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Restoration of Anterior Tooth Fractures Using Silicone Key Method: 3 Case Report (CASE REPORT)

Sema YAZICI AKBIYIK, Dilan AYLUÇTARHAN, Üyesi Elif Pınar BAKIR, Şeyhmus BAKIR

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ORIGINAL RESEARCH PAPER

Evaluation of The Effect of Insulin Resistance on Pancreatic Exocrine Functions in Obese Patients With Fecal Elastase-1 Levels

Geliş Tarihi: 16.11.2020, Kabul Tarihi: 20.12.2020

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Abstract

Objective: *We aimed to show whether insufficiency develops in pancreatic exocrine functions since the insulin resistance period or not.*

Method: *We measured the anthropometric parameters, blood glucose profile parameters and fecal elastase-1 levels of a total of 65 obese patients with 35 insulin resistance and 30 without insulin resistance. Body mass indexes (BMI) Homeostasis of model assessment insulin resistance indexes (HOMA-IR) were calculated. Exocrine pancreatic insufficiency (EPI) was diagnosed with a fecal elastase-1 concentration (FE1) of less than 200 mg/g (ELISA).*

Results**:** *A statistically significant difference was not observed between the mean FE-1 levels between the groups. (p> 0.05). No statistically significant difference was observed between the distribution of mild and severe low FE-1 levels of the IR and Non-IR groups (p> 0.05) Table 3.*

Conclusion: *Our study revealed that the presence of insulin resistance does not cause any change in FE-1 levels in obese patients.*

Keywords: *pancreatic exocrine function, insulin resistance, fecal elastase-1*

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Introduction

While endocrine and exocrine functions are known as two separate functions of the pancreas, the possible link between these two functions within the same anatomy has always attracted attention among researchers[1]. Therefore, studies have been carried out to show that exocrine pancreatic insufficiency (EPI) may occur in patients with diabetes mellitus (DM)[2]. However, the mechanism has not been fully revealed.

There are studies showing the development of EPI in DM patients[2,3] as well as studies showing that DM develops secondary to physical damage in the pancreas after acute or chronic pancreatitis[4]. DM that develops after pancreatitis is even referred to as pancreatic DM[5].

In the diagnosis of EPI, which should be kept in mind in prolonged dyspeptic complaints, difficult and invasive methods were previously used. The diagnosis is made with low fecal elastastasis -1 (or pancreatic elastase-1) (FE-1) currently, which is a proteolytic enzyme that is checked by enzyme-linked immunosorbent assay (ELISA) method[6].

With the increasing prevalence of obesity all over the world, deterioration in blood glucose regulation and insulin resistance are more common in individuals. We determined that the relationship between DM and the development of EPI has been investigated many times, but there is no data for the period in which IR, also known as the pre-DM period, developed.

Our aim in this study was to show whether EPI developed during the insulin resistance period, which is known as the pre-DM period, and to show whether there is a connection between these two functions of the pancreas from the early damage period of the pancreas.

Method

Data of 65 obese patients aged 16-69 who applied to our internal medicine outpatient clinics with dyspeptic complaints between January 2018 and June 2019 and were evaluated for pancreas enzyme deficiency were retrospectively evaluated. These 65 patients were divided into two groups according to the presence of insulin resistance, as the insulin-resistant group (IR) and the non-insulin-resistant (Non-IR) group.

Patients with a history of acute or chronic pancreatitis, diabetes mellitus,malignancies, and pregnants were not included in the study. In addition, patients with a history of alcohol consumption of >20 g/day and those receiving hormone replacement therapy, kortikosteroid or antidiabetic medication were also excluded.

The study was approved by the Medipol University Ethics Committee (10840098-604.01.01-E.15454) and conducted in accordance with the Declaration of Helsinki.

Laboratory and clinical measurements

Blood samples taken from the patients after 10 to 12 hours of fasting were analyzed. Laboratory data, including the levels of serum glucose, insulin and HbA1c were recorded. Height, weight and waist circumference measurements of all participants were made. Fecal elastase was measured by using an enzyme-linked immunosorbent assay (ELISA) and the presence of fat in stool was assessed using the steatocrit.

Definitions

Diabetes mellitus

The diagnosis of diabetes mellitus was defined by the presence of any of the following items using the criteria updated in American Diabetes Association 2020[7].

1. Fasting blood glucose of 126 mg / dl or higher
2. HbA1c value of 6.5% or above
3. Random blood glucose> 200

Obesity

Body mass index (BMI) is calculated as measured body weight (kg) divided by measured height squared (m^2). A BMI over 30 was defined as obesity[8].

Insulin resistance

Homeostasis model of assessment (HOMA) was used for the diagnosis of insulin resistance [9]. Insulin resistance index (HOMA-IR) was calculated according to the formula: fasting insulin (microU/L) x fasting glucose (mg/dL) /405. HOMA-IR> 2.5 was accepted as insulin resistance[9].

Pancreatic enzyme insufficiency

FE-1 test was used to evaluate exocrine pancreatic function. The reference concentration for FE-1 in feces was as follows[10]:

1. Normal exocrine pancreatic function: presence of enzyme> 200µg / g in stool
2. Exocrine pancreatic dysfunction: presence of enzyme <200µg / g in stool

Statistical analysis

The conformity of the data to normal distribution was tested with the Shaphiro wilk test, Student t test was used to compare normally distributed features in individuals with and without insulin resistance, and Mann Whitney u test was used to compare non-normally distributed features in individuals with and without insulin resistance. Relationships of categorical variables were analyzed

using Pearson and Exact Chi-square tests. As descriptive statistics, mean ± standard deviation for numerical variables, number and% values for categorical variables were given. SPSS Windows version 24.0 package program was used for statistical analysis and $p < 0.05$ was considered statistically significant.

Results

The demographic and anthropometric characteristics of the participants are presented in Table 1. There was no significant difference between the groups in terms of age, height and BMI ($p > 0.05$). However, a statistically significant difference was observed between the gender distributions of IR and Non-IR groups ($p = 0.024$). While the number of male patients is high in the IR group, the number of female patients is higher in the Non-IR group. The mean waist circumference and body weight of the IR group were statistically significantly higher than the Non-IR group (p values respectively; $p = 0.0001$, $p = 0.045$).

The mean glucose, insulin, HOMA-IR values of the IR group were found to be statistically significantly higher than the Non-IR group ($p = 0.0001$). The average HbA1c values of the IR group were found to be statistically significantly higher than the Non-IR group ($p = 0.014$) Table 1.

A statistically significant difference was not observed between the mean FE-1 levels between the groups. ($p > 0.05$) Table 1. In addition, no statistically significant difference was observed between the distribution of FE-1 levels of the IR and Non-IR groups ($p > 0.05$) Table 2.

The correlation coefficient between the level of FE-1 was examined. No statistically significant relationship was found ($p = 0.312$) (Figure 1).

Discussion

Simultaneous dysfunction can be seen in both functions of the pancreas, which has both endocrine and exocrine functions. As DM can be seen after pancreatitis[4], there have been studies showing that both type 1 and 2 DM patients develop EPI[1,3]. Many theories have been proposed regarding how EPI develops in DM[1].

In the study conducted by Yilmaztepe et al. with 32 diabetic patients and 12 healthy controls, it was found that 28% of type 2 diabetic patients had a decrease in exocrine function and no decrease was observed in control subjects[1]. In our study, although the rate of EPI in the IR group was determined to be 25.7%, there was no statistically significant difference between the rate of EPI in the Non-IR group (10%). This may be because both groups in our study included obese patients and were not

compared with patients with normal BMI. In previous studies, the incidence of EPI was reported to be between 5.4%[12] and 56.7%[13], consistent with our results (35.7%).

Since gender distributions were not homogeneous in both groups in our study, it should be considered that FE-1 levels may differ between genders. This may be the reason why there was no difference in FE-1 levels between the groups.

Since our study was not designed prospectively, there is no data regarding the presence of malabsorption in these patients. The gender distributions were not homogeneous in both groups in our study.

While there are many studies investigating EPI in DM, it is the first study evaluating EPI in insulin resistance known as the period of pre-DM. In this respect, it is the strength of our work that it sheds light on prospective studies.

In conclusion, our study revealed that the presence of insulin resistance does not cause any change in FE-1 levels in obese patients. However, larger studies should be planned in patients with insulin resistance and obesity in which pancreatic exocrine dysfunction could potentially be seen, compared with healthy controls with larger participation.

Authors' contributions: Both authors have contributed significantly to the conception, design, acquisition, analysis and interpretation of the data in this study. All of them were involved in the preparation of the article or its critical revision for important intellectual content, and everyone gave the final approval of the version to be published.

Ethical Statement: All authors declare that the study was conducted in accordance with the World Medical Association Helsinki "Ethical Principles for Medical Research Containing Human Subjects". The study was approved by the Medipol University Ethics Committee (10840098-604.01.01-E.15454) and conducted in accordance with the Declaration of Helsinki.

Conflict of Interest: The authors did not report any conflicts of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Yilmaztepe A, Ulukaya E, Ersoy C, Yilmaz M, Tokullugil HA. Investigation of fecal pancreatic elastase-1 levels in type 2 diabetic patients. The Turkish journal of gastroenterology : the official journal of Turkish Society of Gastroenterology 2005;16:75-80.
2. Bytzer P, Talley NJ, Leemon M, Young LJ, Jones MP, Horowitz M. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults. Archives of internal medicine 2001;161:1989-96.
3. Radlinger B, Ramoser G, Kaser S. Exocrine Pancreatic Insufficiency in Type 1 and Type 2 Diabetes. Current diabetes reports 2020;20:18.
4. Tu J, Zhang J, Ke L, Yang Y, Yang Q, Lu G, Li B, Tong Z, Li W, Li J. Endocrine and exocrine pancreatic insufficiency after acute pancreatitis: long-term follow-up study. BMC gastroenterology 2017;17:114.
5. Hardt PD, Brendel MD, Kloer HU, Bretzel RG. Is pancreatic diabetes (type 3c diabetes) underdiagnosed and misdiagnosed? Diabetes care 2008;31 Suppl 2:S165-9.
6. Dominici R, Franzini C. Fecal elastase-1 as a test for pancreatic function: a review. Clinical chemistry and laboratory medicine 2002;40:325-32.
7. (ADA) TADA. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes care 2020;43:S14-s31.
8. Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, Toplak H. European Guidelines for Obesity Management in Adults. Obesity facts 2015;8:402-24.
9. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
10. Löser C, Möllgaard A, Fölsch UR. Möllgaard. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. Gut, 1996. 39(4): p. 580-6.
11. Altay M. Which factors determine exocrine pancreatic dysfunction in diabetes mellitus? World journal of gastroenterology 2019;25:2699-705.
12. Vujasinovic M, Zaletel J, Tepes B, Popic B, Makuc J, Epsek Lenart M, Predikaka M, Rudolf S. Low prevalence of exocrine pancreatic insufficiency in patients with diabetes mellitus. Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al] 2013;13:343-6.
13. Cavalot F, Bonomo K, Perna P, Bacillo E, Salacone P, Gallo M, Mattiello L, Trovati M, Gaia E. Pancreatic elastase-1 in stools, a marker of exocrine pancreas function, correlates with both residual beta-cell secretion and metabolic control in type 1 diabetic subjects. Diabetes care 2004;27:2052-4.

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ORIGINAL RESEARCH PAPER

The Effect of Dimethyl Sulfoxide on Chromosomal Abnormalities in Human Peripheral Blood Lymphocytes

Geliş Tarihi: 09.10.2020, Kabul Tarihi: 05.12.2020

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Abstract

Objective: *The main aim of this study was to examine the effects of dimethyl sulfoxide (DMSO) on chromosomal abnormalities in human peripheral blood lymphocytes.*

Methods: *Peripheral blood samples were collected from two healthy men and two healthy women. Then, in vitro studies were conducted with these blood samples , and the results were cytogenetically analyzed . There were two groups: a DMSO group and a control group. DMSO and control medium were added to the samples at 24 hours and 48 hours.*

Results: *A total of 800 metaphases were examined in this study. Depending on the increase in the number of groups and the time of application, an increase in chromosomal abnormalities was observed, and these were recorded.*

Conclusion: *In many previous studies, the effects of DMSO have been examined in various tissues and the body, but there are fewer studies about the effects on chromosomes. In this study, we researched the effects of DMSO, except for negative effects and toxicity, on chromosomal abnormalities.*

Key Words: *DMSO, Cytogenetics, Chromosomal abnormality*

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Introduction

Dimethyl sulfoxide (DMSO) is an amphipathic molecule with a highly polar domain and two nonpolar groups. These properties make it soluble in both aqueous and organic media. Therefore, DMSO is a remarkably efficient solvent for water-soluble compounds and disrupts hydrogen bonds (1).

DMSO, which is commonly used in several human therapeutic situations, such as drug-delivery systems, cryopreservation of autologous peripheral blood stem cells, and embolization of cerebral aneurysms or arteriovenous malformations (AVMs), has a variety of biological actions that have made it a focus of numerous studies (2, 3).

Although DMSO has occasionally been proposed to be neuroprotective and oxidative and induce behavioral alterations, its mechanisms of action remain unclear (4).

It has been reported to alter the permeability of the cell wall and facilitate the transport of substances across membranes (5).

Studies conducted by Chaloupka showed that DMSO tends to be angiotoxic and neurotoxic (6, 7).

DMSO is an organic compound that has a plethora of biological actions, including antioxidant, anti-inflammatory, antinociceptive, and radioprotective effects (8, 9).

It has also been shown to modify enzyme activity, change the secondary structure of both DNA and RNA, affect the mitotic cycle of normal dividing cells, and impede cell membrane-bound electron transfer systems (10-12).

Based on this information, the effects of DMSO on chromosomal abnormalities have to be strictly examined.

Method

In this study, we used peripheral blood samples, which were collected from two 25-year-old men and two 25-year-old women. Before the blood was collected, the individuals had not smoked or taken any drugs in the previous six months. The individuals who gave blood were healthy and had no chromosomal abnormalities.

The lymphocytes from the samples were analyzed in vitro. The concentration of DMSO that was added to the tubes was calculated at 3.7 µl DMSO for every 1 ml. For the control group, a nutrition medium was added instead of DMSO (13, 14).

Blood microculture

Medium	5 ml
Blood	0.25 ml
Phytohemagglutinin	0.10 ml
Total	5.35 ml

According to that, the amount of DMSO used for each tube was as follows: 3.7x5.35=20 µl. The amount of DMSO added to the tubes at a specified time was calculated. In the control group, the nutrition medium that was used instead of DMSO was HAM's F-10, and this medium was added to the tube at the same time that was specified .

Normally, the in vitro blood culture period is 72 hours. In our study, two different times were chosen: 24 hours after starting the blood culture (A) and 48 hours after starting the blood culture (B). DMSO and medium were added to the tubes at these times. For every four tubes that were created, a total of 16 tubes were prepared.

Group A (at 24 hours/48 hours exposure)

Group B (at 48 hours/24 hours exposure) (Table-1)

Table-1: Added material- Time table

TIME→	**24'TH HOUR**	**48'TH HOUR**
ADDED MATERIAL↓	**-A-**	**-B-**
MEDIUM (NUTRIEN MIXTURE)	**CONTROL -A-**	**CONTROL –B-**
DMSO	**DMSO -A-**	**DMSO -B-**

A modified microculture technique was used in this study. The lymphocyte microculture technique is a method of chromosome preparation. Afterward, all phase chromosomes were obtained and prepared for examination (15, 16).

The chromosomes were stained on microscope slides after microculture. Giemsa banding was used to stain the samples. For a flat Giemsa stain, 5 ml Giemsa was added to 95 ml distilled water, and a coating buffer was prepared. Microscope slides were stained in the buffer for 5 minutes and then washed and dried.

Metaphases were examined on light microscopy, and the results were noted on a form. The first examination employed a 10X ocular lens, and the metaphases were marked. Then , an immersion was used, and the metaphases were examined at 100X magnification. Afterward, all examination results were checked and noted on the form again. A total of 50 metaphases were examined for each tube, and a total of 800 (16X50) metaphases were examined.

Results

The metaphases examined in the control and DMSO groups were compared and recorded. Existing chromosomal abnormalities included fractures, gaps, deletion, duplication, endoreduplication, fragments, dicentric chromosomes, and satellite association.

In the examined metaphases of samples to which DMSO was added, more abnormalities were found. There were 4.5% more abnormalities in the DMSO group than in the control group. According to these results, DMSO is one of the causes of chromosome abnormalities (Table-2).

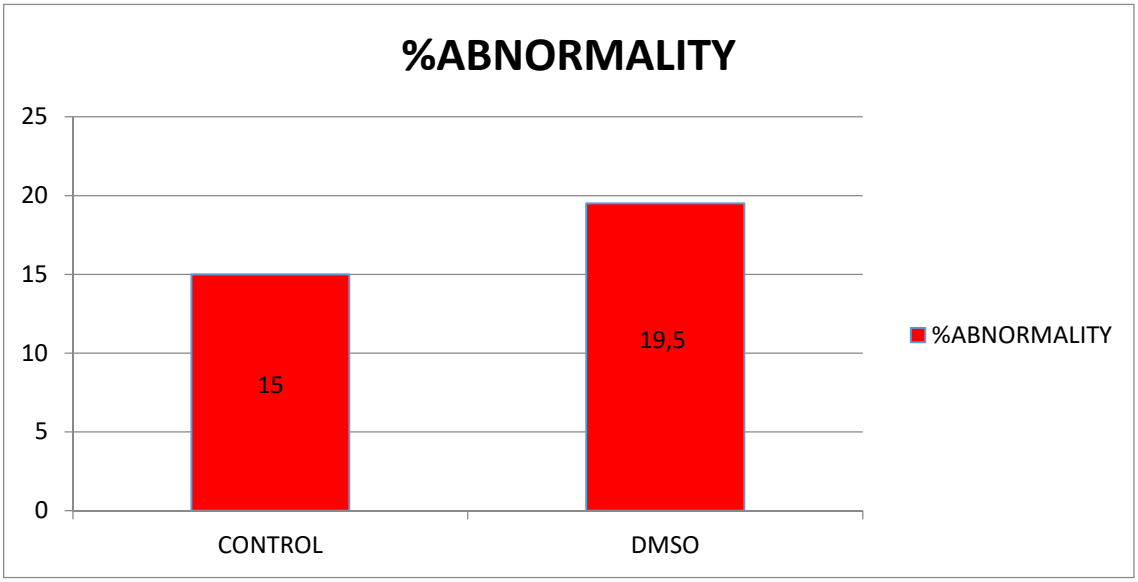
Table-2: % Chromosome abnormality (Fixed time). ap<0.001 compared with the control group. The data were analyzed using the student's t test.

	Control	**DMSO**
Examined metaphases	400	400
Normal metaphases	340	322
Abnormal metaphases	60	78 [a]
% Abnormal metaphases	15	19,5

Chromosome fractures and gap abnormalities are more commonly found in the metaphase plate. There were more abnormalities in the A-B and C chromosome groups, compared with in execution time abnormality increments.. There were a few minor deletions in the metaphase plate.

Abnormalities are structural and numerical, and there are more structural abnormalities than numerical abnormalities. Many of the abnormalities are structural.

In the control group, the rate of abnormalities was 15%, and after DMSO was added, the abnormalities increased to 19.5% (Graphic -1).



Graphic-1: % abnormality graphic (Fixed time)

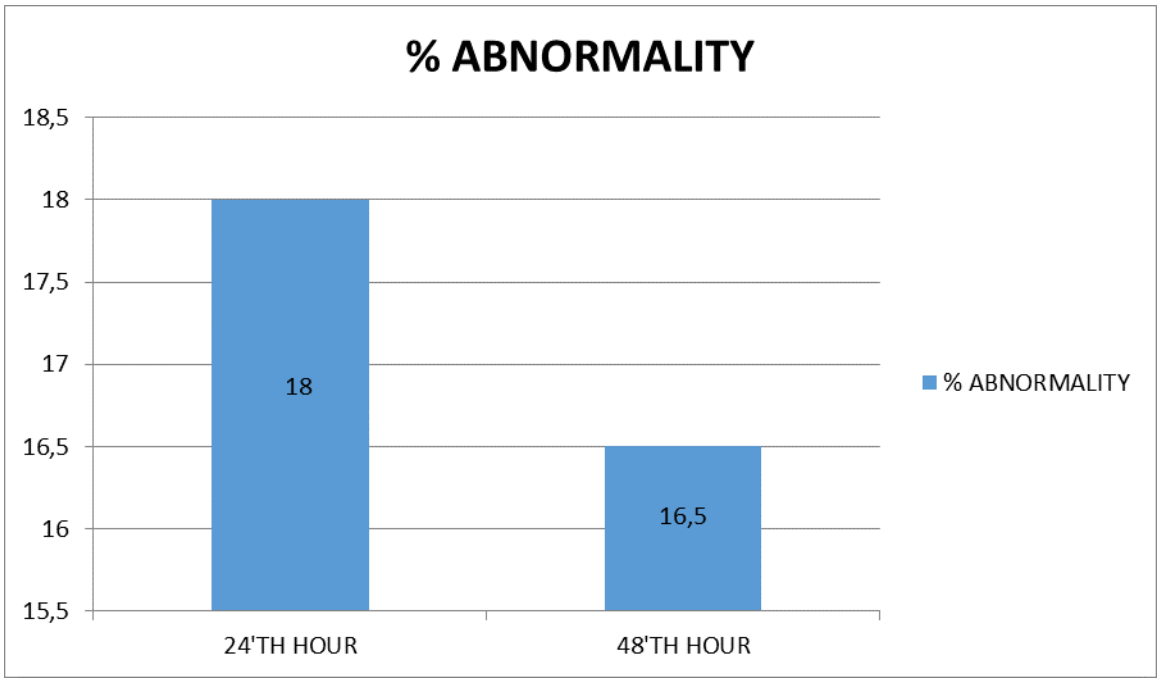
The periods that were determined were 24 hours (for the 48-hour application) and 48 hours (for the 24-hour application). DMSO and control solution were added to tubes at the determined time .

As the application time increased, the quantity of abnormalities increased. At 48 hours after application, there were 72 abnormal metaphases, whereas at 24 hours after application, there were 66 abnormal metaphases. According to the results increasing in the application time affected abnormalities %2.5 (Table3)

Table-3: Chromosome abnormalities % (active ingredient fixed).). The data were analyzed using the student's t test.

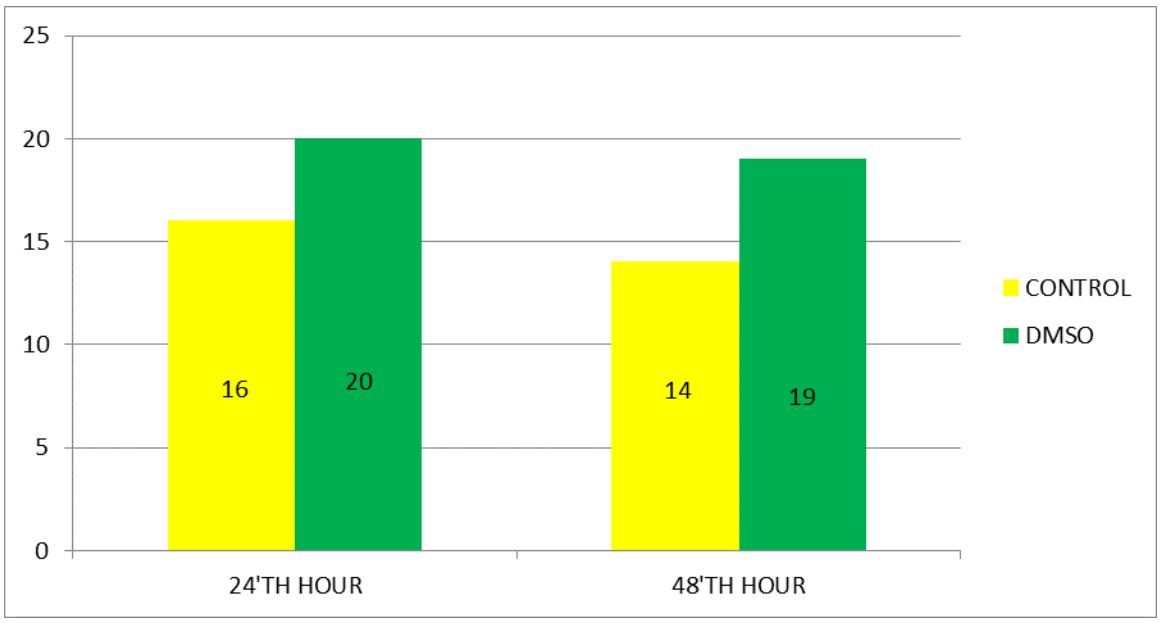
	24'th hour (48 hours application)	**48'th hour (24 hours application)**
Examined metaphases	400	400
Normal metaphases	328	334
Abnormal metaphases	72	66
% Abnormal metaphases	18	16.5

About the data with increasing application time, abnormality and aberrations are increased (Graphic-2).



Graphic-2: % Abnormality (active ingredient fixed)

According to the graphics, there is a linearly proportional between active ingredient-increasing application time and % abnormality (Graphic-3).



Graphic-3: % Abnormality (depend on time and active ingredient)

Discussion

In this study all data were noted to the form that was created before. preparations were examined and finding information analyzed.

Numerical chromosome aberrations were detected at levels too low to be ignored.

Abnormalities of groups were calculated and compared. In control group abnormality is %15 on the other hand the application of DMSO increased abnormality and the result is %19.5. A statistically significant difference was found between patient and control groups.($^{a}p<0.001$) According to the results, DMSO affected chromosome abnormality and increase percentage of anomaly.

There was no statistically significant difference between the application time groups. ($p>0.05$)

As a result, DMSO is effective on chromosome anomalies. However, the DMSO's application time causes anomaly, but it does not represent a statistically significant difference.

References

1. Santos NC, Figueira-Coelho J, Martins-Silva J, Saldanha C. Multidisciplinary utilization of dimethyl sulfoxide: pharmacological, cellular, and molecular aspects. Biochem Pharmacol. 2003;65(7):1035-41.

2. Dudeck O, Jordan O, Hoffmann KT, Okuducu AF, Tesmer K, Kreuzer-Nagy T, et al. Organic solvents as vehicles for precipitating liquid embolics: a comparative angiotoxicity study with superselective injections of swine rete mirabile. AJNR Am J Neuroradiol. 2006;27(9):1900-6.

3. Jacob SW, Herschler R. Pharmacology of DMSO. Cryobiology. 1986;23(1):14-27.

4. Bakar B, Kose EA, Sonal S, Alhan A, Kilinc K, Keskil IS. Evaluation of the neurotoxicity of DMSO infused into the carotid artery of rat. Injury. 2012;43(3):315-22.

5. Nasrallah FA, Garner B, Ball GE, Rae C. Modulation of brain metabolism by very low concentrations of the commonly used drug delivery vehicle dimethyl sulfoxide (DMSO). J Neurosci Res. 2008;86(1):208-14.

6. Chaloupka JC, Vinuela F, Vinters HV, Robert J. Technical feasibility and histopathologic studies of ethylene vinyl copolymer (EVAL) using a swine endovascular embolization model. AJNR Am J Neuroradiol. 1994;15(6):1107-15.

7. Chaloupka JC, Huddle DC, Alderman J, Fink S, Hammond R, Vinters HV. A reexamination of the angiotoxicity of selective injection of DMSO in the swine rete embolization model. AJNR Am J Neuroradiol. 1999;20(3):401-10.

8. Ashwood-Smith MJ. Radioprotective and cryoprotective properties of dimethyl sulfoxide in cellular systems. Ann N Y Acad Sci. 1967;141(1):45-62.

9. Jacob SW, Wood DC. Dimethyl sulfoxide (DMSO). Toxicology, pharmacology, and clinical experience. Am J Surg. 1967;114(3):414-26.

10. Sams WM, Jr., Carroll NV. Cholinesterase inhibitory property of dimethyl sulphoxide. Nature. 1966;212(5060):405.

11. Archer JM, Shilkin KB, Papadimitriou JM, Walters MN. Interaction of dimethylsulfoxide and ascorbic acid on fibroblasts of rats. Proc Soc Exp Biol Med. 1967;126(2):354-6.

12. Hervas JP, Gimenez-Martin G. Dimethyl sulphoxide effect on division cells. Experientia. 1973;29(12):1540-2.

13. A I. Tamiflu'nun insan periferal lenfositlerinde in vitro genotoksik ve sitotoksik etkileri.: Cukurova Üniversity; 2009.

14. Rencüzoğulları E, Topaktaş MJFvMBD. The relationship between quantities of bromodeoxyuridine and human peripheral blood with determination of the best differential staining of sister chromatids using chromosome medium-B. 1991;5(3):19-24.

15. N B. Tıbbi Genetik. 7 ed: Nobel-İstanbul; 1999.

16. G L. Sitogenetiğin Temelleri: Meteksan-Ankara; 1990.McGovern TW. Dermatose Due to Plants. In: Bolognia JL, Schaffer VJ, Cerroni L, eds. Dermatology. 4th Edition. Philadelphia, Elsevier, 2018:17,286.

Figures

Figure-1: Deletion

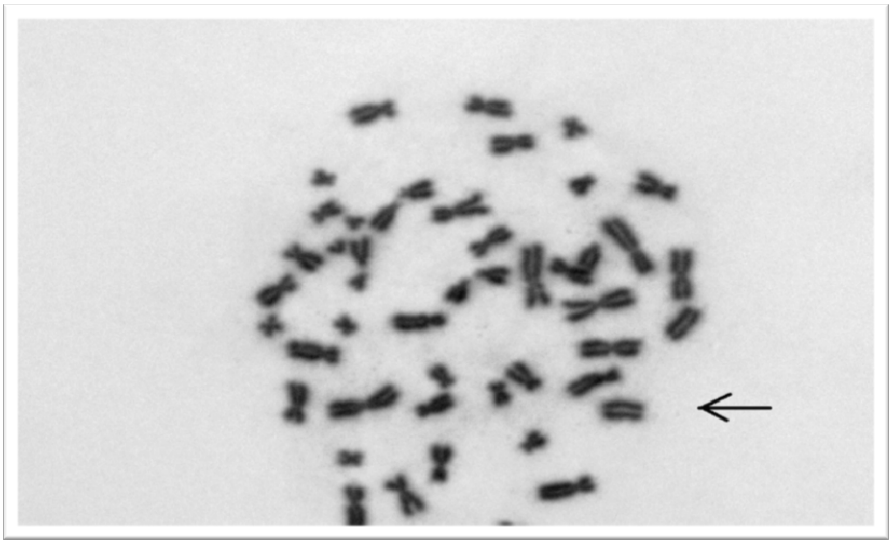


Figure-2: Acentric chromosome

Figure-3: Chromatid gap

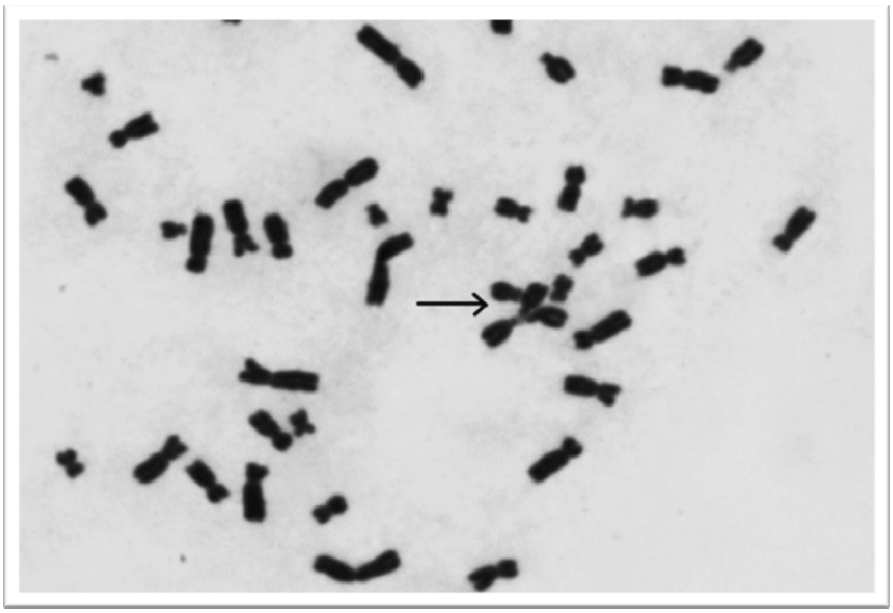


Figure-4: Satellite association

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ORIGINAL RESEARCH PAPER

Mortality Analysis of Patients with Lupus Nephritis

Geliş Tarihi: 21.10.2020, Kabul Tarihi: 05.12.2020

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Abstract

Lupus nephritis (LN), which is an important clinical finding of systemic lupus erythematosus (SLE), may lead to death if not treated. In our study, we aimed to investigate the causes of mortality, 5-year and 10-year survival rates, and standardized mortality ratios (SMR) of patients with LN. 73 LN patients were included in the study. Age, gender, diagnosis, treatment, laboratory and pathology data of these patients were retrospectively scanned and recorded.

63(86.3%) female and 10(13.7%) male LN patients were included in the study. The most prevalent clinical criteria detected in these patients were proteinuria 73(100%). During the follow-up period, death occurred in 4(5.5%) patients. The 5 and 10-year survival rate of the patients was calculated as 95.7% and 94.0% respectly. Cox regression analysis revealed that the prognosis of the disease was significantly more mortal in male patients compared to the female patients [p = 0.01, HR = 19.248]. On the other hand, SMR was determined as 5.52 in SLE patients with LN, which indicates a higher SMR compared to the general population.

Our study is the first LN mortality series study in Turkey. The mortality rates determined in our study were found to be comparable to the mortality rates reported in the literature. Male gender was determined as the risk factors associated with LN in terms of mortality. Hence, male LN patients should be followed up more closely.

Key Words: *Systemic lupus erythematosus, Lupus nephritis, Mortality*

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Introduction:

SLE is a chronic autoimmune disease of unknown cause that can affect almost any organ in the body. LN is detected in approximately 50 percent of SLE patients and is an important cause of morbidity and mortality[1]. In today's world, the survival time of LN patients has been significantly prolonged compared to the past due to factors such as better socio-economic conditions, early diagnosis, improvements in immunosuppressive and supportive treatments. Infections remain a major cause of mortality, whereas cardiovascular complications have been a major cause of late mortality in the event of longer patient survival[2-4].

Whether the mortality rate in patients with LN is higher compared to the mortality rate in the general population can be calculated by SMR[5]. It has been reported in the literature that the SMR of SLE patients without LN is 2.4 times higher than the general population, whereas the SMR of SLE patients with LN was 6.0 times higher than the general population[3-6]. The mortality rate in patients with SLE in our country has been studied[7], however there has been no study to date, in which the mortality in patients with LN in our country was investigated. Therefore, in our study, we aimed to investigate the causes of mortality, 5-year and 10-year survival rates, and SMR of patients with LN.

Material&Method:

73 patients that applied to University of Health Sciences Gazi Yaşargil Training and Research Hospital Rheumatology Outpatient Clinic during the period of 2010 to 2020 and who were diagnosed with LN as substantiated by biopsy were included in the study. Age, gender, diagnosis, treatment, laboratory and pathology data of these patients were retrospectively scanned and recorded. All patients were re-evaluated in terms of their SLE diagnosis using the 2019 EULAR (European League Against Rheumatism) / ACR (American College of Rheumatology) classification criteria and their diagnoses were confirmed[8]. The SLEDAI and ACR Damage Index of the patients were calculated. Vital records (birth and death) of patients were obtained from the Turkish Statistical Institute[9,10]. Statistical analyses were performed using the SPSS V21.0 (SPSS Inc., Chicago, IL) software. Chi-square test was used to compare the categorical data, whereas Fisher's exact test was also used in cases deemed necessary. Cumulative survival curves were created using the Kaplan-Meier method and the difference between curves was tested using the log-rank test. Univariate and multivariate Cox regression analysis was used to determine the independent factors affecting survival. Values of $p<0.05$ have been considered statistically significant. The ethics committee approval

required to conduct the study has been obtained from University of Health Sciences Gazi Yaşargil Training and Research Hospital.

Results:

A total of 73 SLE patients, 63 (86.3%) of whom were female and 10 (13.7%) of whom were male, were included in our study. The mean age of the patients was calculated as 30 ± 10.7 years. The most prevalent clinical criteria detected in these patients were proteinuria, which was detected in 73 (100%) patients, arthritis, which was detected in 56 (76.7%) patients, and photosensitivity, which was detected in 49 (67.1%) patients. On the other hand, the most prevalent immunological criteria detected in these patients were ANA (antinuclear antibody) positivity, which was detected in 72 (98.6%) patients, anti-ds(double stranded)DNA positivity, which was detected in 55 (75.3%) patients, and low complement C3 (component-3), which was detected in 44 (60.3%) patients. Detailed data are given in **Table 1**. The pathology results of our study indicated that 35 (47.9%) patients had class IV LN, 16 (21.9%) patients had class III LN, 10 (13.7%) patients had class V LN, 8 (11.0%) patients had class II LN, 3 (4.1%) patients had class I LN, and 1 (1.4%) patient had class VI LN.

Table 1: Basic clinical and laboratory characteristics of SLE patients

Age, male/female/general, (mean ±sd)	30.7±11.5 / 28±8.7/30±10.7
Female, n(%)/Male, n(%)	63 (86.3) / 10 (13.7)
Duration of illness (month)	138.1±126.4
Death, n(%)	4 (5.5)
Arthritis, n(%)	56 (76.7)
Photosensitivity, n(%)	49 (67.1)
Raynaud, n(%)	20 (27.4)
Malar rash, n(%)	30 (41.1)
Diskoid rash, n(%)	8 (11.0)
Oral aphthae, n(%)	32 (42.5)
Pleurit, n(%)	11 (15.1)
Pericarditis, n(%)	7 (9.6)
Alopecia, n(%)	11 (15.1)
Neurological involvement, n(%)	6 (8.2)
Proteinuria (>500 mg/day) , n(%)	73 (100)
Active sediment,n(%)	49 (67.1)
Hemodialysis, n(%)	3 (4.1)
Leukopenia, n(%)	32 (43.8)
Lymphopenia, n(%)	28 (38.4)
Hemolytic anemia, n(%)	7 (9.6)
Thrombocytopenia, n(%)	10 (13.7)
ANA, n(%)	72 (98.6)
Anti-dsDNA, n(%)	55 (75.3)
Anti-ro, n(%)	18 (24.7)

Anti-sm, n(%)	10 (13.7)
Low C3, n(%)	44 (60.3)
Low C4, n(%)	39 (53.4)
Direct coombs, n(%)	17 (23.3)
SLICC/ACR Damage İndeks, mead±sd	1.16±1.45
SLEDAI, mean±sd	17.63±8.52

n: number, sd: standard deviation

In terms of comorbidity, it was determined that 15 (24.7%) patients had hypertension and 5 (6.8%) patients had diabetes; whereas in terms of medication, it was determined that 72 (98.6%) patients were using hydroxychloroquine, 70 (95.9%) patients were using steroid, 47 (64.4%) patients were using azathiopurine and cyclophosphomide. Detailed data are given in **Table 2**.

Table 2: Risk factors and use of medication in patients with systemic lupus erythematosus (SLE)

Hypertension, n(%)	15 (24.7)
Diabetes, n(%)	5 (6.8)
Hypothyroidism, n(%)	2 (2.7)
Hyperlipidemia, n(%)	4 (5.5)
Steroid, n(%)	70 (95.9)
Hydroxychloroquine, n(%)	72 (98.6)
Azathiopurine, n(%)	47 (64.4)
Mycophenolate Mofetil, n(%)	33 (45.2)
Cyclophosphomide, n(%)	47 (64.4)
Methotrexate, n(%)	3 (4.1)
Cyclosporine, n(%)	6 (8.2)
Rituximab, n(%)	12 (16.4)
Acetylsalicylic acid, n(%)	20 (27.4)
Anticoagulant, n(%)	3 (4.1)

The mean disease duration of the patients was calculated as 138.1 ± 126.4/month. Death occurred in 4 (3 male, 1 female) patients (5.5%) out of the 73 patients during the course of the disease. Considering the causes of death, it was determined that 1 patient died due to central nervous system involvement, 1 patient died due to heart failure, 1 patient died due to development of acute myeloid leukemia, and 1 patient died due to sepsis. The detailed clinical and laboratory characteristics of 4 patients who had died are given in **Table 3**. The 5-year survival rate of the patients was calculated as 95.7%, whereas the 10-year survival rate of the patients was calculated as 94.0% (**Figure 1**).

Table 3: Clinical and laboratory characteristics and causes of death of patients who had died

Age/ Gender	Duration of illness (months)	DM/HT	Lupus Nephritis Class	Neurological involvement	Hemolytic anemia	Thrombocytopenia	Pleurit / Pericarditis	Anti-dsDNA	Treatment	Cause of death	SLEDAI	SLICC/ACR Damage Index
37/F	64	-/-	4	+	-	+	+/-	+	Steroid, Hydroxychloroquine, Cyclosporine, Cyclophosphomide	cns involvement	26	4
31/M	5	-/-	2	-	+	-	+/+	-	Steroid, Hydroxychloroquine, Azathiopurine, Cyclophosphomide	Heart failure	12	1
26/M	26	-/-	3	-	-	-	-/+	-	Steroid, Hydroxychloroquine, Azathiopurine, Cyclophosphomide	AML	23	2
24/M	8	-/-	4	-	-	-	-/-	+	Steroid, Hydroxychloroquine, Mycophenolate Mofetil , Rituximab, Cyclophosphomide	Sepsis	18	1

CNS: Central nervous system, AML: Acute myeloid leukemia

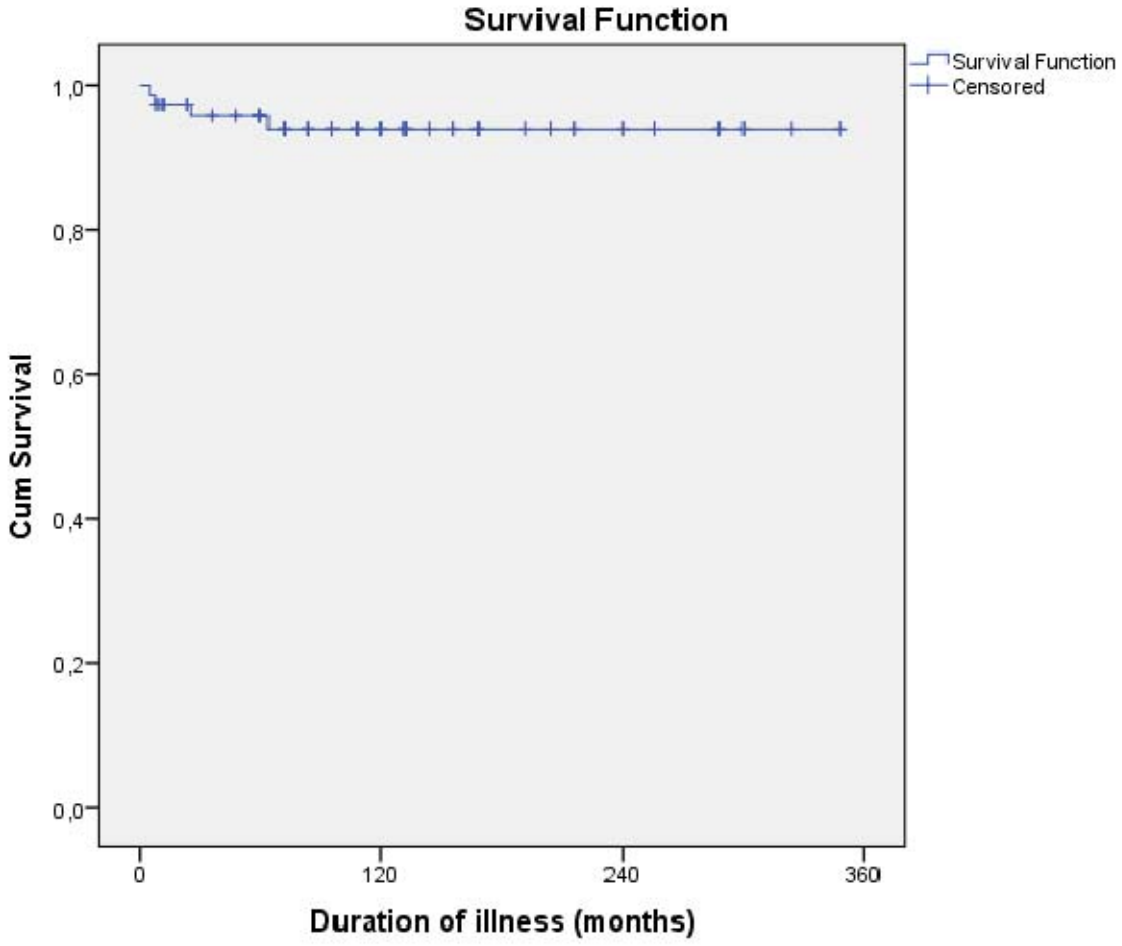

Figure 1: Survival analysis in patients with LN

Cox regression analysis revealed that the prognosis of the disease was significantly more mortal in male patients compared to the female patients [p = 0.01, HR (Hazard Ratio) = 19.248], and in patients with pericarditis compared to the patients without pericarditis (p = 0.02, HR = 9.822). Interestingly, deaths were statistically significantly higher in those without photosensitivity (p = 0.01, HR = 0.004). Univariate Cox regression analysis did not reveal any significant difference between the survivors and the deceased in terms of LN classes and other clinical, laboratory and treatment characteristics. In multivariate cox regression analysis, only gender was found to have a significant effect on mortality (HR: 13.856, p= 0.02). Detailed data are given in **Table 4**.

Table 4: Univariate and Multivariate Cox regression analysis of mortality and clinical parameters in patients with lupus nephritis

	Univariate analysis		Multivariate analysis	
Risk Factor	HR (95% CI)	p	HR (95% CI)	p
Age	0.992 (0.904-1.088)	>0.5		
Gender	19.248 (1.999-185.334)	0.01	13.856 (1.347-142.572)	0.02
Diabetes	0.045 (0.000-1297014.287)	>0.5		
Hypertension	0.032 (0.000-558.735)	>0.5		
Oral aphthae	0.018 (0.000-61.007)	>0.5		
Malar rash	0.021 (0.000-77.419)	>0.5		
Arthritis	0.800 (0.083-7.7705)	>0.5		
Lymphopenia	0.472 (0.049-4.562)	>0.5		
Hemolytic anemia	3.165 (0.329-30.492)	>0.5		
Thrombocytopenia	1.844 (0.191-17.792)	>0.5		
Pericadial effusion	9.822 (1.374-70.233)	0.02	0.237 (0.028-1.997)	0.18
Photosensitivity	0.004 (0.004-81.817)	0.01	204158.960 (0.000-2.181E+180)	0.95
SLEDAI	1.016 (0.908-1.137)	>0.5		
SLICC/ACR Damage Index	1.268 (0.767-2.095)	>0.5		

HR: Hazard Ratio, CI: 95% Confident Interval

The survival rate of the general population has been 95.72% during the period between 2008 and 2017 according to the statistics of the Turkish Statistical Institution[9,10], whereas the survival rate of patients with LN in our cohort was determined as 94.0%. On the other hand, SMR was determined as 5.52 in SLE patients with LN, which indicates a higher SMR compared to the general population.

Discussion:

LN is a serious cause of morbidity and mortality in patients with SLE. Nonetheless, today, the 5-year survival rate associated with LN today is 99.3%[4], which indicates a substantial improvement compared to the 5-year survival rate associated with LN, which was 44% in the 1950s[11]. Many factors have contributed to the said improvement observed in the survival rate associated with LN, including early diagnosis, easy access to healthcare, advances in immunosuppression therapy, dialysis, transplantation, and treatment of comorbidities.

Our literature review revealed that there has been a few studies, in which mortality rates associated with LN were studied; however none of these studies included any results from Turkey. Therefore, our cohort study is the first study, in which the mortality of patients with LN in Turkey was studied. In our study, the 5-year survival rate of the patients was calculated as 95.7%, whereas the 10-year survival rate of the patients was calculated as 94.0%. In comparison, in the literature, the 5-year survival rates were reported within the range of 44% to 99.3%[3,4,11,12] and the 10-year

survival rates were reported within the range of 88% to 93%[3,4,12] which are similar to the results of our study.

In our study, SMR was determined as 5.52 in SLE patients with LN, which indicates a higher SMR compared to the general population. In comparison, the SMRs of patients with LN have been reported as 6[3] and 6.8[13] in the literature. Despite the fact that life expectancy of patients with LN has increased in recent years[4], the mortality rate in patients with LN remains still high compared to the mortality rate in general population.

Death occurred in 4 of the patients included in our study. Their causes of death were determined as cardiovascular complications, malignancy, neurological involvement and infection. Similar causes of death have been reported in patients with LN in the literature[4,14]. Ethnic origins and socio-economic status of the patients are among the factors that have to be taken into consideration in assessing the SLE-related mortality. In our cohort, however, all patients were from the same ethnic background, thus we did not need to take ethnic origins of the patients into account when assessing the SLE-related mortality. On the other hand, we could not evaluate the SLE-related mortality in terms of the socio-economic status of the patients, since a complete set of relevant data were not available.

In our study, male gender, pericarditis and lack of photosensitivity were determined as the risk factors associated with LN in terms of mortality. However, in the multivariate cox regression analysis, only gender was found to have a significant effect on mortality (HR: 13.856, $p = 0.02$). In comparison, in the literature, male gender has been associated with twice as higher mortality rates in patients with LN compared to the female gender[15,16]. However, we did not come across any study in the literature, in which the effect of pericarditis and lack of photosensitivity on LN-related mortality has been studied.

Although it is known that high disease activity index is an indicator of mortality in patients with LN[17] in our cohort, univariate Cox regression analysis did not reveal any increase in LN-related mortality, neither in patients with class IV (diffuse proliferative) LN nor in those with high SLEDAI scores. Therefore, we have concluded that active inflammatory and proliferative kidney changes maintain their importance in the selection of treatment and do not cause an increase in LN-related mortality in the long-term.

Conclusion: Our study is the first LN mortality series study in Turkey. The mortality rates determined in our study were found to be comparable to the mortality rates reported in the literature. Male gender was determined as the risk factors associated with LN in terms of mortality. Hence, male LN patients should be followed up more closely.

References

1. Danila MI, Pons-Estel GJ, Zhang J, Vila LM, Reveille JD, Alarcon GS. Renal damage is the most important predictor of mortality within the damage index: data from LUMINA LXIV, a multiethnic US cohort. Rheumatology (Oxford). 2009;48: 542-5.

2. Ippolito A, Petri M. An update on mortality in systemic lupus erythematosus. Clin Exp Rheumatol. 2008;26:S72-9.

3. Yap DY, Tang CS, Ma MK, Lam MF, Chan TM. Survival analysis and causes of mortality in patients with lupus nephritis. Nephrol Dial Transplant. 2012;27: 3248-54.

4. Ichinose K, Kitamura M, Sato S et al. Factors predictive of long-term mortality in lupus nephritis: a multicenter retrospective study of a Japanese cohort. Lupus. 2019;28:295-303.

5. Yavuz Ş. Sistemik Lupus Eritematozus ve Mortalite. Türkiye Klinikleri. 2018:102-4.

6. Bernatsky S, Boivin JF, Joseph L et al. Mortality in systemic lupus erythematosus. Arthritis Rheum. 2006;54:2550-7.

7. Pamuk ON, Akbay FG, Donmez S, Yilmaz N, Calayir GB, Yavuz S. The clinical manifestations and survival of systemic lupus erythematosus patients in Turkey: report from two centers. Lupus. 2013;22:1416-24.

8. Aringer M, Costenbader K, Daikh D et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol. 2019;71:1400-12.

9. Ölüm Nedeni İstatistikleri [https://data.tuik.gov.tr/Bulten/Index?p=Olum-ve-Olum-Nedeni-Istatistikleri-2019-33710]

10. Adrese Dayalı Nüfus Kayıt Sistemi Sonuçları [https://tuikweb.tuik.gov.tr/PreHaberBultenleri.do;jsessionid=pT27fntc1TPshcphN2cqf9XGPbtpYRp8R30DNpCscjzfrtN0skQ2!-608163093?id=30709]

11. Cameron JS. Lupus nephritis. J Am Soc Nephrol. 1999;10:413-24.

12. Teh CL, Phui VE, Ling GR, Ngu LS, Wan SA, Tan CH. Causes and predictors of mortality in biopsy-proven lupus nephritis: the Sarawak experience. Clin Kidney J. 2018;11:56-61.

13. Faurschou M, Dreyer L, Kamper AL, Starklint H, Jacobsen S. Long-term mortality and renal outcome in a cohort of 100 patients with lupus nephritis. Arthritis Care Res (Hoboken). 2010;62:873-80.

14. Bultink IEM, de Vries F, van Vollenhoven RF, Lalmohamed A. Mortality, causes of death and influence of medication use in patients with systemic lupus erythematosus vs matched controls. Rheumatology (Oxford). 2020.

15. Kasitanon N, Magder LS, Petri M. Predictors of survival in systemic lupus erythematosus. Medicine (Baltimore). 2006;85:147-56.

16. Pattanaik SS, Muhammed H, Chatterjee R et al. In-hospital mortality and its predictors in a cohort of SLE from Northern India. Lupus. 2020;29:1971-7.

17. Momtaz M, Fayed A, Wadie M et al. Retrospective analysis of nephritis response and renal outcome in a cohort of 928 Egyptian lupus nephritis patients: a university hospital experience. Lupus. 2017;26:1564-70.

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ORIGINAL RESEARCH PAPER

Adolescents with Migraine Experience More Daytime Dysfunction than Other Counterparts: A Descriptive Cross-Sectional Study

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Abstract

Objective: *This study examined circadian rhtyhm factors of adolescents with primary headaches and its relation with perceived quality of life and sleep quality as well.*

Method: *Adolescents aged 14-18 years with primary headaches were examined via International Physical Activity Questionnaire-Short Form (IPAQ-SF), World Health Organization Quality of Life-Short Form (WHOQOL-BREF), Biological Rhythm Interview of Assesment in Neuropsychiatry Scale (BRIAN) and Pittsburg Sleep Quality Index (PSQI). SPSS 17.0 was used for statistical analyses. $p<.05$ was accepted as significant.*

Results: *Of 101 adolescents with primary headaches and 97 healthy counterparts were included. Adolescents with primary headaches had similar circadien pattern of sleep, physical and social activity and eating habits, as well as perceived quality of life and sleep quality compared to the healthy counterparts (for all variables $p>.05$). In terms of specific headaches, there was a significance for having migraine in terms of higher daytime dysfunction, a subscale of PSQI ($F(2) = 4.209$, $p = .016$) and lower environmental quality of life, a subscale of WHOQOL-BREF ($F(2) = 5.034$, $p = .007$.*

Conclusion: *Migraine affects daytime functioning and environment's quality of life perceived. Countermeasures related to improving daytime functions of adolescents with migraine could result in better quality of life perceived.*

Keywords: *migraine, BRIAN, QoL, sleep, adolescent*

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Introduction

Primary headaches are one of the debilitating disorders that affect adolescence's quality of life and their sleep quality. Physical inactivity, smoking, and lifestyle factors are previously reported as preventable risk factors for primary headache in adolescents[1].

Biological rhythm is a homeostatic factor to equilibrium of the body functions including circadian rhythm as the most important one. Disrupted biological rhythm as a contributor factor in primary headaches, on the other hand, are relatively less studied subjects in adolescents.

The aim of this study is to examine should primary headaches are affected by circadian factors.

Material and Methods

Adolescents aged 14-18 years whom they admitted to Ankara Training and Research Hospital Child Neurology department between April 2018 and April 2019 were examined. Adolescents whose headache was fulfilled by one of the primary headaches using with International Headache Society's International Classification of Headache Disorders (ICHD-3, 2013) criteria[2] constituted primary headache group and others who had not any specific neurological disorder as healthy counterparts.

Inclusion criteria for both groups were the following; Normal neurological findings of cranial MRI or computerized tomography, normal EEG results, not having any organic, genetic or syndromic disorder related to the headache, mental retardation, and agreed to join this study. These participants were consultated to the child psychiatry department to evaluate their mental status. Psychiatric diagnoses were carried out according to the DSM-5 (APA, 2013) criteria[3] by the child psychiatrists[2].

Tools Used

Demographic variables were recorded. Body-mass index (BMI) were categorized as <18.5 kg/m^2 as underweight, ≥18.5-<24.9 kg/m^2 normal, ≥25-<29.9 kg/m^2 overweight, and ≥30 kg/m^2 obese based on WHO for 5-19 years. Physical activity were examined via International Physical Activity Questionnaire- Short Form (IPAQ-SF)[4], quality of life (QoL) was assessed with World Health Organization-QoL-Short Form (WHO-QoL-BREF) scale[5], circadian rhythm was assessed by Biological Rhythm Interview of Assesment in Neuropsychiatry Scale (BRIAN)[6,7] and sleep quality was examined with Pittsburg Sleep Quality Index (PSQI).[8,9]

International Physical Activity Questionnaire-Short Form (IPAQ-SF): The questionnaire is based on the calculation of the metabolic equivalent (MET) value which is spent by evaluating the short form of physical activity of at least 10 minutes in terms of frequency, duration (minutes) and severity in the last 7 days. 1 MET = indicates the amount of oxygen used by the person at rest (in sitting state) (3.5 ml/O_2/kg). The form consists of four parts under walking, moderate physical activity and very severe physical activity. The total MET value of the activity of each section is calculated by calculating the values in minutes and days of the efficacy of the activity (3.3 MET for walking, 4 MET for moderate physical activity and 8 MET for severe physical activity). Sum of three items point total MET value and it is categorized as "inactive" if a total weekly MET value is less than 600, 600-3000 MET as "minimally active" and more than 3000 MET as "highly active". Turkish validation of this scale was conducted by Saglam et al in 2010.[4]

World Health Organization Quality of Life-Short Form (WHOQOL-BREF): The health-related quality of life scale was developed by WHO and validated by reliability by Eser et al., in 1999.[5] The scale measures physical, psychological, social and environmental well-being and consists of 26 questions. The scale does not have a total score. Since each field independently expresses the quality of life in its field, the area scores are calculated between 4-20. The higher the score, the better the quality of life.

Biological Rhythm Interview of Assesment in Neuropsychiatry Scale (BRIAN): Developed by Giglio et al (2009), the scale measures daily cyclic rhythm and functionality of patients.[6] The 4-item Likert consists of 21 items and five sub-headings as sleep (5-item), activity (5-item), social (4-item), eating habits (4-item) and dominant biorhytm (3-item). Last three items are not added to the total score. High scores indicate irregularity in biological rhythm. Turkish validity and reliability study of it was carried out by Aydemir et al (2012).[7] Croanbach alpha internal consistency was detected as .798. Croanbach alpha of item-test correlations were found to be from .697 to .781.

Pittsburg Sleep Quality Index (PSQI): A 24-item scale that questions sleep quality and sleep-related disorders during a one-month period was developed by Buysse et al. (1989).[8] These include 7 sub-components: Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. Each component is rated at 0-3 points. The total score of the 7 components gives the total score of the scale that ranges

from 0 to 21. If the total score is greater than 5, it indicates "poor sleep quality". The reliability of the Turkish version was performed by Agargun et al. (1996).[9] Croanbach alpha internal consistency was detected as .782. Croanbach alpha of item-test correlations were found to be from .398 to .758.

Ethical approval was obtained from the Local Committee of Ankara Training and Research Hospital (document numbered with 28.03.2018/0040/400). Written consent were obtained from adolescents themselves.

Power analysis (G-Power 3.1, Kiel-Germany, 2017) of this study with 90% power, 5% error rate and effect size of 0.5 with 1:1 distribution revealed that 90 adolescents would be sufficient for each group.

Statistical analysis: SPSS 17.0 (Chicago Inc., 2008) program was used for statistical analyses. Continuous variables were defined as mean, standard deviation, minimum-maximum values and categorical ones as frequency (n) and percentage (%). Normality of the continuous variables was examined via Kolmogorov-Smirnov test. For comparisons of the continuous variables, Student t test or ANOVA were used. Categorical variables were compared using the χ^2 test. Pearson correlation analysis were used for scale scores with other independent variables. $p<.05$ was accepted as significant in dual comparisons and $p<.017$ for triple comparisons.

Results

Of 198 adolescents aged 14-18, mean age was 15.9 years, 78.3% (n = 155) of them were girls and 21.7% (n = 43) were boys. Primary headaches group (n=101) included 73.3% (n = 74) of tension-type headache and 26.7% (n = 27) of migraine. Of 70.2% (n = 139) had normal BMI. Of 10.6% of all (n = 21) were active-smoking and 45.5% (n = 90) of all were reaching their school via walking. Of 34.3% (n = 68) were physically inactive.

Evaluating the effect of having tension-type or migraine type headache on scale scores compared to the healthy group revealed that three groups were similar in terms of demographics including age, BMI scores, smoking status, reaching to school, except gender (for all variables $p>.05$, see Table 1).

Table 1. *Comparisons of variables between tension-type, migraine and healthy groups.*

	Primary Headaches (n = 101)				
	Healthy control	**Tension-type**	**Migraine**	**Statistics**	
	n = 97	**n = 74**	**n = 27**	**F or χ2**	**P value**
Age (years)[a]	15.8 (1.3)	15.8 (1.3)	16.1 (1.0)	.690	.503
Gender, n (%)					
Girls	86 (88.7)	49 (66.2)	20 (74.1)	12.763	.002
Boys	11 (11.3)	25 (33.8)	7 (25.9)		
BMI (kg/m²)[a]	20.9 (3.7)	21.4 (3.5)	22.6 (3.3)	2.233	.110
BMI categories, n (%)					
Underweight	16 (16.5)	17 (23.0)	3 (11.1)		
Normal	73 (75.3)	47 (63.5)	19 (70.4)		
Overweight	4 (4.1)	9 (12.2)	5 (18.5)		
Obese	4 (4.1)	1 (1.4)	0		
Smoking, n (%)					
Not-smoking	86 (88.7)	68 (91.9)	23 (85.2)	1.047	.593
Active smoking	11 (11.3)	6 (8.1)	4 (14.8)		
Reaching school, n (%)					
On motor vehicle	54 (55.7)	37 (50.0)	17 (63.0)	1.438	.487
On foot	43 (44.3)	37 (50.0)	10 (37.0)		
Scales					
IPAQ-SF activity, n (%)					
Inactive	34 (35.1)	24 (32.4)	10 (37.0)		
Minimally active	46 (47.4)	34 (45.9)	12 (44.4)	.571	.966
Highly active	17 (17.5)	16 (21.6)	5 (18.5)		
WHO-QoL-BREF[a]					
Physical health	15.7 (2.8)	16.1 (2.9)	15.2 (3.3)	1.032	.358
Psychological health	15.4 (2.8)	15.9 (3.1)	14.5 (3.9)	2.068	.129
Social relationship	15.9 (4.1)	16.3 (3.7)	16.1 (3.1)	.232	.793
Environment	16.0 (2.7)	16.9 (2.1)	15.1 (3.1)	5.034	.007
BRIAN[a]					
BRIAN-Sleep	12.9 (3.2)	12.3 (3.1)	13.4 (3.1)	1.461	.234
BRIAN-Physical activity	9.2 (3.3)	9.5 (3.5)	9.4 (2.7)	.215	.807
BRIAN-Social activity	8.6 (2.8)	8.1 (2.5)	8.3 (3.2)	.755	.471
BRIAN-Eating pattern	8.2 (2.6)	8.7 (3.3)	9.2 (3.0)	1.141	.322
BRIAN-Total	39.1 (8.9)	38.7 (9.7)	40.4 (9.0)	.345	.708
PSQI[a]					
Sleep quality	1.4 (0.9)	1.1 (0.7)	1.5 (0.7)	3.075	.048
Sleep latency	0.8 (0.7)	0.9 (0.7)	1.0 (1.0)	.402	.669
Sleep duration	0.9 (1.0)	0.8 (1.0)	1.0 (1.0)	.332	.718
Sleep efficiency	0.8 (0.7)	0.8 (0.7)	1.0 (0.6)	.473	.624
Sleep disturbances	1.6 (0.8)	1.6 (0.8)	1.8 (0.8)	.535	.586
Sleep medication	0.1 (0.3)	0.1 (0.5)	0.2 (0.6)	1.202	.303
Daytime dysfunction	1.4 (0.8)	1.1 (0.7)	1.5 (0.7)	4.209	.016
Total PSQI scores	7.2 (3.5)	6.7 (3.8)	8.2 (3.7)	1.650	.195
PSQI categories, n (%)					
Normal (0-5)	32 (33.0)	32 (43.2)	6 (22.2)	4.290	.117
Poor (6-21)	65 (67.0)	42 (56.8)	21 (77.8)		
DSM-5 diagnosis, n (%)					
None	91 (93.8)	59 (79.6)	20 (74.1)	10.434	.005
Yes	6 (6.2)	15 (20.3)	7 (25.9)		

[a]: Mean (standard deviation), BMI: Body mass index, IPAQ-SF: International Physical Activity Questionnaire- Short Form, WHO-QoL-BREF: World Health Organization Quality of Life-Short Form, BRIAN: Biological Rhythm Interview of Assesment in Neuropsychiatry, PSIQ: Pittsburg Sleep Quality Index

In all sample (n = 198), boy gender proportion were significantly higher ($\chi 2$ (2) = 12.763, p = .002) due to the fact that boys with tension-type headache was higher compared to the non-specific headache (33.8% vs. 11.3, $\chi 2$ (1) = 12.722, P<.001).

Three groups also similar with physical activity categories, WHO-QoL-BREF of physical, psychological, and social scores, BRIAN total and sub-scales, all PSQI total and subscales.

Daytime dysfunction were significantly higher in migraine group (F(2) = 4.209, p = .016). Environment and Environment-TR QoL scores were significantly lower in migraine group than that of tension-type headache or non-specific headache group (F(2) = 5.034, P = .007 and F(2) = 5.753, P = .004, respectively, see Table 1).

Psychiatric disorder was found in 6.2% of non-specific headache group, whereas this rate was 20.3% in adolescents with tension-type headache and 25.9% in migraine group ($\chi 2$ (2) = 10.434, p = .005). Comparison of psychiatric disorder among three groups revealed that migraine group had significantly higher rate psychiatric disorder compared to the healthy group (25.9% vs. 6.2%, $\chi 2$ (1) = 8.770, P = .003).

Circadian rhythm examination of the adolescents with headache revealed that biological rhythm scores based on BRIAN scale are significantly and negatively correlated with physical, psychological, social, environmental (both single and combined with national item scores). In addition, circadien rhythm scores was found to be positively correlated with sleep quality index scores (see Table 2).

Table 2. *Biorhythm profiles of adolescents with headache evaluated via BRIAN scale with others.*

	Physical QoL	**Psychological QoL**	**Environmental QoL**	**PSQI-T**
BRIAN-Total	-.335**	-.388**	-.257**	.448**
BRIAN-Sleep	-.270**	-.297**	NS	.346**
BRIAN-Activity	-.293**	-.301**	-.258**	.345**
BRIAN-Social	-.260**	-.311**	-.244**	.386**
BRIAN-Eating pattern	-.174*	-.253**	NS	.266**

QoL: Quality of life, PSQI-T: Pittsburg Sleep Quality Index

Discussion and Conclusion

Primary headaches are one of the debilitating disorders in adolescents in terms of quality of their life and their sleep quality. Physical inactivity and smoking are previously reported risk factors for primary headaches. In our sample, everyone in ten was active smoker and about a third was

physically inactive. These two factors, however, were found to be similar in primary headache group with healthy controls implying that physical inactivity and smoking are not likely to have a direct causative effect on headache.

Sleep quality is another factor effecting headache as previously shown by Bruni et al. (2008) in a total of 1073 non-clinical sample of children and adolescents[10]. Similar with physical inactivity, sleep quality scores obtained by PSQI scale were same in adolescents with primary headaches and healthy counterparts. Besides this, migraine had significantly deteriorated sleep quality compared to the tension type headache subjects or healthy adolescents. Adolescents with migraine also had lower environmental quality of life scores suggesting that there is an important relation between subjects with migraine and their environmental factors as a negative factor effecting adolescents' life daily.

As regards gender, girls are more likely to be with non-specific headache whereas boys are at risk primary headache especially for tension-type. Environment subscale of general quality of life is affected in tension-type headache and daytime dysfunction of sleep quality is significantly higher in migraine.

Last thing to mention is that psychiatric disorders was found in primary headache group in general and migraine group. This result might be explaining the outcome that adolescents with migraine are more affected by sleep quality index and subjective environmental quality of life evaluation.

There is one limitation for this study as this is a cross-sectional sample and because of this, findings could not be generalized. Nonetheless, this study is very first one examining circadian pattern of headache and its effect on whether there is a difference between having a primary headache or not

Conclusion:

In conclusion, circadian disfunctions are correlated with subjective lower quality of life and deteriorated sleep quality in adolescents with both primary headaches and healthy subjects. Other factors besides the primary headaches that have might an effect on these circadian factors as well as perceived quality of life or quality of life general worth examining whether they are likely to be a causative for these factors. Futher studies with larger samples are to be needed.

References

1. Lehmann S, Milde-Busch A, Straube A, von Kries R, Heinen F. How specific are risk factors for headache in adolescents? Results from a cross-sectional study in Germany. Neuropediatrics 2013; 44(1):46-54. doi: 10.1055/s-0032-1333432.

2. Headache Classification Committee of the International Headache Society (HIS). The International Classification of Headache Disorders. 3rd edition (beta version). Cephalalgia 2013; 33(9):629-808.

3. American Psychiatric Association (APA). Diagnostical and Statistical Manual of Psychiatric Disorders, Fifth Edition, Washington DC., 20134.

4. Saglam M, Arikan H, Savci S, Inal-Ince D, Bosnak-Guclu M, Karabulut E, et al. International physical activity questionnaire: reliability and validity of the Turkish version. Percept Mot Skills 2010; 111(1):278-284.

5. Eser E, Fidaner H, Fidaner C, Eser SY, Elbi H, Göker E. Psychometric properties of the WHOQOL-100 and WHOQOLBREF. J Psychiatry Psychol Psychopharmacol 1999; 7(2): 23-40.

6. Giglio LM, Magalhaes PV, Andreazza AC, Walz JC, Jakobson L, Rucci P, et al. Development and use of a biological rhythm interview. J Affect Disord 2009; 118:161-165.

7. Aydemir O, Akkaya C, Altınbaş K, Kora K, Sücüllüoğlu D, Akdeniz F, et al. Reliability, and validity of Turkish version of Biological Rhythms Interview of Assessment in Neuropsychiatry. Anatolian Journal of Psychiatry 2012; 13:256-261.

8. Buysse DJ, Reynolds CF, Monk TH. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989; 28:193- 213.

9. Agargun MY, Kara H, Anlar O. Pittsburgh Uyku Kalitesi İndeksi'nin Geçerliği ve Güvenirliği. Turk Psikiyatri Derg 1996; 7:107-11. [In Turkish]

10. Bruni O, Russo PM, Ferri R, Novelli L, Galli F, Guidetti V. Relationships between headache and sleep in a non-clinical population of children and adolescents. Sleep Med 2008; 9(5):542-548.

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CASE REPORT

Clinical and Trichoscopic Characteristics in a Case of Congenital Triangular Alopecia

Geliş Tarihi: 14.12.2020, Kabul Tarihi: 24.12.2020

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Abstract:

Congenital triangular alopecia (CTA) is a rare, asymptomatic, non-inflammatory and non-scarring form of alopecia with triangular, ovoid or lancet shape that is generally localized at frontotemporal region of scalp. It mostly appears at birth or within the first 9 years of age. Here, we presented a 9-months-old boy who had triangular-shaped, congenital alopecia involving the right fronto-temporo-parietal region and diagnosed as congenital triangular alopecia considering clinical and trichoscopic features that did not respond topical steroids and traditional treatment modalities. With this case, we wanted to remind how CTA is diagnosed in trichoscopic examination using a dermatoscope, accompanying symptoms and syndromes and treatment approaches in patients with CTA.

Keywords: *Congenital triangular alopecia, non-scarring alopecia, trichoscopic, dermatoscope*

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Introduction

Congenital triangular alopecia (CTA) is a rare disorder. It's a form of congenital, asymptomatic, non-inflammatory and non-scarring alopecia having a triangular, ovoid or lancet shape that is confined to the scalp. The lesion is often seen at the frontotemporal region of the scalp. The disease is also termed Brauer nevus. Its incidence is reported as 0.11% [1]. Its etiopathogenesis is unknown. Here, we aimed to present a case of congenital triangular alopecia and related trichoscopic findings.

Case Report

A 9-months-old boy presented to our outpatient clinic with a triangular, hair-free area at the scalp. In history, it was found out that the lesion was present since birth without enlargement in size and that hair in the area remained as thin hair without thickening. There was no history of trauma in the patient. It was also found out that the patient was treated with topical steroid ointment/lotion and traditional therapies (topical garlic administration) but did not respond. In dermatological examination, a triangular alopecia area was observed at the right fronto-temporo-parietal region (Figure 1). No erythema, induration or scarring was detected in the lesion area. In trichoscopy, terminal hair was seen in the areas surrounding alopecia area while vellus hair was observed in follicular ostia in the alopecia area (Figure 2). There was no yellow or black dot or dystrophic hair. Physical examination and development were normal. As parents declined biopsy, CTA was diagnosed by clinical and trichoscopic findings.

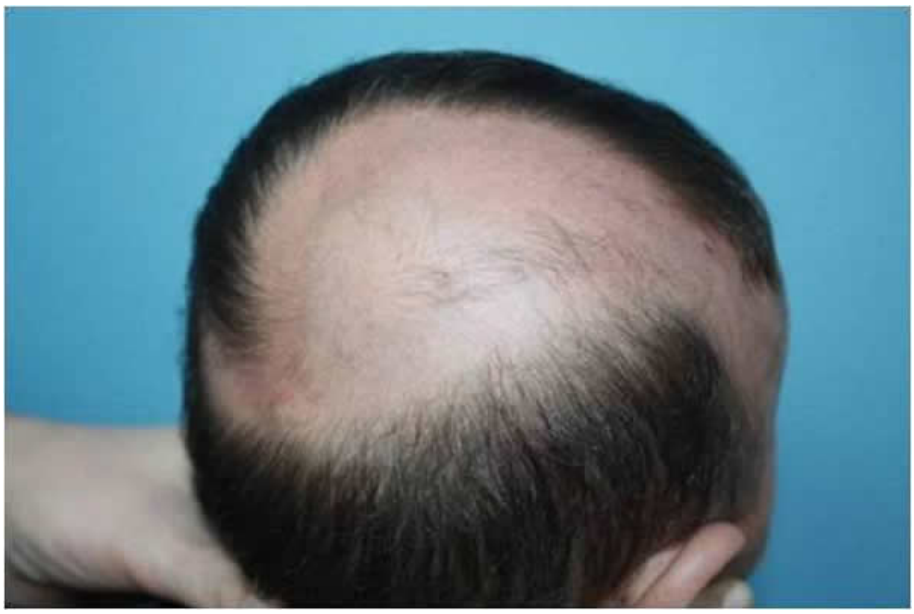

Figure 1. *A triangular, non-inflammatory, non-scarring alopecia in right fronto-temporo-parietal area at the scalp.*

Figure 2. *Vellus hair seen in normal follicular ostia in trichoscopic examination (Digital dermatoscope [Mole Max II] original magnification x20).*

Discussion

CTA generally appears at birth or within the first 9 years of life; however, there're cases of adult onset[2]. There's no gender preponderance. Although it is generally sporadic, there are reports of familial cases[3]. There are publications proposing that it's caused by a neuroectodermal disorder during embryonic period or suggesting that it is due to post-zygotic mutation and should be classified within epidermal nevus group[4]. There's localized miniaturization in follicles. However, the stimulus causing miniaturization is unknown[5].

Although it's typically localized at the frontotemporal region, it may be rarely seen at frontoparietal and occipital region. It's generally unilateral; however, it may also be bilateral[1]. The alopecia area is stable without progression and remains lifelong. There are no concurrent skin findings such as erythema, squamous changes, follicular pustules, discoloration or atrophy[4].

Trichoscopic examination using a hand-held polarized light dermatoscope or digital dermatoscope reveals short vellus hairs of varying length and white hairs in the normal follicular ostia in CTA[6, 7]. Vellus hairs are a non-specific but highly sensitive marker for CTA. In the interfollicular area, the presence of arborizing vessels and honeycomb pigment pattern has been reported as additional findings observed in some cases. The hair pull test is negative in CTA. Inui et al., proposed 4-item diagnostic criteria for CTA; i) triangular or lancet-shaped patch of alopecia on the frontotemporal scalp; (ii) vellus hairs surrounded by a normal terminal hair area with trichoscopically normal follicular openings; (iii) trichoscopically the lack of yellow dots, black dots, tapering hair, broken hair and loss of orifice; and (iv) persistence without significant hair growth for 6 months after

clinically or trichoscopically confirming the presence of vellus hair. It has been reported that using these diagnostic criteria, unnecessary biopsy from children with CTA can be prevented[7].

In histopathological examination, epidermis, dermis and total number of follicles are normal. However, terminal hair is replaced by vellus hair with miniaturization of follicles[2, 6]. Peribulbar inflammation is seen in alopecia areata which should be kept in mind in differential diagnosis while no inflammation is observed in congenital triangular alopecia[5].

In differential diagnosis, alopecia areata, alopecia mucinosa, tractional alopecia, trichotillomania, tinea capitis, primary cicatricial alopecia, aplasia cutis, androgenic alopecia, pressure alopecia and nevus sebaceous should be considered[1, 8].

CTA may be associated with syndromes such as phacomatosis pigmentovascularis, Klippel-Trenaunay syndrome, LEOPARD syndrome, Pai syndrome, Turner Syndrome[1, 9, 10]. In addition, in CTA, caf***é***-au-lait patches, multipl lentigines, mental retardation, epilepsy, Dandy-Walker malformation, spina bifida, cardiac, osseous and dental abnormalities, congenital dislocation of the hip, hydronephrosis, hypospadias, tracheo-oesophageal fistula, iris naevus, leuconychia, dysaesthesia within hairless areas can be found[1, 3, 9, 10].

CTA is an asymptomatic disease with a stable course, there's no effective treatment and in most cases therapeutic intervention is not required, unnecessary treatments such as steroids should be avoided. In the literature, cases with better cosmetic outcomes were reported following hair implant[8] and surgical resection[1]. Partial success has been reported with topical minoxidil[1, 5]. A patient who benefited from minoxidil treatment and experienced recurrence of alopecia after treatment discontinuation was reported. It has been suggested that minoxidil treatment may be effective by preventing follicle miniaturization in CTA[5]. We also started 2% topical minoxidil therapy in our patient.

With this case, we wanted to remind that it's easy to diagnose CTA with trichoscopic examination using a dermatoscope, patients with CTA should be examined in detail in terms of accompanying findings and syndromes, and steroids are not used in the treatment.

References

1. Li VCY, Yesudian PD. Congenital triangular alopecia. Int J Trichology. 2015; 7 (2): 48-53.
2. Trakimas CA, Sperling LC. Temporal triangular alopecia acquired in adulthood. J Am Acad Dermatol. 1999; 40: 842-844.
3. Ruggieri M, Rizzo R, Pavone P, Baieli S, Sorge G, Happle R. Temporal triangular alopecia in association with mental retardation and epilepsy in a mother and daughter. Arch Dermatol. 2000; 136: 426-427.

4. Patrizi A, Morrone P, Fiorentini C, Bianchi T. An additional familial case of temporal triangular alopecia. Pediatr Dermatol. 2001; 18: 263-264.
5. Bang CY, Byun JW, Kang MJ, et al. Successful treatment of temporal triangular alopecia with topical minoxidil. Ann Dermatol. 2013; 25: 387-388.
6. Karadag Kose O, Gulec AT. Temporal triangular alopecia: significance of trichoscopy in differential diagnosis. J Eur Acad Dermatol Venereol. 2015; 29 (8): 1621-1625.
7. Inui S, Nakajima T, Itami S. Temporal triangular alopecia: Trichoscopic diagnosis. J Dermatol. 2012; 39: 572-574.
8. Chung J, Sim JH, Gye J, et al. Successful hair transplantation for treatment of acquired temporal triangular alopecia. Dermatologic Surgery. 2012; 38 (8): 1404-1406.
9. Park SW, Choi YD, Wang HY. Congenital triangular alopecia in association with congenital heart diseases, bone and teeth abnormalities, multiple lentigines and caf***é*** -au lait patches. Int J Dermatol. 2004; 43: 366-367.
10. Gupta A, Khurana A, Malhotra P, Sardana K. Congenital triangular alopecia associated with Phakomatosis Pigmentovascularis Type II along with Klippel Trenaunay Syndrome. Indian Dermatol Online J. 2019; 11 (1): 91-93.

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CASE REPORT

Intrauterine Testiscular Torsion: A Case Report

Geliş Tarihi: 15.12.2020, Kabul Tarihi: 22.12.2020

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Abstract

Neonatal testicular torsion, especially intrauterine testicular torsion (IUTT) is so rare. In testicular torsion, hard testicular tissue is felt in physical examination. Doppler ultrasonography is a sensitive method in diagnosis. Testicle can be rescued in only 0-5% cases even with urgent surgery exploration in IUTT treatment. In this paper, a newborn case with IUTT, who was administered orchiectomy on the first day of life, is presented.

In the first examination of healthy term baby were detected big bilateral scrotums. The skin of right scrotum was darker than normal, hard mass in scrotum was felt. Right testicle was harder than contralateral testicle and placed higher. Paratesticular structures were not exactly distinguished. Other examination findings were normal. In scrotal doppler ultrasonography, right testicle was seemed heterogeneous with decreased parenchymal echo. There is no bloodstain in right testicle. The torsion was first considered and operated. Torsion was detwisted, orchiectomy was applied, fixation was applied to contralateral testicle. The patient was discharged on 2 day after the operation.

Testis torsions seen in postnatal period must be discussed even though they are admitted as surgically urgent due to the recovery of testis. The torsion cases being generally healthy, term and normal-weight babies decreases the risks.

Keywords: *Intrauterine testicular torsion, orchiectomy, testicular fixation, newborn, surgery.*

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Introduction

Neonatal testicular torsion, divided in two as those formed in intrauterine period and the ones that occur in post birth period, has a prevalence of 6,1/ 100000 [1], accounting for 10-12% of childhood testicular torsions [2]. Intrauterine torsion is, on the other hand, a rather rare condition and was first identified in 1897. Although its etiology has not been entirely enlightened, hyperactive cremasteric reflex, non- provision of sufficient in-utero fixation of tunica vaginalitis to scrotal wall, hard delivery, breech delivery, big baby, and multiple pregnancy are stated to be the factors carrying risk [3, 4]. Unlike intravaginal torsions seen in big child, it is generally of extravaginal character. Only 0-5% of the testicles torsioned before birth can be rescued [2]. Yet, it should be kept in mind that in cases with NTT, shortening of the time between diagnosis and operation is of vital significance in terms of rescuing the testicle [5, 6].

In this paper, a newborn on whom orchiectomy and contralateral testicle fixation was applied because of intrauterine testicular torsion was proposed, and the importance of carrying out a detailed genital organ examination at the first physical examination, urgent surgery operation and contralateral testicular fixation have been discussed.

Case

The first and fifth apgar scores of the baby, born in 38th week with C-section from the first pregnancy of the mother at the age of 25, were 8 and 9. There was not a different pathological follow-up report in the mother during pregnancy except for hypertension that came up in the period close to delivery. In the physical examination, baby's weight was 3070 g, height was 49 cm, head circumference was 34,2 cm and body temperature was 36 ºC. As seen in Picture 1 shot after the permission was taken by the family, his bilateral scrotums were big and in the left scrotum was hydrocele. Left testicle was 8x8mm. The skin of right scrotum was darker than normal and 15x15mm hard mass in the scrotum was felt (Figure 1). Right testicle was harder than the contralateral testicle and placed higher. Paratesticular structures were not exactly distinguished. Other physical examination findings were natural. In preoperative laboratory examination, complete blood count, blood glucose, blood gas, and liver and kidney functions were normal. In scrotal Doppler ultrasonography, it was detected that both testicles were in scrotum, right testicle was 9x14 mm, left testicle was 7x10mm. Parenchymal echogenity and bloodstain of left testicular was normal, and there was minimal fluid measuring 3,7mm in the left peritesticular region. Right testicular seemed heterogeneous with decreased parenchymal echo and there was anechoic cyctic

space (Figure 2). There was not bloodstain in the right testicular. In accordance with Doppler ultrasonography findings, torsion was first considered. In the patient operated at the fourth hour of his life, right spermatic cord was determined to make three complete turns. Torsion was detwisted and testicle was covered by gauge bandage with physiological saline solution, waiting for 25 minutes, but testicular bloodstain was observed not to recover (Figure 3). Hematoma and necrotic tissue was discharged from testicular capsule, and orchiectomy was applied and fixation was applied to contrlateral testicle. The patient on whom no complication was observed after the operation was discharged on the second day after the operation.

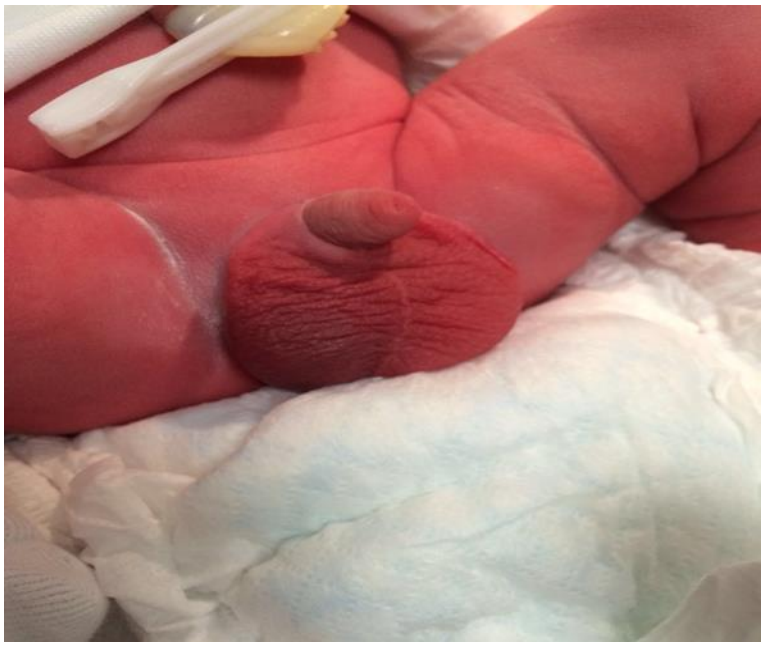

Figure 1. *Color change on the right scrotum skin*

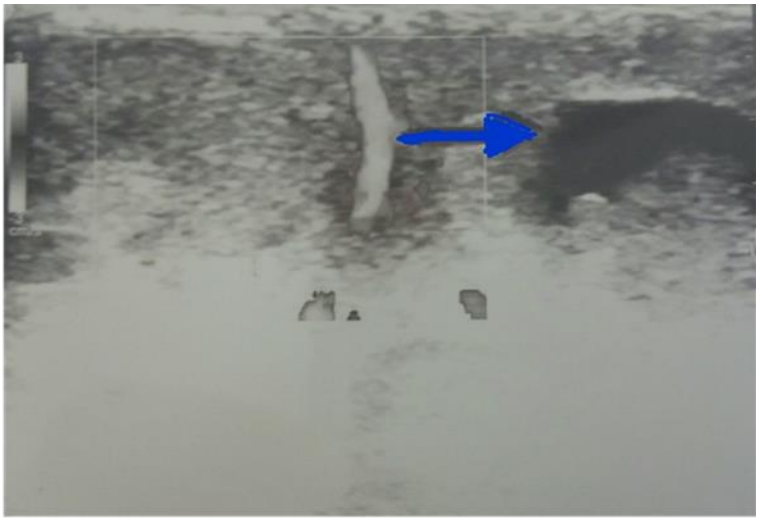

Figure 2. *Decreased heterogeneous appearance in the righ testicle parenchymal echo on ultrasonography and anechoic cyctic space (blue arrow) in the center.*

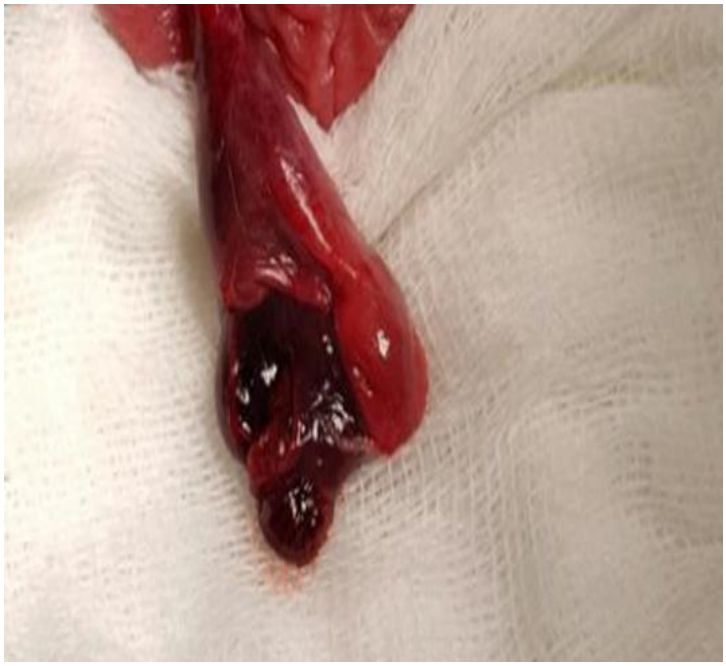

Figure 3. *The gross appearance of the testicle. Hemoragical and necrotic appearance of the outer skin draws attention.*

Discussion

72% of NTTs in literature is intrauterine and the rest have been diagnosed in the fist month [2, 3]. Our patient was accepted to be inutero testicle torsion because a mass in the testicle was found in the first examination after birth. Unlike intravaginal torsions seen in adolescents and adults, 2/3of newborn torsions are extravaginal [7]. In a review studying neonatal torsion cases, it is reported that 90,6% of them are extravaginal, 5,4% are intravaginal; 48% are on the left, 44% are on the right and 8% of them are bilateral [8]. In intravaginal torsion, the testicle twisted in tunica vaginalitis (bell clapper deformity) and this predisposing anomaly frequently exists in the other testicle. In extravaginal torsion, testicular and tunica structures twist together around spermatic cord axis. Finding spermatic cord in a spiral position during surgery supports this opinion [2]. Spiral cycles are generally in two turns and can go up to a complete turn [2]. This condition shows that bots testicles are under risk [2]. In our patient three complete turns were detected.

Etiology of IUTT has not been entirely enlightened, yet it has been stated that the situations increasing intrauterine stress such as hyperactive cremaster reflex, insufficient attachment of tunica vaginalitis on scrotum, hard delivery, breech delivery, big baby, and multiple pregnancy are factors creating risk [4, 9, 10, 11]. We did not find out any apparent risk factor. In a study made by

Kaye et al., vaginal delivery was also shown as a risk factor and 90%of the cases were born through vaginal delivery [2]. Counterlateral hyrocele is often determined in IUTT cases [3]. This can be a reactional situation depending on ischemic attacks caused by torsions as they can be coincidental phenomena [7]. In 11 case-series by Al-salem [5], counterlateral hyrdocele determined in 6 cases (60%) was present in our patient as well.

Doppler ultrasonography is a sensitive method in diagnosis. Although there can be enlarged, heterogeneous-avascular normal volume testicle on ultrasonography, small hyperecogenic testicle can be seen [12]. The existence of enlarged testis makes us think that it developed previously in two conditions in which torsion is more acute. It can be indicated that the bloodstaining of testis gets reduced with nuclear scintigrapy [2, 13]; yet, the sensitivity of scintigraphy is remarkably low during the first age [1].

There is no agreement on pathophysiology of testis torsion, necessity and timing of surgery and management of contralateral testis. Immediate or late scrotal exploration can be made by doing or without doing orchiectomy; in addition, "contralateral" orchiopexy can be made or is not made. Leaving necrotic testis in its place in unilateral torsion can damage contralateral testis through antisperm antibody reproduction theoretically[2].

Testis torsions seen in postnatal period must be discussed even though they are admitted as surgically urgent due to the recovery of testis. Although there can be general risks depending on anesthesia, torsion cases being generally healthy, term and normal-weight babies decreases the risks. Early surgery enables exploration diagnosis to be clarified and other rare reasons. (benign and malign tumors, hematocele) to be excluded [5]. However, in bilateral torsion, urgent surgery is advised for the purpose of preserving the rest healthy testis tissue [2].

Unfortunately, testis cannot be recovered in most of the cases even with proper surgical exploration [1]. Intrauterine testicular torsion can take place in the period close to delivery or during the delivery. For this reason, testis tissue can be recovered even though it is intrauterine torsioned. Al-salem [5] stated that, in his series of 11 cases, three torsioned testicles can be preserved through urgent surgical operation. Olguner et al. [6] sai that they applied urgent surgery on their patients, who came with postnatal right scrotal swelling at the 28th hour and on whom they determined bilateral hypoperfusion on technetium 99m pertechnetate scintigraphy, and rescued non-necrotic testis by detorsioning it. In a review, it was stated that the rescue rate of testis was 8,96% in newborn testis

torsions but this rate rose up to 21,7% in those applied urgent surgeries [8].

Three ways to follow as a general strategy are not operating contralateral, retarded orchiopexy or making orchiopexy in urgent conditions [14]. Considering the fact that insufficient attachment of tunica vaginalitis to scrotum causes extravaginal torsion, the first 1-2 month period in which this attachment can be ensured is risky in terms of torsion [3, 15]. Bilateral torsion is rare but triggering factors have come to be emphasized with the recently increasing case reports. Therefore, it is common to apply fixation on the healthy side in order to prevent bilateral testis loss [2, 5]. In our case unilateral orchiectomy and contralateral fixation was applied.

Because testis has a chance of being rescued, even though little, newborn testis torsion must be kept in mind in the distinguishing diagnosis of newborn scrotal masses, and genital organ examination must be made carefully without any retard. Also, there is need for studies revealing whether there is any damage in solitary testis in adolescence or adulthood in the children left with single testis after torsion.

References

1. John CM, Kooner G, Mathew DE, Ahmed S, Kenny SE. Neonatal testicular torsion-a lost cause? Acta Paediatr 2008; 97: 502.
2. Kaye JD, Levitt SB, Friedman SC, Fronca I, Gitlin J, Palmer LS. Neonatal torsion: a 14-year experience and proposed algorithm for management. J Urol 2008; 179: 2377-2382.
3. Djahangirian O, Ouimet A, Saint-Vil D.Timing and surgical management of neonatal testicular tortions. J Pediatr Surg 2010; 45: 1012-1015.
4. Brandt MT, Sheldon CA, Wacksman J, Matthews P. Prenetal testiculartorsion: principles of management. J Urol 1992; 147: 670.
5. Al-Salem AH. Intrauterine testicular torsion: a surgical emergency. J Pedia Surg 2007; 42: 1887-1891.
6. - Olguner M, Akgur FM, Aktuğ T, Derebek E. Bilateral asnynchronous perinatal testicular torsion: a case report. j pediatr Surg 2000; 35: 1348-1349.
7. Serdaroğlu E, Takcı Ş, User R, Güçer Ş, Yiğit Ş, Yurdakök M. İntrauterin testis torsiyonu: Bir vaka takdimi. Çoçuk Sağlığı ve Hastalıkları Dergisi 2011; 54: 223-226.
8. Nandi B, Murphy FL. Neonatal testicular torsion : a systematic literature review. Pediadr Surg Int 2011; 27: 1037-1040.
9. Celik FC, Aygun C , Aycicek T. et al. A newborn with antenatal testis tortion: Turk Pediatri Ars 2014; 49: 254-256
10. Harper L, Gatibelza ME, Michel JL, et al. The return of the solitary testis. J Pediatr Urol 2011; 7: 534-537.

11. Baglaj M, Carachi R. Neonatal bilateral testicular torsion : a plea for emergency exploration. JUrol 2007; 177: 2296-2299.
12. Traubici J, Daneman A, Navarro O, Mohanta A, Garcia C. Original report. Testicular torsion in neonates and infants: sonographic features in 30 patients. ARJ Am J Roentgenol 2003; 180: 1143.
13. Driver CP, Losty PD. Neonatal testicular torsion. Br j Urol 1998; 82: 855.
14. Roth CC, Mingin GC, Ortenberg J. Salvage of bilateral asynchronous perinatal testicular torsion. J Urol 2011; 185: 2464-2468.
15. Guerra LA, Wiesenthal J, Pike J, et al. Management of neonatal testicular torsion: which way to turn? Can Urol Assoc J 2008; 2: 376-379.

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CASE REPORT

Restoration of Anterior Tooth Fractures Using Silicone Key Method: 3 Case Report

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Abstract: *The most important problem encountered after dental caries is undoubtedly injuries to primary and permanent teeth. Trauma affecting the oral cavity can affect the soft tissues of the lips, cheeks, tongue and floor of the mouth and the structures that form the temporomandibular joint. Luxation injuries are the most common traumatic tooth injury in primary dentition, while crown fractures are more frequently reported in permanent teeth. Traumas cause functional and aesthetic problems in the patient, and this aesthetics, making an ideal restoration to prevent loss of function is extremely important for the patient's psychology. Composite restorations provide conservative solutions in young individuals compared to veneer or other prosthetic restorations. Although composite restorations of permanent incisors with crown fractures are not seen as complicated cases, attention should be paid to the tooth contours that will facilitate function and aesthetics. In this study, restoration of three clinical cases with crown fracture by direct composite resin applications is described.*

***Key words**: Silicone key method, tooth fractures, composite resin*

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Introduction

The most important factor that causes the loss of dental tissue after caries is trauma (1). Although dental traumas are frequently seen in humans, they constitute 5% of all injuries that require treatment (2). Among the most common causes of dental trauma are falling in the preschool period, fighting during puberty and traffic accidents, and sports activities in adolescence (1). The teeth most affected by these traumas are the maxillary incisors due to the protrusive positioning of the teeth (3). While crown fractures are the most common traumatic dental injury in permanent teeth, luxation injuries are more common in primary teeth (2). Injuries caused by dental traumas vary from enamel cracks to maxillofacial fractures. There are different treatment alternatives for the rehabilitation of these injuries (4, 5). When deciding on the treatment procedure, many factors such as the root development status of the traumatized tooth, the age of the patient, the time after the trauma, the degree of displacement or mobility, and whether the fracture line includes pulp should be evaluated together (6, 7).

There are many indirect and direct treatment options for anterior tooth crown fractures, both prosthetically and conservatively. Composite resin restorations (direct and indirect) are thought to be the best option for these treatments because they are applied with the principle of minimal tooth tissue removal (8). It can be applied using methods such as direct composite resin restorations, transparent matrix bands, ready-made strip crowns and free modeling technique (9). Although the use of transparent tape is considered to be a simple and fast technique, obtaining an anatomical form is quite difficult, and more time is required for finishing and polishing (10). Strip crown method; It is a form of restoration made through ready-made transparent crowns. The disadvantage of this method is that the anatomical form cannot be fully formed and sufficient contact cannot be provided with the adjacent tooth depending on the thickness of the strip crown (10). Free modeling technique is a form of restoration where composite resin is applied as layering and no matrix system is used. However, in order to achieve an ideal restoration in this application, good hand manipulation and many applications are required. In order to facilitate this method of application and make it more applicable, it has been suggested to use the silicone guide technique, in which the palatal contour can be obtained by mock-up method (10, 11). It is possible to obtain the color harmony and contour of the restoration as close to nature by using the incremental method through the special matrix impression obtained from silicon (9).

The aim of this case report is to describe the rehabilitation of an uncomplicated crown fracture with direct composite restoration using a silicone key.

Case Reports

Case 1: A 19-year-old female patient applied to the Dicle University Faculty of Dentistry Restorative Dentistry Department, five days after the trauma she suffered due to a crown fracture. It was learned in the medical history of the patient that she did not have any systemic disease and her primary complaint was the impaired aesthetic appearance of her tooth in the area exposed to trauma. No findings were found in the soft tissues in the external examination. In the oral examination, fractures were found in the left upper central and lateral teeth (Figure 1a). It was determined that the relevant tooth was vital, not sensitive to percussion and palpation, and was not mobile. No periapical pathology, root fracture or alveolar fracture was detected in the radiological examination. The patient was offered ceramic laminate veneer, porcelain crown, and indirect composite resin restoration treatment alternatives. However, due to the patient's socioeconomic status and her desire to be treated in a short time, it was decided to be restored using direct composite resin. It was explained that we could apply the treatment to the patient with the help of a silicone key in order to provide a better aesthetic appearance and harmonize shape and contact formation of the fracture tooth with the symmetrical tooth in the arch.

After the consent of the patient, impression was taken from the patient's upper jaw with silicone impression material and a plaster model was obtained. On the plaster model, the fracture tooth was restored, it was adapted to the adjacent teeth, and a silicone key was obtained by measuring on the plaster. Before starting the treatment, composites of different shades were placed in the middle third of the central tooth and polymerized using the button technique. After choosing the appropriate composite color, isolation was provided with a rubber dam. The carious areas at the interface of the upper right and upper left central teeth of the patient were cleaned and restoration was planned together with the fractured area. Minimally invasive beveling was performed. Etching was done with 37% orthophosphoric 8acid (Scotchbond; 3M ESPE, USA) and teeth were isolated from acid with teflon tape. After the universal adhesive agent (3M ESPE, Single Bond Universal, Germany) was applied, a thin layer of A2E (Enamel) composite resin (3M Filtek Ultimate, USA) was placed on the silicon key to form a palatal wall, placed on the tooth and polymerized (Figure 1b). Restoration was performed using dentine layering with medium A2B (Body) (3M Filtek Ultimate, USA) color to imitate natural tooth tissues, and A2E for enamel layering. Temporary surface macro-morphology was drawn on the surface of each tooth and surface macro texture was created using a yellow banded diamond bur at low speed and dry conditions. Interdental polishing was done with interface abrasives of different grades from thick to thin (Epitex, GC, Japan). Marginal

roundings and line angles were created using polishing discs in different grades from thick to thinest (Sof-Lex, 3M ESPE, USA). The surfaces were roughly polished with a spiral, rubber polishing disc. Surface micro-texture was created with a red banded diamond bur at very low speed, in one direction and in dry conditions. The rubber dam was removed and occlusal relationships were checked (Figure 1c). It was found that the treatment result was satisfactory for both the patient and the physician.

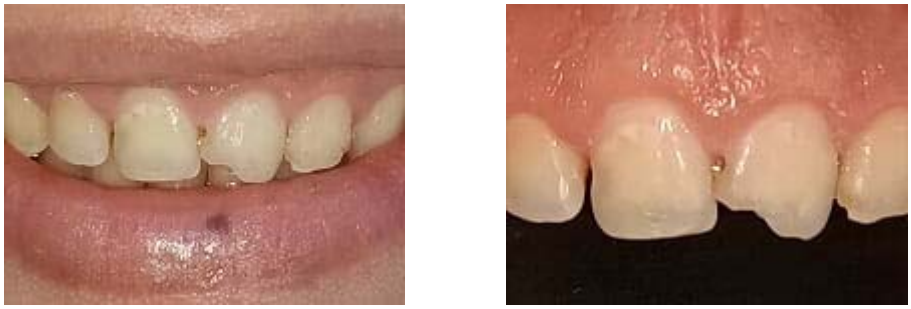

Figure 1a: Intraoral view of Case 1 before treatment

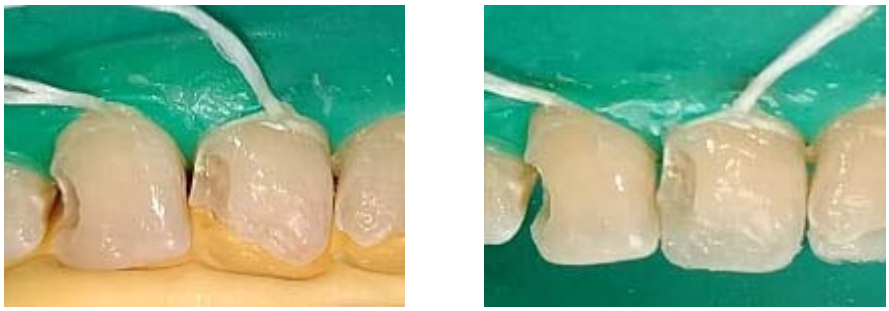

Figure 1b: Placing a silicone key and forming a palatinal wall (Case 1)

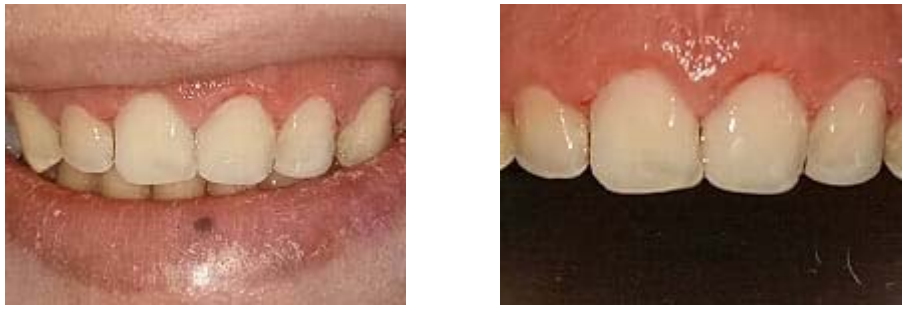

Figure 1c: Intraoral view of Case 1 after treatment

Case 2: A 20-year-old male patient applied to Dicle University Faculty of Dentistry Restorative Dentistry department for a crown fracture one week after his trauma. It was learned in the medical history of the patient that he did not have any systemic disease and his primary complaint was the impaired aesthetic appearance of his tooth in the area exposed to trauma. No findings were found in the soft tissues in the external examination. In the oral examination, fractures were found in the upper central teeth (Figure 2a). It was determined that the relevant tooth was vital, not sensitive to

percussion and palpation, and was not mobile. No periapical pathology, root fracture or alveolar fracture was detected in the radiological examination. Treatment options in Case 1 were presented to the patient. However, due to the patient's socioeconomic status and his desire to be treated in a short time, it was decided to be restored using direct composite resin. It was explained that we could apply the treatment to the patient with the help of a silicone key in order to provide a better aesthetic appearance and the compatibility of the fracture tooth with the symmetrical tooth in the arch (shape harmony and contact formation). The closure of the diastema was not included in the restoration planning because the patient thought it gave a natural appearance and did not approve of the treatment. After patient consent, the silicone key was obtained as described in Case 1. Before starting the treatment, composites of different shades were placed in the middle third of the central tooth and polymerized using the button technique. After choosing the appropriate composite color, isolation was provided with a rubber dam. The color of the composite resin used, treatment stages, finishing and polishing procedures were performed as described in Case 1 (Figure 2b). The rubber dam was removed and occlusal relationships were checked (Figure 2c). It was found that the treatment result was satisfactory for both the patient and the physician.

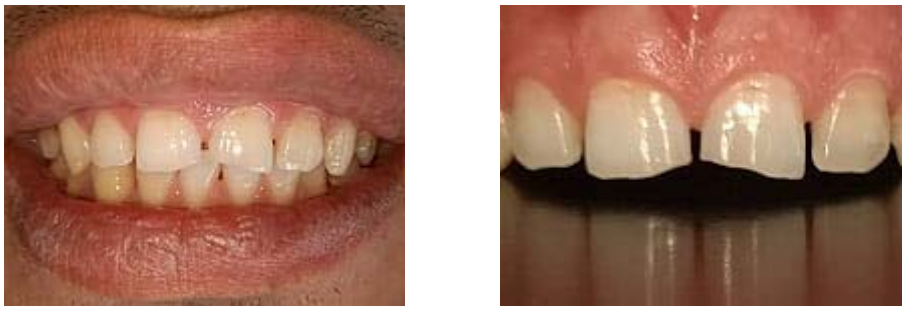

Figure 2a: Intraoral view of Case 2 before treatment

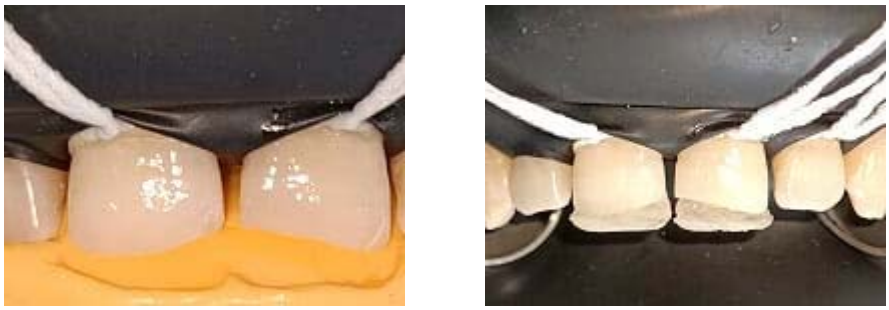

Figure 2b: Silicon key placement and creation of palatinal wall (Case 2)

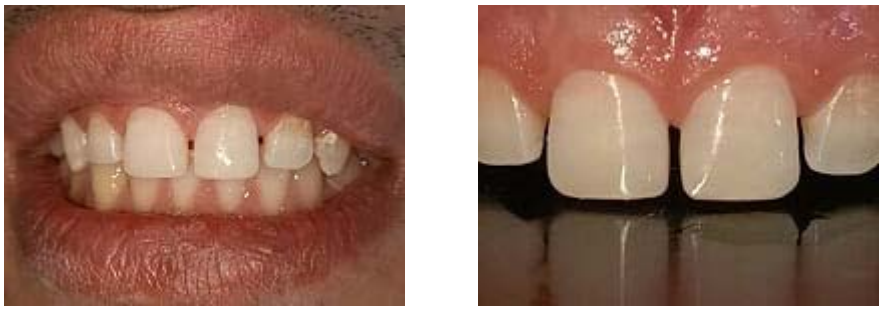

Figure 2c: Intraoral view of Case 2 after treatment

Case 3: A 23-year-old female patient applied to Dicle University Faculty of Dentistry Restorative Dentistry department for a crown fracture one week after the trauma. It was learned in the medical history of the patient that she did not have any systemic disease and her primary complaint was the impaired aesthetic appearance of her tooth in the area exposed to trauma. No findings were found in the soft tissues in the external examination. In the oral examination, a fracture was found in the right upper central tooth (Figure 3a). It was determined that the relevant tooth was vital, not sensitive to percussion and palpation, and was not mobile. No periapical pathology, root fracture or alveolar fracture was detected in the radiological examination. Treatment options in Case 1 were presented to the patient. However, due to the patient's socioeconomic status and her desire to be treated in a short time, it was decided to be restored using direct composite resin. With the consent of the patient; While planning the restoration of the tooth, an acceptable gap was left between the teeth due to the possibility that the mesiodistal size being wider than normal may adversely affect the appearance and the metal-supported porcelain crown in the adjacent tooth could not be changed. It was explained that we could apply the treatment to the patient with the help of a silicone key in order to provide a better aesthetic appearance and harmonize shape and contact formation of the fracture tooth with the symmetrical tooth in the arch. After patient consent, the silicone key was obtained as described in Case 1. Before starting the treatment, composites of different shades were placed in the middle third of the central tooth and polymerized using the button technique. After choosing the appropriate composite color, isolation was provided with a rubber dam. The color of the composite resin used, treatment stages, finishing and polishing procedures were performed as described in Case 1 (Figure 3b). The rubber dam was removed and occlusal relationships were checked (Figure 3c). It was found that the treatment result was satisfactory for both the patient and the physician.

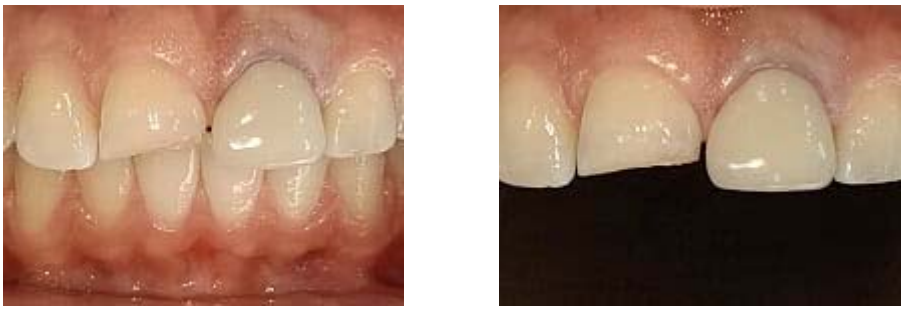

Figure 3a: Intraoral view of Case 3 before treatment

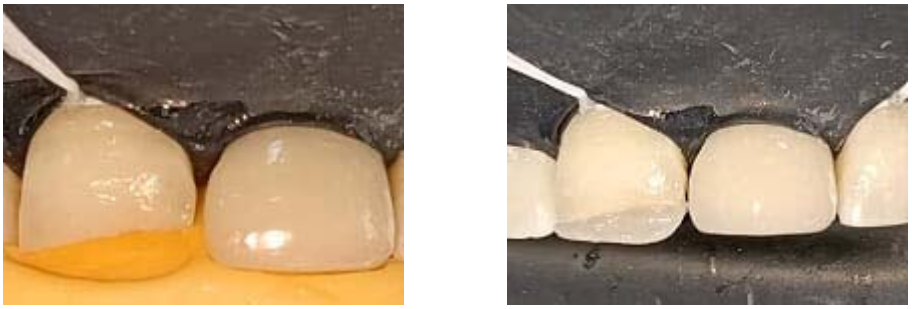

Figure 3b: Silicon key placement and creation of palatinal wall (Case 3)

Figure 3c: Intraoral view of Case 3 after treatment

Discussion

Any trauma that affects the head and face can cause various damage to the teeth and their supporting tissues. The severity of the trauma and the type of injury determine the degree of harm (12). Dental traumas mostly affect the upper middle incisors and this is followed by the upper lateral incisors. Luxation and crown fracture are more common types of dental trauma. While crown fractures are frequently observed in the 11-14 age range, luxation is observed in the 7-10 age range (13).

In crown fractures, the type of treatment and the prognosis afterwards depend on the amount of fracture and the amount of dental tissue it contains. The prognosis of crown fractures that do not involve pulp opening depends primarily on the condition of the periodontal ligament and the surface area of the opened dentin (14). In a study conducted on the prognosis of enamel dentin crown fractures, it was reported that 99% of the tooth was vital in these fractures without luxation injury,

and there was canal obliteration in 1% and no necrosis (15). Different treatment methods can be applied in uncomplicated crown fractures. The choice of treatment method depends on the location of the fracture line. Treatment of uncomplicated crown fractures can be restored prosthetically or conservatively. Many types of treatment have been used in uncomplicated crown fractures until today. In conservative treatment methods, if the pulp is not exposed, the farcture piece can be placed or if there is no farcture piece, direct restoration can be done with composite resins of the appropriate color (16). If it contains 2/3 or more of the fracture crown, it is recommended that the restoration be restored with radical support with a post (17). Restoration with composite resin is a conservative treatment method that replaces the lost tissue without touching the healthy tooth tissue. The use of current composite resins with the incremental method enables the creation of all surface properties of the tooth (18).

In the incremental method, it is easier to create the shape and contour of the tooth and to harmonize the color with the use of silicone keys. Although the time spent for silicone guides seems to be a disadvantage, the color harmony and contour of the restoration can be obtained as close to nature (9).

Porcelain crowns are another treatment option for crown fractures, depending on the location of the fracture and the amount of missing teeth. Today, it has become easier to make with CAD / CAM technology. However, the disadvantages include the difficulty of repair, the inability to change color after bonding, and the inability to polish easily such as composite filling materials when their brightness is lost (19).

Conclusion

Long-term clinical and radiological follow-up is important in terms of early diagnosis of dental injuries in the form of crown fractures in teeth, application of the correct treatment procedure and possible complications that may occur. Direct composite restorations are a type of treatment with lower cost compared to prosthetic treatments and providing patient satisfaction in terms of functionality and aesthetics. In these cases, it has shown that composite resin restorations can be a simple and effective procedure for the treatment of anterior traumatized teeth with promising aesthetic and functional results.

References

1. Yanıkoğlu N, Bayındır F. Restorative materials used in post-core production and their properties. Atatürk University Faculty of Dentistry Journal 2003-2004;13-14:39-47.

2. Andreasen JO, Andreasen FM, Andersson L. Textbook and color atlas of traumatic injuries to the teeth, 4th edn. Oxford, UK: Wiley-Blackwell; 2007.

3. Dündar A, Öztürk B. Five-Year Follow-up of Complicated Crown Fracture Treatment. Turkey Clinics J Dental Sci Cases 2015;1(4):276-80.

4. Ünlü N, Karabekiroğlu S, Tunçdemir MT. Treatment Methods Applied in Crown Fractures in Traumatized Teeth. Turkey Clinics J Dental Sci-Special Topics 2014;5(2):35-40.

5. Yaşa E, Yaşa B, Yıldızeli D, Aral CA. Rehabilitation of traumatized teeth with a multidisciplinary approach in an adolescent patient: a case report. Selcuk Dent J, 2016; 3: 27-33.

6. Robertson A, Andreasen FM, Andreasen JO, Noren JG. Long Long-term prognosis of crown-fractured permanent incisors. The effect of stage of root development and associated luxation injury. Int J Paediatric Dent 2000;10:191-199.

7. Öktem ZB, Özer L. Vital Pulp Treatment in Complicated Crown Fractures: A Case Report. ADO Clinical Sciences Journal Volume: 3, Issue: 2, 2009 Pages: 380-384.

8. Korkut B, Yanıkoglu F, Tağtekin D. Aesthetic Approaches to Defects in the Anterior Region with Direct Composite Resin Restorations: 3 Case Reports. J Dent Fac Atatürk Uni , Supplement: 6, Year: 2012, page :7-15.

9. Felippe LA, Monteiro S Jr, De Andrada CA, Ritter AV. Clinical strategies for success in proximoincisal composite restorations. Part II: Composite application technique. J Esthet Restor Dent. 2005; 17: 11-21.

10. Croll TP, Bullock GA. Bonded resin-based composite crown restoration of diminutive lateral incisors. Comp Contin Educ Dent. 2002; 23: 550-559.

11. Vanini L. Light and color in anterior composite restorations. Pract Periodontics Aesthet Dent. 1996; 8: 673–682.

12. Flores, MT; Andersson, L; Guidelines for the management of traumatic dental injuries. III. Primary teeth. Dental Traumatology, 2007, 23, 196-202.

13. Ünal M, Tugut F, Demir H. Three-Year Follow-up of Traumatic Complicated Crown Fracture and Lateral Luxation Treatment: Case Report. Ataturk Univ. Dentist. Fak. Journal. Volume: 23, Issue: 3, Year: 2013, Page: 380-384.

14. Uslu G, Özyürek T, Kocak İ. Multidisciplinary Treatment of Teeth with Crown Root Fracture. Turkey Clinics J Dental Sci Cases 2016;2(1):31-4.

15. Pala K, Doğan S, Er O. Apexification Treatment of Young Permanent Tooth with Traumatic Complicated Crown Fracture: Case Report. Journal of Health Sciences 20(2) 150-154, 2011.

16. Pusman E, Cehreli ZC, Altay N, Unver B. Fracture resistance of tooth fragment reattachment: effects of different preparation techniques and adhesive materials Dent Traumatol. 2010;26:9–15.

17. Özkanoğlu S, Akın EGG, Hubbezoğlu İ. Fiber Post Supported Composite Restoration in a Case of Complicated Crown Fracture: A Case Report. Cumhuriyet Dental Journal: 2018; 21(3)

18. Santos GC Jr, Santos MJ Jr, Rizkalla AS, Madani DA, El-Mowafy O. Overview of CEREC CAD/CAM chairside system. Gen Dent. 2013;61(1):36-41.

19. Demir F, Oktay EA, Karaoğlanoğlu S , Aydın N, Toksoy Topçu F , Bilgeç E. Aesthetic Smile With Direct Composite Resin Lamina Restorations: Two Case Reports. Ankara Med J, 2018;(2):246-53