the guidelines updated by the Ministry of Health in 2019.*
Method: *This survey is a descriptive study applied to pediatric infectious diseases research workers and pediatricians. In the study, a questionnaire form prepared by researchers consisting of questions about sociodemographic features (n:5), knowledge level about tuberculosis (n:20), experience and approaches (n:13) was used.*
Results: *Fifty physicians participated in the study. The average age of participants was 36 years, and 90% of them were women. It was observed that physicians participating in the study had sufficient knowledge of tuberculosis. In terms of their experiences about tuberculosis, it was learned that m. tuberculosis culture (86%), acid-fast-bacilli test (82%), chest radiography (78%) and tuberculosis polymerase chain reaction (66%) were used most frequently for the diagnosis of pulmonary tuberculosis. Most common form of non-pulmonary tuberculosis was lymphadenitis (84%), and the most challenging condition in the treatment of tuberculosis was drug side effect (78%). When drug resistance was questioned, it was seen that 60% of the physicians encountered drug resistance, and the most common drug resistance was against isoniazid (54%). The isolation measures applied to tuberculosis patients were single room admission, and use of a N95 mask in 80%, an ultraviolet protected lamp use in 22% , and negative pressure room monitoring in 32% of the cases.*
Conclusion: *In our country, tuberculosis still retains its importance. For this reason, the information should be updated with in-service training on issues such as diagnosis, treatment, drug resistance and prevention methods.*

Keywords: *Tuberculosis, pediatric infectious diseases, approach, level of knowledge*

ÖZ

Amaç: *Bu araştırma ile çocuk enfeksiyon hastalıkları yan dal araştırma görevlisi ve uzman hekimlerinin tüberküloz tanı ve tedavisinde yaklaşımlarının ve bilgi düzeylerinin 2019 yılında Sağlık Bakanlığı tarafından güncellenen rehber eşliğinde değerlendirilmesi amaçlanmıştır.*
Yöntem: *Bu çalışma çocuk enfeksiyon hastalıkları araştırma görevlisi ve uzman hekimlerine uygulanan tanımlayıcı tipte bir araştırmadır. Çalışmada, araştırmacılar tarafından hazırlanan sosyodemografik özellikler ile ilgili 5 soru, tüberküloz bilgi düzeyi ile ilgili 20 soru, deneyim ve yaklaşımlar ile ilgili de 13 sorudan oluşan anket formu kullanılmıştır.*
Bulgular: *Araştırmaya 50 hekim katılmıştır. Katılımcıların yaş ortalaması 36 yıl olup, %90'ı kadındır. Çalışmaya katılan hekimlerin çoğunlukla tüberküloz bilgi düzeylerinin yeterli olduğu gözlenmiştir. Tüberküloz deneyimleri açısından, pulmoner tüberküloz tanısında en sık tüberküloz kültür (%86), asidorezistan basil bakısı (%82), akciğer grafisi (%78) ve tüberküloz polimeraz zincir reaksiyonu (%66) kullanıldığı öğrenildi. En sık karşılaşılan non-pulmoner tüberküloz formu lenfadenit (%84), tüberküloz tedavisinde en çok zorlanılan durum ise ilaç yan etkisi (%78) olarak bulundu. İlaç direnci sorgulandığında, hekimlerin %60'ının ilaç direnci ile karşılaştıkları görüldü, en sık karşılaşılan ilaç direncinin ise izoniazid (%54) olduğu belirtildi. Tüberküloz hastalarına uygulanan izolasyon önlemleri, %80 tek kişilik odaya alma ve N95 maske, %22 ultraviyole korumalı lamba kullanımı, %32 negatif basınçlı odada izlem idi.*
Sonuç: *Ülkemizde tüberküloz halen önemini korumaktadır. Bu nedenle tanı, tedavi, ilaç direnci ve korunma yöntemleri gibi konularda meslek içi eğitimlerle bilgilerin güncellenmesine devam edilmelidir.*

Anahtar kelimeler: *Tüberküloz, çocuk enfeksiyon hastalıkları, yaklaşım, bilgi düzeyi*

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INTRODUCTION

Tuberculosis continues to be an important public health problem worldwide. According to the 2019 tuberculosis global report of the World Health Organization (WHO), the estimated number of cases with tuberculosis in 2018 was 10 million, including 1.1 million children. and 230,000 children and 1.5 million people died due to tuberculosis in 2018 [(1)]. In our country, the incidence of tuberculosis per 100,000 population was 14.6 in 2017 and 14.1 in 2018 [(2)].

Tuberculosis control has been called the "tuberculosis war" for a hundred years in our country. Continuing the follow-up and treatment of smear-positive patients and their contacts is of great importance in tuberculosis control. Since children usually contract tuberculosis bacilli from adult patients with tuberculosis, the problem of tuberculosis in childhood is one of the most important indicators of the effectiveness of tuberculosis control programs in adults. For this reason, the knowledge level of pediatric infectious diseases physicians who will diagnose tuberculosis in children, regulates their treatment. Besides, follow up period of the patients should be of sufficient length.

In our country, guidelines are prepared to provide a standard approach for tuberculosis control practices, diagnosis and treatment standards, and the recording and reporting system to be used. The first guidelines for tuberculosis in Turkey were published in 1932 [(3)]. Guidelines containing standards for the diagnosis and treatment of tuberculosis were published by the Ministry of Health in 1998, 2003 and 2011 [(4)]. Finally, this guideline was updated in 2019 [(5)]. In this study, we planned to evaluate the approaches and level of knowledge about tuberculosis of 50 pediatric infectious diseases research workers and pediatricians who are members of the Pediatric Infectious Diseases and Immunization Association, in line with the recently published guidelines.

MATERIAL and METHOD

This survey is a descriptive study applied to pediatric infectious diseases research workers and specialists. The research population was composed of the members of the pediatric infectious diseases association. The sample was not selected for the research. A website or face-to-face questionnaire forms were used in the study. Participation in the survey was on a voluntary basis.

A questionnaire form prepared by the researchers was used as a data collection tool. Questionnaire form contained questions about sociodemographic characteristics (n:5), knowledge level about tuberculosis (n:20), and experiences and approaches (n:13). The questions regarding the level of knowledge on tuberculosis were prepared based on the Tuberculosis Diagnosis and Treatment Guideline updated by the Ministry of Health in 2019 [(5)].

Regarding the level of knowledge of tuberculosis, the participants were asked the questions related to the criteria used for the definitive diagnosis of tuberculosis, the other tests and features used for the diagnosis, the indications of the interferon-gamma release assay (IGRA), contagious forms of tuberculosis, the duration of the contagiousness, contact approach, diagnosis of latent tuberculosis, treatment and follow-up, side effects of antituberculostatic drugs and follow-up of these side effects, indications of corticosteroid use, alternative approaches in patients who did not comply with antituberculostatic drug treatment, drug sensitivity tests and drug-resistant tuberculosis, follow-up of the baby born to a mother with tuberculosis, tuberculosis screening in patients using anti-tumour necrosis factor drugs (anti-TNF) and required isolation methods in patients with tuberculosis.

Regarding the experiences and approaches of the participants in cases of tuberculosis, they were asked questions related to the hospital isolation methods, the tests they used in diagnosis, the conditions they had difficulty in treatment, the drug resistance type they mostly encountered, the tuberculosis treatment they applied for HIV-positive patients, the applications they performed for the contact healthcare workers, and tuberculosis screening before immuno-suppressive therapy.

Statistical evaluation was performed using SPSS,

version 19.0 (IBM company, USA) program, mean, standard deviation, number and percentage were used in defining the data. The approval for the conduction of the study was obtained from the local ethics committee.

RESULTS

Fifty physicians participated in the study. The average age of participants was 36 years (range: 24-48 years), and 90% (n:45) of them were women. Twenty-seven (54%) pediatric infection subspecialists and 23 (46%) pediatric infection research workers were included in the study. The physicians were working in the field of pediatric infection for one (n:11; 22%), 1-3 (n:15; 30%), 3-5 (n:9; 18%) , 5-10 (n:7; 14%), and ≥ 10 (n:8; 16%) years. The physicians were working in a university hospital (n:27; 56%), in a training and research hospital (n:21; 42%), and in a state hospital (n:1; 2%) (Table 1).

Table 1. Sociodemographic characteristics of physicians.

Female / Male	**n (%)**
	45/5 (90/10)
Age (years), median (range)	36 (28-48)
Branch	**n (%)**
Pediatric infectious diseases research worker	27 (54)
Pediatric infectious diseases specialist	23 (46)
Years of working	**n (%)**
0-1	11 (22)
1-3	15 (30)
3-5	9 (18)
5-10	7 (14)
≥10	8 (16)
Health institution	**n (%)**
University Hospital	28 (56)
Training and Research Hospital	21 (42)
Public Hospital	1 (2)

When asked, 58 (96%) participants knew that the definitive diagnostic test of tuberculosis is a bacterial susceptibility test performed on Lowenstein-Jensen selective culture medium, and 98% (n:49) of them knew that larynx is the site of infection Besides, 56% (n:28) of them gave correct answers to the question related to the indication of IGRA in a patient with a negative tuberculin skin test (TST) result.

Twenty-eight (56%) participants correctly responded to the question about the time when the infectiousness ends in patients receiving tuberculosis treatment by marking the options of undergoing the effective treatment for at least 3 weeks, by indicating decrease in symptoms, and by observing smear test positivities at least 8 hours apart and negative sputum smear test results obtained at least 3 consecutive in the morning or 3 consecutive days.

In the question about the use of nucleic acid amplification test (NAAT) in the diagnosis of tuberculosis, 84% (n:42) of the physicians knew that negative NAAT did not exclude the diagnosis of tuberculosis. However, the question of which laboratory test is not necessary before treatment of a patient diagnosed with tuberculosis, was responded correctly by 22 (44%) participants who selected bleeding diathesis among the options of liver function tests, erythrocyte sedimentation rate, anti-HIV, hepatitis B and C screening, fasting blood glucose, HbA_1c, and bleeding diathesis.

When the study participants contacted with contagious tuberculosis patient (s) were asked about the indications for preventive treatment, 92% of the physicians (n: 46) correctly answered that preventive treatment should be initiated in the babies born to a mother with tuberculosis, individuals under the age of 35 with negative TST results and normal chest radiography or IGRA positivity and normal chest radiography. Thirty physicians (60%) knew correctly the preventive treatment to be selected and its duration that consisted of isoniazid for 6 or 9 months, rifampicin for 4 months and moxifloxacin for 9 months. Eleven (22%) physicians did not know that moxifloxacin treatment was among the preventive drug options in cases of contact with resistant tuberculosis patients, which is the new information in the latest guideline. Thirty-three (66%) physicians were informed about this most currently updated information that preventive treatment should be initiated again in people who previously received preventive treatment for any reason but had a history of contact in a new close environment.

Forty-three (66%) physicians knew that pyrazinamide causes hyperuricemia as a response to the question concerning antituberculosis drugs and

their side effects. To the question inquiring if antituberculostatic drug treatment has a minor side effect that does not require discontinuation of the treatment, 29 (58%) physicians correctly chose the option of hypersensitivity reactions.

Thirty-two (64%) participants knew correctly what to do in the presence of hepatotoxicity in a patient receiving antituberculosis treatment. Accordingly, they stated that the drug should be discontinued if the transaminase values exceeded 5 times the upper limit value of normal regardless of the presence of any symptom and if the bilirubin value exceeded 1.5 mg/dL or the patient's clinic required emergency treatment. They indicated that in these patients non-hepatotoxic treatment should be initiated and viral hepatitis should be considered in the differential diagnosis in cases where transaminases are at a very high level. Forty-seven (94%) patients knew the indications of corticosteroid use in the treatment of tuberculosis.

Thirty-six (72%) patients were informed about the alternative approaches to the patients who did not comply with the antituberculosis treatment. The conditions that should be considered as multi-drug resistance were known correctly by 47 (94%) physicians, but only 30 (60%) study participants answered correctly to the question concerning the definition of multi-drug resistant tuberculosis, and the development of resistance to isoniazid and rifampicin Twenty-eight (56%) participants knew correctly that the drug sensitivity test should be performed at the beginning of treatment and if bacterial reproduction continues on the 3rd month.

Thirty-seven (74%) physicians correctly knew that whether the babies born to a mother with tuberculosis had of had not tuberculosis, the isoniazid treatment should be completed to 6 months, regardless of the TST results.

Thirty-four (68%) patients correctly knew how to perform tuberculosis screening tests in patients using anti-TNF drugs, and stated that clinical screening tests should be performed every 3, radiological screening studies every 6, TST/IGRA every 12 months.

Twenty-two (44%) physicians were not informed about isolation measures of the patient with tuberculosis, and did not know that the patient who came out of the ward did not need to wear an N95 mask.

When physicians' approaches to diagnosis and treatment were evaluated, the indicated proportions of study participants had correct knowledge about the use of tuberculosis culture (86%), acid-fast bacilli (AFB) smear tests (82%), chest radiography (78%) and tuberculosis polymerase chain reaction (PCR) (66%). Ten percent of the physicians, all of whom were first-year research workers in the department of pediatric infectious diseases, stated that they had not diagnosed anyone with tuberculosis before. It was observed that TST, chest radiography and IGRA were used in the diagnosis of latent tuberculosis in immunosuppressed individuals (74%). The most common type of non-pulmonary tuberculosis was lymphadenitis (84%), followed by bone, joint (56%) and central nervous system tuberculosis (34%). Treatment of tuberculosis was extremely difficult in cases of drug side effects (78%), patient noncompliance (56%) and drug resistance (26%). Sixty percent of the study participants encountered drug resistance, and the most common drug resistance was against isoniazid (54%). As screening tests of the healthcare workers in contact with tuberculosis patients, most frequently (64%) annual TST + chest radiography and in suspected cases sputum AFB controls were performed. When the isolation measures applied to tuberculosis patients were questioned, 80% of the physicians stated that they used a single-bed isolation rooms and N95 mask, and 22% of them used ultraviolet (UV) protected lamps. It was learned that 32 % of the patients were monitored in the negative pressure rooms, and 88 % of them for 24 hours. To the question" Do you feel safe in terms of preventive measures while monitoring tuberculosis patients?," 20 (40%) physicians responded as "yes most of the time", 36% (n:18) of them as "never" and 24% (n:12) of them as " sometimes".

DISCUSSION

Although tuberculosis is a preventable and treatable disease, it continues to be an important cause of morbidity and mortality in children and adolescents. Each child diagnosed with tuberculosis in society is an indicator of a new outbreak and that tuberculosis disease is not well controlled in that society. For this reason, pediatric infectious diseases physicians dealing with childhood tuberculosis must have good knowledge and experience concerning tuberculosis. It was observed that the physicians involved in this study were mostly experienced and sufficiently knowledgeable about tuberculosis.

The definitive diagnosis of pulmonary tuberculosis in children is made by showing tuberculosis bacilli in sputum [5]. Diagnostic methods such as ARB and PCR might shorten the time to diagnosis. In our study, 96% of the physicians correctly answered the question of how the definitive diagnosis of tuberculosis was made In another study, 83.6% of pediatric research workers gave correct responses to that question [6]. When the experiences of the physicians participating in the study were questioned, it was found that they mostly used culture, AFB, PCR, TST and radiological imaging for the diagnosis of tuberculosis.

In our country, TST is used extensively in tuberculosis screening. However, TST can be affected by many factors such as BCG vaccine, immunity of the individual, application and interpretation technique of the screening tests [7]. IGRA has been used frequently in recent years, and its use is recommended in immunosuppressed patients with negative TST results or those using immunosuppressive drugs, and in TST-positive patients with poor prognosis but without any risk factor for tuberculosis disease to rule out false positivity [5]. In our study, 56% of the patients had an accurate knowledge about the indication of IGRA in patients with TST-negativity. This lower rate shows that IGRAs are still not performed routinely in most hospitals in our country, so there is a lack of knowledge and experience in this respect.

Preventive treatment is given to patients who have contact with infectious patients without active disease, children with latent infection, and babies born to mothers with tuberculosis. In preventive treatment, isoniazid (10 mg/kg, maximum 300 mg) is used daily for 6 months. This period is 9 months in immunocompromised children. In case of resistance to isoniazid, rifampicin is given for 4 months (10 mg/kg daily, maximum 600 mg) [5]. There is no randomized controlled study on an effective preventive treatment regimen in children in contact with patients with multi-drug resistant tuberculosis. In quinolone-sensitive cases, use of either moxifloxacin or levofloxacin is recommended for 9 months. Alternatively, quinolone + ethambutol treatment is recommended [8]. In our study, although most (92%) of the participants correctly knew the indications for preventive treatment, among the options of preventive treatment, scarce number of these physicians heard about moxifloxacin which was attributed to the fact that most of the physicians did not encounter cases with resistant tuberculosis and therefore did not have up-to-date knowledge of resistant tuberculosis treatment. Because adults with resistant tuberculosis have an important place in our country, we think that in-service training on current issues should be done.

Extrapulmonary tuberculosis is more common in children than adults, especially with younger age, due to the high risk of lymphohematogenous spread. Tuberculous lymphadenitis is the most common form of extrapulmonary tuberculosis [9]. In the study of Coşar et al. [10] evaluating childhood tuberculosis, the rate of extrapulmonary tuberculosis was 38.6% and the frequency of tuberculous lymphadenitis was 11.7%. In another study, the most common forms of extrapulmonary tuberculosis in children were found in decreasing order of frequency as lymphadenopathy, bone, meninges, and miliary tuberculosis, respectively [11]. When physicians' experiences about extrapulmonary tuberculosis were questioned in our study, they indicated that they mostly (84%) encountered lymphadenitis followed by bone joint (56%) and central nervous system tuberculosis (34%).

It is important to identify tuberculosis patients in

the community, to treat these patients regularly and to complete their treatment within the appropriate time. Drug side effects are among the most important issues that make compliance difficult. Children tolerate tuberculostatic drugs better than adults, and side effects such as hypersensitivity, visual impairment, hepatotoxicity or hearing loss that require interruption of treatment are less common in children [5]. Despite this, drug side effect (78%) was found to be the most difficult situation in the treatment of tuberculosis by the physicians participating in our study followed by patient compliance (56%) and drug resistance (26%). The lack of special drug formulations for children and the fact that the flavours of the drugs are not palatable for children are factors that reduce patient compliance to treatment [5]. Drug resistance is another factor that makes tuberculosis control difficult. In patients who use the drug irregularly or discontinue it, and in cases of tuberculosis accompanied by a human immunodeficiency virus infection, single or multi-drug resistance can occur. This form of tuberculosis, which is also passed on to children as a result of the contact of children with these patients, complicates the diagnostic process and selection of appropriate treatment . In our study, 60% of the physicians encountered drug resistance, and they most commonly reported drug resistance against isoniazid (54%).

Many studies have demonstrated that tuberculosis is seen more often in healthcare workers in our country than the general population. It is known that nurses and medical staff in hospitals most often contract tuberculosis bacilli [12]. A series of precautions should be taken by the health institutions to prevent transmission of tuberculosis which include measures taken by management, engineering measures and personal protective measures [5]. One of the preventive measures implemented by the management is to screen the health personnel for tuberculosis periodically. In this study, it was found that as the screening tests of health workers contracting tuberculosis bacilli, most frequently (64%) annual TST + chest radiography + and sputum control for ARB in suspected cases were performed. Engineering measures are related to the effective installation and use of isolation rooms and ventilation systems. It is recommended that rooms with contagious tuberculosis patients be under negative pressure [5]. Another practice is to install UV lamps in rooms, corridors and sections where tuberculosis patients are present [5]. Using a mask is among the personal protective measures. A 95% effective filtering N system (N-95) mask is recommended as a protective measure against tuberculosis bacilli [5]. It was determined that more than half of the physicians participating in the study did not have a negative pressure room in the institution where they worked, UV lamps were less frequently applied, and usually N95 masks were used.

The approach and level of knowledge of pediatric infectious diseases physicians about tuberculosis have not been evaluated in the literature before. Since a suitable sampling selection technique is not used, it cannot be said that the number of participants represents all physicians working in this field. On the other hand, in studies evaluating the knowledge level of healthcare professionals about tuberculosis, it was observed that the knowledge level of pediatric residents, infectious diseases and clinical microbiology specialists was sufficient [6,13].

In conclusion, pediatric infectious diseases physicians continue to encounter tuberculosis patients frequently. Although they don't receive any special training on tuberculosis during their education, they mostly have sufficient knowledge and experience on tuberculosis. Since tuberculosis still maintains its importance in our society, we think that it will be beneficial to continue updating the information with in-service training on diagnosis, treatment, drug resistance and prevention methods.

Ethics Committee Approval: S.B.Ü İzmir Dr. Behçet Uz Pediatrics and Surgery Training and Research Hospital Clinical Research Ethics Committee approval was obtained (02.07.2020/144).
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Research Article

Is There a Relation Between Vitamin B_{12} Levels and Headaches in Children and Adolescents?

Çocuk ve Ergenlerdeki Baş Ağrılarının Vitamin B_{12} Düzeyleri ile İlişkisi var mı?

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ABSTRACT

Objective: *Primary headaches are common and benign discomforts both in children and adolescents. However, they have a negative influence on the quality of life. This retrospective study aimed to determine the relationship between vitamin B_{12} results and primary headaches in Turkish children.*
Methods: *Demographical features, headache types, laboratory results, including vitamin B_{12}, were assessed retrospectively. Headache types were categorized as tension-type headache, migraine, and unclassified headache according to the International Classification of Headache Disorders-beta version (ICD-3 beta). Patients with seconder headaches, anemia, and macrocytosis were excluded.*
Results: *The study group consisted of 133 (86 female, 47 male) patients with headache and a control group of 103 (57 female, 46 male) healthy children. There was no significant difference in terms of age and gender between groups ($p>0.05$). Vitamin B_{12} levels in tension-type headache, migraine, and unclassified headache groups were significantly lower ($p<0.0001$) than in the control group. Logistic regression has identified lower vitamin B_{12} levels than 400 pg/ml as an independent risk factor for headache (OR: 3.212, 95% CI: 1.850-5.576).*
Conclusion: *We conclude that lower vitamin B_{12} levels than 400 pg/mL may be associated with tension-type headache, migraine, and unclassified headache.*

Keywords: *Vitamin B_{12} levels, unclassified headache, migraine, tension-type headache, cobalamin deficiency, the pain-reducer effect of vitamin B_{12}*

ÖZ

Amaç: *Primer baş ağrıları, çocuk ve ergenlerde sık görülen benign patolojiler olmalarına rağmen, yaşam kalitesi üzerine olumsuz etki gösterirler. Bu retrospektif çalışma, çocuk ve ergenlerde vitamin B_{12} düzeyleri ile primer baş ağrıları arasındaki ilişkiyi incelemeyi amaçlamıştır.*
Yöntem: *Demografik özellikler, baş ağrısı tipleri ve vitamin B_{12} düzeylerini içeren laboratuvar sonuçları retrospektif olarak kaydedildi. Baş ağrısı tipleri International Classification of Headache Disorders-beta version (ICD-3 beta) kriterlerine göre; gerilim tipi, migren ve sınıflandırılamayan tipte baş ağrısı olarak sınıflandırıldı. Sekonder baş ağrısı, anemisi ve makrositozu olan olgular dışlandı.*
Bulgular: *Çalışma grubu; 133 hasta (86'si kız, 47'si erkek) ve 103 (57'si kız, 46'sı erkek) sağlıklı kontrol olmak üzere toplam 236 kişiden oluşmaktaydı. Hasta ve kontrol grupları arasında yaş ve cinsiyet açısından anlamlı farklılık saptanmadı ($p>0.05$). Vitamin B_{12} düzeyleri gerilim tipi, migren tipi ve sınıflandırılamayan tipte baş ağrısı gruplarının tamamında kontrol grubuna göre anlamlı olarak düşük saptandı ($p<0.0001$). Lojistik regresyon analizi sonrasında vitamin B_{12} düzeyinin 400 pg/ml'nin altında olmasının baş ağrısı için bağımsız bir risk faktörü olduğu saptandı (OR: 3.212, 95% CI: 1.850-5.576).*
Sonuç: *Vitamin B_{12} düzeylerinin 400 pg/mL'nin altında olmasının gerilim tipi, migren tipi ve sınıflandırılamayan baş ağrıları ile ilişkili olabileceğini düşünmekteyiz.*

Anahtar kelimeler: *Vitamin B_{12} seviyeleri, sınıflandırılamayan baş ağrısı, gerilim tipi baş ağrısı, kobalamin eksikliği, vitamin B_{12}'nin ağrı kesici etkisi*

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INTRODUCTION

Headaches are common chronic neurological disorders, both in children and adolescents [1]. Intracranial mass, trauma, infection, metabolic, or vascular diseases should be considered as they may be life-threatening conditions for secondary headache [2]. Although primary headaches are benign, they may have negative impacts on patients' quality life [3]. Tension-type headache (TTH) is a common cause of primary headaches in children. Though the exact pathological mechanism of TTH is unclear, both muscular and psychogenic factors are thought to be related to TTH. Migraine is another common cause of recurrent primary headaches in children and has a significant impact on school attendance and family dynamics [4]. Pediatric migraine differentiates from adult migraine in response to treatment and its presentation. Under the new classification, bilateral location and shorter duration of attacks are currently revised for children in the diagnosis of migraine headaches [5]. Although migraines are divided into six categories, migraine with aura and migraine without aura are the most important and frequently seen subtypes. Headaches that differ from almost all types of headaches are classified as unclassified headaches.

There is some evidence supporting the use of comprehensive elimination diets in the prevention of migraine and other headache types. Various comprehensive elimination diets have been discussed in the literature including diets containing high folate, low fat, ketogenic diets, modified Atkins diets, and high omega-3 / low omega-6 diets [6]. There are also some reports supporting folate, vitamin B_2, vitamin B_6, vitamin B_{12} supplements in the treatment of migraine. Evidence exists that diets rich in folate and vitamin B_6/B_{12} supplements may prevent attacks of migraines, especially in people with certain gene variants of enzymes involved in homocysteine metabolism [7].

Anemia is a common health problem. Numerous studies exist regarding the negative impact of iron deficiency anemia (IDA) on psychomotor development [8]. Moreover, some reports have pointed out the association between headache and anemia [9]. Vitamin B_{12} is a water-soluble vitamin B that participates in DNA synthesis and plays a role in cell division, proliferation, and nerve myelination. Vitamin B_{12} deficiency is a common nutritional problem, especially in developing countries. Developmental delay, irritability, weakness, failure to thrive, paresthesia, sensory deficits, loss of deep tendon reflexes, movement disorders, hypotonia, seizures, and paralysis are the manifestations of vitamin B_{12} deficiency [10]. The prevalence may be as high as 40% in children in developing countries due to malnutrition, and inadequate intake is the most common cause of vitamin B_{12} deficiency [11]. The main systems of the human body affected by vitamin B_{12} deficiency are the hematological system, nervous system, skin, and mucous membranes. Numerous neurological disorders have been reported related to vitamin B_{12} deficiency. Moreover, studies on the relationship between headache and vitamin B_{12} deficiency have been increasing [12-15]. In the current study, we aimed to determine the relationship between vitamin B_{12} levels, and headache types in Turkish children and adolescents.

MATERIAL and METHOD

Study design and subject

We have obtained the approval of the local ethics committee (Date: 03/20/2019 No:2019-03/03) in line with the principles outlined in the Second Declaration of Helsinki. Due to the retrospective design of the study, the waiver of consent was not required by the ethics committee. This retrospective study was conducted from January 2018 to July 2018 in the department of pediatric neurology clinic of a state hospital, and included 133 cases aged between 5-18 with complaints of headache. Headache types, demographic features, and laboratory results were assessed retrospectively. Since the most frequent headache types in children were migraines, TTH, and unclassified headache, headache types were specified in these categories and categorized according to the International Classification of Headache Disorders-beta version (ICDH-3 beta).

Patients were excluded if they had a chronic disease, secondary headache with specific pathology detected on examination such as hypertension or detected on magnetic resonance imaging (MRI) like an intracranial mass or hydrocephalus. The control group consisted of 103 healthy children aged between 5-18 years without a headache or history of a chronic disease or drug use. The control group was chosen from the healthy children outpatient clinic among those who had no history of headache and underwent complete blood count (CBC), vitamin B_{12} analyses in the previous two weeks. The results were extracted from the electronic database. Demographic features and laboratory results of the patients and the healthy controls were compared according to headache types. Serum vitamin B_{12} levels were analyzed by electrochemiluminescence (ECLIA) immunoassay. Serum vitamin B_{12} level <400 pg/ml was defined as deficiency. Patients with anemia and macrocytosis were excluded from the study.

Statistical analysis

SPSS-22 (Statistical Package for Social Sciences) was used for statistics of the study. The Kolmogorov-Smirnov test was applied to quantitative data to detect conformity to the normal distribution, and values were stated as median and interquartile range. The differences among four groups regarding numerical variables were estimated by Kruskal-Wallis test and pairwise comparisons were compared using Tamhane tests. Chi-square test was applied to compare the categorical variables between groups, and a value of $p<0.05$ was accepted as statistically significant.

RESULTS

The study group comprised 133 patients (86 female, 47 male) and 103 (57 female, 46 male) healthy children. The most frequent headache types in the study group were TTH (42.1%), unclassified headache (30%), and migraine (27.8%). Demographic results are summarized in Table 1. Vitamin B_{12} results of 133 patients were extracted from the electronic database. Serum median vitamin B_{12} levels in the children with TTH, migraine, unclassified headache, and control groups were 315 (162.7) pg/ml, 313 (132) pg/ml, 284.7 (154.85) pg/ml, and 405 (238) pg/ml respectively. Vitamin B_{12} levels were significantly lower in TTH, migraine, and unclassified headache groups than in the control group. ($p<0.0001$) (Table 1). The logistic regression analysis has demonstrated vitamin B_{12} deficiency (<400 pg/ml) as an independent risk factor in children for headache (OR: 3.276, 95% CI:1.889-5.683, Table 2).

Table 1. Demographics, hemoglobin, MCV and vitamin B_{12} results of the headache and control groups.

	Tension-type headache (n=66, 25%)	Migraine (n=46, 17.4%)	Unclassified headache (n=48, 18.2%)	Control Group (n=103, 39.1%)	Pα-value
Age (years)*	11 (3)	12 (5)	12 (5)	13 (6)	0.151
Female	46 (69.7%)	25 (54.3%)	25 (56.3%)	57 (55.3%)	0.236
Male	20 (30.3%)	21 (45.7%)	21 (43.8%)	46 (44.7%)	0.343
Hemoglobin*	13.9 (1.15) mg/dL	13.9 (1.2) mg/dL	13.8 (1.5) mg/dL	13.6 (1.5) mg/dL	0.761
MCV*	81.45 (6.78) fL	81.7 (5.20) fL	81.8 (6.10) fL	82.7 (5.6) fL	<0.0001
Vitamin B_{12}*	300 (188) pg/ml**	313 (131) pg/ml**	278 (152.6) pg/ml**	405 (238) pg/ml	

**Median, (interquartile range), α: the difference of numerical variables between four groups obtained by Kruska Wallis and pairwise comparisons by Tamhane test*

***Vitamin B_{12} levels were significantly lower in tension-type, migraine, and unclassified headache groups than in the control group (pα<0.0001)*

p1α=0.001, difference between control and tension-type headache groups

p2α=0.005, difference between control and migraine groups,

p3α=0.01, difference between control and unclassified headache group,

p4α=0.999 difference between tension-type headache and migraine groups,

p5α=0.767 difference between tension-type headache and unclassified headache groups.

Table 2. Multiple logistic regression model for vitamin B_{12} deficiency.

		95% CI		
	Odds Ratio	Lower limit	Upper Limit	p-value
Vitamin B_{12} deficiency (<400 pg/ml)	3.276	1.889	5.683	<0.0001

The logistic regression has demonstrated vitamin B_{12} deficiency (<400 pg/ml) as an independent risk factor in children for headache (OR: 3.276, 95% CI:1.889-5.683).

DISCUSSION

Headache is one of the most common symptoms among children and adolescents who are admitted to emergency services, pediatrics, and pediatric neurology clinics [16]. There is a high prevalence of psychological comorbidity related to headache disorders, which significantly decreases the quality of life, with the severity of impairment being dependent on headache type [3]. Therefore, this issue is an important public problem. Although there are studies regarding the relationship between vitamin B12 deficiency and various neurological manifestations [10,17-20], studies on the relationship between vitamin B_{12} deficiency and headaches should be conducted. Hence, the present study hypothesizes that there may be an association between headache and vitamin B_{12} deficiency. The major outcomes of the current study were i) TTH was the most frequent headache type (42.1%) of the study group ii) vitamin B_{12} levels were significantly lower in TTH, migraine, and unclassified headache groups than in the control group (p<0.0001) (Table 1). iii) Vitamin B12 level lower than 400 pg/ml is an independent risk factor for headache (OR: 3.212, 95% CI:1.850-5.576) (Table 2). In the present study, the most frequent headache type was TTH. Tension-type headaches recurred at intervals of more (n=38), and less than 15 days (n=18) a month. Among migraineurs, the history of aura was present in 14 cases. Unclassified headache differed as for all headache features from both migraine and TTH. The common features were mild intensity and short duration (<1 hour) in patients who were categorized as unclassified headaches. These symptoms were similar to undifferentiated headaches, which were previously described by Wöber et al. [21].

Although there is generally no sex difference in prepubertal children, adult women suffer from migraines more frequently than adult men [22]. Some epidemiological studies have shown that the prevalence of migraine increases with age until a peak is reached during the fourth decade of life; thereafter, the prevalence declines [23,24]. According to a study performed in school children between the ages of 7 and 17 years in Kayseri, the prevalence of recurrent headache was 47.5%, and the estimated prevalence rates of unclassified headache, migraine and TTH were 4.6%, 7.2%, and 7.8%, retrospectively. In children older than 15 years, the frequency of migraine and TTH significantly increased [25]. Jin et al. [26] found a higher prevalence of headaches in the 12 and 15 year age groups. In the current study, headache episodes recurred in 42.1%, 27.8%, and 30% of children with TTH, migraine, and unclassified headache groups, respectively (Table 1). There were no statistically significant differences between headache types and age.

Vitamin B_{12} deficiency can present with various neurological manifestations during infancy, childhood, and adulthood. Neurological symptoms are attributable to pathology in the peripheral nerves, posterior, and lateral columns of the spinal cord and brain. When we browse through the symptomatology in infancy, slowly progressive manifestations such as motor delay, apathy, and developmental regression, and acute neurological events such as seizure or involuntary movement disorders may also be seen [27]. Besides, vitamin B_{12} has antinociceptive effects with some resultant clinical outcomes [28,29]. A possible explanation of the antinociceptive mechanism of vitamin B_{12} comes from interactions with prostaglandin synthesis, including cyclooxygenase (COX) enzymes. Although animal studies exploring the direct effects of vitamin B_{12} on COX enzyme are lacking, in murine models dextran sodium sulfate-induced colitis showed that a methyl-deficient diet (excluding vitamin B_{12}, folate, and choline) leads to a significant upregulation of COX_2 in the intestines after exposure

to dextran sulfate. Probably, vitamin B_{12} may have a role in the regulation of COX_2 levels during inflammatory challenges [30]. Hosseinzadeh et al. [31] performed a hot plate and abdominal pain studies. In these studies, mice showed mild and moderate reduction in pain in response to the administration of vitamin B_{12}. Hot plate pain study testing involves central COX mechanism, whereas abdominal writhing measures peripheral COX enzyme effects, suggesting that vitamin B_{12} may have both central and peripheral COX inhibitory features. Another possible antinociceptive mechanism of vitamin B_{12} involves neurotransmitters. Evidence shows that homocysteine decreases noradrenaline and 5-hydroxytryptamine synthesis. Additionally, it is well known that vitamin B reduces homocysteine levels. Lowering homocysteine levels with vitamin B might regulate neurotransmitter synthesis in individuals with high homocysteine levels, which may contribute to neurotransmitter-moderated antinociceptive effects [32]. In the current literature, the pain-reducing effect of vitamin B_{12} is observed in conditions of chronic pain including diabetic neuropathy, postherpetic neuralgia, low back pain, and aphthous ulcers with significant beneficial results [33,34]. Some studies have exhibited the relationship between vitamin B_{12} and headaches. Çalik et al. [12] performed a prospective study with 75 TTH patients and a control group of 49 healthy children. Serum vitamin B_{12} levels were significantly lower in patients with TTH than in the control group. Moreover, 66.6 % of the patients in the headache group with vitamin B_{12} deficiency also had an anxiety disorder. They suggested that there was a high incidence of vitamin B_{12} deficiency in those with TTH and anxiety disorder. Furthermore, some reports have shown the relationship between neuropsychiatric disorders such as depression and vitamin B_{12} deficiency. In the previous studies a possible mechanism has been suggested indicating the role of vitamin B_{12} in the synthesis of S-adenosyl methionine, which is an important methyl donor for the production of monoamine transmitters [35]. Togha et al. [13] performed a case-control study in 70 adult patients with migraine and 70 healthy adult cases. Serum vitamin B_{12} levels were significantly lower in patients with migraine than in the control group ($p=0.07$), whereas migraineurs had higher levels of MMA ($p=0.027$). They suggested that patients with lower levels of vitamin B_{12} and higher levels of MMA had higher odds of migraine. Aydın et al. [14] performed a retrospective study in children and adolescents, including 65 migraineurs and 87 healthy cases. They found a statistically significant difference between the migraine group and the control group, in terms of levels of vitamin B_{12} and folic acid ($p=0.008$, $p<0.0001$). Abu-Shanab et al. [15] performed a study in 485 patients and found that recurrent headaches were significantly related to lower vitamin B_{12} levels.

The reference range for vitamin B_{12} was 201-1100 pg/ml. Nevertheless, serum vitamin B_{12} levels between 201-400 pg/ml have frequently been found in both metabolically and clinically significant vitamin B_{12} deficiency due to frank depletion of B_{12} stores [36]. Thus, we accepted the adequate level for serum vitamin B_{12} as ≥400 pg/ml. In the current study, the median vitamin B_{12} levels were <400 pg/ml in all types of headache groups, and we also observed significantly lower vitamin B_{12} levels in TTH, migraine, and unclassified headache groups when compared to the control group ($p<0.0001$). The probable mechanisms of the linkage between headache and vitamin B_{12} deficiency involve the neurotransmitter-moderated antinociceptive effect of vitamin B_{12}, and the role of vitamin B_{12} to control COX_2 levels during the inflammatory challenges. The results of the present study regarding the relationship between TTH, migraines, and lower vitamin B_{12} levels support the results of the previous studies mentioned. Moreover, we also found an association between the unclassified headache, and lower vitamin B_{12} levels.

One of the limitations of our study was its retrospective design. The other limitations were the lack of clinical results regarding post-treatment follow-up and a small number of study patients. Randomized double-blind placebo-controlled studies are needed on this issue.

The current study, one of the few studies in this field, has shown not only the relationship between vitamin B_{12} deficiency and TTH but also the linkage

between migraine, unclassified headache, and lower vitamin B_{12} levels. We suggest that vitamin B_{12} levels lower than 400 pg/ml are significant independent risk factors for headache. The probable mechanism might be related to neurotransmitter-moderated pathways and interactions with prostaglandin synthesis, as found in previous investigations. Therefore, vitamin B_{12} should be analyzed in patients with TTH, migraine, and unclassified headache.

Ethics Committee Approval: Cumhuriyet University Non-Interventional Clinical Research Ethics Committee approval was obtained (20.03.2019/03/03).

Conflict of Interest: The authors declare no competing interest.

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Research Article

Awareness and Knowledge of Children With Asthma Who Treated With Subkutan Immunotherapy

Subkutan İmmunoterapi Uygulanan Astımlı Çocukların Farkındalık ve Bilgi Düzeyi

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ABSTRACT

Objective: *Asthma is one of the most common chronic diseases of childhood. Many studies have shown that education positively affects asthma control and patients' quality of life. In this study, it was aimed to measure the awareness levels of children who have been under observation for a long time and who underwent Allergen Specific Immunotherapy (AIT).*
Methods: *Patients with asthma, asthma & allergic rhinitis and/or rhinoconjunctivitis who received subcutaneous AIT between July 2019 and December 2019 were included in our prospective case-control study. A questionnaire was applied to each patient, in which both the levels of awareness related to their disease and AIT, as well as their knowledge of the allergens and prevention measures they were sensitive to were measured. The results were examined. Age, gender, type of allergic diseases, allergen type, AIT time were evaluated statistically.*
Results: *82 cases (48 boys and 34 girls) were included in the study. The number of patients who know the name of the disease correctly is 68 (82.9%); The number of patients who knew allergens to be sensitive was found to be 47 (57.3%). It was observed that 15%-72% of the cases had information about asthma disease. Age, gender and diseases of the patients were not statistically different.*
Conclusion: *In our study, it was observed that our children were highly aware of especially about sports and environmental protection methods. It is essential to raise awareness of patients and parents for increase treatment success and control the asthma.*

Keywords: *Asthma, awareness, immunotherapy, knowledge*

ÖZ

Amaç: *Astım çocukluk çağının en sık görülen kronik hastalıklarından biridir. Yapılan birçok çalışmada eğitimin, astım kontrolünü ve hastaların yaşam kalitesini olumlu yönde etkilediği gösterilmiştir. Bu çalışmada uzun süredir izlem altında olan ve Alerjen Spesifik İmmünoterapi (AIT) programı nedeniyle sık sık bir araya gelinen çocukların hem hastalıkları ve AIT ile ilişkili farkındalık düzeylerinin ölçülmesi hedeflenmiştir.*
Yöntem: *Prospektif, olgu kontrol çalışmamıza, Çocuk Alerji Polikliniği'ne Temmuz 2019-Aralık 2019 tarihleri arasında subkutan AIT uygulanan astım, astım&alerjik rinit ve/veya rinokonjonktivitli hastalar dahil edildi. Her hastaya hem hastalıkları ve AIT ile ilişkili farkındalık düzeylerinin, hem de duyarlı oldukları alerjenler ve korunma önlemleri ile ilgili bilgilerinin ölçüldüğü bir anket uygulandı. Anket sonuçları üzerinde yaşın, cinsin, alerjik hastalık tipinin, uygulanan alerjen tipinin, AIT süresinin etkisi olup olmadığı araştırıldı.*
Bulgular: *Çalışmaya toplam 82 olgu (48 erkek ve 34 kız) alındı. Hastalığının tam olarak adını bilen olgu sayısı 68 (%82.9), duyarlı olduğu alerjeni bilen olgu sayısı ise 47 (%57.3) olarak saptandı. Olguların %15-72'sinin astım hastalığı ile ilgili bilgi sahibi olduğu görüldü. Hastalara ait yaş cinsiyet ve sahip olduğu hastalıklar arasında istatistiksel olarak anlamlı fark saptanmadı.*
Sonuç: *Araştırmamızda özellikle spor ve çevresel korunma yöntemlerini içeren konular hakkında çocuklarımızın farkındalığının yüksek olduğu görülmüştür. Astım semptomlarının azaltılması ve kontrolünün sağlanması için tedavi uygulamaları ile beraber, tedaviye uyumu arttırmak için hasta ve ailelerin bilinçlendirilmesi ve bu eğitimin devamlılığının sağlanması esastır.*

Anahtar kelimeler: *Astım, farkındalik, immünoterapi, bilgi düzeyi*

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INTRODUCTION

Asthma is one of the most common chronic childhood diseases with a reported worldwide prevalence of between 1.4% and 21.5% [1-3]. The reported prevalence of asthma in children in Turkey is e 6-15%, with one in around 10 children known to have asthma [4,5]. Allergic asthma is more common in children, and necessitates the elimination of the causative allergen and the regulation of environmental circumstances as known triggers, along with medical treatment and allergen specific immunotherapy (AIT) [6,7]. Among these, AIT is the single treatment modality that induces the development of immune tolerance and that may change the course of the disease [7].

Allergen-specific immunotherapy involves the application of a standard allergen extract to which the patient has been established to be clinically sensitive, starting at a low dose and in gradually increasing doses so as not to cause adverse effects. This is an efficacious treatment that is directed to the etiology, and is used in allergic rhinitis, allergic asthma and allergic reactions to bee venom [8]. It has long been used successfully for the treatment of children with asthma.

Patient education, close collaboration with the patient and AIT are required for the efficacious treatment of asthma. Education has been shown to positively affect the control of asthma and the quality of life of patients in many studies performed to date [9]. In those with asthma in the pediatric age group, patient awareness of the disease and its treatment course has been observed to be low, despite the long-term follow-up and the intense use of medication [10]. Furthermore, studies of the general population, primary school teachers and parents of children with asthma have reported the level of awareness and knowledge also of those groups about asthma to be low [11-13].

The quality of life of children and disease management may be improved through school-based asthma education programs that include also family members [14,15]. The present study measures the level of awareness of children on long-term follow-up, who were met frequently due to the AIT program, on both their diseases and AIT, and also their level of knowledge on the allergens to which they are sensitive and the ways to protect themselves against them.

MATERIALS and METHODS

Patient Population

Patients with asthma, and asthma/allergic rhinitis and/or rhinoconjunctivitis who received subcutaneous AIT between July 2019 and December 2019 at the Pediatric Allergy Outpatient Clinic of the Izmir SBU Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital were included in this prospective case-control study. Asthma and allergic rhinitis diagnoses were based on international guidelines. Allergic sensitivity was detected through skin prick tests (SPT) and/or the measurement of serum-specific IgE levels. The indications and contraindications of subcutaneous AIT were evaluated considering the recommendations of the American Academy of Allergy Asthma and Immunology.

Study Design

Sociodemographic data, such as the age and gender of the children included in the study, their age at the time of the asthma diagnosis, accompanying atopic diseases, duration of follow-up allergens to which they were sensitive, age at the start of AIT, duration of AIT, laboratory results and the content of the AIT extracts applied were recorded. All patients took part in a survey measuring their level of awareness of their disease and AIT, and also their knowledge on the allergens to which they are sensitive, along with preventative approaches. Patients who received no AIT and who dropped out of the AIT program, or whose AIT was stopped due to the onset of side effects were excluded from the study. The effects of age, gender, type of allergic disease and duration of AIT on the results of the survey were evaluated.

Subcutaneous allergen immunotherapy

Standardized depot extracts supplied by Allergopharma (Reinbeck, Germany), including

aluminum hydroxide; and by ALK-Abellò (Madrid, Spain), including calcium phosphate and Stallergenes (Antony Cedex, France), all of which are commercially available in Turkey, were used in the study.

Survey

The applied survey was created by Al-Harbi AS et al. (2016) (Structured Asthma Knowledge Questionnaire) after being adapted into Turkish [12]. The applied survey is presented in Table 1.

Ethical Approval

The study was approved by the Clinical Research Ethics Board of Dr. Behçet Uz Child Diseases and Pediatric Surgery and Research Hospital (Decision date July 18, 2019, and number 2019/267-110).

Statistical Analysis

The data were analyzed using SPSS for Windows (Version 15.0. Chicago, SPSS Inc.). For the continuous variables, the data were expressed as mean±standard deviation or median, based on the type of distribution as normal or non-normal. Chi-square and Mann-Whitney U tests were applied for the comparison of parametric values with normal and homogeneous distribution or nonparametric variables.

RESULTS

A total of 82 cases were included in the study (48 male; 34 female), with a mean age and mean duration of follow-up of 162.2±36.9 months and 67.7±23.9 months, respectively. The age at the start of subcutaneous AIT and the duration of follow-up for AIT were 133.3±36.9 months and 67.7±23.9 months, respectively.

An evaluation of the medical records of the patients revealed a median eosinophil count of 350/

Table 1. Statements made to patients in the survey, and the correct answers.

Questions	Correct answers
1. Asthma is a chronic disease that manifests with exacerbations following exposure to allergens.	True
2. Genetic and environmental factors play role in the course of asthma.	True
3. Is there a difference between asthma and chest allergies in children?	No
4. Asthma is a potentially dangerous disease.	True
5. Signs of asthma are dyspnea and night coughs.	True
6. Fever, sore throat and nasal discharge are among the symptoms of asthma.	False
7. A child with severe asthma symptoms cannot speak in sentences, cannot lie on his/her back, and changes in behavior may be seen, such as temper.	True
8. Frequent use of antibiotics prevents long-term lung damage.	False
9. An increase in respiratory system infections may cause changes in the course of asthma.	True
10. House dust, seasonal changes and sudden environmental changes, such as cold air, may lead to changes in the course of asthma.	True
11. Direct or indirect exposure to cigarette smoke may cause asthma exacerbations.	True
12. Asthma patients will have a better outcome if they visit a physician regularly.	True
13. A patient with asthma should refrain from physical activity and sports.	False
14. Patients with asthma should refrain from such foods as fish, eggs and bananas.	False
15. Physicians should inform patients about the indications of asthma and plan the patient's management of the disease, including what to avoid and what to refrain from.	True
16. A patient with asthma should be informed how to manage his/her disease.	True
17. The treatment of asthma is unnecessary in children under 6 years of age.	False
18. A patient with asthma may stop the drugs he/she uses after treatment for an exacerbation.	False
19. A patient with asthma may use the drugs of another patient without consulting a doctor.	False
20. Steam (nebulizer) is a better asthma treatment than drugs taken through a mask or tube drugs.	False
21. A patient with asthma does not need a mask when using drugs if she/he is less than 5 years old.	False
22. A patient with non-severe asthma may be treated by a primary care physician.	True
23. Asthma drugs can be addictive.	False
24. Asthma prevention drugs may have serious side effects when used to treat conditions other than exacerbations.	False
25. Special centers should be established in order to raise awareness of, and to provide for the better treatment of asthma.	True
26. Asthma may lead to absenteeism from school.	True

Table 2. Demographic data and laboratory results of patients.

	Patients n (%)
Gender	
Girl	10 (47.6%)
Boy	11 (52.4%)
Diagnosis distribution	
Asthma	43 (52.4%)
Asthma + Allergic Rhinitis and/or Rhinoconjunctivitis	39 (47.6%)
Sensitization	
House dust mites	20 (24.4%)
Pollen	30 (36.6%)
Mold	3 (3.7%)
Multiple	29 (35.4%)
Content of the SKIT Used	
House dust mite allergens	29 (35.4%)
Pollen allergens	42 (51.2%)
Mold allergens	3 (3.7%)
Multiple allergens	8 (8.9%)
Eosinophil count /mm^3 (median, min-max)	350 (29-5410)
Percentage of eosinophils (%) (median, min-max)	4.3 (0.7-22)
IgE level (IU/L) (median, min-max)	191 (5-2000)
Age of the Patient (Months, mean±SD)	162.2±36.9
Mean Age at Diagnosis (Months, mean±SD)	65.3±28.2
Duration of Follow-up (Months, mean±SD)	67.7±23.9
Age at Start of IT (Months, mean±SD)	133.3±36.9
Duration of IT (Months, mean±SD)	28.4±10.3

Table 3. Distribution of patient responses to questions.

Questions	Correct n (%)	False n (%)	No response n (%)
1	64 (78%)	18 (22)	0 (0%)
2	75 (91.5%)	3 (3.7%)	4 (4.9%)
3	15 (18.3%)	65 (79.3%)	2 (2.4%)
4	72 (87.8%)	9 (11%)	1 (1.2%)
5	73 (89%)	8 (9.8%)	1 (1.2%)
6	37 (45.1%)	39 (47.6%)	6 (7.3%)
7	31 (37.8%)	47 (57.3%)	4 (4.9%)
8	63 (76.8%)	14 (17.1%)	5 (6.1%)
9	27 (32.9%)	49 (59.8%)	6 (7.3%)
10	73 (89%)	6 (7.3%)	3 (3.7%)
11	77 (93.9%)	2 (2.4%)	3 (3.7%)
12	75 (91.5%)	5 (6.1%)	2 (2.4%)
13	74 (90.2%)	5 (6.1%)	3 (3.7%)
14	63 (76.8%)	16 (19.5%)	3 (3.7%)
15	69 (84.1%)	10 (12.2%)	3 (3.7%)
16	73 (89%)	8 (9.8%)	1 (1.2%)
17	75 (91.5%)	5 (6.1%)	2 (2.4%)
18	12 (14.6%)	68 (82.9%)	2 (2.4%)
19	45 (54.9%)	34 (41.5%)	3 (3.7%)
20	73 (89%)	7 (8.5%)	2 (2.4%)
21	59 (72%)	22 (26.8%)	1 (1.2%)
22	61 (74.4%)	17 (20.7%)	4 (4.9%)
23	50 (61%)	28 (34.1%)	4 (4.9%)
24	55 (67.1%)	24 (29.3%)	3 (3.7%)
25	21 (25.6%)	60 (73.2%)	1 (1.2%)
26	70 (85.4%)	10 (12.2%)	2 (2.4%)

mm^3, median eosinophil percentage of 4.3% and median total IgE level of 191 kU/L. Among the patients, 43 (52.4%) and 39 (47.6%) were followed-up for asthma and asthma & allergic rhinitis and/or rhinoconjunctivitis, respectively.

Following in vivo and in vitro allergy tests, 53 cases (64.6%) were found to be monosensitized and 29 (35.4%) to be polysensitized. The distribution of the allergens to which the patients were sensitive was as follows: 20 cases, to house dust and mite mixture (24.4%); three cases to Alternaria alternata (3.7%); 15 cases to meadow pollens (18.3%); and 15 cases tree mixtures (18.3%).

The extracts used in the subcutaneous AIT included a single allergen in 74 cases (91.1%) and multiple allergens in eight cases (8.9%). Subcutaneous AIT was applied in 29 cases using a house dust mite mixture (35.4%), 42 cases using meadow pollen (51.2%), three cases using Alternaria (3.7%) and eight cases using more than one allergen (8.9%) (Table 2).

Of all patients, 68 (82.9%) were able to state the exact name of his/her disease, while 47 (57.3%) could name the exact allergen to which he/she was sensitive. The distribution of the responses given by the patients to the survey statements is shown in Table 3. Around 15-72% of the cases were found to have knowledge of asthma, while 6-68% gave incorrect responses to the statements related to the treatment and follow-up of asthma. No relationship was identified between the given responses and the age, gender and the disease of the child.

DISCUSSION

Asthma is a chronic repetitive disease of the respiratory tract that is frequently characterized by symptoms such as cough, dyspnea and feeling of chest tightness. It is exacerbated by many conditions, such as respiratory tract infections, exercise, allergens such as dust mites, and pollens and cigarette smoke. The patient's knowledge of the clinical features of

their disease and the precautions to avoid, and treatments for exacerbations will aid in the control of asthma, and the prevention of acute exacerbations and complications [16,17].

The children's level of knowledge of their disease and the allergens to which they were sensitive, and who were met frequently, was found to be higher than their knowledge of preventive measures. Some 82% of the cases knew exactly the name of their disease, although their general level of knowledge of asthma was found to vary between 15% and 72%. Sleath BL et al. [18] reported the rate of correct answers of the patients related to their diagnosis as 21%, and the level of knowledge of the patients on preventive measures, treatment and follow-up of 1-11%.

It is essential to raise the awareness of patients about their disease and drug treatments to decrease their symptoms and the need for medication, as a means of raising their quality of life. Furthermore, collaborating with the patients and their families is a fundamental aspect of treatment, and asthma management plans prepared following this approach will increase the efficacy of the asthma pharmacotherapy [19]. In the present study, however, the patients gave incorrect responses to 6-68% of the statements about the treatment and follow-up of asthma. In a study by Al-Harbi AS et al. [13], 59.5% of patients gave correct responses to the statements. The fundamental nature of patient and family collaboration and education as a means of asthma control has been noted in many studies [19]. Raising awareness of the disease and an appropriate lifestyle can be greatly beneficial for asthma patients, being low-cost, as such information is easily accessible, thus increasing compliance. Accordingly, efforts to increasing awareness through school-based education programs, and through the web and social media, have been introduced, and many education and information programs providing instruction in drug use, emergency disease action programs and asthma lifestyle changes have been established.

Families, clinicians and school nurses should create support circles so as to ease asthma care. Complaints that asthma can interfere with daily life activities by causing school absenteeism, activity intolerance and frequent hospital and emergency service visits and thus might have negative effects on the quality of life of both the child who has the disease and his/her caregivers [19]. Clark NM et al.'s [20] study included a total of 416 children in the study group and 419 in the control group from seven different schools, all of whom had been diagnosed with asthma. The study evaluated the efficacy of school-based family education programs related to asthma and its management. After 24 months, the children who had received focused education were found to be able to better control their symptoms at day and night, and to have better disease management associated with asthma exacerbation. Similarly, Bartholomew et al. [21] in their study of 1,730 children with asthma from 60 primary schools, reported increased knowledge of the children about the disease and better emergency action plan skills. Furthermore, less absenteeism and hospital presentations were determined in the children compared to the control group; however, no change in the general disease status was observed. It is essential to ensure adequate communication between asthma patients and healthcare workers, and to provide continuity of patient education, as such education should minimize any fears or worries patients may have about their treatment and follow-up. The information provided should be suitable for the level of education and the lifestyle of the patient to ensure compliance, and continuity in education should be ensured. These issues should also be reviewed during follow-up visits with tests of the knowledge of the patient, and any weak areas should be addressed [22,23]. The present study found the knowledge of the patients about the symptoms of asthma to be better than their knowledge of the treatment and emergency management applications, and so a hospital-based education program was planned to be implemented.

Various approaches to patient education have been devised, and the use of technology has been shown to have particularly beneficial effects on patients with asthma. Web-based asthma self-management systems and social media have been demonstrated to increase public awareness, to

improve the quality of life of people with asthma, to decrease the symptoms and exacerbations of asthma, and to improve compliance, especially in adults [24].

Inadequate compliance with inhaled steroid treatments in patients with asthma results in poor clinical results and more applications to health services. The efficacy and safety of interventions aimed at increasing compliance with inhaled corticosteroids have been evaluated in many studies, and various applications have been developed for individuals with chronic disease, such as drug reminders, diet compliance reminders, and applications that support and ease the management of their diseases. One particular study reported findings that may support the self-management of chronic diseases involving cell phone messaging applications [25]. Therefore, identifying easier approaches to informing patients about the status of chronic diseases such as asthma, controlling for compliance with drug treatments and informing of results, and ensuring the continuation of the process might be considered part of the treatment in long-term follow-ups. In the present study, the knowledge of the children with asthma about the need for drug treatments, the management of exacerbations and the methods of drug use was observed to be inadequate. Education programs making use of verbal seminars and brochures were planned, although it has not yet been possible to assess their long-term effects. Furthermore, tested lifestyle interventions, including activities in support of nutrition, and those encouraging physical activity, yoga and massage, have been observed to increase the compliance of asthma patients to drug treatment [26]. In a study evaluating the awareness of the benefit of lifestyle changes in asthma management [27], just a 5-10% loss of weight in obese patients with asthma was found to improve their quality of life and asthma control, while meditation applications and breathing exercises were found to decrease stress and anxiety, and to improve the respiratory rate and muscle relaxation. Improvement was reported in FEV1 from 88% to 75% ($p < 0.001$), as well as a relief in symptoms from 10% to 72% ($p<0.01$) [28]. In the present study, the awareness of the children of the benefits of sport and environmental prevention methods was found to be high, providing correct responses to the statements in these fields at a rate of 90% (Table 3).

In conclusion, activities to raise awareness in patients and their families, and to ensure the continuation of education programs, in addition to the treatment applications, should be developed so as to decrease asthma symptoms and to support disease control.

Ethics Committee Approval: Dr. Behçet Uz Pediatrics and Pediatric Surgery and Research Hospital Clinical Research Ethics Committee approval was obtained (18.07.2019 and 2019/267-110).

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Research Article

Mean Platelet Volume/Platelet Count Ratio as a Diagnostic Marker in Children with Acute Appendicitis

Akut Apandisitli Çocuklarda Tanısal Belirteç Olarak Ortalama Trombosit Hacmi/Trombosit Sayısı Oranı

Inanc Karakoyun
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ABSTRACT

Objective: *The objective of this research was to evaluate the diagnostic value of mean platelet volume/platelet count (MPV/PC) ratio in pediatric acute appendicitis.*
Methods: *This retrospective study included a total of 310 patients, 176 in the uncomplicated appendicitis group, 80 in the complicated appendicitis group, and 54 in the nonspecific abdominal pain (NSAP) group. C-reactive protein (CRP) level, white blood cell (WBC) count, absolute neutrophil count (ANC), MPV, PC, and MPV/PC ratio were compared between the groups.*
Results: *WBC and ANC levels differed significantly between the groups (P<0.001 in all pairwise comparisons). CRP levels in the complicated appendicitis group were higher than in the NSAP and uncomplicated appendicitis groups (P<0.001 for both comparisons). There was a negative correlation between MPV and PC (r= -0.434, P<0.001). Both PC and MPV/PC ratio were able to distinguish cases of complicated appendicitis from NSAP (P=0.047 and P=0.045, respectively) and from cases of uncomplicated appendicitis (P=0.010 and P=0.045, respectively). Areas under the ROC curve for CRP, WBC, ANC, MPV, PC, and MPV/PC ratio were 0.640, 0.690, 0.727, 0.553, 0.541, and 0.546, respectively.*
Conclusion: *According to the results of our study, MPV/PC ratio can be used in addition to the conventional markers to discriminate cases of complicated appendicitis.*

Keywords: *Appendicitis, biomarkers, mean platelet volume/platelet count ratio, pediatrics*

ÖZ

Amaç: *Bu çalışmanın amacı pediatrik akut apandisitte ortalama trombosit hacmi/trombosit sayısı (MPV/PC) oranının tanısal değerini değerlendirmektir.*
Yöntem: *Bu retrospektif çalışma, komplike olmayan apandisit grubunda 176, komplike apandisit grubunda 80 ve nonspesifik karın ağrısı (NSAP) grubunda 54 olmak üzere toplam 310 hastayı içermektedir. C-reaktif protein (CRP) düzeyi, beyaz kan hücresi sayısı (WBC), mutlak nötrofil sayısı (ANC), MPV, PC ve MPV/PC oranı gruplar arasında karşılaştırıldı.*
Bulgular: *WBC ve ANC düzeyleri gruplar arasında anlamlı farklılık gösterdi (tüm ikili karşılaştırmalarda P<0.001). Komplike apandisit grubunda CRP düzeyleri NSAP ve komplike olmayan apandisit gruplarından daha yüksekti (her iki karşılaştırma için de P <0.001). MPV ve PC arasında negatif bir korelasyon vardı (r=-0.434, P<0.001). Hem PC hem de MPV/PC oranı, komplike apandisit vakalarını NSAP (sırasıyla P=0.047 ve P=0.045) ve komplike olmayan apandisit vakalarından (sırasıyla P=0.010 ve P=0.045) ayırt edebildi. CRP, WBC, ANC, MPV, PC ve MPV/PC oranı için ROC eğrisi altındaki alanlar, sırasıyla 0.640, 0.690, 0.727, 0.553, 0.541 ve 0.546'dır.*
Sonuç: *Çalışmamızın sonuçlarına göre, komplike apandisit vakalarını ayırt etmek için geleneksel belirteçlere ek olarak MPV/PC oranı kullanılabilir.*

Anahtar kelimeler: *Apandisit, biyobelirteçler, ortalama trombosit hacmi/trombosit sayısı oranı, pediatri*

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INTRODUCTION

Acute abdominal pain in children is a common cause of emergency department (ED) admissions and represents a challenge for physicians who conduct the initial evaluation [1]. Although acute abdominal pain is usually a self-limiting process, in a small proportion of cases (1-8%) it is associated with a serious condition that requires surgery, such as appendicitis [1,2].

Acute appendicitis is the most common abdominal surgical emergency in the pediatric population [3] and an early diagnosis can reduce the incidence of perforation, postoperative complications, mortality, length of hospital stay, and costs [4]. However, early diagnosis of appendicitis is a challenging issue even today, because the clinical signs and symptoms presented in the ED may be nonspecific and misleading, particularly in younger children [5].

Although ultrasound and computed tomography (CT) have improved diagnostic accuracy in acute appendicitis, these imaging modalities have some disadvantages [6]. CT has over 95% sensitivity and specificity in the diagnosis of acute appendicitis, but also requires exposing children to ionizing radiation [7]. Abdominal ultrasound also offers good specificity and specificity (88% and 94%, respectively) without the negative effects of radiation, but its diagnostic value is operator-dependent [8].

In recent years, biomarkers have been used in addition to imaging techniques as noninvasive tools for diagnosing disease and predicting prognosis [9]. White blood cell (WBC) count, absolute neutrophil count (ANC), and C-reactive protein (CRP) are traditional parameters routinely use either alone or in combination by physicians in ED [10]. However, the diagnostic sensitivity and specificity values reported for these markers are highly variable, raising questions regarding their ability to enable physicians to accurately and reliably rule out or confirm the diagnosis of acute appendicitis [11]. Although leukocytosis is present in 70% of patients with acute appendicitis, the presence of leukocytosis in other acute abdominal complaints decreases the sensitivity and specificity of this test [12]. In addition, large fluctuations in CRP sensitivity (40-99%) and specificity (27-90%) led researchers to seek new biomarkers [13].

Platelet indices including mean platelet volume (MPV) and platelet count (PC) are routinely reported parameters in complete blood count (CBC) analysis and have been investigated for the diagnosis of acute appendicitis, but the results are variable [14-17]. It has been suggested that there is an inverse relationship between these two parameters and that their ratio, rather than their individual values, is superior in terms of diagnostic potential [18].

Our aim in the present study was to evaluate the utility of MPV/PC ratio in pediatric patients presenting to the ED with suspected acute appendicitis. To the best of our knowledge, MPV/PC ratio has not been evaluated previously in suspected acute appendicitis in the pediatric population.

MATERIAL and METHOD

Subjects and study design

This retrospective study was conducted in patients who presented to the ED of a tertiary hospital between January 1, 2016 and January 1, 2019 with complaints of abdominal pain. A total of 310 patients under 18 years of age were included in the study. Three groups were formed: nonspecific abdominal pain (NSAP), uncomplicated appendicitis, and complicated appendicitis. The NSAP group consisted of patients with nonspecific abdominal pain who were observed for 24 to 48 hours and discharged (n=54). The NSAP patients were contacted by phone after discharge to ensure that appendicitis did not develop. Patients with obvious symptoms of urinary tract infection, gastroenteritis, and respiratory system infections were excluded from the study. Patients who underwent appendectomy and were confirmed as having focal, suppurative, or phlegmonous appendicitis in the pathology report were included in the uncomplicated appendicitis group (n=176). Those whose appendectomy pathology report indicated gangrenous or perforated appendicitis were included in the complicated appendicitis group (n=80). Patients with negative appendectomy and other surgical pathologies were excluded from the uncomplicated and complicated appendicitis groups.

Analyzed laboratory parameters

CRP, WBC, ANC, MPV, and PC results were obtained from the laboratory information system, and MPV/PC ratio was calculated from MPV and PC values. Analysis of WBC, ANC, MPV, and PC, which are CBC subparameters, were

performed by electrical impedance method (Coulter LH 780, Beckman Coulter Inc., CA, USA); CRP was analyzed turbidimetrically by an automated procedure (AU640 autoanalyzer, Beckman Coulter Inc., CA, USA). Total coefficient of variation was <3.3 for CBC parameters, and <5 for CRP.

Statistical analysis

SPSS version 22.0 (SPSS Inc., Chicago, USA) software package was used for statistical analyses. Results of the Shapiro-Wilk test indicated that the data were not normally distributed, and the nonparametric Mann–Whitney U test was used for statistical analyses. Chi-square test was used for sex-based comparison of the groups. Results were given as median (interquartile range). Cut-off, sensitivity, specificity, and area under the curve (AUC) values of the analyzed markers were determined by receiver operating characteristic (ROC) curve analysis. Correlations between the laboratory markers were identified with Spearman rank correlation test. Results with P<0.05 were considered statistically significant.

Ethical considerations

The study was approved by the local ethics committee (Resolution Number 2019/8-11, dated May 08, 2019).

RESULTS

The demographic characteristics and laboratory findings of the patients with acute appendicitis and those

Table 1. The demographic characteristics and laboratory findings of patients with acute appendicitis and those with nonspecific abdominal pain.

Parameter	NSAP (n=54)	Uncomplicated appendicitis (n=176)	Complicated appendicitis (n=80)	P
Age, years	13.0 (9.0-15.0)	11.0 (8.0-14.0)	11.0 (8.0-14.0)	0.131* 0.156† 0.738‡
Gender Female, n(%)	28 (51.9%)	59 (33.5%)	29 (36.3%)	0.050
WBC (x10^3/µL)	11.6 (8.6-16.8)	14.9 (12.4-18.8)	17.9 (14.7-21.5)	<0.001* <0.001† <0.001‡
ANC (x10^3/µL)	7.4 (5.2-12.5)	12.3 (9.1-15.7)	15.2 (12.6-18.3)	<0.001* <0.001† <0.001‡
CRP (mg/L)	10.1 (1.3-29.9)	12.0 (4.0-33.1)	85.8 (35.4-140.0)	0.274* <0.001† <0.001‡
MPV (fL)	8.0 (7.5-8.7)	7.9 (7.4-8.5)	7.9 (7.2-8.7)	0.587* 0.315† 0.519‡
PC (x10^3/µL)	285.5 (237.5-375.0)	295.0 (251.5-343.0)	319.0 (272.8-384.3)	0.750* 0.047† 0.010‡
MPV/PC	0.0296 (0.0208-0.0363)	0.0271 (0.0222-0.0341)	0.0264 (0.0200-0.0305)	0.645* 0.045† 0.045‡

**NSAP vs. Uncomplicated appendicitis; †NSAP vs. Complicated appendicitis; ‡Uncomplicated appendicitis vs. Complicated appendicitis; Data were presented as median (25th-75th percentile); P value <0.05 was considered statistically significant; Statistically significant P values shown in bold.*

Abbr: NSAP, Nonspecific abdominal pain; n, number; WBC, White blood cell count; ANC, Absolute neutrophil count; CRP, C-reactive protein; MPV, Mean platelet volume; PC, Platelet count.

with NSAP are summarized in Table 1. There was no difference in age between the groups (NSAP vs. uncomplicated appendicitis p=0.131, NSAP vs. complicated appendicitis p=0.156, uncomplicated appendicitis vs. complicated appendicitis p=0.738). There was no difference in sex distribution between the three groups (P=0.050).

PC levels in the complicated appendicitis group were higher than in the other two groups (NSAP vs. complicated appendicitis p=0.047, uncomplicated appendicitis vs. complicated appendicitis p=0.010).

The median value of our candidate marker MPV/PC ratio was 0.0296 in the NSAP, 0.0271 in the uncomplicated appendicitis, and 0.0264 in the complicated appendicitis group. These median values were able to distinguish cases of complicated appendicitis from NSAP (p=0.045) and uncomplicated appendicitis cases (p=0.045).

WBC and ANC, markers routinely used in the diagnosis of acute appendicitis, showed significant differences in all pairwise comparisons (p<0.001). CRP levels were also higher in the complicated appendicitis group than in the other two groups (NSAP vs. complicated appendicitis P<0.001, uncomplicated appendicitis vs. complicated appendicitis p<0.001).

The diagnostic capacities of the laboratory markers were evaluated using ROC curve analysis (Table 2, Figure 1). The AUC of ANC indicated good discrimination between NSAP and acute appendicitis (AUC=0.727, p<0.001), while the AUC of WBC and CRP showed fair discrimination (AUC=0.690, P<0.001; AUC=0.640, P<0.001, respectively). AUC of MPV, PC, and MPV/PC ratio showed poor discrimination (AUC=0.553, p=0.424; AUC=0.541, p=0.391; and AUC=0.546, p=0.336, respectively) [19].

According to Spearman correlation analysis, there was a negative correlation between MPV and PC (r=-0.434, P<0.001) (Table 3).

DISCUSSION

There is an ongoing debate regarding the usefulness of laboratory tests in the diagnosis of acute appendicitis [20]. In this study, we evaluated the diagnostic value of MPV/PC ratio in children with acute appendicitis, which to the best of our knowledge is the first examination of this parameter for acute appendicitis in this age group.

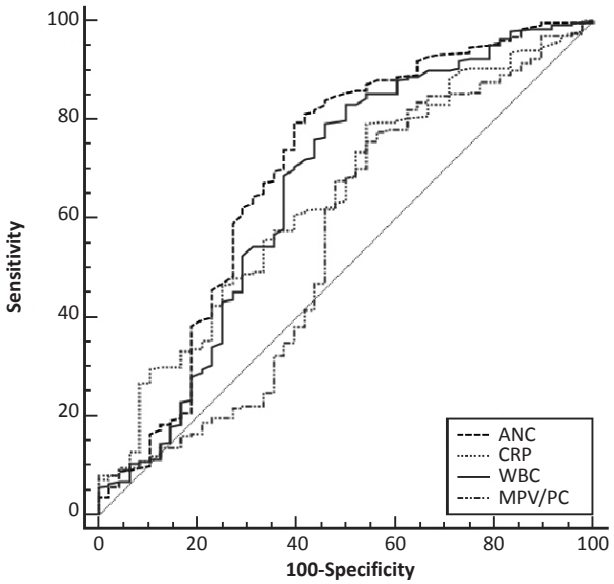

Figure 1. Receiver operating characteristic curves of markers for discrimination of patients with acute appendicitis and those with nonspecific abdominal pain.

Abbr: WBC, White blood cell; ANC, Absolute neutrophil count; CRP, C-reactive protein; MPV, Mean platelet volume; PC, Platelet count.

Table 2. Cut-off values and diagnostic performance characteristics of markers in the differential diagnosis of patients with acute appendicitis and those with nonspecific abdominal pain.

	Cut-off value	Sensitivity, (%)	95% CI	Specificity (%)	95% CI	AUC (95% CI)	P*
WBC (x10^3/µL)	> 11.9	83.6	78.5 - 87.9	55.6	41.4 - 69.1	0.690 (0.635 - 0.741)	<0.001
ANC (x10^3/µL)	> 9.5	79.3	73.8 - 84.1	64.8	50.6 - 77.3	0.727 (0.674 - 0.776)	<0.001
CRP (mg/L)	> 4.7	79.2	73.6 - 84.1	45.8	31.4 - 60.8	0.640 (0.582 - 0.694)	<0.001
MPV (fL)	≤ 7.1	15.6	11.4 - 20.7	94.4	84.6 - 98.8	0.553 (0.476 - 0.589)	0.424
PC (x10^3/µL)	> 257	74.2	68.4 - 79.5	44.4	30.9 - 58.6	0.541 (0.484 - 0.598)	0.391
MPV/PC	≤ 0.0320	73.8	68.0 - 79.1	44.4	30.9 - 58.6	0.546 (0.489 - 0.603)	0.336

**Significance of AUC; P value <0.05 was considered statistically significant; Statistically significant P values shown in bold.*
Abbr: CI, Confidence interval; WBC, White blood cell; ANC, Absolute neutrophil count; CRP, C-reactive protein; MPV, Mean platelet volume; PC, Platelet count; AUC, Area under curve.

Table 3. Correlations of markers that evaluated in the diagnosis of acute appendicitis.

Markers		ANC	CRP	MPV	PC	MPV/PC
WBC	r	0.948	0.614	- 0.160	0.284	- 0.273
	P	<0.001	<0.001	<0.001	0.496	<0.001
ANC	r		0.643	- 0.102	0.217	- 0.201
	P		<0.001	0.023	<0.001	<0.001
CRP	r			- 0.155	0.080	- 0.104
	P			0.001	0.098	0.032
MPV	r				- 0.434	0.702
	P				<0.001	<0.001
PC	r					- 0.937
	P					<0.001

P value <0.05 was considered statistically significant; Statistically significant P values shown in bold.
Abbr: WBC, White blood cell count; ANC, Absolute neutrophil count; CRP, C-reactive protein; MPV, Mean platelet volume; PC, Platelet count; r, Correlation coefficient.

MPV and PC are among the 18 to 22 subparameters determined in CBC analysis, depending on the analyzer used. The utility of MPV/PC ratio has been investigated in many diseases including hepatocellular carcinoma, lung cancer, obstructive sleep apnea syndrome, and acute ischemic stroke [21-24]. The interest in platelets and related indices is based primarily on growing evidence of their key role in inflammation. Platelets have been shown to produce and store large amounts of inflammatory mediators, communicate with and activate different cells, and are themselves activated by various proinflammatory mediators via surface receptors [25]. In our study, the higher platelet counts in patients with complicated appendicitis compared to NSAP support the role of platelets in the inflammatory process. Another finding of our study was that the group with the most severe inflammation had the highest CRP and PC levels.

MPV, a measure of platelet size, is one of the most widely used markers of platelet function and is believed to reflect the inflammatory burden in various diseases [26]. Different mechanisms have been proposed to explain the relationship between MPV and the inflammatory process. Interleukin (IL)-6 is a well-known acute phase reactant inducer whose concentration correlates with CRP and degree of inflammation, and higher IL-6 levels have been demonstrated in acute appendicitis [27,28]. It has been hypothesized that conditions associated with high inflammatory marker activity may also decrease MPV values, and thus decreased MPV may indicate the intensity of the inflammatory process. Overproduction of proinflammatory cytokines and acute phase reactants may suppress platelet size by inhibiting megakaryopoiesis, resulting in the release of small platelets from the bone marrow [28]. In the present study, we observed lower MPV levels in the appendicitis groups compared to the NSAP group, but the differences were not statistically significant.

There is only one study in the literature evaluating MPV/PC ratio in acute appendicitis, which was conducted in adults. Biricik et al. detected no difference in MPV/PC ratio between healthy controls and acute appendicitis cases [29]. In contrast to their findings, we determined in the present study that changes in MPV and especially PC ultimately affected the MPV/PC ratio in complicated appendicitis. Although the decrease in MPV was not significant in patients with complicated appendicitis, this change was found to affect the significance of MPV/PC ratio, albeit to a limited degree. According to our results, MPV/PC ratio at a cut-off value of 0.0320 was able to distinguish cases of acute appendicitis from NSAP with 73.8% sensitivity and 44.4% specificity. We also noted an inverse correlation between MPV and PC.

Leukocyte count is commonly used in the diagnosis of acute appendicitis, with high leukocyte count recognized as helpful in the early diagnosis of acute appendicitis. On the other hand, ANC is usually associated with bacterial infections. In previous studies, sensitivity and specificity of WBC were reported as 67-97.8% and 31.9-90.8%, and those of ANC as 68.6-98.9% and 33.1-91%, respectively. In our study, WBC and ANC levels were high in the acute appendicitis group and consistent with the literature [14].

CRP is another frequently used test to guide clinical evaluation of acute appendicitis. It is an acute phase reactant that is synthesized in the liver and released into the bloodstream in response to tissue damage. CRP measurement is practical, fast, and cost-effective. Previous studies in the literature have reported a sensitivity of 40-94% and specificity of 38-87% [30]. In our study, CRP was elevated in patients with complicated appendicitis and its diagnostic sensitivity and specificity values were consistent with the literature. Despite low sensitivity and specificity, one of the main findings of our study is that the traditional

markers (CRP, WBC, and ANC) had better AUC and P values, thus remaining the first choice to distinguish complicated appendicitis cases from NSAP.

There are several limitations of this study. First, there were fewer cases of NSAP and complicated appendicitis than uncomplicated appendicitis during the study period. We were able to contact only a small number of patients after discharge due to reasons such as having an incorrect phone number on file or getting no response, which reduced the size of our NSAP group. Second, similar to other retrospective studies, we cannot completely rule out the impact of selection bias.

In conclusion, early diagnosis of acute appendicitis in children is important to reduce morbidity and mortality rates. According to the results of our study, MPV/PC ratio can be used in addition to traditional markers as a guide for ED physicians to discriminate cases of complicated appendicitis.

Ethics Committee Approval: Approval was obtained from the ethics committee of Tepecik Training and Research Hospital with decision number 2019/8-11.

Conflict of Interest: The Authors declare that there is no conflict of interest.

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Informed Consent: Since our study was retrospective, informed consent was not obtained from the patients.

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Research Article

Evaluation of Inhaled Nitric Oxide Use in Patients with Pediatric Acute Respiratory Distress Syndrome

Pediatrik Akut Respiratuar Distres Sendromu Tanılı Hastalarda İnhale Nitrik Oksit Kullanımının Değerlendirilmesi

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ABSTRACT

Objective: *Nitric oxide therapy is not routinely used in the treatment of pediatric acute respiratory distress syndrome (PARDS), but it is recommended to be used as an adjunctive therapy in some selected cases. In our study, we aimed to discuss patients with PARDS who were treated with inhaled nitric oxide (iNO) therapy.*
Methods: *The data of patients who were hospitalized in the pediatric intensive care unit with a diagnosis of PARDS and received iNO treatment between January 2016 and January 2018 were retrospectively analyzed. Age, gender, length of stay, mortality, number of days on mechanical ventilation, use of vasoactive drugs, mortality scores, lactate levels, OI (oxygenation index), PaO_2/FiO_2, methemoglobin levels, iNO administration time, echocardiographic findings and underlying primary diseases were recorded.*
Results: *It was determined that 9 patients who were followed up with the diagnosis of PARDS were given iNO treatment. Except for one patient, they were diagnosed with pneumonia developing on the basis of chronic disease and PARDS secondary to septic shock. Five patients died while receiving iNO therapy. Seven patients were ventilated with iNO in addition to conventional mechanical ventilation methods. Two patients who died were ventilated with HFOV (high frequency oscillatory ventilation). In 3 of 9 patients, inhaled nitric oxide treatment was successful.*
Conclusion: *Although inhaled nitric oxide treatment is a known treatment used in different diseases, the level of its effect in PARDS patients continues to be investigated. We think that this treatment can be beneficial when applied in selected patients and experienced centers.*

Keywords: *Pediatric acute respiratory distress syndrome, inhale nitric oxide, pediatric intensive care unit*

ÖZ

Amaç: *İnhale nitrik oksit (iNO) tedavisi, pediatrik akut respiratuar distres sendromu (PARDS) tedavisinde rutin kullanılmamakla beraber bazı seçilmiş vakalarda ek tedavi yöntemi olarak kullanılması önerilen bir tedavidir. Çalışmamızda inhale nitrik oksit tedavisi alan PARDS tanılı hastaları tartışmayı amaçladık.*
Yöntem: *Ocak 2016 - Ocak 2018 tarihleri arasında çocuk yoğun bakım ünitesinde yatan PARDS tanısı İNO tedavisi alan ve alan hastaların dosyaları geriye dönük olarak incelendi. Yaş, cinsiyet, kalış süresi, mortalite, mekanik ventilasyonda geçen gün sayısı, vazoaktif ilaç kullanımı, mortalite skorları, laktat seviyeleri, OI (oksijenasyon indeksi), PaO_2/FiO_2 oranı, methemoglobin düzeyleri, iNO uygulama süresi, ekokardiyografik bulgular ve altta yatan birincil hastalıklar kaydedildi.*
Bulgular: *PARDS tanısıyla izlenen 9 hastaya iNO tedavisi uygulandığı saptandı. Bir hasta hariç diğerleri kronik hastalık zemininde gelişen pnömoni ve septik şoka sekonder PARDS tanısı almışlardı. Beş hasta, iNO tedavisi alırken eksitus gelişti. Yedi hasta konvansiyonel mekanik ventilasyon yöntemlerine ek olarak iNO ile solutuldu. Eksitus olan 2 hasta HFOV (high frequency oscillatory ventilation) ile solutuldu. 9 hastanın 3'ünde inhale nitrik oksit tedavisi başarılı olmuştu.*
Sonuç: *İnhale nitrik oksit tedavisi farklı hastalıklarda kullanılan bilinen bir tedavi olmasına rağmen, PARDS hastalarındaki etki düzeyi araştırılmaya devam etmektedir. Seçilmiş hastalarda ve deneyimli merkezlerde uygulandığında bu tedavinin faydalı olabileceğini düşünüyoruz.*

Anahtar kelimeler: *Pediatrik akut respiratuar distres sendromu, inhale nitrik oksit, pediatrik yoğun bakım ünitesi*

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INTRODUCTION

Pediatric acute respiratory distress syndrome (PARDS) was presented at PALICC (Pediatric Acute Lung Injury Consensus Conference), revised and classified in 2015 with its latest definition. PARDS is a picture that causes severe hypoxemic respiratory failure by causing pulmonary gas exchange disorder. Healthy lungs regulate fluid movement by protecting alveoli with a small amount of interstitial fluid. However, with lung damage, excess fluid accumulation begins in the interstitium and alveoli. This results in impaired gas exchange, decreased compliance, and increased pulmonary artery pressure. One of the most important features of PARDS is hypoxemia and is associated with the severity of the disease [1-3]. In pediatric patients, treatment planning is made by calculating the oxygenation index with arterial blood gas measurement [4]. Inhaled nitric oxide (iNO) is successfully applied in the treatment of PPH (persistent pulmonary hypertension), especially in newborns and is a molecule that can cause relaxation in vascular smooth muscles and consequently vasodilation [5]. It is used as a supportive agent in selected PARDS cases to benefit from vasodilation and vascular regeneration effects. Also iNO, T_h (T helper) is also known to reduce the inflammatory response by changing balance on cells. This immunomodulatory effect is also considered as the mechanism of action that can benefit patients with PARDS [6]. In this study, we wanted to share our experiences on iNO recovery therapy used in selected PARDS cases, not a routine treatment.

MATERIAL and METHOD

In the Dr. Behcet Uz Pediatric Diseases and Surgery Training and Research Hospital pediatric intensive care unit, there are 24 pieces of 3rd-stage pediatric intensive care beds, 2 pediatric intensive care specialists, 5 pediatric intensive care minor assistants, 5 pediatric assistants and 49 nurses. In our hospital, specialist training is given in both the branch of pediatric health and diseases and the fellowship of pediatric intensive care. The annual number of patient hospitalizations in our unit is around 300 patients.

The study was performed by retrospectively examining the files in our pediatric intensive care unit between 2016-2018, diagnosed with PARDS and undergone iNO treatment. The ethics committee file of our study was approved by the ethics committee unit of our hospital with the number of 2019/357.

Each patients' age, gender, duration of ICU stay (days), mortality, number of mechanical ventilator days, vasoactive drug use, mortality scores (PRISM IV, pSOFA), baseline lactate levels, baseline OI (oxygenation index), baseline PaO_2/FiO_2 (partial arterial oxygen pressure/fraction of inspired oxygen) rate, methemoglobin levels measured at follow-up, duration of iNO administration, echocardiographic findings, underlying diseases were recorded.

Pediatric ARDS diagnostic criteria are determined as; findings of new involvement in the lung parenchyma with lung injury developing in the last 7 days, the rate of arterial oxygen saturation (SpO_2) to the fraction of inspired oxygen (FiO_2) being as ≤264 and the ratio of PaO_2 to FiO_2 being as ≤300 under the support of non-invasive and invasive mechanic ventilation; provided that the are not related to the perinatal period. In addition to these criteria, new cases of lung parenchyma involvement that cannot be explained by these diseases are among the diagnostic criteria in patients with cyanotic congenital heart diseases, chronic lung diseases and left ventricular dysfunction. After diagnosis of pediatric ARDS, oxygenation index and PaO_2/FiO_2 measurements are calculated for severity grading and decision of treatment modalities. The oxygenation index (FiO_2×mean airway pressure×100/PaO_2) is calculated by the formula [4]. All patients in our study were diagnosed with PARDS according to these criteria.

Inhaled nitric oxide treatment was initiated in cases where adequate oxygenation could not be achieved with conventional mechanical ventilation strategies (cases with PaO_2/FiO_2≤110 and OI> 16) [4,7]. Inhaled nitric oxide treatment was applied intratracheally and continuously during mechanical

ventilation with NOxBOX (Kent, England) brand device. Treatment was initiated at a dose of 5 ppm. The dose was increased to maximum 25 ppm according to clinical response [8]. Following the initiation of inhaled nitric oxide treatment and ensuring adequate oxygenation, adjustments were made to FiO_2, PEEP and volume targets in conventional mechanical ventilation settings. In patients who received inhaled nitric oxide treatment for at least 24 hours, and in cases where it did not benefit before exitus, or in case of improvement, the iNO level was gradually decreased down to 5 ppm and cut according to the patient's MV settings and OI (Figure 1). Although the daily methemoglobin levels of patients receiving inhaled nitric oxide therapy should be monitored, we also evaluated methemoglobinemia along with oxygenation parameters by taking blood gases 4 times with an interval of 6 hours depending on the clinical status of our patients. Values lower than 5% were considered appropiate for methemoglobin [8]. All of our patients were evaluated with echocardiography by cardiology department before iNO treatment for the risk of developing pulmonary hypertension secondary to lung injury. However, in our study, patients' other accompanying heart failure, other therapies used for heart failure and other pulmonary hypertension treatment methods were not evaluated.

RESULTS

It was found that 9 patients who were monitored with the diagnosis of PARDS in pediatric intensive care were given iNO treatment. Demographic data, hospitalization, mortality scores and blood lactate-methemoglobin levels of the patients are shown in Table 1. Five of the patients were male and four were female. Their ages ranged from 2 months to 204 months. Except for one patient, the others were diagnosed with PARDS secondary to septic shock and pneumonia developing on the basis of chronic disease. In one patient, there was no known chronic disease and it was followed up in our clinic primarily with the diagnosis of PARDS secondary to acute community-acquired lower respiratory tract infection.

Mechanical ventilator variables, oxygenation parameters and measurements (before iNO) of the patients are given in Table 2.

Duration of stay in the mechanical ventilator, vasoactive drug use, diagnosis of pulmonary hypertension (PH) by echocardiography, duration of iNO treatment and prognosis are shown in Table 3 for all patients.

Methemoglobin level was measured at a maximum of 1.8%. The number of patients diagnosed PH (pulmonary hypertension) by echocardiography was 3 (cases 4,8,9). Patients with a pulmonary gradient of 25 mmHg and above measured from the

Table 1. Demographic data, mortality scores and blood lactate-metHB levels of cases.

Patient No	Age (months)	Gender	Diagnosis	Length of stay (day)	PRISM IV (Score/percent)	pSOFA	Blood lactate level (mmol/L)	MetHB (%)
1	8	Male	Severe combined immunodeficiency	56	28 (73.4)	11	2.6	1.3
2	24	Male	Neurometabolic Disease	5	22 (44.3)	9	1.5	1.8
3	6	Male	Severe combined immunodeficiency	15	26 (64.6)	12	3.5	1.8
4	48	Female	Mucopolysaccharidosis type1	78	24 (54.6)	11	1.8	1.1
5	12	Female	Acute lymphocytic leukemia	5	26 (64.6)	10	1.9	1.5
6	7	Male	No Chronic Diseases	18	17 (22)	7	3.4	1.4
7	24	Female	Metabolic disease	76	18 (25.8)	8	1.5	1.3
8	204	Female	Cellular type immune deficiency	27	24 (54.3)	10	1.4	1.7
9	2	Male	Intracranial Hemorrhage	3	20 (35.7)	10	4.5	1.2

Pediatric Risk of Mortality (Prism IV), The Pediatric Sequential Organ Failure Assessment (pSOFA), MetHB (Methemoglobin percentage).

Table 2. Mechanical ventilator parameters and measurements of patients.

	Mv mode	Mv (day)	iNO initial peak	iNO initial MAP	OI	PaO_2 / fiO_2	Additional treatment	iNO initial PEEP
1	VC-SIMV	46	38	24	28	85	HFO	14
2	VC-SIMV	5	40	24	30	80	-	13
3	PC-SIMV	10	35	22	21	103	HFO	13
4	VC-SIMV	20	36	22	18	118	-	12
5	PC-SIMV	4	42	25	35	70	-	15
6	VC-SIMV	10	32	20	22	90	-	12
7	VC-SIMV	15	37	23	26	72	-	13
8	PC-SIMV	4	38	22	20	110	-	14
9	VC-SIMV	2	36	20	33	60	-	12

VC-SIMV (Volume-controlled synchronized intermittent mandatory ventilation), PC-SIMV (Pressure-controlled synchronized intermittent mandatory ventilation), iNO (inhaled nitric oxide), OI (Oxygenation index), PaO_2 / FiO_2 (partial arterial oxygen pressure /fraction of inspired oxygen), iNO (inhaled nitric oxide), MAP (mean airway pressure).

Table 3. Duration of therapy, vasoactive drug use and prognosis.

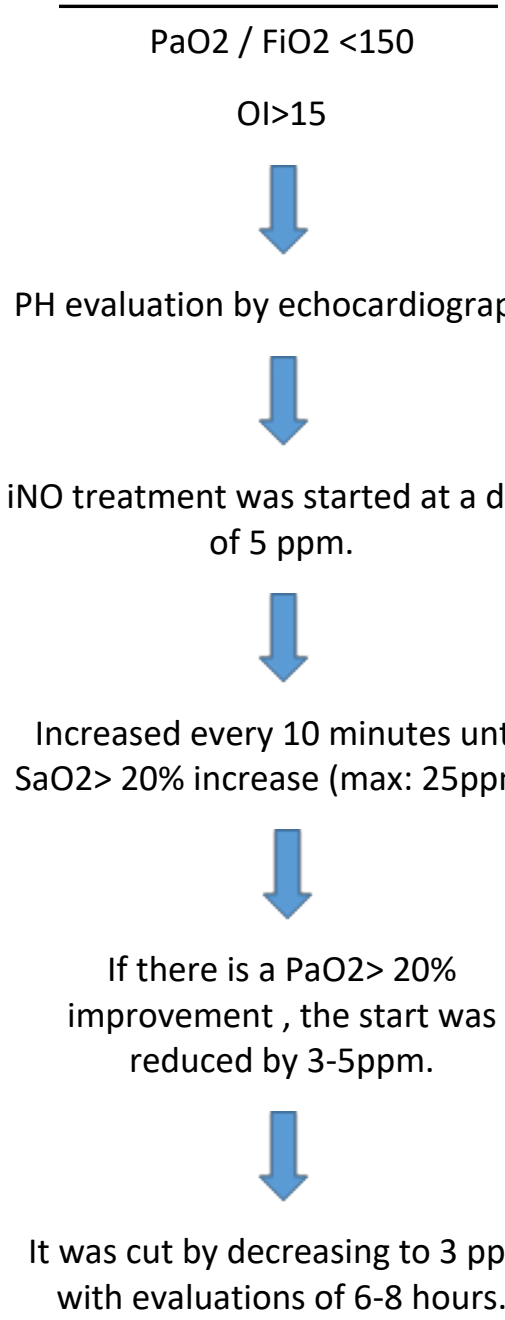
Patient No	MV period (hours)	Vasoactive drug	Echocardiographic PH diagnosis	iNO Duration (Hour)	Mortality (result)
1	1100	+	-	638	Yes
2	116	+	-	91	Yes
3	236	+	-	88	Yes
4	710	+	+	475	No
5	91	+	-	70	Yes
6	232	+	-	156	No
7	353	+	-	114	No
8	90	+	+	45	Yes
9	47	+	+	10	Yes

iNO: inhaled nitric oxide, MV: Mechanical ventilator, PH: Pulmonary hypertension.

tricuspid valve were considered meaningful for PH. Pulmonary gradient measured in other patients was calculated as normal (<25 mmHg). The EF (ejection fraction) values were minimum 58%, maximum 75%, average 65% (± SD 1.8).

The iNO treatment of our patients was started with 5 ppm and the maximum dose was up to 25 ppm. In the reduction phase, it is reduced by 5 ppm every 6-8 hours and treatment was discontinued at the 3ppm level (Figure 1). In five patients, while iNO treatment continued at a dose of 20-25 ppm, the exitus developed.

In our study, 7 patients were ventilated with conventional mechanical ventilation methods and cases number ''1'' and ''3'' were ventilated with HFOV (high frequency oscillatory ventilation) with iNO treatment. The patients were diagnosed with PARDS according to the PARDS diagnostic criteria in PALICC. In the follow-up of these patients, despite the use of 100% oxygen and high MV pressure levels, if oxygen saturation could not be increased above 85% or OI was higher than 16 and PaO_2/FiO_2 was lower or equal to 110, iNO treatment has been initiated. Except for cases 6 and 9, our patients who received inhaled nitric oxide treatment had no indication for ECMO due to their underlying diseases and current iNO treatment was continued. Patient number nine died due to additional morbidity other than PARDS and the clinical status of the patient was not suitable for ECMO due to intracranial hemorrhage during approximately 10 hours of follow-up. The other patient, who did not have any chronic disease but developed PARDS secondary to pneumonia, was successfully treated with the correct MV strategy and additionally inhaled nitric oxide treatment, and was disconnected from the ventilator and discharged. In the clinical follow-up of this patient, ECMO was considered before the start of iNO, but iNO treatment



PaO_2/FiO_2: Partial arterial oxygen pressure/fraction of inspired oxygen, PH: Pulmonary Hypertension
Ppm: One unit per million; parts per million

Figure 1. iNO treatment algorithm.

was continued due to the rapid response to conventional MV therapy administered with iNO and improvement in blood gas oxygenation levels.

It was observed that vasoactive drugs were used in all of our patients. A case of multiorgan failure developing secondary to PARDS clinic developed in cases 1, 3, 6 and 9. The inotropic need of all patients supports the clinical picture that patients were accompanied by septic shock and cardiogenic shock. In 4 of our patients (cases 1,3,5,8) who died, primary or secondary developing immune deficiencies were present and they were at risk for infection. In addition to these cases, inotropic treatment was implemented in cases 6 and 9 due to septic shock. In our patients number 2, 4 and 7, inotropic treatment was given when systolic dysfunction was observed besides the existing neurometabolic disease.

It was observed that the findings of one of the three patients who were diagnosed with PH by echocardiography and received iNO treatment regressed (case 4) and two patients resulted in exitus (cases 8, 9). Of the 6 patients who were not diagnosed with PH echocardiographically, 2 were successfully treated and discharged, and the other 4 resulted in exitus.

DISCUSSION

Inhaled nitric oxide treatment; Although it is not recommended to use routine in adult ARDS and pediatric ARDS for the last 20 years, it is an accepted treatment method for rescue from extracorporeal life support or for bridging in severe PARDS cases. When the treatment options of our patients were evaluated, it was seen that inhaled nitric oxide treatment could be an important option as a savior in the PARDS developed on the basis of chronic disease. In our study, the high mortality rate was attributed to the fact that the severe baseline clinical features of the patients we lost due to their existing diseases were more severe compared to other patients.

Inhaled nitric oxide causes vasodilation by increasing cGMP (cyclic guanosine monophosphate) on pulmonary vascular smooth muscle. Pulmonary vasodilation reduces intrapulmonary shunt, improves ventilation / perfusion rate and improves oxygenation. Vasodilation effect is utilized in pulmonary hypertension [9]. One of the known side effects of inhaled nitric oxide is that it may cause coagulopathy

because it induces partial inhibition of platelet aggregation [10,11]. In our study, none of the nine patients had coagulopathy. In our case with intracranial hemorrhage, this was a condition that developed independently before the iNO treatment. In our study, iNO doses not exceeding 25 ppm may be a reason why methemoglobinemia didn't develop. In the literature, this risk has been reported to increase at doses of 40 ppm and above [12]. In addition, there is no definite information about the maximum duration of iNO treatment. In the reports for the usages of INO due to PPHN with newborns, it was stated that it was used for 14 days and it was suggested to investigate the causes of alveolar capillary dysplasia in longer periods [13]. In patients 1, 4, and 6 of our patients, iNO treatment was continued for more than 7 days, as we considered the pathogenesis of PARDS, apart from its benefit for PH, and we saw an improvement in oxygenation. In meta-analyzes from adult studies, it has been reported that iNO treatment provides improvement in oxygenation in the first 24 hours (PaO_2/FiO_2), while in some studies this period could be extended up to 96 hours [14,15].

Epidemiologically evaluated, studies show that ARDS is less common in children than adults, compared with pediatric ARDS, high mortality may be due to higher incidence of multiple organ failure in adults, whereas in children, respiratory failure due to lung pathology is observed rather than multiple organ failure. It may be thought that lung selective treatment may provide more survival advantages in children than adults [9,16,17].

Studies on recovery treatments for pediatric acute respiratory distress syndrome are also ongoing. Despite published inadequate meta-analysis, it has been reported that combinations of HFOV, prone position treatments and iNO use may be more effective than monotherapy [18]. In our patients, prone positions were applied in combination with iNO in others (due to the risk and difficulty in positioning) except in cases number 8 and 9. A daily prone position duration of 10-12 hours was targeted and a change of position was applied every 4-6 hours.

In a meta-analysis in adults, 12 studies were examined and the effect of nitric oxide on ARDS was investigated in 1237 patients in total. As a result, it was concluded that routine use in acute lung injury (ALI) and acute respiratory distress syndrome does not have a positive effect on mortality. It is stated in the same meta-analysis that there may be some factors that can cause this situation. The first of these factors is that lung damage is not the only reason for the deterioration in oxygenation, and additional morbidity could be a contributing agent as well, the second, cause of mortality of patients is multiple organ failure rather than refractory hypoxemia and the third factor is that the MV strategies applied during iNO treatment damaged the lung and the effects of iNO treatment could be overwhelmed by the lung damage [19]. The development of multiple organ failure also increases mortality in patients with pediatric acute respiratory distress syndrome. Causes of mortality of the PARDS patients who use inhaled nitric oxide can also be examined separately and the level of primary effects of hypoxemia on mortality should be investigated. In addition to the implementation of lung-specific treatments, treatment of the underlying disease is also required. As one of the reasons for not benefiting from inhaled nitric oxide treatment, it should be considered that there may be lung damage due to recurrent hospitalization and mechanical ventilation in children with chronic disease.

In PARDS patients with pulmonary hypertension and right ventricular dysfunction, iNO therapy should be considered as a bridge or rescue therapy. Depending on the patient's clinical condition and response, it can be predicted that this treatment before ECMO may benefit mortality, considering that it can improve hypoxia in a short time.

As a result; As said in the pediatric acute lung injury consensus conference (PALICC) recommendations, not as a routine, iNO was used only in selected PARDS cases that we monitored in our clinic. In the development of PARDS treatments in children, every clinic should share the treatment preferences they have applied and experienced in line with international guidelines and treatment modalities should be strengthened. We think that

more data should be collected in order to better understand the issue of which patients can benefit in the pediatric age group and the role of iNO.

Ethics Committee Approval: S.B.Ü İzmir Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee approval was obtained (19.12.2019/17-08).

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Research Article

Serum 25-Hydroxy-Vitamin D and Vitamin B12 Levels in Childhood Alopesia Areata

Selcen Kundak
Ayşe Kutlu

Alopesi Areatalı Çocuklarda Serum Vitamin D ve Vitamin B12 Düzeyleri

ABSTRACT

Objective: *Alopecia areata (AA); is a sudden onset, non-scaring hair loss. Twenty percent of cases are children.Although it is thought to be related to genetic predisposition, inflammation, immunological processes or psychological triggers, its pathophysiology is still not fully understood. This study was planned to investigate the levels of serum 25-hydroxy vitamin D, vitamin B12, thyroid-stimulating hormone (TSH) and free T4 FT4) in children with AA and compare the results with age-matched healthy individuals.*
Methods: *A retrospective medical record review was carried out in an outpatient dermatology clinic in a tertiary medical center between January 1,2013 and December 31, 2017. The study included 520 patients (ages 0-18 years) who received a clinical diagnosis of AA.106 patients with AA met the inclusion criteria. Patients in the control group (n=106) were selected among children aged 0-18 years without any medical and/or psychiatric diagnosis. Both past medical and family medical history were also noted. Results of laboratory tests including vitamin D, vitamin B12, TSH, FT4, and thyroid auto-antibodies were noted.*
Results: *There was no significant difference between the patient and control groups in terms of mean age. Mean age of onset was 8.0 years. The number of boys and girls in both the patient and control groups were 55 and 51. Serum levels of FT4 and TSH in patients with AA were significantly higher than the control group. Both vitamin D and vitamin B12 levels of the patients with AA were significantly lower than the control group.*
Conclusion: *Although its role in etiopathogenesis is not understood, the importance of monitoring both vitamins and thyroid functions in childhood AA cases is obvious.*

Keywords: *Alopecia areata, Vitamin D, Vitamin B12, TSH, FT4*

ÖZ

Amaç: *Alopesi areata (AA); ani başlangıçlı, skar bırakmayan saç dökülmesidir. Olguların %20'si çocuktur. Genetik yatkınlık, inflamasyon, immünolojik süreçler veya psikolojik tetikleyiciler ile ilişkili olduğu düşünülse de, patofizyolojisi hala tam olarak anlaşılamamıştır. Bu çalışma; alopesi areatalı çocuklarda vitamin D, vitamin B12, tiroid stimulan hormon (TSH) ve serbest T4 (fT4) düzeylerini araştırmak ve sonuçları aynı yaş grubundaki sağlıklı bireylerle karşılaştırmak için planlandı.*
Yöntem: *1 Ocak 2013 ve 31 Aralık 2017 tarihleri arasında üçüncü basamak sağlık merkezinde dermatoloji kliniğine ayaktan başvuran hastalarda tek merkezli retrospektif tıbbi kayıt incelemesi yapıldı. Çalışmaya klinik tanısı alopesi areata (AA olan 520 hasta (0-18 yaş) çalışmaya alındı. AA'lı 106 hasta dahil edilme kriterlerini karşıladı. Kontrol grubundaki hastalar(n=106) herhangi bir tıbbi ve/veya psikiyatrik tanısı olmayan 0-18 yaş arası çocuklar arasından seçildi. Hem tıbbi geçmişleri hem de aile tıbbi geçmişleri kaydedildi. 25 hidroksi-D vitamini, B12 vitamini, TSH, FT4 ve tiroid oto-antikorlarını içeren laboratuvar testlerinin sonuçları kaydedildi.*
Bulgular: *Hasta ve kontrol grubu arasında ortalama yaş açısından anlamlı fark yoktu. Ortalama başlangıç yaşı 8 idi. Hem hasta hem de kontrol grubundaki kız ve erkeklerin sayısı 55 ve 51'dir. AA hastalarında serum FT4 ve TSH düzeyleri kontrol grubuna göre anlamlı olarak yüksek bulundu. AA'lı hastaların hem D vitamini hem de B12 vitamini düzeyleri kontrol grubundan anlamlı olarak düşüktü.*
Sonuç: *Etyopatogenezdeki rolü henüz anlaşılmamış olsa da, çocukluk çağı AA vakalarında hem D hem de B12 vitaminlerini ve tiroid fonksiyonlarını izlemek önemlidir.*

Anahtar kelimeler: *Alopesi areata, Vitamin D, Vitamin B12, TSH, FT4*

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INTRODUCTION

Alopecia areata (AA) is a tissue-specific autoimmune disease. It constitutes 0.7% - 3.8% of all dermatoses encountered in dermatology practice. Its estimated lifetime risk of occurrence ranges between 1.7% -2% [1,2]. AA is mainly a T-cell mediated autoimmune disease of hair follicles. Circulating macrophages and Langerhans cells may also target hair follicles [3,4]. Accumulation of CD4 + T cells around the hair follicles supports the autoimmune origin of the disease. Abnormal expression levels of HLA I and II and its coexistence with other dermatoses are findings that reinforce autoimmune etiology of AA [5,6].

Apart from autoimmunity, many possible etiologic factors have been suggested for AA. High rates of familial transmission of AA suggest a genetic background. Indeed, at least one first-degree relative of 25% of the children with AA has been reported in the literature [4]. Vitamins and thyroid hormones are among the other markers investigated as possible etiological factors of AA. Due to their fundamental role in innate and acquired immunity, vitamin D, vitamin B12 and thyroid hormones have been investigated in many autoimmune and inflammatory diseases including AA. The 25-hydroxy vitamin D acts by binding to its receptors in the cell nuclei. The presence of vitamin D receptor in hair follicles, dermal papilla, and keratinocytes revealed the possible relationship between vitamin D levels and hair growth [7,8]. Although not as much as vitamin D, cobalamin (vitamin B12) is also involved in the development of hair follicles. As a coenzyme, vitamin B12 contributes to nucleic acid production in the proliferative phase of hair follicles [9]. Similarly, the role of thyroid hormones in hair stem cell development and hair cycle has suggested that T3 and T4 levels may be important in the etiopathogenesis of AA [10].

In order to reveal the possible relationship between serum levels of vitamins, thyroid hormones and AA, many studies have been conducted in adult individuals [11,12]. Nevertheless, there are few studies investigating the relationship between AA and these parameters in pediatric cases. In this respect, our study has a critical importance. Therefore, the current study was planned to investigate the serum levels of 25-hydroxy vitamin D, vitamin B12, TSH, and FT4 in children with AA and age-matched healthy controls.

MATERIALS and METHODS

We retrospectively reviewed the medical records of 520 patients diagnosed with AA who were followed up at the dermatology outpatient clinic of the University of Health Sciences Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, between January 1, 2013 and December 31, 2017. Out of 520 patients, 106 patients met the inclusion criteria. Records of 106 patients diagnosed with AA between the ages of 0-18 in our dermatology outpatient clinic were included in the study. In order to increase the homogeneity of the study group and to exclude factors that may affect the results, very strict inclusion criteria were applied. The main inclusion criterion was the absence of any psychiatric problem. For this reason, all children diagnosed with AA were subjected to psychiatric evaluation. In the child psychiatry consultation, those who did not have any psychiatric disease or a psychogenic trigger before the onset of the disease were included in the study. Other criteria for inclusion in the study were as follows: (i) alopecia areata should be the first episode, (ii) the lesion should involve less than 25% of the scalp. All lesions were on the scalp and Severity of Alopecia Tool (SALT) score was used to evaluate disease severity according to the extent of hair loss (S0: no hair loss; S1: <25%; S2: 25%-49%; S3: 50%-74%; S4: 75%-99%; and S5: 100% scalp hair loss), (iii) disease duration < 1 year, (iv) and lack of any additional skin disease and history of family skin disease such as alopecia areata, vitiligo, or psoriasis, etc. The patients with abnormal thyroid function test results or anti-T or anti-M antibody levels in the AA or control groups were excluded from the study.

Patients in the control group were selected among children aged 0-18 years without any medical and/or psychiatric diagnosis. The number and gender distribution of the patients in the control group were similar to those of the patient group. The data

Table 1. Serum levels of vitamin D, vitamin B12 and thyroid hormones in cases with AA and controls.

Parameters	SAMPLING AA/Control	AA Median (min-max)	CONTROL Median (min-max)	z	p
Age (years)	106/106	8.03 (1.3-17.3)	8.0 (3.08-16.16)	-0.703	0.482
FT4 (ng/dL)	103/77	1.09 (0.06-1.39)	1.06 (0.78-1.42)	-2.140	0.032
TSH (mIU/L)	103/77	1.99 (0.51-5.61)	1.56 (0.63-3.97)	-2.242	0.025
D vit (µg/L)	106/106	20.8 (5.9-42.3)	25.0 (15.3-48.2)	-4.941	0.000
B12 vit (ng/L)	103/72	364 (142-937)	429 (207-983)	-2.984	0.003

collection was approved by the local ethics committee (University of Health Sciences Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital Local Ethics Committee/374). The data on biochemical and hormonal tests were obtained from the medical records. Past laboratory records were examined and serum levels of FT4, TSH, vitamins D and B12 were determined. For homogenity in terms of vitamin D levels the results obtained during summer period in the patient and control groups were evaluated. Concentrations of 25-hydroxy vitamin D (lower limit; 15 µg/L), vitamin B12 (lower limit; 187 ng/L), TSH (lower limit; 0.54 mIU/L) and FT4 (lower limit; 0.7 ng/dL) were determined using electro-chemiluminescence immunoassay (ECLIA) method.

Statistical analysis

Statistical analyses were performed by using SPSS 20.0 software (SPSS Inc. Chicago, IL, USA). Descriptive statistics were used to define demographic and clinical variables of all participants. Categorical variables were compared with chi-square test. The normality of the data distribution was checked with the Kolmogorov-Smirnov test. Since the distribution of the sample group was not normal, Mann-Whitney U test was performed in binary comparisons. The $p<0.05$ was considered as statistically significant.

RESULTS

Gender distribution was equal in both patient and control groups. Both the patient, and the control groups consisted of 55 boys, and 51 girls There was no significant difference between the patient and control groups in terms of mean age. Median age of AA patients was 8.0 years. Although the cases with normal TFT results in the patient and control groups were included in the study, serum levels of FT4 and TSH in patients with AA were significantly higher than the control group. Both vitamin D and vitamin B12 levels of the patients with AA were significantly lower than the control group (Table 1).

Lower limits of reference values of our laboratory were 187 ng/L for vitamin B12, and 15 µg/L for vitamin D (patients with available summer period measurements were included in the study). The patient and the control groups were compared in terms of vitamin B12 and vitamin D deficiencies. In the AA group 7 (7/103) patients had vitamin B12 levels below 187 ng/L , while vitamin B12 deficiency was not detected in the healthy group (0/72). The number of patients with vitamin B12 deficiency in the AA group was significantly higher than the control group (χ^2: 5.097 p=0.024). When the study participants were grouped according to their vitamin B 12 levels, 30 patients (30/103) in the AA,and 7 (7/72) patients in the control group had vitamin B12 levels below 300 ng/L. As a result, the number of patients with vitamin B12 levels below 300 in the AA group was significantly higher than the control group (χ^2=6.764 p=0.009).

Considering the vitamin D values of the groups, in the AA group 25 (25/106) patients had vitamin D levels below 15 µg/L, whereas none of the cases in the control group had vitamin D values below 15 µg/L (0/106). The number of patients with vitamin D deficiency was significantly higher in the AA group compared to the control group (χ^2: 28,342 p<0,0001).

The presence of thyroid disease and absence of autoimmune thyroiditis were the study inclusion

criteria. Even when TSH and FT4 values were within normal limits, both FT4 and TSH levels were statistically significantly higher in the AA group compared to the control group (n=103/77; z=-2,140, p=0.032; z=-2.224, p=0.025)

DISCUSSION

Alopecia areata (AA) is a common autoimmune disorder which is characterized by sudden onset of focal well-circumscribed hair loss without signs of significant inflammation and scarring. In the literature, various hypotheses related to etiopathogenesis of AA are encountered. One of the most accepted hypotheses is the "immune privilege collapse" hypothesis. Healthy hair follicle epithelium does not express major histocompatibility complex (MHC) class I and II molecules [13,14]. For this reason, the hair follicle is considered as an immune privileged area. The mechanism that initiated the presentation of various antigens in the anagen phase hair follicle epithelium to T cells by antigen presenting cells is still unknown. The loss of the immune privilege of the anagen hair bulb is important in AA pathogenesis. IFN-γ which is a proinflammatory cytokine is prominently expressed in lesional skin of the patients with AA [14-16]. It is thought that IFN-γ induces the expression of MHC class I molecules and triggers the presentation of autoantigens. The autoantigens presented from the anagen hair follicle structure are recognized by C8 + T lymphocytes, then the attack to the anagen hair follicle epithelium begins with the help of CD4 + T lymphocytes [15- 17]. Because CD8 + T lymphocytes are cytotoxic, their presence in the hair follicle interrupts hair growth easily with resultant development of inflammatory process [14,16-19]. It has been shown in many studies that vitamin D impedes the secretion of proinflammatory cytokines and inhibits inflammation by restraining Th1 and Th17 cells. There is an increase in proinflammatory cytokines, especially IFN-γ, in vitamin D deficiency [14,15]. Vitamin D may contribute to maintenance of the immune privilege by decreasing the production of IFN-γ. Additionally, triggers such as emotional stresses, minor skin traumas, infectious agents also seem likely to cause an intrafollicular increase in IFN-γ on the background of genetic susceptibility [14,15,17,20-25].

A second hypothesis is the production of autoantibodies specific to the hair follicle. IL 6 is a proinflammatory cytokine that increases in vitamin D deficiency [13]. IL 6 induces an increase in IgG. The presence of autoantibodies specific to hair follicles does suggest that such autoantibodies may provide clues as to the antigenic targets for T cells. Vitamin D has been shown to inhibit the conversion of B cell precursors to plasma cells and to modulate humoral immunity [15,17,22].

As is seen, vitamin D deficiency can trigger AA through many mechanisms of the immune system. Studies have shown the presence of a relationship between vitamin D deficiency and autoimmune disease [15,17]. Vitamin D supplementation improves the immune response by inhibiting Th1 cell activity in AA [23]. Although there is strong evidence that vitamin D is both anti-inflammatory and immunoregulatory [23,26,27], the mechanism of its effect on autoimmunity is not understood [26-28]. Low levels of vitamin D have also been found in many autoimmune diseases [26-32].

A collapse in immune-privilege environment of the hair follicle initiates the development of AA [23, 27]. Similarly, the lack of micronutrients impairs the normal course of hair follicle cycles [27,33]. There are multiple reasons to suspect a role for vitamins in rapidly dividing hair follicle. Given their role in the development of a normal hair follicle and in immune cell function [27], a growing number of investigations have sought to determine whether serum levels of 25-hydroxy vitamin D and vitamin B12 may differ in children with AA. Studies have demonstrated relations between vitamin D deficiency and autoimmune disease [23]. Vitamin D supplementation improves the immune response by inhibiting Th1 cell activity in AA [23]. Decreased levels of vitamin D in cases with systemic lupus and rheumatoid arthritis support the relationship between autoimmunity and this vitamin [34,35].

Studies investigating serum levels of vitamin D in patients with AA have reported that serum vitamin D

levels were significantly lower in AA patients compared to healthy controls [36,37] Similar to other studies in the literature, in our study, vitamin D levels of AA cases were found to be significantly lower than controls. Vitamin D levels were found to be less than 15 µg/L in 25 of 106 patients with AA (25/106). In the control group, none of the study participants had vitamin D values below 15 µg/L (0/106). Most studies reported low levels of vitamin D in both summer and winter periods [36,37]. In our study, summer values of vitamin D were taken into account and relatively lower levels were noted. In contrast to previous studies, Thompson et al. found no association between AA development and high or low vitamin D levels. In addition, they reported that vitamin D supplementation did not prevent development of AA [28].

In contrast to vitamin D, there is limited evidence to suggest that vitamin B12 levels decrease or increase in AA cases. In terms of vitamin B12, a possible relation between AA and vitamin B12 deficiency is predicated on the autoimmune nature of pernicious anemia. In the present study, in the control group none of the cases (0/72), while in the AA group 7 (103) patients had vitamin B12 values below 187 ng/L. In contrast to our study, studies investigating possible relationship between vitamin B12 levels and AA did not identify any such differences in vitamin B12 levels of patients compared to control subjects [12,38]. Concordantly, Ertugrul et al. measured holotranscobalamine, vitamin B12, folate and homocysteine levels in 75 patients with AA and control subjects. They did not find any significant differences between two groups regarding these parameters. The current literature failed to show the relationship between vitamin B12 deficiency and AA, but our study was the first with the largest sample in childhood and found that vitamin B12 levels in children diagnosed with AA were significantly lower than healthy ones. Vitamin B12 deficiency was also found statistically significantly more often in children with AA. More research seems to be needed to understand the relationship between vitamin B12 and AA.

In addition to autoimmune and genetic predisposition AA has been linked to thyroid disorders [39]. Thyroid hormones are known to play an important role in the synthesis of mesenchymal stem cells located at the base of hair follicles. Both T3 and T4 hormones induce hair follicle stem cell niche and contribute to renewed life cycle of the hair follicle [10]. Hence, the close relationship between the hair follicle and thyroid hormones suggests that one of the underlying causes of the development of AA may be thyroid diseases.

The incidence of thyroid disease varies in patients with AA. However, despite the high prevalence of thyroid disease in patients with AA,no clear association was noted between thyroid dysfunction and the type and severity of AA. Moreover, no relation was found between thyroid disorders and family or medical history of subjects with AA [40]. In the current study, we found that serum levels of TSH and FT4 were significantly higher in AA group than in the control group. Increased serum TSH and FT4 levels may contribute to the development of AA. However, since there is no significant correlation between AA outcomes and TSH and FT4 levels, it is not rational to perform thyroid fuction tests routinely. Our suggestion is supported by other studies. Hollowell et al. reported that TFT results were abnormal in 10 to 15% of healthy individuals [41]. Similarly, Patel et al. reported that routine thyroid function screening should be restricted to AA patients with a history of Down syndrome or atopy, a family history of thyroid disorders, or clinical findings of thyroid dysfunction [11].

Current study has consistently demonstrated lower vitamin D and vitamin B12 levels in patients with AA. Although present study is limited by its retrospective nature and single-center site, our results showed statistically significant decrease in vitamin D and vitamin B12 levels but significant increase in circulating TSH and FT4 levels in participants with AA. Overall, present study revealed an association between vitamin D and B12 status and risk of developing AA.

Ethics Committee Approval: SBÜ. Izmir Dr. Behçet Uz Children's Diseases Training and Research Hospital has been approved by the Clinical Research Ethics Committee (27.02.20 / 36).

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Case Report

Y Shaped Colonic Duplication Mimicking Intestinal Volvulus: A Case Report and Review of Literature

Volkan Sarper Erikci

İntestinal Volvulusu Taklit Eden Y Şekilli Kolonik Duplikasyon: Olgu Sunumu ve Literatür İncelemesi

ABSTRACT

Enteric duplications are rare congenital anomalies found anywhere from mouth to anus. Colonic duplications constitute about 13% of all enteric duplications. In this report a 6-year-old boy with chronic abdominal pain for a duration of last 2 years requiring intermittent hospital admissions was diagnosed as colonic duplication mimicking intestinal volvulus. Clinical findings are nonspecific and definitive diagnosis can only be made during surgical intervention and surgical treatment is advocated for all duplications. The topic is discussed under the light of relevant literature with a brief a brief literature review.

Keywords: *Colonic duplication, intestinal volvulus, children*

ÖZ

Enterik duplikasyonlar nadir anomaliler olup ağızdan anüse kadar herhangi bir yerde gözlenebilir. Kolonik duplikasyonlar enterik duplikasyonların %13'ünü oluşturur. Bu çalışmada 2 yıldır devam eden kronik karın ağrılı 6 yaşında erkek çocuğu sunulmaktadır. Sık hastane yatışları mevcut olan olgumuzda intestinal volvulusu taklit eden kolonik duplikasyon saptanmıştır. Bu olgularda klinik bulgular nonspesifik olup kesin tanı ancak cerrahi girişim sırasında konulur ve cerrahi tedavi tüm duplikasyonlar için önerilmektedir. Konu hakkındaki literatür incelenerek kolonik duplikasyonlar gerekli bilgiler verilerek tartışılmaktadır.

Anahtar kelimeler: *Kolonik duplikasyon, intestinal volvulus, çocuklar*

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INTRODUCTION

Enteric duplications ("ED") are rare congenital anomalies and can occur anywhere in the gastrointestinal tract from mouth to anus [1]. Sites of involvement include ileum (33%), esophagus (20%), colon (13%), jejunum (10%), stomach (7%), and duodenum in 5% of cases (2-4). More than 80% of patients present before the age of 2 years and findings in presentations vary from case to case. These include nonspecific findings like; abdominal pain and mass, acute abdomen or intestinal obstruction like volvulus, or intussuception and rectal bleeding [5-7]. The aim of this study is to present a case with Y shaped colonic duplication presenting like intestinal volvulus and to discuss the topic with regard to relevant literature and to give a brief literature review. CASE A 3-year-old boy with a complaint of abdominal pain and vomiting was admitted to our clinic. He had a chronic abdominal pain for a duration of last 2 years requiring intermittent hospital admissions. The physical examination revealed that the boy was dehydrated and tachycardic. Resuscitation with IV fluid and electrolyte was commenced promptly. He had a moderate abdominal distention and laboratory tests were within normal range. Standing abdominal X-ray showed large air collection at the middle abdomen with multiple gas filled, grossly dilated bowel loops (Figure 1). Abdominal ultrasonography (US) reported a diffuse collection of fluid in the abdominal cavity at the region of hepatorenal, pelvic, and superior to bladder. Urgent computerized tomography (CT) scan of the abdomen revealed findings compatible with an intestinal volvulus located periumbilically at the right of mid abdominal line (Figure 2). Emergent laparotomy was performed and a tubular bowel seg-

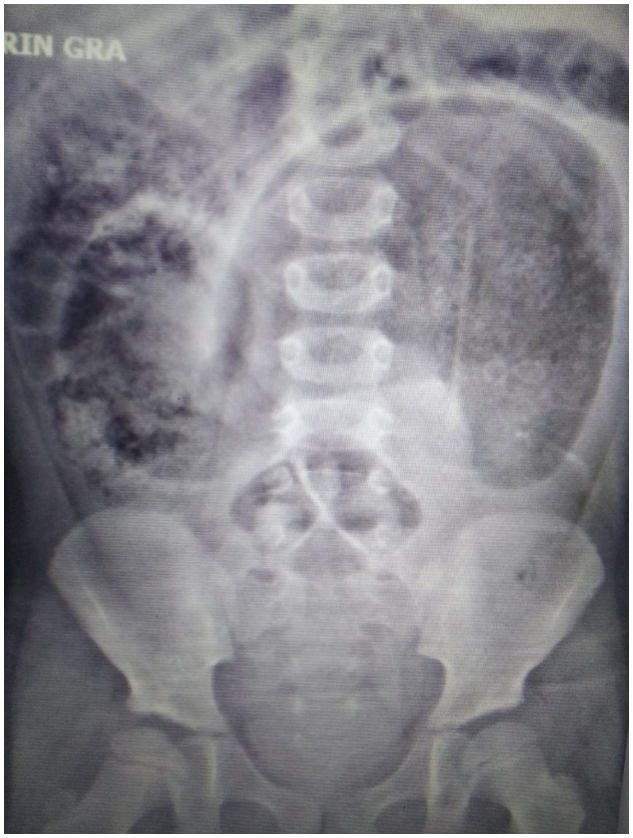

Figure 1. Standing abdominal X-ray showing large air collection in the abdomen with multiple gas filled, grossly dilated bowel loops.

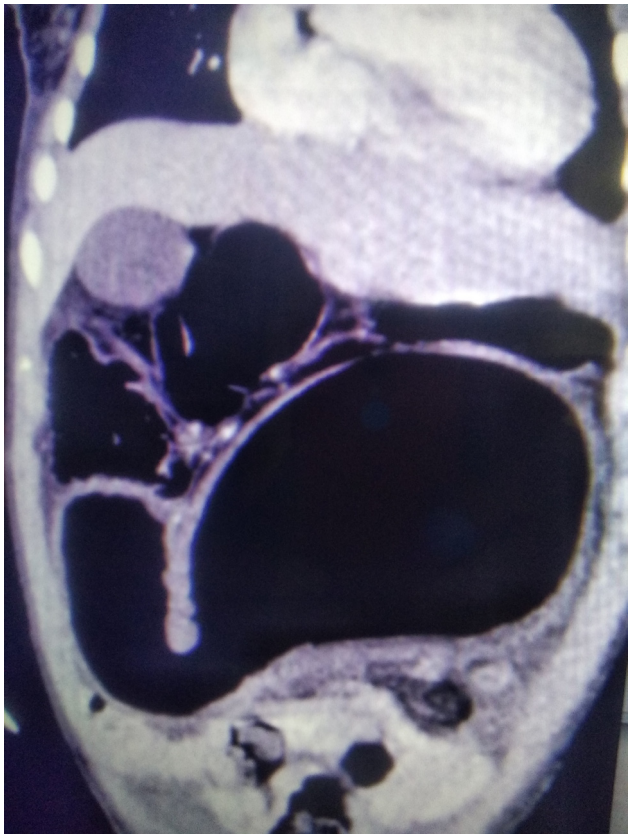

Figure 2. Abdominal CT scan showing intestinal volvulus in the abdominal cavity.

ment originating from ascending colon, measuring 21.5x5x8 cm with a dilated blind end floating freely in the abdominal cavity together with hemorrhagic fluid collection were found. Duplicated colonic segment was found to be congested and twisted 360° anticlockwise around mesentery with caecum and appendix found in the right lower quadrant (Figure 3). After detorsion of the volvulus, in addition to an incidental appendectomy, resection of colonic duplicated segment was performed with the aid of linear 6 cm stapler device (Figures 4 and 5). A second suture layer with 4/0 polyglicolic acid was performed for reinforcement of stapler suture line at the resection site in the native colon. Histopathologic examination of the excised specimen revealed a colonic duplication containing all layers of large intestine without evidence of ectopic or abnormal tissue. For a possibility of concomitant urinary, cardiac and vertebral anomalies, the patient was evaluated accordingly and had no accompanying anomalies. The child did well post operation and was commenced on oral feeds on the 4th postoperative day and discharged on 7th postoperative day. He is disease free and gaining weight with no symptoms.

DISCUSSION

Alimentary tract duplications in children are rare congenital anomalies commonly seen under the age of 2 years as an acute abdomen or bowel obstruction [8,9]. The incidence of gastrointestinal duplications is 1 in 4500 autopsies [10]. The first report of ED was made by Calder in 1733 and the term “Duplications of the Alimentary Tract” was coined by Ladd in 1937 [6,11]. In a meta analysis comprising 580 cases, it was found that 80% of lesions occured in the abdomen and 20% in the chest [12]. There are numerous terms for defining these masses including; enterogenous cysts,

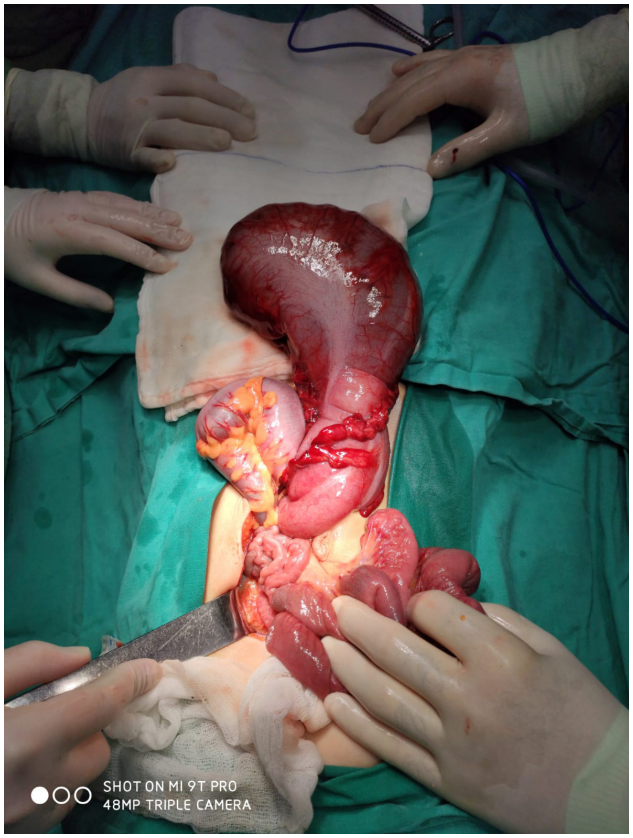

Figure 3. Peroperative view. Note the duplicated congested colonic segment was detorsed.

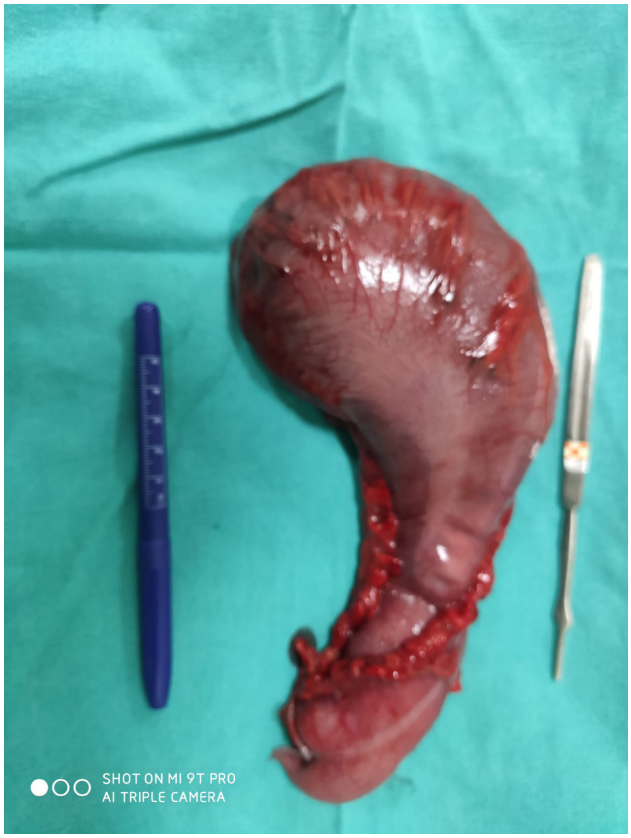

Figure 4. Postoperative view of the resected duplicated colonic segment.

giant diverticula, ileal or jejuna duplex, and unusual meckel diverticula [7]. The etiology of EDs is still unclear and it is believed that it occurs between 4th and 8th weeks of gestation [13]. There are several proposed theories to explain the pathophysiology of EDs suggesting that the origin of ED can be multifactorial. These are the theories of split notochord, luminal recanalisation, partial twinning, persistent embryonic diverticula, and intrauterine vascular accident [2,3,14-16]. EDs have 3 characteristics in common; epithelial lining containing alimentary mucosa, smooth muscle envelope, and close attachment with gastrointestinal tract showing common wall [13]. Structurally, they can be cystic in 80% and tubular in 20% of cases. Cystic duplications are not related to adjacent intestinal lumen whereas tubular lesions may be related to adjacent colonic lumen adjacent as in our case [17]. It has been reported that ectopic tissue is present in 25-30% of duplicated specimens and most common types of ectopic tissues are gastric followed by pancreatic tissue [6]. Presentation of colonic duplication is variable and asymptomatic in 10% of patients and can be discovered accidentally at surgery [18]. Vague abdominal pain and distention, vomiting, constipation or failure to thrive may be observed. As an emergency setting, the children may present with an acute intestinal obstruction due to intussuception or volvulus as in the presented case. If there is ectopic gastric tissue in the epithelial lining of duplicated colon, rectal bleeding may be observed. Extra gastrointestinal anomalies including genital, urinary or cardiovascular systems have been reported in 80% of patients with colonic duplications [19,20]. Our patient did not reveal any finding related to these systems. Imaging findings may be helpful in diagnosing colonic duplications in children. Plain abdominal X-ray is usually nonspecific and shows features of intestinal obstruction and air filled intestinal loops.

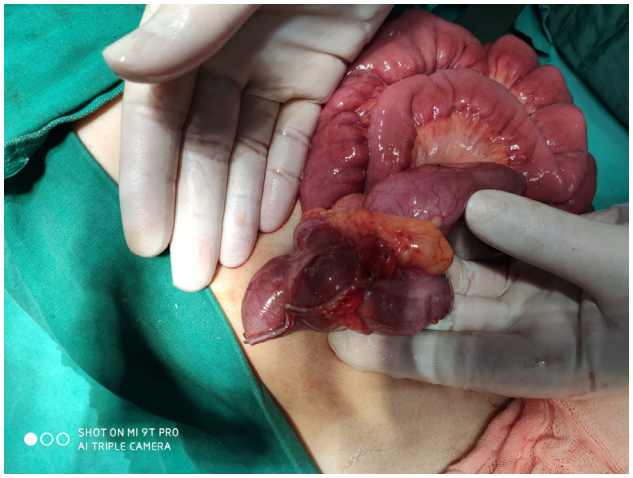

Figure 5. Postoperative view. Note resection of colonic duplication and an incidental appendectomy was performed.

Ultrasonography ("US") is the imaging modality of choice in the diagnosis of ED but is operator dependent. Classical findings of uncomplicated cystic EDs are the presence of a cyst adjacent to the gut with double-wall or muscular sign (gut signature sign) but US may be non-helpful in diagnosing tubular duplications [13]. Sonographic finding in the presented case is nonspecific and includes massive abdominal fluid collection in the abdominal cavity. Due to ionizing radiation computerized tomography (CT) is not typically performed to evaluate the EDs but may depict location and extension of duplication and anatomical relationship with surrounding structures as well as complications like volvulus [13]. CT finding in our case was an intestinal volvulus necessitating urgent surgical intervention. The treatment in colonic duplications is surgical excision of the duplicated intestinal segment. The aims of surgery are to relieve the symptoms, to eliminate the risks of complications like volvulus, intussuception or bleeding from an ectopic gastric mucosa. Resection of duplicated colonic segment can also decrease the risk of adenocarcinoma because the occurence of adenocarcinoma in the duplicated colon is higher than duplications located at any other locations [21,22]. Other surgical treatment options especially in extensive tubular colonic duplications include cyst marsupialisation, partial cystectomy, and mucosal stripping. In conclusion, colonic duplications especially Y shaped lesions in children may be a challenge for clinicians with regard to not the surgical treatment but the clinical diagnosis because these cases usually can not be diagnosed usually without surgical intervention. Significant morbidity and even mortality may be observed if these patients are left untreated. A high index of suspicion is necessary to recognize this anomaly and clinicians should keep this entity in their minds in children with nonspecific complaints of gastrointestinal tract including abdominal pain, vomiting or intestinal obstruction and these children should be provided treatment and care promptly for an uneventful recovery.

Conflict of Interest: None.

Informed Consent: Obtained from the patient's relatives.

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Case Report

Nekrobiosis Lipoidica in a Pediatric Patient

Pediatrik Bir Hastada Nekrobiyozis Lipoidika

Gözde Emel Gökçek
Özge Şeyda Saka
Emine Çölgeçen
Murat Borlu
Özlem Canöz

ABSTRACT

Necrobiosis lipoidica is a rare chronic granulomatous disease that has historically been associated with diabetes mellitus, but recently it is thought to be secondary to microangiopathic changes. We report a necrobiosis lipoidica case of a five-year-old girl with diabetes since the age of two, because it is exceptionally unusual in pediatric diabetes. Necrobiosis lipoidica should be considered in pediatric patients with slowly expanded erythematous plaques and patches. This will help protect the patient from other important diabetic microangiopathic complications, such as nepropathy and retinopathy and also malignant progression, such as squamous cell carcinoma.

Keywords: *Necrobiosis lipoidica, type 1 diabetes, children, diabetes, granulomatous dermatitis*

ÖZ

Nekrobiyozis lipoidika, tarihsel olarak diabetes mellitus ile ilişkilendirilmiş olan, ancak son zamanlarda mikroanjiyopatik değişikliklere ikincil olduğu düşünülen, nadir görülen kronik granülomatöz bir hastalıktır. Bu yazıda, iki yaşından beri diyabeti olan, beş yaşındaki bir kız çocuğunda görülen nekrobiyozis lipoidika vakasını sunuyoruz, çünkü nekrobiozis lipoidika pediatrik diyabette nadir görülen bir durumdur. Yavaş yavaş genişleyen, eritemli plak ve yamaları olan pediyatrik hastalarda, nekrobiyozis lipoidika ayırıcı tanıda muhakkak düşünülmelidir. Böylece hastanın nepropati ve retinopati gibi diğer önemli diyabetik mikroanjiyopatik komplikasyonlardan ve ayrıca skuamöz hücreli karsinom gibi malign dönüşümlerden korunmasına yardımcı olabiiriz.

Anahtar kelimeler: *Nekrobiyozis lipoidika, tip 1 diyabet, çocuk, diyabet, granülomatöz dermatit*

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INTRODUCTION

Necrobiosis lipoidica (NL) is an uncommon chronic granulomatous disease traditionally linked to diabetes mellitus (DM). Recent studies have shown that microangiopathy is significantly involved in the pathogenesis of NL. Patients with NL present with erythematous papules and atrophic telangiectatic patches, especially on the lower extremities. Necrobiotic xanthogranuloma, granuloma annulare and other granulomatous diseases should be considered at differential diagnosis. Biopsy is also useful during diagnosis [1]. NL occurs in ~75% of patients with clinical DM or in whom DM will develop subsequently, but it is unusual in paediatric diabetes. However, NL in paediatric patients is linked to an increased risk of diabetic nephropathy and retinopathy [2], such that its diagnosis is of particular importance. We describe a diabetic patient with NL and discuss the case in light of previous reports in

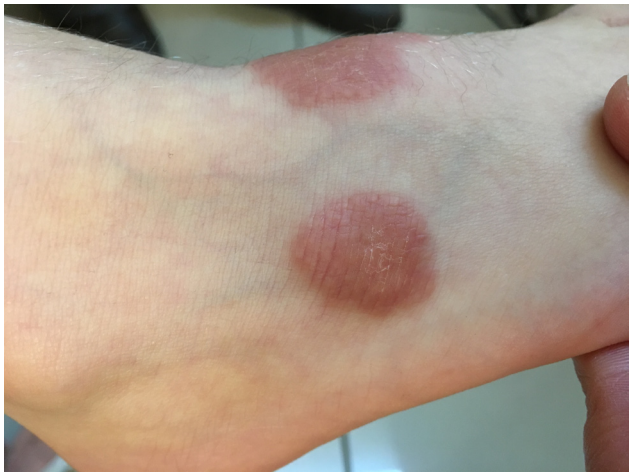

Figure 1. Circular, indurated red plaque, measuring 1 x 0.8 cm on foot.

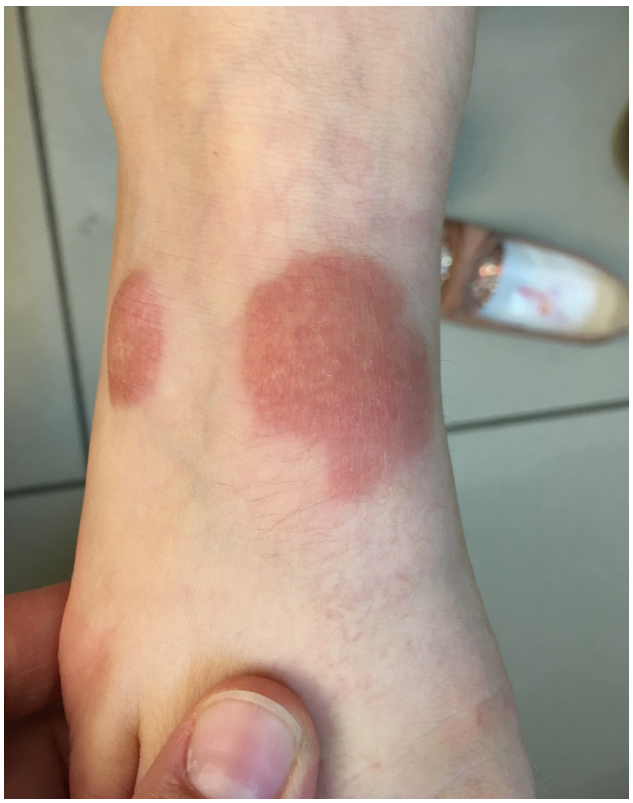

Figure 2. The other well-defined, indurated red plaque, measuring 2 x 2 cm on dorsum of foot.

the literature.

CASE REPORT

A 5-year-old girl with type 1 DM diagnosed at the age of 2 years developed diabetic ketoacidosis. She had no family history of DM and was being followed-up by the paediatric endocrinology department of our hospital. Her HbA1c value was 7.8. She had undergone annual screening for microangiopathic complications, but neither microalbuminuria nor retinopathy was detected. The patient's diabetes was currently under control with insulin. Two distinct, persistent plaques, both containing a depressed central area and an elevated purple peripheral ring, were observed on the top of her right foot. One of the lesions appeared as a circular, indurated red plaque 1 cm × 0.8 cm in size (Figure 1) and the other as a 2 cm × 2 cm red plaque (Figure 2). Both plaques began as painless, reddish papules which gradually expanded to form plaques over a 6-month period.

Biopsy of the plaques from the superficial to deep dermis led to a diagnosis of NL, based on the presence of degenerate collagen fibres containing CD 68 (+) epithelioid histiocytes and moderately necrotic, multinuclear giant cells (Figure 3).

The plaques were successfully treated, resolving almost completely in response to 1 week of topical steroid therapy.

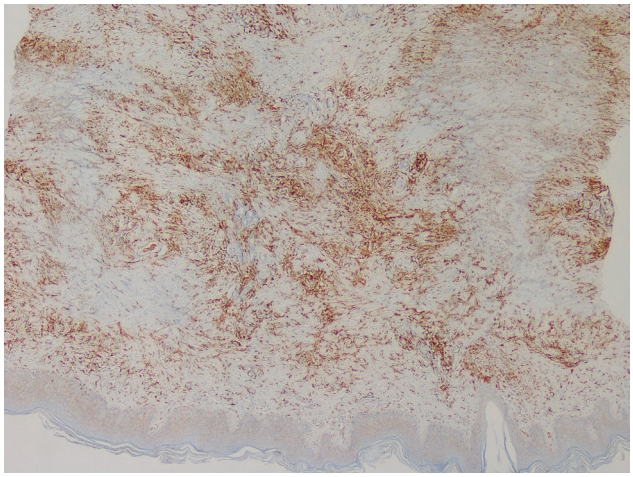

Figure 3. Degenerated collagen fibers containing CD 68 (+) epithelioid histiocytes and middle necrotic, locally multinuclear giant cells.

DISCUSSION

Necrobiosis lipoidica is a chronic granulomatous dermatosis with a reported prevalence among dia-

betic adults of 0.3%. However, it may also occur in patients in whom no indication of impaired glucose metabolism is observed. NL is particularly frequently seen in women, with the onset generally occurring in early or middle adulthood [1]). There are only a few case reports of NL developing in childhood. However, it developed in our 5-year-old patient with DM.

NL is an idiopathic entity that has been attributed to vascular disruption involving immune complex deposition or microangiopathic changes concluding with collagen degradation [3].

Although NL is more common in diabetic patients, it is not pathognomonic for DM. Özkur et al. [4] described a non-diabetic 14-year-old girl who presented with an asymptomatic, 7 cm × 5 cm, single red plaque located in the interscapular region that had gradually enlarged over 5 years. Our patient had two distinct, persistent plaques, both containing a depressed central area and an elevated purple peripheral ring, on the top of her right foot.

Reports of a link between NL and diabetes in the paediatric age group are limited. Dereci et al. [5] described the case of a 13-year-old girl with type 1 DM who presented with a slowly enlarging erythematous patch on her leg. The patient's blood glucose level was not under control despite subcutaneous insulin treatment. After topical steroid therapy and glucose control, the lesion resolved, as in our patient.

Marchetti et al. [6] reported a case of granuloma annulare involving the bilateral ankles and NL in the left pretibial region in a 12-year-old girl, both of which appeared prior to a diagnosis of maturity-onset diabetes of the young (MODY). Following a detailed analysis of similar cases reported in the literature, the authors conclude that NL is more common in type 1 DM (6.5%) and MODY (2.8%) than in type 2 DM (0.4%). Our patient had been diagnosed with type 1 DM at 2 years of age.

Paediatric patients are more likely to develop severe complications and morbidity secondary to NL. Ulceration, sometimes with subsequent infection, is seen in 25–33% of patients with NL. Although malignant ulceration is a rare entity, it should nevertheless be suspected in the event that the ulcer fails to resolve with conservative treatment. This was the case in a 28-year-old woman with type 1 DM who presented with established DM, with a history of squamous cell carcinoma in a region of NL involvement 11 years previously [7]. Neither ulceration of the plaques nor malignancy developed in our patient, but further follow-up would be advisable.

In their study of children with NL, Verroti et al. [8] found a higher prevalence of persistent microalbuminuria and retinopathy in those with NL compared to those without NL. The authors concluded that NL may be a clue to the presence of nephropathy and retinopathy, both in children and adults. Neither of these pathologies were detected in our patient.

The treatment of NL may be problematic and is often unsuccessful. Topical or intralesional steroids have been shown to be capable of ameliorating inflammation and sclerosis. Other alternatives include the use of systemic hydroxychloroquine, antiplatelet agents, cyclosporine, thalidomide, clofazimine, anti-tumour necrosis factor agents, fumaric acid esters, PUVA or UVA1 photodynamic therapy, tacrolimus and pentoxifylline. In our patient, the plaques responded well to topical steroid therapy. Given the long-term risk in NL of malignant progression to squamous cell carcinoma, patients should be followed up intermittently after treatment.

CONCLUSION

NL is a chronic degenerative disease of unknown aetiology involving the dermal connective tissue. It is mostly seen in diabetic patients, especially adults. However, it should also be considered in paediatric patients who present with slowly enlarging erythematous plaques and patches. The early identification and treatment of NL may aid the prevention of other diabetic microangiopathic complications as well as ulceration of the lesions and subsequent squamous cell carcinoma development.

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Informed Consent: The patient's parents in this manuscript had given written informed consent to the publication of their case details.

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