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Comparison of Hemogram Parameters in Febrile Seizures Types

Febril Nöbet Tiplerinde Hemogram Parametrelerinin Karşılaştırılması

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ABSTRACT

Aim: Febrile seizures (FS) are among the most common neurological emergencies during childhood and clinically classified into two types, being simple febrile seizures (SFS) and complicated febrile seizures (CFS). The differentiation between FS types is important, in that they are associated with different morbidity and mortality risks and it is based on the clinical characteristics of each seizure, however there is currently no laboratory test that can guide this differentiation. In this study, the relationship between FS types and hemogram parameters was evaluated and potential use of these parameters in differential diagnosis was investigated.

Material and Methods: This retrospective study included a total of 133 patients whose first FS met the criteria of an FS, and whose hemogram results were available. The American Academy of Pediatrics criteria were used to confirm the diagnosis. The patients were divided into two groups as SFS and CFS.

Results: Hemoglobin (Hb), hematocrit (HCT), mean platelet volume (MPV), neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) differed significantly between two groups ($p<0.001$, $p=0.002$, $p=0.033$, $p<0.001$, $p<0.001$, respectively), while no significant difference was identified in total blood count parameters. Moreover, MPV was significantly higher in CFS group than in SFS group.

Conclusion: This is one of the few studies investigating the potential relationship between hemogram parameters and FS types in children. We believe that, although they do not ensure a clear differentiation, Hb, MPV, NLR and PLR may be useful to clinicians in differentiating between FS types, particularly in patients with an unclear seizure history.

Keywords: Febrile seizures; simple; complicated; hemogram.

ÖZ

Amaç: Febril nöbetler (FN) çocukluk çağında en sık görülen nörolojik aciller arasındadır ve klinik olarak basit febril nöbetler (BFN) ve komplike febril nöbetler (KFN) olmak üzere iki tipte sınıflandırılır. FN tiplerinin ayrımı, farklı morbidite ve mortalite riskleriyle ilişkili olması ve her nöbetin klinik özelliklerine dayanması nedeniyle önemlidir, ancak şu anda bu farklılaşmaya yol gösterecek laboratuvar testi bulunmamaktadır. Bu çalışmada FN tipleri ve hemogram parametreleri arasındaki ilişki incelenmiş ve bu parametrelerin ayırıcı tanıda potansiyel kullanımı araştırılmıştır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya, FN kriterlerine uyan, ilk defa FN geçiren ve hemogram sonuçlarına ulaşılabilen toplam 133 hasta dahil edildi. Tanıyı doğrulamak için Amerikan Pediatri Akademisi kriterleri kullanıldı. Hastalar BFN ve KFN olmak üzere iki gruba ayrıldı.

Bulgular: Her iki grup arasında hemoglobin (Hb), hematokrit (HCT), ortalama trombosit hacmi (MPV), nötrofil lenfosit oranı (NLO) ve trombosit lenfosit oranı (TLO) değerleri anlamlı şekilde farklıyken (sırasıyla $p<0,001$; $p=0,002$; $p=0,033$; $p<0,001$; $p<0,001$) diğer tam kan sayımı parametrelerinde ise anlamlı bir farklılık yoktu. Ayrıca, KFN grubunda MPV, BFN grubuna göre anlamlı derecede yüksekti.

Sonuç: Bu çalışma çocuklarda hemogram parametreleri ile FN tipleri arasındaki potansiyel ilişkiyi araştıran az sayıdaki çalışmadan biridir. Hemoglobin, MPV, NLO ve TLO'nun kesin bir ayrım sağlamasa da özellikle nöbet hikayesi net olmayan hastalarda klinisyenlere FN tiplerinin ayırt edilmesinde yardımcı olacağını düşünmekteyiz.

Anahtar kelimeler: Febril nöbetler; komplike; basit; hemogram.

INTRODUCTION

Febrile seizures (FS) are among the most common neurological emergencies seen during childhood. The commonly accepted criteria for FS include a fever higher than 38°C, absence of a central nervous system infection or inflammation, lack of an underlying metabolic abnormality that may cause convulsions, and absence of a previous history of afebrile seizures in children aged 6-60 months. FS is seen in 2-5% of all children, and its incidence peaks at the age of 18 months. FSs are clinically classified into two types, being simple febrile seizures (SFS) and complicated febrile seizures (CFS). SFSs were defined as primary generalized seizures that lasted for less than 15 minutes and did not recur within 24 hours. CFSs were defined as focal, prolonged (≥15 minutes), and/or recurrent within 24 hours (1). SFS and CFS account for 80% and 20% of all febrile seizures, respectively (2).

It is important to differentiate between the different types of FSs, as they are associated with different risks of morbidity and mortality (3), and this differentiation is made based on the clinical characteristics of each seizure, as there is currently no laboratory test that can guide this differentiation. The majority of previous studies about FS in literature focus on the risks of FS, the development of epilepsy, recurrence and prophylaxis of the disease. In the present study, we investigate the relationship between FS types and hemogram parameters, and evaluate the potential use of these parameters in differential diagnosis.

MATERIAL AND METHODS

A total of 133 patients aged between 6 and 60 months who referred to the pediatric emergency care unit of the Bülent Ecevit University Medical Faculty between January 2009 and January 2017 with their first FS, and whose hemogram results were available, were included in the study. Ethics committee approval was obtained from the Bülent Ecevit University Medical Faculty Research Hospital Ethics Committee, with approval date 08.03.2017 and protocol number 2017-29-08/03. Medical data of the patients was reviewed retrospectively, and the American Academy of Pediatrics (AAP) criteria was used to confirm the diagnosis of FS. According to AAP criteria; FS is a seizure accompanied by fever (≥38°C), without central nervous system infection, occurring in infants and children between the ages of 6 to 60 months. SFSs were defined as primary generalized seizures that lasted for less than 15 minutes and did not recur within 24 hours. CFSs were defined as focal, prolonged (≥15 minutes), and/or recurrent within 24 hours. Patients were divided into two groups as SFS and CFS (1).

A lumbar puncture was performed in patients with signs of meningeal irritation and no fever focus. Then patients with negative growth cultures were included in the study. Patients who were suffered from afebrile seizures, with cerebral palsy and/or mental retardation, and those who had experienced a previous FS were excluded from the study.

Laboratory Analysis

The hemogram parameters, measured from peripheral blood obtained at the initial presentation, were evaluated. White blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), mean erythrocyte volume (MCV), hematocrit (HCT), erythrocyte distribution width (RDW), platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) were recorded. NLR was calculated by dividing the neutrophil count by the lymphocyte count, and PLR was calculated by dividing PLT by lymphocyte count. Patients were considered anemic if Hb values were 10.5 gr/dl and lower in the 6-24 months age group and 11.5 g/dl or lower in the 25-60 months age group (4).

Statistical Analysis

Statistical analyses were performed with SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) and MedCalc 19.0.6 (demo version). Distribution of data was determined by Shapiro-Wilk test. Continuous variables were expressed as mean±standard deviation, categorical variables as frequency and percent. Categorical variables were compared using Pearson's Chi-square test. Independent samples t test was used for Hb and HCT and Mann-Whitney U test was used for the rest of the hemogram parameters to compare two groups in terms of continuous variables. A receiver operating characteristic (ROC) analysis was constructed to determine the best cut-off value to predict the outcome. A p value of less than 0.05 was considered statistically significant for all tests.

RESULTS

The study included 133 (57 girls, 76 boys) patients whose medical files were reviewed retrospectively. The patients were evaluated in two groups, as those with SFS (n=105, 78.9%) and those with CFS (n=28, 21.1%). The mean age and gender distribution were not significantly different between two groups (p=0.812, p=0.830, respectively). In terms of age distribution, 21.1% (n=28) of the cases were younger than 12 months, 52.6% (n=70) were aged between 13 and 24 months, 15.8% (n=21) were aged between 25 and 36 months, 6.0% (n=8) were aged between 37 and 48 months and 4.5% (n=6) were older than 48 months. The seizure types did not differ significantly between the age groups (p=0.254, Table 1).

While Hb (p<0.001), HCT (p=0.002), MPV (p=0.033), NLR (p<0.001) and PLR (p<0.001) values were statistically significantly different between the two groups, no significant difference was noted in the total blood count parameters. Of all the patients, 36.1% (n=48) had anemia, and 29.5% (n=31) of those were in the SFS and 60.7% (n=17) were in the CFS group. Table 2 shows the mean hemogram parameter values in each group.

Table 1. Age and gender distribution of febrile seizure types

	SFS (n=105)	CFS (n=28)	p
Age (month), mean±SD	21.63±11.54	24.28±16.13	0.812
Age, n (%)			
≤12	21 (20.0)	7 (25.0)	
13-24	56 (53.2)	14 (50.0)	
25-36	19 (18.1)	2 (7.1)	0.254
37-48	6 (5.7)	2 (7.1)	
≥49	3 (2.9)	3 (10.7)	
Gender, n (%)			
Girl	44 (41.9)	13 (46.4)	0.830
Boy	61 (58.1)	15 (53.6)	

SFS: Simple febrile seizure, CFS: Complicated febrile seizure, SD: Standard deviation

When the strength of markers in predicting CFS was evaluated, the area under curve (AUC) values were found to be low and similar. AUC values of NLR-PLR and Hb-MPV were not significantly different (p=0.970 and p=0.314, respectively). Table 3 shows the cut-off, AUC, sensitivity, specificity, 95% confidence interval (CI) and p values of the Hb, HCT, MPV, NLR and PLR parameters for predicting CFS, while the ROC curves are presented in Figures 1 and 2.

Table 2. Hemogram parameters according to groups

Hemogram Parameters	SFS (n=105)		CFS (n=28)		p
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
WBC ($\times10^3/mm^3$)	13.71±5.90	13.30 (4.80-35.00)	14.45±8.59	12.45 (3.70-37.10)	0.858
RBC (10^6/mL)	4.45±0.38	4.46 (3.38-5.40)	4.25±0.54	4.36 (2.30-5.18)	0.074
Hb (g/dL)	11.40±1.03	11.40 (8.70-13.70)	10.50±1.05	10.45 (8.40-12.20)	<**0.001**
HCT (%)	33.46±2.81	33.70 (26.70-39.50)	31.45±3.30	33.70 (23.70-37.00)	**0.002**
MCV (fl)	75.31±5.51	76.00 (56.60-83.90)	74.35±8.25	74.30 (56.70-102.70)	0.128
RDW (%)	14.94±1.96	14.60 (12.10-25.00)	15.56±2.19	14.95 (12.60-20.80)	0.132
PLT ($10^3/\mu L$)	310.81±113.48	300.00 (113.00-873.00)	294.14±104.28	278.00 (144.00-585.00)	0.347
PCT (%)	0.223±0.071	0.214 (0.090-0.530)	0.221±0.070	0.205 (0.125-0.422)	0.747
PDW (%)	16.51±0.62	16.50 (15.20-18.40)	16.82±0.72	16.70 (15.90-18.70)	0.072
MPV (fl)	7.32±0.88	7.20 (5.80-9.70)	7.70±0.94	7.65 (5.70-9.10)	**0.033**
NLR (%)	3.80±3.49	2.81 (0.26-21.00)	8.90±8.12	5.75 (1.52-35.43)	<**0.001**
PLR (%)	125.20±96.94	102.66 (22.11-683.30)	200.72±118.41	162.50 (52.88-456.00)	<**0.001**

SFS: Simple febrile seizure, CFS: Complicated febrile seizure, SD: Standard deviation, Min: Minimum, Max: Maximum, WBC: White blood cell count, RBC: Red blood cell count, Hb: Hemoglobin, HCT: Hematocrit, MCV: Mean erythrocyte volume, RDW: Erythrocyte distribution width, PLT: Platelet count, PCT: Plateletcrit, PDW: Platelet distribution width, MPV: Mean platelet volume, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio

Table 3. The results of ROC analysis

Hemogram parameters	Cut-off value	Area Under Curve	Sensitivity	Specificity	%95 Confidence Interval	p
Hb	≤10.5	0.709	57.14	80.00	0.624-0.784	**<0.001**
HCT	≤31.5	0.669	50.00	76.19	0.582-0.748	**0.002**
MPV	>6.9	0.632	85.71	39.05	0.544-0.714	**0.034**
NLR	>5.6	0.724	57.14	83.02	0.640-0.798	**<0.001**
PLR	>141.9	0.727	71.43	76.19	0.642-0.800	**<0.001**

Hb: Hemoglobin, HCT: Hematocrit, MPV: Mean platelet volume, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio

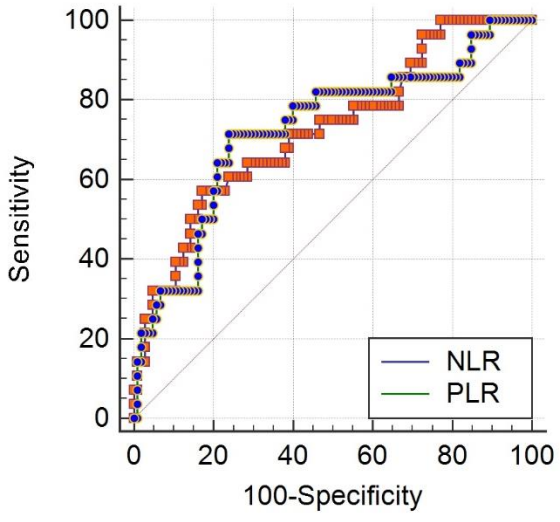

Figure 1. Comparison of ROC curves for neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR)

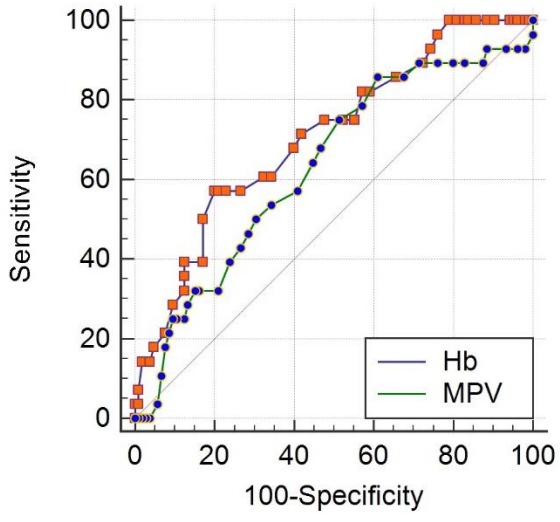

Figure 2. Comparison of ROC curves for hemoglobin (Hb) and mean platelet volume (MPV)

DISCUSSION

Based on a clinical diagnosis, FSs are classified into two types as SFS and CFS (1). Both conditions are generally not expected to have long-term consequences on motor or cognitive development, although CFS has been associated with a slightly higher rate of epilepsy (5). The clinical differentiation of FS types may be further complicated by ineffective anamnesis provided by the families in a state of panic, as well as the change in or complete resolution of physical examination findings at admission due to anticonvulsive treatments administered to the patients during their transfer to hospital. Both seizure types require different approaches and management strategies, and it is therefore important to define the type of each seizure (1,6). The majority of studies about FS in the literature focus on the risks associated with FS, the development of epilepsy, FS recurrence, treatment and prophylaxis. Aside from clinical identification, some recent studies have evaluated the role of laboratory parameters in the differentiation of FS types. It has been suggested that there is currently no laboratory test with a specifically proven value in the management of a child having FS, and these tests only become helpful when accompanied by symptoms and findings of an important disease. While no investigation has been recommended for SFS, it is recommended that clinicians should carry out further investigations in patients with CFS due to the potential long-term risks (7). In the present study, we made a retrospective evaluation of the medical files of patients to investigate the potential use of hemogram parameters in the differentiation of FS types. The mean age of the overall study population was 22.19±12.62 months and FSs were most frequently experienced by patients younger than 24 months of age. These results are consistent with previously reported findings (8,9). The incidence of FS reaching a peak and overlapping that of iron deficiency anemia (IDA) is most commonly seen between the ages of 12 and 24 months (10). Elemental changes such as iron deficiency are considered to play a role in the development of FS (11), leading to the relationship between anemia and FS being investigated in several studies (12-14). Pisacane et al. (15) were the first to investigate this relationship in children of similar age groups, and suggested that iron deficiencies facilitated the development of seizures. In studies carried out in Iran and Pakistan, the odds of IDA occurring in children with a history of FS were found to be 1.27 and 1.93-fold higher, respectively, than the control group (12,16). The SFS and seizure-free pyretic disease groups were compared in another study, and the rate of IDA was found to be significantly different in favor of SFS (17). In contrast, there have been other studies in which no significant relationship was identified between anemia and FS (13,18). In the limited number of studies in our country investigating the relationship between IDA and FS (14,19), IDA is reported in 35-48% of children with FS. In a study by Ozaydın et al. (20), IDA was found to be more common among patients with CFS when compared to SFS, and CFS was also associated with lower Hb, HCT and MCV values. Due to its retrospective design, it was not possible to evaluate the etiology of anemia in the present study. Of all the patients, 36.1% had anemia, and 64.6% of those were in the SFS group, and 35.4% were in the CFS group. The mean Hb and HCT values were found to be low in the CFS group, and this low level was considered significant. A ROC analysis identified the cut-off Hb and HCT levels for CFS as 10.5 g/dl and 31.5%, respectively. Previous studies have suggested that anemia may increase the rate of FS development, or may even trigger FS. In the present study, although the number of patients with anemia was lower in the CFS group than in the SFS group, the mean Hb value was still lower in the CFS group. It is not possible here to speculate on the relationship between anemia and FS development due to the retrospective design of the present study and absence of a control group, although the Hb value may be considered a useful marker in the differentiation of seizure types.

RDW is a routinely used test to define the etiology of anemia, and is an index that automatically measures the heterogeneity of erythrocytes. Moreover, RDW has been shown to be positively correlated with inflammatory markers in the presence of certain diseases (such as cardiovascular and autoimmune diseases and cancer) and can therefore be considered as a potential inflammatory marker (21). In a study by Goksugur et al. (22), RDW was shown to be a simple, effective and practical marker for the differentiation of FS types, while another study has reported that RDW was not significantly helpful in the differentiation of FS types (23). In the present study, the mean RDW value was elevated in the CFS group, although the difference between two groups was not statistically significant. As RDW may be influenced by several parameters, including the method of measurement, additional prospective studies including larger patient groups are required to better understand the role of RDW in differentiating between seizure types.

There is evidence that inflammatory cells and proinflammatory cytokines play significant roles in the etiopathogenesis of febrile seizures, as inflammation enhances neuronal excitability in the brain and decreases seizure threshold. Platelets have been shown to play critical roles not only in hemostasis, but also in the immune system and in inflammation, and there have been studies investigating the relationship between platelet indexes and FS (24). Platelet indexes, including PLT, MPV, PDW and PCT, are all markers of platelet activity, and the MPV reflects the size of platelets and the rate of platelet production in bone marrow. This can be considered as an easily accessible marker of platelet activation that does not result in any additional cost, and the method has been investigated related to several diseases as a marker of platelet activation and the severity of inflammation (22-24). A study investigating the relationship between febrile seizure types and MPV considered epilepsy as an inflammatory disease of the brain, and demonstrated significantly lower MPV values in the presence of CFS. A ROC analysis was indicated that the optimum cut-off MPV level for CFS as 8.25 fL (20). Contradicting of the findings of this study, a study by Ozkale et al. (25) investigating the relationship between platelet indexes and FS found that the increased platelet cycle in the CFS group, decreased PLT and the markedly increased MPV value, was considered to play a significant role in the prediction of FS severity in children. In two further studies it was reported that decreases or increases of MPV were not significantly different between the two types of FS (22,26), but that

MPV was significantly higher in the CFS group than in the SFS group. The corresponding cut-off value for MPV was 6.9 fL and this level had 85.71% sensitivity and 39.05% specificity for use in the differential diagnosis of CFS and SFS (AUC=0.632). We believe that further studies should be made involving larger patient populations, as previous studies have demonstrated different MPV cut-off values.

PDW is a marker of platelet volume variation, and increases in the presence of platelet anisocytosis. PCT, on the other hand, is the ratio of total platelet volume to total blood volume. While an MPV decrease or increase has been associated with febrile seizures in some studies, only a few studies have investigated PDW in FS. In the study by Ozkale et al. (25), MPV and PDW values measured one hour after a seizure were found to be higher in the CFS group than in the SFS group, while no difference between the two groups was identified after one month. The increased MPV and PDW values were thought to reflect the increased severity of inflammation in the CFS group. In the present study, PCT and PDW were not significantly different between the two groups.

The ratio of neutrophils and platelets to lymphocytes, which may be used as stand-alone inflammatory markers, can also be helpful as markers of early inflammation (27). The physiological response of circulating leukocytes under various stress conditions is characterized by an increase in the neutrophil count and a decrease in the lymphocyte count. Zahorec R. (28) showed that neutrophil and lymphocyte counts (absolute and/or relative percentages) and their ratios, as markers of systemic inflammation, are easily-measured parameters that may reflect disease severity. In addition, there have been several studies in literature investigating the relationship between the NLR value and different clinical conditions, such as pneumonia, acute abdomen, and chronic liver failure (29,30). Recent studies have also evaluated the role of NLR in differentiating febrile seizure types, and it has been indicated that NLR has a potential value in FS management (22,24). In the present study, NLR was significantly different between the two groups, and a ROC analysis showed that an NLR cut-off value of 5.58 had a sensitivity and specificity of 57.14% and 83.02%, respectively. Cut-off values for NLR were reported as 2.134 in the study by Yigit et al. (24) involving 142 patients, while these values were reported as 1.98 in the study by Goksugur et al. (22), including 112 patients. Despite the number of patients in the present study being similar to previous studies, we identified a higher cut-off value in this study. We believe that NLR may serve as a useful guide for clinicians as an objective, cheap and easily calculated parameter that is used routinely in clinical practice and it does not incur any additional costs.

Like NLR, the PLR is also an effective and simple thrombo-inflammatory marker that may reflect inflammation. It has been suggested to use as a predictive and prognostic parameter in several conditions, including cardiovascular diseases, pneumonia, Hepatitis B and C, vestibular neuritis, thyroid disorders and malignancies, and has also been associated with gestational diabetes mellitus, acute appendicitis, preeclampsia, recurrent pregnancy loss and preterm delivery in pregnant women (30-32). PLR was significantly different between the two groups in the present study, and a ROC analysis showed a cut-off PLR value as 141.9. The PLR is also an objective and cheap parameter that can be easily calculated and used routinely in clinical practice.

When the AUC for NLR-PLR and Hb-MPV were compared in the present study, no significant differences were noted. Accordingly, we believe that all of these parameters are suitable for the differentiation of the two seizure types.

In conclusion, this is one of the few studies investigating the relationship between hemogram parameters and FS types in children. Although this study has a relatively small sample size, we believe that our findings may help clinicians in using Hb, MPV, NLR and PLR parameters to differentiate between FS types, particularly in patients with an unclear seizure history. Moreover, rather than using platelet, WBC or lymphocyte counts alone, a simultaneous evaluation of PLR and NLR values would appear to be more appropriate for the assessment of inflammation. As this study was performed retrospectively on a relatively small patient group, and demonstrated conflicting results with previous studies, we stress that larger prospective studies are required on this matter.

Conflict of Interest: Authors declared no conflict of interest.

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Prenatal Genetic Diagnostic Test Outcomes in Van Province and Nearby Cities in Eastern Turkey

Van ve Çevresinde Bulunan Türkiye'nin Doğu İllerindeki Prenatal Genetik Test Sonuçları

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ABSTRACT

Aim: The aim of this study is to retrospectively evaluate the indications and karyotype results of amniocentesis and chorion villus sampling performed in Health Sciences University, Van Education and Research Hospital, Department of Perinatology.

Material and Methods: In this study, 157 patients who underwent amniocentesis and 58 patients who performed chorion villus sampling procedure for different indications in our perinatology clinic between March 2017 and March 2019 were evaluated retrospectively. A spinal needle of 22-Gauge for amniocentesis procedure and a 20-Gauge spinal needle for chorionic villus sampling were used.

Results: Genetic abnormality was detected in 14.6% of amniocentesis (n=23) and 34.5% of chorion villus sampling cases (n=20). Twenty (87.0%) of the chromosomal anomalies detected in amniocentesis and 18 (90.0%) of the anomalies detected in chorionic villus sampling were numerical anomalies. The most common chromosomal anomaly of these numerical anomalies was trisomy 21. The most common indication for patients who underwent amniocentesis and chorionic villus sampling was abnormal ultrasound findings, followed by high risk in triple or quadruple test.

Conclusion: Amniocentesis and chorion villus sampling are commonly performed invasive tests for prenatal diagnosis of genetic diseases. The indications of amniocentesis and chorion villus sampling procedures and the rate of genetic anomaly detected as a result of genetic analysis applied to these samples in our clinic were compatible with literature. It is thought that this study will contribute to the literature since this is the first study that evaluates the results of amniocentesis and chorion villus sampling in Van and nearby cities.

Keywords: Amniocentesis; chorion villus sampling; chromosomal anomaly.

ÖZ

Amaç: Bu çalışmanın amacı, Sağlık Bilimleri Üniversitesi Van Eğitim ve Araştırma Hastanesi Perinatoloji Kliniğinde gerçekleştirilen amniyosentez ve koryon villus örneklemelerinin endikasyon ve karyotip sonuçlarının retrospektif olarak değerlendirilmesidir.

Gereç ve Yöntemler: Bu çalışmada, Mart 2017 ve Mart 2019 tarihleri arasında perinatoloji kliniğimizde çeşitli endikasyonlar ile amniyosentez uygulanan 157 hasta ve koryon villus örnekleme işlemi yapılan 58 hasta geriye dönük olarak incelendi. Amniyosentez işlemi için 22 Gauge spinal iğne ve koryon villus örneklemesi için ise 20 Gauge spinal iğne kullanıldı.

Bulgular: Amniyosentez yapılan olguların %14,6'sında (n=23) ve koryon villus örneklemesi yapılan vakaların ise %34,5'inde (n=20) genetik anomali saptandı. Amniyosentez sonucunda saptanan kromozom anomalilerinin 20'si (%87.0) ve koryon villus örneklemesi sonucunda saptanan anomalilerin ise 18'i (%90,0) sayısal anomali idi. Bu sayısal anomaliler arasında en sık saptanan kromozom anomalisi trizomi 21 idi. Amniyosentez ve koryon villus örneklemesi yapılan hastalarda en sık endikasyon anormal ultrason bulguları olup bu endikasyonu üçlü veya dörtlü testte risk yüksekliği takip etmekte idi.

Sonuç: Amniyosentez ve koryon villus örneklemesi, genetik hastalıkların prenatal tanısında sıklıkla kullanılan invaziv yöntemlerdir. Kliniğimizde amniyosentez ve koryon villus örnekleme endikasyonları ile örneklere uygulanan genetik analiz sonucu saptanan genetik anomali oranı literatür ile uyumlu idi. Bu çalışmanın, Van ve çevre illerdeki amniyosentez ve koryon villus örnekleme sonuçlarının değerlendirildiği ilk çalışma olması nedeniyle literatüre katkı sağlayacağı düşünülmektedir.

Anahtar kelimeler: Amniyosentez; koryon villus örneklemesi; kromozom anomalisi.

INTRODUCTION

Invasive prenatal tests are crucial to detect genetic diseases during pregnancy (1). It provides genetic information to detect chromosomal anomalies found in the fetus in the early stages of pregnancy and enables the patients to decide on termination or birth of the fetus with the anomaly (2). There are indirect (non-invasive) methods including first trimester screening test (nuchal translucency (NT), free beta-hCG, PAPP-A), second trimester screening test (triple and quadruple screening tests) and fetal DNA determination on maternal circulation which form non-invasive techniques to determine the risk of genetic anomalies (3-5).

Chorionic villus sampling (CVS), amniocentesis and cordocentesis are performed in different gestational weeks to provide the precise diagnosis. CVS is performed between the 11st and 14th gestational weeks. CVS is a more preferable test over amniocentesis since it provides early diagnosis (6). Amniocentesis is the most frequently used prenatal invasive test to detect the fetal chromosomal anomalies. Although it is appropriate to perform amniocentesis between the 14th and 22nd weeks, the most suitable period for the process is between the 16th and 17th weeks at which culture success and fetal cell growth is the highest. Advanced maternal age, recurrent abortions, history of chromosome anomaly, stillbirth, parents with chromosome anomaly, high risk in maternal serum screening tests, abnormal ultrasound finding and family request are indications for amniocentesis. Even though prenatal invasive tests have some complications including amnion fluid leakage, vaginal bleeding, uterine contraction and fetal loss, it is known that complication rates are inversely proportional with experience of the clinicians and it is regarded as a reliable method with acceptable complication rate (7). Cordocentesis is another invasive method which is preferred after 21st gestational week and the advantage of cordocentesis is that it provides early culture result and it can be used in late cases or in failed amniocentesis cases (1).

In this study, we evaluated indications, cytogenetic analysis and results of CVS and amniocentesis performed in the eastern of Turkey.

MATERIAL AND METHODS

In this study, data of 215 pregnant patients, who were admitted to the Perinatology Clinic of Health Sciences University, Van Education and Research Hospital from March 2017 to March 2019 and created the sampling of amniocentesis and chorion villus with various indications, was evaluated retrospectively. The data was examined with regard to indicative distribution and karyotype results of invasive procedures. Genetic counseling was given to all patients about the procedure before invasive operations. Ethic committee approval was taken from Van Education and Research Hospital, the approval number: 2019/07, date: 04.04.2019. Complications that may occur during and after the procedure were described to each patient and her husband, and written approval forms were signed by all couples. Detailed ultrasonographic evaluation including fetus biometric measurements, fetal heartbeat, and placenta localization was performed for all the patients before the procedure, and skin cleaning with povidone-iodine was provided before procedure as well. 10-15 microgram placenta sample was obtained using 1 Gauge spinal needle for CVS with the aid of the injector and transported to the transport medium. It was entered through the gestational sac from where it was the farthest to fetus and the largest to amniotic pocket with 22 Gauge sharp tip spinal needle in case of amniocentesis. The first aspirated amniotic fluid of 2 cc expelled out in order to decrease maternal contamination risk; amniotic fluid was aspirated to 2 separate injectors at 1 cc per pregnancy week. Both procedures were performed with USG-guidance. After these procedures, all patients were enable to listen to fetal heart beat; fetal viability was proven. Patients were monitored for possible complications after operation. Post-processing rhogam practice was done to patients who had Rh incompatibility.

All fetal samples were sent to the Department of Medical Genetics for genetic examination under proper circumstances. Two cultures were made for each fetal sample and 2 preparations were prepared on average. The preparations were painted with G banding method with the aid of Giemsa and Trypsin, and in average 20 metaphases were examined for each sample on microscope and imaging system. Metaphases were examined by at least two analyzers; numerical and structural anomalies in chromosomes were named and recorded according to the International System for Human Cytogenetic Nomenclature (ISCN).

Statistical Analysis

Descriptive statistics were used to summarize the data, and given as mean±standard deviation, median (minimum-maximum), and number (percentage). Statistical analyses were made using Excel 2019.

RESULTS

Invasive procedures were performed to 215 patients who were admitted to the Perinatology Clinic of Van Education and Research Hospital, Health Sciences University between March 2017 and March 2019. The amniocentesis was performed to 157 (73.0%) patients and CVS to 58 (27.0%) patients. Our patients were between the ages of 16-52, and the mean age was 31.05±7.31 years. Seventy three (34.0%) of the patients were 35 years and older. While mean week of gestation was 17 weeks and 3 days (17.42±1.54) in amniocentesis patients, it was 12 weeks and 4 days (12.57±0.95) in CVS patients.

The indications for performing the invasive procedures were defined as increased risk in maternal serum screening tests, increase in NT, abnormal ultrasound findings and others (advanced maternal age, IUGR, history of baby chromosomal abnormality, family history). The indications for amniocentesis of the 157 patients analyzed were the presence of pathological findings in ultrasonography (n=80, 50.9%), high risk in triple or quadruple screening tests (n=46, 29.3%), increased NT (n=11, 7.0%), high risk in combined test (n=10, 6.4%), and some other causes (n=10, 6.4%). Also, indications for the CVS were the presence of increased NT (n=22, 37.9%), pathological ultrasound findings (n=21, 36.2%), high risk in combined test (n=12, 20.7%) and other causes (n=3, 5.2%). Data on the distribution of indications for amniocentesis and CVS were shown in Table 1.

Table 1. Distribution of indications for amniocentesis and chorionic villus sampling, n (%)

Indication	Amniocentesis (n=157)	CVS (n=58)
High risk in combined test	10 (6.4)	12 (20.7)
High risk in triple or quadruple test	46 (29.3)	0 (0.0)
Increased NT thickness	11 (7.0)	22 (37.9)
Abnormal findings in ultrasound	80 (50.9)	21 (36.3)
Other	10 (6.4)	3 (5.1)

CVS: Chorionic Villus Sampling, NT: Nuchal Translucency

Chromosomal anomaly was detected in 43 (20.0%) patients in total. Of these, 23 (10.7%) patients were amniocentesis cases and 20 (9.3%) patients were CVS cases.

Moreover, in our amniocentesis results, chromosomal anomaly was identified in 17 (21.3%) of the 80 patients for whom the procedure was performed due to pathological USG finding; in 3 (6.5%) of 46 patients who have high risk of triple or quadruple screening tests; in 2 (20.0%) of 10 patients who have high combined risk; in 1 (9.1%) of 11 patient who have increased NT thickness. In terms of chromosomal changes, numerical anomaly were detected in 20 (87.0%) of 23 patients; only in 3 (13.0%) of them had structural anomaly. Trisomy 21 (n=11, 47.8%) was the most common numerical anomaly, followed by trisomy 18 (n=3 13.0%). Trisomy 13, triploidy, Turner Syndrome, structural changes belong to X chromosome were the other chromosomal abnormalities. Also, one patient was performed the ESCO2 gene analysis due to the presence of pathologic USG findings and diagnosed as Roberts Syndrome. Rates of chromosomal anomalies according to the indications for amniocentesis were shown in Table 2.

In the CVS results; chromosomal anomaly was detected in 9 (40.9%) of 22 patients for whom the invasive procedure was performed due to increased NT; in 8 (38.1%) of 21 patients who had pathologic USG findings; in 2 (16.7%) of 12 patients who had high risk of combined test; in 1 (33.3%) of 3 patients who performed CVS due to other indications. In the 18 (90.0%) of 20 patients having chromosomal changes, numerical anomaly was detected, but the rest of the patients (n=2, 10.0%) had structural anomaly. The most common numerical anomalies were trisomy 21 (n=5, 25.0%) and trisomy 18 (n=3, 15.0%) respectively, similar to the results of amniocentesis. Trisomy 13, trisomy 14, trisomy 7, triploidy, Turner syndrome and tetrasomy 12p were among the other chromosomal abnormalities. Rates of chromosomal anomalies according to the indications for CVS were shown in Table 3.

The amniocentesis and the CVS were performed successfully at the first attempt in 56 patients, at the second attempt in 2 patients. No patients needed more than two attempts. The sufficient placenta sample was obtained in all CVS patients at the first entry. There were not any complications after the both procedures. The karyotype results could not be obtained from two patients (0.9%) performed CVS due to culture failure.

DISCUSSION

Prenatal diagnostic methods have been implemented since the 1950s in order to determine genetic anomalies during the pregnancy (8). Especially after 1980s, both CVS and amniocentesis have been performed under USG-guidance which also resulted in the increase in success rate of the processes (9,10). While amniocentesis is the most frequently used invasive prenatal diagnostic method due to low complication rate and high culture reproduction success; the CVS is the gold standard of prenatal diagnosis in the first trimester which enables to detect the possible genetic disorders of the fetus in the earliest period (11,12). The most common indications of CVS are; increased risk of first trimester screening test, increased NT, pathological USG findings, advanced maternal age, recurrent abortions in the family or a baby history with chromosomal anomaly (12,13). The reliability of CVS is accepted as 99.5%, but false negativity or positivity may be seen due to maternal contamination or placental mosaicism (14). Procedure-related pregnancy loss, increased risk of extremity defect in early week procedures are the common complications of

Table 2. Distribution of karyotype results according to the indications for amniocentesis

Indication	Normal	Trisomy 21	Trisomy 18	Structural anomaly	Others
High risk in combined test	8 (80.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (10.0)
High risk in triple or quadruple test	43 (93.5)	2 (4.3)	0 (0.0)	0 (0.0)	1 (2.2)
Increased NT thickness	10 (90.9)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal findings in ultrasound	63 (78.7)	7 (8.7)	3 (3.7)	3 (3.7)	4 (5.0)
Other	10 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 3. Distribution of karyotype results according to the indications for chorionic villus sampling

Indication	Normal	Trisomy 21	Trisomy 18	Structural anomaly	Others
High risk in combined test	10 (83.3)	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)
Increased NT thickness	13 (59.1)	3 (13.6)	1 (4.5)	1 (4.5)	4 (18.2)
Abnormal findings in ultrasound	13 (61.9)	1 (4.8)	2 (9.5)	1 (4.8)	4 (19.0)
Other	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)

CVS (15,16). In our study, the most common CVS indication was the increase in NT (37.9%), followed by the presence of pathological findings in USG (36.3%), increased risk in the first trimester combined test (20.7%) and some other reasons (5.1%). Bilen et al. (12) in a study with 42 patient who performed CVS observed that the most common indication of the procedure was advanced maternal age (33.3%) followed by increased risk in the first trimester screening test (26.2%) and presence of abnormality in ultrasonography (19%). In our study, maternal age over 35 was present in 12 of 58 patients who underwent CVS, but in these patients there were increased risk in the first trimester screening test or abnormal USG findings as well. Dağlar et al. (17) showed that increased risk of first trimester combined test (80%) was the most common CVS indication followed by advanced maternal age (13.3%). On the other hand, in a study of Oztas et al. (18) in the 354 patients who were performed CVS, increased risk of combined screening test (68.6%) was the most common indication for the procedure; followed by the increase in NT (19.2%).

Amniocentesis is the most commonly used invasive method in fetal genetic diagnosis. The indications of the procedure are the advanced maternal age, the increased risk results in maternal serum screening tests, pathological USG findings, history of having baby with the chromosomal anomaly, chromosomal anomaly in the parents and desire of the family (19). Although the most common indication is defined as the advanced maternal age in many studies, abnormal screening test result is the most common indication recently (20-23). This change about the indications was attributed to the increase in the reliability of screening tests and that the American Society of Obstetricians and Gynecologists (ACOG)'s January 2007 paper suggesting that screening tests should be performed for all pregnant women independent of the maternal age (24). In a study by Acar et al. (25) in 3721 amniocentesis cases, the most common indication was determined as the increased risk in maternal screening test (45.1%), followed by advanced maternal age (35.8%) and abnormal USG findings (15.8%). On the other hand, Tasdemir et al. (26) reported that the advanced maternal age was the most common indication (40.4%), whereas the increased risk in the maternal serum screening test was the second common indication (38.9%) in a study with 1429 cases. Gündüz et al. (27) observed that the advanced maternal age, which is the most common indication for 4-year prenatal cytogenetic studies, replaced its position to increased risk in triple testing in time. Similarly, the most common indication was found to be increased risk in triple screening tests in a study by Türkyılmaz et al. (28) that was performed in 481 patients. Furthermore, in a study by Serin et al. (29) that was performed in 561 cases, the most common indication was increased risk in triple screening tests (65.59%), followed by abnormal ultrasound findings (14.26%). In our study, presence of pathological finding in USG was the most common indication (50.9%). This indication was followed by increased risk in triple test (29.3%), increase in NT (7.0%), increased risk in the combined test (6.4%) and other causes (6.4%). Similarly, the most common indication was found to be pathological finding (29.4%) in USG in the study of Lostchuck et al. (30) that was performed in 16152 patients. The number of the patients who were performed invasive testing with indication of the advanced maternal age was not significantly high since most of these patients had also increased risk in screening tests or abnormal USG findings. Dilek et al. (31) applied to yield and cost analysis to the patients that underwent amniocentesis between the years of 2000-2005. It was emphasized that the efficacy of amniocentesis alone with advanced age indication was not enough; USG imaging and serum screening tests should be used together with this indication which supported our findings as well.

In our study, 134 of the patients had normal karyotype in total 157 cases that performed amniocentesis (85.4%). Chromosomal anomaly was present in 23 of the patients; 20 (87.0%) of them were numerical anomalies and 3 (13.0%) of them were structural anomalies. Trisomy 21 is the most frequently chromosomal anomaly among numerical anomalies. Trisomy 18 and trisomy 13 followed this anomaly. In the studies which were reporting the results of amniocentesis, it was seen that chromosomal anomaly rate varies between 1.5% and 14.3% in the literature (32). Stoll et al. (33) and Eddleman et al. (34) mentioned in their studies that the frequency of chromosomal anomaly was increased in the presence of fetal anomaly varying the rates between 4% and 27%. Fu et al. (35) showed that frequency of chromosomal anomaly was 18% in patients with pathologic findings in ultrasound while, this rate was reported as 27.1% in the study of Dallaire et al. (36). In our study, 80 of the patients of total 157 cases who were performed amniocentesis had abnormal findings in USG and high rate of chromosomal anomaly (14.6%) correlates with the literature.

In this study, 38 of 58 CVS cases (65.5%) had normal karyotype. Chromosomal anomaly was present in the 20 patients; 18 of them were numerical anomalies and 2 of them were structural anomalies. Trisomy 21 was the most common numerical chromosomal anomaly followed by trisomy 18, trisomy 13, triploidy, Turner Syndrome and trisomy 14. Daglar et al. (17) showed that the chromosomal anomaly rate was 26.6% in CVS cases and 20% of them had numerical anomaly. In the study by Bilen et al. (12) in 42 CVS cases, chromosomal anomaly rate was reported as 35.7%, and the most common anomaly was trisomy 21 in 53.5% of the cases.

As a result; in our study the abnormal karyotype rate was 14.6% in 157 amniocentesis samples, and 34.5% in 58 CVS samples. There were no false negative or false positive results. Maximum two attempts were performed to the patients; thus, sufficient amniotic fluid and placenta samples were obtained. Fetal loss occurred in one patient who were performed CVS had also hydrops fetalis during the procedure. In our study, it was determined that abortion rate after CVS was 1.7% which is similar to the literature and there was not any complication after amniocentesis (16). Recently, some methods such as fetal DNA screening in the maternal blood have been developed and they are recommended to be used to detect fetal chromosomal anomalies. However, this cell free DNA testing (NIPT) can only be used as a screening test (37), and invasive tests are required for confirmation of the result (38). This is the first study analyzing the data of Van and nearby cities on the amniocentesis and CVS results and we thought that it will shed light on future studies.

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The Effect of the Ministry of Health's Periodic Free Drug Policy on Smoking Cessation Polyclinic

Sağlık Bakanlığının Dönemsel Ücretsiz İlaç Politikasının Sigara Bırakma Polikliniğine Olan Etkisi

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ABSTRACT

Aim: The aim of this study is to evaluate the effect of periodic free drug applications of the Ministry of Health on Smoking Cessation Polyclinic (SCP) and the success rates of the treatment methods used.
Material and Methods: A total of 1861 patients applied to SCP in a county state hospital in Şanlıurfa between January 1 and December 31, 2017 were included in this study. Patients not smoke for at least six months were accepted as non-smokers. Each patient was followed up for at least six months. The data was calculated as number and percentage.
Results: According to months the highest application was seen in December. In July and November, there was a significant decrease in the number of patients applying to SCP. It was determined that 80.0% of the patients received behavior therapy, 20.0% received pharmacological treatment. Utilization of pharmacological treatment was the lowest in July with no patient and the highest in November with 96.8%. The rate of quitting with pharmacological treatment was 27.4% while this rate was 18.9% with behavioral therapy.
Conclusion: The Ministry of Health's periodic free drug application policy has a direct impact on SCPs. This may be the reason for resistance in patients to smoking cessation with behavioral therapy. Smoking cessation treatments should be provided throughout the year. It is recommended that free drug treatments include all drugs and supply from pharmacies through report. We think that with these arrangements, the compliance of patients to treatment and their determination to quit smoking will increase.
Keywords: Behavior therapy; health policy; pharmacotherapy; smoking; smoking cessation

ÖZ

Amaç: Bu çalışmanın amacı Sağlık Bakanlığı'nın dönemsel ücretsiz ilaç uygulamalarının Sigara Bırakma Polikliniği (SBP)'ne olan etkisi ve kullanılan tedavi yöntemlerinin başarı oranlarının değerlendirilmesidir.
Gereç ve Yöntemler: Bu çalışmaya 1 Ocak ve 31 Aralık 2017 tarihleri arasında Şanlıurfa'da bulunan bir ilçe devlet hastanesinde SBP'ye başvuran toplam 1861 hasta dahil edildi. En az altı ay boyunca sigara içmeyen hastalar sigarayı bırakmış olarak kabul edildi. Her hastanın en az altı ay süreyle takibi yapıldı. Elde edilen veriler sayı ve yüzde olarak hesaplandı.
Bulgular: Aylara göre en yüksek başvurunun Aralık ayında olduğu görüldü. Temmuz ve Kasım aylarında ise SBP'ye başvuran hasta sayılarında belirgin bir düşme vardı. Hastaların %80,0'inin davranış terapisi aldığı, %20,0'sinin ise farmakolojik tedavi aldığı tespit edildi. Farmakolojik tedavi uygulaması en düşük hiç hastanın olmadığı Temmuz ayında ve en yüksek ise %96,8 ile Kasım ayında idi. Farmakolojik tedavi ile bırakma oranı %27,4 iken davranış terapisi ile bırakma oranı ise %18,9 idi.
Sonuç: Sağlık Bakanlığı'nın dönemsel ücretsiz ilaç uygulama politikası SBP'yi direkt olarak etkilemektedir. Bu durum, hastalarda davranış terapisi ile sigara bırakmaya karşı bir direnç nedeni olabilmektedir. Sigara bırakma tedavilerinin yıl boyu karşılanması gereklidir. Ücretsiz ilaç tedavilerinin tüm ilaçları kapsaması ve rapor karşılığı eczanelerden temini yoluna gidilmesi önerilir. Bu düzenlemeler ile hastaların tedaviye uyumu ve sigara bırakma kararlılığının artacağını düşünmekteyiz.
Anahtar kelimeler: Davranış tedavisi; sağlık politikası; farmakoterapi; sigara içme; sigarayı bırakma

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INTRODUCTION

Smoking is an important public health problem, and there has been no sign of improvement. It results in social and economic harm, is responsible for numerous diseases, and decreased quality of life. Cigarette addiction treatment is important for public health, preventive medicine, and chest diseases (1,2). Even simply explaining the harms of smoking and recommending a patient to quit may increase the likelihood of smoking cessation (3). With respect to cessation therapies, behavioral training and pharmacotherapy are two proven approaches to therapeutic support (3,4). The aim of this study was to evaluate the application of The Ministry of Health's periodic free drug delivery policy, the methods and success rates of treatments used in Smoking Cessation Polyclinic (SCP).

MATERIAL AND METHODS

This is a retrospective registry-scan design study performed between January 1, 2017 and December 31, 2017. A total of 1861 patients who had applied to the SCP of Şanlıurfa Ceylanpınar County State Hospital were included in the study. Quarterly reports of 1861 patients admitted to the SCP were evaluated. Drug therapy and behavior training were recorded in terms of supportive therapy. The data were organized as quarterly reports requested by the Ministry of Health. Persons who did not smoke for at least six months were considered as nonsmoker who quit smoking. For this reason, regardless of which month they applied, patients were followed up for at least six months. This study was approved by the Harran University Ethical Committee (01.02.2018; session: 02; decision no: 08).

Statistical Analysis

Descriptive statistics of the data were calculated as numbers and percentages in quarterly periods for each treatment method.

RESULTS

Of the 1861 patients admitted to the SCP, 1489 (80.0%) were received behavior therapy and 372 (20.0%) were received pharmacological treatment (Table 1). When the distribution of treatment modalities by months was examined, it was observed that the lowest number of pharmacological treatment was in July with no patient and the highest number was in November with 60 (96.8%) applicants. Behavior therapy was at its lowest in November with 2 (3.2%) patients and highest in July with 34 (100%) patients (Table 1).

When the smoking cessation status of the patients admitted to the SCP was examined according to treatment methods, 102 (27.4%) of the 372 patients received pharmacological treatment were shown to have quit smoking since three months while 102 (27.4%) patients had not quit smoking, and there were 168 (45.2%) patients with unknown status (Table 2).

When the smoking cessation status of the patients who had applied to the SCP and received behavioral therapy was examined, of the total 1489 patients, 282 (%18.9) had quit smoking while 672 (45.1%) of them continued to smoke. The number of patients with unknown status was 535 (35.9%) among patients who had received behavioral therapy (Table 3).

Table 1. Monthly distribution of treatment modalities of patients admitted to smoking cessation polyclinic, n (%)

	Pharmacological Treatment	Behavior Therapy	Total
January	1 (0.8)	130 (99.2)	131
February	4 (3.1)	125 (96.9)	129
March	11 (6.5)	157 (93.5)	168
April	21 (15.8)	112 (84.2)	133
May	20 (13.8)	125 (86.2)	145
June	32 (22.7)	109 (77.3)	141
July	0 (0.0)	34 (100)	34
August	51 (20.1)	203 (79.9)	254
September	45 (35.4)	82 (64.6)	127
October	42 (29.8)	99 (70.2)	141
November	60 (96.8)	2 (3.2)	62
December	85 (21.5)	311 (78.5)	396
Total	372 (20.0)	1489 (80.0)	1861

Table 2. Three monthly smoking cessation status of patients receiving pharmacological treatment, n (%)

	Stopped	Not stopped	Unknown	Total
Jan-Mar	12 (75.0)	4 (25.0)	0 (0.0)	16
Apr-Jun	25 (34.2)	10 (13.7)	38 (52.1)	73
Jul-Sep	20 (20.8)	46 (47.9)	30 (31.3)	96
Oct-Dec	45 (24.1)	42 (22.5)	100 (53.5)	187
Total	102 (27.4)	102 (27.4)	168 (45.2)	372

Jan-Mar: January to March, Apr-Jun: April to June, Jul-Sep: July to September, Oct-Dec: October to December

Table 3. Three monthly smoking cessation of patients receiving behavior therapy, n (%)

	Stopped	Not stopped	Unknown	Total
Jan-Mar	88 (21.4)	274 (66.5)	50 (12.1)	412
Apr-Jun	87 (25.1)	80 (23.1)	179 (51.7)	346
Jul-Sep	32 (10.0)	167 (52.4)	120 (37.6)	319
Oct-Dec	75 (18.2)	151 (36.7)	186 (45.1)	412
Total	282 (18.9)	672 (45.1)	535 (35.9)	1489

Jan-Mar: January to March, Apr-Jun: April to June, Jul-Sep: July to September, Oct-Dec: October to December

DISCUSSION

In our study, the number of patients who applied to the SCP in one year was 1861. Behavior therapy was not conducted in November, while pharmacological treatment was highest at 96.8%. In July, no patient was given pharmacological treatment. The rate of patients receiving behavior therapy was 80.0% and pharmacological treatment was 20.0%. With respect to pharmacological treatment, it was found that 27.4% had stopped smoking, 27.4% had not quit and their status was unknown in the 45.2% of patients. With regard to behavior therapy, 18.9%

had quit, 45.1% had not and no determination could be made for 35.9% of the patients.

At the end of one year, smoking cessation success rates were found to be 30% in a study by Bakkevic et al. (5), 37.4% in a study by Yaşar et al. (6), and 27.9% in a study by Çelik et al. (7). Our study showed lower smoking cessation rates at the end of three months compared these studies.

While there is one smoking cessation outpatient clinic in South Africa (8), the number in Turkey was 25 in 2002 and had exceeded to 400 in recent years (1). The extensive healthcare service provided at these outpatient clinics includes the distribution of some 300000 pharmacotherapy drugs free of charge - as such, it is important that these resources are used efficiently within the context of public health strategies (9). In our hospital, smoking cessation counseling was provided to 1861 patients at the SCP. Our relatively low smoking cessation rates might be explained by some factors related both subjects and SCPs. Pıçakçıefe et al. (10) reported that the most frequent applications to the SCP were in the spring. In our study, the highest number of applications was in the December. The high level of pharmacological treatment in November and the exceptionally high level of admissions to the SCP in December coincided with the Ministry of Health's free distribution of smoking cessation drugs. The refusal of behavior therapies by these patients can only be explained by their requests for pharmacological treatment.

As pharmacotherapy is expensive and was provided by free of charge by the Ministry of Health, there is evidence to suggest that patients have attempting to secure the drug in advance for later use (11).

In their study, Berkeşoğlu et al. (12) found that the success rate for quitting was 30.9% among those receiving free medication provided by the Ministry of Health, while the success rate for treatment in the paid group was 18%. Similar studies reported no difference in smoking cessation rates between those in receipt of paid/free medication (13,14).

In the most comprehensive study involving smoking cessation medications in China, 43% of the patients received pharmacotherapy (15). In our study, only 20.0% of patients received pharmacotherapy.

In the literature, the combination of pharmacotherapy and behavior education treatment resulted in a one-year cessation rate of 52.3%, and a rate of 14.0% for behavior therapy alone (12). In our study, the combination of pharmacotherapy and behavior therapy resulted in a cessation rate of 27.4%, whereas 18.9% of the patients who received only behavior therapy were successful in stopping smoking.

It has been shown that with respect to smoking cessation rates, that encouraging patients to stop has a better outcome than making no recommendations at all (16). A high level of patient compliance has also been shown to be effective in the patient's successfully stopping smoking (17-19). Although there is evidence to suggest that encouraging patients to stop smoking (by issuing coupons, paying cash, and giving gifts) results in an improvement in both short and long term success rates, debates continue on this matter (20). Encouraging the patient as well as his or her physician are other issues discussed in relation to these processes (21).

Most smokers perceive deterioration in their quality of life over time (11). They then try to quit smoking to halt this downward trend, however, most of these efforts fail (22). Smoking cessation will be more effective if such patients know that professional support is available and that pharmacotherapy support will be provided when necessary (23).

A number of findings in our study about SCP have been reported previously in the literature. These are:

- The Ministry of Health's periodic unpaid drug delivery policy is applied in a different city, different month in the year;
- Some of the smoking cessation drugs are not in stock while some are also plentiful.
- Admissions for the use of drugs in the months when they are declared to be free of charge or to take drugs for later use indirectly leads to rejection of behavior therapy;
- If the SCP is the only program in the health center, the performance of the attending physician will vary from month to month, as such, the motivation of follow-up of patients or of those who have been recently admitted to the program may decrease.
- Lack of regular follow-up of patients and insufficient supportive treatment may lead to resistance and hopelessness, such as the idea that patients will not be able to quit smoking despite the use of behavior or pharmacotherapy.
- Monitoring of the use of smoking cessation drugs, addressing possible questions, and eliminating problems will increase compliance and stability of treatment.

As a result, a behavior therapy in patients who want to quit smoking is important. In addition to behavior support, pharmacotherapy may positively affect treatment success. The periodic free drug delivery policy of the Health Ministry directly affects the SCP and may result in resistance on the part of patients to behavior therapies. Like other medicines used in the treatment of chronic diseases, smoking cessation treatments should be supplied year-round by pharmacies on the production of a report. In addition, in order to follow-up the patient and increase the success of cessation treatments, the drugs should be supplied in packages of 2-weeks duration. We think that with these arrangements, the compliance of patients to treatment and their determination to quit smoking will increase.

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Gynecomastia Treatment with Liposuction: Clinical Experience

Liposuction ile Jinekomasti Tedavisi: Klinik Deneyim

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ABSTRACT

Aim: Gynecomastia is the visible enlargement of the male breast tissue either due to physiologic, pathologic or drug-related causes. Physiological and pathological gynecomastia occurs because of the derangement of the estrogen and androgen metabolism. Drug-related gynecomastia is seen when using drugs affecting this hormone metabolism as well as a side effect of different drugs. Successful treatment of gynecomastia was reported with medical treatment and cessation of the possible causative drugs especially in early period, and with direct excision, endoscopic subcutaneous mastectomy and excision with liposuction treatments in the late period.

Material and Methods: In this study, we reported our results of gynecomastia treatment with suction assisted wet liposuction in 3 different planes using 3 different thickness cannulas in Grade I, II and III patients. Forty five patients were operated between 2009 and 2019 using this technique in our clinique. All patients were followed for up to a minimum of 6 months to observe the complication rate and the final aesthetic result.

Results: Within the 45 patients evaluated in this study, the complication rate was 6.7%, the success rate of the operation was 93.3% and the patient satisfaction was 91.1%. Gynecomastia treatment in general -especially liposuction- was reviewed and our results were evaluated based on the literature results.

Conclusion: There are many different options for gynecomastia treatment. In this study, we concluded that in Grade I, II, and III patients good results can be achieved and patient satisfaction is high in gynecomastia treatment with wet liposuction.

Keywords: Endocrine breast diseases; gynecomastia; liposuction; body contouring

ÖZ

Amaç: Jinekomasti fizyolojik, patolojik veya ilaca bağlı nedenlerle erkeklerdeki normal meme dokusunun görünür hale gelecek kadar büyümesidir. Fizyolojik ve patolojik jinekomasti östrojen ile androjen metabolizmasındaki bozulmadan dolayı ortaya çıkmaktadır. İlaca bağlı jinekomasti ise yine bu hormonal metabolizmayı etkileyen hormonlar dışında farklı ilaç gruplarında da yan etki olarak görülebilmektedir. Jinekomasti tedavisinde özellikle erken dönemde medikal tedavi ve neden olabilecek ilaçların kesilmesi, daha ileri dönemlerde ise direkt eksizyon, endoskopik subkutan mastektomi, liposuction yöntemleri ile eksizyon gibi çeşitli yöntemlerle başarılı sonuçlar bildirilmiştir.

Gereç ve Yöntemler: Bu çalışmada Evre I, II ve III hastalarda 3 farklı planda 3 farklı kalınlıkta kanüller ile aspirasyon destekli ıslak liposuction (suction assisted wet liposuction) tekniği ile jinekomasti tedavi sonuçlarımızı sunmaktayız. Bu teknik ile kliniğimizde 2009 ile 2019 arasında 45 hasta opere edilmiştir. Tüm hastalar operasyon sonrasında komplikasyon oranlarının ve nihai estetik sonucun gözlemlenebilmesi için postoperatif dönemde en az 6 ay takip edilmiştir.

Bulgular: Bu çalışmada değerlendirilen 45 hastada komplikasyon oranı %6,7, operasyon başarı oranı %93,3 ve hasta memnuniyeti %91,1 idi. Jinekomasti tedavisinde başta liposuction olmak üzere diğer mevcut tedaviler gözden geçirilmiş ve çalışmamızdaki sonuçlar literatür eşliğinde değerlendirilmiştir.

Sonuç: Jinekomastinin cerrahi tedavisinde mevcut çok sayıda farklı yöntem bulunmaktadır. Bu çalışmada ıslak liposuction yöntemi ile jinekomasti tedavisinde Evre I, II ve III hasta grubunda başarılı sonuçlar elde edildiği ve hasta memnuniyetinin yüksek olduğu gösterilmiştir.

Anahtar kelimeler: Endokrin meme hastalıkları; jinekomasti; liposuction; vücut şekillendirme

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INTRODUCTION

Male breast tissue is composed of small amount of ductal and stromal tissue instead of the glandular tissue found in female breast (1). Gynecomastia is the benign proliferation of these ductal and stromal tissues due to derangement of estrogen/androgen balance (2,3). This proliferation subsequently increases the visibility of normally invisible male breast tissue (4). The incidence of gynecomastia is reported as 32-70% in the literature, and 50% of cases occur bilaterally (1,5,6). In Turkey, Neyzi et al. (7) reported this incidence as 7% between ages 9 to 17 whereas Güvenç et al. (8) reported as 19.6% unilaterally and 34.6% bilaterally. There is no identifiable etiologic cause in 25% of gynecomastia cases and the remaining possible causes may be classified as physiological, pathological or drug-related (6). Derangement of hormonal balance in favor of estrogen may cause physiological or pathological gynecomastia (4,6). Common gynecomastia causes are listed in Table 1 (3,5,9). There are six different types of grading systems for gynecomastia. In Table 2, the three most commonly preferred grading systems -Cordova-Moschella, Rochrich, Simon- are listed (9-11). In our clinic, we prefer to use the Simon Classification as it is simple and practical (Table 2). Gynecomastia treatment is planned according to the grade of the disease, the nature of the breast tissue and the duration of symptoms. Even though the disease may regress especially in adolescents, treatment may be necessary as it causes pain and tenderness along with

Table 1. Causes of gynecomastia (3,5,9)

Physiological gynecomastia
• Neonatal period
• Adolescent period
• Senile period
Pathological gynecomastia
• Hypogonadism
• Testicular tumor
• Pituitary tumor
• Adrenal tumor
• Bronchogenic carcinoma
• Thyrotoxicosis
• Cirrhosis
• Kidney failure
Pharmacological gynecomastia
• Antibiotics (metronidazole, ketoconazole, minocycline, isoniazid)
• Hormones (estrogens, gonadotropins, androgens)
• Antiandrogens (spiranolactone, cimetidine, ketoconazole, flutamide, nilutamide, leuprolide)
• Cancer chemotherapy agents (alkylating agents, methotrexate, vinca alkaloids)
• Cardiovascular agents (verapamil, nifedipine, diltiazem, digoxin, captopril, enalapril, spironolactone, minoxidil)
• Antiulcer drugs (cimetidine, ranitidine, omeprazole)
• Psychiatric drugs (methyldopa, reserpine, anxiolytic drugs, haloperidol)
• Dopamine blockers (phenothiazides, meclopromide, domperidone)
• Central nervous system agents (tricyclics, diazepam, phenytoin, diethylpropion)
• Drugs (Mariuana, heroin, methadone, amphetamines)
• Anti-tuberculosis agents (isothiazide, ethionamide, thiacetazone)
• Other (Amiadorone, Clomiphene, Etretinate, Omeprazole, Penicillamine, Theophylline)

Table 2. Comparison of different classifications of gynecomastia

Cordova-Moschella (2006) (10)	Grade I	Increase in diameter and protrusion limited to the areolar region
	Grade II	Hypertrophy of all the structural components of the breast The nipple-areola complex is above the inframammary fold
	Grade III	Hypertrophy of all the structural components Nipple-areola complex at the same height as or about 1 cm below the inframammary fold
	Grade IV	Hypertrophy of all the structural components Nipple-areola complex more than 1 cm below the inframammary fold
Rochrich (2003) (9)	Grade I	Minimal hypertrophy (<250 g) without ptosis, Primary glandular, Primary fibrous
	Grade II	Moderate hypertrophy (250-500 g) without ptosis, Primary glandular, Primary fibrous
	Grade III	Severe hypertrophy (>500 g), Grade I ptosis
	Grade IV	Severe hypertrophy (>500 g), Grade II or III ptosis
Simon (1973) (11)	Grade I	Minor enlargement, no redundant skin
	Grade IIa	Moderate enlargement, no redundant skin
	Grade IIb	Moderate enlargement with minor skin redundancy
	Grade III	Gross breast enlargement with marked skin redundancy

psychological symptoms (6). The treatment may be planned as medically or surgically regarding the grade of the disease. Surgical treatment modalities are classified as liposuction or excisional methods chosen on patient characteristics (12). The effective results of these various treatment modalities in different patient groups are well documented in the literature (9,13-15). In this study, we present the results of our treatment method as liposuction using varying thickness cannulas in different tissue planes alone or with short scar excision in Simon Grade I, II and III patients (Figure 1). The advantages and disadvantages of this technique are discussed along with the relevant literature.

MATERIAL AND METHODS

Between 2009 and 2019, 45 gynecomastia patients were operated by liposuction +/- short scar excision in the Department of Plastic Reconstructive and Aesthetic Surgery at Abant İzzet Baysal University. The study was approved by Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee by the number 2019/300 and dated 19.12.2019. Written informed consent was obtained from all patients. Thirty-eight of the patients were primary and seven had previously been operated in other centers and presented with unsatisfactory results. Eight of the 38 patients were evaluated as Grade I, twenty-six as Grade II, and four as Grade III (Figure 1). Fat volume obtained by liposuction was calculated as minimum 100 cc and maximum 1000 cc from the total of two breasts and the mean was 540 cc. The results were evaluated by photographs of the patients by 3 surgeons; averaged and classified as inadequate, good, and excellent. When all three surgeons reached a different result, they were asked to re-evaluate. The patients were also asked to evaluate their satisfaction as inadequate, good, and excellent.

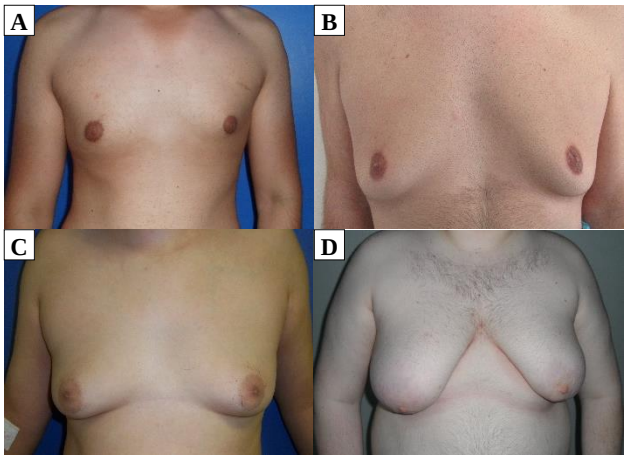

Figure 1. Gynecomastia patients from our clinic, Simon **A)** Grade I, **B)** Grade IIa, **C)** Grade IIb and **D)** Grade III

Table 3. Postoperative results (minimum of 6 months)

	Surgeon evaluation	Patients' evaluation
Inadequate	3 (6.7%)	4 (8.9%)
Good	7 (15.5%)	13 (28.9%)
Excellent	35 (77.8%)	28 (62.2%)

Surgical Technique

The operation can be performed under local, sedation or general anesthesia. The patient's planning is done before the operation while the patient is standing. For wet technique, liposuction solution is prepared by adding 1000 cc ringer lactate + 2% lidocaine + 1:1000 epinephrine. The solution is then injected into the preoperatively marked region (Figure 2A). For liposuction, two incisions are made for the cannula entry with 11 blade, one on the edge of the nipple and the other on the lateral side of the breast; additional incisions can be made if necessary. Ten minutes after the injection, liposuction is performed first to the deep region with 4 mm cannula, then to the superficial layer with 3 mm cannula and to the subareolar region with 2 mm cannula (Figure 2B, C, D, E). At the end of the operation, if the gland remains under the nipple, the liposuction incision at the border of the nipple is expanded to 1 cm and the gland is easily excised from here (Figure 2F). After sutures are placed on the incisions, dressing is performed and moderate pressure is applied to the thorax with elastic bandage. All patients were mobilized early in the postoperative period and postoperative drains were not used.

RESULTS

Seroma was seen in 2 patients as early complication and late complication was not seen except inadequate result. Results were excellent in 35 patients, good in 7 patients, and inadequate in 3 patients (Figures 3, 4, 5 and 6). In the evaluation, 93.3% of the surgical results were found to be successful. Three patients who were found to be inadequate underwent revision; in two of these patients who had Grade III gynecomastia preoperatively, minor periareolar skin excision was added, and in one patient the skin retraction was corrected surgically. The patient satisfaction rate was 91.1%. The results are summarized in Table 3.

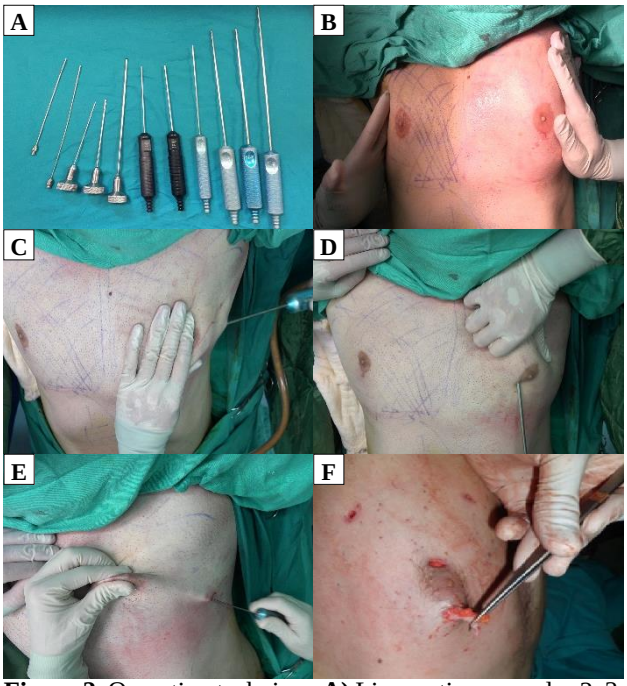

Figure 2. Operation technique **A)** Liposuction cannulas 2, 3, 4 mm; **B)** Inflating breast tissue with solution, wet technique; **C-E)** Liposuction procedure with 3 different cannulas in 3 different planes; **F)** Excision of the remaining glandular tissue by extending the periareolar incision to 1 cm

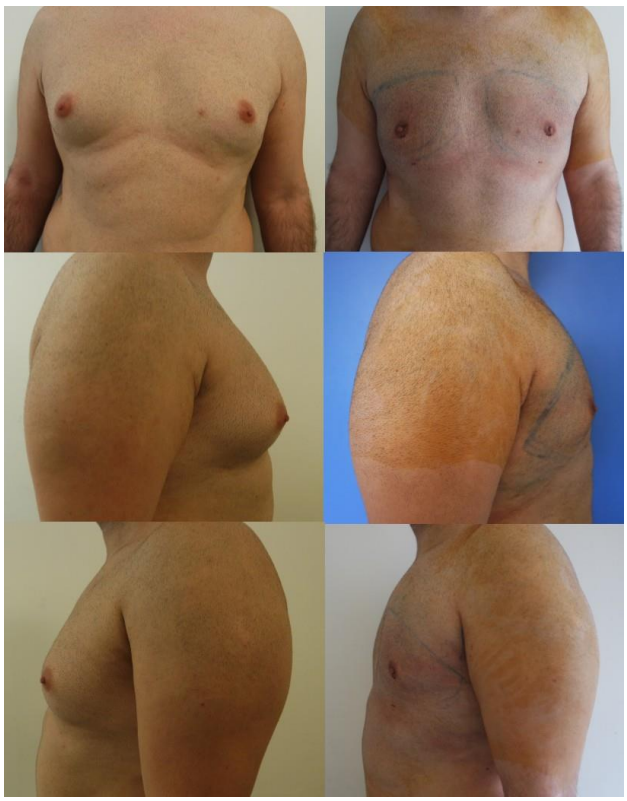

Figure 3. Gynecomastia patient, preoperative and 1 day postoperative images

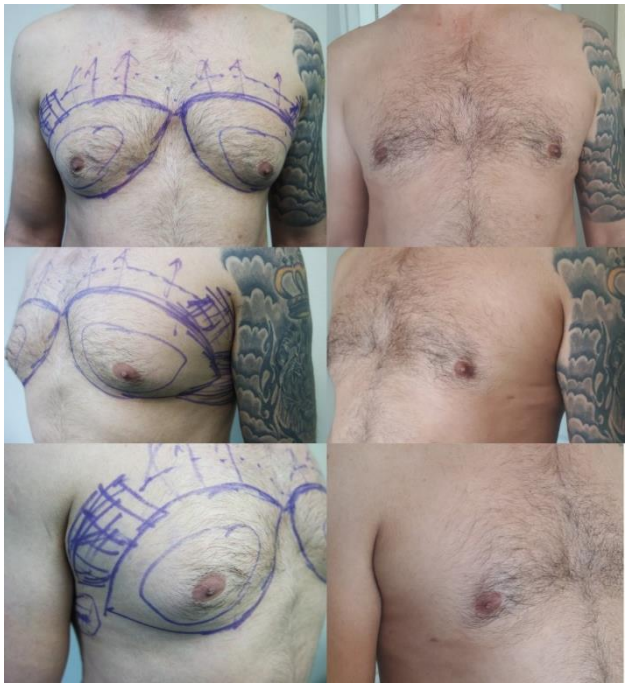

Figure 4. Gynecomastia patient, preoperative and 6 months postoperative images

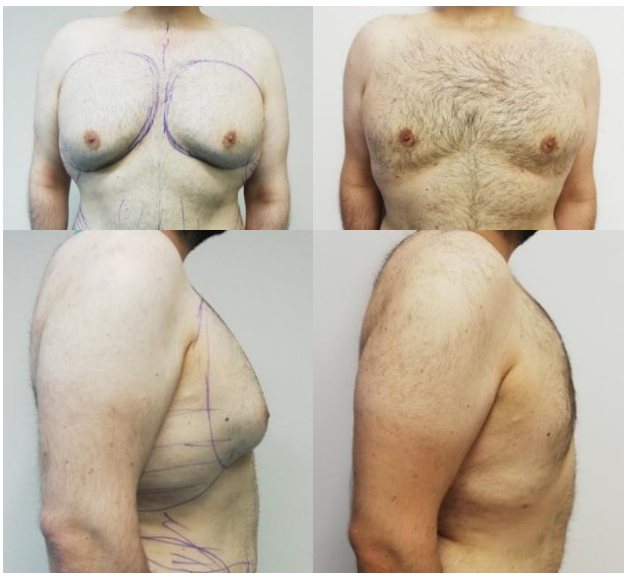

Figure 5. Gynecomastia patient, preoperative and 1 year postoperative images

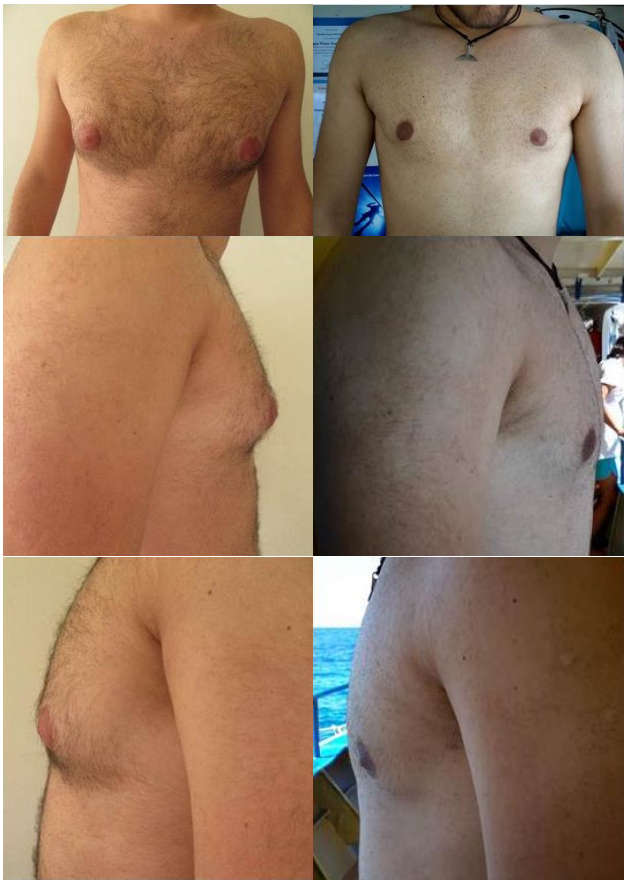

Figure 6. Revision gynecomastia patient, pre-revision and 9 months postoperative images

DISCUSSION

Gynecomastia is the increased visibility of breast tissue that normally exists in men, after benign proliferation due to physiological, pathological or drug-related reasons (12). Physiological gynecomastia is seen in neonates, adolescents, and the elderly. Gynecomastia in the newborn regresses within one year at the latest, while gynecomastia seen in adolescence and old age becomes fibrotic and permanent, especially when it exceeds a year (3).

When the patient is admitted to the outpatient clinic due to gynecomastia, the drugs used by the patient should be

questioned, the presence of real gynecomastia should be confirmed by physical examination and imaging methods, hormone profile should be requested and physical examination must include testicular examination (6). Physical examination may reveal an increase in the areola diameter, a deterioration of the thorax profile due to breast enlargement, abnormal localization of the inframmamarian fold, ptosis and asymmetry where nipple areolar complex may fall to the fold level or inferior (10). While the causes of gynecomastia are excluded, it should be kept in mind that men may also have breast cancer and this possibility should be ruled out (5). The growth in male breast cancer is usually unilateral and is found as a hard and painless mass anywhere in the breast. In addition, there are signs such as retraction on the skin or nipple and discharge from the nipple. Biopsy can be performed from the mass if necessary to exclude cancer (9).

Treatment Options

The aim of gynecomastia treatment is to achieve normal body image with minimal surgical scar as well as pain relief (16). During the adolescent period, gynecomastia occurs in different degrees, which regressed within a few months to years. In this period, the pathogenesis of gynecomastia is related to high plasma estradiol compared to testosterone (2,17). Gynecomastia in adolescents should not be operated until 3 years have passed and it is decided that spontaneous regression is no longer possible (2). Although gynecomastia seen in adolescence may regress spontaneously, treatment should be planned considering the psychological effect of the condition (16). Especially in adolescent gynecomastia, if accompanied by obesity, the existing fat tissue will increase the prominence of gynecomastia, weight loss should also be recommended in these circumstances (16). In addition, in case of obesity, pseudogynecomastia may also be seen with increased adipose tissue in the breast (5). Clinically, it is possible to obtain information about the nature of the breast tissue by palpation and ultrasonography examination (6). In gynecomastia seen in adults, operation is indicated if gynecomastia continues for more than a year or one year after the underlying cause has been corrected (6).

Medical Treatment

In medical treatment, especially in adolescent gynecomastia, drugs such as tamoxifene, raloxifene, clomiphene that block specific estrogen effects in mammary tissue with serum estrogen receptor modulator effects, danazol which has the effect of androgen receptor agonist, and anastrazole or testolactone which inhibit estrogen production can be tried (2,5,6,18,19). It has been shown that these medications reduce pain associated with gynecomastia but provide a minimal reduction in gynecomastia size (18). In addition, if gynecomastia persists for more than a year, medical treatment will not be effective because the breast tissue becomes fibrotic (6,20).

Surgical Treatment

The aim of surgical treatment for gynecomastia is to make the chest area aesthetically pleasing and while achieving this goal, to hide the surgical scar as much as possible, to protect the nipple sensation and to minimize skin irregularities (15). Current surgical treatment options include minimally invasive methods, surgical excision, or both (21). Skin excision can also be planned depending on whether the skin is excessive or not (16). Surgical treatment can be performed under local anesthesia with sedation, under local anesthesia alone or under general anesthesia (20). Open surgical excision techniques using semicircular periareolar incision have high morbidity (22). Minimally invasive methods include suction assisted liposuction, power assisted liposuction, ultrasound assisted liposuction, laser assisted liposuction and vacuum assisted minimally invasive or endoscopic subcutaneous mastectomy (2,22,23). Suction assisted liposuction may sometimes not be sufficient alone, because the male breast structure contains more fibrous septum than female breast tissue (11). Ultrasound assisted liposuction and power assisted liposuction are more effective in the treatment of gynecomastia than conventional suction assisted liposuction. When the ultrasonic method is applied to the subdermal plan close to the skin, it may provide retraction of the excess skin, but the major disadvantage is the possibility of thermal damage to the surrounding skin (2,11). In a systematic review by Fagerlund et al. (5), surgical excision combined with liposuction was reported to be the most permanent outcome and the least complication rate. Abdelrahman et al. (20) reported that they achieved acceptable results in 92% of patients with Grade I and II gynecomastia after suction assisted liposuction with fat-disrupting cannulas. In our clinical series, we achieved similar success rates in the literature in patients who underwent liposuction alone or minimal subareolar gland removal when necessary. Devices used in ultrasonic (Vaser), laser and other assisted liposuction techniques are expensive and not available in all clinics. The advantages of the presence of such devices cannot be denied, but the costs cannot be covered by every patient. It is possible to achieve successful results with classical wet liposuction technique by using rigorous working technique and by using different thickness cannulas at different stages of the procedure. There is a local anesthetic in the fluid given for liposuction, so local anesthesia under sedation will be sufficient for the majority of patients. This is the most commonly used method in our experience. While the patient is in deep sedation, fluid injection is completed in 10-15 minutes, and then the operation is completed with local anesthesia in 45-90 minutes.

The most common complications reported in the literature after surgical treatment of gynecomastia are hematoma in early period and inadequate excision in late period. In addition to these, early complications include ecchymosis, fat necrosis and seroma, infection, deep vein thrombosis, pulmonary embolism, and late complications include deformities of the nipple areolar complex like inverted nipple (11,15,18). In a study by Zavlin et al. (21), the rate of surgical complications in 204 pediatric and 1583 adult gynecomastia patients was reported to be 3.9% and 1.9% respectively. Fagerlund et al. (5) reported a postoperative complication rate of up to 20% in different surgical techniques. In our series, seroma was seen in 3 patients (6.7%) as early complications and inadequate excision in 3 patients (6.7%) as late complications. This is a low complication rate compared to the reported rate in the literature.

Vacuum lipoplasty (vacuumroller LPG massage) or ultrasound-guided lipoplasty (ultrasonic cavitation devices) can be used to shape the remaining tissues and skin excess after liposuction treatment of gynecomastia

(10). Cryolipolysis and radiofrequency treatments can be used primarily in patients with pseudogynecomastia as well as shaping the remaining tissue after surgical treatment (18).

CONCLUSION

In the treatment of gynecomastia, different methods are recommended according to the duration of the disease, the etiological cause, the amount and characteristics of the available breast tissue, the presence of excess skin, and the location of nipple areolar complex. The fact that there are so many factors affecting the choice and success of treatment makes it difficult to apply a standard management in every gynecomastia patient. Classical wet liposuction technique yielded good reproducible results in our patients with Grade I, II and III gynecomastia; with a success rate of 93% and patient satisfaction rate of 91.1%. The advantages of the technique are short hospitalization, return to normal life in the early period, low complication rate, low cost and aesthetically acceptable results. For this reason, liposuction method applied to different tissue planes with different thickness cannulas is a preferable treatment method in the treatment of patients with Grade I, II and III gynecomastia. Gynecomastia is treated with low complication rates and highly satisfactory results with standard liposuction techniques.

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Evaluating the Anxiety Levels of Parents of Children Underwenting Hypospadias Surgery

Hipospadias Cerrahisi Geçiren Çocukların Ebeveynlerinin Kaygı Düzeyinin Değerlendirilmesi

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ABSTRACT

Aim: Hypospadias is an anomaly in which urethral meatus is located more proximally. Its treatment is surgery. Children undergoing hypospadias surgery are much more prone to emotional disorders than the other surgical procedures. In this study, it was aimed to evaluate the emotional and temperament characteristics of the parents of children undergoing hypospadias surgery and normally circumcised.
Material and Methods: All voluntary parents of children with hypospadias surgery and of children with normal circumcision were included in this study. A semi-structured sociodemographic data form, The Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A), State-Trait Anxiety Inventory (STAI) I-II, and Beck Depression Scale (BDS) were used to collect data from these parents.
Results: There was no significant difference between the parents in terms of sociodemographic and clinical characteristics. When the parents of children with hypospadias and normal circumcision were compared in terms of TEMPS-A temperament scale scores, STAI total and I-II subscale scores, and BDS scores, no statistically significant difference was found.
Conclusion: Hypospadias is a complex biological development defect. In men who underwent hypospadias surgery, sexual dysfunctions that develop in further period usually develop on psychological grounds. Parents' anxiety levels should be taken into consideration and everyone should act together in management process of hypospadias, operation of which is planned in early period and may have many effects in the future. We think that the study we have done with parents in this area may guide to other studies.
Keywords: Anxiety; parents; hypospadias; children; surgery.

ÖZ

Amaç: Hipospadias, üretral meanın daha proksimalde lokalize olduğu bir anomalidir. Cerrahi olarak tedavi edilir. Hipospadias cerrahisi geçiren çocuklar, duygusal bozukluklara diğer cerrahi yöntemlere göre daha fazla yatkın olmaktadırlar. Bu çalışmada normal sünnet yapılan ve hipospadias cerrahisi geçiren çocukların ebeveynlerinin duygusal ve karakteristik mizaçlarının değerlendirilmesi amaçlanmıştır.
Gereç ve Yöntemler: Bu çalışmaya hipospadias cerrahisi geçiren çocukların ve normal sünnet yapılan çocukların ebeveynlerinden gönüllü olanların tümü dahil edilmiştir. Ebeveynlerden veri toplamak için yarı yapılandırılmış sosyodemografik veri formu, Memphis, Pisa, Paris ve San Diego Mizaç Değerlendirme Anketi (The Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire, TEMPS-A), Durumluluk-Süreklilik Kaygı Envanteri (State-Trait Anxiety Inventory, STAI) I-II ve Beck Depresyon Ölçeği (BDÖ) kullanılmıştır.
Bulgular: Ebeveynler arasında klinik ve sosyodemografik özellikler açısından anlamlı bir fark yoktu. Hipospadiaslı olan ve normal sünnet olan çocukların ebeveynleri TEMPS-A mizaç ölçeği puanları, STAI toplam ve I-II alt ölçek puanları ve BDÖ puanları açısından karşılaştırıldığında da istatistiksel olarak anlamlı bir fark bulunmadı.
Sonuç: Hipospadias karmaşık bir biyolojik gelişme defektidir. Hipospadias ameliyatı geçiren erkeklerde, ileriki dönemde gelişen cinsel işlev bozuklukları genellikle psikolojik nedenlerle gelişir. Ebeveynlerin kaygı düzeyleri dikkate alınmalı ve operasyonu erken dönemde planlanan ve gelecekte birçok etkisi olabilecek olan hipospadias tedavi sürecinde herkes birlikte hareket etmelidir. Bu alanda ebeveynlerle yaptığımız bu çalışmanın diğer çalışmalara rehberlik edebileceğini düşünüyoruz.
Anahtar kelimeler: Kaygı; ebeveynler; hipospadias; çocuk; cerrahi.

INTRODUCTION

Hypospadias is an anomaly in which urethral meatus is located more proximally on the anterior aspect of the penis. The cause of this anomaly seen in one of 300 boys is unknown and its treatment is surgery (1). Surgical management of hypospadias is generally completed in childhood. It is thought that in patients with hypospadias, psychological, psychosexual and psychosocial problems may be seen not only during treatment but also in adolescence and adulthood. While preliminary studies support this thought, most of the controlled studies conducted in recent years indicate that hypospadias cases do not differ from their controls. There are inconsistencies in the results of the research due to the fact that patients are being less traumatized as a result of changes in surgical technique and applications and treatment can be completed at much earlier ages (before 30 months) compared to the past (2-5).

Children undergoing hypospadias surgery are much more prone to emotional disorders than the average population (6-8). There are some studies about children and their emotional disorders in the literature, but there is no study about emotional disorders of parents with children undergoing hypospadias surgery. In this study, we aimed to present the emotional and temperament characteristics of the parents in the evaluation of this disorder in children by comparing the parents of children undergoing hypospadias surgery and of children who are normally circumcised, in terms of some sociodemographic and clinical variables, anxiety levels and affective temperament characteristics.

MATERIAL AND METHODS

Approval of Adnan Menderes University Ethics Committee was obtained (approval no: 2018/1413 and approval time: 07.06.2018). The aims and the all procedures of the study were explained to both parents of the hypospadias and circumcision groups by a trained psychiatrist.

Participants

Forty six parents of children with hypospadias and 50 parents of children with normal circumcision (aged 18 and older, with written consent, and those without any communication and comprehension difficulties that may prevent the administration of the study scales) who admitted to Department of Pediatric Surgery of Adnan Menderes University between June 2018 and June 2019 were included to in the study.

Data Collection Tools

A semi-structured sociodemographic data form, The Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire-(TEMPS-A) temperament scale, State-Trait Anxiety Inventory(STAI) I-II and Beck Depression Scale (BDS) were used during the interview with 46 parents of children with hypospadias and 50 parents of children with normal circumcision.

Sociodemographic Data Form for Family and Child: In this form, parents of children with hypospadias and of children with normal circumcision were questioned in terms of their child's future sexual life and sexual orientation, besides sociodemographic characteristics about child and his family. The form was filled in by parents.

State-Trait Anxiety Inventory (STAI) I-II: According to Two-Factor Anxiety Theory, Spielberger et al. (9) divided anxiety into two as State and Trait Anxiety. State Anxiety is the anxiety that occurs when a dangerous, undesirable situation is encountered. Trait Anxiety is an anxiety that exists when there is no objective reason, and when there is, it is disproportionately long-term and violent with this situation (10). Every person feels anxiety when he/she thinks it is dangerous. Fear and anxiety caused by dangerous conditions are considered as temporary and normal anxiety experienced by the individual. It is called State Anxiety. When the stress is intense, the state anxiety level increases, and when the stress disappears, it falls. Some consistently live in uneasiness and are often unhappy. This type of anxiety, which does not depend on the dangers directly from the environment, is endogenous. Individuals feel anxiety if they think that their core values are threatened or if they interpret the situations they are in as stressful. It is called Trait Anxiety. Continuous anxiety is steady and it is generally stated that it is a personal trait (11).

The Temperament Evaluation Scale (The Temperament Evaluation of Memphis, Pisa, Paris and San-Diego Autoquestionnaire, TEMPS-A): It was developed by Akiskal et al. (12) to evaluate the dominant affective temperament. The questionnaire consists of 100 questions designed to determine depressive, hyperthymic, irritable, cyclothymic and anxious temperaments. The person responds to the questions as yes or no, considering his or her whole life. To determine the presence of dominant depressive (19 questions), cyclothymic (19 questions), hyperthymic (20 questions), irritable (18 questions) and anxious (24 questions) temperament characteristics in an individual, cut points are 13, 18, 20, 13 and 18 points respectively. The validity and reliability studies of the Turkish version were performed by Vahip et al. (11). Test-retest reliability of the Turkish form calculated separately for each temperament trait is between 0.73-0.93, and the Cronbach-alpha coefficient is between 0.77-0.85. TEMPS-A was applied to patients aged 16 years and older and to their mothers.

Beck Depression Scale (BDS): Scale developed by Beck et al. (13) and is used to determine the risk for depression and to measure the level and intensity change of depression symptoms. It includes 21 self-evaluation sentences. Point interval ranges from 0 to 63. Validity and reliability of the Turkish form was made by Hisli N. (14).

Statistical Analysis

Data obtained from the study were analyzed with SPSS 20 statistical package. The normal distribution of the numerical data was examined using Shapiro-Wilk test, and homogeneity of variances using Levene test. Independent samples t or Mann-Whitney U test was used to compare two groups according to normality assumption. Categorical data were analyzed with Pearson chi-square or Fisher's exact test, as appropriate. Two-way analysis of variance was used to investigate both main and interaction effects of group and gender. Descriptive statistics were summarized as mean±standard deviation or median (minimum maximum), and frequency and percentage, as appropriate. A p value equal to or below 0.05 level was considered as statistically significant.

RESULTS

A total of 96 parents with a mean age of 35.6±7.0 (range, 21 to 57) years, 46 of whose child were underwent hypospadias and 50 were underwent normal circumcision were included in the study. There was no significant difference between the parents of normal circumcision and hypospadias groups in terms of age, gender, marital status, employment status, and region of residence (Table 1).

There were 1 (3.8%) parent with a psychiatric diagnose in normal circumcision group and 2 (4.5%) parents in hypospadias group, and no significant difference was found between the groups (p=0.606). Information of parents about hypospadias was higher in hypospadias (n=37, 80.4%) group compared to normal circumcision (n=29, 58.0%) group (p=0.018). Concern of parents about child's homosexuality were not significantly different between the groups in general (p=0.227). Although there was no statistically significant difference between groups, two parents (one mother and one father) in the hypospadias group were concerned about child's homosexuality, while none of the parents in the normal circumcision group. Additionally, concern about child's sexuality was found lower in hypospadias (n=12, 26.1%) group compared to normal circumcision (n=23, 46.0%) group (p=0.043). When concerns of parents examined separately, as mothers and fathers, it was observed that similar results were obtained for comparison of groups. On the other hand, when mothers and fathers are compared each other in each group, it was seen that there was no significant difference, that is, being a mother or father does not affect these concerns (Table 2).

We have also found no differences in affective temperament and BDI scales. There were no significant differences between the mothers and fathers of the children with hypospadias and normal circumcision groups with regard to depression, anxiety scores, and affective temperaments.

When the effect of normal circumcision and hypospadias groups, and parent's gender effect evaluated together, there was no significant interaction in terms of STAI-I (p=0.379), STAI-II (p=0.867) and total (p=0.673) scale points. While there was no significant difference between normal circumcision and hypospadias groups (p=0.500, p=0.291 and p=0.811, respectively), it was observed that being a mother or father in general was not statistically significantly affect the scale points (p=0.980, p=0.071 and p=0.278, respectively). Parents of hypospadias group regardless of being a mother or father had lower scale points compared to normal circumcision group in terms of STAI-II and total scores, except STAI-I score. Fathers of children with hypospadias had highest STAI-I score, while mothers of them had the lowest, even lower than the parents of normal circumcision group (Table 3, Figure 1).

When the effect of information about hypospadias and parent's gender effect on STAI scale evaluated together, there was no significant interaction in terms of STAI-I (p=0.537), STAI-II (p=0.779) and total (p=0.588) scale points. While there was no significant difference between parents with and without information about hypospadias (p=0.514, p=0.700 and p=0.873, respectively), it was observed that being a mother or father in general was not statistically significantly affect the scale points (p=0.201, p=0.587 and p=0.655, respectively). Fathers of hypospadias group regardless of having information about hypospadias had higher scale points compared to mothers in terms of STAI-I and total scores, except STAI-II score. Additionally, fathers of children not having information about hypospadias had highest STAI-I and total scores, while mothers of them had the lowest regardless of having or not any information about hypospadias (Table 4, Figure 2).

Table 1. Comparisons of parents in normal circumcision and hypospadias groups in terms of sociodemographic

	Normal circumcision (n=50)	Hypospadias (n=46)	p
Gender, n (%)			
Female	24 (48.0)	24 (52.2)	0.683
Male	26 (52.0)	22 (47.8)	
Marital status, n (%)			
Single	0 (0.0)	0 (0.0)	
Married	46 (92.0)	46 (100)	0.118
Divorced/widow	4 (8.0)	0 (0.0)	
Employment, n (%)			
Employed	29 (58.0)	27 (58.7)	0.945
Unemployed	21 (42.0)	19 (41.3)	
Place of residence, n (%)			
Urban	24 (48.0)	22 (47.8)	0.986
Rural	26 (52.0)	24 (52.2)	
Age of parent (years), Mean±SD	35.7±6.3	35.6±7.7	0.903
Age of child (months), Median (IQR), min-max	32 (77) 6-163	47 (74) 14-168	0.088
Number of children, Median (IQR), min-max	2 (1) 1-3	2 (1) 1-6	0.380

SD: Standard Deviation, IQR: Inter Quartile Range, min: Minimum, max: Maximum

Table 2. Comparisons of parents in terms of clinical characteristics according to the group and gender, n (%)

		Normal circumcision	Hypospadias	p_c
Any psychiatric diagnoses	**Mother***	0 (0.0)	1 (4.2)	0.312
	Father#	1 (3.8)	1 (4.5)	0.904
	p_r	0.332	0.950	
	Total	1 (2.0)	2 (4.3)	0.606
Information about Hypospadias	**Mother***	13 (54.2)	18 (75.0)	0.131
	Father#	16 (61.5)	19 (86.4)	0.054
	p_r	0.598	0.464	
	Total	29 (58.0)	37 (80.4)	**0.018**
Concerns about child's sexuality	**Mother***	12 (50.0)	6 (25.0)	0.074
	Father#	11 (42.3)	6 (27.3)	0.278
	p_r	0.586	0.861	
	Total	23 (46.0)	12 (26.1)	**0.043**
Concerns about child's homosexuality	**Mother***	0 (0.0)	1 (4.2)	0.312
	Father#	0 (0.0)	1 (4.5)	0.458
	p_r	---	0.950	
	Total	0 (0.0)	2 (4.3)	0.227

*: there were 24 mothers both in normal circumcision and hypospadias groups, #: there were 26 fathers in normal circumcision group and 22 in hypospadias group, p_c: p value for comparison of column proportions in each gender and group, p_r: p value for row comparisons (comparison of mother and father) in same group

Table 3. Comparisons of parents in terms of state-trait anxiety scale according to the group and gender

		Normal circumcision	Hypospadias	p
STAI-I	**Mother***	36.04±8.09	34.58±8.17	0.980
	Father#	35.69±9.07	37.24±7.48	
	p	0.500		0.379
	Total	35.86±8.53	35.82±7.88	
STAI-II	**Mother***	42.63±6.23	39.75±9.38	0.071
	Father#	41.08±10.72	37.62±5.71	
	p	0.291		0.867
	Total	41.82±8.80	38.76±7.87	
STAI	**Mother***	78.67±12.28	74.33±14.89	0.278
	Father#	76.77±16.53	74.86±10.41	
	p	0.811		0.673
	Total	77.68±14.53	74.58±12.85	

STAI: State-Trait Anxiety Scale, *: there were 24 mothers both in normal circumcision and hypospadias groups, #: there were 26 fathers in normal circumcision group and 22 in hypospadias group

Table 4. Comparisons of parents of children with hypospadias in terms of state-trait anxiety scale according to the gender and having information about hypospadias

		Information (+)	Information (-)	p
STAI-I	**Mother***	34.56±8.48	34.67±7.89	0.201
	Father#	36.67±7.87	40.67±3.51	
	p	0.514		0.537
	Total	35.61±8.13	36.67±7.14	
STAI-II	**Mother***	40.28±8.55	38.17±12.34	0.587
	Father#	37.67±5.98	37.33±4.61	
	p	0.700		0.779
	Total	38.97±7.39	37.89±10.03	
STAI	**Mother***	74.83±13.81	72.83±19.18	0.655
	Father#	74.33±10.86	78.00±7.94	
	p	0.873		0.588
	Total	74.58±12.25	74.56±15.88	

STAI: State-Trait Anxiety Scale, *: there were 18 mothers having information about hypospadias and 6 not having, #: there were 19 fathers in having information about hypospadias and 3 not having

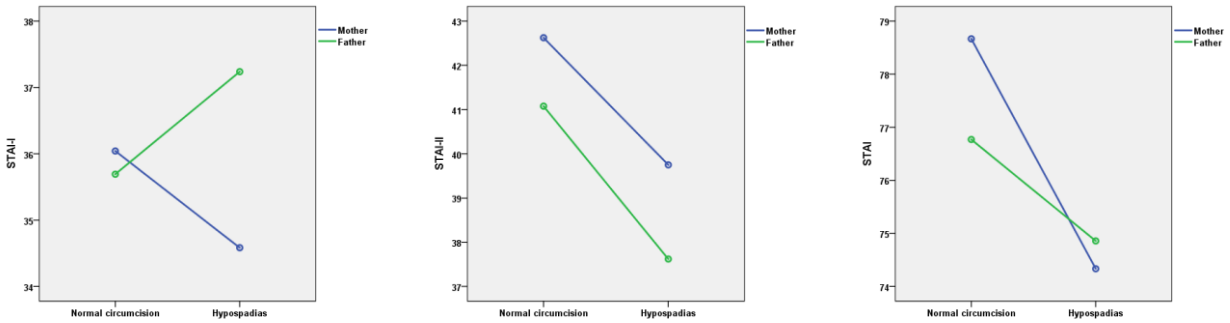

Figure 1. State-trait anxiety scale points according to the group and gender

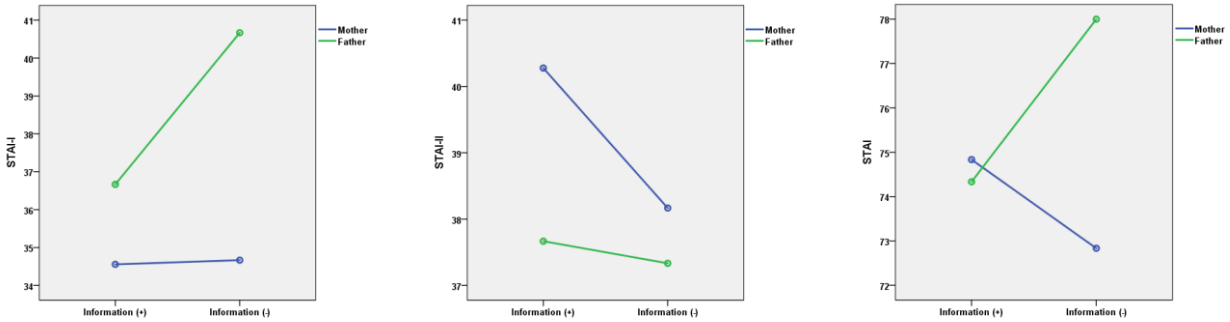

Figure 2. State-trait anxiety scale points according to the gender and information about hypospadias

DISCUSSION

Detection of hyperthymic temperament in fathers of circumcision group was the most remarkable result obtained from the parents of children with hypospadias and of children with normal circumcision. Hyperthymic temperament has characteristics such as optimism, extroversion, sociality and self-confidence (15). It may be thought that fathers in the circumcision group are more optimistic and social and thus may help to reduce the stress of their children compared to the hypospadias group. Conversely, it may be thought that fathers in the hypospadias group may not help enough to reduce the stress of their children.

Yıldırım et al. (16) have shown in a study conducted with ankylosing spondylitis (AS), a significant relationship between BAI and BDI scores and depressive, cyclothymic, irritable, and anxious temperaments. This result suggests that affective temperament except hyperthymic temperament could be a risk factor for depression and anxiety in AS patients. But in our study, fathers of normal circumcision children have higher trait anxiety scores accompanying hyperthymic temperament. In another study conducted by Fıstıkçı et al. (17) hyperthymic temperament scores were higher in Panic Disorder patients. This result suggests that hyperthymic temperament could be a risk factor for trait anxiety in fathers of normal circumcision children.

There are very limited studies on hypospadias and its long-term outcomes. Most of these studies are on the anatomy and function of the penis, and sexual dysfunction. The general opinion obtained from all studies is that hypospadias surgery before the age of 5.5 makes a positive psychological contribution to the child (18). In another study conducted on Turkish children, it was found that the most important parameter of the emotional effect detected in children underwent hypospadias surgery was the age of surgery (19). Personality traits of the child, how the child is prepared for circumcision in pre-circumcision period, and physical problems experienced during and after operation may play a role in circumcision causing psychiatric disorders in some children. How families perceive circumcision and reflect it to their children can also be an important factor. When the groups in our study were evaluated, it was observed that the age of the children in the circumcision group and hypospadias group were similar and homogenous, and the mean age was 5 years in accordance with the literature. While it is stated that psychological trauma in children can be prevented with relatively early surgery, there are no studies on parents in the literature. However, it may be thought that parents of children undergoing hypospadias surgery at small ages may get really stressed. In other words, surgery performed at an early age may cause an increase in the psychological trauma of the parents. However, when the two groups were evaluated in our study, we found that the age distribution was homogenous and there was no statistically significant difference depending on the age in the evaluation of anxiety status.

Especially the temperament traits of mothers play an important role on child. The irritable temperament traits of mother are important in terms of both the quality of maternal support child perceived and angry and impulsive parent relationship (20). Irritable temperament traits are also characterized by impaired social function and interpersonal relationships. In our study, we found that the mothers of the hypospadias group showed no irritable temperament trait. From this point of view, we think that there was no statistically significant difference in temperament characteristics between mothers in both groups because they were informed about the hypospadias since birth and they were prepared for the operation process.

It is a known fact that social media is widely used today. In a study conducted on social media, after 736 cases were examined with hypospadias, it was detected that 7.1% (n=52) of them was remained untreated. As a result of this study, it can be seen that patients or their parents are still hesitating for hypospadias surgery and do not have the necessary operation done. Although there are various risks such as sexual dysfunction, cosmetic problems in the penis and even infertility, surgical stress in patients or parents caused by the operation planned to be performed may be the reason why 7.1% of patients are not having operation (21). In our study, parents who abstained from the operation and therefore developed serious anxiety disorders did not bring their children and therefore were not included in the study. In fact, study with parents of children with hypospadias in the whole society, not only with parents of children underwent surgery, may have different results. The fact that our study was performed only with the parents of children with hypospadias who accepted the operation can be considered as one of the limitations of the study.

Depression and emotional status in children are directly influenced by behavior, attitude and socioeconomic status of parents (22). In our study, we did not find any socioeconomic difference between the parents of hypospadias and circumcision groups.

Hypospadias is a complex developmental defect and all patients are treated with different techniques and it requires special expertise and knowledge. In men who underwent hypospadias surgery, sexual dysfunctions that develop in further period usually develop on psychological basis (23-25). Due to insufficient information acquired on the internet and social media, anxiety level of parents usually increases. In our study, detection of hyperthymic temperament character in the circumcision group compared to the hypospadias group, especially in fathers, supports this situation.

As a result, parents' anxiety levels should be taken into consideration and everyone should act together in management process of hypospadias which have many effects in the future. We think that this study which was done with the family of children operated for hypospadias may guide to other studies.

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Evaluation of Cognitive Functions in Obstructive Sleep Apnea Syndrome

Obstrüktif Uyku Apne Sendromunda Bilişsel Fonksiyonların Değerlendirilmesi

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ABSTRACT

Aim: The aim of this study is to evaluate patients with Obstructive Sleep Apnea Syndrome (OSAS) in terms of various cognitive functions and determine the relationship between cognitive functions with anxiety and depression levels.

Material and Methods: This cross-sectional study was conducted between June 15, 2019 and December 15, 2019 and included 34 OSAS patients and 28 healthy volunteers between the ages of 18-65 with at least primary education. All participants underwent overnight recording of polysomnography. Patients were evaluated using sociodemographic data form, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Montreal Cognitive Assessment (MoCA) and the Stroop Color and Word Test (SCWT).

Results: There was no significant difference between the OSAS and control group in terms of age and gender. OSAS patients had significantly higher depression and anxiety scores compared to the control group. OSAS patients showed poor performance in naming, attention, abstract thinking, and delayed recalling compared to the control group. OSAS patients completed Stroop tests 1, 3, and 5 in a longer amount of time than the control group. Cognitive functions were found to have a significant negative correlation with apnea hypopnea index, BDI, and BAI scores.

Conclusion: OSAS was found to have a different effect on each subcomponents of cognitive function. Furthermore, it was determined that many negative factors caused by OSAS may play a role in cognitive involvement in OSAS. Further studies are warranted to shed light on the ethiopathogenesis of this subject.

Keywords: Stroop; attention; memory; abstract thinking; neurocognitive function.

ÖZ

Amaç: Bu çalışmanın amacı Obstrüktif Uyku Apne Sendromu (OUAS) hastalarını birçok bilişsel fonksiyon açısından değerlendirmek ve OUAS hastalarının bilişsel fonksiyonları ile anksiyete ve depresyon düzeyleri arasındaki ilişkiyi ortaya koymaktır.

Gereç ve Yöntemler: Bu kesitsel çalışmaya 15 Haziran 2019 ve 15 Aralık 2019 tarihleri arasında yapıldı ve 18-65 yaş arası en az ilkokul mezunu 34 OUAS hastası ve 28 sağlıklı gönüllü dahil edildi. Tüm katılımcıların bir gece boyunca polisomnografi kayıtları alındı. Tüm katılımcılara sosyodemografik veri formu, Beck Depresyon Ölçeği (BDÖ), Beck Anksiyete Ölçeği (BAÖ), Montreal Bilişsel Değerlendirme (MoCA) ve Stroop Renk ve Sözcük Testi (SCWT) uygulandı.

Bulgular: OUAS ile kontrol grubu arasında yaş, cinsiyet açısından anlamlı fark yoktu. OUAS hastalarının depresyon ve anksiyete ölçek puanları kontrol grubuna göre anlamlı şekilde daha yüksekti. OUAS hastalarının adlandırma, dikkat, soyut düşünme ve gecikmeli hatırlama performansları kontrol grubuna göre daha düşük idi. OUAS hastaları Stroop 1, 3 ve 5 testini kontrol grubundan daha uzun bir sürede tamamladı. Bilişsel fonksiyonların apne hipopne indeksi, BDÖ ve BAÖ skorları ile negatif yönde anlamlı bir korelasyonu olduğu bulundu.

Sonuç: OUAS'ın bilişsel fonskiyonların her bir alt birleşeni üzerinde farklı bir etkisinin olduğu saptandı. Ayrıca OUAS'daki bilişsel etkilenmenin altında, OUAS'ın neden olduğu birçok olumsuz faktörün rolü olabileceği tespit edildi. Bu konunun etyopatogenizin daha açık hale gelmesi için ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Stroop; dikkat; hafıza; soyut düşünme; nörokognitif fonksiyon.

INTRODUCTION

Obstructive Sleep Apnea Syndrome (OSAS) is a disease characterized by obstructions in the upper respiratory tract causing cessations of breathing. Repeated pauses in breathing disrupt the integrity of sleep, preventing deep and restful sleep and causing excessive sleepiness during the day. At the same time, cessations in breathing often reduce oxygen saturation in the blood, causing emergence or aggravation of many diseases (1-4). One epidemiological study conducted in Switzerland reported that 50% of males between the ages of 49-68 were affected by OSAS (5). Peppard et al. (6) published a study evaluating the OSAS prevalence of two different periods, 1988-1994 vs. 2007-2010. This study asserted that 13% of men and 6% of women between the ages of 30-70 had moderate to severe OSAS. In addition, an increased risk of 48% for men and 44% for women compared to the 1988-1994 period was reported.

It has been theorized that the primary and secondary outcomes of obstructive breathing during sleep lead to changes in the control of cognition, emotion, learning, memory, and executive functions (7,8). Following this theory, few studies have shown that cognitive functions are affected in OSAS patients. On the other hand, the extent to which cognitive functions are affected has yet to be clarified (9,10).

Although some theories about cognitive impairment in OSAS have been proposed, the pathogenesis of this association has not been fully elucidated (9). Depression and anxiety are also known to have negative effects on cognitive function (11-13). Higher rates of depression and anxiety have been reported in OSAS patients compared to healthy control subjects (14-17).

This study aims to conduct a multifaceted evaluation of cognitive functions and determine the relationship between anxiety and depression levels and cognitive functions in OSAS patients.

MATERIAL AND METHODS

This cross-sectional case-control study was conducted simultaneously at the neurology and pulmonary diseases outpatient clinics of Yozgat Bozok University Medical School between January 15 and December 15, 2019. The study was conducted in accordance to the principles of the Helsinki Declaration and written informed consent was obtained from all participants. Yozgat Bozok University Local Ethics Committee approved the study protocol (Protocol Number: 2017-KAEK-189_2019.06.26_06 and Date: 26.06.2019).

Study Population

A total of 34 OSAS patients and 28 healthy volunteers between the ages of 18-65 were included in the study. People with at least primary education, and mental capabilities to complete the questionnaires and comprehend the scope of the study were included.

People with alcohol-substance and caffeine addiction, chronic physical disease, shift workers, pregnant and breastfeeding women, those with neurologic disease other than OSAS, lung diseases, infectious disease, and endocrine and systemic diseases were excluded from the study. OSAS patients who were receiving Continuous Positive Airway Pressure (CPAP) therapy were also excluded from the study.

The control group consisted of 28 healthy volunteers who were age and gender-matched with the OSAS group. The control group was also subjected to the exclusion criteria listed above; and also subjects with apnea/hypopnea index (AHI) of 5 and higher in polysomnography (PSG) was excluded from the study.

Detailed clinical history of the patients and the control group was obtained. Systemic physical and neurological examinations were performed. Height and weight measurements were recorded and body mass indexes (BMI) were calculated. PSG was performed on all participants. According to PSG results, participants were divided into two groups: OSAS patients and healthy volunteers.

Polysomnography (PSG) Evaluation

Patients who report snoring, witnessed apnea, and daytime sleepiness are evaluated for OSAS. These patients are asked to undergo overnight PSG in order to diagnose OSAS. PSG was performed using 31-channel ALICE 6 LDe (Respironics, PA, USA) at the sleep laboratory of the pulmonary department of the tertiary hospital.

The PSG recordings included electroencephalograms, electrooculograms, electromyograms for chin and leg movements, electrocardiograms, body position via thoracic belt, snoring sounds, oronasal airflow, arterial oxygen saturation via pulse oximetry, and respiratory efforts via chest and abdominal belts.

Sleep stages, movement events and respiratory parameters were scored according to the standard criteria of the American Academy of Sleep Medicine (AASM) version 2.5 published in 2018 (18). Sleep was scored manually in 30-second epochs. Drop in airflow amplitude ≥90% relative to the basal amplitude lasting ≥10 seconds was defined as apnea while hypopnea was accepted as a ≥30% decrease in airflow amplitude relative to the baseline values for ≥10 seconds with either an associated oxygen desaturation ≥3% or arousal. The AHI was calculated using the total number of apneas and hypopneas divided by total sleep time in hours. AHI <5/h was accepted as the control group while AHI ≥5/h was accepted as having OSAS. The OSAS group was divided into three subgroups as mild (5≤AHI<15), moderate (15≤AHI<30), and severe (AHI>30).

Data Collection Tools

Both groups were administered sociodemographic data form, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Montreal Cognitive Assessment (MoCA), and the Stroop Color and Word Test (SCWT).

Sociodemographic Form: The data collection form was developed by the researchers for study purposes and included questions related to the life stories of the participants. It included general information of patient and control groups. The form was applied at initial admission and collected data related to age, sex, marital status, education level, place of residence, habits, and medications used by the participants.

Beck Depression Inventory (BDI): The BDI was developed by Beck et al. (19) in order to evaluate bodily, emotional, cognitive, and motivational symptoms observed in depression. Total score ranges between 0-63, in which 0-9 indicates minimal, 10-16 mild, 17-29 moderate, and 30-63 severe depression. The scale's Turkish validity and reliability study was conducted by Hisli N. (20).

Beck Anxiety Inventory (BAI): The BAI was developed by Beck et al. (21) to measure the person's frequency of anxiety symptoms. Total score ranges between 0-63, in which 8-15 indicates mild anxiety, 16-25 moderate anxiety, and 26-63 severe anxiety. The scale's Turkish validity and reliability study was conducted by Ulusoy et al. (22).

Montreal Cognitive Assessment (MoCA): The MoCA test was developed as a fast screening test for mild cognitive impairment. MoCA evaluates various cognitive domains including attention and concentration, executive functions, memory, language, visuo-constructional skills, abstract thinking, calculations, and orientation. Maximum test score is 30. Cut-off score of 21 and higher is considered normal. Selekler et al. (23) conducted the Turkish validity and reliability study.

Stroop Color and Word Test (SCWT): The SCWT is used to evaluate attention and mental control, shift in reaction mechanism, and ability to resist interference. The Stroop test uses four white cards. The first card contains color names printed in black letters over a white background. The second card shows color names printed in different colors that are inconsistent to the color name; for example, the word "red" is printed in yellow. This card is the main stimulus and the most critical part of the test. The third card consists of 0.4 cm diameter circles printed in different colors. The fourth card contains neutral words (much, thin, if, middle, etc.) printed in different colors. The Stroop test is based on stimuli and responses of the participant to these stimuli. The first and second cards assess reading and information-processing speed; the second, third, fourth and fifth cards assess focused attention; the fourth and fifth cards assess selective attention; and the fifth card measures executive functions of locking and inhibition. At the end of the test, number of errors, number of self-corrections, and test completion time are determined (24). The Stroop test is used to evaluate executive functions. Its fundamental purpose is to measure the perceptive configuration and capability to shift response when under an impairing effect. Other measured attributes include information-processing speed and attention. This test is accepted as the most selective test to evaluate the inhibition of mis-matched stimulus and is sensitive to damage to the left frontal lobe, especially the orbitofrontal cortex. The Turkish validity and reliability study of the test has been conducted (25).

Statistical Analysis

Statistical analysis was performed using the SPSS® 22.0 package program. Descriptive statistics of the data were calculated. Shapiro-Wilk test was used to assess normality distribution. Student's t-test was use to compare normally distributed data between two groups. Mann-Whitney U test was used in two group comparisons of data without normal distribution. Chi-square test was used to compare categorical variables. Pearson's correlation test was used to assess data with normal distribution and Spearman's correlation test was used for data without normal distribution. A p value of less than 0.05 was considered statistically significant.

RESULTS

There was no significant difference between the OSAS (n=34) and control group (n=28) according to age, gender, or BMI. The OSAS group had significantly higher BDI and BAI scores compared to the control group (p=0.005 and p=0.019, respectively). Sociodemographic and psychological test results of the OSAS and control groups are presented in Table 1.

According to AHI classification, 35.3% (n=12) of OSAS patients had mild OSA, 38.2% (n=13) moderate OSA, and 26.5% (n=9) severe OSA. Polysomnographic data and results of the OSAS patients and control group are presented in Table 2.

Table 1. Sociodemographic characteristics and psychological test results of the OSAS patients and control group

	Control (n=28)	OSAS (n=34)	p
Age, years	41.57±10.14	44.88±8.04	0.157
Gender, n (%)			
Female	8 (28.6)	10 (29.4)	0.942
Male	20 (71.4)	24 (70.6)	
Education, years	9.89±3.37 11 (3) [5-15]	10.82±3.13 11 (7) [5-15]	0.308
BMI	31.33±5.11	30.49±3.98	0.467
Smoking, n (%)	13 (46.4)	16 (47.1)	0.961
BDI	5.61±4.96 5.5 (6.5) [0-23]	10.35±7.50 9.5 (7.5) [0-34]	**0.005**
BAI	6.29±5.65 5.5 (7.5) [0-24]	11.09±8.69 8.5 (10.5) [0-40]	**0.019**

OSAS: Obstructive Sleep Apnea Syndrome, BMI: Body Mass Index, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory, descriptive statistics given as mean±standard deviation and median (interquartile range) [minimum-maximum]

Table 2. Polysomnographic data and results of the OSAS patients and control group

	Control (n=28)	OSAS (n=34)
Total Recording time, (minutes)	385.32±53.04	406.87±46.16
Total Sleep Time, (minutes)	311.69±77.33	324.67±62.27
Sleep Efficiency, (%)	80.96±13.99	79.64±11.62
Sleep Latency, (minutes)	12.64±12.99	17.15±15.08
REM Latency, (minutes)	123.78±69.03	133.12±76.62
Wake Time During Sleep Period	60.98±54.24	65.02±39.22
Sleep Stage 1, (minutes)	8.25±3.16	11.19±4.67
Sleep Stage 2, (minutes)	199.75±60.81	210.23±66.56
Sleep Stage 3, (minutes)	67.02±26.75	51.73±28.25
REM Stage, (minutes)	34.01±21.99	40.51±23.49
Right side sleep time, (minutes)	108.29±99.51	90.06±83.39
Left side sleep time, (minutes)	52.84±60.56	80.79±69.68
Supine sleep time, (minutes)	120.16±85.92	135.03±94.22
Prone sleep time, (minutes)	15.47±26.00	9.29±26.46
AHI Total, (n/hour)	2.48±1.28	27.52±22.19
AHI REM, (n/hour)	4.46±6.48	30.98±26.07
AHI NREM, (n/hour)	2.34±1.45	29.07±23.86
LEFT AHI, (n/hour)	2.09±3.16	21.18±24.98
RIGHT AHI, (n/hour)	1.16±1.56	11.30±16.32
PRONE AHI, (n/hour)	0.08±0.39	7.17±22.52
SUPINE AHI, (n/hour)	2.92±2.66	40.73±33.96
Minimum O_2 Saturation, (%)	86.53±4.89	79.12±10.74
Mean O_2 Saturation, (%)	92.74±3.02	91.25±4.57
Oxygen Saturation Index, (%)	5.69±4.98	34.51±24.59

OSAS: Obstructive Sleep Apnea Syndrome, AHI: Apnea Hypopnea Index

Mean overall MoCA score was 21.38±5.01 for the OSAS patients and 25.32±3.28 for the healthy control group; there was a significant difference between the groups (p=0.001). According to MoCA subdomains, OSAS patients had significantly lower naming, attention, abstract thinking, and delayed recall scores compared to the control group (p=0.028, p<0.001, p=0.047 and p<0.001, respectively). The OSAS patients had lower executive, language, and orientation scores compared to the control group, but these differences were not statistically significant (p=0.088, p=0.402 and p=0.242, respectively). MoCA scores of the OSAS patients and control group are presented in Table 3.

Comparison of the OSAS and control groups according to Stroop times showed that OSAS patients had longer Stroop 2 and 4 times but these differences was not statistically significant (p=0.090 and p=0.099, respectively). Stroop 1, 3 and 5 times were significantly longer in OSAS patients compared to the control group (p=0.028, p=0.008 and p<0.001, respectively). There was no significant difference between the OSAS group and control group according to correction and error results. Stroop test results of the OSAS and control groups are presented in Table 4.

There was a statistically significant low negative correlation between MoCA total score and AHI (r=-0.404, p=0.001). MoCA total score were found to have a statistically significant moderate negative correlation with BDI (r=-0.568, p<0.001) and BAI (r=-0.530, p<0.001) scores. There was a moderate positive correlation between Stroop 5 time and AHI (r=510, p<0.001). Stroop 5 time was found to have a statistically significant low positive correlation with BDI (r=0.487, p<0.001) and BAI (r=0.407, p=0.001) scores. Correlation analysis of AHI, BDI, BAI, MoCA and Stroop test is presented in Table 5.

DISCUSSION

The primary finding of this observational study was that OSAS had a negative effect on cognitive functions and this effect had different degrees of extent on different domains of cognition. In addition, OSAS patients were found to have higher rates of depression and anxiety compared to the control group. Impaired cognitive function showed correlation with AHI as well as depression and anxiety.

Hypoxia due to OSAS has been found that it could cause major damage to the central nervous system. Reduced oxygen saturation may result in decreased protective vascular mechanisms and increased vasoconstriction, which may lead to the development of structural and functional changes in the brain (26,27). The anterior frontal cortex, which is highly susceptible to hypoxia,

Table 3. MoCA scores of the OSAS patients and control group

	Control (n=28)				OSAS (n=34)				p
	Mean±SD	Median	IQR	Min-Max	Mean±SD	Median	IQR	Min-Max	
Executive	4.07±0.85	4	1.75	2-5	3.61±1.04	4	1.25	2-5	0.088
Naming	2.61±0.49	3	1	2-3	2.26±0.62	2	1	1-3	**0.028**
Attention	4.77±1.23	6	1	2-6	3.94±1.13	4	2	2-6	**<0.001**
Language	1.96±1.14	2	2	0-3	1.76±1.10	2	2	0-3	0.402
Abstract thinking	1.53±0.69	2	1	0-2	1.09±0.9	1	2	0-2	**0.047**
Delayed recall	3.93±1.05	4	2	2-5	2.82±0.97	3	2	1-5	**<0.001**
Orientation	5.96±0.89	6	0	5-6	5.88±0.32	6	0	5-6	0.242
Total MoCA	25.32±3.28	25	5	19-30	21.38±5.01	21.5	7.75	11-29	**0.001**

MoCA: Montreal Cognitive Assessment, OSAS: Obstructive Sleep Apnea Syndrome, SD: Standard Deviation, IQR: Interquartile Range, Min: Minimum, Max: Maximum

Table 4. Stroop test results of the OSAS patients and control group

	Control (n=28)				OSAS (n=34)				p
	Mean±SD	Median	IQR	Min-Max	Mean±SD	Median	IQR	Min-Max	
Stroop 1 (Time)	11.35±2.75	11.5	2.75	7-20	12.56±2.12	12.5	3	9-20	**0.028**
Stroop 1 (Error)	0.07±0.38	0	0	0-2	0.15±0.44	0	0	0-2	0.261
Stroop 1 (Correction)	0.00±0.00	0	0	0-0	0.03±0.17	0	0	0-1	0.364
Stroop 2 (Time)	12.21±4.56	11.5	5.75	7-25	13.09±2.44	13	4	9-18	0.090
Stroop 2 (Error)	0.07±0.26	0	0	0-1	0.12±0.41	0	0	0-2	0.787
Stroop 2 (Correction)	0.04±0.19	0	0	0-1	0.08±0.29	0	0	0-1	0.406
Stroop 3 (Time)	13.14±4.34	12	5	7-25	15.32±2.81	15.5	3.5	10-21	**0.008**
Stroop 3 (Error)	0.11±0.42	0	0	0-2	0.29±0.52	0	1	0-2	0.059
Stroop 3 (Correction)	0.11±0.41	0	0	0-2	0.24±0.49	0	0	0-2	0.155
Stroop 4 (Time)	20.50±6.56	19	10	10-35	23.71±7.27	24	13.25	10-37	0.099
Stroop 4 (Error)	0.68±1.02	0	1.75	0-3	0.76±0.92	1	1	0-4	0.457
Stroop 4 (Correction)	0.57±0.92	0	1	0-3	0.65±0.73	0.5	1	0-2	0.389
Stroop 5 (Time)	26.57±8.65	27.5	14.75	10-41	35.82±10.10	38	12.5	12-50	**<0.001**
Stroop 5 (Error)	2.07±2.39	1.5	2.5	0-10	2.35±1.39	2	2.25	0-6	0.094
Stroop 5 (Correction)	1.39±1.61	1	2	0-6	1.71±1.19	2	1.25	0-5	0.155

OSAS: Obstructive Sleep Apnea Syndrome, SD: Standard Deviation, IQR: Interquartile Range, Min: Minimum, Max: Maximum

Table 5. Correlation analysis of AHI, BDI, BAI, MoCA and Stroop test

		AHI	BDI	BAI
Executive	r	-0.154	-0.453	-0.337
	p	0.232	**0.001**	**0.007**
Naming	r	-0.383	-0.479	-0.489
	p	**0.002**	**<0.001**	**<0.001**
Attention	r	-0.398	-0.501	-0.449
	p	**0.001**	**<0.001**	**<0.001**
Language	r	-0.133	-0.340	-0.309
	p	0.302	**0.007**	**0.015**
Abstract thinking	r	-0.370	-0.460	-0.448
	p	**0.003**	**<0.001**	**<0.001**
Delayed recall	r	-0.419	-0.391	-0.378
	p	**0.001**	**0.002**	**0.002**
Orientation	r	-0.215	-0.434	-0.530
	p	0.094	**<0.001**	**<0.001**
MoCA total	r	-0.404	-0.568	-0.530
	p	**0.001**	**<0.001**	**<0.001**
Stroop 1 time	r	0.211	0.568	0.510
	p	0.100	**<0.001**	**<0.001**
Stroop 2 time	r	0.142	0.346	0.023
	p	0.273	**0.006**	0.289
Stroop 3 time	r	0.280	0.510	0.398
	p	**0.028**	**<0.001**	**0.001**
Stroop 4 time	r	0.284	0.560	0.420
	p	**0.025**	**<0.001**	**0.001**
Stroop 5 time	r	0.510	0.487	0.407
	p	**<0.001**	**<0.001**	**0.001**
AHI	r	----	0.452	0.368
	p		**<0.001**	**0.003**
BDI	r	0.452	---	0.899
	p	**<0.001**		**<0.001**
BAI	r	0.368	0.899	---
	p	**0.003**	**<0.001**	

AHI: Apnea Hypopnea Index; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; MoCA: Montreal Cognitive Assessment

seems to be the most affected region of the brain (28). In addition, grey matter volume loss in basal ganglia has been identified in OSAS patients (29,30). Reduced information processing and psychomotor speed, difficulty switching between tasks, and difficulty in preventing predominant responses in OSAS patients was also reported (31). It is noteworthy that studies showing the neuroanatomical regions affected in the literature from the above sentences also coincide with studies showing clinical results. Our study found that Stroop 1, 3, and 5 times were longer in OSAS patients compared to the control group, while Stroop 5 time had the highest correlation with AHI value. The fundamental feature of the Stroop test is that it measures the perceptive configuration of cognition under impairment, the capability to shift response, and the speed of information processing. Stroop test is also highly sensitive to frontal cortex damage. Evaluation of information in the literature in conjunction with our study results suggests that our findings are indicative of damage in the frontal region. Although increasing evidence over the past decade confirms our findings, it should be noted that the underlying pathophysiology linking OSAS and cognitive involvement is still controversial (32).

Depression and anxiety are common among OSAS patients (33,34). On the other hand, Gupta et al. (35) showed increased prevalence of OSAS in individuals with major depressive disorder and post-traumatic stress disorder. Clinical studies have indicated that the relationship between OSAS and depression is multifactorial (36). Inanç et al. (37) showed that BDI and BAI scores of the patients with OSAS were higher than the healthy control group. However, there are also studies that did not find an association between the OSAS with anxiety and depression (17,38). Depression, even in its mildest forms, has been associated with reduced cognitive functions (12,39). Depending on its duration and severity, anxiety has been known to cause cognitive disorders including deficits in cognitive flexibility and decision-making (40,41). Our study found higher levels of anxiety and depression in OSAS patients compared to the control group and also detected a correlation between cognitive functions and anxiety and depression. When evaluated in this regard, the results of our study may suggest that anxiety and depression associated with OSAS may be the cause of poor cognitive performance.

In addition, it should not be forgotten that OSAS patients have excessive daytime sleepiness. Sleepiness plays a role in the development of cognitive dysfunction, especially attention and executive functions (42,43). It is also noteworthy that daytime sleepiness may have contributed to the low cognitive performance of our patients. It has been reported that even short-term CPAP treatment has shown a positive effect on neurocognitive functions in OSAS patients (44,45). On the other hand, it also indicates that structural damage is not a single factor.

CONCLUSION

In conclusion, the results of this study imply that OSAS has different effects on various domains of cognitive function and that many negative factors caused by OSAS may play a role in cognitive involvement associated with OSAS. It should be kept in mind that further studies are warranted to more clearly illustrate the ethiopathogenesis of this subject. In addition, we believe long-term follow-up of cognitive status before and during CPAP therapy will provide significant contributions to our understanding of the irreversibility and extent of reversibility of cognitive involvement in OSAS.

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Predictors of Severe and Permanent Disability in Children Evaluated in Health Boards: A Single-Center Study

Özürlü Sağlık Kurulunda Değerlendirilen Çocuklarda Ağır ve Sürekli Özürlülüğün Yordayıcıları: Tek Merkezli Bir Çalışma

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ABSTRACT

Aim: The aim of this study is to determine the severe and permanent disability of the children evaluated in the disabled health boards and to evaluate the predictors of severe and permanent disability.
Material and Methods: Records of 1482 children who were referred to a university hospital health board for disability between the years 2013-2018 were screened retrospectively.
Results: More than half (52.2%) of the children had a single psychopathology. 83.5% of the cases were severely disabled and 66.5% were permanently disabled. Severely disabled children were significantly more likely to have psychiatric, pediatric, neurological, orthopedic and otorhinolaringologic disorders. Permanent disability was significantly more frequent among patients with pediatric, ophthalmologic and cardiac disorders while children with psychopathologies were significantly less likely to have permanent disability. Mental retardation/intellectual developmental disorder levels differed in rates of permanent disability with pair-wise comparisons revealing that severe mental retardation/intellectual developmental disorder was the main factor. Severe disability was significantly more common among children younger than 8 years while permanent disability was more common among children >3 years. Children with psychopathology were 4.1 times more likely to have severe disability and this further increased to 15.3 for those with mental retardation/intellectual developmental disorder.
Conclusion: This is the first study to evaluate the factors that affecting the decisions of permanent and severe disabilities in disability health boards. Comprehensive results have been achieved despite low generalizability. To provide consistent reports, further and multicenter studies on factors associated with severe and permanent disabilities in children are needed.
Keywords: Disability; disabled children; intellectual disability; disability evaluation.

ÖZ

Amaç: Bu çalışmanın amacı özürlü sağlık kurullarında değerlendirilen çocuklarda ağır ve sürekli özürlüğü belirlemek ve ağır ve sürekli özürlülüğün yordayıcılarını değerlendirmektir.
Gereç ve Yöntemler: Bir üniversite hastanesinin özürlü sağlık kuruluna 2013-2018 yılları arasında başvuran 1482 çocuğa ait kayıt geriye dönük olarak değerlendirildi.
Bulgular: Çocukların yarısından fazlasında (%52,2) bir psikopatoloji saptandı. Olguların %83,5'i ağır özürlü ve %66,5'i ise sürekli özürlüydü. Ağır özürlü olan çocuklarda psikiyatrik, pediatrik, nörolojik, ortopedik bozukluklar ve kulak burun boğaz ile ilişkili bozukluklar görülme olasılığı anlamlı şekilde daha fazlaydı. Pediatrik, oftalmolojik ve kardiyak bozuklukları olan çocuklar arasında sürekli özürlülük anlamlı şekilde daha fazla iken, psikopatolojisi olan çocuklarda sürekli özürlülük görülme olasılığı anlamlı olarak daha düşüktü. Mental retardasyon/entelektüel gelişimsel bozukluk düzeylerinin sürekli özürlülük oranları açısından çift yönlü karşılaştırmalar ile farklılaşması ağır mental retardasyon/entelektüel gelişimsel bozukluğun ana faktör olduğunu ortaya koymuştur. Ağır özürlülük 8 yaşından küçük çocuklar arasında anlamlı şekilde daha yaygın iken sürekli özürlülük ise 3 yaşından büyük çocuklar arasında daha yaygındı. Psikopatolojisi olan çocuklarda ağır özürlülük görülme olasılığı 4,1 kat daha fazlaydı ve bu durum mental retardasyon/entelektüel gelişimsel bozukluğu olanlar için 15,3'e kadar yükselmiştir.
Sonuç: Bu çalışma özürlü sağlık kurullarında sürekli ve ağır özürlülük kararlarını etkileyen faktörleri değerlendiren ilk çalışmadır. Genellenebilirliği düşük olmasına rağmen kapsamlı sonuçlar elde edilmiştir. Çocuklarda sürekli ve ağır özürlülükle ilişkili faktörlerle ilgili tutarlı raporların verilebilmesi adına daha fazla ve çok merkezli çalışmalara ihtiyaç vardır.
Anahtar kelimeler: Engellilik; engelli çocuklar; entellektüel engellilik; engellilik değerlendirmesi.

INTRODUCTION

Disability is defined as any impairment, activity limitations, or participation restrictions that result from the health condition or from personal, societal, or environmental factors in typical daily activities and interactions in the individual's life (1).

The Global Burden of Disease study estimates that the number of persons with disabilities over the age of 15 is approximately 975 million (19.2%) through the world, while the World Health Survey reports this number as 785 million (15.6%) (2). According to a nation-wide disability survey conducted in 2002 in Turkey, while the people with disabilities constitute 12.3% of the total population, the disabled population aged between 0 and 19 is about 8.8% of the total population (3).

In Turkey, disabled children and adolescents are brought by their parents to the health boards for certification and classification of their impairment. This certification is required in order for them and their families to benefit from the rights of the disabled. Health boards are responsible for providing medical reports on health status, disability rates, educational and social rights and employability of persons (for those >18 years old). The legal basis of these reports is the "Regulation on the Disability Measure, Classification and Health Board Reports for Disabled", which was updated in 2013 and was put into force in 2016 (4). The rate of disability is determined by the percentage (%) corresponding to the rates of disability in this regulation. The ratings are similar to baremas used in various countries and multiple impairments are combined with the Balthazard Formula (5). According to this regulation, persons with a disability rate of 50% or more and who cannot fulfill their daily living activities without the help of others are considered "severely handicapped". The duration of the report is also determined by whether the person's disability is continuous or not (6). However, no clear statements in the regulation exits as to which diseases and under which circumstances will the child be categorized as severely and/or permanently disabled. Discretion on the disabilities remains delegated to the physicians in the health boards for disabled, and it is well known in the clinical practice that there might be differences of opinion and a lack of uniformity exist across the different health boards. This ambiguity leads to discrepancy between reports, the inability of patients to benefit from social and educational rights at the same time, and the increase in objections to reports. Given these reasons, in this study, we aimed to evaluate the sociodemographic and clinical characteristics of children and adolescents who applied to the health board of a tertiary treatment center, and factors affecting severe and persistent disability decisions.

MATERIAL AND METHODS

Records of children aged 18 and younger who were referred to Health Board for Disability of Mersin University Medical Faculty between the years 2013-2018 were screened retrospectively. Age, gender, disability rates, disability-causing illnesses, disabling psychiatric disorders, severe and/or persistent disability, and reporting purposes were examined. Clinical factors and diseases that require decisions of severe and/or persistent disability were assessed. Ethical approval was obtained for this study and that participation involved informed consent (Mersin University Clinical Researches Ethic Committee, approval date 22/02/2018, number 2018/84).

Statistical Analysis

Statistical analyses were conducted with Statistica 13.3.1 software (TIBCO Software Inc., Palo Alto, CA, USA). Quantitative data are summarized in means and standard deviations while categorical data are summarized as counts and frequencies. Chi-square test was used to evaluate bivariate associations between categorical variables. Multiple logistic regression analyses were used to evaluate variables displaying significant associations. For quantitative variables, Receiver Operating Characteristic (ROC) analysis was used to determine appropriate threshold. Two-tailed p value was set at 0.05.

RESULTS

Within the specified time frame 1482 children (63.1% male, n=935) were evaluated by the Health Board for Disability of Mersin University Medical Faculty. Mean age was 6.6±5.0 (range, 0-18) years. There were 172 missing values and all percentages were calculated from 1310 sample size. More than half of the children had a single psychopathology (52.2%, n=684) while 14.8% (n=194) of the children were diagnosed with two or more psychopathologies. Most frequent diagnoses were mental retardation/intellectual developmental disorder (MR/IDD, 52.9%), autism spectrum disorders (ASD, 14.0%) and attention deficit/hyperactivity disorder (ADHD, 4.2%). Although the Turkish regulation suggests using Developmental Delay for children <6 years old rather than MR/IDD, those groups were conflated for this analysis. Grades of MR/IDD in order of frequency were mild (n=422, 32.2%), moderate (n=294, 22.4%) and severe (n=141, 10.8%). Additionally Borderline Intellectual Functioning was observed in 37 (2.8%) of the patients.

Among the whole sample severe disability was found in 83.5% (n=1238) and permanent disability was found in 66.5% (n=986). Severely handicapped children were significantly more likely to have psychiatric ($p<0.001$), otorhinolaringologic ($p<0.001$), pediatric ($p<0.001$), neurological ($p<0.001$) and orthopedic ($p=0.007$) disorders. Among psychopatologies; severe disability was significantly more common among those with MR/IDD ($p<0.001$) and those with mild/moderate and severe MR/IDD ($p<0.001$). Children with severe disability were significantly younger than those without ($p<0.001$). Area Under Curve (AUC) was significant and 8 years emerged as a significant but weak cut-off to distinguish severe disability (AUC=0.670, $p<0.001$, Figure 1).

Permanent disability was significantly more frequent among patients with pediatric, ophthalmologic and cardiac disorders ($p<0.001$) while children with psychopatologies were significantly less likely to have permanent disability ($p<0.001$). MR/IDD levels differed in rates of permanent disability ($p<0.001$) with pair-wise comparisons revealing that severe MR/IDD was the main factor ($p<0.001$). Children classified as permanently disabled were significantly older ($p<0.001$). ROC analysis revealed that children <3 years old were provided with temporary reports while those >3 years were more likely to be diagnosed with permanent disability (AUC=0.700, $p<0.001$, Figure 2).

Logistic regression analysis revealed that for this sample (Hosmer-Lemeshow test was used for model evaluation and model fits was good, HW=12.899, p=0.075), children with psychopathology were 4.060 times more likely to have severe disability (95% CI=1.558-10.580, p=0.004) and this further increased to 15.305 for those with MR/IDD (95% CI=7.112-32.937, p<0.001, Table 1).
The probability of receiving permanent report rises by 4.324 times as the age increases (95% CI=3.282-5.698, p<0.001). The probability of having a psychiatric condition is 0.535 times lower than for those who are not on a permanent report (95% CI=0.360-0.796, p=0.002, Table 2).

DISCUSSION

This retrospective chart-review study aimed to evaluate socio-demographic and clinical features of patients applying to the health board of a university hospital and to determine predictors of severe and permanent disabilities. As a result, we found that more than half of the sample had psychopathologies while severe and permanent disabilities were common. Severe disability was significantly more common among children younger than 8 years while permanent disability was common among children >3 years. In the Turkish literature, studies related to health board reports for disabled (HBRD) examined the sociodemographic characteristics and frequency of disability of the patients in general, but no study was conducted to evaluate the factors affecting severe and permanent disability decisions in HBRD.
Previous studies from Turkey reported that male children and those with psychopathologies were significantly more frequent among HBRD applications (7-9). Another study involving 1112 children reported that most common diagnoses were global developmental delay (61.1%) and ASDs (15.0%) for the <6 years, while most common diagnoses were MR/IDD (61.9%) and learning disorders (2.8%) for >6 years (8). Another study found that most frequent diagnoses were MR/IDD (36.1%), learning disorders (20.2%) and ASDs (11.1%) among its sample of HBRD applications (10). Similar to those reports, we also found a preponderance of males and those with psychopathologies among our sample. Also, similarly most common diagnoses in our sample were MR/IDD, ASDs and ADHD.
Previous studies from Turkey reported that most frequent reason of application to HBRD was to receive a special education report for Individual Education Plans (IEPs) (8,10-13). However, the most common reason of application in our study was procuring financial aids (i.e. 75.0%) while special education reports for IEPs formed only 23.4% of the reasons. This difference may be due to the facts that previous studies focused on children with mental disorders only (11-14), and that the high rates of severe disability in our study (i.e. 83.5%). The parents in

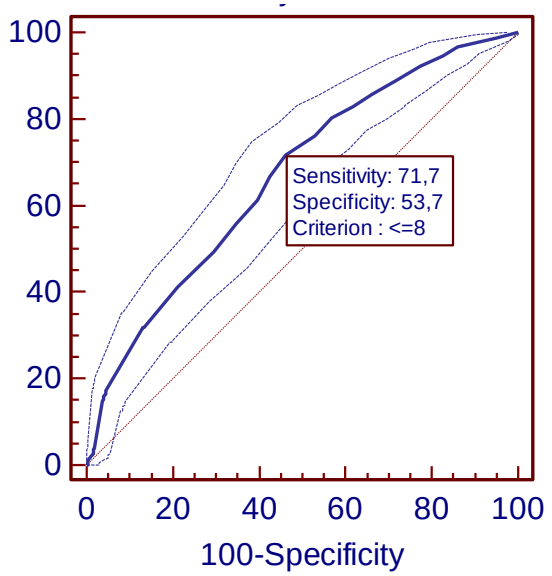

Figure 1. Receiver operating characteristics curve to determine age for severe disability

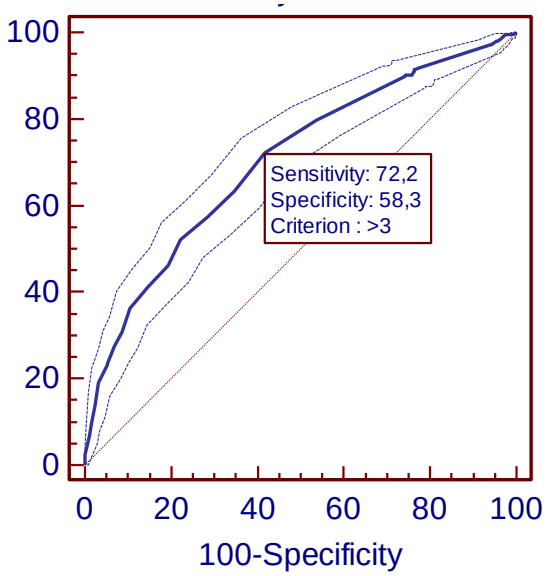

Figure 2. Receiver operating characteristics curve to determine age for permanent disability

Table 1. Factors affecting odds of severe disability

	OR	95% CI	p
Age	1.590	1.027-2.456	**0.037**
Otorhinolaringologic	2.692	1.150-6.302	**0.022**
Psychopathology	4.060	1.558-10.580	**0.004**
MR/IDD	15.305	7.112-32.937	**<0.001**
Pediatric	7.734	4.485-13.337	**<0.001**
Neurologic	2.021	1.070-3.818	**0.030**
Orthopedical	1.261	0.715-2.222	0.423

OR: Odds Ratio, CI: Confidence Interval

Table 2. Factors affecting odds of permanent disability

	OR	95% CI	p
Age	4.324	3.282-5.698	**<0.001**
Psychiatric condition	0.535	0.360-0.796	**0.002**
MR	0.722	0.490-6.514	0.100
Cardiac	2.841	1.942-4.156	**<0.001**
Pediatric	4.452	3.043-6.514	**<0.001**
Ophthalmologic	2.735	1.736-6.514	**<0.001**

OR: Odds Ratio, CI: Confidence Interval

our sample may have focused on financial aids for their children's disability and neglected the rehabilitation process. This hypothesis should be evaluated with further studies using interviews with parents for aims of their applications.

Rates of severe and permanent disability in previous studies vary according to sampling sources (9,13,15,16). According to Global Burden of Disease, the rate of severe disability in children aged between 0 and 14 was 0.7% and the rate of moderate to severe disability was 5.1% (15). In another study from Turkey, which conducted a chart review of children's HBRDs rates of severe and permanent disability were 45.9% and 17.6%, respectively (13). The authors interpreted those results as reflecting the relative rarity of chronic disorders in childhood as well as the unwillingness of clinicians to ascribe “permanence” to disabilities in children who after all were undergoing rapid development (13). Contrarily, a study of HBRDs from a university hospital in 2015 reported that rate of permanent disability among children as 77.0% (9). In another study of adults receiving HBRDs (n=795), rates for severe and permanent disability were reported as 39.4% and 64.2%, respectively (16). Another study on a different adult sample reported severe and permanent disability among 56.7% and 57.6%, respectively (9). In our study 83.5% of the sample were severely disabled while 66.5% of the patients were classified as having permanent disability. Those rates were higher than those previously reported and may reflect sampling bias as well as accepted clinical practice within the institution.

According to the 2010 TURKSTAT data, the most common reason for applying for HBRDs is mental disorders (17). When the frequency of diagnosis was determined from other areas except psychiatry, it was found that the diagnosis was most related to neurological problems (cerebral palsy 18.6%, epilepsy 12.4%, (8). Another study reported that 13.7% of their sample had seizures and 36.1% of cases had motor dysfunction (7). When the distribution of disturbances that cause disability among children applying for HBRDs is examined, another group reported that the most frequent disorders were mental/psychological/behavioral, followed by musculoskeletal and nervous system disorders, respectively (13). Another study also confirmed those results and reported that applicants for HBRDs mostly had musculoskeletal disorders and mental illnesses (18). Patients with musculoskeletal disorders may also be more likely to have severe and permanent disability (19). In our study, children with psychiatric, ear/nose/throat, pediatric, neurological and orthopedic disorders were more severely disabled than those without. Also, severe disability is most likely with pediatric disorders and mental disorders (especially MR/IDDs). Our results support and extend those from previous studies in that musculoskeletal disorders in children may be severely disabling along with other disorders. Among mental disorders, MR/IDDs may be especially disabling.

It is known that a majority of the MR/IDDs in the community are mild (i.e. 85.0%) although rates in clinical populations may differ (18). Reflecting those results, mild MR/IDDs formed 32.2% of our population while the rests were moderate (i.e. 22.4%) or severe (10.8%). This difference may reflect later recognition and better functioning of milder MR/IDDs as well as elevated medical/psychiatric comorbidities is more severe MR/IDDs. According to the Turkish regulations, people whose disability rate is 50.0% or more and who depend on help to perform their daily living activities are considered to have "severe disability" (6). Also, according to Turkish barema mild MR/IDDs have a disability rating of 50.0% while moderate (70.0%), severe (90.0%) and profound (100%) MR/IDDs are assigned greater disability ratings. In our study, severe disability was related with mild/moderate and severe MR/IDDs. This may reflect the fact that daily independent functioning rather than Intellectual Quotients in structured tests is more important in assessing disability. Also, toddlers and infants who naturally depend on others for their daily functioning are not adequately covered in the present regulation and may be assigned severe disability.

A common approach in HBRDs in Turkish institutions is to provide permanent reports in life-long disorders (such as MR/IDDs and ASDs) depending on severity and the age of the applicant. Provision of permanent reports in such cases protects the family and the disabled child against repeated applications (11). In our study, pediatric, ophthalmologic, and cardiac disorders were found to have a high rate of permanent reports, but those with psychiatric disorders were found to have significantly lower rates. This may be related to the fact that the diagnostic stability of psychiatric diseases is lower than that of organic diseases. There is a need for further studies in this area. Additionally we found that permanent disability reports in the institution we studied were given in severe MR/IDD cases, while mild MR/IDD patients received temporary records. This may be due to the child's developmental stage, change in diagnostic status with rehabilitation as well as the desire of the physician to keep the hope of the parents alive and the need for follow-up depending on the variability of diagnostic stability.

In our study, ROC analysis for severely handicapped and persistent handicap indicated that the cut-off point was identified as 8 years for severe disability and 3 years for permanent disability. Those aged 8 years and younger were severely disabled, and those older than 3 is in the permanent reports group. This may reflect greater dependence on assistance of others for daily functioning in younger children as well as greater severity of disorders. Also, diagnostic stability may increase with greater age allowing reports for permanent disability. Supporting this position we found that as the age increases, the likelihood of receiving permanent disability reports increases by 4.324 times. Diagnostic variability of psychopathology is also reflected by the fact that permanent disability is more likely with non-psychiatric and less likely with psychiatric disorders.

Our results should be evaluated within their limitations. Firstly, the results are limited to a single-center and the patients reporting for HBRDs and may lack generalizability to other centers and other populations. Secondly, this is a chart review study and further, objective information on functioning (i.e. quality of life, psychometric scales and instruments) may have enriched our results. Regardless of those limitations our results suggest further avenues of research on factors associated with severe and permanent disabilities in children. Further, more detailed studies on this subject are required.

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Changes in Bone Mineral Density after Kidney Transplantation

Böbrek Nakli Sonrası Kemik Mineral Yoğunluğundaki Değişiklikler

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ABSTRACT

Aim: The aim of this study was to evaluate changes in lumbar and femoral bone mineral density (BMD) in the post-transplant period.
Material and Methods: A total of 69 consecutive adult (>18 years of age) patients who underwent kidney transplantation between Jan 2016 and Jul 2019 were included in this retrospective study. The demographic features and laboratory findings of the patients (serum corrected calcium, phosphorus, alkaline phosphatase, creatinine, eGFR, i-parathormone and 25(OH) D vitamin levels) were recorded. BMD was evaluated by dual energy X-ray absorptiometry (DEXA).
Results: According to the DEXA results, lumbar and femoral T scores were -1.1±1.3 and -1.1±1.1, respectively. Lumbar assessment revealed osteoporosis in 12 (17.4%) patients and osteopenia in 24 (34.8%) patients. Femoral assessment revealed osteoporosis in 7 (10.1%) patients and osteopenia in 29 (42.0%) patients. The first year, 1-2 year and >2 years follow up data revealed osteoporosis in 4.3%, 5.8% and 7.2% of patients in the lumbar region and in 2.9%, 2.9% and 4.3% of patients in the femoral region, respectively. There was no significant difference in cumulative steroid dose between patients with BMD loss in the lumbar (p=0.197) and femoral (p=0.971) region and patients with normal BMD measurement. In addition, no significant relation was observed between the induction therapy and loss of BMD in the lumbar region (p=0.671) and femur (p=0.126).
Conclusion: As a result, 25(OH) D vitamin deficiency is quite common in transplant patients and the loss of BMD is observed especially in the lumbar region in the first year after transplantation.
Keywords: Kidney transplantation; bone mineral density; lumbar region; femoral; vitamin D.

ÖZ

Amaç: Bu çalışmanın amacı böbrek nakil sonrası dönemde lomber ve femoral kemik mineral yoğunluğundaki (KMY) değişiklikleri değerlendirmektir.
Gereç ve Yöntemler: Bu retrospektif çalışmaya, Ocak 2016 ve Temmuz 2019 tarihleri arasında böbrek nakli yapılan ardışık 69 erişkin (>18 yaş) hasta dahil edildi. Hastaların demografik özellikleri ve laboratuvar bulguları (serum düzeltilmiş kalsiyumu, fosfor, alkalen fosfataz, kreatinin, eGFR, i-parathormon ve 25(OH) D vitamin düzeyi) ile ilgili veriler kaydedildi. KMY, dual enerji X-ray absorbsiyometri (DEXA) ile değerlendirildi.
Bulgular: DEXA sonuçlarına göre, lomber ve femoral T skorları sırasıyla -1,1±1,3 ve -1,1±1,1 idi. Lomber değerlendirmede 12 (%17,4) hastada osteoporoz ve 24 (%34,8) hastada osteopeni saptandı. Femoral değerlendirmede 7 (%10,1) hastada osteoporoz ve 29 (%42,0) hastada osteopeni saptandı. İlk yıl, 1-2 yıl ve >2 yıl takip verilerine göre, sırasıyla lomber bölgede hastaların %4,3, %5,8 ve %7,2'sinde, femurda hastaların %2,9, %2,9 ve %4,3'ünde osteoporoz saptandı. Lomber bölge (p=0,197) ve femurda (p=0,971) KMY kaybı tespit edilen hastalar ile KMY ölçümü normal olan hastalar arasında kümülatif steroid dozu açısından anlamlı bir fark yoktu. Ayrıca hastaların almış olduğu indüksiyon tedavisi ile lomber bölge (p=0,671) ve femurda (p=0,126) gelişen KMY kaybı arasında anlamlı bir ilişki görülmedi.
Sonuç: Sonuç olarak, nakil hastalarında 25(OH) D vitamini eksikliği oldukça yaygındır ve özellikle nakilden sonraki ilk yıl lomber bölgede belirgin olmak üzere KMY kaybı görülmektedir.
Anahtar kelimeler: Böbrek nakli; kemik mineral yoğunluğu; lomber bölge; femur; vitamin D.

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INTRODUCTION

Problems related to bone mineral density (BMD) is one of the complications associated with life-long immunosuppressive therapy in kidney transplant patients. This condition increases the length of hospital stay, treatment cost, and mortality and morbidity rates due to the increased fracture risk in kidney transplant recipients (1). Data from the two major studies on fracture and mortality rates in post-transplant patients revealed the incidence of fractures to be 3.4-3.8% and the 1-year mortality risk after fracture to be 9.0-11.0%, depending on the risk factors (2,3). Several factors have been implicated in the etiology of bone mineral disorders develop after kidney transplantation including immunosuppressive drugs along with duration of chronic renal failure, type and duration of dialysis, pre-transplant bone disease (secondary hyperparathyroidism, osteomalacia, mixed bone disease, adynamic bone disease), diabetes mellitus, smoking, physical inactivity, menopause, fracture history, malnutrition, post-transplant persistent hyperparathyroidism and 25(OH) vitamin D deficiency (4,5). Immunosuppressive drugs, especially corticosteroids, reduce the number and activity of osteoblasts, increase osteoclastic activity and suppress bone formation resulting in rapid bone loss and increasing fracture risk via dose-dependent inhibition of growth hormone release and insulin-like growth factor-1 synthesis. Moreover, these agents cause negative calcium balance by decreasing intestinal absorption and increasing renal excretion of calcium (6). Calcineurin inhibitors can also cause high bone turnover, especially leading to trabecular bone loss. The combined use of cyclosporine (CsA) and glucocorticoid leads to bone loss by inhibiting osteoblast differentiation and enhancement. Tacrolimus (Tac) has been shown to cause osteopenia in animals, but there is limited data regarding its effect on bones in humans (5,7,8). Sirolimus, rapamycin, mycophenolate mofetil and azathioprine treatments were shown to have minimal effect on bone mass, and in vitro studies, everolimus has been shown to prevent bone resorption by inhibiting osteoclast cathepsin-K expression (9,10).

There are studies showing that the risk of fractures increases as BMD decreases in transplant patients (11,12). In this study, our aim was to show BMD changes in lumbar and femoral region in the post-transplant period.

MATERIAL AND METHODS

A total of 69 consecutive patients older than >18 years of age, who underwent kidney transplantation between January 2016 and July 2019 were included in this retrospective study. The blood biochemistry analysis was performed in routine controls including corrected serum calcium, phosphorus, alkaline phosphatase, creatinine, eGFR, i-parathormone and 25(OH) D vitamin level.

The study protocol was approved by the Ufuk University Faculty of Medicine Clinical Trials Ethics Committee (dated 16.12.2019 and numbered 5) and was conducted in accordance with the principles of Helsinki Declaration. Informed consent was obtained from all participants after informing them to participate in this research.

The 25(OH) D vitamin levels of the participants were studied by High Performance Liquid Chromatography (HPLC) method and vitamin D status was categorized as vitamin D deficiency (<20 ng/mL), vitamin D insufficiency (20-30 ng/mL), and normal vitamin D levels (>30 ng/mL, 13).

Anti-thymocyte globulin (Grafalon Neovii), one of the antilymphocyte antibodies, was given in 100 mg/g dose for 3 days as induction therapy on demand. All patients were started on prednisolone (0.8 mg/kg/day, oral) after intravenous 1500 mg methyl-prednisolone treatment. Prednisolone was given as 30 mg/day, 20 mg/day and 5 mg/day, in the first month, in the second month and after the third month, respectively. In maintenance therapy, calcineurin inhibitor (Tac or Cs-A) and an antiproliferative agent (mycophenolate mofetil, maximum 2 g/day or mycophenolate sodium, maximum 1440 mg/g) were used in combination with prednisolone therapy. Cs-A (6 mg/kg/day, 2 oral doses daily) and Tac (0.1 mg/kg/day, 2 oral doses daily) blood levels were titrated as needed to achieve target levels. In case of acute organ rejection, renal biopsy was performed and treatment (pulse methyl-prednisolone, anti-thymocyte globulin, plasmapheresis and intravenous immunoglobulin treatments alone or in combination) was performed according to Banff criteria.

Bone mineral densitometry was evaluated by dual energy X-ray absorptiometry (DEXA). The shooting time and radiation dose were determined as 60 seconds and 42 μGy for lumbar region and femur. Results were determined as T score [defines the difference between the patient's BMD and the mean BMD of the standard young adult (20-30 years old) population as standard deviation (SD) and expresses peak bone mass] and Z score (standard deviation of difference of patient's BMD results with the mean BMD of controls in the same gender and age group). The T score ≤-2.5 SD was accepted as osteoporosis, and T score <-1.0 and >-2.5 SD was accepted as osteopenia.

Statistical Analysis

The Kolmogorov-Smirnov test was used to follow normal distribution of variables. For the variables assumed to be normally distributed, inter-group comparisons were made by Independent samples t-test, while Mann Whitney U test was used for non-normally distributed variables. Spearman's rank correlation analysis was used to test the relation between cumulative steroid dose and 25(OH) D vitamin levels and BMD measurements. Chi-square test was used to the test the relationships among the categorical variables. The p value <0.05 was considered as statistically significant. The statistical analyses were performed with SPSS v.22.

RESULTS

Overall, 24.6% (n=17) of the patients were female and 75.4% (n=52) were male. The mean age of the patients was 40.7±13.8 (range, 17.0 to 64.0) years, body mass index was 26.6±5.0 (range, 18.7 to 42.5) kg/m^2, and post-transplant follow-up duration was 20±12 (range, 1 to 41) months. The evaluation of patients' diseases underlying end-stage renal disease to be chronic glomerulonephritis in 23 (33.3%) patients, hypertension in 12 (17.4%) patients, diabetic nephropathy in 9 (13.0%) patients, secondary amyloidosis in 8 (11.6%) patients, chronic tubulointerstitial nephritis in 3 (4.3%) patients, nephrolithiasis in 2 (2.9%) patients, polycystic renal disease in 2 (2.9%) patients and vesicoureteral reflux in 1 (1.4%) patient. The etiology of end-stage renal disease was unknown in 9 (13.0%) patients. When classified according to the reference values, there were 3 (4.3%) patients with normal 25(OH) vitamin D

levels, 11 (15.9%) patients with 25(OH) vitamin D insufficiency and 55 (79.7%) patients with 25(OH) vitamin D deficiency. The type of dialysis, tissue compliance number, transplantation type, the features of immunosuppression induction and maintenance treatment, rejection development and laboratory values of the patients are demonstrated in Table 1.

The mean T score for the lumbar region was -1.1±1.3 (range, -3.3 to 2.1), while the mean T score for the femur was -1.1±1.1 (range, -3.4 to 1.3). In lumbar region evaluation, osteoporosis was detected in 12 (17.4%) patients and osteopenia was detected in 24 (34.8%) patients. Five (41.7%) of 12 patients who developed osteoporosis and 11 (45.8%) of 24 patients who developed osteopenia received induction therapy. Looking at the relationship between lumbar region BMD loss and induction therapy; loss of BMD was observed in 16 (55.2%) of the 29 patients given induction therapy, whereas BMD loss was observed in 20 (50.0%) of the 40 untreated patients (p=0.671). According to femur measurements, osteoporosis was detected in 7 (10.1%) patients and osteopenia in 29 (42.0%) patients. Three (42.9%) of 7 patients who developed osteoporosis and 9 (31.0%) of 29 patients who developed osteopenia received induction therapy. Considering the relationship between BMD loss and induction therapy in the femoral region; while BMD loss was observed in 12 (41.4%) of the 29 patients who received induction therapy, bone loss was observed in 24 (60.0%) of the 40 patients who did not receive induction therapy (p=0.126). There were 4 (5.8%) patients with osteoporosis in both regions and 14 (20.3%) patients with osteopenia. Overall, 24 (34.8%) patients had normal BMD. Fracture was noted in none of the patients during follow-up period (Table 2). Follow up data on BMD losses with respect to DEXA measurements of lumbar and femur area are shown in Table 3, Figure 1 and Figure 2. Follow up data on osteoporosis development in the first year, 1-2 years and >2 years revealed lumbar osteoporosis rates of 4.3%, 5.8% and 7.2%, respectively, and femoral osteoporosis rates of 2.9%, 2.9% and 4.3%, respectively. In addition, at the end of the first year, BMD loss in the lumbar region was higher than in the femur region, and the frequency of osteoporosis showed a cumulative increase in the post-transplant period.

Overall, 20 (29.0%) patients developed acute rejection and therefore received 1500 mg of methyl-prednisolone in addition to standard steroid treatment. When patients were evaluated in terms of the relationship between cumulative steroid dose and BMD; there was no significant difference in cumulative steroid dose between patients with BMD loss and with normal BMD measurement in the lumbar region (p=0.197). In the femur region, there was no significant difference in cumulative steroid dose between patients with BMD loss and patients with normal BMD measurement (p=0.971, Table 4).

The evaluation of relation between 25(OH) vitamin D levels and BMD of the patients revealed no significant difference in 25(OH) vitamin D levels between patients with BMD loss and normal BMD measurement (p=0.909) in the lumbar region. There was also no significant difference in 25(OH) Vitamin D levels in patients with BMD loss and in patients with normal BMD measurements in the femur region (p=0.177, Table 4).

Table 1. Demographic characteristics of patients, n=69

Gender, n (%)	
Female	17 (24.6)
Male	52 (75.4)
Age (year)	40.7±13.8
BMI (kg/m^2)	26.6±5.0
Dialysis type, n (%)	
Preemptive	37 (53.6)
Hemodialysis	30 (43.5)
Peritoneal dialysis	2 (2.9)
Transplantation type, n (%)	
Live	66 (95.7)
Cadaveric	3 (4.3)
MM, n (%)	
0 MM	5 (7.2)
1 MM	4 (5.8)
2 MM	10 (14.5)
3 MM	24 (34.8)
4 MM	11 (15.9)
5 MM	8 (11.6)
6 MM	7 (10.1)
Immunosuppression, n (%)	
Tac+MMF	68 (98.6)
CsA+MMF	1 (1.4)
Induction treatment, n (%)	
ATG	28 (40.6)
Basiliximab	1 (1.4)
Non-inducted	40 (58)
Transplantation time (month)	20.0±12.0
Cumulative prednisolone dose (mg)	6450.0±2486.8
25(OH) vitamin D (ng/mL)	11.1±10.0
PTH (ng/L)	148.3±217.5
Ca (mg/dL)	9.3±0.4
P (mg/dL)	3.4±0.6
ALP (U/L)	76.0±27.2

BMI: Body Mass Index, MM: Miss-Match number, MMF: Mycophenolate mofetil, Tac: Tacrolimus, CsA: Cyclosporine-A, PTH: Parathyroid Hormone, Ca: Calcium, P: Phosphorus, ALP: Alkaline phosphatase, ATG: Anti-thymocyte Globulin

Table 2. Patients' lumbar and femur BMD evaluations

		Lumbar			
		Normal	Osteopenia	Osteoporosis	Total
Femur	Normal	24 (34.8)	8 (11.6)	1 (1.4)	33 (47.8)
	Osteopenia	8 (11.6)	14 (20.3)	7 (10.1)	29 (42.0)
	Osteoporosis	1 (1.4)	2 (2.9)	4 (5.8)	7 (10.1)
	Total	33 (47.8)	24 (34.8)	12 (17.4)	69 (100)

BMD: Bone Mineral Density

Table 3. Lumbar and femur BMD evaluations according to follow-up duration

	Region	**1-12 month**	**12-24 month**	**>24 month**
Normal BMD	Lumbar	7 (38.9)	10 (41.7)	16 (59.3)
	Femur	9 (50.0)	10 (41.7)	14 (51.8)
Low BMD	Lumbar	11 (61.1)	14 (58.3)	11 (40.7)
	Femur	9 (50.0)	14 (58.3)	13 (48.2)
Osteopenia	Lumbar	8 (44.4)	10 (41.7)	6 (22.2)
	Femur	7 (38.9)	12 (50.0)	10 (37.0)
Osteoporosis	Lumbar	3 (16.7)	4 (16.6)	5 (18.5)
	Femur	2 (11.1)	2 (8.3)	3 (11.2)

BMD: Bone Mineral Density

Table 4. Effect of cumulative steroid dose and 25(OH) Vitamin D levels on BMD

		Normal BMD (n=33)		BMD Loss (n=36)		p
		Mean±SD	Median (Q_1-Q_3)	Mean±SD	Median (Q_1-Q_3)	
Cumulative Steroid Dose (mg)	Lumbar	6777±2232	6750 (5550 - 8250)	6125±1922	6075 (4275 - 7500)	0.197
	Femur	6427±2302	6450 (5100 - 8150)	6445±1901	6225 (5325 - 7725)	0.971
25(OH) Vit D (ng/mL)	Lumbar	13.8±11.4	12.3 (7.5 - 16.4)	14.1±8.6	11.1 (7.5 - 19.6)	0.909
	Femur	12.3±6.3	10.4 (7.5 - 15.5)	15.6±12.3	12.6 (7.3 - 21.5)	0.177

BMD: Bone Mineral Density, SD: Standard Deviation, Q_1: 1st Quartile, Q_3: 3rd Quartile

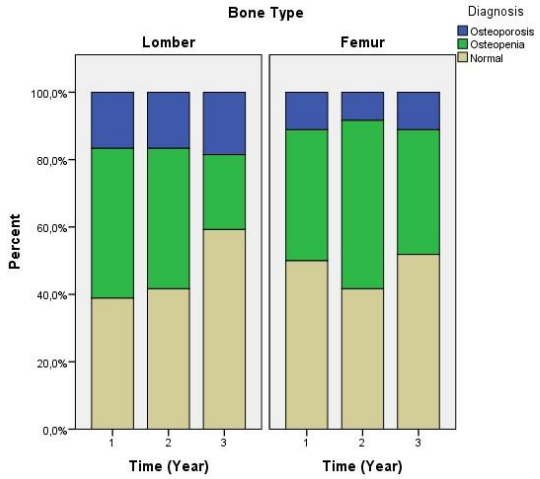

Figure 1. Evaluation of BMD in terms of normal, osteopenia and osteoporosis according to duration of follow-up

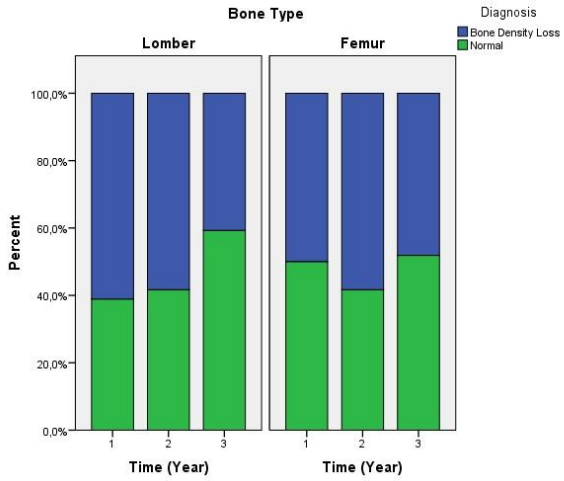

Figure 2. Evaluation of BMD changes of patients by years

In addition, there was no significant correlation between 25(OH) vitamin D levels and lumbar BMD measurement (r_s=0.036, p=0.771), and between 25(OH) vitamin D levels and femur BMD measurement (r_s=-0.015, p=0.905).

DISCUSSION

Our findings revealed more extensive BMD loss in the lumbar vs. femur region at the end of the first year than the following years and a cumulative increase in the frequency of osteoporosis in the post-transplantation period. The ratio of patients with adequate 25(OH) vitamin D levels was calculated as 4.3% (n=3). The majority of patients (79.7%, n=55) had 25(OH) vitamin D deficiency. There was no relation between cumulative steroid dose and BMD loss. Also, no statistically significant relationship was shown between induction therapy and loss of BMD.

Although BMD loss is seen both in the lumbar region and in the femoral neck in the first 6 months of the transplantation, the most intense BMD loss is seen in the lumbar region. BMD loss in the femoral neck becomes prominent after 6 months by follow-up (14). Similar to our study, in the study of Julian et al. (15), 20 post-transplant patients were evaluated and BMD loss was shown to be more intense in the lumbar region in the first 6 months. This can be explained by the different bone structure of lumbar and femur regions. Lumbar region consists mainly of trabecular bone and is a region sensitive to steroid effect. For this reason, BMD loss in the first 6 months is the highest in this region, when glucocorticoid therapy is used at the maximum doses. Femoral neck, on the other hand, is sensitive to hyperparathyroidism as it contains cortical bone. The effects of high parathyroid hormone on femur are long-lasting, as it may take years for the recovery of parathyroid gland hyperplasia after transplantation (16).

Similar to our study, in the literature, it has been shown that BMD loss or osteoporosis during the post-transplantation period reached the highest level in the first 6 months, and continue at a lower rate in the 6-12 months. Although it varies according to the series, the BMD reduction rate in the post transplantation period has been shown to be 5.5-19.5% for the first 6-month and 2.6-8.2% for the second 6-month (17). In the study by Trabulus et al. (18), osteoporosis was reported in 15.3% of patients in the first year, in 37.5% between 1-3 years, and in 41.6% between 3-5 years.

Vitamin 25(OH) D levels, together with calcium and phosphorus metabolism, is one of the factors affecting development, structure and function of the musculoskeletal system. Moderate or severe 25(OH) D vitamin deficiency has been demonstrated in kidney transplant recipients. This situation varies according to seasons, countries and age. In the studies investigated 25(OH) D vitamin levels of the recipients, the ratio of patients with adequate vitamin 25(OH) D levels was reported to be 3-12%, similar to our findings (4.3%) (19,20).

In a study of 86 transplant patients followed for 38.3±14.8 years after transplantation, those who received >5600 mg steroids and those who received <3300 mg steroids were compared and it was shown that the cumulative steroid dose did not increase the risk of bone fracture (21). In a similar study, 59 patients (31 patients with osteoporosis, 28 patients without osteoporosis) were followed up for 8.5±3.1 years after transplantation, and authors reported no significant difference between patients with vs. without

osteoporosis in terms of cumulative steroid doses (11). However, data from the United States Renal Data System (USRDS) revealed that the fracture risk decreased by 31% without increasing acute rejection risk in patients who were discharged from hospital by discontinuing steroid treatment (22). Chandran et al. (23) showed a negative correlation between cumulative steroid doses and BMD in a 5-year study with 164 renal transplant patients. In a study of 68 transplant patients, >40% of patients were shown to have lumbar BMD loss in first 11 months and bone loss was closely related to the cumulative steroid dose (24).

The limitations of the current study are retrospective design, lack of detailed information on patients' mineral and bone disorders associated with chronic renal disease before transplantation, and lack of data on control BMD measurements after treatment.

CONCLUSION

In conclusion, 25(OH) vitamin D deficiency is commonly encountered in transplant patient population, while BMD loss is also evident, particularly within the first post-transplant year and in the lumbar region. However, no relationship has been demonstrated between induction therapy and loss of BMD. Conflicting data exists in the literature regarding the effects of cumulative steroid doses and immunosuppressive treatments on BMD. Further studies are needed to address BMD, potential treatments and treatment outcome in transplant patients.

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Evaluation and Management of Severe Childhood Anemia: A Single Center Experience

Derin Çocukluk Çağı Anemisinin Değerlendirilmesi ve Yönetimi: Tek Merkez Deneyimi

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ABSTRACT

Aim: The aim of this study was to determine the frequency of iron deficiency anemia in patients with severe anemia, and to investigate and compare the difference in the hematological parameters between patients with and without iron deficiency anemia.
Material and Methods: A total of 119 patients diagnosed with severe anemia between January 2012 and July 2014 were retrospectively analyzed in this study. Demographic and clinical characteristics of severe anemia patients were evaluated. Patients were evaluated in terms of iron deficiency anemia, and clinical characteristic and laboratory findings of the patients with and without iron deficiency anemia were compared.
Results: Of the 119 cases 49 (41.2%) were male and 70 (58.8%) were female, mean age was 6.7±6.2 years. Various comorbidities were present in the patients. In all patients, the group with a hemoglobin value below 6 g/dL had a significantly lower platelet count than those equal to or above 6 g/dL (p=0.037). It was found that 52 (43.7%) of all cases had iron deficiency anemia and 27 (51.9%) of them were aged 5 to 18 years. Patients with iron deficiency anemia had lower ferritin level (p<0.001) than patients without iron deficiency anemia, while platelet count was higher in patients with iron deficiency anemia (p=0.001).
Conclusion: In patients with severe anemia, a significant decrease in platelet count was found with hemoglobin value below 6 g/dL. In order to reduce the need for red blood cells transfusion, early diagnosis of iron deficiency anemia is important and iron supplementation should be given earlier.
Keywords: Severe anemia; childhood; iron deficiency anemia; blood transfusion.

ÖZ

Amaç: Bu çalışmanın amacı derin anemisi olan hastalarda demir eksikliği anemisi sıklığını belirlemek ve demir eksikliği anemisi olan ve olmayan hastalar arasında hematolojik parametrelerdeki farklılığı incelemek ve karşılaştırmaktır.
Gereç ve Yöntemler: Bu çalışmada Ocak 2012 ve Temmuz 2014 tarihleri arasında derin anemi tanısı almış olan toplam 119 hasta geriye dönük olarak incelendi. Derin anemi hastalarının demografik ve klinik özellikleri değerlendirildi. Hastalar demir eksikliği anemisi açısından değerlendirildi ve demir eksikliği anemisi olan ve olmayan hastaların klinik özellikleri ve laboratuvar bulguları karşılaştırıldı.
Bulgular: Yüz on dokuz olgunun 49 (%41,2)'u erkek, 70 (%58,8)'i kız olup ortalama yaş 6,7±6,2 yıl idi. Hastalarda çeşitli eş zamanlı hastalıklar vardı. Tüm hastalarda, hemoglobin değeri 6 gr/dL'nin altında olan grup, 6 gr/dL'ye eşit ve üstünde olanlara göre anlamlı şekilde daha düşük trombosit sayısına sahipti (p=0,037). Tüm vakaların 52 (%43,7)'sinde demir eksikliği anemisi olduğu bulundu ve bunların 27 (%51,9)'si 5 ile 18 yaş arasında idi. Demir eksikliği anemisi olan hastaların ferritin düzeyi demir eksikliği anemisi olmayan hastalara göre daha düşük (p<0,001) iken, trombosit sayısı ise demir eksikliği anemisi olan hastalarda daha yüksekti (p=0,001).
Sonuç: Derin anemili hastalarda, hemoglobin değerinin 6 g/dL'nin altında olması durumunda trombosit sayısında anlamlı düşüş saptanmıştır. Eritrosit transfüzyonu ihtiyacını azaltmak için, demir eksikliği anemisinin erken teşhisi önemlidir ve demir takviyesi daha erken yapılmalıdır.
Anahtar kelimeler: Derin anemi; çocukluk çağı; demir eksikliği anemisi; kan transfüzyonu.

INTRODUCTION

Anemia is defined as a hemoglobin and hematocrit value with two standard deviations below the mean for a certain age, with a confidence limit of 95% (1). In 2011, the World Health Organization (WHO) has reported cut-off points to classify anemia as mild, moderate, and severe (2). Severe anemia is defined as a hemoglobin level below 7 g/dL in children aged 6 to 59 months, and below 8 g/dL in other age groups. According to data from the WHO, half of the children diagnosed with anemia in developing countries have iron deficiency anemia while severe anemia is uncommon (3). However, the mortality of severe anemia can be increased by infections, malnutrition, poverty, and low availability of health care. It is very important to diagnose the cause of the anemia before any blood transfusions so that the appropriate treatment strategy can be determined (4). The aim of this study was to determine the frequency of iron deficiency anemia in patients hospitalized for severe anemia, to evaluate characteristics of the patients with iron deficiency anemia, and to investigate and compare the hematological parameters between the patients with and without iron deficiency anemia.

MATERIAL AND METHODS

A total of 119 patients hospitalized for severe anemia between January 2012 and July 2014 at Düzce University Medical Faculty, Departments of Pediatrics were retrospectively evaluated. Information was obtained retrospectively from the patient charts and by contacting the families by phone. All patients had severe anemia according to their age group reference value at the time of first admission. The age range was 2.5 months to 17.5 years, and divided into three groups as <6 months, 6 months to 5 years and 5 to 18 years. The lower limit of hemoglobin for severe anemia was accepted as 7 g/dL in children under 6 months of age, 7 g/dL in children aged 6 months to 5 years, and 8 g/dL in those older than 5 years (2).

Demographic and clinical characteristics of patients with severe anemia were evaluated. Severe anemia patients were divided into two groups according to hemoglobin values as the patients with a hemoglobin value above or below 6 g/dL, and these groups were compared in terms of laboratory values.

All the patients were evaluated in terms of iron deficiency anemia, demographic and clinical characteristics of the patients detected with iron deficiency anemia were also evaluated. Severe anemia patients were divided again into two groups as the patients with and without iron deficiency anemia. Two groups with and without iron deficiency anemia were compared in terms of their complaints, laboratory values and other clinical characteristics.

Blood indices contained hemoglobin, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), red blood cell distribution width (RDW), white blood cell (WBC) and platelet count were evaluated.

This study was approved by the Clinical Research Ethics Committee of Düzce University Medical Faculty on 25.04.2013 with decision number 2013/401 and was conducted according to the Helsinki Declaration principles.

Statistical Analysis

The normality assumption for continuous variables was examined using Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous data were summarized with mean and standard deviation or median and interquartile range, as appropriate, according to normality assumption. Categorical variables were summarized as frequency and percentage. Independent Samples t test or Mann-Whitney U test was used to compare two groups in terms of continuous variables depending on whether the normality assumption was provided. Pearson chi-square or Fisher's exact tests were used to evaluate the relationships between categorical variables. A receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic predictive ability and cut-off values of the continuous variables. Statistical analyzes were performed with the SPSS v.22 statistical package and a p value equal to or less than 0.05 was considered as statistical significance level.

RESULTS

Characteristics of Children with Severe Anemia

One hundred nineteen children aged between 0.25 and 17.5 with a mean of 6.7±6.2 years had a hemogram value that was consistent with severe anemia. There were 49 (41.2%) male and 70 (58.8%) female patients. The patients were divided into three age groups as below 6 months, 6 months to 5 years and 5 to 18 years containing 5 (4.2%), 61 (51.3%) and 53 (44.5%) patients, respectively. The complaints of children with severe anemia were loss of appetite in 81 (68.1%), rapid fatigue in 76 (63.9%), weight loss in 46 (38.7%), pica in 9 (7.6%), and parasites in 2 (1.7%).

The severe anemia in study group was due to various disorders. Of the three most common causes, iron deficiency anemia was present in 52 patients (43.7%), chronic disease anemia in 29 patients (24.4%), and bleeding in 21 patients (17.6%). Microangiopathic hemolytic anemia was detected in 5 (4.2%), leukemia in 2 (1.7%), hereditary spherocytosis in 4 (3.4%), thalassemia major in 1 (0.8%), sideroblastic anemia in 1 (0.8%), and megaloblastic anemia in 1 (0.8%), as the other less common causes (Table 1). There were 2 (1.7%) patients diagnosed with transient erythroblastopenia of childhood. In addition to the main diagnoses evaluated above, 14 (11.8%) patients had iron deficiency anemia or iron deficiency, 8 (6.7%) patients had vitamin B12 deficiency, and 1 (0.8%) patient had folate deficiency.

Table 1. Differential diagnosis of severe anemia patients

Etiology of Anemia	n (%)
Iron deficiency anemia	52 (43.7)
Chronic disease anemia	29 (24.4)
Bleeding	21 (17.6)
Hemolytic anemia	5 (4.2)
Hereditary spherocytosis	4 (3.4)
Leukemia	2 (1.7)
Childhood transient erythroblastopenia	2 (1.7)
Thalassemia major	1 (0.8)
Megaloblastic anemia	1 (0.8)
Chemotherapy	1 (0.8)
Sideroblastic anemia	1 (0.8)

Laboratory Parameters of Children with Severe Anemia

Of the 119 patients 32 (26.9%) had a hemoglobin value below 6 g/dL. The platelet counts were statistically significantly higher in patients with a hemoglobin value equal to or above 6 g/dL compared to below 6 g/dL (p=0.037). There was no statistically significant difference in terms of blood indices except platelet counts between two groups (Table 2).

Characteristics of Children with Severe Iron Deficiency Anemia

A total of 52 (43.7%) cases with iron deficiency anemia were detected. Monthly income was 1500 Turkish liras (TL) or less in 40 (76.9%) of these cases. This information was obtained by contacting the families by phone.

Fecal occult blood test results were present for 27 (51.9%) patients with iron deficiency anemia. The fecal occult blood test was positive in 4 (7.7%) cases. The tissue transglutaminase IgA assay was found to be elevated in 1 (1.9%) patient (who also had celiac disease). The mean hemoglobin level was 10.5±1.9 g/dL at the 10-month follow-up. None of the severe iron deficiency anemia patients died.

Vitamin B12 deficiency was found in 5 (9.6%) severe iron deficiency patients while folate deficiency was present in 1 (1.9%) patient. Among the iron deficiency anemia patients, 14 (26.9%) had inadequate intake, 10 (19.2%) had abnormal uterine bleeding, and 13 (25.0%) had bleeding. Two patients (3.8%) had von Willebrand's disease, 3 (5.8%) had menorrhagia, and 1 (1.9%) had bleeding from esophageal varices.

Organomegaly or pathological lymphadenomegaly was not found in any patient with severe iron deficiency. Systemic diseases were detected in 23 (44.2%) iron deficiency anemia patients and included pulmonary diseases (bronchiolitis, pneumonia, tuberculosis) in 7 (13.5%) cases, neurological diseases (migraine, epilepsy, hydrocephalus, meningitis, cerebral palsy, mental retardation) in 6 (11.5%) cases, renal diseases (renal cyst, pelviectasis) in 5 (9.6%) cases, congenital heart disorders (atrial septal defect, etc.) in 2 (3.8%) cases, gastrointestinal bleeding in 2 (3.8%) cases, and celiac disease in 1 (1.9%) case. Oral iron was administered to all of the cases in the iron deficiency group.

Comparison of Severe Anemia Patients with and without Iron Deficiency Anemia

There was anorexia in 33 (63.5%) of the patients with iron deficiency and in 48 (71.6%) of the patients without iron deficiency anemia (p=0.342). Quick fatigue was present in 30 (57.7%) of the patients with iron deficiency and 46 (68.7%) of the patients without iron deficiency anemia (p=0.217). There was weight loss in 17 (32.7%) of the patients with iron deficiency anemia and 29 (43.3%) of the patients in the group without iron deficiency (p=0.239). A history of a parasitic infection was present in 2 (3.8%) subjects in the iron deficiency anemia group but none of the patients without iron deficiency anemia. A history of pica was statistically significantly more common in patients with iron deficiency anemia (p=0.041), there were 7 (13.5%) patients in the group with iron deficiency anemia and 2 (3.0%) patients in the group without iron deficiency anemia.

Evaluation of the blood indices of the iron deficiency anemia patients revealed a mean hemoglobin value of 6.7±0.9 g/dL and a median leukocyte count of 7.3x10³/mm³. Mean hemoglobin value was 6.4±1.3 g/dL and median leukocyte count was 7.8x10³/mm³ in patients without iron deficiency anemia, and there was no significant difference between groups in terms both of these parameters (p=0.113 and p=0.314, respectively). The median platelet count was 360x10³/mm³ in patients with iron deficiency anemia and it was significantly higher than patients without iron deficiency anemia (232x10³/mm³, p=0.001). There was a significant difference between two groups in terms ferritin (p<0.001). The median ferritin level was 10 ng/mL in patients with iron deficiency anemia and 170 g/dL in patients without iron deficiency anemia. The mean MCH value was 17.3±3.5 pg and the mean MCHC value 28.8±1.9 % in patients with iron deficiency anemia, while these parameters were 26.4±5.9 pg and 31.9±4.2 % in patients without iron deficiency anemia, respectively. Both the MCH and MCHC values were significantly lower in patients with iron deficiency anemia (both p values were <0.001). In patients with iron deficiency anemia, MCV values with a mean of 58.9±7.8 fL was detected as significantly lower compared to the patients without iron deficiency anemia (81.1±14.4 fL, p<0.001). The mean RDW value were 19.9±3.9 % in patients with iron deficiency anemia and 16.9±6.5 % in patients without iron deficiency anemia; and RDW value was higher in patients with iron deficiency (p=0.004, Table 3).

Table 2. Comparison of the hematology values of patients with a hemoglobin value below and above 6 g/dL

	<6 g/dL (n=32)	≥6 g/dL (n=87)	p
MCV (fL)	72.7±15.5	70.9±16.3	0.586
MCH (pg)	21.9±7.7	22.6±6.4	0.656
MCHC (gr/dL)	29.6±5.4	30.8±2.8	0.263
RDW	18.9±5.9	17.9±5.6	0.416
WBC (x10³/L)	7.5 (4.6-11.5)	7.7 (5.8-12)	0.519
Platelet (x10³/mm³)	198 (82-382)	303 (185-430)	**0.037**
Ferritin (ng/mL)	15 (7-157)	40 (10-276)	0.286

MCV: Mean Cell Volume, MCH: Mean Cell Hemoglobin, MCHC: Mean Cell Hemoglobin Concentration, RDW: Red Blood Cell Distribution Width, WBC: White Blood Cell

Table 3. Comparison of the patients with and without iron deficiency anemia

	IDA (n=52)	Non-IDA (n=67)	p
Hemoglobin (g/dL)	6.7±0.9	6.4±1.3	0.113
MCV (fL)	58.9±7.8	81.1±14.4	**<0.001**
MCH (pg)	17.3±3.5	26.4±5.9	**<0.001**
MCHC (gr/dL)	28.8±1.9	31.9±4.2	**<0.001**
RDW	19.9±3.9	16.9±6.5	**0.004**
WBC (x10³/L)	7.3 (5.5-9.9)	7.8 (5.2-13.3)	0.314
Platelet (x10³/mm³)	360 (234-492)	232 (114-356)	**0.001**
Ferritin (ng/mL)	10 (3-21)	170 (37-464)	**<0.001**

IDA: Iron Deficiency Anemia, MCV: Mean Cell Volume, MCH: Mean Cell Hemoglobin, MCHC: Mean Cell Hemoglobin Concentration, RDW: Red Blood Cell Distribution Width, WBC: White Blood Cell

The cut-off value for the diagnosis of severe iron deficiency anemia was calculated as ≤66.5 for MCV (AUC=0.913, 95% CI=0.858-0.969, p<0.001) and ≥17.9 for RDW (AUC=0.787, 95% CI=0.704-0.870, p<0.001). Sensitivity and specificity values were 71.2% and 74.6% for RDW, while these values were 92.4% and 86.6% for MCV, respectively (Figure 1).

Transfusion in Severe Anemia

One hundred nine (91.6%) patients in total and 42 (80.8%) patients in iron deficiency group required packed red blood cell transfusions because of co-morbid cardiorespiratory distress. Additionally, in the group of severe iron deficiency anemia 7 (13.3%) patients had worsening respiratory distress because of previous pulmonary disease.

DISCUSSION

Severe anemia is an important global health problem and is most frequent in developing countries (4). Severe anemia prevalence is below 2.5% worldwide, except in African countries (5). We used the most recent criteria for anemia as published by the WHO in 2011 for the cut-off values. Iron deficiency is the most common cause of anemia in children with a prevalence in the general population exceeding 50% in countries with low socioeconomic status (6,7). In our current study, iron deficiency anemia (43.7%) was the leading cause similarly. A study conducted in 1994 on severe anemia in childhood reported that 36.2% of the cases were diagnosed with iron deficiency anemia, 29.7% with malignancies and 12.3% with hemolytic anemia. The most common cause of severe anemia was reported as iron deficiency, followed by chronic disease and hemorrhage. And this study reported a higher rate of severe anemia in the group aged between 0-2 years (9). However, in our current study, the anemia rate was higher in children aged 6 months to 5 years compared to the other age groups studied. In another study conducted in 2005, 44.5% of the patients with severe anemia aged 6 months to 6 years were diagnosed with iron deficiency anemia and 31% with anemia due to inflammation. This study also concluded that low socioeconomic level played a role in iron deficiency and severe anemia (10). We found that the family's monthly income was below 1500 TL in most of the patients with iron deficiency anemia, as in this report.

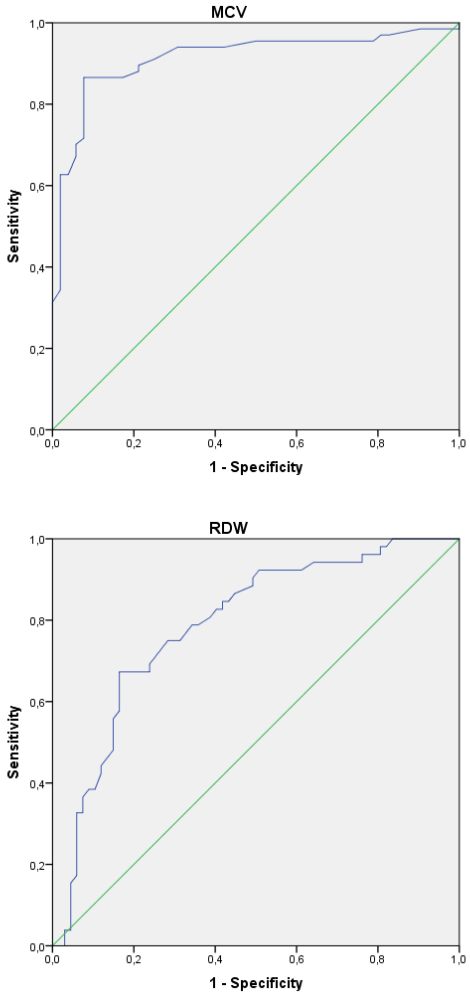

Figure 1. ROC (Receiver Operating Characteristics) curves for MCV (Mean Cell Volume) and RDW (Red Blood Cell Distribution Width)

A study conducted in 2014 evaluated 28 hospitalized patients with severe anemia (hemoglobin <7 g/dL) and iron deficiency anemia. The age range was 4 to 18 years and 42.8% of the adolescents were admitted with bleeding. Severe anemia due to iron deficiency was seen especially in the adolescent group, with less than half associated with bleeding, while the red meat consumption history suggested nutritional deficiency in all patients (11). The age groups were similar to our study but bleeding was not prominent in the etiology of our severe iron deficiency anemia patients. Another study from India in 2014 included 69440 adults and children. The hemoglobin concentration was the lowest in children aged 6-30 months. Microcytic anemia was the most common anemia type in children and women. Iron deficiency was the most common etiology of severe anemia, as in our study (12). A total of 55 severe anemia and iron deficiency anemia patients were evaluated in a study and 23 (45%) severe anemia patients diagnosed incidentally during a healthy child examination (13). In a study from US in 2014, a total of 64 severe anemia and iron deficiency anemia patients aged 13 to 36 months were evaluated and emphasized that the necessary precautions should be taken to avoid severe iron deficiency in infants aged 15 months and over (14). In our study, iron deficiency anemia was most frequently found in children aged 6 months to 5 years.

Reactive thrombocytosis is usually seen in iron deficiency anemia (15). Thrombocytopenia may also occur. We found thrombocytopenia at a rate of 15.4% and thrombocytosis at a rate of 28.8% in the children with severe anemia and iron deficiency anemia, similar to the rates reported in the literature. In a study on 4 children evaluating severe anemia has reported platelet levels below $50x10^3/mm^3$ in all the cases (16). We found the platelet count to be significantly lower in patients with a hemoglobin level <6 g/dL compared to those with ≥6 g/dL. Although the hemoglobin cut-off value for RBCs transfusion varies according to the child's age, transfusion is not indicated if the clinical condition is stable (17,18). Our patients with the criteria of severe anemia received transfusions if they showed heart failure symptoms or were in respiratory distress due to a pulmonary disorder.

Our results gave similar results with the study conducted by Keskin et al. (19) in terms of specificity and sensitivity of RDW; in cases with RDW elevation, prophylactic dose

iron replacement can be performed. In our study, cases with severe anemia were divided into two group as those with and without iron deficiency anemia. We found that, the sensitivity and specificity of RDW to diagnose iron deficiency anemia in patients with severe anemia was 71.2% and 74.6% while these values were 92.4% and 86.6% for MCV, respectively. We concluded that iron replacement would prevent severe iron deficiency anemia by early diagnosis of iron deficiency in patients with high RDW and low MCV.

The distribution of the etiologies for severe anemia in this study was different when compared to other studies from developing countries. Still, iron deficiency, a potentially preventable medical problem, was the leading cause. The use of RBCs transfusions in almost a third of children with iron deficiency anemia may result in unnecessary transfusion-related complications. The association of RBCs transfusions with underlying disease and a higher MCV value affect the physicians' decision process. Improved attempts for the prevention of iron deficiency anemia in all children and improvements in the guidelines for RBC transfusion in children presenting with severe anemia are needed.

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Spontaneous Perforation of Jejunal Ulcer

Spontan Jejunal Ülser Perforasyonu

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ABSTRACT

Spontaneous perforation of the nonspecific small bowel ulcer is a rarely seen condition that causes acute abdomen and mostly diagnosed perioperatively. A 72-year old female patient was admitted to emergency service with abdominal pain. Her physical examination was compatible with acute abdomen and peritonitis. Abdomen computerized tomography showed free air under the right diaphragm. She was operated with a presumptive diagnosis of gastrointestinal perforation. An isolated jejunal perforation on the opposite side of the mesentery was found perioperatively. A biopsy was taken, and the perforation was repaired with primary sutures. The patient died in the intensive care unit due to pulmonary complications on the fifth postoperative day. Although the biopsy was taken from the superficial tissue, it was consistent with an ulcer. Nonspecific jejunal ulcer perforations can be life-threatening because of the delayed diagnosis. Especially in elderly patients, it should be kept in mind as a cause of acute abdomen.
Keywords: Jejunal ulcer; acute abdomen; perforation.

ÖZ

Non spesifik spontan ince bağırsak ülser perforasyonu akut karına neden olan ve çoğunlukla perioperatif olarak tanı alan, nadir görülen bir durumdur. Yetmiş iki yaşında kadın hasta karın ağrısı yakınması ile acil servise başvurdu. Yapılan fizik muayenesi akut batın ve peritonit ile uyumluydu. Çekilen abdomen bilgisayarlı tomografide sağ diyafram altında serbest hava saptandı. Hasta gastrointestinal perforasyon ön tanısı ile operasyona alındı. Operasyon sırasında jejunum ansında antimezenterik yüzde perforasyon alanı saptandı. Bu alandan biyopsi alındı ve perforasyon primer suturasyon ile onarıldı. Hasta pulmoner komplikasyonlar nedeniyle postoperatif beşinci gün yoğun bakım ünitesinde exitus oldu. Alınan biyopsi yüzeyel olmakla birlikte ülser tanısını desteklemekteydi. Non spesifik jejunal ülser perforasyonları gecikmiş tanı nedeniyle hayatı tehdit edici olabilir. Özellikle ileri yaş hastalarda bir akut karın nedeni olarak akılda tutulmalıdır.
Anahtar kelimeler: Jejunal ülser; akut karın; perforasyon.

INTRODUCTION

Ulcerative perforations are most commonly occur in the stomach and duodenum. Jejunal perforation due to the primary ulcer is a sporadic condition (1,2). The disease has unknown etiology (1). Although the etiology is unclear, trauma, jejunal diverticulitis, malignancy, arteriosclerosis, drugs, infections, advanced age, superior mesenteric arterial occlusion, and the nonspecific ulcers are associated with the disease (2,3). Nonspecific small bowel ulcers are rare and can be life-threatening due to delayed diagnosis, and at the time of admission, patients might have a perforation as in our case.

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CASE REPORT

A 72-year old female patient was admitted to the emergency department with abdominal pain, vomiting, and nausea persisting for two days. She had a medical history of hypertension and chronic obstructive pulmonary disease but no history of operation. She also mentioned chronic using of diclofenac sodium for osteoarthritis. The patient's temperature was 38.3°C, blood pressure was 78/56 mm Hg, pulse rate was 101/min, and respiratory rate was 19/min. On physical examination, there were signs of peritoneal irritation in all quadrants of the abdomen with rebound tenderness. Laboratory data were as follows; white blood cell count was 3600/mm^3, platelet count was decreased, and the value was 114000/mm^3, liver function tests were increased (AST: 263, ALT: 144) and kidney functions tests and high lactate level which was counted at 3.6. Abdomen computerized tomography showed massive intraabdominal free gas and perihepatic fluid (Figure 1). The patient was diagnosed with perforation, and immediate surgical exploration was performed based on the diagnosis of the acute abdomen. Due to patients' impaired general condition and comorbidities, inotropic agents were initiated perioperatively. During explorative laparotomy, purulent fluid was observed in all four quadrants of the abdomen and pelvis. There were no perforations observed in the stomach, duodenum, ileum, or colon, and also no ischemia finding, which indicates mesenteric vascular disease. An isolated jejunal perforation with a diameter of 5 mm on the opposite side of the mesentery, which was located 70 cm distal of the ligament of Treitz, was detected (Figure 2). The jejunal ulcer was macroscopically similar to a perforated peptic ulcer. The perforated area was repaired with primary sutures due to the patients' impaired general condition and sepsis clinic. Postoperatively the patient was followed up with the support of inotropic drugs and mechanical ventilator in the intensive care unit. On the fifth postoperative day, the patient had sudden respiratory arrest secondary to pulmonary embolism and died in the intensive care unit. Written informed consent was obtained from the patient before the treatment, surgery, and publication.

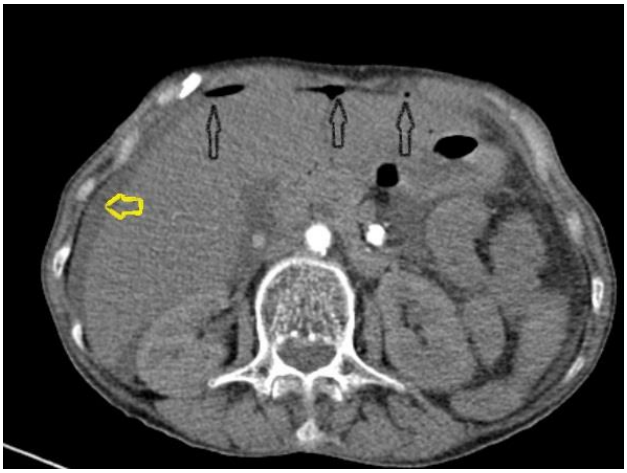

Figure 1. Abdomen computerized tomography showed; amount of free air in abdomen which was showed by black arrows and perihepatic fluid which was marked with yellow arrow

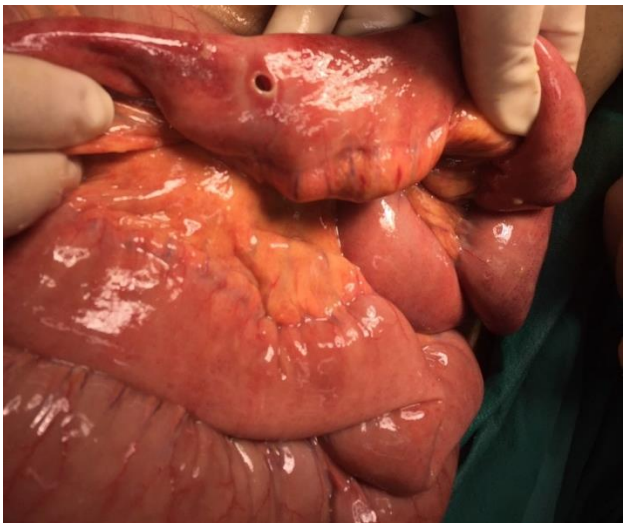

Figure 2. Perioperative finding; a jejunal perforation was detected 70 cm distal to the ligament of Treitz

DISCUSSION

Spontaneous perforation of the small intestine is a rare condition with an incidence of 1/350000 (1,2). In the small intestines, perforation due to ulceration mostly occurs in the duodenum, followed by the ileum and jejunum (1,2).

Spontaneous perforation of the small intestine requires immediate diagnosis and surgical treatment. It has various underlying etiologies such as jejunal diverticulitis, Crohn's disease, celiac disease, advanced age, arteriosclerosis, superior mesenteric arterial occlusion, malignancy, advanced age, radiation, focal gastric mucous membrane ectopy, and jejunal ulceration in case of gastroenterostomy partial gastric resections with a very short efferent loop to the jejunojejunostomy, and a nonspecific primary ulcers (1,3). Also, Chlorothiazide, antineoplastics and immunosuppressive, enteric-coated potassium chloride, and nonsteroidal anti-inflammatory drugs (NSAID) have been implicated in the etiology of spontaneous perforation of the small intestine (2,4). In addition, cytomegalovirus, human immunodeficiency virus, salmonella, tuberculosis, *Tropheryma whipplei*, histoplasmosis, *Entamoeba histolytica*, and viral, bacterial, parasitic, fungal intestinal infections have been shown to play a role in the etiology (3,4).

Among these etiologic factors, nonspecific jejunal ulcer (NJU) is extremely rare. In our case, the patient had no history of trauma, surgery, radiation, or antineoplastic drugs. The inflammatory diseases were excluded due to the unremarkable results of the colonoscopy, which was performed one year ago for anemia. Gastroscopy was compatible with *Helicobacter pylori* negative antral gastritis. Infectious causes, such as CMV IgM, HIV, and Salmonella, were also tested since the patient had a sudden clinical progression and death, and all were reported as negative. In our presented case for the etiology of JUP, the patient had the risk factors of advanced age and diclofenac sodium use, as mentioned by Matsumoto et al. (5) and Maiden L. (6). Maiden L. (6) supported the intestinal mucosal damage in healthy volunteers by using NSAID via capsule endoscopy. The study shows that not only the long term of use of NSAID but also 14 days of NSAID use

could cause mucosal breaks (29%). In addition 3% of the sample had free luminal blood and 2% had strictures.

The symptoms and signs of jejunal ulcers are nonspecific, such as abdominal pain, nausea, constipation, or diarrhea. The disease generally becomes symptomatic with the complications of an ulcer such as perforation, peritonitis, intraabdominal abscess, and intestinal obstruction. Patients with jejunal perforation due to NJU generally are admitted to the emergency service with acute onset abdominal pain with signs of peritonitis, nausea, fever, and vomiting, as in our case.

Laboratory tests for the jejunal ulcer perforation are not disease-specific. In the radiological examination of complicated NJU, chest X-Ray can show sub-diaphragmatic free air. Although the imaging studies, especially computerized tomography, can be helpful, a perforated jejunal ulcer is mostly diagnosed perioperatively, as in our case.

Most of the studies and case reports suggest that surgical treatment for complicated NJU is the first choice for treatment. Our case had needed an urgent surgical intervention and primary suture repair can be a first quick treatment choice. Primary suture repair, resection, and anastomosis or an ostomy may also be performed depending on the intraoperative findings and general condition of the patient via open surgery or laparoscopic methods (1,2).

In conclusion, perforation of NJU which can be life-threatening due to the delayed diagnosis must be kept in mind as a cause of acute abdomen. After the initial diagnostic evaluation, an urgent surgical intervention must be performed, especially in elderly patients with a history of NSAID use.

Informed Consent: Written informed consent was obtained from the patient for treatment, surgery, and publication at the time of hospital admission.

Conflict of Interest: All the authors declare no conflict of interest.

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Minimally Invasive Interventions Used with the Guidance of SPECT/CT in the Treatment of Mediastinal Parathyroid Adenomas

Mediastinal Paratiroid Adenomlarının Tedavisinde SPECT/BT Rehberliğinde Uygulanan Minimal İnvazif Girişimler

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ABSTRACT

Locating and removing ectopic parathyroid tissue may result in more than 20% failure. Seven cases which were detected by single photon emission computed tomography/computed tomography (SPECT/CT) imaging with Tc-99m sestamibi and treated with minimally invasive surgical methods were presented. The cases that underwent SPECT/CT due to high parathormone (PTH) level after total/subtotal parathyroidectomy operation, and detected to have mediastinal ectopic parathyroid were included. The success of the surgery was assessed with preoperative and postoperative PTH levels. Video-assisted thoracic surgery (VATS) was performed on five of the cases and video-assisted mediastinoscopy (VAM) was performed on remaining two. The mean age was 52.4±19.0. There were six women and one man. Mediastinal adenomas ranging from 1.5 to 6 cm in size, were successfully treated after single attempt. If the mediastinal ectopic parathyroid adenomas are fully localized before surgery, it can be treated with minimally invasive surgical methods.
Keywords: Ectopic parathyroid; parathormone; single photon emission computed tomography.

ÖZ

Ektopik paratiroid dokusunun yerini saptamak ve çıkarmak %20'nin üzerinde başarısızlıkla sonuçlanabilmektedir. Tc-99m sestamibi ile yapılan tek foton emisyon bilgisayarlı tomografi/bilgisayarlı tomografi (single photon emission computed tomography/computed tomography, SPECT/CT) görüntülemesinde saptanan ve minimal invaziv cerrahi yöntemler ile tedavi edilen yedi olgu sunulmuştur. Total/subtotal paratiroidektomi operasyonu sonrası yüksek parathormon (PTH) seviyesi nedeni ile SPECT/CT uygulanan ve mediastende ektopik paratiroid saptanan olgular dahil edilmiştir. Cerrahinin başarısı preoperatif ve postoperatif PTH düzeyleri ile değerlendirildi. Beş olguya video yardımlı toraks cerrahisi (video-assisted thoracic surgery, VATS), diğer ikisine video yardımlı mediastinoskopi (video-assisted mediastinoskopi, VAM) uygulandı. Ortalama yaş 52,4±19,0 idi. Altı olgu kadın, bir olgu erkek idi. 1,5 ile 6 cm arasında değişen mediastinal adenomlar tek denemeden sonra basit girişimler ile başarılı bir şekilde tedavi edildi. Mediastinal ektopik paratiroid adenomu ameliyat öncesi tam olarak lokalize edilebilirse minimal invaziv cerrahi yöntemlerle tedavi edilebilir.
Anahtar kelimeler: Ektopik paratiroid; parathormon; tek foton emisyon bilgisayarlı tomografi.

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INTRODUCTION

Primary hyperparathyroidism (HPT) is a disease characterized by hypercalcaemia, hypophosphatemia and excessive bone resorption resulting from excessive parathormone (PTH) release from the parathyroid gland. The cause is parathyroid adenomas in 85% of patients, parathyroid hyperplasia in 15% and more rarely parathyroid carcinoma in 1-2%. Treatment of parathyroid adenoma is surgical (1). Ectopic parathyroid tissue is a rare entity that causes severe metabolic problems (2).

Presented as a poster at 8th National Thoracic Surgery Congress (April 23-26, 2015, Antalya, Turkey).

About 5-10% of the parathyroid adenomas, which are the cause of HPT, are ectopic (1). The locations of ectopic parathyroid adenomas are frequently retroesophageal, paraesophageal, mediastinal, intrathymal or in carotid sheath (3).

Surgical success depends largely on the preoperative determination of the gland's localization. Today, various imaging modalities are used in preoperative imaging of parathyroid adenomas. These methods include ultrasound (USG), radionuclide methods such as Tc-99m methoxyisobutylisonitrile (MIBI), Tc-99m tetrofosmin scintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI) (4,5). Ectopic parathyroid adenomas are usually found in the parathymic or thymic tissue at the anterior mediastinum. Cervical USG cannot help in the preoperative locating of these lesions. Today, the radionuclide imaging with 99mTc-sestamibi scan accompanied by single photon emission computed tomography/computed tomography (SPECT/CT) is the most commonly used method for detecting adenomas. USG is also commonly used (6). In cases where the first attempt fails, reoperations increase morbidity because there are adhesions in the tissues. Since the parathyroid scintigraphy can also be used to examine the mediastinum, the accuracy of the scintigraphy in this area is high. In some recent studies it has been show that Technetium 99m MIBI parathyroid scintigraphy can be used for the localization of parathyroid pathologies. Kedarisetty et al. (7) state that the sensitivity and specificity of SPECT/CT for parathyroid adenomas are reported to be 77% and 71%, respectively.

CASE REPORTS

Seven patients with/without the history of total/subtotal parathyroidectomy operation who underwent SPECT/CT with Tc-99m sestamibi due to high PTH level and who had mediastinal ectopic parathyroid adenomas between January 2015 and September 2018 were included in the study. Five cases were performed video-assisted thoracic surgery (VATS) and the remaining two were video-assisted mediastinoscopy (VAM). The success of the surgery was assessed with preoperative and postoperative PTH levels. All procedures were carried out following the rules of the Declaration of Helsinki. Informed written consents were taken from all patients.

There were six women and one man whose mean age was 52.4±19.0 (range, 23-73) years. Preoperative and postoperative serum PTH and calcium values of the cases are given in Table 1. Mediastinal adenomas, ranging from 1.5 to 6 cm in size, were successfully treated after single attempt. Three of the cases were secondary HPT patients who underwent hemodialysis due to chronic renal failure. There were two cases with thyroid pathology. Surgical complications developed in two cases (1 hoarseness, 1 empyema). Both cases with complications were hemodialysis patients. Persistent hypocalcemia was seen in one of the cases. One of the patients had a history of operation due to parathyroid carcinoma in 2017. This patient's parathyroid adenoma resected with VATS and although the postoperative blood PTH level decreased, the normal PTH levels could not be reached. Some examples of parathyroid adenomas that were detected in SPECT/CT were shown in Figure 1 and 2.

DISCUSSION

The treatment of PHP was including bilateral neck exploration, identification of all parathyroid glands, and removal of pathologically enlarged glands. Recently, unilateral surgical approach and focal exploration with the help of localization studies have been accepted (8). In a case presented by Fatimi et al. (9), a mediastinal ectopic parathyroid adenoma at the anterior mediastinum was resected with VATS. They also stated that VATS is a safe and effective procedure for the resection of ectopic mediastinal parathyroid adenoma.

Imaging in HPT can be performed by parathyroid scintigraphy (PS), USG, CT and MRI, but the most recommended two methods are PS and USG. However, imaging should not be used to diagnose HPT but to identify the location of the lesion in biochemically proven HPT patients. The only management method for HPT patients is the surgical treatment. As a result of the switch from examination of four parathyroid glands by bilateral neck exploration to minimally invasive surgical procedures, precise location of the lesion prior to surgery has become one of the most important factors in the success of the operation (2). VATS technique can be used for parathyroidectomy and it has some advantages over sternotomy or thoracotomy like short operative time and better visualization of the tumor (10).

We also used Tc-99 MIBI PS, which is recommended for precise localization. USG is inadequate when ectopic adenomas are identified. The location of ectopic parathyroid adenomas is frequently retroesophageal,

Table 1. General characteristics and outcomes of the cases

Case	Age	Gender	Primary Disease	Dimension of ePT (mm)	Surgical Method	Complication	Preop PTH	Postop PTH	Preop Ca	Postop Ca
1	23	Female	CRF, Hypothyroidism	15	VAM	hoarseness	1350	6.5	12.20	9.60
2	39	Female	CRF	20	VAM	-	1270	71.0	9.80	5.30
3	46	Female	CRF	22	VATS	empyema	2200	190	8.90	5.60
4	69	Female	Hyperthyroidism	38	VATS	-	1650	126	10.20	7.50
5	71	Female	Hyperthyroidism	65	VATS	-	1460	92.4	12.40	8.60
6	46	Male	Hyperparathyroidism	60	VATS	-	259.30	1.2	10.70	10.00
7	73	Female	Hyperparathyroidism	65	VATS	-	953.50	86.48	12.43	8.27

ePT: Ectopic Parathyroid Adenoma, PTH: Parathormone, Ca: Calcium, CRF: Chronic Renal Failure, VAM: Video-assisted Mediastinoscopy, VATS: Video-assisted Thoracic Surgery

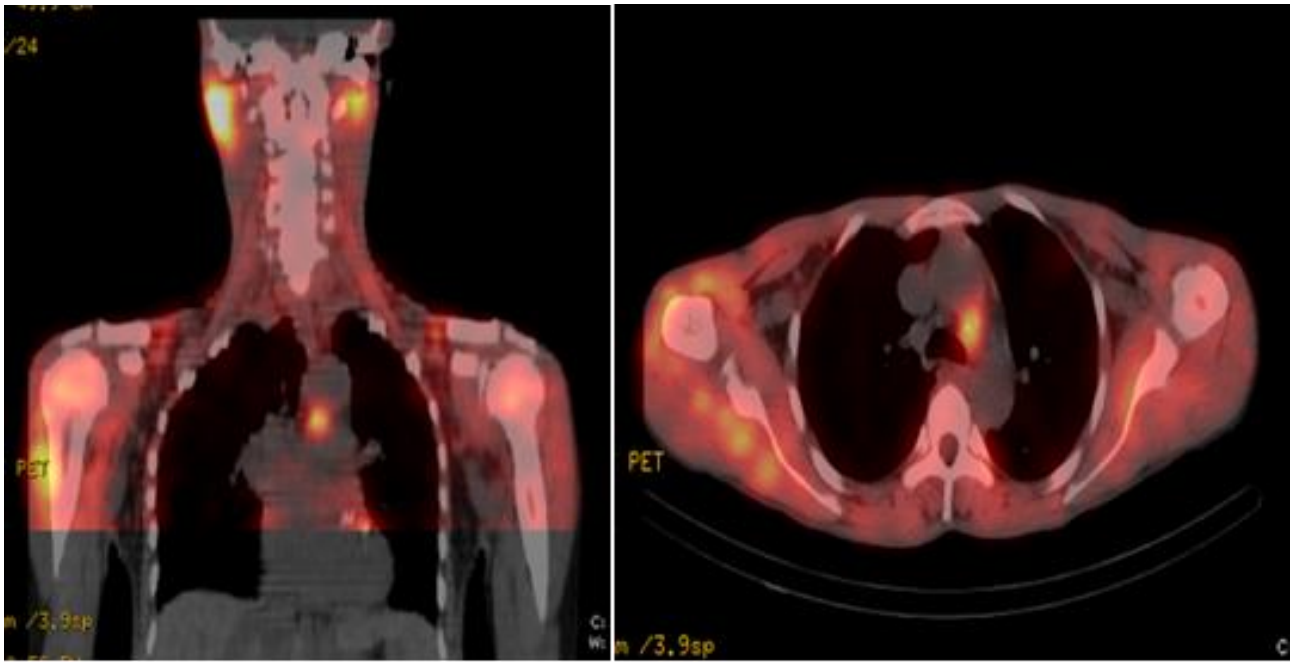

Figure 1. Ectopic parathyroid tissue located in left paratracheal area

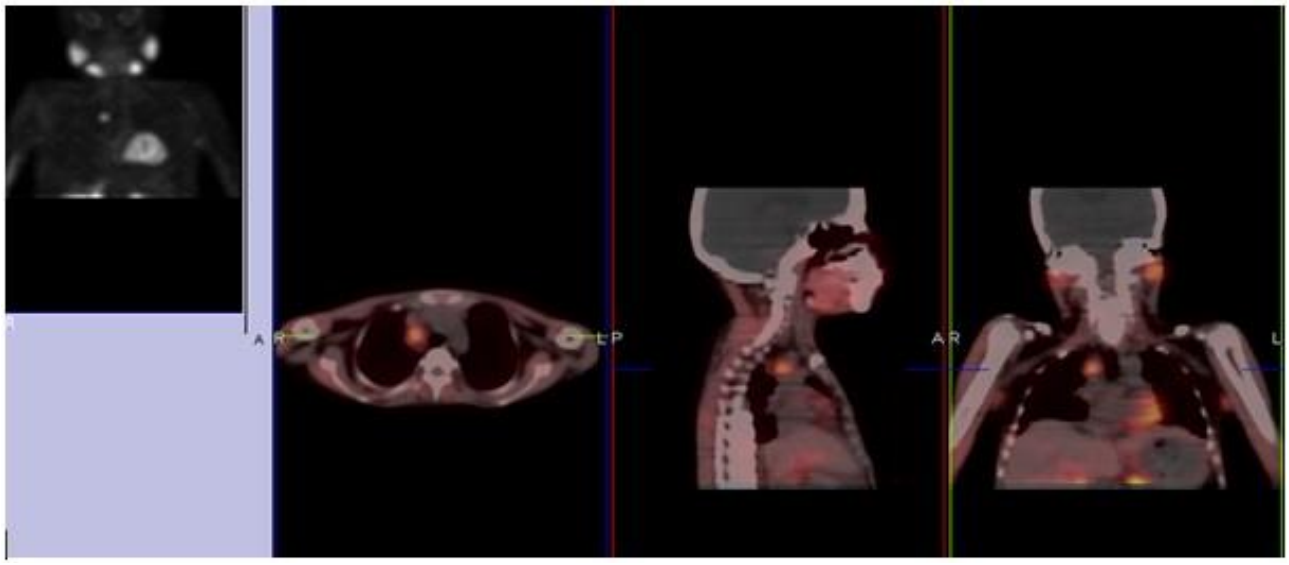

Figure 2. Ectopic parathyroid tissue located in right upper paratracheal area

paraesophageal, mediastinal, intrathymal or in carotid sheath (3). Locations of the cases were lower and upper paratracheal in our study.

Better cosmetic results can be obtained up to 90% using minimally invasive surgical methods and small incisions in solitary adenomas. In addition, some other advantages have been reported with minimally invasive surgical methods such as; reduction of complications including recurrent nerve damage and postoperative hypocalcemia, shortening of operation and hospitalization time and ensuring earlier healing. Equally successful results to the classical method were achieved by minimally invasive surgical methods (11,12). Lihara et al. (13) presented 8 cases with parathyroid adenomas that were applied VATS and no complication were seen in any patient. Hoarseness developed in 1 case, and postoperative hypocalcemia developed in 2 cases as postoperative complications in our series; both of the cases with hypocalcemia were hemodialysis patients due to chronic renal failure.

The most important factor affecting the success of minimally invasive surgery is the correct location of the lesion (14). We also detected the location correctly with Tc-99 m MIBI PS in 6 cases. We think that Tc-99m MIBI is safe for lesion detection.

If the mediastinal ectopic parathyroid adenoma is fully localized before surgery, it can be treated with minimally invasive surgical methods. Especially in the case of secondary HPT, the risk of surgical complications is high.

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A Cause of Rectal Mass: Diffuse Large B-Cell Lymphoma

Bir Rektal Kitle Nedeni: Diffüz Büyük B-Hücreli Lenfoma

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ABSTRACT

The most commonly seen pathological type of rectal cancer is adenocarcinoma. The involvement of the colorectal tract with diffuse large B-cell lymphoma is a very rare clinical condition. A-65-year old man was admitted with complaints of weight loss and hematochezia. A rectal mass that mimicked rectal carcinoma was diagnosed by rectal examination and supported by the colonoscopy. The final report of the rectal mass biopsy reported as rectal lymphoma. Thoracoabdominal computed tomography was showed rectal wall thickening which surrounded small lymph nodes. Additional examinations didn't reveal any evidence of infiltration to other organs. The patient diagnosed as primary rectal lymphoma and chemotherapy was started by the hematology department. Rare pathologies such as rectal lymphoma must be kept in mind in the differential diagnosis of rectal mass cases. Since both rectal carcinoma and rectal lymphoma have similar appearances in clinical and radiological studies, it is difficult to make a differential diagnosis.
Keywords: Rectal lymphoma; rectal mass; diffuse large B-cell lymphoma.

ÖZ

Rektum kanserinin en sık görülen patolojik tipi adenokarsinomdur. Diffüz büyük B-hücreli lenfomanın kolorektal sistem tutulumu çok nadir görülen bir klinik durumdur. Atmış beş yaşında erkek hasta kilo kaybı ve hematokezya şikayetleri ile başvurdu. Rektal muayene ile rektal karsinomu taklit eden bir kitle teşhis edildi ve kolonoskopi ile desteklendi. Rektal kitle biyopsisinin nihai raporu rektal lenfoma olarak raporlandı. Çekilen torakoabdominal bilgisayarlı tomografi rektum çevresinde küçük lenf nodları ve rektum duvarında kalınlık artışı olduğunu gösterdi. Yapılan ek tetkikler başka bir organ tutulumu olmadığını gösterdi. Hasta primer rektum lenfoma tanısı aldı ve hematoloji bölümü tarafından kemoterapi başlandı. Rektal kitle vakalarının ayırıcı tanısında rektal lenfoma gibi nadir patolojiler akılda tutulmalıdır. Hem rektal karsinom hem de rektal lenfoma klinik ve radyolojik çalışmalarda benzer görünümlere sahip olduğundan, ayırıcı tanı zordur.
Anahtar kelimeler: Rektal lenfoma; rektal kitle; diffüz büyük B-hücreli lenfoma.

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INTRODUCTION

Primary rectum lymphoma (RL) is a rare tumor that constitutes about 0.2 - 0.6% of all colorectal tumors (1). Diffuse large B cell lymphoma (DLBCL) subtype is the most common subtype of colorectal lymphoma (1). RLs are diagnosed in advanced stages due to nonspecific symptoms and clinical presentations that are not specific to the disease. Although surgical resection is often possible in the management of RL, the choice of medical therapy and surgical treatment is still controversial, and optimal treatment has not yet been described. Here, we aimed to present an elderly male patient, diagnosed with DLBCL of the rectum that managed medically, with the current light of the literature.

CASE REPORT

A 65-year-old male patient without any history of chronic disease or previous operation presented with a complaint of weight loss, anorexia and rectal bleeding for 3 months. The rectal examination of the patient revealed a palpable mass which fixed to the rectal wall. A colonoscopic examination revealed a rectal mass lesion with necrotic tissues covering more than half of the lumen approximately 2-4 cm proximal from the dentate line. Histopathological sections showed a neoplastic lymphocytic infiltrate of moderate to large size with nucleolar prominence (Figure 1). The cells that make up this infiltrate are positive for CD20 (Figure 2), Bcl2 and MUM1. Furthermore, most of these cells are Bcl6 positive. These cells were negative with CD5, CD10, cyclin D1, and pan-cytokeratin. Ki67 proliferative index was 40%. The case was reported as DLBCL with morphological and immunohistochemical findings. In thoracoabdominal computed tomography (CT), no pathological findings or other organ involvements were observed except for the increase in thickness in the rectal wall and peripheral lymphadenopathies around the rectum wall. The patient was referred to the hematology department to receive chemotherapy treatment. Written informed consent was obtained from the patient for publication and any accompanying images.

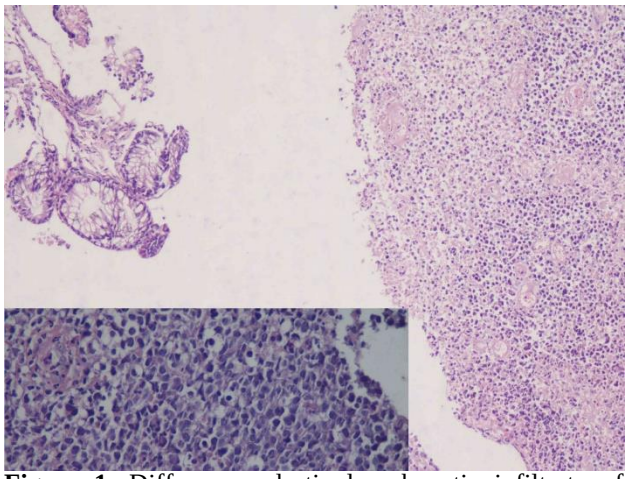

Figure 1. Diffuse neoplastic lymphocytic infiltrate of moderate to large size with nucleolar prominence, hematoxylin eosin, 100x (inlet, 400x)

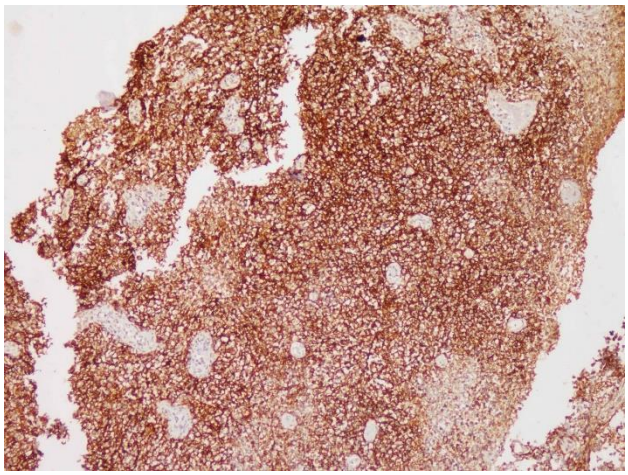

Figure 2. Diffuse CD20 positivity, 100x

DISCUSSION

Colorectal lymphoma is an extremely rare disease. The incidence of RL is 0.2-0.6% of all colonic carcinomas and 10-15% of all primary lymphomas of the gastrointestinal tract (1,2). The most common colon placement of lymphoma is cecum with a rate of 70%, followed by the rectum and ascending colon (2). Although gastrointestinal lymphoma has been correlated with immune deficiency, immunosuppression, and inflammatory bowel disease, our case did not have any chronic disease or history of operation to support it (1,2). The patient had five criteria supporting gastrointestinal lymphoma defined by Dawson et al. (3). No superficial lymph node was detected in the physical examination of him. Although abdominal CT supports the localized lymphadenopathies around the rectum, spleen and liver involvement and mediastinal lymphadenopathy were not seen in the thorax and abdominal CT. No pathological findings were observed about white blood cells in laboratory tests (3). Since both rectal carcinoma and RL have similar appearances in clinical and radiological studies, it is difficult to make a differential diagnosis. However, in this case, CT and histopathological examination guided us to distinguish between RL and rectal carcinoma. Although surgical resection is the basis of treatment in non-metastatic resectable rectal cancer, therapeutic treatment of RL remains uncertain due to the rarity of it. Although there are studies indicating that radical surgical resection or even local resection is more useful in the treatment of RL, many authors consider medical management to be the primary treatment (4,5). In RL, the correct diagnosis of the disease directly affects the patient's prognosis and the choice of treatment to be administered to the patient. In the treatment of RL, the patient may have a chance to cure without the need for surgery. In conclusion, the fact that RL is very rare and the clinical signs and symptoms are very similar to rectal carcinoma causes a great difficulty in diagnosing of the disease. Differentiation of RL from rectal carcinoma is important because staging, treatment, and prognosis are different from each other. Prospective randomized controlled trials with larger patient series are needed to identify risk factors for the RL and determine the most appropriate treatment method.

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Liver Transplantation in a Patient with Absent Inferior Vena Cava: Case Report

İnferior Vena Cava Bulunmayan Bir Hastada Karaciğer Transplantasyonu: Olgu Sunumu

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ABSTRACT

Transplantation procedure used if the recipient and donor do not have a special anatomical variation today; left lateral segment in the pediatric age group, and right lobe in the adult age group. Biliary atresia in children and various liver diseases like metabolic events in adults are the major causes of liver transplantation. Liver transplantation is challenging in the patients with congenital vascular anomalies. Infrahepatic interruption of the inferior vena cava (IVC) is a rare congenital anomaly with the incidence of 0.6% to 2% and mostly found with congenital heart disease. In this study we tried to report a 58-year old male patient with a diagnosis of decompensated liver cirrhosis caused by the hepatitis B virus (HBV) who was hospitalized for the first time for living donor liver transplantation.
Keywords: Liver transplantation; inferior vena cava (IVC); congenital anomalies.

ÖZ

Günümüzde alıcı ve vericinin özel anatomik bir varyasyonunun yokluğunda kullanılan transplantasyon prosedürü; pediatrik yaş grubu için sol lateral segmentin alınması, erişkin yaş grubunda ise sağ lobun kullanılmasıdır. Çocuklarda biliyer atrezi, erişkinlerde ise metabolik olaylar gibi çeşitli karaciğer hastalıkları karaciğer transplantasyonu için başlıca nedenlerdir. Karaciğer transplantasyonu, konjenital damar anomalisi olan hastalar için oldukça zor bir işlemdir. İnferior vena cavadaki, infrahepatik kesinti %0,6 ile %2 oranında gerçekleşen oldukça nadir bir konjetinal anomalidir ve genellikle konjenital kalp hastalığı ile birlikte görülür. Biz bu çalışmada, hepatit B virüsü (HBV) zemininde gelişen dekompanse karaciğer yetmezliği tanısı olan ve canlı vericiden karaciğer nakli için ilk kez hastaneye yatışı yapılan 58 yaşındaki erkek hastayı takdim etmek istedik.
Anahtar kelimeler: Karaciğer transplantasyonu; inferior vena cava (IVC); konjenital anomaliler.

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INTRODUCTION

Infrahepatic interruption of the inferior vena cava (IVC) with azygos or hemiazygos substitution has been reported generally in children (1). Infrahepatic interruption of the IVC is a rare congenital anomaly with the incidence of 0.6% to 2% and mostly found with congenital heart disease (2). Although liver transplantation (LT) in children with biliary atresia and polysplenia syndrome accompanying IVC anomalies have been routinely performed, to the best of our knowledge only one single deceased donor LT in an adult patient with developmental interruption of the IVC with hemiazygos substitution was reported. In this study we report for the first time a living donor liver transplantation (LDLT) in an adult patient with developmental interruption of the IVC with hemiazygos substitution and its' technical details.

CASE REPORT

A 58-year old male patient with a diagnosis of decompensated liver cirrhosis caused by the hepatitis B virus (HBV) was hospitalized for LT. Physical examination revealed splenomegaly and atrophic liver with ascites. MELD point was 15. Abdominal computed tomography (CT) showed atrophic and cirrhotic liver, interruption of the IVC with hemiazygos substitution (Figure 1).

An LDLT from his daughter was planned. At the laparotomy a diffuse nodular and atrophic liver with ascites was observed. After the liver was liberalized from its ligaments the developmental interruption of the IVC with hemiazygos substitution was observed. The hepatic veins were draining into the right atrium at the suprahepatic level. The donor hepatectomy was performed with a 990 gr of the right liver graft with the 4 mm and 5 mm veins draining the segment V, 7 mm vein draining the segment VIII and 10 mm size inferior hepatic vein. The drainages of the segments V, VIII and inferior hepatic vein were performed with the implant of cadaveric iliac arteries into the 10 cm segment of the cadaveric aortic graft at the back-table (Figure 2).

The inferior opening of the aortic graft was closed and the LT was completed (Figure 3).

Post treatment course of the patient was uneventful and he was discharged at post-transplant day 14. In his 6-months post treatment follow-up, liver is functioning well without any complication (Figure 4).

The patient was informed and consent was taken for the case report.

DISCUSSION

Systemic anomalous venous return is a heterogeneous group of vascular malformation in terms of clinical and anatomical (3). These anomalies may arise out of numerous variations of four main veins which are superior vena cava (SVC), IVC, vena azygos and hepatic veins (4). Interruption of IVC but continuity of venous return through vena azygos usually accompanies other cardiac congenital anomalies; it is rare to be seen as isolated congenital vascular anomaly (5).

According to its embryological origin, three pairs of fetal veins are formed with fusion, regression and mid-section anastomosis of system in 6^{th} to 8^{th} week of IVC gestation.

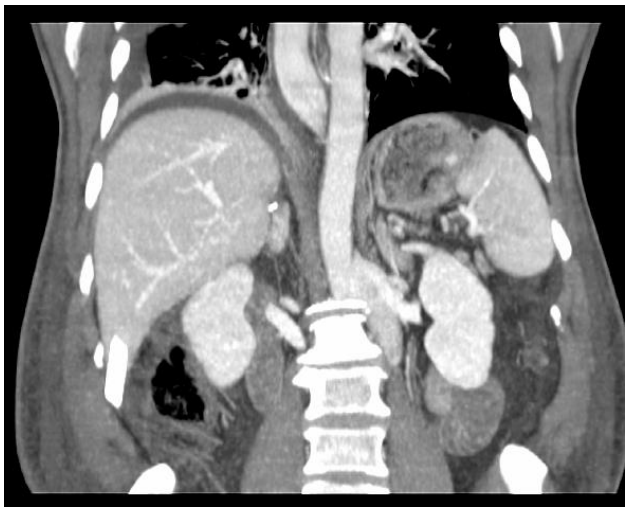

Figure 1. Transposition of Inferior Vena Cava prior to operation is shown in figure

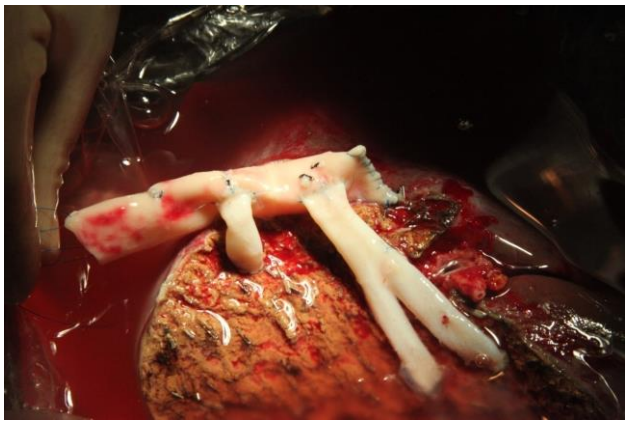

Figure 2. Liver drained with aortic graft and iliac grafts in back-table procedure and liver tissue in pre-transplantation phase with 5^{th} and 8^{th} segments are shown.

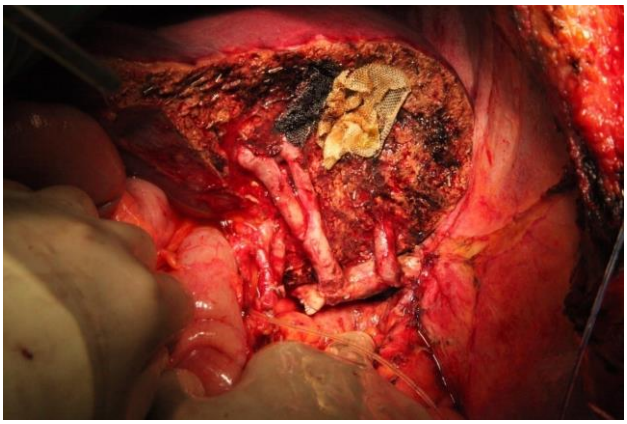

Figure 3. Transplanted liver and grafts after perfusion are shown in figure

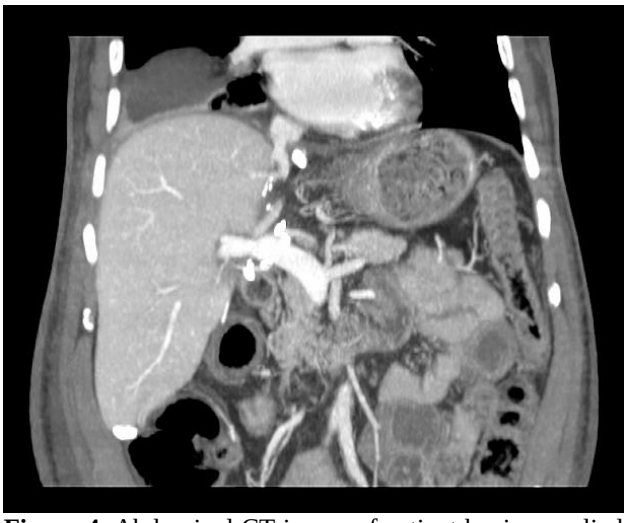

Figure 4. Abdominal CT image of patient having applied LT procedure and completed Inferior Vena Cava transposition

Those veins contain two posterior, two sub-cardinal and two supra-cardinal veins. According to its embryological origin, IVC is consisted of four segments as hepatic, prerenal, renal and postrenal. The most frequent anomaly is the lack of infrahepatic segment of IVC and its drainage into the right atrium or SVC through azygos (4,6). According to Chuang et al. (7), normal IVC is developed with an open right supra-cardinal vein and regression of the left one (type B). Exact opposite situation of that is resulted with transposed IVC (type C). Continuity of both supra-cardinal vein openings means duplication of IVC (type B, C). Most of IVC anomalies are asymptomatic. However, there is cyanoses in anomalies where IVC is drained into left atrium, besides that in anomalies caused due to lack of infrarenal segment of IVC, relapsing deep vein thrombosis in sub-extremities may cause bilateral venous failure (5,8).

The only effective treatment of end stage liver failure is LT. LT from live donors is widespread in many countries like Turkey in which there are some difficulties about obtaining organs from cadavers. Compared to cadaveric liver transplantation; it has superiorities like effective operation opportunity for patients, lesser graft ischemia periods and eliminating waiting-list deaths (9). Donors and receivers having IVC anomalies may be appropriate patients for transplantation surgery (10). However, it is important to diagnose existing anomalies of this kind of patients prior to operation and plan the surgery to be held according to this situation (11). As a result, although it is obvious that transplantation surgeons may encounter these kinds of cases, we think that the surgical procedures defined in this case may be a guide for this type of patients.

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A Rare Cause of Acute Abdomen in Pregnancy: Internal Herniation

Gebelikte Nadir Bir Akut Batın Nedeni: İnternal Herniasyon

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ABSTRACT

Internal herniation is one of the rare causes of intestinal obstruction. The most common causes of intestinal obstruction are adhesive bridges, volvulus, and invagination. The classic triad frequently seen in the clinic includes colic type abdominal pain, nausea/vomiting and absences of gas passage and defecation. It is very difficult to diagnose internal herniation during pregnancy due to the inability to see all clinical findings together, to confuse the findings with obstetric pain, and to the possible fetal side effects due to the application of radiological diagnostic methods. Because of high maternal and fetal mortality risk, it is important to make an early diagnosis and perform surgical intervention without any delay if necessary. In all pregnant women presenting with a diagnosis of acute abdomen, intestinal obstruction and the possibility of the internal herniation that may cause this clinical picture should be kept in mind.
Keywords: Pregnancy; intestinal obstruction; internal herniation.

ÖZ

İnternal herniasyon, intestinal obstrüksiyonunun nadir görülen nedenlerinden biridir. İntestinal obstrüksiyona en sık yol açan nedenler; adeziv bantlar, volvulus ve invajinasyondur. Klinikte sıklıkla görülen klasik triadı, kolik tarzında karın ağrısı, bulantı/kusma ve gaz gayta deşarjının olmamasıdır. Klinik bulguların hepsinin birlikte görülmeyebilmesi, bulguların obstetrik ağrılar ile karışabilmesi ve radyolojik tanı yöntemlerinin uygulanmasına bağlı oluşabilecek olası fetal yan etkiler nedeniyle gebelikte internal herniasyon tanısının konulması oldukça zordur. Yüksek maternal ve fetal mortalite riski nedeniyle erken tanı konulması ve cerrahi müdahale gerekli ise vakit kaybetmeden uygulanması önemlidir. Akut batın ön tanısı ile başvuran tüm gebelerde, intestinal obstrüksiyon ve bu klinik tabloya neden olabilecek internal herniasyon tanısı akılda tutulmalıdır.
Anahtar kelimeler: Gebelik; intestinal obstrüksiyon; internal herniasyon.

INTRODUCTION

Internal herniation is defined as the protrusion of intestinal loops from fossa, foramen or mesenteric defects in the abdominal cavity and it is one of the uncommon causes of small bowel obstruction (1). The fusion defect of the mesentery and posterior parietal peritoneum creates the potential hernia orifice. It can occur congenitally or acquired depending on inflammation, trauma and previous surgery, like gastric by-pass for bariatric treatment and liver transplantation (2). The most frequent causes of intestinal obstruction are adhesive bridges, volvulus, and invagination. Internal herniation accounts for 0.6-5.8% of intestinal obstruction (3). Paracaecal herniation is a rare type of internal hernia and it constitutes 2% of all internal herniation cases (4). Intestinal obstruction is most frequently seen; in the second trimester of the pregnancy when the uterus becomes an abdominal organ, at the end of the third trimester when fetal head engagement occurs and during the early postpartum period when the dimension of uterus changes abruptly. In this article, we aimed to present a 32-year-old pregnant woman diagnosed with internal herniation at the paracecal region, which is a very rare cause of small bowel obstruction. Internal herniation must

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be remembered in the differential diagnosis of intestinal obstruction, particularly for patients without a history of previous surgical intervention or trauma.

CASE REPORT

A 32-year-old pregnant woman, gravida 5, para 4, applied to the emergency department with severe abdominal pain at 39 2/7 gestational week. The patient whose pregnancy controls had been followed up in another health center had common abdominal pain especially located in the epigastric area. The patient did not have a prior history of abdominal surgery. In the ultrasonographic examination; single and live fetus was determined and its biometric measurements were compatible with 37 gestational weeks. The amniotic index was normal and placental pathology was not detected. Routine laboratory tests were performed. Vaginal examination revealed a 2 cm cervical opening, nonstress test (NST) was reactive and minimal irregular contractions were observed. Blood pressure measurements were within normal limits. Liver enzymes, cardiac enzymes, other biochemical parameters and complete blood count results were within normal limits. Echocardiography and electrocardiography were evaluated as normal. The patient stated that nausea and vomiting complaints began following severe abdominal pain and she had never experienced such excruciating abdominal pain before. It was thought that the complaints of the patient were neither obstetric nor cardiac, but were likely to be due to gastrointestinal system pathology. The patient's oral intake was stopped and intravenous hydration and anti-acid treatment were initiated. Upon a little regression of her complaints, the decision was made for the initiation of the birth process and induction was performed. The patient whose previous deliveries were vaginal, followed-up with continuous NST monitoring. Approximately 5 hours after the onset of induction, a 2860-gram girl baby with a 7/9 Apgar score was delivered through normal vaginal delivery.

Due to the aggravation of abdominal pain after delivery, the whole abdominal ultrasonography was performed and dilated jejunal loops were noted. In the direct abdominal radiograph, dilated jejunal loops were also observed. The patient was consulted with the general surgery department. On abdominal examination, abdominal distension and defense were detected while rebound was negative. The patient underwent a contrast-enhanced computed tomography (CT) scan and the ileocecal region was found to be switched to the upper right quadrant and an ileus image which developed probably due to a co-existent internal herniation was observed (Figure 1). A plain radiograph of the abdomen was repeated due to the increase of nausea and vomiting and the persistence of abdominal pain. Evaluation of the radiograph confirmed the diagnosis of ileus (Figure 2). Since CRP values kept increasing and the clinical findings of the patient did not improve, the decision was made for surgical intervention 48 hours after delivery. A lower abdominal median incision was made and intestines were exposed. During the intraoperative observation, dilated jejunal loops were noted. A 15-cm intestinal segment at the 5-6 cm proximity of terminal ileum was strangulated between the ring-like foramen in the mesentery, and its blood supply was deteriorated (Figure 3). After the band in mesentery was

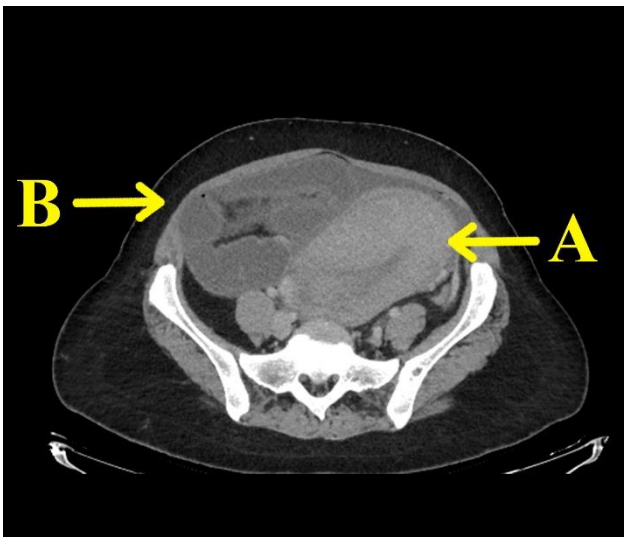

Figure 1. A) Postpartum uterus, **B)** Dilated jejunal loops

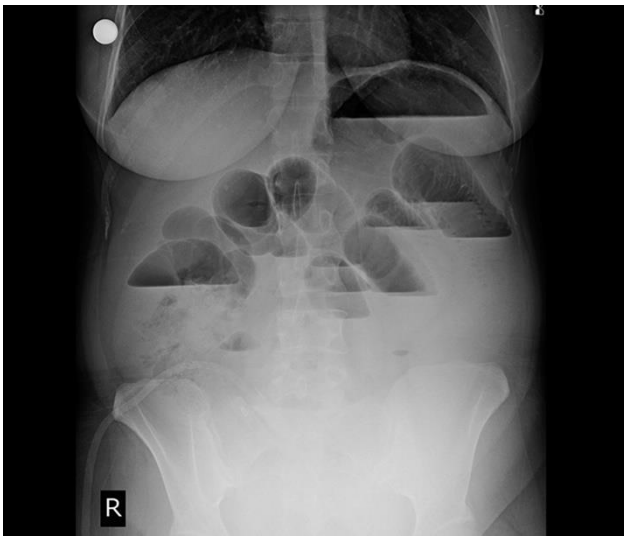

Figure 2. Direct abdominal radiograph showed air-fluid levels in small bowel

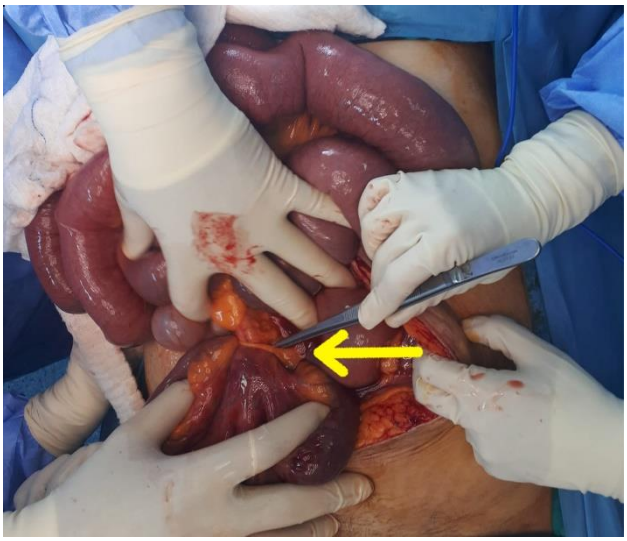

Figure 3. Strangulated intestinal segment between the ring-like foramen in mesentery and deteriorated blood supply

excised, the intestines were repositioned in their natural configuration. Heat was applied to the intestines for a time and they were re-evaluated for the restoration of vascular circulation. After observation of restoration of the circulation and blood supply, intestinal peristalsis re-started, and its color began to be clearer, the segmental intestinal recession was not performed. After insertion of a drain in the abdomen, the surgical procedure was finished. On the 2nd postoperative day, the intestinal gas passage occurred. The patient's clinical and laboratory values improved in the follow-up, and she was discharged from the hospital on the 6th postoperative day. The informed consent form was obtained from the patient.

DISCUSSION

Internal herniation is described as the protrusion of small bowel loops and the mesentery through visceral defects or peritoneal and mesenteric aperture into a compartment in the abdominal and pelvic cavity (3). Internal herniation is one of the rare causes of intestinal obstructions and it is seen in men three times as often as in women (2). Peritoneal or mesenteric defects may not only be congenital but may be acquired due to inflammation, trauma or surgery. The history of previous surgery should remind of acquired causes. An internal herniation, congenital or acquired, accounts for 0.6-5.8% of the small intestine obstructions (3).

Paraduodenal herniations are the most frequent form of internal herniations, and they constitute about 53% of all internal hernias (5). The other types of internal herniations are trans-mesenteric, paracaecal, transomental and foramen Winslow herniations. Paracaecal herniation comprises 2% of all the internal herniation cases (4). Even though classical paraduodenal hernia has been defined as the most frequent form of internal herniation, transmesenteric hernias have recently gained a higher incidence, presumably due to the increasing frequency of surgical interventions in which a Roux-en-Y loop is constructed (6).

Pregnancy does not increase the incidence of intestinal obstruction. Although intestinal obstruction is a common condition seen by general surgeons, it is extremely challenging to establish the diagnosis during pregnancy. The diagnosis may be masked due to some circumstances that can be seen during pregnancy such as abdominal distension, nausea and vomiting, tension pain of the ligamentum rotundum, uterine contractions, and leukocytosis. Colic type pain due to intestinal obstruction may be mistaken for uterus contractions.

Avoiding examinations involving radiation such as direct radiography and computerized tomography in pregnancy may cause a delay in the diagnosis. The findings in intestinal obstruction do not exhibit any remarkable differences between pregnant and non-pregnant women. Classical triad is colic type abdominal pain, nausea and vomiting, and the absence of intestinal gas passage and defecation. All of these three findings may not be seen together. These findings may be accompanied by increased bowel sounds and abdominal tenderness during the physical examination.

Intestinal obstruction most commonly occurs in the second trimester of the pregnancy when the uterus becomes an abdominal organ, at the end of the third trimester when the fetal head is engaged, and in the early postpartum period when the size of the uterus decreases abruptly (5). In our case, symptoms appeared at the end of the third trimester and the severity increased in the early postpartum period.

In the diagnosis, abdominal ultrasonography, direct radiography and computerized tomography can be utilized. The fact that radiological imaging methods involving radiation are not preferred during pregnancy also causes a delay in diagnosis. However, the risk of maternal and fetal mortality due to delayed diagnosis is higher than the risks associated with radiation exposure. Abdominal ultrasonography can be considered as the first choice diagnostic modality since it is a noninvasive method devoid of radiation risk. When the final diagnosis cannot be established, the other imaging methods must be utilized at once. Abdominal tomography is the imaging modality of choice for the investigation of acute abdominal conditions (7). The accuracy of CT in the detection of small bowel obstruction possesses a sensitivity and specificity of 94-100% and 90-95%, respectively (8). Thereby, it accelerates the therapeutic processes due to its high potential to establish the diagnosis and to document the severity and the etiology of the illness correctly. The direct signs of a closed-loop at CT are a U- or C- shaped, fluid filled, distended intestinal loop or a radial array of distended loops with stretched and thickened mesenteric vessels converging to a central point. Thus, a cluster of dilated loops or a 'sac-like appearance' of crowded small bowel loops must recall internal herniation (9). Identification of air-fluid levels, diminished or absent colon gas, dilated small intestinal loops and dilatation of caecum are significant radiological findings (8). In our case, we evaluated the patient initially with abdominal ultrasonography before methods based on radiation and determined the pre-diagnosis observing dilated jejunal loops. After the delivery, our diagnosis was confirmed with tomography.

During the treatment, firstly dehydration and electrolyte imbalance must be restored while the patient is under observation with nasogastric decompression. Owing to the rare occurrence, treatment for internal herniation following surgery is still under debate. The recent Bologna guidelines imply conservative management for 48-72 h in an otherwise healthy patient who do not display any signs consistent with strangulation or peritonitis. Nevertheless, if there is no improvement in the clinical picture during an observation period of 48-72 hours, patients with strangulation or CT findings consistent with intestinal ischemia must be treated with urgent open surgery (10).

Its prognostic mortality rate is more than 50% unless treated (3). In laparotomy, a lower abdominal median incision should be preferred, and an appropriate surgical technique should be performed considering the underlying causes. Any delay in the diagnosis can lead to incarceration and a serious situation that can result in bowel necrosis. The fundamental principles of the treatment are both reduction of herniation and repair of the defect. Following the restoration of bowel passage, intestinal loops are expected to return to their natural color. Very rarely, in the event of the development of ischemia, bowel resection may be necessary. Laparoscopic surgery is a technically challenging procedure with relatively low success rates, particularly without clear preoperative

diagnosis and imaging for recognition of the orifice of the hernia (11).

In every pregnant woman presenting with an acute abdomen, the intestinal obstruction must be kept in mind in the differential diagnosis. As in our case, even in patients who had not undergone any abdominal surgery before, internal herniation, one of the rare causes of intestinal obstruction, should be considered in the presumptive diagnosis. In the absence of all clinical findings of intestinal obstruction, radiological imaging methods must be used appropriately to overcome the diagnostic challenge. Avoidance of the delay of surgical treatment in patients with persistent symptoms after decompression will help to decrease the maternal and fetal mortality rates.

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Renal Amyloidosis in a Common Variable Immune Deficiency Patient with Autoimmune Complications

Otoimmun Komplikasyonlarla Seyreden Yaygın Değişken İmmün Yetmezlik Hastasında Renal Amiloidoz

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ABSTRACT

Common variable immune deficiency (CVID) is a rare primary immunodeficiency disorder that is characterized by defective antibody production and inadequate B cell differentiation. While frequently recurrent respiratory tract infections are the most prominent clinical feature in CVID patients, CVID is a heterogeneous immune deficiency disorder that involves many systems and organs such as lymphoid hyperplasia, autoimmune cytopenia, chronic lung diseases, granulomatous diseases and susceptibility to malignancy. This may lead to delay in diagnosis and immunoglobulin replacement therapy, not being able to receive antibiotics at the appropriate dose and time, chronic inflammation, and therefore secondary amyloidosis. In this case report it is aimed to present a CVID patient with autoimmune complications and developing renal amyloidosis during follow-up.
Keywords: Common variable immune deficiency; renal amyloidosis; chronic inflammation.

ÖZ

Yaygın değişken immün yetmezlik (YDIY), bozulmuş antikor üretimi ve yetersiz B hücresi farklılaşması ile karakterize nadir görülen bir birincil immün yetmezlik tablosudur. Her ne kadar YDIY hastalarında sık tekrarlayan solunum yolu enfeksiyonları en belirgin klinik durum olsa da; YDIY, lenfoid hiperplazi, otoimmün sitopeni, kronik akciğer hastalıkları, granülomatöz hastalıklar ve maligniteye yatkınlık gibi birçok sistem ve organı etkileyen heterojen bir immün sistem bozukluğudur. Bu durum, tanı ve immünoglobulin replasman tedavisinde gecikmeye, uygun dozda ve zamanda antibiyotik alınamamasına, kronik inflamasyona ve dolayısıyla sekonder amiloidoza yol açabilir. Bu vaka sunumunda, otoimmün komplikasyonla seyreden bir YDIY olgusu ve takip sırasında gelişen renal amiloidoz tablosunun sunulması amaçlanmıştır.
Anahtar kelimeler: Yaygın değişken immün yetmezlik; renal amiloidoz; kronik enflamasyon.

INTRODUCTION

Common variable immune deficiency (CVID) is a rare primary immune deficiency (PID) disorder that is thought to affect 1 in 25000 people, with defective antibody production characterized by inadequate B cell differentiation (1). Since the most prominent clinical feature in CVID patients is frequently recurrent respiratory tract infections, CVID is a heterogeneous disorder that involves many systems and organs such as lymphoid, autoimmune cytopenia, chronic lung diseases, granulomatosis diseases, and predisposition to malignancy (2,3). The main laboratory finding is hypogammaglobulinemia. Amyloidosis is a heterogeneous group of diseases characterized by the accumulation of proteins, many of which are soluble in plasma, as abnormally insoluble fibrils in the extracellular space. Amyloidosis cases can be presented with very different clinical presentations depending on the localization, type and quantity of accumulated proteins. Accumulated amyloid fibrils are relatively stable and resistant to proteolysis. Due to their ability to bind Congo red dye, they show pathognomonic apple-green double refraction under polarized light (4). Although the first studies showing the development of amyloidosis in patients with

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hypogammaglobulinemia date back half a century (5,6), the diagnosis of amyloidosis is rarely defined in CVID patients because of insufficient level of PID awareness, delayed diagnosis and the necessity of an invasive procedure such as a biopsy to diagnose (7). Lederman et al. (8) showed none of 96 X-Linked Agammaglobulinemia (XLA) patients were found to have amyloidosis, while Hermaszewski et al. (1) stated that renal amyloidosis was found in only 2 patients out of 44 XLA patients in a study conducted in 1993. Mostly, because of the underlying inflammatory processes, amyloidosis has been reported in adult patients diagnosed with CVID, XLA and hypogammaglobulinemia. In this case we aimed to present a CVID patient with autoimmune complications and the progression of renal amyloidosis was determined.

CASE REPORT

For the first time in October 2013, 50 years old male patient consulted to the hospital with the complaint of weakness, fatigue, yellowing of the skin and darkening in the urine. The hemoglobin: 4.3 g/dl, mean corpuscular volume (MCV): 110.1 fl, indirect bilirubin: 6.6 mg/dl, direct and indirect Coombs were (+) and splenomegaly (spleen: 155 mm) was detected in laboratory results. Therefore, the patient hospitalized with a preliminary diagnosis of autoimmune hemolytic anemia and patient's complaints and laboratory findings were fixed with steroid treatment.

The patient, who did not have any complaints for about 4 years, was hospitalized again in May 2017 due to abdominal pain and low hemoglobin values. The patient was diagnosed as chronic autoimmune hemolytic anemia when hepatosplenomegaly was detected on physical examination, and hemoglobin: 6.4 g/dl, reticulocyte: 19.94%, MCV: 106.7 fl, lactate dehydrogenase (LDH): 492 U/L, indirect bilirubin: 3.03 mg/dl.

In addition to hepatosplenomegaly, multiple lymph nodes with the largest one measuring 18x11 mm in the parailiac and paraaortic area in abdominal computed tomography (CT) and tubular bronchiectasis in the right middle lobe of the lung were detected. In positron emission tomography (PET)/CT scan, mild hypermetabolic lymph nodes have been reported throughout the body; primarily lymph node measuring 25x10 mm in the right axillary region (SUV max: 4.83), 16 mm in diameter in the left axillary region (SUV max: 4.33) and approximately 16 mm in the right parailiac area in the intra-abdominal region (SUV max: 10.83). In the bone marrow examination performed with a preliminary diagnosis of lymphoma, it is reported that no CD34 + blastic cell increase was observed, and the samples did not have sufficient features for the diagnosis of lymphoma. As a result of the lymph node biopsy, it was reported that the lymph nodes were reactive and there was no staining in favor of amyloid with crystal violet and Congo red (Figure 1). In addition to these findings, the patient was consulted to our clinical immunology department upon the decrease in total protein and gamma globulin levels. The family history of the patient did not reveal any valuable information. There were no siblings or children who died at an early age. During the examinations, the patient had panhypogammaglobulinemia. Albuminuria was not detected in his 24-hour urine samples. In the peripheral lymphocyte subgroup analysis, CD19 + B cell ratio was found to be low with 3.5% and IgD-IgM-CD27 + B cell ratio with 0.5% (Figure 2). Immunoglobulin analyses were repeated after 1 month and panhypogammaglobulinemia was observed to be persistent (Table 1). After the secondary reasons that would cause hypogammaglobulinemia were excluded, the patient was considered as lymphoid hyperplasia to secondary CVID and 400-600 mg/kg^3 weeks intravenous immunoglobulin (IVIG) treatment was started. Azithromycin 500 mg/week was started for bronchiectasis. Blood samples sent for advanced genetic research.

After receiving immunoglobulin treatment for about 2 years, IgG levels started to decrease in the follow-ups. The patient was being investigated for secondary losses and no diarrhea was detected in the history. In the 24-hour urine, 1940 mg/day albuminuria was detected. Kidney biopsy was conducted to the patient who was evaluated by the nephrology department, regarding etiology of albuminuria. Renal amyloidosis was detected as a result of biopsy (Figure 3). According to the recommendations of the nephrology department, ramipril 2.5 mg 1x1 p.o. and colchicine 0.5 mg 3x1 p.o. were initiated for renal proteinuria.

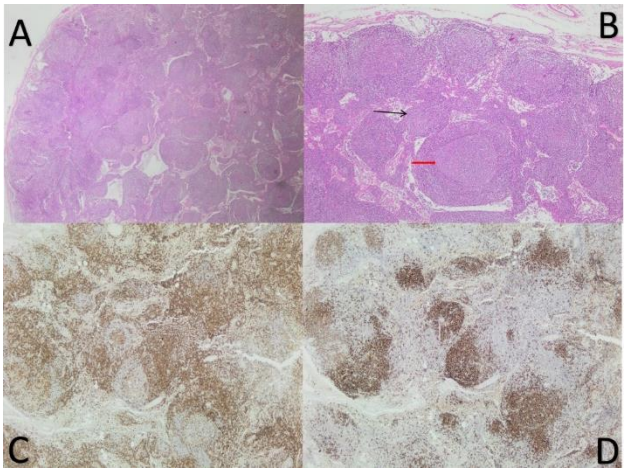

Figure 1. Patient's lymph node biopsy samples **A)** Lymph node surrounded by thin fibrous capsule, containing follicles of various shapes and sizes, (Hematoxylin-Eosin (HE) x20), **B)** Secondary follicle (red arrow) structures containing primary (black arrow) and germinal center (HEx20), **C)** Immunhistochemical CD3 staining (x40), **D)** Immunhistochemical CD23 staining (x40)

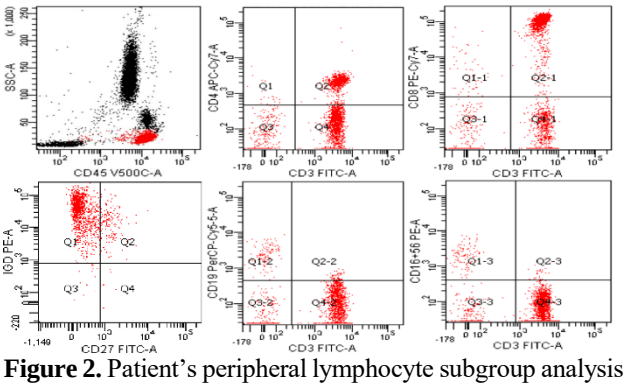

Figure 2. Patient's peripheral lymphocyte subgroup analysis

Table 1. Patient's clinical and laboratory features

	Normal values	October 2013	May 2017	May 2018 (with IVIG treatment)
Hemoglobin	12.1-17.2 (g/dl)	**4.3**	**6.4**	13.9
Reticulocytes	%		**19.9**	
MCV	80-100 (fl)	**114**	**106.7**	83.4
Neutrophils	1500-7.300 (/mm³)	6400	**6550**	**10090**
Lymphocytes	800-5500 (/mm³)	2310	**5790**	4490
Platelets	150-400 (1000x/mm³)	229	220	221
Total/indirect bilirubin	(mg/dl)	**7.2/6.6**	**3.6/3.03**	1.17/0.37
LDH	135-225 U/L	**452**	**492**	**237**
Indirect Coombs		positive	positive	
Direct Coombs		IgG-pos	IgG-pos	
IgG	7-17 (g/L)		**1.35**	**1.69 → 1.89 → 4.35**
IgM	0.4-2.3 (g/L)		**0.19**	**0.186**
IgA	0.7-4 (g/L)		**0.261**	**0.261**
IgE	0-100 (g/L)			
IgG1	4.05-10.11 (g/L)		**0.856**	
IgG2	1.69-7.86 (g/L)		**0.335**	
IgG3	0.11-0.85 (g/L)		**0.0345**	
IgG4	0.03-2.01 (g/L)		**0.0543**	
Tetanus antibody	≥0.5 (IU/ml)		**0.01**	
Anti-Hepatitis B	0-10 mIU/ml		33.13	
$CD3^+$ T cells (%)	48-82.6%		89	91
$CD4^+$ T cells (%)	23-52.6%		27.6	27
$CD8^+$ T cells (%)	12.8-40.2%		60.6	61
$CD19^+$ B cells (%)	6.3-20.8%		**3.5**	**3**
CD 16-56^+ T cells (%)	5-31.3%		**3.1**	**3**
$IgD^+IgM^+CD27^-$ B cells (%) Naive B cells			85.3	97
$IgD^-IgM^-CD27^+$ B cells (%) Switched Memory B cells			**0.5**	**0.8**
Isohemagglutinin	≥1/4	Anti-A: 1/4		
Anti-HIV		(-)	(-)	

IVIG: Intravenous Immunoglobulin, MCV: Mean Corpuscular Volume, LDH: Lactate Dehydrogenase, CD: Cluster of Differentiation, HIV: Human Immunodeficiency Virus

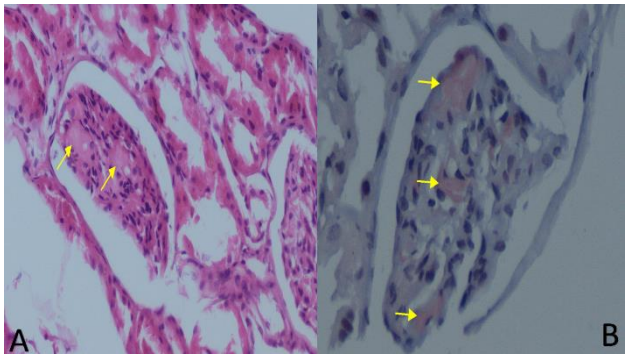

Figure 3. Patient's renal biopsy samples **A)** Amyloid deposits in glomerulus (HEx10), **B)** Amyloid deposits in glomerulus (Congo red x20)

DISCUSSION

While recurrent respiratory tract infections are the most prominent clinical feature in CVID patients, CVID is a heterogeneous immune deficiency disorder that involves many systems and organs such as lymphoid hyperplasia, autoimmune cytopenia, chronic lung diseases, granulomatous diseases, and susceptibility to malignancy (2,3,9). This may lead to delay in diagnosis and immunoglobulin replacement therapy, not being able to receive antibiotherapy at the appropriate dose and time, chronic inflammation, and therefore secondary amyloidosis (10). In addition, treatment and follow-up incompatibility and presence of bronchiectasis also contribute to the development of amyloidosis (11). Renal amyloidosis often presents itself with nephrotic albuminuria and renal insufficiency. Although frequent infections and increased autoimmunity are well defined and expected complications in CVID, renal pathologies are rarely reported in this patient group, and current literature are mostly in the form of case reports (1,11-15).

Meysman et al. (16) reported XLA patient with persistent diarrhea due to systemic amyloidosis in 1993. In 1996, Kotilainen et al. (17) reported a case of nephrotic syndrome due to systemic amyloidosis associated with frequent infections and inadequate immunoglobulin replacement in a 49-year-old patient who was followed for hypogammaglobulinemia for 18 years. Due to the nephrotic syndrome of the patient, higher dose and more frequent intervals of IVIG infusion were required for infection control. In our patient, nephrotic albuminuria was detected after the diagnosis of CVID and this prevented the effective and stable serum immunoglobulin levels by causing renal loss of the replaced immunoglobulins. It may be beneficial to undergo subcutaneous replacement in cases of gastrointestinal or renal loss for the patients receiving immunoglobulin replacement therapy (18).

Amyloidosis can be accumulated in all body organs and systems and the kidneys are the most frequently affected organs, but renal amyloidosis is a rare clinical disorder. Esteve et al. (19) conducted a study for 12-year survey in Spain and they found the incidence of AA amyloidosis to be 12.2 per million population. Arslan et al. (12) presented the first case of renal and pulmonary amyloidosis for CVID patients in 2014. In clinical follow-up, patient did not comply with immunoglobulin replacement and prophylactic antibiotic treatment so the presentation of renal amyloidosis causing abdominal acid, pleural effusion, and pretibial edema was poorly defined. In same patient, pulmonary amyloidosis is diagnosed with biopsy applied within 1 year and associated severe lung complications and pulmonary hypertension was progressed (12).

Balwani et al. (20) reported a patient who has been suffering from respiratory infection and diarrhea for twenty years, receiving at least 1 hospitalization history every year for pneumonia, 9 months of anti-tuberculosis treatment due to pulmonary tuberculosis. After developing nephrotic albuminuria due to renal amyloidosis, hypoalbuminemia and pedal oedema, this patient could be diagnosed with CVID. Renal amyloidosis has been associated with previous tuberculosis infection and chronic inflammation due to recurrent lung infections. The bronchiectasis present in our patient can also be accepted as an indication that the patient has been exposed to chronic persistent inflammation for a long time. In the same year, Esenboğa et al. (11) reported a patient with chronic diarrhea, frequent sinopulmonary infections, and hypogammaglobulinemia and diagnosed with CVID. Although rectal and gingival biopsies are negative in terms of amyloidosis, amyloidosis was detected in renal biopsy.

In conclusion, even if immunoglobulin replacement therapy reduces the frequency of infection; controlling of infections, prophylactic antibiotic therapy, immunoglobulin replacement at appropriate doses and intervals, and regular clinical follow-up are very important for preventing amyloidosis, which is a rare but mortal complication in CVID patients. In addition, sudden reductions in serum IgG levels, difficulties in obtaining stable and effective trough IgG levels should suggest possible secondary losses in these patients, and clinicians should not ignore the possibility of renal amyloidosis in these patients.

Informed consent was obtained from the patient.

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- DOI is the only acceptable online reference.

Article:

Al-Habian A, Harikumar PE, Stocker CJ, Langlands K, Selway JL. Histochemical and immunohistochemical evaluation of mouse skin histology: comparison of fixation with neutral buffered formalin and alcoholic formalin. J Histotechnol. 2014;37(4):115-24.

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Book:

Buckingham L. Molecular diagnostics: fundamentals, methods and clinical applications. 2nd ed. Philadelphia: F.A. Davis; 2012.

Book Chapter:

Altobelli N. Airway management. In: Kacmarek R, Stoller JK, Heuer AJ, editors. Egan's fundamentals of respiratory care. 10th ed. St. Louis: Saunders Mosby; 2013. p.732-86.

YAZARLARA BİLGİLENDİRME

BİLİMSEL SORUMLULUK

Bilimsel yayıncılık standartları açısından, gönderilecek makaleler, Uluslararası Tıbbi Dergi Editörler Kurulu (ICMJE), Dünya Tıbbi Editörler Birliği (WAME) ve Yayın Etik Kurulu (COPE) kriterlerine uygun olarak hazırlanmalıdır.

- Gönderilecek makalelerde araştırma ve yayın etiğine uyulması zorunludur. Makalelerin sorumluluğu yazarlarına aittir.
- Makalelerin daha önce hiç bir yerde yayınlanmamış ve/veya yayınlanmak üzere değerlendirme sürecinde olmaması gerekir.
- Değerlendirme sürecinin başlaması için makaleler, tüm yazarlar tarafından imzalanmış Telif Hakkı Devir Formu ile birlikte gönderilmelidir. Yazar sıralaması için Telif Hakkı Devir Formu'ndaki imza sırası dikkate alınır.
- Sorumlu yazar, tüm yazarlar adına makalenin son halinin sorumluluğunu taşır.

ETİK SORUMLULUK

- "İnsan" öğesini içeren tüm çalışmalarda Helsinki Deklerasyonu Prensipleri'ne (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) uygunluk aranır. Bu tip çalışmalarda yazarların, GEREÇ VE YÖNTEMLER bölümünde çalışmayı bu prensiplere uygun olarak yaptıklarını, kurumlarının etik kurullarından onay ve çalışmaya katılmış insanlardan "bilgilendirilmiş olur" (informed consent) aldıklarını belirtmeleri gerekmektedir.
- Çalışmada "Hayvan" öğesi kullanılmış ise yazarların, GEREÇ VE YÖNTEMLER bölümünde Guide for the Care and Use of Laboratory Animals (https://grants.nih.gov/grants/olaw/guide-for-the-care-and-use-of-laboratory-animals.pdf) prensipleri doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmeleri gerekmektedir.
- Olgu sunumlarında hastalardan "bilgilendirilmiş olur" (informed consent) alınmalıdır.
- Etik kurul onay bilgisi GEREÇ ve YÖNTEMLER bölümünde kurul adı, onay tarihi ve sayısı ile birlikte belirtilmelidir.
- Eğer çalışmada direkt-indirekt ticari bağlantı veya maddi destek veren kurum mevcut ise yazarlar; kullanılan ticari ürün, ilaç, firma vb. ile ticari hiçbir ilişkisinin olmadığını veya varsa nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar), editöre sunum sayfasında belirtmelidirler.
- Yazarlar çalışma ile ilgili kişisel ve finansal tüm ilişkilerin bildirilmesinden sorumludur. Makalenin başvurusu ve/veya değerlendirmesi ile ilişkili herhangi bir çıkar çatışması olup olmadığının açıkça beyan edilmesi gerekmektedir.
- Makalelerin bilimsel ve etik kurallara uygunluğu yazarların sorumluluğundadır.

BAŞVURU DOSYALARI

Makaleler aşağıda belirtilen şekilde ayrı dosyalar halinde sisteme yüklenmelidir.

Telif Hakkı Devir Formu: Başvuru sırasında sistemden alınacak Telif Hakkı Devir Formu tüm yazarlar tarafından makaledeki yazar sıralamasına uygun şekilde imzalanmış olmalıdır.

Başvuru Mektubu: Makalenin türü, daha önce hiç bir yerde yayınlanmamış ve/veya yayınlanmak üzere değerlendirme sürecinde olmadığı, varsa çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve bu kuruluşların yazarlarla olan ilişkileri (yoksa olmadığı) belirtilmelidir. Makalenin konusuyla ilgili olarak önerilen, yazarlarla ve kurumlarıyla ilgisi olmayan en az iki hakemin adları, akademik unvanları, kurumları, iletişim bilgileri ve e-posta adresleri yazılmalıdır. Editörlerin hakemleri seçme hakkı saklıdır.

Başlık Sayfası: Makalenin başlığını (İngilizce ve Türkçe), 40 karakteri geçmeyen kısa başlık, tüm yazarların adlarını, akademik unvanlarını, ORCID® numaralarını, kurumlarını, e-posta adreslerini ve ayrıca sorumlu yazarın adını, yazışma adresini, telefon numarasını, e-posta adresini içermelidir. Makale daha önce bilimsel bir toplantıda sunulmuş ise toplantı adı, tarihi ve yeri (yoksa sunulmadığı) belirtilmelidir.

Ana Metin: Makalenin başlığı (İngilizce ve Türkçe), 40 karakteri geçmeyen kısa başlık, Öz (İngilizce ve Türkçe), Anahtar kelimeler (İngilizce ve Türkçe), Ana Metin (gönderilen makalenin türüne uygun olarak bölümlere ayrılmış), Kaynaklar, Tablolar ve Şekil açıklamaları yer almalıdır.

Etik Kurul Onay Belgesi: Tüm araştırma makaleleri için Etik Kurul Onay Belgesi ayrı bir dosya olarak yüklenmelidir.

Not: Makalede şekil, resim veya fotoğraf varsa bunların da her biri ayrı birer dosya olarak yüklenmelidir.

MAKALE TÜRÜNE GÖRE KULLANILMASI GEREKEN BÖLÜMLER

Araştırma Makalesi

BAŞLIK (İngilizce ve Türkçe), KISA BAŞLIK, ÖZ (İngilizce ve Türkçe), Anahtar kelimeler (İngilizce ve Türkçe), GİRİŞ, GEREÇ VE YÖNTEMLER, BULGULAR, TARTIŞMA, SONUÇ, KAYNAKLAR

ÖZ ve ABSTRACT çeviri açısından uyumlu olmalı ve her biri kendi içinde 200-250 kelime arasında olmalıdır.

ABSTRACT, "Aim, Material and Methods, Results, Conclusion" şeklinde yapılandırılmalıdır.

ÖZ, "Amaç, Gereç ve Yöntemler, Bulgular, Sonuç" şeklinde yapılandırılmalıdır.

Derleme (Sadece Davetli)

BAŞLIK (İngilizce ve Türkçe), KISA BAŞLIK, ÖZ (İngilizce ve Türkçe), Anahtar kelimeler (İngilizce ve Türkçe), GİRİŞ, Konu ile İlgili Alt Başlıklar, SONUÇ, KAYNAKLAR

ÖZ ve ABSTRACT çeviri açısından uyumlu olmalı ve her biri kendi içinde 150-200 kelime arasında olmalıdır.

Olgu Sunumu

BAŞLIK (İngilizce ve Türkçe), KISA BAŞLIK, ÖZ (İngilizce ve Türkçe), Anahtar kelimeler (İngilizce ve Türkçe), GİRİŞ, OLGU SUNUMU, TARTIŞMA, KAYNAKLAR

ÖZ ve ABSTRACT çeviri açısından uyumlu olmalı ve her biri kendi içinde 100-150 kelime arasında olmalıdır.

Diğer

Bu üç temel makale türü dışındaki (editöre mektup, editöryel yorum/tartışma vb.) yazıların hazırlanmasında da genel yazım kuralları geçerlidir. Bu tür yazılarda başlık ve öz bölümleri yoktur. Kaynak sayısı 5 ile sınırlıdır. İthaf olunan makale sayı ve tarih verilerek belirtilmelidir. Yazının sonunda yazarın ismi, kurumu ve adresi yer almalıdır. Mektuba cevap, editör veya makalenin yazarları tarafından, yine dergide yayınlanarak verilir.

YAZARLARA BİLGİLENDİRME

YAZIM KURALLARI
- Makaleler Microsoft Word® belgesi olarak hazırlanmalıdır.
- Sayfa kenarlarında 2,5 cm boşluk bırakılmalıdır.
- Sayfa numaraları sayfanın sağ alt köşesine yerleştirilmelidir.
- Tüm metinler 12 punto Times New Roman karakteri kullanılarak çift satır aralığı ile sola hizalanmış olarak yazılmalıdır.

ANAHTAR KELİMELER
- Anahtar kelime sayısı en az 2 olmalı, kelimeler birbirlerinden noktalı virgül (;) ile ayrılmalıdır.
- Türkçe anahtar kelimeler Türkiye Bilim Terimleri (TBT)'ne (http://www.bilimterimleri.com), İngilizce anahtar kelimeler Medical Subject Headings (MESH)'e (http://www.nlm.nih.gov/mesh/MBrowser.html) uygun olarak verilmelidir.

İSTATİSTİKSEL YÖNTEMLER
- Tüm araştırma makaleleri biyoistatistik açıdan değerlendirilmeli ve uygun plan, analiz ve raporlama ile belirtilmelidir. Bu makalelerde, GEREÇ VE YÖNTEMLER bölümünün son alt başlığı "İstatistiksel Analiz" olmalıdır.
- Bu bölümde çalışmada kullanılan istatistiksel yöntemler ne amaçla kullanıldığı belirtilerek yazılmalı, istatistiksel analiz için kullanılan paket programlar ve sürümleri belirtilmelidir.
- p değerleri ondalık üç basamaklı (p=0,038; p=0,810 vb.) olarak verilmelidir.
- Makalelerin biyoistatistik açıdan uygunluğunun kontrolü için ek bilgi www.icmje.org adresinden temin edilebilir.

KISALTMALAR
- Terim ilk kullanıldığında parantez içinde kısaltmayla birlikte açık olarak yazılmalı ve tüm metin boyunca aynı kısaltma kullanılmalıdır.
- Uluslararası kullanılan kısaltmalar Bilimsel Yazım Kurallarına uygun şekilde kullanılmalıdır.

TABLOLAR VE ŞEKİLLER
- Metinde ilgili cümlenin sonunda (Tablo 1) ve/veya (Şekil 1) şeklinde belirtilmelidir.
- Tablolar (başlıklarıyla birlikte) ve şekiller (açıklamalarıyla birlikte) kaynaklardan sonra ve her biri ayrı bir sayfada olacak şekilde metnin sonuna eklenmelidir.
- Tablo başlıkları tablo üstünde (Tablo 1. Tablo başlığı), şekil açıklamaları ise şeklin altında (Şekil 1. Şekil açıklaması), ilk harfleri büyük olacak şekilde yazılmalıdır.
- Tablolarda ve şekillerde kısaltma veya sembol kullanılmış ise altında dipnot olarak açıklanmalıdır.
- Şekiller ve fotoğraflar, .png, .jpg vb. formatta ve en az 300 dpi çözünürlükte ayrı dosyalar halinde yüklenmelidir.
- Şekil ve fotoğraf alt yazıları, son tablonun olduğu sayfadan sonra, ayrı bir sayfada sırasıyla verilmelidir.
- Daha önce basılmış şekil, resim, tablo, grafik vb. kullanılmış ise yazılı izin alınmalı ve açıklama olarak belirtilmelidir. Bu konudaki hukuki sorumluluk yazarlara aittir.

TEŞEKKÜR
- Eğer çıkar çatışması/çakışması, finansal destek, bağış ve diğer bütün editöryel (İngilizce/Türkçe değerlendirme) ve/veya teknik yardım varsa, bu bölümde, KAYNAKLAR bölümünden önce belirtilmelidir.

KAYNAKLAR
- Kaynaklar, kullanım sırasına göre numaralandırılmalı ve metin içinde ilgili cümlenin sonunda parantez içinde numaralarla (1) veya (1,2) veya (3-5) şeklinde verilmelidir.
- Kaynaklar dizini, metin içinde kaynakların kullanıldığı sıraya göre oluşturulmalıdır.
- Yazar sayısı 6 veya daha az ise tüm yazarlar belirtilmeli, 7 veya daha fazla ise ilk 6 yazar belirtildikten sonra "et al." eklenmelidir.
- Kongre bildirileri, kişisel deneyimler, basılmamış yayınlar, tezler ve internet adresleri kaynak olarak gösterilmemelidir.
- DOI tek kabul edilebilir online referanstır.

Makale:

Al-Habian A, Harikumar PE, Stocker CJ, Langlands K, Selway JL. Histochemical and immunohistochemical evaluation of mouse skin histology: comparison of fixation with neutral buffered formalin and alcoholic formalin. J Histotechnol. 2014;37(4):115-24.

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