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Editorial

The Journal of Experimental Medicine provides numerous scientific reports to its readers for nearly 39 years. The main objective of the journal has published high quality works without interruption; I regret to inform you that the publication process of the journal had been delayed for a short period of time due to some technical problems. With the happiness of taking over again, I would like to give good news to our readers that publication process starts again with this issue. My sincere gratitude to all authors who submitted their nice and high quality work for publication in the journal, and thanks to the reviewers of journal for their contributions during evaluation processes and thanks to technical staff of the journal and also thanks to the dean of medical faculty for his unlimited support to the journal.

Suleyman Kaplan, PhD
Editor in Chief

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Clinical Research

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Association of gamma-glutamyl transpherase activity with electrocardiographic indicators in coronary artery disease patients

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ABSTRACT

Gamma-glutamyl transpherase (GGT) plays an important role in atherogenesis through its activity in oxidative processes, which has been demonstrated in clinical studies. The connection between serum GGT activity and noninvasive arrhythmia indicators in patients with coronary artery disease (CAD) is investigated in the present study. We examined patients (n = 254, 174 males, mean age 62 ± 8) diagnosed with coronary artery disease on the basis of clinical and angiographic findings. All patient data were assessed, including serum GGT activity, biochemical measurements, and demographic and electrocardiographic features. A positive correlation was found between GGT levels and P-wave dispersion ($r = 0.299$, $p < 0.0001$); however, there was a negative correlation between GGT and ejection fraction ($r = 0.216$, $p < 0.001$). On the other hand, no correlation was found between GGT and the following: Sokolow-Lyon voltage, Cornell voltage, Cornell product, corrected QT, and QT dispersion (p values are 0.728, 0.892, 0.551, 0.069, and 0.146, respectively). When the patients were grouped according to gender, a significant association of GGT with P-wave dispersion and ejection fraction was observed in both of the groups. Nonetheless, a significant correlation between GGT and QTc was only found in the female group. In this study, we found that increased GGT activity was correlated with P-wave dispersion. These results indicate that there might be an increased risk of arrhythmias especially the atrial fibrillation in this patient population.

1. Introduction

Gamma-glutamyl transpherase (GGT) is a common test that is used as a liver function indicator and plays an important role in antioxidant defense systems. The main function of GGT is to provide intracellular support for glutathione precursors, which work as intracellular antioxidants, and to catalyze the first step in the degradation of GSH (Whitfield, 2001). The results of clinical studies on individuals with coronary artery disease (CAD) show that GGT activity is directly associated with the oxidative process that contributes to atheromatous plaque formation (Lee et al., 2004; Paolicchi et al., 2004; Emdin et al., 2005; Ulus et al., 2007; Bradley et al., 2014; Kunutsor et al., 2014). GGT appears to be a strong predictor of acute coronary events aside from cardiovascular risk factors (Paolicchi et al., 2004; Ulus et al., 2007; Bradley et al., 2014; Kunutsor et al., 2014).

Apart from coronary artery disease, arrhythmias, especially atrial fibrillation, are frequently seen in clinical practice and cause deterioration in quality of life, morbidity, and mortality.

The risk of arrhythmia can be decreased by various treatment options in patients showing increased risk factors.

In the present study, the association of serum GGT activity with electrocardiographic data was investigated in the CAD population.

2. Material and methods

Patient selection

Data from randomly selected patients who had diagnostic coronary angiography at our institution were analyzed. A total of 254 patients with angiographically diagnosed CAD were included in the study. The clinical presentation was acute coronary syndromes (ACS) in 170 patients. Forty percent (n=68) of patients with ACS were diagnosed as unstable angina (UA), whereas others (60%, n=102) were diagnosed as acute myocardial infarction (MI; all of them were non-ST elevation MI). We performed coronary angiography in 84 patients because of suspected coronary artery disease (exercise stress test and thallium scintigraphy were positive in 60 and 24 patients, respectively). Patients with other cardiac diseases (valvular heart disease, atrial fibrillation, congenital heart disease and aortic aneurysm) who underwent coronary angiography were not included in the study.

CAD was diagnosed via an angiogram and detection of at least 50% stenosis in epicardial coronary arteries or their major branches was considered as CAD. The exclusion criteria for the study were as follows: a history of liver disease, chronic alcohol use, bundle branch block, the presence of a permanent pacemaker, preexcitation syndrome, antiarrhythmic medication use, interventricular and intraventricular conduction delays, and the presence of angina symptoms during recording. Patients with blood pressure in excess of 140/90 mmHg or receiving antihypertensive treatment were considered hypertensive. Likewise, patients with a history of diabetes mellitus, antidiabetic medication use, or a fasting blood glucose level of 126 mg/dl or more were considered diabetic. Prior to every procedure, signed consent was obtained from all of the patients.

GGT measurement

Serum GGT levels were measured at 37 °C by means of an enzymatic calorimetric test using a Roche/Hitachi analyzer. L-gamma-glutamyl-3-carboxy-4-nitroanilide was used as substrate (Mannheim, Germany) (Persijn and van der Slik, 1976). In our laboratory, the normal reference value of the GGT level for a healthy individual was 7-49 U/l.

Electrocardiographic evaluation

All of the patients had a 12-lead resting ECG in a supine position recorded using an analog system. The recording rate was 50 mm/sec with a 10mm/mV gain. The measurements were obtained using a millimetric ruler by an investigator who was unaware of the patient data (The CSE Working Party, 1985). All parameters were measured in all leads and for two consecutive cycles, and the average value was taken for each lead. Sokolow-Lyon voltage (SLV) was calculated as the sum of the S-wave voltage in the V1 or V2 leads and the R-wave voltage in V5 or V6 (the higher of the two) (Sokolow and Lyon 1949). Cornell voltage (CV) was measured in millimeters as the sum of the R-wave voltage in the aVL lead and the S-wave voltage in the V3 lead. Cornell product (CP) was calculated by multiplying the duration of QRS and CV (millimeter x millisecond) (Molloy et al., 1992).

The beginning of the P-wave was considered as the joint between the isoelectric line and first prominent upward or downward incline of the trace. The return of the trace to the isoelectric line was defined to be the end of the P-wave. The difference between the longest and shortest P-waves was defined as P-wave dispersion (PWD).

QT interval was obtained through manual measurement of the time between the beginning of the QRS complex and the point of return to the isoelectric line (the end of the T-wave) in milliseconds. Corrected QT (QTc) was obtained by correcting the QT interval based on the patient's heart rate (QT interval / $\sqrt{}$ (RR interval)). QT dispersion (QTd) was defined as the difference between the longest and the shortest QT in each derivation.

Echocardiography

Echocardiographic evaluation was done in the left lateral decubitus position (Vingmed System V, Horten, Norway). The measurements of the left ventricle diameter, wall thickness, and ejection fraction (EF) were obtained according to the device manual (Cheitlin et al., 1997).

Coronary Angiography

Coronary angiographies were carried out using Siemens Axiom Artis (Munich, Germany) digital angiography equipment. Selective coronary angiography was performed via the right femoral artery by using the Judkins technique. Coronary arteries were imaged by utilizing right and left anterior oblique views with cranial and caudal positions. At least 50% stenosis in epicardial coronary arteries or their major branches was defined as CAD. Coronary angiographies were evaluated and reported by at least two experienced cardiologists who did not have information about the study.

Statistical analysis

Continuous variables were expressed as mean ± SD. The

distribution of continuous variables for normality was tested using the Kolmogorov-Smirnov test. Logarithmic conversion was performed for non-normally distributed variables based on this evaluation. The groups were compared using the Student t test, while the Pearson test was used to evaluate the association between the constant variables. The indicators of GGT activity were investigated using an analysis of multi-variable regression. A p value less than 0.05 was considered statistically significant.

Reproducibility analysis was performed for intra-observer and inter- observer variability at electrocardiographic measurements (Sokolow-Lyon voltage, Cornell voltage, Cornell product, Corrected QT, QT dispersion, P-wave dispersion) and ejection fraction.

3. Results

A total of 254 patients (174 males, mean age 62 ± 8 years) with angiographically diagnosed CAD were included in the present study. The risk factors for coronary artery disease were diabetes in 76 (29.9%) patients, hypertension in 123 (48.4%) patients, and smoking in 121 (47.6%) patients.

A positive correlation was found between GGT levels and PWD ($r = 0.299$, $p < 0.0001$); however, there was a negative correlation between GGT and EF ($r = 0.216$, $p < 0.001$). On the other hand, no correlation was found between GGT and the following: SLV, CV, CP, QTc, and QTd (p values are 0.728, 0.892, 0.551, 0.069, and 0.146, respectively).

When the patients were grouped according to gender, a significant association of GGT with PDD and ejection fraction was observed in both of the groups. Nonetheless, a significant correlation between GGT and QTc was only found in the female group (Table 1).

Table 1. Correlation of GGT level with electrocardiographic parameters and ejection fraction in the female and male groups.

	Male		Female	
	r	p value	r	p value
GGT activity				
Sokolow-Lyon voltage (mm)	- 0.070	0.374	0.056	0.660
Cornell voltage (mm)	- 0. 029	0.712	0.062	0.622
Cornell product (mm.sc)	- 0.021	0.792	0.142	0.261
Corrected QT (msc)	0.123	0.121	0.245	**0.049**
QT dispersion (msc)	0.070	0.380	0.138	0.276
P-wave dispersion (msc)	0.284	**< 0.0001**	0.275	**0.031**
Ejection fraction (%)	- 0.182	**< 0.05**	- 0.309	**0.013**

A comparison between the electrocardiographic parameters and ejection fraction in both genders revealed that PWD was higher and the ejection fraction was lower in the male group (Table 2).

Table 2. Comparison of electrocardiographic parameters and ejection fraction between female and male patients.

	Female (n = 80)	Male (n = 174)	p
Age	64.6 ± 8.3	58.5 ± 10.5	**< 0.001**
GGT activity (u/I)	30.1 ± 21.3	41 ± 33.4	**< 0.001**
Sokolow-Lyon voltage (mm)	18.7 ± 8.9	20.1 ± 9.1	0.283
Cornell voltage (mm)	13.9 ± 6.2	15.2 ± 6.9	0.191
Cornell product (mm.sc)	1263.0 ± 768.7	1378.9 ± 818.1	0.323
Corrected QT (msc)	421.7 ± 54.6	407.2 ± 67.7	0.123
QT dispersion (msc)	39.3 ± 19.4	44.6 ± 31.8	0.215
P-wave dispersion (msc)	30.1 ± 14.7	39.9 ± 39.4	**0.045**
Ejection fraction (%)	56.0 ± 10.8	53.0 ± 12.2	**0.088**

Similarly, it was found that there was a positive correlation of GGT activity with PWD in the nonsmoker group ($r = 0.360$, $p < 0.0001$), but it correlated negatively with the EF in the same group ($r = -0.211$, $p = 0.028$). On the other hand, GGT activity only correlated with PWD in the smoker subgroup ($r = 0.194$, $p = 0.045$).

Reproducibility analysis results were as follows: Intra-observer variability was 2.4% for Sokolow-Lyon voltage criteria, 3.1% for Cornell voltage criteria, 4.9% for Cornell product, 5.0% for QT dispersion, 5.7% for P-wave dispersion, 4.6% for Ejection fraction. Inter-observer variability was 3.5% for Sokolow-Lyon voltage criteria, 3.8% for Cornell voltage criteria, 6.2% for Cornell product, 6.5% for QT dispersion, 6.4% for P-wave dispersion, 7.3% for Ejection fraction.

4. Discussion

A variety of research studies have determined raised GGT activity in the progression of atherosclerosis, which is associated with oxidative stress (Paolicchi et al., 2004; Emmin et al., 2005; Ulus et al., 2007; Bradley et al., 2014). GGT appears to be a strong predictor of acute coronary events besides cardiovascular risk factors. Epidemiological evidence from recent studies demonstrates that GGT, which is generally used in hepatobiliary disease and the use of alcohol, can be used as a prognostic marker for mortality and morbidity from cardiovascular disease (Karlson et al., 2000, Emdin et al., 2001; Ruttmann et al., 2005; Wannamethee et al., 2008).

There are studies suggesting that GGT is a predictor of cardiac mortality or non-fatal myocardial infarction, especially in patients who had ischemi which was identified as coronary atherosclerosis, and a history of myocardial infarction (Paolicchi et al., 2004; Ruttmann et al., 2005; Lee et al., 2007; Lee et al., 2009, Patterson et al., 2015).

The studies, which were carried out on an apparently healthy general population, demonstrate that GGT is a strong predictor of acute coronary events,

independently of other cardiovascular risk factors (Lee et al., 2006; Meisinger et al., 2006; Kunutsor et al., 2015).

Our results demonstrate that GGT activity only relates to one of the non-invasive arrhythmia indicators, PWD. In our study, higher PWD but lower EF was found in male compared to female patients. Assessment of smoking and nonsmoking patients based on the GGT activity showed that GGT activity was associated with PWD in both of the groups.

Prolongation of interatrial and intraatrial conduction, along with nonhomogeneous conduction of sinus stimulus, is considered an indicator of atrial fibrillation risk (Dilaveris et al, 2000; Tukek et al.,2001; Perzanowski et al., 2005). It is known that increased PWD and prolongation of maximum P-wave duration are non-invasive signs of heterogeneous and unstable electric activity, and this can trigger atrial reentry. Prolongation of the P-wave duration reflects the changes to the atrial substrate. Even though there is a higher prevalence of coronary artery disease in patients with atrial fibrillation (Kannel et al., 1982; Krahn et al., 1995; Lip and Beevers, 1995), atrial fibrillation is less prevalent in patients with CAD (Haddad et al., 1978; Cameron et al., 1988). Numerous studies note the role of inflammation (Aviles et al., 2003; Van Wagoner, 2008; Ozaydın, 2010) and the rise in C-reactive protein levels in atrial fibrillation patients (Chung et al., 2001; Watanabe et al., 2005). Similarly, it is reported that systolic dysfunction rather than ischemia may lead to atrial fibrillation in coronary artery disease patients (Lokshyn et al., 2000). Left ventricle dysfunction can lead to the development of atrial fibrillation due to electro-mechanic feedback and neurohormonal activation (Van den Berg et al., 1997). When increased oxidative stress in atrial fibrillation is considered (Neuman et al., 2007), the association between PWD and GGT activity suggests that the oxidative process is effective in the development of atrial fibrillation. The positive correlation between GGT and PWD and the negative correlation between GGT and EF are parallel findings in our study. These findings can be explained by the frequent concomitance of decreased left ventricle function and atrial arrhythmias. There are studies showed that association of GGT activity and atrial fibrillation. (Tekin et al.,2013; Alonso et al., 2014)

In this study, we found that increased GGT activity was correlated with P-wave dispersion. These results indicate that there might be an increased risk of arrhythmias especially the atrial fibrillation in this patient population. However, prospective, larger and long-term studies are necessary to obtain more accurate conclusions.

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Reliability and validity of the Turkish version of the Florida shock anxiety scale

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ABSTRACT

The aim of the study is to translate the Florida Shock Anxiety Scale (FSAS) into Turkish and probe the reliability and validity of this scale in a Turkish sample of Implantable Cardioverter Defibrillator (ICD) patients. The current study is a methodological cultural adaptation study. The Florida Shock Anxiety Scale was developed to measure fear associated with ICD shocks. The FSAS is composed of 10 items and originally was validated with two sub-factors. The current study was conducted in two different university hospital cardiology clinics in İzmir. One hundred and fifteen ICD recipients completed the FSAS. Content validity was evaluated with opinions of nine experts and between expert opinions about items of the scale was not found to be statistically significant different (p= 0.066), indicating agreement about relevant content. At the end of the confirmatory factor analysis it is concluded to use a one factor model. The factor loads of the items were found between 0.27 and 0.78. The correlation coefficient of the scores of each item and the scale score was r=0.37 - 0.77. Cronbach's alpha coefficient was found as 0.83. Pearson's correlation value was found as r=0.903 in retest (p= 0.000). Overall, results revealed that Turkish version of FSAS is a reliable and valid instrument in a Turkish sample.

1. Introduction

Implantable Cardioverter Defibrillators (ICDs) are used for preventing sudden cardiac death, ventricular tachycardia or fibrillation through the use of anti-tachycardia pacing and high energy shock. It is an electronic device that continuously observers heart rate and rhythm. If an abnormal heart rhythm is detected by the ICD, it gives energy in the form of electrical impulses or shock to the heart muscle, which helps the heart to return its normal (sinus) rhythm (American Heart Association, 2012). Unfortunately, patients usually experience this shock as painful and distressing (Magyar-Russell et al., 2011; Ford et al., 2012). A big amount of ICD and pacemaker patients can face some psychological symptoms such as anxiety and/or depression, which can affect their adjustment to the device (Kuijpers et al., 2002; Malm and Hallberg, 2006; Magyar-Russell et al., 2011).

ICD patients who experience shock or the knowledge of this function may increases the concerns about prospective shocks and it is known that the prevalence of anxiety is higher in this group than the general population. Finally, shock anxiety may turn in to a clinically significant anxiety disorder which

is associated with shock distressing (Magyar-Russell et al., 2011; Ford et al., 2012). The unpredictable and uncontrollable ICD shocks are one of the most distressing factors which lead poor psychological adjustment (Sears and Conti, 2002). In some of the studies that determine the ICD patients level of anxiety, generally Hospital Anxiety Depression Scale (HADS) (Keren et al., 2011; Magyar-Russell et al., 2011; Wilson et al., 2012) and State-Trait Anxiety Inventory (STAI) (Kohn et al., 2000; Kamphuis, et al., 2003; Dunbar et al., 2009; Kuhl et al., 2009; Pedersen and Spek, 2009; James et al., 2012;) were used. The scales are generally used to diagnose anxiety scales, but they are not specific for ICD patients. The Florida Shock Anxiety Scale (FSAS) was developed to be a sensitive quantitative metric of ICD shock-related anxiety for use in electrophysiology clinics and research (Kuhl et al., 2006).

The original FSAS validation showed that the reliability and validity of this specific measure of shock anxiety was acceptable. Two factors was emerged in factor analysis with the 66% variance. The first factor assessing fear or anxiety, which was related to the consequences of shock, and the second factor assessing fear or anxiety about triggering a shock. Thus, factor 1 was labeled as consequence factor and factor 2 was labeled as triggering factor. One item (fearing getting angry or upset will cause the ICD to fire) did not load on any factor (Kuhl et al., 2006).

At the end of the reliability analyses, the strong support for the factor structure was found (Cronbach's $\alpha = 0.91$; split-half = 0.92; test-retest total score = 0.79, $P < 0.01$). The consequence factor had high reliability ($\alpha = 0.88$) than the triggers factor had ($\alpha = 0.74$) (Kuhl et al., 2006).

The FSAS has been used as a shock anxiety measure globally in Canada (Vazquez et al., 2010), Australia (Keren et al., 2011), China (Chair et al., 2011) and America (Ford et al., 2012). In Chinese study, the crohnbach alpha is found 0.81, in American study it is found 0.89 (Chair et al., 2011; Ford et al., 2012). The measure it has been assessed in a primarily female participant sample (Kuhl et al., 2006) given the predominately-male participant sample of the initial evaluation in the United States (Vazquez et al., 2008). It hasn't been studied in Turkey yet. The purpose of the study is to adapt the Florida Shock Anxiety Scale (FSAS) into Turkish and probe the reliability and validity of this scale.

2. Materials and methods

Setting and sample

This methodological cultural adaptation study was conducted in two different university hospital cardiology clinics in İzmir between March 2012 and March 2013. Patients were recruited during an outpatient cardiology clinic and were at least three months post implant, able to speak and understand Turkish, older than 18 years old. Patients with serious medical illnesses, cognitive dysfunction, or a history of psychiatric illness and hearing impairment were excluded in the study. The total number of 115 participants completed the questionnaire.

Outcome measure

The final sample of 115 patients completed the questionnaire, such as the FSAS and the demographic questions.

Florida Shock Anxiety Scale

The Florida Shock Anxiety Scale (FSAS) is a brief tool which was provide a quantitative measure of ICD shock-related anxiety. It was designed by an interdisciplinary team including electrophysiology and clinical psychology. The scale consists of 10 items and two subscales. The anxiety related to the consequences of device called consequence factor and the anxiety related to triggering device shock called trigger factor. Each item was rated on a 5-point Likert scale from 1 (not at all) to 5 (all of the time). Higher total scores indicated higher shock anxiety. The total score is calculated by summing the items. A patient who scores 3 or higher on any item should receive counseling related to his specific concerns. The reliability analyses revealed strong support for the factor structure; the Cronbach's α of the overall items was 0.91, split half was 0.92, and the test-retest score was 0.79, $P < 0.01$. The reliability of the consequence subscale was high with Cronbach's $\alpha = 0.88$ and the Cronbach's α of the trigger subscale = 0.74.20 (Kuhl et al., 2006).

Demographic questions

This form is comprised of patients' socio-demographic features: Age, sex, social insurance, educational status, marital status, occupation, economic condition and descriptive features: Duration of ICD implantation, number of ICD shocks, ICD indication and sudden cardiac death experience.

Statistical analysis

Analysis was conducted using descriptive statistics and appropriate reliability and validity statistical tests using the Statistical Package for the Social Services (SPSS) 15.0 (SPSS Inc., Chicago, IL) and the LISREL program. For the content validity expert opinions were assessed through Kendall W analysis. For construct validity confirmatory factor analysis was used (LoBiondo-Wood et al., 2005; Şimşek, 2007; Harrington, 2009). Pearson's Product-Moment Correlation Coefficient was used for reliability analysis, also item total score correlation and Cronbach alpha analysis. Test-retest measurement was assessed using Pearson Correlation

and a dependent t-test with ten days interval (Karasar, 2000; Gözüm and Aksayan, 2003). For retest, fifteen days following the first administration, the FSAS was given to 30 patients again.

Ethical considerations

This study conformed to the Helsinki Declaration of Human Rights and respected the individual rights of the participants. Written permission was taken to adapt the FSAS into Turkish and to use the instrument in this study. This study was approved by the ethical review boards at the authors'institution (and each hospital). Written consent was obtained from each participant. Following informed consent, patients were asked to complete the questionnaire and demographic data sheet.

3. Results

Descriptive statistics

The total sample of the study was 115. Patients were mostly male (70.4%) and had a mean age of 59.63 ± 15.03 (min=25, max=94) years. Most of the patients were graduated from primary school (47.8%), married (87.8%) and retired (64.3%) (Table 1).

The FSAS mean score of the patients was 18.25±8.84 (min=10, max=46).

Table 1. Characteristics of participants (n=115).

Validity Analysis			
Characteristics	**Mean**	**SD**	**Min-Max**
Age	59.63	15.03	25-94
Implantation duration (month)	33.53	29.65	20 days-120 months
Number of shocks	5.52	14.00	0-100
	N	**%**	
Gender			
Female	34	29.6	
Male	81	70.4	
Education			
İlliterate	5	1.7	
Literate	2	4.3	
Primary education	55	47.8	
Secondary education	12	10.4	
High school	19	16.5	
University and higher	22	19.1	
Marital status			
Married	101	87.8	
Single	14	12.2	
Occupation			
Housewife	21	18.3	
Officer	5	4.3	
Worker	5	4.3	
Retired	74	64.3	
Self-employed	8	7.0	
Other	2	1.7	
Economic condition			
Income < expense	57	49.6	
Income = expense	53	46.1	
Income > expense	5	4.3	
Social insurance			
Yes	114	99.1	
No	1	0.9	

Translation of FSAS

First, the instrument was translated from English to Turkish. Language validity of the scale was analyzed as the first step of the research conducted to test the validity of the scale for the Turkish society. Scale was translated into Turkish by all researchers and two different translation offices. The researchers reviewed the initial Turkish version of the scale and then recruited one Turkish version of the FSAS. The forward-translated version was then back-translated by a professional bilingual translator unfamiliar with either the English or the Turkish versions of the FSAS to ensure the accuracy of the translation. and the original form and the translated English form were checked by the researchers. Forward-translated and back-translated instruments and the choice of words was discussed until a final version was composed (Karasar, 2000; Gözüm and Aksayan, 2003). The translated Turkish version submitted to the expert opinion (four faculty members from the Faculty of Nursing, one head nurse from the coronary intensive care unit, one head nurse from the Department of Cardiology, one cardiology assistant doctor, one psychiatry assistant doctor and one cardiology professor) for an analysis of its content validity. Experts were asked to rate each item in the Turkish version of the FSAS based on relevance, clarity, and simplicity on a scale of one (not appropriate at all) to ten (completely appropriate). Acquiring the final form with expert opinions, the scale was used in pre-interviews conducted with 15 patients. Scores of the nine experts were evaluated using the Kendall W analysis, and no statistically significant difference was found among the scores. As a result, it was determined that expert scores were consistent with one another. The overall Cronbach's α of the Turkish version FSAS used in this study was 0.83.

Construct validity

Confirmatory factor analysis. The suitability of data was assessed prior to conducting factor analysis. The Kaiser-Meyer-Olkin value was 0.86 and Bartlett's test of sphericity reached statistical significance χ^2= 319,033 p= 0.000, thus supporting the factorability of the correlation matrix.

In order to determine if the two-factor exploratory factor analysis model found by Kuhl and associates during the initial development of the FSAS (Kuhl et al., 2006) could be replicated, an exploratory model specifying the two factors was initially estimated. Estimation of the two-factor exploratory model with factors obliquely rotated using promax revealed a different pattern of loadings. Specifically, FSAS items 2,5,6,7,8,9 loaded on consequence factor in the original form whereas in Turkish form the 4,5,7,8,9,10 items loaded on consequence factor. The 1,4,10 items loaded on trigger factor whereas in Turkish form 1,2,3,6 items

loaded on trigger factor. In the original form of FSAS third item (fearing getting angry or upset will cause the ICD to fire) did not significantly load on either factor. But in the Turkish form, it is loaded on trigger factor. On the FSAS, items are grouped under specific meanings. For example; Factor 1, including fearing that the device would not fire, fearing being alone when device fires, fearing a rapid heartbeat, having unwanted thoughts about firing, fearing consequences of touching others, and fearing creating a scene if the device were to fire. Although these are all diverse items, a common underlying theme seems to be fears related to consequences associated with device shock. Therefore, this factor could be labeled the consequence factor. On the other hand, the three items that loaded on Factor 2 appear to be more related to triggering device shock (fearing sexual activity, fearing exercise, and fearing not knowing when the device would fire); thus, Factor 2 could be labeled the trigger factor. But in this study the items that loaded on these factors did not meet these meanings (Kuhl et al., 2006). Therefore, the analysis was done again with single factor model (Fig. 1).

At the end of these analyses, it was concluded that the two-factor model did not meet the meanings that the original items have. Thus, a one factor model was used.

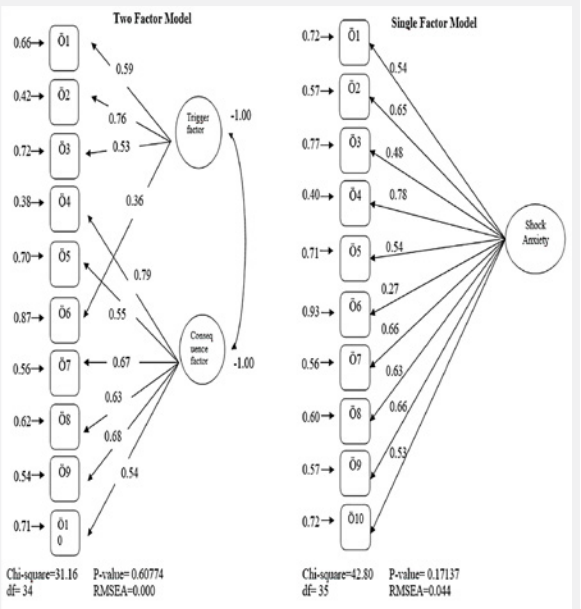

Fig. 1. Comparison of the second-order and single-factor models of the Florida Shock Anxiety Scale

Consistency values were determined as follows: "chi square=42.80", "Root Mean Square Error of Approximation (RMSEA)= 0.044", "Standardized Root Mean Square Residual (SRMR)= 0.055", "Comparative Fit Index (CFI)= 0.98", "Non-Normed Fit Index (NNFI)= 0.98", "Normed Fit Index (NFI) = 0.93", "Goodness of Fit Index (GFI) = 0.93". The factor loading was between 0.27-0.78.

Reliability

Internal consistency analysis

When item-total score correlations of 10 items were examined in the reliability analysis of the FSAS, it was found to be 0.37 - 0.77 at a statistically significant level ($p < 0.001$) (Table 2). In the analysis conducted to test the internal consistency, Cronbach alpha coefficient was 0.83.

Table 2. Item-Total Score Correlations of Florida Shock Anxiety Scale (n= 115).

FSAS Items	Item-total Score Correlations (r)*	p
Characteristics	**Mean**	**SD**
I am scared to exercise because I am scared that it will increase my heart rate and cause my device to fire.	**.645**	**.000**
I am afraid of being alone when the ICD fires and I will need help.	**.736**	**.000**
I do not get angry or upset because it may cause the ICD to fire.	**.592**	**.000**
It bothers me that I do not know when the ICD will fire.	**.774**	**.000**
I worry about the ICD not firing sometimes when it should.	**.586**	**.000**
I am afraid to touch others for fear that I will shock them if the ICD fires.	**.366**	**.000**
I worry about the ICD firing and creating a scene.	**.686**	**.000**
When I note my heart beating rapidly, I worry that the ICD will fire.	**.679**	**.000**
I have unwanted thoughts of my ICD firing.	**.654**	**.000**
I do not engage in sexual activity because it will cause my ICD to fire	**.526**	**.000**

Test-retest reliability

To determine whether or not there were differences in the mean scores obtained from the scale between the first and second administration, the scale was evaluated using the t-test in dependent groups. No statistically significant differences were found ($p > 0.05$, p=0.344).

When the relationship between scores obtained from first and second administration was evaluated with Pearson correlation analysis, it was determined that there was a very strong, positive, and statistically significant relationship between test-retest scores (r=0.903, p=0.000) (Table 3).

Table 3. Test-retest Scores of Participants (n=30).

Scale	FSAS score	Correlation	Analisis results			
	First implementation X ± SS	Second implementation X ± SS	r	p	t	p
FSAS	**16.40± 7.05**	**16.97± 7.47**	**.903**	**.000**	**-.963**	**.344**

4. Discussion

We evaluated a Turkish version of the Florida Shock Anxiety Scale and confirmed the reliability and validity in a Turkish sample of ICD patients. Consistent with recent research with the FSAS (Ford et al., 2012), this tool may better reflect a one factor measure of shock

anxiety. These results are promising because shock anxiety remains an important aspect of the care of ICD patients to reach exhaustive health outcomes.

Our confirmatory factor found that the original subscales and their meanings did not identically match with our results. In this study, at the end of CFA it was determined that factor loads of all items were between 0.27 and 0.78. CFA recommends that each item should have a model-data fit coefficient value of at least 0.30 and above (Harrington, 2009). The sixth item model-data fit coefficient is below 0.30. The reason for this low is thought to be the patients' lack of information about the ICD device functions. During data collection patients questions about this item and received answers showed a lack of information. This item has a high correlation with other items and when this item is removed the structure validity of the scale is corrupted. Thus this item has decided to not remove from the scale by the authors.

Goodness of fit statistics should also be at the desired level in the confirmatory factor analysis. In the chi-square test performed as the fit statistic, it was determined that chi-square fit value was significant (x2/df=1.22 (42.80/35). The fact that this value is two or less means that it is a good model. However, the fact that this value is five or less shows us that the model has an acceptable goodness of fit (Tavşancıl, 2005; Harrington, 2009). In this study model-data fit was found to be good.

The other tests that used to measure goodness of fit are Root Mean Square Error of Approximation (RMSEA), Standardized Root-Mean-Square Residual (SRMR), Comparative Fit Index (CFI), Non-Normed Fit Index (NNFI) (Şimşek, 2007; Harrington, 2009). The fact that RMSEA is equal to or less than 0.080 and p value is lower than .05 (that it is statistically significant) means a good fit (Şimşek, 2007; Harrington, 2009), while a value equal to or less than 0.10 indicates a poor fit (Harrington 2009). In this study, RMSEA value was found 0.04. This value indicates data consistent with the model.

A value of SRMR lower than .10 and CFI, NNFI values equal to or more than 0.90 indicate that there is fit in the scale (Şimşek, 2007; Harrington, 2009). In this study, SRMR, CFI, and NNFI values indicated a good fit. Results of this study support the construct validity of the Turkish version of the FSAS and that it is a valid instrument for use in Turkish samples.

In this study, the FSAS demonstrated acceptable internal consistency. One of the methods used to evaluate the internal consistency in the adapted scales in terms of reliability is the item analysis. Even though sufficiency level of item-item score correlation coefficients displays variety in the literature, in general, minimum level is accepted as .20 items with reliability coefficients between .30 and .40 are considered as "good", while items having reliability coefficients above 40 are reported as ideally distinctive, and thus reliable (Gözüm and Aksayan, 2003; Tavşancıl, 2005). In this study, item-item score correlation coefficients were 0.37 - 0.77.

In our study, Cronbach Alpha coefficient of the scale was found to be within highly reliable (0.83). Test-retest analysis is one of the most frequently used reliability analyses and evaluates the invariance characteristic of the measurement tool. Obviously, there was consistency between measurements performed at specific intervals as there was not a difference between test-retest score averages, test-retest reliability coefficient was r=0.903, and there was a statistically positive and highly significant relationship between test-retest scores (Tavşancıl, 2005; Polit and Beck, 2008). The Turkish FSAS was found to have a high level of reliability.

The current study revealed that Turkish version of Florida Shock Anxiety Scale is a reliable and valid instrument in a Turkish sample. Consistent with recent research with the FSAS, this tool may better reflect a one factor measure of shock anxiety. Since it is a brief scale, it is easy to use and practical. In addition, it is a device-specific scale to evaluate ICD patients' shock-related anxiety and can used in the clinical practices and research in Turkey.

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Analysis of patients admitted to the emergency service for warfarin complication and determination of their levels of knowledge and requirements of knowledge about warfarin use

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ABSTRACT

Warfarin is a cumarol derivative anticoagulant. It shows its effect by antagonizing the effects of Vitamin K. Warfarin is metabolized in the liver. International normalized ratio has been developed in the monitorization of warfarin. It is a drug which has a limited therapeutic index. The difference in sensitivity for therapy dose among individuals depends on the genetic polymorphism of the two enzymes in the liver. The objective of our study was to assess the information about the demographic characteristics, complications, treatments and the related factors of the patients who were admitted to our emergency service for high INR in routine controls and of the cases who had bleeding due to warfarin overdose. Of the 18-year-old and older patients who were admitted to our emergency service with a complaint related to warfarin use and who had been using warfarin on admission and patients who had an INR value of over 3.0 although the patient had no complaints, those who accepted to participate in the study were included in the study. The results of the demographic characteristics, complications and treatments of the 59 patients included in the study were in parallel with the literature. The rate of patients' being informed was found as 61%. Although difference was found when the demographic data of the informed and non-informed groups and their answers to the questions asked for warfarin information level were compared, no statistically significant difference was found ($p>0.005$). This brings to mind that the information given to patients at the time of first prescription is not sufficient and it does not turn into a regular training.

1. Introduction

Warfarin is the most used oral anticoagulant. It blocks the Vitamin K dependent clotting factors and coagulation inhibitors. Warfarin is metabolized in the liver (Alay et al., 2011). Warfarin is a widely used coumarin anticoagulant prescribed for patients with venous thrombosis and pulmonary embolism, chronic atrial fibrillation and prosthetic heart valves (Guven et al., 2012).

Initially, prothrombin time (PT) was used in warfarin monitorization. In time, international normalized ratio (INR) was developed to eliminate the heterogeneity which occurred due to the use of different tissue thromoplastins in this measurement. The difference in sensitivity for therapy dose among individuals depends on the genetic polymorphism of the two enzymes in the liver. These enzymes are hepatic cytochrome P-450 2Cp (CYP2C9) and Vitamin K

epoxide reductase complex 1 (VKORC1). In addition, warfarin is known to interact with a great number of drugs since its metabolism occurs through CYP2C9. At the same time, substances such as red pepper, fish oil and daisy can increase INR and cause bleeding. Warfarin's most important and most frequent side effect is bleeding. Recently, the increase in the number of patients who are admitted to the emergency service due to warfarin related complications is remarkable. One of the most important reasons of this is the prevention of stroke in atrial fibrillation patients and the increase in the frequency of use due to the increase in valve operations (Altuntas et al., 2013). Besides the absence of special anticoagulant clinics in our country, there are also no standard patient education approaches among clinics that prescribe and follow warfarin use and pharmacology polyclinics (Yaka et al., 2011). The objective of our study was to assess the information about the demographic characteristics, complications, treatments and the related factors of the patients who were admitted to our emergency service for high INR in routine controls and of the cases who had bleeding due to warfarin overdose.

2. Material and methods

Our study was conducted at Adnan Menderes University, Faculty of Medicine, Emergency Service between July-December 2015 after local ethical board approval (2015/614) was taken. Of the 18-year-old and older patients who were admitted to our emergency service with a complaint related to warfarin use and who had been using warfarin on admission and patients who had an INR value of over 3,0 although the patient had no complaints, those who accepted to participate in the study were included in the study (Dentali et al., 2006; Eroğlu et al., 2011). Demographic data of the patients included in the study such as age and gender and their PT/INR levels, treatments and results were recorded in the study form. Questions were asked to patients who agreed to participate in the study or to their relatives in order to assess their information about warfarin treatment and the answers were recorded in the study form.

Statistical evaluation

Statistical analysis of the data was performed by using Kruskal-Wallis and Chi-square tests. The level of significance was considered as $p<0.05$. When significant differences were found among groups, pairwise comparisons were performed between groups in order to detect the groups from which the differences originated.

3. Results

The average age of the 59 patients included in the study was 68.1 ± 11.3 years. 27 (45.8%) of the patients were men, while 32 (54.2%) were women (Table 1). 26 (44%) of the patients used warfarin due to coronary artery diseases and arrthymia, 15 (25.4%) used warfarin due to valve replacement, 6 (10.2%) used warfarin due to cerebrovascular disease, 4 (6,8%) used warfarin due to deep vein thrombosis, 3 (5.1%) used warfarin due to pulmonary thromboembolism and 5 (8.5%) used warfarin due to other reasons.

Table 1. Demographic data and laboratory results of patients and groups.

	Total Patients n=59 (%100)	Group 1 n=36 (%61)	Group 2 n=23 (%39)	p
Age (years)	68.1 ± 11.3	69.56 ± 10.25	65.83 ± 12.70	0.249
Female	32 (%54.2)	21 (%58.3)	11 (%47.8)	0.433
Male	27 (%45.8)	15 (%41.7)	12 (%52.2)	
INR	9.7 ± 1.8	4.7 ± 11.60	4.66 ± 2.08	0.860
Hemoglobin (gr/dl)	10.8 ± 2.5	10.91 ± 2.56	10.86 ± 2.47	0.901

Nineteen patients (32.2%) were admitted to the emergency service for high INR, 4 (6.8%) were admitted due to ecchymosses on the skin, 4 (6.8%) were admitted due to gingival bleeding, 3 (5.1%) were admitted due to intracerebral bleeding, 4 (6.8%) were admitted due to stomach ache, 3 (5.1%) were admitted due to hematuria and 3 (5.1%) were admitted due to internal joint bleeding.

While the average INR of the patients on admission to the emergency service was 9.7 ± 1.8, INR of 10 patients were too high to be measured and the average hemoglobin was 10,8 ± 2,5 gr/dl (range between 4.2-10.8 gr/dl) (Table 1). The average warfarin use time of the patients was 5.1 ± 5.5 months (range between 0.1-20 months). 32 patients (54.2%) were given fresh frozen plasma (FFP) treatment, 4 patients (6.8%) were given erythrocyte suspension (ES), 6 patients (10.2%) were given ES+FFP, 2 patients (3.2%) were given prothrombin complex, 1 patient (1.7%) was given Vitamin K, 1 patient (1.7%) was given total blood, while 13 patients (22%) were not given any treatment. 39 (66.1%) patients were hospitalized in the services while 4 (6.1%) were hospitalized in the intensive care and 16 (16.1%) were discharged from the emergency service. While 84.7% of the patients had a chronic comorbid disease, 93.2% used comorbid drugs regularly.

The patients were grouped in 2 in terms of being informed about warfarin. While Group 1 consisted of 36 (61%) patients who were informed about warfarin, Group 2 consisted of 23 (39%) patients who were not informed. When the groups were compared in terms of their demographic data, laboratory results, ways of using warfarin and their answers for questions of level of drug information, no significant difference was found ($P>0.005$) (Table 2).

Table 2. Answers of patients and groups to the questions about their ways of warfarin use and their drug information levels

	Total Patients n=59 (%100)	Group 1 n=36 (%61)	Group 2 n=23 (%39)	p
State of education (none)	24 (%40.7)	15 (%41.7)	9 (%9.1)	0.665
Does the patient take the drug himself/herself? (No)	22 (%46.3)	9 (%25)	12 (%52.2)	0.035
Does the patient know the reason for Warfarin use? (No)	15 (%25.4)	6 (%16.7)	9 (%39.1)	0.055
Does the patient know the Warfarin dose? (No)	17 (%28.8)	6 (%16.7)	11 (%47.8)	0.011
Does the patient know Warfarin complications? (No)	36 (%61)	17 (%47.2)	19 (%82.6)	0.007
Does the patient have regular INR follows? (No)	16 (%27.1)	6 (%16.7)	10 (%43.5)	0.0 25
Does the patient mention warfarin use on admission to hospital? (No)	7 (%11.9)	2 (%5.6)	5 (%21.7)	0.063
Has the patient been informed about Warfarin use? (No)	23 (%39)	0	23 (%39)	

4. Discussion

Warfarin is a cumarol derivative oral anticoagulant. At least 48-72 hours are needed for it to show its full effect. Its bioavailability is close to 100%. Bile juice is required for its absorption from the gastrointestinal system. Since it is dependent on albumin on the plasma with a rate of 99%, its renal elimination is slow. Plasma half-life time is 36 hours (Eroglu et al., 2012). The gene of the major protein component of VKOR is found in the complex subunit 1, known as VKORC1. Mutations in this gene have been associated with a deficiency in vitamin-K-dependent clotting factors, resulting in increased sensitivity to warfarin or warfarin resistance or insensitivity (Turkdogan et al., 2013).

In Acar et al.'s study (2012) study, 64% of the patients were women, while 36% were men and the average age was 67.5 years. In Yaka et al. (2011)'s study, 62.3% of the patients were women, while 37.7% were men and the average age was 64±14 years. Our results were in parallel with the literature.

In Eroğlu et al. (2011)'s study, warfarin therapy was started on 50% of the patients due to atrial fibrillation, on 10% due to deep vein thrombosis, on 10% due to pulmonary embolism and on 30% due to valvular heart disease. In Alay et al. (2011)'s study, warfarin was used due to cardiac valve replacement in 30 patients, vascular thrombosis in 13 patients, cardiac thrombosis in 3 patients, atrial fibrillation in 13 patients and pulmonary embolism in 1 patient.

The results of our study were similar to the results in literature. In Eroğlu et al. (2011)'s study, hematuria was found in 26% of the patients, rectal bleeding or darkening in stools color was found in 36%, brusing on the skin was found in 13%, nasal bleeding was found in 10% and high INR was found in the controls of 6.6% and hemarthrosis was found in 6.6%. In Alay et al.'s study (2011), the most frequent was gastrointestinal bleeding (33.3%), followed by mucosal bleeding (21.7%), urinary system bleeding (13.3%), intraabdominal bleeding (10%), vaginal bleeding (10%), intracranial bleeding (5%), lower gastrointestinal bleeding (3.3%), pericardial bleeding (1.7%) and intramuscular hematoma (1.7%). The results of our study were in line with the literature.

In three study the average INR level was measured as 9.46, 13.42 and 7.2 respectively (Alay et al., 2011; Eroğlu et al., 2011; Eroglu et al., 2012). In our study, the average INR level was measured as 9.7 ± 1.8, which was in line with the literature.

The current approach to warfarin-related bleeding is primarily warfarin discontinuation of use, risk status of the patient and K vitamins according to the presence of the bleeding, fresh frozen plasma transfusion and protombin complex concentrates should be given (Acar et al., 2011). In Eroğlu et al. (2011)'s study, intravenous Vitamin K treatment was given to 83% of the patients, FFP treatment was given to 76% and erythrocyte suspension treatment was given to 43%. In Acar et al. (2011)'s study, erythrocyte and fresh frozen plasma transfusion was given to 11 (30%) patients, only frozen plasma transfusion was given to 19 (53%) patients, while 6 (17%) patients did not need any kind of transfusion. The treatments given in our study were similar to those in literature.

In Mercan and Enç (2011)'s study, it was found that 51.8% of the patients had a comorbid disease that required regular drug use other than warfarin, while 73.7% were found to have a drug or drug group they used all the time. In our study, comorbid disease and additional drug use rates were high, which was in line with the literature.

In our study, 40.7% of the patients were illiterate. Similar to the results of our study, 33.3% and 33.6% of the patients were found to be illiterate in literature (Beyan et al., 2010; Yaka et al., 2011). In Yaka et al. (2011)'s study, 64.8% of the patients stated that they had been informed about warfarin. In our study, the ratio of being informed was 61%. Although difference was found when the demographic data of the informed and non-informed groups and their answers to the questions asked for warfarin information level were compared, no statistically significant difference was found ($p>0.05$). This brings to mind that the information given to patients at the time of first prescription is not sufficient and it does not turn into a regular training.

Warfarin-induced complications may not be decreased with only through education or the factors that influence it since the warfarin metabolism has genetic, drug and different food interactions. As well as the information given to patients during prescription, complications

can be solved through a compact approach which includes regular monitorization, genetic predisposition and repetitive education. This compact approach can be built through pharmacology polyclinics formed by primary care physicians and hospitals.

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Demographic characteristics and psychiatric disorders of sexually abuse children: An analysis of 343 cases

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ABSTRACT

The aim of this study was to examine demographic characteristics and psychiatric diagnosis of sexually abused children and adolescents who referred for forensic examination to Child and Adolescent Psychiatry outpatient clinic. We retrospectively reviewed records of 343 children and adolescent aged 3-18 years who exposure to sexual abuse between January 2010 and 2013 by judicial authority. In all cases, age, gender, educational status, intelligence level, type and frequency of abuse, degree of familiarity of abuser and psychiatric diagnosis according to DSM-IV-TR classification were evaluated. The mean age of cases was 13.46±3.1 years. Majority of cases were girls (78.7%). It was found that 77.8% of the cases were between 12 and 18 years of age. The most common type of sexual abuse was touching and/or friction (51.6%). Majority of cases was exposed to sexual for once (57.4%). The abusers were all male, and 85.1% were known to their victim. It was found that rate of early marriage was 10.5%. The rate of mental retardation was found as 7.3%. Psychiatric disorders were determined in 71.4% of the cases, post traumatic stress disorder (37.6%) and depression (13.1%) were the most common psychiatric disorders. Given the fact that abuse has negative impact on mental health of children, long-term management should be stressed in such cases. Increasing awareness about child sexual abuse and its damaging effects is very important. Great significance should be given to the treatment and rehabilitation of the cases. İn addition, preventive measures must be taken.

1. Introduction

Sexual abuse is an important problem that negatively affects physical, mental and social development of child. Child abuse can be encountered worldwide and it is now understood that its frequency is rather high when this issue is comprehensively evaluated. Actual statistical data regarding sexual abuse at childhood is unclear, as there are number of unreported or unregistered cases as much as those reported. It is thought that the reasons of this include inability of the child to talk about the abuse experienced, not believing or distrusting the child when he/she told and not reporting to public authorities by family despite recognition of abuse (Johnson 2004; Finkelhor et al., 2001; Friedrichet et al., 2001). According to population studies, 4.9% of men and 12-35% of women experience undesirable sexual experiences (Putnam, 2003). In a recent meta-analysis including 55 studies from 24 countries, sexual abuse

incidence was reported as 3-17% in boys and 8-31% in girls (Barth et al., 2013). It has been reported that sexual abuse rate is 1.5-3-fold higher among women (Finkelhor, 1994). In a study on 1955 college students in Turkey, it was reported that 13.4% of the cases were exposed to sexual abuse, including incest experience in 1.8% of the cases (Alikasifoglu et al., 2006). Sexual abuse can be classified into two main groups as those involving or not involving physical contact. Sexual abuse is considered in a wide spectrum including exhibitionism, voyeurism, inappropriate sexual conversations, sexual penetration, attempting sexual penetration, oral-genital contact, direct or indirect (over clothing) touching to genital areas, interfemoral penetration, exposure of a child to adult sexual activity or pornography, sexual exploitation (use in prostitution or pornography) (Johnson, 2004; Kaufman, 2007; Glazer, 2008).

In the literature, it has been reported that children and adolescents exposed to abuse display several psychiatric disorders extending from childhood to adult life (Nickel et al., 2004; Kaufman, 2007; Csorba, et al., 2012). In a review by Kendall-Tacket et al. (1993), it was found that victims of sexual abuse displayed psychiatric symptoms by 64-79% (Kendal-Tackett et al., 1993). Several psychiatric disorders resulting from sexual abuse may be seen in children, including post traumatic stres disorder (PTSD), anxiety disorder, depression, adjustment disorder, dissociative experiences, self-harmand suicidal behaviors, sleep disorders, impaired self-esteem, aggressive behavior, mood disorders, behavioral and sexual behavior disorders, elimination disorders, alcohol and substance abuse and eating disorders (Putnam, 2003; Johnson, 2004; Kaufman 2007; Maniglio, 2009; Fergusson, 2013).

In our country, data are limited regarding frequency and distribution of definite and formal abuse cases as well as frequency of psychological trauma related to abuse and effects of abuse.

In this study, it was aimed to identify demographic characteristics and psychiatric diagnosis in children and adolescents who referred to Child and Adolescent Psychiatry outpatient clinic at Kahramanmaraş province with exposure to sexual abuse between 2010 and 2013 by judicial authority for forensic examination.

2. Material and methods

This study was conducted by reviewing records of children and adolescents aged 3-18 years who exposed to sexual abuse and referred to Child and Adolescent Psychiatry outpatient clinic of Kahramanmaraş Obstetrics& Gynecology & Children hospital 2010 and 2011 and those referred to Child and Adolescent Psychiatry Department of Kahramanmaraş Sütçü İmam University, Medicine School in 2012 and 2013 by judicial authorities. Kahramanmaraş, the region of this study, is among highly populated cities of Turkey with a population of 1,075,706 comprising different cultures. In all cases, age, gender, educational status, intelligence level, type and frequency of abuse, degree of familiarity of abuser and psychiatric diagnosis according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) classification were evaluated. Wechsler Intelligence Scale for Children (WISC-R) was used in children older than 6 years, while Ankara Developmental Screening Inventory (ADSI) was used in those younger than 6 years for assessment of intelligence levels.This study was approved by Ethics Committee of Kahramanmaraş Sütçü İmam University Medical Faculty.

Statistical analysis

SPSS for Windows version 17.0 was used for statistical analysis. Frequencies and percentages of the categorical variables were calculated. Comparisons of the subgroups were made by Chi square test. A p value less than 0.05 was considered significant.

3. Results

In this study, 343 children adolescents who are victims of sexual abuse were evaluated. Of the cases, 265 (77.3%) were girls and 78 (22.7%) were boys, with a female to male ratio of 1:3. Mean age was found as 13.46±3.1 years ranging 3 and 18 years. Mean age was found as 14.03±2.7 years among girls and 11.53±3.5 years among boys. Of the cases, 22.2% (n=76) were at childhood (3-11 years of age), while 77.8% (n=267) were at adolescent age (12-18 years of age). When educational status was considered, it was found that 100 children (29.2%) weren't going to school, while 81 children (23.6%) were at elementary school and 89 children (25.9%) were at secondary school. It was found that 73 children (21.3%) at high school. 13,7% (47 cases) were the children of divorced families (Table 1).

Table 1. Demographic characteristics of sexual abuse victims.

	Victims	
Preporties	**n**	**(%)**
Gender		
Female	265	(77.3)
Male	78	(22.7)
Age Groups (years)		
3–11	76	(22.2)
12-18	267	(77.8)
Victims' educational status		
Not going to school	100	(29.2)
Elementary school	81	(23.6)
Secondary school	89	(25.9)
High school	73	(21.3)
Intelligence level		
Normal intelligence level	318	(92.7)
Mental retardation	25	(7.3)

Family status		
Nuclear family	281	(81.9)
Divorced	47	(13,7)
The dead mather or father	15	(4,4)
Phsyical violence		
Yes	34	(9,9)
No	309	(81,2)
Presence of psychiatric disorders in the family members	26	(7,6)
Case proportion according to years		
Year 2010	40	(11.7)
Year 2011	76	(22.2)
Year 2012	102	(29.7)
Year 2013	125	(36.4)

When type of sexual abuse was considered, it was found that touching and/or friction (51.6%; n=177) were most common type; followed by vaginal penetration in 84 cases (24.5%) and anal penetration in 67 cases (19.5%). It was found that touching and/or friction (n=151; 57.0%) was most common type of sexual abuse in girls, whereas anal penetration (n=51; 65.4%) in boys. 9.9% (n=34) of cases were exposed to physical violence in addition to sexual abuse (Table 2).

Table 2. Type and frequency of sexual abuse.

	Victims		
	Female n (%)	**Male** n (%)	**Total** n (%)
Type of sexual abuse			
Touching and/or friction	151(57)	26 (33.3)	177 (51.6)
Vaginal penetration	84 (31.7)	0	84 (24.5)
Anal penetration	16 (6)	51 (65.4)	67 (19.5)
Vaginal and anal penetration	6 (2.7)	0	6 (1.7)
Verbal harassment	4 (1.5)	0	4 (1.2)
Oral penetration	2 (0.7)	0	3 (0.9)
Exhibitionism	2 (0.7)	1 (1.3)	2 (0.6)
Frequency of sexual abuse			
Single abuse event	145 (54.7)	52 (66.7)	197 (57.4)
Repeating abuse event	120 (45.3)	26 (33.3)	146 (42.6)

It was found that a single abuse event was experienced in majority of the cases (57.4%; n=197), whereas there was repeating abuse in 42.6% (n=146) of the cases.

It was found that 14.9% (n=51) of abusers was a stranger, while majority (85.1%; n=292) was a previously known person. It was found that abuser was boyfriend in 69 cases (20.1%), teacher in 31 cases (9.0%); (this rate was found to be higher as one teacher involved in many events including students), partner (early marriage) in 36 cases (10.5%) and acquaintance (neighbor, grocery, distant relative, school staff,cousinetc.) in 138 cases (39.4%). It was found that 5.2% of the cases exposed to incest relationship (father, brother, step father, uncle), where majority of incest cases (94.4%; n=17) were girls. Of the incest cases, 11 cases (3.2%) involved father, whereas 4 cases (1.2%) involved brother; 2 cases (0.6%) involved step father; one case (0.3%) involved uncle (Table 3).

Table 3. The relationship between victims and abuser

	Victims		
	Female n (%)	**Male** n (%)	**Total** n (%)
Abuser			
Acquaintance (neighbor, grocery, distant relative, school staff, cousin etc)	68 (25.7)	70 (89.7)	138 (39.4)
Boyfriend	69 (26.0)	0	69 (20.1)
Teacher	28 (10.6)	3 (3.8)	31 (9.0)
Stranger	47 (17.7)	4 (5.1)	51 (14.9)
Partner (Early marriage)	36 (13.6)	0	36 (10.5)
Incest			
Father	10 (3.8)	1(1.9)	11 (3.2)
Brother	4 (1.5)	0	4 (1.2)
Step father	2 (0.7)	0	2 (0.6)
Uncle	1 (0.4)	0	1 (0.3)

When it was assessed according to years, there were 40 cases (11.7%) in 2010, 76 cases (22.2%) in 2011; 102 cases (29.7%) in 2012 and 125 cases (36.4%) in 2013 (Table 1).

When intelligence level was assessed by using WISC-R and ADSI in cases older and younger than 6 years of age, respectively, it was found that there was normal intelligence level in 92.7% (n=318), whereas mental retardation in 7.3% (n=25) of the cases (Table 1).

A psychiatric disorder was found in 71.4% of the cases exposed to sexual abuse according to DSM-IV-TR diagnostic criteria. It was found that there was PTDS in 129 (37.6%), major depression in 45 (13.1%), adjustment disorder in 34 (9.9%), anxiety disorder in 21 (6.1%) and acute stress disorder in 16 (4.7%)) of the cases. No psychiatric diagnosis was found in 98 cases (28.6%) after sexual abuse (Table 4).

Table 4. Psychiatric disorders diagnosed in the victims.

	Victims		
	Female n (%)	**Male** n (%)	**Total** n (%)
Psychiatric disorders			
Post traumatic stress disorder	96 (36.2)	33 (42.3)	129 (37.6)
Depression	32 (12.1)	13 (16.7)	45 (13.1)
Adjustment disorder	20 (7.5)	14 (17.9)	34 (9.9)
Anxiety disorder	18 (6.8)	3 (3.8)	21 (6.1)
Acute stress disorder	14 (5.9)	2 (2.6)	16 (4.7)
No psychiatric diagnosis	85 (32.1)	13 (16.7)	98 (28.6)

4. Discussion

In this study, we assessed 343 children and adolescents aged 3-18 years who were victims of sexual abuse and referred to Child and Adolescent Psychiatry department during 4-years period by judicial authorities for forensic evaluation regarding whether there is a disruption in their mental health. Although sexual abuse is observed

in children from all ages, mean age at first exposure to sexual abuse was 8-12 years (Finkelhor 1994). In our study, mean age was found as 13.46±3.1 in agreement with above-mentioned studies. Again, it was also determined that mean age was higher among girls than boys in agreement with previous studies (Putnam, 2003; Kaufman 2007; Cengel-Kültür et al., 2007; Bahali et al., 2010; Köse et al., 2011). It is thought that being at adolescent age for girls and being more commonly at streets for boys in this age could be a risk factor for abuse (Köse et al., 2011). In addition, it is thought that higher mean age at girls can be due to the fact that younger girls are more strictly protected when compared to boys and higher number of adolescent girls experiencing early marriage. In several studies from Turkey, it was reported that majority of sexual abuse victims are older than 12 years of age, while some studies suggested that cases were younger than 12 years of age (Fis et al., 2010; Bahali et al., 2010; Köse et al., 2011). In our study, it was found that 77.8% (n=267) were older than 12 years of age. It is thought that improved perception and awareness about sexual abuse among adolescents can cause increase in reporting rates (Glazer, 2008). In addition, the fact that prepubertal children are more strictly protected by parents may be another factor that plays roles in lower sexual abuse rate in children younger than 12 years of age.

In our study, it was found that there were 265 girls (77.3%) and 78 boys (22.7%). In the literature, it has been reported that girls are more commonly victims of sexual abuse when compared to boys (De Voe and Coulborn-Faller, 1999; Finkelhor, 1994; Putnam 2003; Walrath et al., 2003; Pereda et al., 2009; Köse et al., 2011; Barth et al., 2013). The finding that 77.3% of cases were girls in our study supports the data that girls are more commonly exposed to sexual abuse. It is thought that the relatively lower rates detected in boys could be related to unwillingness for sharing experiences due to perception that seeking help for this reason is an improper behavior for mankind and concerns about being considered as homosexual (Pereda et al., 2009). In our study, it was found that adolescent girls were commonly exposed to sexual abuse. In the literature, it has been reported that girls experiencing loss of one or both parents and those with lower socioeconomic status, poorer maternal education level, behavioral disorders, lower success rates, learning disorders and impulsivity are at higher risk for sexual abuse (Walrath et al., 2003; Butler, 2013).

In our study, it was found that approximately one-third of sexually abused children weren't going school. It was found that, of 100 sexually abused children, 10 children weren't going to school as they were younger than 6 years of age, while 90 children weren't going to school due to several reasons. Our study supports the previous studies which reported that sexual abuse is more common in adolescent girls not going to school (Walrath et al., 2003). In addition, in this study, the reasons for not going school included withdrawal from school by parents or leaving school by their own decision, leaving school due to academic failure, not sending girls to school by parents and early marriage.
Several studies have reported that the majority of abusers are male and generally (30.1–82%) previously known to or acquainted with the victim (Cattaneo et al., 2007; Pinera-Lucatero et al., 2008; Syengo-Mutisya et al., 2008). In agreement with this, all the abusers in our study were male and 85.1% were known to the victim, while 14.9% were strangers.These findings indicate that child sexual abuse committed by previously known individuals is more likely to be disclosed. This may be attributed to people who are known and related having easier access to children, and to children not suspecting such people and trusting them more easily. In various studies from Turkey, incest rate was reported as 1.8–31.1 % among sexual abuse cases presented to child and adolescent psychiatry (Alikasifoglu et al., 2006; Bahali et al., 2010; Fis et al., 2010; İmren et al., 2013; Yildirim et al., 2014). The incest rate was found as 5.2% in our study. As known, incest is the most challenging type of abuse in terms of recognizing or reporting and this causes varying frequency rates of incest in different studies. Father is the most common abuser in incest abuse cases (Finkelhor 1994; Cengel-Kültür et al., 2007; Kaufman 2007; Yildirim et al., 2014). In our study, the abuser was father in 11 of 18 incest cases in agreement with literature. Child victims of incest generally do not disclose their experiences, usually due to feelings of shame, fear guilt, and other causes. In addition, families that are aware of abuse suffered by children prefer to cover the matter up, again from a variety of concerns. In cases of incest, which generally remains hidden for such reasons, the abuse lasts longer and is recurrent, and judicial complaints are made later compared too their cases (Pintello 2001; Gunduz 2011; Yildirim et al, 2014)

Marriages at childhood are also considered as abuse. These marriages are denoted by different terms such as "early marriage", "child bride" or "child marriage". According to legal arrangements in our country, individuals under 18 years of age aren't allowed to marry. Such marriages are established with religious but not legal act of marriage. In such cases, presentation to our clinical occured as a result of notification to judicious authorities by healthcare facilities which provide prenatal maternal follow-up or delivery services to these cases. In our study, rate of cases experienced early marriage was 10.5% (n=36). Mean age was 15.7±1.1 in these cases. This

finding suggests that younger children still are given to marriage despite legal arrangements.

In studies from Turkey, it has been reported that most common type of abuse is touching-fondling-friction (Fis et al., 2010; Köse et al., 2011; İmren et al., 2013). In our study, touching and/or friction (n=177; 51.6%) was most commonly reported type of sexual abuse in agreement with those studies; followed by vaginal penetration (n=84; 24.5%) and anal penetration (n=67;19.5%). One study evaluating 83 cases of child sexual abuse reported abuse involving penetration at a level of 35% and that additional physical violence was also present in 10.8% of these 83 cases (Fis et al., 2010). In our study, 6.9% of cases were subjected to physical violence. The most common type of sexual abuse was touching and/or friction and vaginal penetration in girls, whereas anal penetration and touching and/or friction in boys. The rarest type of sexual abuse was oral penetration in 2 girls.

The psychological effects of sexual abuse on children may vary depending on relationship between children and abuser, type of abuse, duration of abuse, presence of physical violence, presence of physical harm, sex, age and developmental stage of child, psychological characteristics of child and psychological development of child before sexual abuse (Kendal-Tackett et al., 1993; Johnson 2004; Maniglio 2009; Hornor 2010; Davies and Jones, 2013). Psychiatric disorders in children caused by abuse may occur immediately after event or years after (Nickel et al., 2004; Csorba et al., 2012). In a review, the long term effects of child sexual abuse was reported prevalence levels of PTSD of between 33% and 86% and prevalences of major depression of between 13% and 88% in child abuse cases (Polusny and Follette, 1995). In our study, a psychiatric disorder was detected in 71.4% (n=245) of victims of sexual abuse. It was found that there was PTDS in 129 (37.6%), major depression in 45 (13.1%), adjustment disorder in 34 (9.9%), anxiety disorder in 21 (6.1%) and acute stress reactions in 16 (4.7%) of the cases. No psychiatric diagnosis was found in 98 cases (28.6%) after sexual abuse. These findings are consistent to literature (Kendal-Tackett et al., 1993; Polusny and Follette, 1995; Bahali et al., 2010; Hornor 2010; İmren et al., 2013). In our study, cases without psychiatric disorders included adolescent girls who were exposed to abuse by their boyfriends in the form of touching and/or friction with their own consent, those experiencing early marriage with their own consent, victims of abuse in the form of touching 1-2 years ago, and victims of abuse in the form of sexual play. In the follow-up studies, it has been reported that 10-20% of children not expressing signs of psychiatric disorder may subsequently have psychiatric disorder depending on personal characteristics, parental or social support and environmental factors (Putnam, 2003). It is thought that psychiatric disorder couldn't be detected in short-term in some cases; thus, such cases should be followed to monitor long-term effects of sexual abuse.

In our study, mental retardation was detected in 7.3% (n=25) of the cases. In the studies from Turkey, rate of mental retardation has been reported between 7.4 % and 35.5% (Cengel-Kültür et al., 2007; Bahali et al., 2010; Köse et al., 2011). These rates suggest that individuals with mental retardation are at risk for sexual abuse. It has been reported that children with mental retardation may accept the proposal for a sexual relationship or sexual approaches without understanding the likelihood of sexual exploitation because of positive response to interest and affection, or inability of judgment and assessment (Morano, 2001). Moreover, children with mental retardation may experience difficulty when assessing or reporting the event. Thus, it is thought that sexual abuse events are underestimated in children with mental retardation since sexual abuse is experienced but not timely reported in such cases. However, it is also possible that parents behave in more protective manner in Kahramanmaraş province, which can be a protective factor against sexual abuse

In our study, annual number of cases between 2010 and 2013 were found as 40, 76, 102 and 125 respectively. It is though that legal orders by judicial authorities for findings of psychiatric examination from child and adolescent psychiatry departments play an important role in significantly increased clinical referrals, although increasing sensitivity, understanding and awareness to abuse cause an increase in clinical referrals. In addition, psychiatric symptoms developing after abuse promote parents to report abuse and seek medical help, which also contribute increasing clinical referrals.

Our study has some limitations. Firstly, data were retrospectively collected, based on hospital records. Secondly, psychosocial stressors other than abuse and data regarding social support weren't systematically assessed. However, data regarding child sexual abuse are stil less than might be expected in Turkey. Therefore, this evaluation of data for 343 children subjected to abuse over a 4-year period contributes to the determination of the characteristics of sexual abuse experienced by children in Turkey.

In conclusion, as adolescent children are more commonly exposed to abuse, attempts should be made to increase awareness about abuse in these children and their parents. In our study, psychiatric disorders prevalence was found to be high in children who were referred for psychiatric assessment after sexual abuse by public authorities. Early marriage is an important problem. We think that educations regarding this issue should be performed and legal arrangements should be made to protect such children. As several psychiatric disorders develop in sexually abused children and adolescents, healthcare providers working in the field of child and adolescent psychiatry should provide close long-term follow-up in these children.

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Assessment of Medicine Faculty Biostatistics Exam with different models

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ABSTRACT

The most important goal of a test is having reliable and valid measurement tools. The purpose of this study is to conduct item analysis to questions for an exam which measures the biostatistics knowledge of students and to assess the Biostatistics Program. The study group consists of a total of 261 students in their second year of Ondokuz Mayıs University Faculty of Medicine. 132 (50.6%) of the students are female, while 129 (49.4%) are male. Item analysis was assessed by using classical method and Rasch analysis. The average value of the test which consisted of a total of 60 multiple choice questions was 47.47± 6.99; the lowest score was 15, while the highest score was 57. KR 20 value was found as 0.86. When all the questions were analyzed with Rasch analysis, item difficulty of 75% of the items was between -1.60 and 1.60. As a conclusion, the exam was found to be reliable and it was shown to be a moderately difficult exam which assessed the knowledge of the students. Future studies are planned to assess Biostatistics teaching in different levels of class.

1. Introduction

Miller's pyramid is the most important component in tracking, measuring and assessing the development of education process and it attracts attention especially in the assessment of health education. While the base of the pyramid forms knowledge and comprehension skills, the top of the pyramid forms performance (Vegada et al., 2016).

During the process of measuring knowledge, multiple choice questions are frequently preferred among different types of measurement tools used for error-free and objective measurement results (Mukherjee and Lahiri, 2015). Multiple choice questions are easy to conduct and classify and they enable an easy assessment of the students taking the exam. Suitably created multiple choice questions measure and analyze knowledge, comprehension and application. They can measure knowledge from a narrow field to a wide field and thus they are the type of questions used most frequently in medicine (Epstein, 2007; Brookhart, 2015).

Having reliable and valid measurement tools is the most important goal of a test. Thus, item analysis is conducted by using the application results of the test (Atılgan et al., 2011; Mukherjee and Lahiri, 2015). Item analysis of multiple-choice questions first of all assesses the quality of the items, while at the same time the test measures the skills in the area. Different

theoretical methods assess whether the items have desired characteristics (Abdalla 2011; Tomak and Bek, 2015). The most frequently used method, Classical Test Theory (CTT) assesses the test as a whole. This method based on correlation assumes that all the questions are equal indicators of an individual's knowledge in that subject (Allen, 2012; Petrillo et al., 2015). An alternative method to this is Rasch analysis, which is one of the Item Response Theory (IRT) models. This method, which was initially developed for educational purposes, can also be used especially to develop psychological assessment tools. When compared with the classical method, Rasch analysis is more stable in different populations (Trakman et al., 2017). In this theory, responses are modeled on individual items. Individual's response on test item shows the characteristics of the item and the individual. It is assumed that the individual's response (test taker's performance) depends on one or more factors, which are called latent characteristics or skills. Each item in the test or questionnaire is assumed to measure an underlying latent characteristic (De Grutijter and Van der Kamp, 2008; Pallant, 2016).

In this study, the purpose was to conduct item analysis and distractor analysis for multiple choice questions which measured the biostatistics knowledge of Ondokuz Mayis University (OMU) Faculty of Medicine students and to assess the Biostatistics Program.

2. Materials and methods

Participants

The study group consists of a total of 261 students in their second year of Ondokuz Mayıs University Faculty of Medicine. 132 (50.6%) of the students are female, while 129 (49.4%) are male.

Measures

The data set used in the study consists of multiple-choice questions for measuring biostatistics knowledge of students during the 2015-2016 academic year. Students' level of knowledge was assessed with a total of 60 questions including basic biostatistics subjects. The topic titles included in the exam were listed as summary of the data, sample, descriptive statistics, statistical significance, error types and hypothesis tests. The questions were prepared by taking the lesson hours into consideration and with content validity and applied on the students.

Analysis

Rasch method was used with CTT for the analysis of multiple-choice questions. In the analysis of the data, NCSS model was used for CTT model, while RUMM programs were used for Rasch model (Hintze, 2007; Andrich et al., 2012).

For multiple choice questions, the stage of creating and analyzing the distractors is very important for a healthy measurement. Distractors are choices given to mislead those who do not know or those who know little (Tarrant et al., 2009; Deepak et al., 2015). A good distractor should consist of expressions which are correct but which do not meet the requirements of the problem and which are incorrect although they seem to be correct. Distractors are reasonable, but clearly incorrect expressions (Collins, 2006; Kilgour and Tayyaba, 2016).

CTT is the most widely and most frequently used item analysis method and it connects some existing structures to hypothetical basis. In this theory, the degree of having a characteristic is found by adding up the answers given to items related to that subject in the scale. The score obtained is the observed score and it consists of the combination of actual score and error score (Crocker and Algina, 2008; Cappelleri et al., 2014). In a reliable measurement, error score will decrease and the observed score will get closer to the real score, in other words, reliability is decreasing the random errors in the measurement on which reliability is conducted. In order to find out the reliability of a measurement tool, internal consistency analyses, item difficulty and item discrimination can be used (Biswas et al., 2015; Abozaid et al., 2017).

Kuder- Richardson 20 (KR-20) coefficient was used to assess the internal consistency of the measurement tool analyzed in this study. KR-20 is used in the assessment of reliability of tests which consist of multiple choice questions the correct answers of which are coded as 1 and the incorrect answers of which are coded as 0 (Brennan 2011).

In the assessment of reliability in terms of items, average values of the items, item difficulty and item discrimination were analyzed (Zaman et al., 2010; Hingorjo and Jaleel, 2012). Item difficulty is the rate of individuals who answer the item correctly (Deepak et al., 2015). Biserial point correlation (rpbis), which is used to find out item discrimination, is a measurement which shows the association between test score and the score of answering the item correctly (Biswas et al., 2015; Abozaid et al., 2017).

Another method used in the study is Rasch analysis. It is the only model in Item Response Theory models which includes item difficulty. The probability of answering an item correctly can be found with the function of the rate of that individual's ability level to item difficulty (Demars, 2010; Petrillo et al., 2015). It has two assumptions as unidimensionality and local independence. The responses given to questions are defined by a unidimensional latent variable and the responses given to questions are independent of each other (Li et al., 2011; Pallant, 2016). With Item Characteristics Curve (ICC) in Rasch analysis, item

response possibility of individuals with different ability levels and difficulty values of the items can be found with graphs (De Grutijter and Van der Kamp, 2008; Trakman et al., 2017).

3. Results

The data obtained from the answers given to 60 multiple choice questions by a total of 261 students were analyzed. The average value of the test was 47.47±6.99; while the lowest score was 15 and the highest score was 57. KR 20 value of the test was 0.86. The questions, which assessed basic biostatistics knowledge, were assessed with CTT and Rasch analysis. Difficulty and discrimination of the questions were found, at the same time how the questions worked was analyzed with distractor analysis. In terms of analysis of all the questions with Rasch analysis, there were 45 (%75) items with an item difficulty between -1.60 and1.60.

The questions which showed different intervals were analyzed in more detail by taking the difficulty and discrimination of the questions into consideration. In variance analysis table, for Item 38 which asked the equivalent of variance value, the correct answer A was given by 141 (54%) students, while the other answers were given as B by 15 (6%) students; C by 49 (19%) students; D by 16 (6%) students and E by 40 (15%) students, respectively. In the assessment conducted with classical method for this question, item difficulty was found as 0.54, while discrimination was found as 0.40. Item difficulty was found as 1.87 with Rasch analysis. Fit residual value was found as -2.02. ICC for Item 38 is given in Fig. 1.

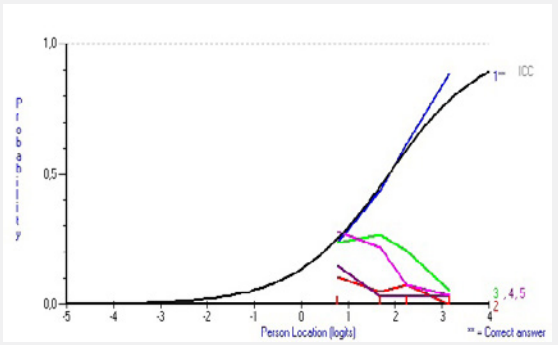

Fig. 1. ICC for Item 38.

The correct answer of Item 39 which assessed hypothesis test was E and it was given by 92 (35%) students, while the other answers were given as A by 12 (5%) students; B by 28 (11%) students; C by 8 (3%) students and D by 121 (46%) students, respectively. With CTT, item difficulty was found as 0.3, while discrimination was found as 0.31. With Rasch analysis, item difficulty was found as 2.70. Fit residual value was -0.42 (Fig. 2).

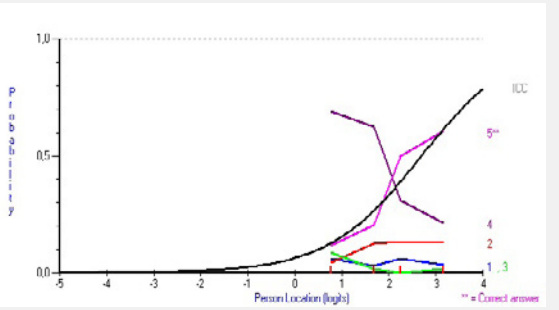

Fig. 2. ICC for Item 39.

The correct answer for Item 56 which assessed the graphic summary of data was C and it was answered correctly by 76 (29%) students. The other answers were given as A by 3 (1%) students, B by 81 (31%) students, D by 15 (6%) students and E by 84 (32%) students. Item difficulty was found as 0.29, while discrimination was found as -0.22. Item difficulty was found as 2.92 with Rasch analysis. Fit residual value was found as 0.64. Rasch analysis of the question is given with Fig. 3.

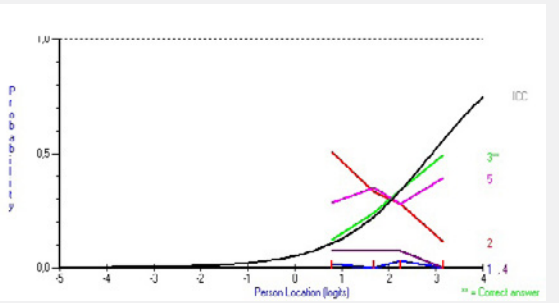

Fig. 3. ICC for Item 56.

The correct answer for Item 37 which assessed variation coefficient was C and it was given by 190 (73%) students, while the answer A was given by 42 (16%) students, B by 5 (2%) students; D by 4 (2%) students and E by 20 (8%) students. CTT assessment showed that item difficulty was 0.73 and discrimination was 0.37. Item difficulty was found as 0.87 with Rasch analysis. Fit residual value was -0.98. ICC for Item 37 is given with Fig. 4.

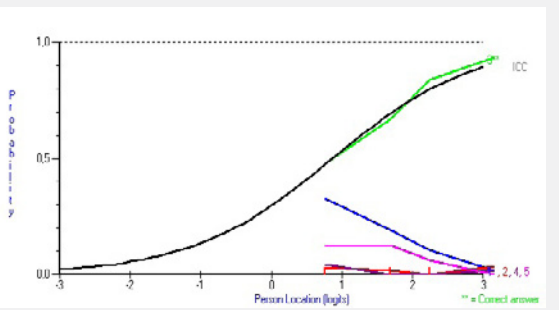

Fig. 4. ICC for Item 37.

The correct answer B for Item 36 which assessed hypothesis knowledge was given by 237 (91%) students, while A was given by 5 (2%) students, C was given by 3 (1%) students, D was given by 14 (5%) students and E was given by 2 (1%) students. In the assessment of this question made with classical method, item difficulty was found as 0.91 and discrimination was found as 0.38. Item difficulty was found as -0.63 with Rasch analysis. Fit residual value was 0.12. ICC for Item 36 is given with Fig. 5.

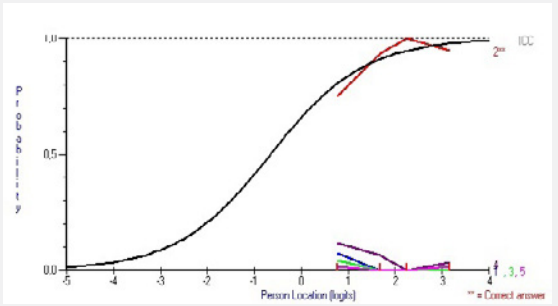

Fig. 5. ICC for Item 36.

4. Discussion

In the second year of their 6-year-long education, students of OMU Medicine Faculty get theoretical and practical classes about biostatistics in the block which includes basic information about biostatistics. The exam at the end of the block which includes multiple choice questions assesses students' level of knowledge and what they have learned.

Multiple choice questions are preferred especially when there are too many people taking the exam, when there is a need for selection and placement, when there are too many questions, when there is a need for quick results and when high reliability and validity is required. These questions which are developed for a specific content provide a consistently tested content (Collins, 2006; Mukherjee and Lahiri, 2015). The disadvantages of these questions are the fact that they are answered by remembering rather than recognizing the questions, there is the factor of luck in answering and developing them are difficult and time consuming. In this question type, since the information is mostly remembered within the item, it is insufficient to measure top level behaviors. This in turn causes negative effect on construct validity (Atılgan et al., 2011).

A test's being valid and reliable will help it to reach its goal. With this study, the test's analyses were conducted in general and on the basis of items (questions) and the characteristics of items which worked well and which did not work well were assessed over a few items.

In the general assessment of the reliability of the exam, KR-20 value was found as 0.86 and it is the equivalent of Cronbach Alpha in the assessment of the reliability of dichotomous questions (DeVellis 2006). A KR- 20 value of over 0.80 is required for a reliable measurement tool and it was found that the exam met this requirement. For KR-20, it is assumed that the questions are not equally difficult, while for KR-21, which is another type of KR, it is assumed that the questions are equally difficult. Thus, KR-20 is more reliable than KR-21 (Brennan 2011).

With assessment based on questions, item difficulty, discrimination and whether the distractors were well built were assessed. In the classical method, as the item difficulty level increases, it is understood that the item gets easier (Abozaid et al., 2017). Although the most ideal values for item difficulty are between 0.5 and 0.6 in an exam, 0.3-0.7 and 0.2-0.8 are recommended intervals (Sim and Rasiah, 2006; Hingorjo and Jaleel, 2012; Biswas et al., 2015). For item discrimination index, values over 0.25 are indicators of discrimination. Values over 0.40 are accepted as perfect, those between 0.30 and 0.40 are accepted as good and those between 0.25 and 0.30 are accepted as acceptable levels of discrimination (Deepak et al., 2015; Abozaid et al., 2017). In assessment with Rasch analysis, as the item difficulty becomes negative, the items become easier, while they become more difficult as it increases positively (De Grutijter and Van der Kamp, 2008; Trakman et al., 2017). Within this context, some questions –which had different difficulty and discrimination and distractor characteristics- were analyzed.

For item 38, item difficulty with CTT was 0.54, which can be accepted as the optimal value and a discrimination value of 0.40 can be assessed as good (Deepak et al., 2015; Abozaid et al., 2017). Since Fit residual values were between -/+ 2.5 for all items, the items were made fit for the model. With Rasch, item difficulty was 1.87, which was over the average (De Grutijter and Van der Kamp, 2008; Pallant, 2016). In terms of distractors, as ability increases, the rate of answering the question correctly also increases and the rate of incorrect answers decreases. According to these, it can be said that Item 38 is a good functioning, ideal item.

With Item 39, degree of freedom was questioned. In the question, degree of freedom (df) was asked for Student t test, the rate of highest distractor was higher than the correct answer and here df value was given for paired t test. With CTT, the difficulty of the question can be said to be acceptable and it can be said to have good discrimination (Biswas et al., 2015). With Rasch analysis, it can be described as a difficult question (Trakman et al., 2017). The important point here is the result that more talented students had higher rates of answering correctly and the highest distractor was marked by students who had lower levels of talent. The question was very distractive for students who had insufficient levels of information.

For Item 56 which was about graphical summary (box graph) in categorical data, the correct answer and the two distractors were answered in similar rates. According to the results obtained with both methods, the question is difficult and it does not have sufficient discrimination (Deepak et al., 2015; Pallant, 2016). It was found that the frequency of the correct answer increased as the level of talent increased, the frequency of the distractor in choice B (histogram answer) decreased as the level of talent increased and the distractor in choice E (line chart answer) was found to be high in high talent level. It was found that the students had superficial knowledge about this subject.

Item 37 which questioned the expression of variability with percentage had values close to the ones an achievement exam should have. Its discrimination can also be considered as good (Hingorjo and Jaleel, 2012). When analyzed with Rasch, it was found that it was an easy question and with ICC it was found that the correct answer was marked easily by the students (Pallant 2016). Since this question about the subject of descriptive analysis-variability measures is among the basic subjects students should know about, the percentage of correct answers can be accepted as normal.

Item 36, which was for the calculation of the expected value with Chi-square test, was found to be an easy question with both methods (De Grutijter and Van der Kamp, 2008; Trakman et al., 2017). In addition, discrimination had a value higher than 0.35 (Deepak et al., 2015; Abozaid et al., 2017). This result shows that this subject which was repeated in the applied lesson as well as the theoretical lesson was comprehended well by the students.

This study analyzed the exam which was conducted for measuring the knowledge of biostatistics lesson which requires the students to have specific basic knowledge during and after their medicine education and assessed the reliability of the exam in general and showed how the questions worked on the basis of item. These assessments made with different theoretical methods were also presented to readers visually with graphs. Since it was not possible to show all of the questions, five items which exemplified different difficulty and discrimination intervals were analyzed more closely.

As a conclusion, the reliability of the exam was revealed and it was shown that the exam was a moderately difficult exam which assessed the knowledge of the students. At the same time, multiple choice questions were assessed with analyses through different methods and their discriminations were analyzed according to different levels of talent.

Biostatistics has an important duty especially in terms of showing the power of evidence in medical practices based on evidence. Medical students need to have sufficient basic knowledge not only to be able to conduct their own practices but also to be able to follow scientific publications. Students should be given sufficient and necessary education during their medical studies and this education should be assessed. Thus, this study will play an important role in organizing the future programs and assessment of Biostatistics Education in different levels of classes is intended in future studies.

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Comparison of Truview EVO2 Videolaryngoscope and Macintosh Laryngoscope in pediatric patients

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ABSTRACT

We aimed to compare Trueview EVO2 laryngoscope and Macintosh laryngoscope in terms of hemodynamic response and intubation conditions for pediatric patients. 100 children aged between 1 month and 4 years were included in the study. Patients were randomly divided into 2 groups. Intubation was performed via Macintosh laryngoscope in Group DL and via Trueview EVO2TM videolaryngoscope in Group VL. Heart rates were similar between the two groups. Systolic, diastolic and mean blood pressures 1 minute after the intubation were significantly higher in Group VL. There was no significant difference between groups in terms of SpO2 levels, TD, airway demand, cricoid pressure or Cormack-Lehane scores. End-tidal CO2 levels were significantly higher in Group VL. Difficulty occurred while inserting the tube in 6 patients in Group VL but in none of the patients in Group DL. Intubation durations were higher in Group VL (17.81±1.31 sec) than in Group DL (17.00±1.20 sec). There was no statistically significant difference in terms of intubation related complications. In pediatric patients, better laryngeal visualization is acquired with Trueview videolaryngoscope but intubation duration prolongs and has no advantage on intubation success.

1. Introduction

Opening the airway and keeping it open is one of the main responsibilities of the anesthetist. Delays in opening the airway may result in irreversible damage or death in the hypoxic and anoxic brain. For this reason, it is the most important task of the anesthetist to assess the airway and make the necessary preparations to ensure that the airway is open and kept open. The continuity of vital functions depends on the opening the airway and keeping it open (Toker, 2012). Despite the new tools and techniques in airway management, endotracheal intubation remains the gold standard in securing the airway (Vlatten et al., 2009).

In pediatric airway management, it is important to know the anatomical differences between a child's and an adult's upper airway. An appropriate history and physical examination, appropriate endotracheal tube and laryngoscopy choice are the key points in pediatric airway management (Infosino, 2002).

Functional residual capacity (FRC) is lower in children due to the fact that the chest wall compliance is more, and the lung compliance is less than that of adults. This decline in FRC limits oxygen reserves in children during apnea periods (Berry and Castro, 2006). Failure of intubation or prolonged duration of

intubation may cause serious complications in children. For this reason, it is important to take control of the airway in a short period of time (Morgan et al., 2008). In this study, we aimed to compare the Truview EVO2TM laryngoscope, a newly developed videolaryngoscope type and not widely used in the pediatric age group, with the Macintosh laryngoscope, which is routinely used, in terms of hemodynamic response and intubation conditions.

2. Material and methods

After the approval of the University Ethics Committee, parents of the patients were informed about the study, and their written approval was obtained.

A total of 100 children aged between 1 month and 4 years with an ASA (American Society of Anesthesiologists) classification of I-II-III were included in the study, which were planned to undergo elective surgery and to be operated under general anesthesia. The patients were randomly divided into two groups.

Group DL: Those that were subject to intubation with Macintoch blade laryngoscope
Group VL: Those that were subject to intubation with Truview EVO2TM videolaryngoscope

Age, gender, weight, height, ASA and thyromental distance (TD) values were recorded in the preoperative examinations of the patients. No premedication was given to the patients. Intubation was performed in both groups by a 5-year specialist student, who used a Truview EVO2TM videolaryngoscope in 30 adult and 20 pediatric patients. During the intubation, head was held in neutral position, and a probe was used.

Patients with oxygen saturation (SpO2) of less than 94% in the preoperative room air or who were expected to have a power airway were not included in the study. Attempts with prolonged intubation durations (longer than 10 minutes) and attempts with incomplete intubation after 3 attempts were considered unsuccessful and were left out of the study. During the intubation procedure, the intubation was considered to be unsuccessful when SpO2 fell below 94%. In such cases, the patient underwent mask ventilation with 100% oxygen, and was switched to alternative methods. After the patients were taken to the operation room, all of them were monitored for heart rate (HR), noninvasive blood pressure, SpO2, and end-tidal carbon dioxide (ETCO2), using the "Preoperative standard monitorization" electrocardiography (ECG).

In both groups, anesthesia induction was started with 6% sevoflurane inhalation anesthesia and 100% oxygen. An additional 0.2 μg/kg/h remifentanil infusion was applied to the anesthesia. Intravenous 0.2 mg/kg cisatracurium was administered to relieve muscles, after seeing that mask ventilation was comfortable, and the lungs were ventilated. Patients were intubated at the end of three minutes of mask ventilation. In both groups, the duration of intubation was recorded as the time elapsed from the time the vocal cords were seen until the ETCO2 was seen on the monitor. The airway demand during mask ventilation and the need for cricoid pressure during intubation procedure were recorded. The number of attempts until reaching the successful endotracheal intubation was recorded. Laryngoscopy intervention was recorded as easy, moderate, difficulty, and impossible. The reasons for intubation difficulty (difficulty in seeing the larynx, difficulty in seeing the tube, difficulty in both) were recorded. Complications (bleeding, laceration, dental damage, etc.) during intubation were recorded.

In both laryngoscopy methods, a glottic image was recorded using the Cormack-Lehane (C&L) scoring system. Scores were recorded as I, II, III, or IV. Cases with C&L scores of III-IV were excluded from the study.

Hemodynamic parameters of the patients including HR; systolic (SBP), diastolic (DBP), mean (MBP) blood pressures; and SPO2 values were recorded preoperatively, at induction, and 1, 2, 3, 4, 5 and 10 minutes after intubation. ETCO2 values were also recorded at 1, 2, 3, 4, 5 and 10 minutes after intubation.

Statistical analysis

In order to determine the sufficient number of cases, the study of Singh et al. (Singh et al., 2009) was referred to. Using the Minitab program, the number of patients in both groups was determined as 50 at a level of $\alpha = 0.05$ with 99% confidence limit and 99% confidence.

Statistical analysis of the data obtained in this study was performed using the "Statistical Package for Social Sciences (SPSS) for Windows 16.0" program. Whether the obtained data were normally distributed was investigated using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare the groups with non-normal distributions. The Chi-square test was used to compare the data obtained by counting.

The data were expressed in means, standard deviations, numbers and percentages. p 0.05 was considered significant.

3. Results

There were no statistically significant differences between the two groups in terms of demographic characteristics (age, height, weight, ASA and gender) (p=0.647, 0.362, 0.129, 0.186, 0.149, respectively). The SpO2 and HR values of the groups were similar (p>0.05). Post-intubation first minute SAB, DAB and OAB measurements were statistically significantly higher in Group VL (Table 1, 2, 3).

Table 1. Groups systolic blood pressures.

	DL (n=49), (ort ± SD)	VL (n=48) (ort ± SD)	P
Preoperative	104.06 ± 15.43	107.08 ± 13.19	0.053
Induction	89.63 ± 12.85	93.04 ± 11.39	0.126
Intubation 1. minute	98.69 ± 13.26	105.45 ± 16.66	0.040
Intubation 2. minute	94.34 ± 12.57	98.12±11.74	0.088
Intubation 3. minute	92.61 ± 12.06	95.22 ± 9.92	0.110
Intubation 4. minute	91.32 ± 11.99	94.27 ± 10.71	0.138
Intubation 5. minute	89.36 ± 12.02	92.33 ± 9.94	0.072
Intubation 10. minute	90.08 ± 11.59	93.02 ± 9.45	0.077

Table 2. Groups diastolic blood pressures.

	DL (n=49), (ort ± SD)	VL (n=48) (ort ± SD)	P
Preoperative	63.22 ± 14.54	66.22 ± 16.07	0.412
Induction	52.61 ± 13.06	53.70 ± 12.41	0.513
Intubation 1. minute	68.85 ± 16.06	79.56 ± 21.32	0.007
Intubation 2. minute	56.85 ± 13.45	59.97 ± 13.01	0.100
Intubation 3. minute	54.24 ± 12.89	56.87 ± 12.60	0.109
Intubation 4. minute	54.12 ± 12.73	55.56 ± 13.68	0.484
Intubation 5. minute	51.46 ± 13.50	55.12 ± 12.81	0.074
Intubation 10. minute	51.16 ± 11.19	55.06 ± 14.43	0.146

Table 3. Groups mean blood pressures.

	DL (n=49), (ort ± SD)	VL (n=48) (ort ± SD)	P
Preoperative	80.34 ± 14.96	83.72 ± 17.30	0.304
Induction	68.10 ± 12.38	70.08 ± 12.77	0.302
Intubation 1. minute	76.85 ± 13.01	82.47 ± 15.16	0.039
Intubation 2. minute	73.20 ± 12.93	75.45 ± 11.99	0.170
Intubation 3. minute	71.22 ± 11.80	72.18 ± 10.83	0.484
Intubation 4. minute	69.61 ± 11.63	72.79 ± 13.14	0.258
Intubation 5. minute	68.20 ± 13.10	71.56 ± 11.02	0.169
Intubation 10. minute	66.63 ± 12.12	71.25 ± 10.71	0.053

In comparison between the groups, ETCO2 values were statistically significantly higher in Group VL at all measurement intervals ($p<0.001$). There were no statistically significant differences between the groups in terms of TD lengths, airway demand, cricoid pressure and Cormack-Lehane score ($p>0.05$) (Table 4).

Table 3. Groups intubation parameters.

	DL (n=49)	VL (n=48)	P
TM Distance (cm) (ort, SD)			
Airway need (n, %)			1.00
Yes	7(%14.3)	6(%12.5)	
No	42(%85.7)	42(%87.5)	
Cricoid pressure (n,%)			1.00
Yes	3(%6.1)	6(%12.5)	
No	46(%93.9)	42(%87.5)	
Cormack - Lehane I (n,%)	37 (%75.5)	38 (%79.2)	0.851
Cormack - Lehane II (n, %)	12 (%24.5)	10 (%20.8)	

During the intubation procedure, difficulties were encountered when guiding the tube in 6 patients in Group VL, while in Group DL, no difficulties were encountered in any patients ($p=0.03$).

Intubation times were significantly longer in Group VL (17.81 ± 1.31 sec) than in Group DL (17.00 ± 1.20 sec) ($p=0.002$).

There was no statistically significant difference in the number of attempts in the intubation process of the groups ($p=0.466$).

In Group VL, 2 patients were excluded – one due to the difficulty of laryngoscopy attempt and SpO2's falling down to 92%, the other due to unsuccessful intubation at the third attempt – and in Group DL, 1 patient was excluded.

4. Discussion

Today, the failures or difficulties in ensuring open airway during anesthesia practice are important causes of anesthesia-related morbidity and mortality. ASA reports difficult intubation as the third most common respiratory-related cause of death and permanent brain damage (Peterson et al., 2005). Compared to adults, intubation is more difficult in pediatric patients because there are significant differences in pediatric airway anatomy and respiratory system, and difficult airway is encountered more often (Kurt et al., 1998). Since pediatric patients have less oxygen reserves, they can rapidly develop hypoxia and then cardiac arrest when encountered with difficult airways. For this reason, it is extremely important to take control of the airline in children in a short period of time.

A line of sight is needed along the blade to see the glottic gap using the direct laryngoscopy; the angle of view is limited to oropharyngeal structures and measured as 15° (Vlatten et al., 2009). It is possible to improve the visibility of the glottis by increasing the visibility with the video camera system placed on the blade tip (Vlatten et al., 2009). The primary role of videolaryngoscopy is to achieve better performance in intubation, which is difficult or even impossible with standard methods (Ozkan, 2011).

Storz Miller 1 videolaryngoscope and the Miller 1 direct laryngoscope were observed on simulating difficult intubated infants (Fiadjoe et al., 2009). 32 pediatric anesthesiologists who participated in the study attempted intubation using random videolaryngoscope and direct laryngoscope. Using direct laryngoscopy, 40% of the anesthetists reported glottic vision as Grade III-IV and the entire videolaryngoscope as Grade I-II. And, the C&L score was significantly higher in direct laryngoscopy. Intubation times were recorded as similar in both groups. In a newborn with Desbuquois syndrome who had hypoplasia and microstomy on the face, and a short neck, C&L score were assessed as Grade IV using laryngoscopy with the Miller 0 blade, then at the second laryngoscopic evaluation the C&L score was graded as Grade III, after that the glottic opening was graded as Grade I using the Miller 1 pediatric videolaryngoscope for endotracheal tube instability, and intubation was performed (Samuel et al., 2008). They reported that videolaryngoscopy is a useful method when encountering a difficult newborn airway.

Hackell performed intubation in three separate cases with difficult airway history using videolaryngoscopy and performed intubation by evaluating the C&L score as Grade I. In the presence of difficult and/or unsuccessful direct laryngoscopy, they have come to the conclusion that videolaryngoscopy methods have proven to be an alternative method for babies in airway management (Hackell et al., 2009).

Vlatten compared the Storz videolaryngoscope and standard direct laryngoscope in children. The C&L score was recorded as a percentage of glottic gap and was found to be 97.5% (60-100%) in direct laryngoscopy and 100% in Storz videolaryngoscope. In the study, reported that Storz videolaryngoscope improved the glottic gap percentage score in children with normal airway anatomy (Vlatten et al., 2009).
The C&L scores were similar in our study. Most adult and pediatric studies with videolaryngoscopy have shown that the wide angle of blade and better visualization of the laryngeal structures on the screen during intubation attempts resulted in better image quality. In our study, however, no statistically significant difference was found between Cormack-Lehane scores in accordance with the study performed by Vlatten et al. (2009). This may be due to the fact that patients that were expected to have airway difficulty in the preoperative evaluation were not included in the study.

Kim have compared Macintosh laryngoscope and GlideScope videolaryngoscope in 203 pediatric patients. The duration of intubation was recorded as 36.0 sec in the group for which the GlideScope videolaryngoscope was used and 23.8 sec in the group for which the direct laryngoscope was used. As a result, they have reached the conclusion that in children, intubation with GlideScope videolaryngoscope required a longer period of time (Kim et al., 2008). In another study, Miller laryngoscope and Truview EVO2TM videolaryngoscope were used for intubation in 50 pediatric patients aged 2-8. The mean duration of intubation was recorded as 6.36 sec in Miller group and 13.8 sec in Truview EVO2TM group. They concluded that Truview EVO2TM improved the laryngoscopic glottic image, but required longer intubation times (İnal et al., 2010). In the other study Miller laryngoscope and the Truview EVO2TM videolaryngoscope were compared in 60 newborn and infants. They reported that the time of intubation was 18.18 sec in the Truview EVO2TM group and 16.30 in the Miller group (Singh et al., 2009). Macnair compared direct laryngoscopy and the Berci-Kaplan videolaryngoscope for airway management in 60 children aged 2-16 years. Intubation times were recorded as 16 (14-20) sec for the direct laryngoscopy group and 22.5 (17.8-35) sec for the videolaryngoscopy group, and the duration of intubation was found to be significantly higher in the videolaryngoscopy group (Macnair et al., 2009) In our study, we found that VL prolonged the duration of intubation, consistent with other studies in adult and pediatric patients. It is thought that this result was caused by the difficulty in guiding the tube by watching on the screen during the attempt of intubation with VL. İnal observed the heart rate changes before and after laryngoscopy in their study and found that heart rate changes in the Miller laryngoscope group were significantly lower than in the Truview videolaryngoscope group. They argued that this was due to the longer duration of intubation with Truview. Moreover, in that study, they found that the change in mean arterial pressure was similar in both groups (İnal et al., 2010). In the other study the changes in hemodynamic parameters were recorded in 200 patients aged 20-50 years using a Trueview videolaryngoscope or a Macintosh laryngoscope. Hemodynamic changes were similar between the groups (Timanaykar et al., 2011). Xue found no significant difference between two groups in terms of hemodynamic response to intubation in the study of Glidescope videolaryngoscope and Macintosh laryngoscopy (Xue et al., 2007). Nishikawa compared the effect of videolaryngoscopy and Macintosh laryngoscope on hemodynamic parameters. In the Macintosh group, they found the systolic blood pressure and heart rate at a significantly higher level (Nishikawa et al., 2009).

There was no significant difference between the groups when HR values were compared in our study. However, in the videolaryngoscopy group, SAD, DAB and OAB values were found to be statistically significantly higher at the initial measurements after intubation. It was thought that the reason for this was due to the lack of experience of the practitioner in using the videolaryngoscope.

In our study, ETCO2 values were also monitored after intubation in both groups. ETCO2 values were higher in the videolaryngoscopy group than in the direct laryngoscopy group. However, although there was statistical difference, this was not considered to be clinically significant because the values of ETCO2 did not reach very high values in the videolaryngoscopy group.

Barak compared Truview videolaryngoscopy and Macintosh laryngoscopy complications in 170 patients who were planned to undergo general anesthesia and found no significant difference in terms of dental injury and postoperative stridor. However, during the intubation period, soft palate injuries and lip bleeding were found to be significant in the Macintosh group. They attributed this to the ease of use of the videolaryngoscope, the lesser exertion of force during use and the practitioner's experience (Barak et al., 2007).

In our study, we did not encounter traumatic complications due to intubation in either group. It is thought that mechanical traumatic complications were not encountered due to conduct of the intubation process by watching on the screen, ease of use of the videolaryngoscope and its better image-rendering. In our age group, Truview videolaryngoscopy did not provide an advantage over intubation success in cases with no expected intubation difficulty in the preoperative evaluations. To the contrary, it was observed to prolong the duration of intubation because of the need for good hand-eye coordination compared to direct laryngoscopy.

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Analysis of orosomucoid and c-reactive protein levels in gingival tissue and serum of rats with experimental periodontitis: Comparison at different time points in disease progression

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ABSTRACT

Acute-phase proteins are thought to trigger periodontal tissue destruction. The core purpose of this study is to analyze the levels of Orosomucoid1 (ORM1) and C-reactive protein (CRP) in gingival tissue and serum of rats with experimental periodontitis. Thirty rats were divided randomly and Group 1 was specified as control group, while the remaining groups were classified as ligature-induced experimental periodontitis groups. Each group was constituted 10 rats and Group 2 was evaluated the impact of ligature for the term of 7 days. Group 3 was classified on the basis of 14 days ligature. With the help of ELISA, gingival tissue and serum samples was utilized for measuring CRP and ORM1 levels. Alveolar bone and attachment loss was statistically higher in all experimental periodontitis groups than those in control group ($P<0.001$). The levels of CRP and ORM1 in gingival tissue were significantly higher in Group 2 than in Groups 1 and 3 ($P<0.05$). Also, a statistically significant positive correlation was found between CRP and ORM1 levels in the gingival tissue ($P<0.001$). The present results reveal that tissue destruction at earlier periods of inflammatory periodontal disease may be associated with ORM.

1. Introduction

Periodontal disease can be regarded as an infectious disease which is mainly caused by periodontal microorganism (Feng and Weinberg, 2006). Severity and progression of the disease is based on the host immune response which can also be observed by the production of mediators including cytokines, prostaglandin, and acute-phase protein (Keles et al., 2012). Acute-phase proteins are effective markers for the identification and evaluation of inflammatory diseases and they are increased in case of microbial infection including periodontitis (Keles et al., 2012).

In case of acute and chronic inflammation, C-reactive protein (CRP) is considered to be the most

accurate marker of acute phase protein and periodontal disease is also linked with significant increase in CRP level (Gornik and Lauc, 2008; Gupta et al., 2015). Significant increase in the level of CRP in gingival tissue and serum is associated with inflammatory reaction which result in excessive production of CPR by hepatocytes (Brito et al., 2013; Lu and Jin, 2010; Shimada et al., 2010).

Orosomucoid (ORM) is an acute-phase plasma protein, which is also termed as alpha-1-acid glycoprotein, and this glycoprotein is inflammation-sensitive (Fournier 2000). In different pathological conditions such as physical trauma, any kind of bacterial infection, the malignant diseases and rheumatoid arthritis (RA), ORM serum concentrations increases many folds in different pathophysiological problems (Fournier et al., 2000; Luo et al., 2015). In the gene expression of ORM, the major regulatory mediators are glucocorticoids, IL-6, and IL-6 related cytokines in liver cells from rat and human (Luo et al., 2015). It is a matter of fact that its main functions are unknown; however, it regulates immunomodulatory and anti-inflammatory functions, inhibits the activation of the polymorphonuclear neutrophil and results in the modulation of monocytes-macrophages dependent secretion of LPS-induced cytokine (Fournier et al., 2000; Sai et al., 2014). Two genes control the expression of ORM and these are ORM1 and ORM2 (Sai et al., 2014). Rangé et al. (2013) demonstrated that ORM is a better inflammatory marker as compared to CRP and the reason behind is that periodontitis is an infectious chronic disease. Though, there is no data regarding comparison of ORM and CRP in the gingival tissue in periodontitis.

Thus, a hypothesis is made that the in the rats with experimental periodontitis, there may be a difference in the gingival tissue and serum level of ORM1 and CRP in different periods. Therefore, the purpose of this study is to analyze the serum and gingival tissue levels of ORM1 and CRP in rats with experimental periodontitis at different periods as well as healthy control group. Also, the relationship between these biomarkers and histomorphometric findings is investigated

2. Material and methods

Animals

The study evaluated a group of fifty Wistar albino rats, each 8 weeks old and weighing between 200-250 grams. The subjects were individually interned within plastic cages at a room temperature of 22±1°C within 50% humidity conditions. The lighting was maintained at a 12:12-h light–dark cycle, with the required food and water being provided ad libitum. The internment of the subjects was ensured to be in compliance with the protocols and guidelines recommended by the Ethical Committee of Animal Research of Bulent Ecevit University, in accordance with Guide for the Care and Use of Laboratory Animals (Protocol No. 2013-13-05/06). Upon stratifying them on the basis of their weights, they were arranged within 3 experimental groups of 10 subjects each. The groupings ultimately consisted of Group 1, healthy control; Group 2 was ligated for 7 days; Group 3 were ligated for 14 days.

Induction of periodontal disease

The experimental periodontitis effect was induced after tying 3.0 sterile silk ligatures within the cervical areas on both the left and the right of the mandibular first molars of individual subjects, barring those animals constituting the control group. Each of the subjects was therefore provided with two ligatures. General anesthesia was used during the procedure, which was intraperitoneally delivered along with 100mg⁄kg ketamine and 0.75mg⁄kg chlorpromazine. The ligatures contributed to periodontal diseases, facilitating the movement and passage of bacteria within the gingival cavities (Brito et al., 2013).

Sample collection

At the conclusion of the experimental phase, the subjects were denied food or water in the evening prior to the concluding day of the study. On the proceeding day, 5mL of venous blood was drained out through cardiac punctures under general anesthesia conditions, which were forwarded for serum analyses. On the conclusion of the study, subjects with experimental periodontitis, and the periodontally healthy rats were all decapitated. Their blood samples were placed within centrifuges (Shimadzu UV160A, SNo:28006648, Kyoto, Japan) at 3000g within room temperatures over a period of 10 minutes, enabling the collection of serums, which were then placed at −70°C prior to analysis. The mandibles were thereafter surgically removed, along with the gingiva within the surroundings. The gingival tissue samples were collected from within the buccal region located within the mandibular right first molars, prior to storage at -700C for subsequent biochemical analysis.

Biochemical analysis

The gingival tissue was blotted, prior to being weighed upon a microbalance. The tissues were cryogenically frozen using liquid nitrogen, before being subsequently grounded manually. This was done by placing them within eppendorf tubes having a required volume of PBS (pH 7.4, 10mM), diluted to 10 mg. tissue/mL PBS. This was sonicated (METU Electromechanical, Serial No.30607, Berlin, Germany) for 10 minutes at +4°C with 220V. On the day of evaluation, homogenates defrosted within the room from the samples were centrifuged (SIGMA 3K30, Serial No.76262, Osterode am Harz, Germany) at +4°C for 5 minutes with 15000g and supernatants were arranged for subsequent CRP

and ORM1 analysis. Gingival tissue and serum CRP and ORM1 concentrations were evaluated using commercially marketed enzyme-linked immunosorbent assay (ELISA) kits (Hangzhou Eastbiopharm Company, Zhejiang, China (Mainland)). The quantum of protein present within the tissues was concluded by the Lowry method (Lowry et al., 1951), with the results expressed as mg. per protein. The conclusions were derived as picogram (pg) of cytokine\mg of protein (pg\mg.protein) within the gingival tissues, and as pg\mL within the serum, barring CRP levels. CRP levels was represented as ng/mg.prot within the gingival tissues, and as ng\mL within the serum.

Histomorphometric analysis

The left of the mandible so detached from within the gingiva was fixated within 10% neutral buffered formalin. The samples collected were decalcified within 8% formic acid (14 days), and subsequently embedded within paraffin. Serialized paraffin sections (5 μm) were concluded from within the mesiodistal aspects within the mandibular first molars. Three of the sections reflective of the central parameters of individual tooth were observed and thereafter stained with hematoxylin and eosin (H&E).

Histomorphometric analysis was concluded utilizing a small microscope (BX50 research microscope, Olympus, Tokyo, Japan). The images were digitized using a camera (DP26 Digital Camera, Olympus, Tokyo, Japan) and subsequently analyzed using software (OLYMPUS DP2-BSW, Center Valley, PA) through a calibrated examiner (B.A.), not knowing the experimental design. As stated within the earlier study (Balli et al., 2014), individual sections were stained with H&E wherein the paramaters assessed included: 1) the percentage of alveolar bone in furcation area, 2) alveolar bone loss (ABL), and 3) clinical attachment level (CAL). The percentage ratios of alveolar bone area upon individual specimens were concluded as a ratio of the alveolar bone area versus the furcation area. The alveolar bone area was concluded as a mix of the trabecular bone area and the bone marrow area in furcation. The levels of the alveolar bone were concluded through a measure of the distances within the cemento-enamel junction (CEJ) and the alveolar bone crest. CAL was concluded to be the distance within the CEJ, versus the coronal extent of the connective tissue attachment to cementum. ABL and CAL values were concluded within mesial and distal regions of the mandibular first molars. All averages of the measurements concluded were utilized towards analyzing the data.

Intra-examiner reproducibility

Prior to histomorphometric analyses, the examiner (B.A.) evaluated 20 specimens twice, with a week's interval between the measures. Bland-Altman plots along with intraclass correlation coefficients were utilized towards concluding the intra examiner agreement and reliability measures (Donatelli et al., 2013). Bland–Altman plots reflected the agreements within the two values concluded within a week's interval in the histomorphometric parameters. The intraclass correlation coefficients (95% confidence interval) were concluded to be 0.981 (0.907-994) relative to the alveolar bone area measures, 0.988 (0.958-0.996) for alveolar bone loss and 0.992 (0.978-0.997) for clinical attachment level.

Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate the normality of the data. One-way analysis of variance and Tukey's post hoc test were employed to evaluate histomorphometric and biochemical parameters within the groups in the aftermath of the normality within the data distribution concluded. SPSS software (SPSS Inc., Chicago, IL, USA), version 19.0 was used for the tests, with $p<0.05$ being considered to be a statistically significant measure.

3. Results

Histomorphometric findings

Values associated the alveolar bone area in the furcation region, ABL, and CAL is stated within Table 1. Major increases within alveolar bone and attachment loss was observed within the experimental periodontitis groups when compared with the healthy control group ($p<0.001$). There were major differences within the experimental periodontitis groupings associated with alveolar bone and attachment loss ($p<0.001$). The alveolar bone area was larger within the experimental group, than in the control group ($p<0.001$). Within the experimental groups, the alveolar bone area within ligated groups over 14 days was much high when compared with the ligated group over 7 days ($p<0.05$). The histologic appearances are reflected within Fig. 1.

Table 1. The percentage of alveolar bone in furcation area, alveolar bone loss, and clinical attachment level.

Groups	Alveolar bone area (%)	Alveolar bone loss (μm)	Clinical attachment level (μm)
Group 1 (n=10)	67.638±4.80	433.459±32.11	114.214±20.43
Group 2 (n=10)	52.003±3.47*	879.644±71.91*	361.153±58.59*
Group 3 (n=10)	44.770±4.84*#	1263.50±45.87*#	708.92±59.68*#

Data are expressed as the mean ± standard deviation.
One-way ANOVA and post-hoc Tukey's test.
$p<0.05$ was considered to be statistically significant.
* Statistically significant difference from group 1(control group) ($p<0.05$)
# Statistically significant difference from group 2 ($p<0.05$)

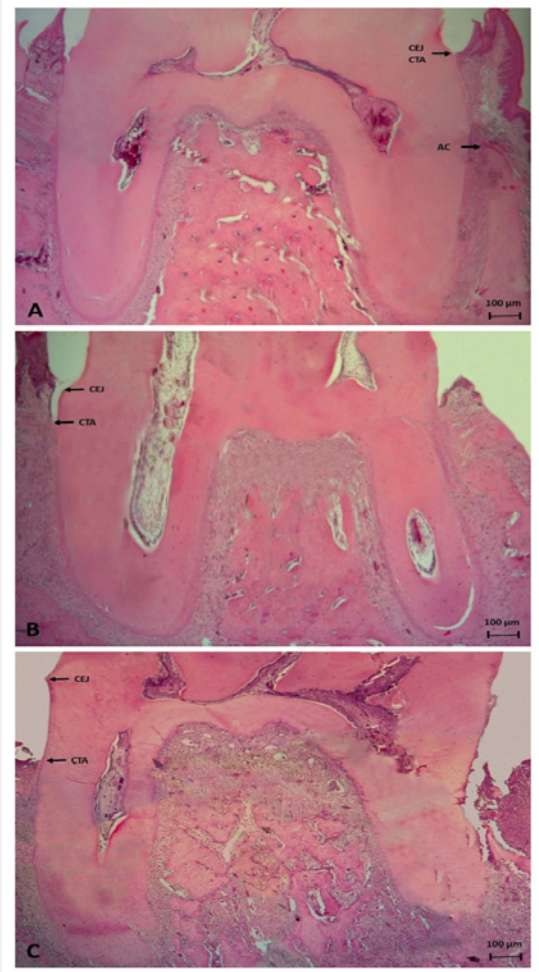

Fig. 1. (A) The sections from the mesio-distal aspects throughout the mandibular first molars in control group (H&E, 4x), (B) The sections from the mesio-distal aspects throughout the mandibular first molars in Group 2 (H&E, 4x), (C) The sections from the mesio-distal aspects throughout the mandibular first molars in Group 3 (H&E, 4x), CEJ: Cemento-enamel junction, CTA: Connective tissue attachment, AC: Alveolar crest.

Biochemical findings

Conclusions against CRP and ORM1 within gingival tissue and serum are reflected in Tables 2. The levels of CRP within gingival tissue and serum were observed to be statistically lower within Group 1 when compared against experimental periodontitis groupings, other than that observed against Group 3 in gingival tissue ($p<0.05$). Major differences were also observed within Group 3 versus Group 2 with regard to the gingival tissue levels associated with CRP, and relative to Group 3 versus Group 2 with regard to the serum levels of CRP ($p<0.05$). Gingival tissue ORM1 levels were observed to be lower within the control group in comparison to that for Group 2. It was nevertheless concluded to be higher within Group 2 when compared to Group 3 ($p<0.05$). Significant variations were not observed within serum ORM1 levels of the experimental periodontitis and within the control group ($p>0.05$).

Table 2. Levels of CRP and ORM1 in rat gingival tissue and serum.

Groups	CRP		ORM1	
	Gingival tissue (ng\mg.prot)	Serum (ng\mL)	Gingival tissue (pg\mg.protein)	Serum (pg\mL)
Group 1 (n=10)	27.53±9.31	22.00±4.38	560.98±94.00	463.76±159.09
Group 2 (n=10)	73.38±14.64*	46.62±5.79*	1155.29±277.58*	459.45±109.71
Group 3 (n=10)	44.18±19.10♯	57.35±6.17*♯	736.57±273.41♯	396.91±160.42

Data are expressed as the mean ± standard deviation.
One-way ANOVA and post-hoc Tukey's test.
$p<0.05$ was considered to be statistically significant.
* Statistically significant difference from group 1(control group) ($p<0.05$)
♯ Statistically significant difference from group 2 ($p<0.05$)

Correlations

The correlation coefficients are stated within Table 3. Upon examining all the groups simultaneously, a strong degree of positive correlation is observed within levels of CRP and ORM1 in gingival tissue ($p<0.001$). Further, strong negative correlations are concluded among the alveolar bone level, alveolar bone area and attachment level ($p<0.001$). There was a positive correlation between serum levels of CRP and histomorphometric values ($p<0.001$).

Table 3. The Pearson correlation (r) among groups with respect to ORM1, CRP levels and alveolar bone loss, alveolar bone area and clinical attachment level in all groups.

		Alveolar bone loss	Clinical attachment level	S CRP	S ORM1	G CRP	G ORM1
Alveolar bone area	r	-0.858**	-0.810**	-0.722**	0.085	-0.199	-0.107
	p	0.000	0.000	0.000	0.555	0.166	0.460
Alveolar bone loss	r		-0.925**	0.708**	-0.219	0.193	0.142
	p		0.000	0.000	0.127	0.180	0.326
Clinical attachment level	r	-0.925**		0.670**	-0.157	0.039	0.011
	p	0.000		0.000	0.275	0.790	0.942
S CRP	r	0.708**	0.670**		0.068	0.330*	0.219
	p	0.000	0.000		0.640	0.019	0.127
S ORM1	r	-0.219	-0.157	0.068		0.093	-0.037
	p	0.127	0.275	0.640		0.521	0.796
G CRP	r	0.193	0.039	0.330*	0.093		0.848**
	p	0.180	0.790	0.019	0.521		0.000
G ORM1	r	0.142	0.011	0.219	-0.037	0.848**	
	p	0.326	0.942	0.127	0.796	0.000	

** Correlation is significant at the 0.01 level.
*Correlation is significant at the 0.05 level.
S, serum; G, gingival tissue; CRP, C-reactive protein; ORM, Orosomucoid

4. Discussion

In the current study, the impact of acute-phase proteins within the incidence of periodontitis was observed, utilizing biochemical analysis processes within four varying experimental periods. The study concluded efficiencies within periodontal tissue breakdown, in addition to alveolar bone loss in periodontitis related to four varying experimental periods relative to histomorphometric analysis. As per our knowledge, this is a pioneering study evaluating the systemic and local levels of ORM within the periodontium utilizing biochemical analysis processes within the context of experimental periodontitis models.

The ligature-induced experimental periodontitis model was utilized within the study. This enabled significant efficiencies in handling, costs and in its similarities to human diseases. Ligature-induced periodontitis within rats is considered amongst the more common experimental models related to periodontitis (Brito et al., 2013). Alveolar bone loss is observed to be markedly observed within 7 days of ligature placement (Sobaniec and Sobaniec-Lotowska, 2000). Within the study, periodontitis was induced through the use of silk thread ligatures over 7 days. Brito et al. (2013) concluded how systemic inflammation markers concluded to basal levels within 28 days after the ligature. It was concluded how rats are greatly adaptable to inflammatory stimuli (Brito et al., 2013). The primary objective of the study using the current model was to evaluate the local effects of the lesions and the systemic consequences too. Hence, the subjects were evaluated for 14 days after the ligature. The current research revealed that in contrast with unligatured control rats, position of ligature led to considerable amount of alveolar bone loss and apical migration of the junctional epithelium. For about fourteen days in the ligated groups there was extensive amount of alveolar bone and attachment loss, which contrasted with our perception of the control and experimental groups. The outcomes are in accordance with the previously conducted studies (Sobaniec and Sobaniec-Lotowska, 2000; Peruzzo et al., 2008; Brito et al., 2013).

According to Gupta et al. (2015), within a day or two after the acute tissue breaks CRP increases in serum or plasma and declines with the resolution of inflammation or disturbance. Amid periodontitis, rise of CRP in serum or plasma have already been noted (Bain et al., 2009; Lu and Jin, 2010). However, it has been indicated by Lu and Jin (2010) CRP is also developing in human gingiva and it constitutively expresses CRP. They demonstrated that human gingiva consists of a local source of CRP and could possibly affect the CRP levels in gingival crevicular fluid (GCF), saliva and serum (Lu and Jin, 2010). Similarly, Maekawa et al. (2011) revealed that in contrast with gingivitis the expression of CRP mRNA was greater in periodontitis tissues. It was expected that the CRP's local expression of in gingival tissues may possibly be a critical factor in the advancement and development of periodontitis (Maekawa et al., 2011). In the same way, the levels of the gingival tissue and serum CRP were considerably low in control group as compared to experimental group according to the current study. Additionally, the variation in levels of CRP in the gingival tissue is observed, where the levels of CRP in the gingival tissue were less in Group 3 that that in Group 2 and there were higher levels of CRP in the serum in Group 3 than that in Group 2. Brito et al. (2013) concurred that within fourteen days serum CRP levels rises after ligature in rats and within 28 days restore to basal level. CRP increases faster with inflammation and quickly decreases after its resolution this is because in contrast with other acute phase proteins CRP has a short half-life (Vermeire et al., 2006). As stated, CRP generated by endothelial cells through pro-inflammatory cytokines is considerably low than that observed in blood (Maekawa et al., 2011). According to literature (Maekawa et al., 2011), our data indicates the rise of CRP levels in gingival tissue of the rats at the onset of inflammation and lowers within fourteen days with resistance to inflammation stimuli of the rat.

The study revealed that for 7 days ORM1 levels in the gingival tissue were greater in the ligated groups than for 14 days in the control group, however no considerable variation was observed in the serum ORM1 levels among groups. Moreover, in the gingival tissue there was a great relationship among ORM1 and CRP levels. Until now, no research has been found on the said subject, hence this is the only research that been conducted which indicates ORM1 levels in the gingival tissue increases with inflammation. According to Range et al. (2013), in mild-moderate periodontitis group ORM in the plasma was lower than the severe periodontitis group. After conformity for age, gender and smoking ORM level (in contrast with CRP and IL-6) was linked with periodontal inflammation severity (Range et al., 2013). Also, the acuteness of periodontitis, in morbidly obese patients, is linked with the rise of orosomucoid levels (Range et al., 2013). Mohmoud and Abbas (2002) indicated that ORM was constantly less on the gingival fluid immunograms, but was unidentified in plasma. According to Hochepied et al. (2003) ORM1 has the ability to systemically and locally release soluble IL-6 (sIL-6) through mononuclear leukocytes. Moreover, determining the level of ORM and identifying its glycoforms is more effective in measuring the intensity of an illness rather than assessing the CRP levels (Luo et al., 2015). It is proposed that ORM1 levels in gingival tissue could help in assessing the pathophysiologic procedures related to periodontitis.

Our research suggests that confined relentless infection may impact universal levels of inflammatory intermediaries. Inflammatory state can be provoked through periodontal infection by raising the levels of gingival of ORMI. Though it serious inflammation has been revealed from the model of the ligature-induced rat periodontitis and is not associated with the chronic illness in humans. Consequently, more research has to be done to explain the correlation of periodontal inflammation and the commitment to the periodontal disease of ORM1 by killing constraints in long haul research constituting bigger sample of patients with CP.

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Case Report

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Neuroendocrine carcinoma of the rectum

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ABSTRACT

Neuroendocrine carcinoma (NEC) of the rectum is rare. Most patients have metastatic disease at the time of diagnosis. These malignancies have a worse prognosis compared with conventional adenocarcinoma, and there is no standard treatment protocol. We report herein a case of NEC of the rectum with a short survival. A 60-year-old female was admitted to the emergency service with jaundice, abdominal pain, back pain and confusion, without a history of rectal bleeding. The imaging studies showed a rectal tumor, abdominal lymphadenopathies, and multiple liver and vertebral metastases. Rectal biopsy was performed. The histopathologic findings were consistent with those of NEC. Palliative radiotherapy was planned for the spinal metastases, but the patient died before completing radiotherapy, within 1 month from diagnosis. In conclusion, these neoplasms show a dramatic course, particularly in metastatic patients, and there is a clear need for studies involving larger numbers of colon and rectum NEC patients.

1. Introduction

Neuroendocrine cells are located diffusely throughout the human body, with most located in the intestinal tract (Vilallonga et al., 2008; Minocha et al., 2014). According to the 2010 World Health Organization (WHO) classification, neuroendocrine neoplasms are classified into three categories as follows: low-grade (Grade 1 = mitotic rate of less than 2 per 10 high-power fields (HPF) and a Ki-67 proliferative index (PI) of less than 2%) neuroendocrine tumor (NET), intermediate-grade (Grade 2 = mitotic rate of 2-20 per 10 HPF and a Ki-67 PI of 3-20%) NET, and high-grade (Grade 3 = mitotic rate of more than 20 per 10 HPF and a Ki-67 PI of more than 20%) NET or neuroendocrine carcinoma (NEC) (Öberg et al., 2012). Large cell and small cell NECs falls within the NET grade 3 category (Minocha et al., 2014).

NEC is extremely rare and constitutes less than 1% of all colon and rectal cancers. However, the incidence of these neoplasms is increasing (Shafqat et al., 2015). The symptoms of these neoplasms are similar but are extremely aggressive and are associated with a high

mortality rate compared with adenocarcinomas (Nojima et al., 2010; Aytac et al., 2013). Most of the patients are metastatic on presentation (Smith et al., 2014; Shafqat et al., 2015). The overall survival at 5 years in patients with metastatic disease is 3-5.5% (Kang et al., 2007; Shafqat et al., 2015).

There have been no prospective studies on or standard treatments developed for patients with NEC of the colon and rectum because of its rarity. Treatments are based on case reports, small retrospective studies, adenocarcinoma of the rectum and small cell carcinoma of the lung (Aytac et al., 2013; Smith et al., 2014; Shafqat et al., 2015). We herein report a rare case of NEC of the rectum that showed a dramatic course.

2. Case report

A 60-year-old woman was admitted to the Ondokuz Mayis University Hospital emergency department with jaundice, inability to remove gas or stool, and abdominal and back pain. Her consciousness was blurred and not cooperative. She was icteric. Her Karnofsky performance status was 40%. There was no history of rectal bleeding. Physical examination revealed hepatomegaly. There was no blood or mass on digital rectal examination. The complete blood count, serum biochemistry and serum tumor marker results were as follows: hemoglobin, 13.3 g/dL (reference range (RR) = 12.00-15.00 g/dL); total bilirubin, 18.21 mg/dL (RR = 0.1-1.5 mg/dL); direct bilirubin, 15.8 mg/dL (RR = 0.00-0.40 mg/dL); aspartate aminotransferase (AST), 117.7 U/L (RR = 8-46 U/L); alanine transaminase (ALT), 80.5 U/L (RR = 7-46 U/L); gamma-glutamyl transferase (GGT), 562 U/L (RR = 5-36 U/L); carcinoembryonic antigen (CEA), 1.02 ng/mL (RR = less than 4.3 ng/mL) and carbohydrate antigen (CA) 19-9, 19.4 U/mL (RR = 0-37 U/mL). The postero-anterior chest X-ray results were normal. Abdominal ultrasonography detected multiple liver masses. Abdomino-pelvic computed tomography (CT) detected hepatomegaly, multiple liver masses, a mass in the 3.5-cm proximal segment of the rectum and pathological enlargement of the perirectal, presacral, paraaortic, portocaval and celiac lymph nodes (Fig. 1).

Sigmoidoscopy showed a mass that completely filled the proximal lumen of the rectum. Biopsy of the rectal mass was performed. Immunohistochemical (IHC) staining of the tumor was positive for synaptophysin and CD56 but negative for chromogranin A (Cg-A). The Ki-67 PI was greater than 20%. The mitotic rate was more than 20 per 10 HPF. These histopathologic findings were consistent with NEC (Fig. 2).

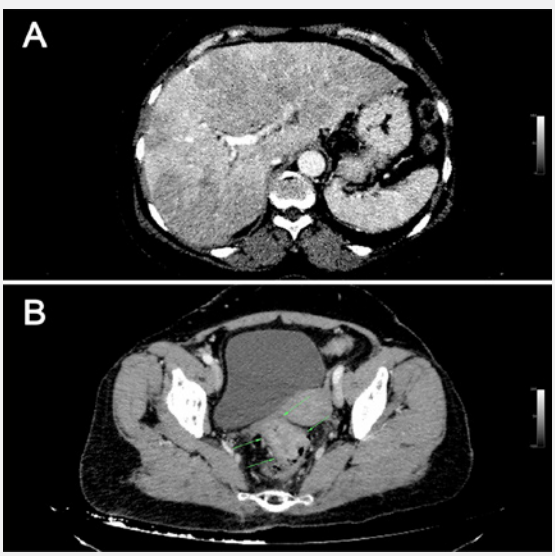

Fig. 1. (A) Computed tomography showing numerous hypodense masses throughout the liver consistent with liver metastasis. (B) Contrast-enhanced computed tomography of the pelvis reveals a rectal mass involving the proximal segment of the rectum (shown with arrows).

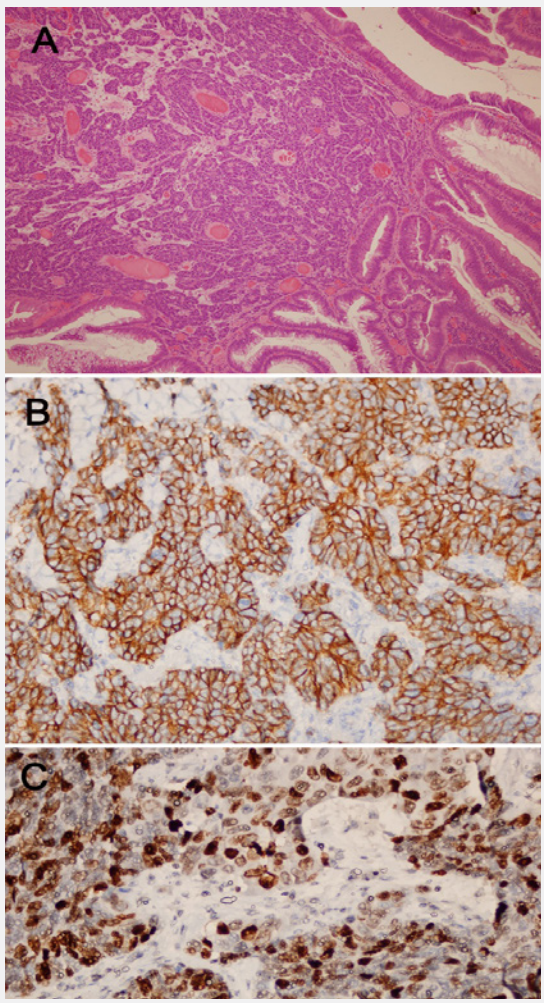

Fig. 2. Pathological findings: hematoxylin and eosin (HE) and immunohistochemistry staining images. (A) HE staining (×100). (B) CD56 immunostaining (×400). (C) Ki-67 immunostaining (×400).

Chest CT was normal after a definite diagnosis. Spinal magnetic resonance imaging was planned due to back pain, and multiple vertebral metastases were detected. Palliative radiotherapy (RT) was planned for the vertebral metastases. The patient died of hepatic failure during RT.

3. Discussion

NEC of the large bowel was first described by Gould and Chejfec in 1978 (Gould and Chejfec, 1978). The most frequent localization of NEC in the large bowel is the rectum, and the reported rates vary between 26.5% and 42% (Smith et al., 2014; Shafqat et al., 2015). Most of the rectal tumors are located in the mid and upper rectum (Aytac et al., 2013). The clinical presentation of rectal NEC is similar to that of adenocarcinoma. The most frequently seen symptoms are abdominal pain, hematochezia, constipation, tenesmus and fecal occult blood. The symptoms of paraneoplastic or carcinoid syndromes and metabolic abnormalities are rarely seen (Vilallonga et al., 2008; Aytac et al., 2013; Minocha et al., 2014). As in our case, most (57.9 - 67%) patients present with metastatic disease, and the liver is the most frequently (51 - 68%) seen site of metastasis at presentation (Okuyama et al., 1999; Miyamoto et al., 2006; Sorbye et al., 2013; Smith et al., 2014).

NEC is diagnosed according to the aforementioned WHO classification, with a high proliferation rate reflected by the number of mitoses and a Ki-67 PI greater than 20% (Öberg et al., 2012). The Ki-67 PI is the best available marker of tumor cell proliferation. It predicts the invasive potential of these neoplasms. Highly proliferating tumors with a Ki-67 greater than 10% have extensive angioinvasion and show high potential for developing into metastatic disease. Additionally, these tumors usually stain positively for one or more neuroendocrine IHC markers such as Cg-A, synaptophysin, neuron-specific enolase (NSE) and CD56 (Minocha et al., 2014). The reported positivity rates of Cg-A, synaptophysin and NSE staining in patients with neuroendocrine neoplasms are 72.62-94%, 76.19-96% and 32.74%, respectively (Sorbye et al., 2013; Zhang et al., 2014). Our case was synaptophysin positive, CD56 positive, and CgA negative and met both criteria of the WHO classification.

The treatment for patients with NEC of the colon and rectum has not been clearly defined. NEC of the colon and rectum is morphologically and phenotypically related to NEC (large and small cell types) of the lung. Therefore, particularly in metastatic patients, cytoreductive chemotherapy (ChT) with platinum-based regimens is generally recommended (Miyamoto et al., 2006; Minocha et al., 2014). However, platinum-based ChT does not provide sufficient benefit in patients with a Ki-67 value less than 55% (Sorbye et al., 2013). There is no established second-line ChT agent for these neoplasms, but the efficacy of temozolomide alone or in combination with capecitabine ± bevacizumab was reported in some retrospective studies (Öberg et al., 2012). Some NECs contain non-neuroendocrine components, such as adenocarcinomas. In such situations, the chemotherapeutic regimen should be chosen according to the predominant cell type in the tumor (Aytac et al., 2014). Surgery is the mainstay of treatment for localized disease but does not provide a survival benefit for metastatic patients (Smith et al., 2014). On the other hand, localized non-small cell NEC patients obtain a survival benefit with surgery, but this is not valid for small cell NEC patients (Shafqat et al., 2015). Postoperative concurrent chemoradiotherapy (CRT) and/or ChT are recommended in patients with a high risk of local recurrence, such as those with positive lymph nodes and a positive resection margin (Miyamoto et al., 2006; Nojima et al., 2010; Aytaç et al., 2014). Prophylactic whole-brain irradiation, as in patients with small cell lung carcinoma, is not recommended due to the rarity of brain metastases (Smith et al., 2014).

The reported 5-year survival rates of patients with these neoplasms at stage I, II, III and IV are 57.4%, 56.4%, 26.3% and 3%, respectively (Shafqat et al., 2015). Poor prognostic factors are small cell histology, increasing age, male gender, stage III-IV tumors, poor performance status, a high platelet count and a high lactate dehydrogenase level (Sorbye et al., 2013; Shafqat et al., 2015). Our patient was admitted with widespread metastatic disease and died within a month before the completion of palliative RT.

In conclusion, NEC of the colon and rectum is extremely rare. Most patients have metastatic disease at the time of diagnosis. These tumors have a worse prognosis than that of conventional adenocarcinoma, and there is no standard treatment protocol. There is a clear need for studies involving a greater number of colon and rectum NEC patients.

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Isolated seminal vesicle metastasis from gastric adenocarcinoma: First case report

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ABSTRACT

A 49-year-old Turkish man underwent subtotal gastrectomy for gastric cancer in February 2010. The cancer was staged as pT4aN0M0R0. The patient received adjuvant chemoradiotherapy per the Intergroup study 0116. Regular follow-up abdominopelvic computed tomography revealed a contrast-enhancing right seminal vesicle lesion 35 months after gastric surgery. Staging evaluation using (18) F-fluorodeoxyglucose positron emission tomography/computed tomography revealed isolated seminal vesicle fluorodeoxyglucose uptake. A right seminal vesiculectomy was then performed. Histologic examination of the seminal vesicle specimen revealed that the sample was similar to the original gastric adenocarcinoma. The tumor board recommended external beam radiotherapy due to the close surgical margin, but the patient refused treatment. Five months after right seminal vesiculectomy, tumor recurrence was found. Tumor excision and left seminal vesiculectomy were performed, and 45 Gy external beam radiotherapy was delivered to the region of recurrence in February 2014. As of January 2016, the patient has had no complaints since the last radiation treatment. In conclusion, we report the first case of isolated seminal vesicle metastasis from gastric adenocarcinoma. Therefore, seminal vesicles should be considered a potential recurrence site in primary gastric adenocarcinoma. The combination of surgery and radiation (45 Gy dose) without chemotherapy appeared to be successful in treating this gastric adenocarcinoma metastasis.

1. Introduction

Gastric cancer (GC) is the fifth most common malignancy and the third leading cause of cancer mortality in both sexes worldwide (Ferlay et al., 2015). Moreover, GC is the second most common gastrointestinal malignancy and is responsible for most gastrointestinal cancer-related deaths worldwide (Morganti et al., 2013). GC usually metastasizes to the liver, lungs, abdominal lymph nodes, bones, and the peritoneum (András et al., 2013). Herein, we report the first case of isolated seminal vesicle (SV) metastasis in a patient with GC after a curative subtotal gastrectomy.

2. Case report

A 49-year-old Turkish man presented to his doctor with gastric complaints in January 2010. Gastroscopy

revealed an ulcer with a diameter of 5 cm at the gastric angulus. A biopsy revealed adenocarcinoma of the stomach. The patient was referred to the Ondokuz Mayis University Medical Faculty Hospital. Staging work-ups, including a complete blood count, comprehensive biochemistry profile, chest computed tomography (CT), and abdomino-pelvic CT, indicated no evidence of metastasis. The patient underwent distal subtotal gastrectomy with lymph node dissection in February 2010. During surgical exploration, a 5×5 cm tumoral mass at the gastric angulus and a suspicious nodular structure in the left lobe of the liver, which was destroyed after palpation, were found. In addition, the tumor had invaded the serosa, and there were no peritoneal implants. Histopathologic examination revealed grade 2 gastric adenocarcinoma (Fig. 1), approximately 45×35 mm in size, and tumor penetration of the serosa (pT4a) with marked perineural and lymphovascular invasion. There were no metastases in any of the 12 removed lymph nodes (pN0). Proximal and distal surgical margins were not involved (R0).

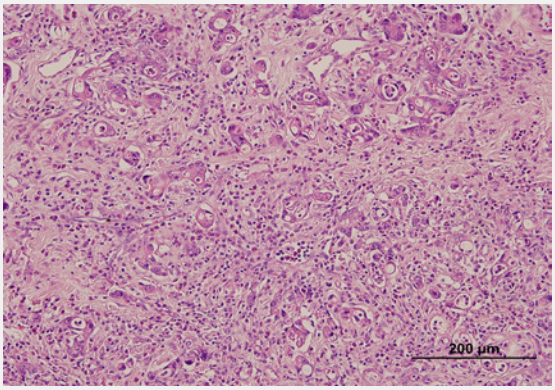

Fig. 1. Hematoxylin-eosin staining (×20) reveals atypical epithelial cells of gastric adenocarcinoma.

Due to suspicious operative findings, positron emission tomography/computed tomography (PET/CT) imaging was performed, and no metastases were detected. The patient was staged as T4aN0M0R0 according to the American Joint Committee on Cancer (AJCC) TNM staging classification for carcinoma of the stomach 7th edition (2010). He was treated with concurrent chemoradiotherapy per the Intergroup study 0116 (Macdonald et al., 2001) until August 2010. After treatment completion, the patient's follow-up was planned at 3-month intervals for the first 2 years, biannually for 2-5 years, and then annually thereafter. Follow-up evaluation for this patient consisted of a physical examination, complete blood count, and comprehensive biochemistry profile at each control period. A chest radiograph was performed once every 6 months. Upper gastrointestinal endoscopy and radiologic imaging were performed as clinically indicated or annually.

A regular follow-up abdominopelvic CT in January 2013 revealed a contrast enhancing right SV nodular lesion without any specific patient complaints. Pelvic magnetic resonance imaging (MRI) also revealed similar findings (Fig. 2).

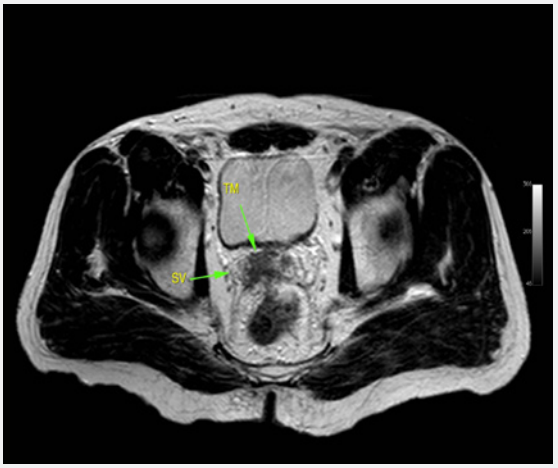

Fig. 2. MRI (T2-weighted) reveals a tumor in the right seminal vesicle with an irregular edge (shown with arrows: TM = tumor, SV = seminal vesicle).

Lastly, PET/CT was performed, and minimal FDG uptake (maximum standard uptake value: 4.05) was seen in the right SV (Fig. 3).

The patient's laboratory tests, including total PSA

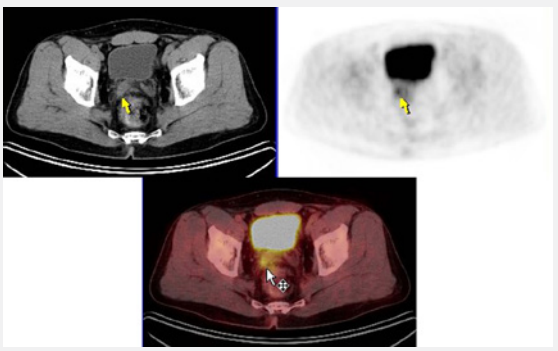

Fig. 3. PET/CT images of right seminal vesicle metastasis.

(0.6 ng/ml), were normal. A transrectal ultrasound-guided biopsy was performed, and histologic examination revealed adenocarcinoma infiltration. A right seminal vesiculectomy was then performed in June 2013. Histopathologic examination revealed that the maximum tumor diameter was 35 mm, and the tumor was less than 1 mm from the painted surgical margin. Immunohistochemical tests revealed that the tumor cells were cytokeratin 20 positive, CDX2 positive, cytokeratin 7 negative, and PSA negative. Intracytoplasmic and luminal muscin presence were revealed using PAS Alcian blue (Fig. 4).

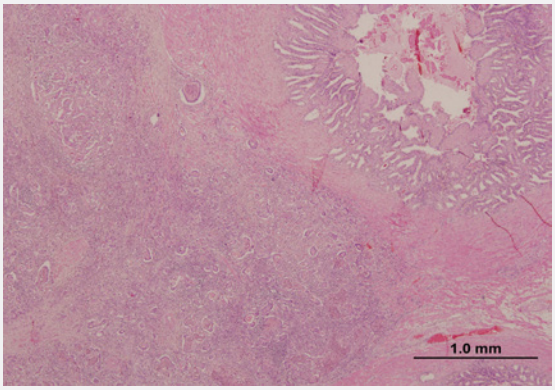

Fig. 4. Hematoxylin-eosin staining (×4) reveals adenocarcinoma infiltration of the seminal vesicle.

Histopathologic characteristics suggested that the tumor had resulted from metastasis of the initial gastrointestinal system adenocarcinoma. Ultimately, the patient was diagnosed with SV metastasis from gastric adenocarcinoma based on medical history and immunohistochemical staining results. The multidisciplinary tumor board recommended adjuvant radiotherapy due to the close surgical margin, but the patient refused and was followed over 3-month intervals. An abdominopelvic MRI was performed in November 2013, and it revealed tumor recurrence between the prostate, bladder posterior wall, rectum anterior wall, and left SV in the right seminal vesiculectomy region. PET/CT was performed in December 2013 and only one hypermetabolic focus in the right seminal vesiculectomy region invading the rectum anterior wall was seen (Fig. 5).

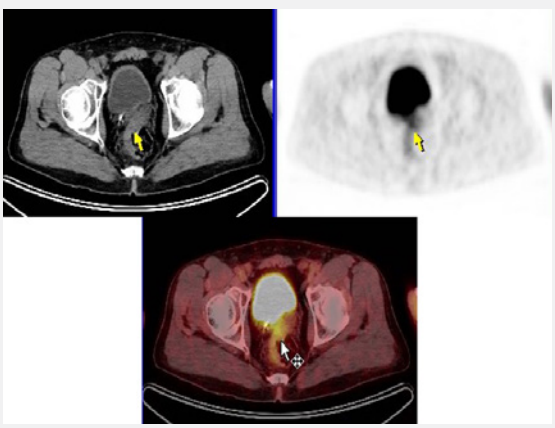

Fig. 5. PET/CT images reveals tumor recurrence at the right seminal vesiculectomy region.

The multidisciplinary tumor board recommended radical surgery involving the rectum, prostate, and SV, but the patient refused due to infertility and impotence risk. In February 2014, the patient consented to a less risky surgery that involved tumor excision and left seminal vesiculectomy. After this decision, an abdominopelvic MRI was performed that revealed local progression to the right seminal vesiculectomy region. Left seminal vesiculectomy and tumor excision were performed in February 2014. Histopathologic examination revealed adenocarcinoma infiltration of the left SV and a positive surgical margin. External beam radiation therapy (EBRT) to the recurrence region was recommended due to disease recurrence and a positive surgical margin. Finally, the patient was treated with 45 Gy EBRT. Chemotherapy was not implemented due to lack of additional metastasis. Regular follow-ups were performed. The patient was alive without further complaints when this report was written in January 2016.

3. Discussion

The mechanism of spread from GC to the SVs is uncertain. The SV is often invaded by locally advanced prostate cancer (Egevad et al., 2007). Secondary involvement of the SV is more common than primary SV cancer (Lee et al., 2007). Secondary malignancy of the SV from non-adjacent sites is extremely rare. In 1956, Dalgaard and Giertson established the following criteria for the diagnosis of primary SV adenocarcinoma: 1) the tumor should be a microscopically verified carcinoma, localized exclusively or mainly to the SV; 2) the presence of other simultaneous primary carcinoma should be excluded; and 3) the tumor should preferably resemble the architecture of the non-neoplastic SV (Gong et al., 2011).

In the case presented here, 1) staging evaluations did not show any lymphatic, peritoneal, or distant metastasis other than SV in 2013; 2) histopathologically, the removed SV tumor (2013) was similar to the original gastric adenocarcinoma (2010). Therefore, hematogenous metastasis appears to be the most likely pathway for SV tumor occurrence.

In conclusion, the SV should be considered a recurrence site in primary gastric adenocarcinoma patients. The differential diagnosis between metastasis and primary SV carcinoma is important for oncologic treatment. The combination of surgery and radiation (45 Gy dose) without chemotherapy seemed to be successful in treating this case of gastric adenocarcinoma SV metastasis.

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Treatment of intra-gestational methotrexate of cesarean scar ectopic pregnancy: A case report

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ABSTRACT

Cesarean scar pregnancy is the localization of uterine out of the cavity. There is a variety of treatment methods of cesarean scar pregnancy. There is not yet a consensus on treatment of scar pregnancy by using a preferred method. A 28-year-old woman applied to our center with the suspicion of pregnancy. A cesarean scar pregnancy that had fetal heart beats consistent with 6 weeks +2 days was determined in the area of incision line of uterus. Methotrexate was injected to the patient with oocyte pick-up needle under transvaginal ultrasonograph. No complication developed after the procedure. The patient was discharged in good health from the hospital the next day and her b hcg levels turned back to normal level.

1. Introduction

Cesarean scar pregnancy is the localization of uterine out of the cavity by surrounding completely with the fibrous tissue of the previous lower uterine segment cesarean scar and myometrium. Deterioration in endometrium and myometrium after cesarean section can set ground for implantation in uterine scar. Early invasion of myometrium is a condition that can cause uterine rupture and excess bleeding in the first trimester (Jurkovic et al., 2003).Because the cases of cesarean increase nowadays and can be detected more easily by ultrasonography, the incidence of such cases has been increasing. Rate of incidence is 1/1800-1/2216 among all pregnancies, and 0.15% among the women having history of cesarean (Chueh HY, 2008).Due to being observed rarely, cesarean scar pregnancies are present as case reports in the literature. In the literature, there is a variety of treatment methods of cesarean scar pregnancy. Treatment options such as local or systemic methotrexate (MTX), expecting treatment, uterine artery embolization, uterine curettage, local potassium chloride (KCl), hysteroscopy, laparotomy or laparoscopic excision, hysterotomy and hysterectomy are reported. Early and true diagnosis, alternative treatment options and combinations are very important for preventing serious complications (Katarzyna

and Ermanno, 2011).There is not yet a consensus on treatment of scar pregnancy by using a preferred method. Generally, such cases are referred to advanced centers for examination and treatment. In our hospital, such cases are successfully treated. The aim of this study was to present a case of cesarean scar pregnancy we treated successfully by administering single dose of methotrexate.

2. Case report

A 28-year-old woman, who was gravida 3 and para 2, had 2 previous cesarean sections. The patient applied to an external center with the suspicion of pregnancy and was referred to our hospital with diagnosis of cesarean incision scar pregnancy during her examination. She was suffering from struma and depression; and was receiving medical treatment for 10 years due to depression. According to her last menstrual period, she was pregnant for 6 weeks +2 days. In the examination, her vital findings were found to be stable. In both transvaginal and abdominal ultrasonography, a cesarean scar pregnancy that had fetal heart beats consistent with 6 weeks +2 days was determined in the area of incision line in the frontal side of uterus. Endometrial cavity and cervix were empty (Fig. 1).

Fig. 1. Ultrasonographic image of endometrial cavity and cervix.

There was no fluid in the douglas. The gestational sac was settled in old uterine scar in the lower segment of uterine and prolonged towards serosa of uterus. The hemogram and routine biochemistry values were determined to be normal in routine examinations of the patient. The possible risks, which could occur such as rupture bleeding if it was not treated, and treatment options were told to the patient and local methotrexate administration was decided. 50 mg local MTX was injected to the patient with oocyte pick-up needle under transvaginal ultrasonography-guided mask anesthesia. No complication was developed during and after the procedure. The patient was discharged in good health from the hospital the next day and called for weekly ultrasonography and b hcg checks until her b hcg levels turned back to normal level.

3. Discussion

Because the rates of cesarean have increased today and advanced ultrasound devices have been used, the incidence and diagnosis rates of cesarean scar pregnancy have increased (Sadeghi, 2010). There are cases of scar pregnancy diagnosed with transabdominal ultrasonography in 16th and 23rd weeks in literature. The diagnosis of our case was made in the 6th week of the pregnancy. The uterus isthmic segment localization of our case had the ultrasonographic diagnosis criteria of scar pregnancy with its reduced myometrial layer between the gestational sac and the bladder (Jurkovic, 2003).

The initial complaints of the patients can be vaginal bleeding or/and stomachache; can be realized during routine follow-ups; and can be asymptomatic. Almost half of the patients in the literature are asymptomatic (Maymon, 2004). It was asymptomatic in our patient and she was not describing any complaint. The diagnosis was made during routine pregnancy examination and the patient was referred to us.

The first treatment of scar pregnancy dates back to 1978 with the removal of lesion tissue (Litwicka, 2011). Even though there are numerous treatment modalities are administered in the literature, there is not yet a consensus on the most appropriate treatment approach of scar pregnancy. In the study conducted Le et al., with 38 patients, they compared uterine artery embolization and methotrexate treatment with a new method they called as “transvaginal surgery”, and determined the method of transvaginal surgery to be more successful in treatment. In this method, they determined a significant decrease in b hcg value and more rapid healing in menstrual cycle (Le et al., 2013). In another study, it was stated that resection of cesarean scar pregnancy and repair of defect, occurring after resection, with laparoscopy and laparotomy was a safe technique (Rotas, 2006). In the study of Godin et al. they treated these cases with intragestational methotrexate, and found that the treatment to be effective due to the high concentration in the sac (Godin, 1997).

We transvaginally administered local methotrexate in the gestational sac in our case. We discharged the patient in good health from the hospital next day. The b hcg levels of our case turned back to normal 1 month later. Consequently, treatment of transvaginal intragestational methotrexate is a short, effective, safe treatment method which protects fertility, does not have any major complication and enables us to avoid surgical procedures such as laparotomy and laparoscopy. However, further studies are needed on an efficient treatment method on this subject.

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Polyhydramnios and pregnancy complicated with Bartter's syndrome: A case report

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ABSTRACT

Bartter syndrome is a renal tubular defect that can be diagnosed prenatally, reports are limited on the prenatal course of pregnancies complicated with the disease in the current literature. In this case review we would like to define and debate on the course of pregnancy complicated with Bartter's syndrome in regard with current literature. Rising levels of polyhydramnios without certain fetal or placental abnormalities should lead us to suspect renal functional disorders like this in which the evaluation of amniotic fluid chloride level is usually diagnostic. A series of amniocentesis' were performed until 34 weeks. Neonatal and subsequent investigations confirmed the diagnosis of Bartter syndrome. The infant was healthy at birth and now, is at 4 years of age under constant follow-up by pediatricians.

1. Introduction

Antenatal Bartter syndrome (ABS) is a rare autosomal recessive renal tubular disorder. The defective chloride transport in the loop of henle draw leads to fetal polyuria hence resulting in severe polihydramnios and premature delivery. Early initiation of the symptoms along with unexplained polyhydramnios often challenges the treating obstetrician. Gradually increasing levels of polyhydramnios without apparent placental or fetal abnormalities should at least give raise suspicions about this entity. Biochemical analysis of amniotic fluid is usually diagnostic. Early recognition, maternal treatment with indomethacin, and amniocentesis can help continue the pregnancy (Nakanishi et al., 2005). Polyhydramnios is dominantly present throughout, the pregnancy especially between 24th and 30th weeks of gestation. During antenatal follow-up growth restriction, nephrocalcinosis, polyuria and events of dehydration and hypercalciuria are characteristics regarding postnatal course (Rodriguez, 2004).

The disease is generally diagnosed during the infancy or early childhood period. Prenatal diagnosis of any affected fetus with Bartter syndrome is substantial for several reasons including, the need to treat polyhydramnios at an early onset and to be prepared for possible premature delivery along with

prompt treatment of symptoms such as blood and urine electrolyte instability at an early time after birth which is especially considered to be essential if we want to decrease the pathological severeness and the occasional alleviations of the disease. In terms of treatment Indomethacin is found to be an effective agent against the gradual raise of polyhydramnios aiding us against premature delivery in Bartter syndrome (Moise et al., 1988). Here in this report we would like to present a case of Bartter syndrome complicated with severe polihydramnios and managed with recurrent drainage

2. Case report

A 22-year-old patient (G2P1A0) with 24 weeks of pregnancy who had her previous pregnancy diagnosed with Bartter syndrome was referred to our clinic. According to the history taken from the patient, her other child is currently 4 years old and in good health under regular observation by pediatrics and also the patient revealed that she and her husband are related on 1st degree. When asked about her current pregnancy, patient reveals that a detailed fetal ultrasonographic scan was taken at 20th week showing no significant anomalies other than polihydramnios with amniotic fluid index more than 32 cm in total with the deepest pool being 15 cm. After admission patient was hospitalized in our clinic administered betametazon for lung maturation and put under close observation including nst (non stres test), biophysical profiling and fetal doppler ultrasonography every 2-3 times a week which were all in normal range.

Series of amniocenteses were carried out in order to control uterine contractions and increasing dyspnea associated with polyhidramnios, respectively at weeks 28, 31 and 33 up to the point where persistent uterine contractions developed at 34th week. The fetus was delivered with cesarean section. A male infant with APGAR scores of 3 at 1st min and 8 at 5th min with a birth weight of 2030 g (10-50 percentile) was delivered. Neonatal course was complicated with hyponatraemia and polyuria. The diagnosis of Bartter Syndrome was confirmed by laboratory findings afterwards. The child is currently doing well, at 4 years of age, since prostaglandin synthetase inhibitors are usually required to control the disease he is receiving Indomethacin therapy and is being followed by pediatricians

3. Discussion

Case reports of pregnancy complicated with Bartter syndrome are rare. This syndrome was primary described in 1962. Onset may be infancy, childhood, in the neonatal period (Amiralok and Dawson, 2000). Polyhydramnios occurs in 1–2.8% of all pregnancies and in some cases the aetiology is not identified. Polyhydramnios usually arises from fetal anomalies (mostly gastro-intestinal), uncontrolled maternal diabetes, chromosomal abnormalities and neural tube defects such as anencephaly. Unexplained severe polyhydramnios is a challenge for obstetricians (Rodriguez, 2004). Consistent with the literature, as in this case, when faced with gradually increasing severe poyhydramnios we would like to emphasise ABS where no other cause can be found. Marked fetal polyuria due to antenatal Bartter syndrome is one of the rarer causes of violent polyhydramnios. Patients with this syndrome usually present in infancy or childhood with chronic pain related to growth restriction or hypokalemia (Tomoyoshi and Toshihide, 2001).

Maternal amniocentesis and indomethacin are the options that consent pregnancy to continue. Indomethacin, by inhibiting prostaglandin synthetase, reduces salt-wasting and maternal administration of indomethacin successfully prevents the advance of polyhydramnios.

However, this therapy might have a risky negative effect. In the fetus, prostaglandin E keeps the patency of the ductus arteriosus. Indomethacin, being a strong inhibitor of prostaglandin synthesis, might bring about constriction of the ductus. Hence, wary clinical and echocardiographic monitoring of the fetus is essential (Bhat et al., 2011). In our case, we didn't use indomethacin, instead we preferred to control polyhydramnios by series of amnio-drainage to buy us enough time to get to 34th week.

Indomethacin and serial amnio-drainage is an effective viable treatment option and especially more efficient together in terms of preventing premature delivery if used carefully.

In conclusion, we would like to say that Bartter syndrome should be considered in severe idiopatic polyhydramnios cases where no other obvious cause is present.

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Perioperative management of giant symptomatic autosomal dominant polycystic kidney disease: A case report

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited systemic disorder characterized by renal cyst enlargement which results in abnormal kidney structure and renal insufficiency. The anaesthesia management of patients with ADPKD is often complex and carries considerable risks of perioperative complications. Safe and successful anaesthesia management requires an increased understanding of ADPKD pathophysiology. We report successful perioperative management of a bilateral open surgical radical nephrectomy on a male patient with giant symptomatic ADPKD. The patient had chronic renal failure and extremely large kidneys. We believe that the description and observations seen in this case will aid in the recognition and anaesthetic management of this syndrome.

1. Introduction

Polycystic kidney disease (PKD) is an inherited genetic disease characterized by progressive cystic formations (Chapman, 2008; Wuthrich et al., 2009). Although the involvement of complex mechanisms in the development of cysts is suggested, ciliary dysfunction is thought to play a role in the main pathology. Cystic expansion progressively enlarges the kidney, leads to intrarenal ischemia and activates the renin-angiotensin-aldosterone system (RAAS). An activated RAAS causes hypertension, related proteinuria, cardiovascular complications and progression to end-stage renal disease. Apart from these, extra renal findings are seen, but they rarely emerge during the early stages of the disease (Chapman, 2008; Wuthrich et al., 2009). Autosomal dominant or recessive genetic inheritance is often seen. Autosomal dominant polycystic kidney disease (ADPKD) is more frequently seen during the fifth and sixth decades of life; it slowly progresses to renal enlargement with a resultant development of renal failure (Chapman, 2008). Its prevalence is nearly 1:800–1:1,000, and constitutes 2.5% of all end-stage renal diseases (Chapman, 2008; Wuthrich et al., 2009). ADPKD is a heterogeneous disease which

develops as a mutation of at least two genes (mutations on chromosomes 16 and 4, chromosomes at PKD1 and PKD2 genes, respectively). As a consequence of these mutations, epithelial de-differentiation, increased cell division and apoptosis and decreased reabsorptive capacity of the kidney are seen. Thus, cyst growth and expansion and, finally, enlarged kidneys and progressive renal injury occur (Chapman, 2008). Clinically, the patient may present with hypertension, flank pain, haematuria and cyst infection. Cysts may develop slowly or rapidly. Generally, the glomerular filtration rate is maintained until 30–40 years of age, and then it quickly worsens (Franz and Reubi, 1983; Wuthrich et al., 2009). During the seventh decade of life, nearly 50% of ADPKD patients become dependent on dialysis (Halvorson et al., 2010).

However, unlike the other forms of the disease, the autosomal recessive form evidences itself more frequently during the neonatal period and during infancy (Capisonda et al., 2003; Guay-Woodford and Desmond, 2003; Kaimori and Germino, 2008). It is seen 20 times less frequently than ADPKD, and its clinical manifestations generally lead to a more severe course (Kaimori and Germino, 2008). It is the most frequently seen renal cystic disease during childhood. Most of the cases are discerned during intrauterine life or at birth. In a seriously affected foetus, oligohydramnios and facial, vertebral and extremity anomalies are frequently seen. Clinically, it is characterized by cystic dilation of the collecting ducts of the kidneys, malformation of the biliary ductal system and hepatic fibrosis and portal hypertension; frequently, during the prenatal period, the foetus is lost secondary to pulmonary hypoplasia and respiratory failure (Zerres et al., 1998; Capisonda et al., 2003; Guay-Woodford and Desmond, 2003).

In our case, we report a successful perioperative management of a bilateral open surgical radical nephrectomy in a male patient. The patient had giant symptomatic autosomal dominant polycystic kidney disease, chronic renal failure (CRF) and extremely large kidneys. The anaesthesia management of patients with ADPKD is complex and carries with it considerable risks of perioperative complications. We believe that the description of this case will help in the recognition and anaesthetic management of this syndrome.

2. Case report

A 52-year-old male patient who had been followed for 20 years with diagnoses of ADPKD and CRF was admitted to the renal transplantation unit. The patient, when he was being prepared for transplantation in the unit, complained of shortness of breath which was found to be related to coronary artery disease. In the cardiology department, a drug-eluting stent was implanted, and in order to prevent stent thrombosis, a dual antiplatelet treatment, employing a combination of acetylsalicylic acid (100 mg/d) and clopidogrel (75 mg/d), was initiated. One week later, he complained of abdominal pain and persistent fever, and a computed tomographic examination revealed intracystic bleeding. Based on the antibiotic susceptibility test results of the cyst contents, meropenem (2x1 g/d) and teikoplanin (1x400 mg/d) were initiated without any effect on his febrile state. Meanwhile, abdominal tenderness developed, and ultrasonography examination demonstrated a cyst rupture. Dual antiplatelet treatment was then discontinued, and a bilateral nephrectomy was planned. His anamnesis revealed the presence of ankylosing spondylitis for 25 years and hypertension for 20 years. He was using a tumour necrosis factor (etanercept 50mg/d) for the treatment of the ankylosing spondylitis and valsartan (160 mg/d), doxazosin (4mg/d) and nifedipin (60mg/d) for the management of his hypertension. It was also learnt that his brother had been followed-up with diagnoses of ADPKD and CRF. Systemic examination was unremarkable (temperature 37.5 °C). His airway was graded as Mallampatti class I with normal neck movements. Preoperatively, excluding his haemoglobin (Hb, 9 g/dL), his blood urea (63 mg/dL), serum creatinine (5mg/dL) levels and other parameters (serum sodium and potassium, blood cell count, liver function tests and coagulation profile) were within normal limits. On an abdominal ultrasonogram, in addition to renal cysts, two small simple hepatic cysts were detected. An electrocardiogram showed sinus rhythm, and a chest X-ray showed normal lung fields. The patient was categorized as ASA III (American Society of Anesthesia). He was informed about all potential risks, and then he provided his consent for all procedures. He was advised to continue antihypertensive medication on the morning of the surgery. The Department of Rheumatology recommended cessation of etanerceptin 15 days prior to the operation because of potential infectious complications. In addition, the cardiology department was again consulted about the patient who discontinued his dual antiplatelet therapy. Accordingly, infusion of thyrofiban at a rate of 12.5 mg/24 hr was initiated up to eight hours before the operation, and re-initiation as soon as possible of dual antiplatelet therapy during the postoperative period was indicated. During the two weeks prior to the surgery, he underwent three sessions of dialysis each week; his blood urea nitrogen, serum creatinine and potassium values were maintained within acceptable ranges. His last haemodialysis was performed 24 hours prior to surgery.

In addition to standard monitorization (pulse oximeter, non-invasive blood pressure, urine output measurement, electrocardiogram and core body temperature), central venous pressure (CVP, measured from the right subclavian vein) and invasive blood pressure (intra-arterial, radial artery) measurements

were performed. Pleth variability index (PVI) was calculated, and total haemoglobin (SpHb) monitorization was carried out. For the estimation of PVI and the measurement of SpHb, a pulse co-oximetry (Rainbow R1 25 Adhesive Sensors, Adult; Masimo Corp., Irvine, CA, USA) probe was used. This probe was placed on the index finger of one hand and connected to a Masimo Radical-7 monitor with PVI software (Masimo Rainbow SET Radical-7 Pulse CO-Oximeter; Masimo Corp., Irvine, CA, USA). Before induction of anaesthesia, his heart rate (HR, 140/min), systemic blood pressure (120/80 mmhg), blood oxygen saturation (SpO2) (98%), SpHb (9 g/dl) and PVI (12%) were estimated. For the induction of anaesthesia propofol (1.5 mg/kg IV), rocuronium (0.6 mg/kg IV) and remifentanil (0.5 mcg/kg/min), infusions were used, and the patient was intubated. Central venous pressure (CVP, 14 cm H2O), urine output (50 ml) and core body temperature (37 °C) were detected as indicated. The surgery was performed with the patient in the supine position and maintenance of the anaesthesia was achieved using desflurane (1 minimum alveolar concentration)/air (1L/min)/oxygen (1L/min), and remifentanil infusion (0.1-0.25 mcg/kg/min). Fluid replacement therapy was adjusted according to pulse oximeter-derived PVI (goal-directed fluid management). Accordingly, PVI values were maintained at 13-14% (Cannesson et al., 2008). After the first hour of the operation, development of hypotension (70/40 mmHg) necessitated initiation of inotropic support (norepinephrine 0.04-0.1 µg/kg/min, and dopamine 4-10 µg/kg/min). During the operation, CVP (14-16 mm Hg), SpHb (9-10 g/dL), core body temperature (36 °C), systolic and diastolic blood pressures (100-110 mmHg and 60-80 mmHg) and heart rate (110-120/min) were maintained within indicated limits. Arterial pH did not drop below 7.25, and decreased ionised calcium level (< 3.5 mg/dl) was treated with infusion of four ampoules of calcium (calcium gluconate levulinate 10%, 10 ml). During the surgery, which lasted five and one-half hours, infusions of various solutions and blood components, including a total of 5000 cc 0.9% sodium chloride, 2000 cc lactated Ringer's solution, 1500 gelofusine (0.04 g/500 ml; B. Braun-Irengun, Istanbul, Turkey), nine units of erythrocyte suspension and 11 units of fresh frozen plasma were made. The polycystic kidneys, which were removed bilaterally, weighed nearly eight kg (Fig. 1 and Fig. 2). At the termination of the operation, the patient was intubated under dual inotropic support and transferred to the intensive care unit (ICU). After nine days in the ICU, the patient was extubated and transferred to the Organ Transplantation Unit. The patient was admitted to a three times per week haemodialysis program and kidney transplantation was planned.

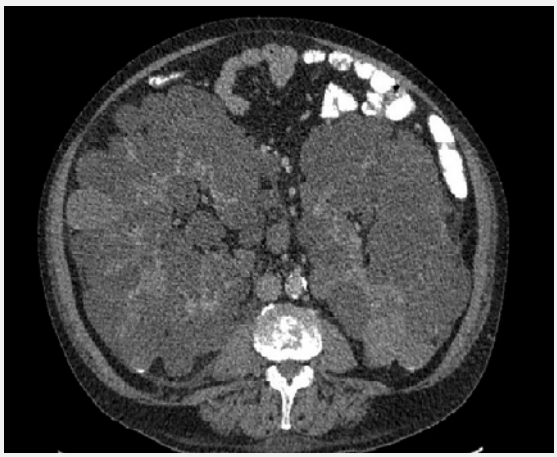

Fig. 1. Computed tomographic scan shows multiple bilateral kidney cysts, resulting in enlargement of the organ.

Fig. 2. Explanted giant polycystic kidneys.

3. Discussion

Although ADPKD is the most prevalently seen inherited disease, it is essentially a systemic disease (Gabow, 1993; Chapman, 2008; Kaimori and Germino, 2008). In addition to the kidneys, it is also seen in the liver (primarily as an extra renal lesion), pancreas, thyroid, subarachnoidal space, seminal vesicles and inguinal hernias (Chapman, 2008; Kaimori and Germino, 2008). In addition, its vascular phenotype can manifest itself as intracranial aneurysms, mitral valve prolapses and biventricular dysfunctions. However, its clinically characteristic features are gradual and include massive cystic enlargement and, finally, the development of renal failure (Chapman, 2008). Because of increased RAAS activity, its earliest symptom is hypertension, which is seen in nearly 60% of the patients (Suvarna and Fernandes, 2011). During the advanced stages of the disease, a decrease in the concentration ability of the kidneys is seen (Arulkumaran et al., 2012). ADPKD is responsible for 8-10% of all cases with end-stage renal

disease (Gabow, 1993). Especially in patients who are diagnosed during its early stage, the coexistence of the male gender and hypertension indicate the progressive course of the disease (Wilson, 2004).

Our patient had hypertension and CRF which had been kept under control for 20 years with medication and with a low-salt and low-protein diet. In patients with CRF, coronary artery disease is frequently (40%) seen because of the presence of hypertension, systolic and diastolic dysfunction, diabetes, dyslipidaemia, peripheral vascular disease and anaemia (Gupta et al., 2004). Our patient had experienced a coronary ischemic attack before transplantation, and as a result of antiplatelet therapy, intracystic bleeding occurred. This, together with infection, worsened the clinical condition of the patient, further leading to the development of end-stage renal disease and azotaemia.

During the preoperative evaluation of such patients, a detailed medical history should be taken, and a thorough physical examination should be performed. Signs and symptoms of uraemia, fluid overload and inadequate dialysis should be emphasized, especially in the presence of comorbidities. Laboratory parameters, such as electrolyte concentrations, acid-base status, urea and creatinine levels, haematocrit, platelet count and coagulation, should be analysed in case dialysis needs to be performed before the operation. Chest radiography is usually helpful to rule out fluid overload, and an electrocardiogram is necessary to assess for changes caused by myocardial ischemia and by electrolyte abnormalities (Maurizio et al., 2012). Blood pressure (below 130/80 mm Hg) and haemoglobin values (≥ 10 g/dL) should be brought to indicated optimal levels (Gupta et al., 2004; Locatelli et al., 2008).

In this patient group, the pharmacokinetic effects of several anaesthetic drugs were significantly altered due to CRF. Since free fractions of hypnotic agents increase, doses used in the induction of anaesthesia should be significantly reduced (SarinKapoor et al., 2007; Wagener and Brentjens, 2010). With this type of patient, after the induction of anaesthesia, hypotension is frequently seen because of autonomic dysfunction, hypovolemia and the preoperative use of angiotensin-converting-enzyme inhibitors. Therefore, in addition to dose reduction, slow titration of anaesthetic and sedative agents is required. In this patient group, because of the high incidence of gastroparesis rapid-sequence induction was frequently used. To this end, rocuronium can be used safely (Maurizio et al., 2012). Since plasma clearance of rocuronium is not affected by renal dysfunction, it can be also used in the maintenance of anaesthesia (Cooper et al., 1995; SarinKapoor et al., 2007). In our case, we used lower doses of propofol and remifentanil for the maintenance of anaesthesia. Rocuronium was the preferred muscle relaxant.

Although the safe use of total intravenous anaesthesia (propofol, remifentanil, and cisatracurium) in the maintenance of anaesthesia in this patient group had been indicated, we preferred to use the combination of an inhalational aesthetic agent (desflurane) and remifentanil (Dahaba et al., 1999). Remifentanil does not have active metabolites and is well tolerated in patients with CRF (SarinKapoor et al., 2007). It has been demonstrated that desflurane can be used in CRF patients without increasing renal dysfunction (Litz et al., 2002; SarinKapoor et al., 2007). Since it is minimally metabolized in the body, even with chronic use, the liberation of inorganic fluoride does not appear to cause renal injury (Maurizio et al., 2012).

Successful perioperative haemodynamic management of these patients is challenging. Intravenous fluid administration should be planned so as to avoid fluid overload or hypovolemia. However, the frequent coexistence of systolic and diastolic left ventricular dysfunction and poorly controlled hypertension causes low cardiac output and large swings in blood pressure. Therefore, these patients often need more advanced haemodynamic monitoring (arterial line, central venous and pulmonary artery catheters or the oesophageal Doppler, stroke volume variation and pulse pressure variation) (Maurizio et al., 2012). In meta-analyses that have been performed, it has been reported that goal-directed fluid therapy for the management of critically ill patients, and the major surgeries of these patients, will decrease organ-specific complications and improve post-operative outcomes (Corcoran et al., 2012; Davies et al., 2013). Herein, haemodynamic targets to be considered are achieved by measuring either cardiac output (CO) or fluid responsiveness. In these measurements, invasive methods (pulmonary artery catheterization) have been replaced by non-invasive methods (stroke volume variation [SVV], pulse pressure variation [PPV] or PVI) (Davies et al., 2013). The Radical-7 PVI that we used in our clinic allows measurement of these parameters. PVI is an algorithm that automatically and continuously measures the variability of the pulse oximeter plethysmographic waveform amplitude during the respiratory cycle in a mechanically ventilated patient (Hood and Wilson, 2011; Siswojo et al., 2014). Thus, we may be able to predict fluid responsiveness in major surgery. The response to the fluid administered to our patient was evaluated by continuous PVI measurements to optimize the patient's fluid status.

Anaesthesia management of nephrectomy for giant polycystic kidneys is challenging. Safe anaesthetic management requires an understanding of APDK pathophysiology and careful patient assessment. The changes in pharmacokinetics and pharmacodynamics of drugs used in the perioperative period must be taken into consideration. However, optimisation of volume status and blood pressure are fundamental to reducing morbidity and mortality.

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Case Report

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Surgical management of isolated true femoral artery aneurysm
True femoral artery aneurysm

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ABSTRACT

Popliteal artery aneurysm are seen more common than femoral artery aneurysms. Common femoral artery (CFA) aneuryms, superficial femoral artery (SFA) aneurysms and profound femoral artery (PFA) aneurysms are relatively rare and incidence rates are 80%, 15% and 5% respectively among the all femoral artery aneurysms and most of them are pseudoaneurysms. True aneurysms are often seen bilaterally (38%) and accompanying popliteal artery aneurysms (%27-44) or abdominal aorta aneurysms (%50-90). These aneuryms can be thrombose, embolize or rupture. Repair is indicated for symptomatic patients. Diameter and extent of the aneurysm are the main indicators for the surgical treatment. We present the successful menagement of a 67 year old male who was presented with left femoral artery aneurym.

1. Introduction

Peripheral artery aneurysm is defined as more than 2 cm increase in diameter or more than %50 expansion in diameter of the artery. Popliteal artery aneurysm are seen more common rather than femoral artery aneurysms. Common femoral artery (CFA) aneuryms, superficial femoral artery (SFA) aneurysms and profound femoral artery (PFA) aneurysms are relatively rare and incidence rates are 80%, 15% and 5% respectively among the all femoral artery aneurysms and most of them are pseudoaneurysms. These pseudoaneurysms are often iatrogenic, associated with syphilitic and mycotic infections or trauma. True aneurysms are often seen bilaterally (38%) or accompanying popliteal artery aneurysms (%27-44) and abdominal aorta aneurysms (%50-90) (Leon et al., 2008). These aneuryms can be thrombose, embolize or rupture. Large aneurysms are mimicing masses and may compress adjacent veins or nerves. Etiologic factors are including atherosclerosis, connective tissue disorders and arteritis. Atherosclerosis is the most common cause of aneurysms. Increased turbulent flow beyond the stenosis in cross joints or dense structures may cause aneurym formation. They are commonly seen in elderly males, often located in the middle third of the artery in the right limb as a focal lesion. These are frequently asymptomatic until reaching a large diameter before the diagnosis was made. The most seen symptoms are localized pain in association with a pulsatile mass, rupture, thrombosis, embolism, deep vein thrombosis, lower limb edema,

claudication or bruising. Rupture of the femoral artery aneurysms are much more seen rather than distal ischemia unlike the popliteal artery aneurysms. Repair is indicated for all symptomatic femoral artery aneurysms. Dublex ultrasound, magnetic resonance angiography, computed tomography angiography and digital substraction angiography can be used for diagnosing. The incidence of thrombosis and embolus for CFA, PFA and SFA were 15%, 45% and 26% respectively (Lawrence et al., 2014). Due to the high incidence of complications, repair should be performed electively when possible.

2. Case report

A 67 year old male was presented with acute left lower limb ischemia although he was taking anticoagulation therapy, was admitted to us. On physical examination his left popliteal and distal pulses were absent and he was found to have a pulsatile mass at the level of the right groin without extension into the thigh. Contralateral pulses were usual. He had a history of aorta-right femoral artery. His blood pressure was 120/80 mmHg and heart rate was 90/minute. Renal function was normal. He had no history of previous trauma to his left lower limb. The remainder of the physical examination was unremarkable. Computed tomography angiography (CTA) scanning revealed 3.2 cm aneurysm of the right CFA and proximal portion of SFA and distal flow was absent (Fig. 1). Routine preparation for surgery was made and informed consent was taken. After proximal and distal ligation of SFA was performed, the patient had undergone bypass from the left external iliac artery to SFA and proximal popliteal artery with a 8 mm PTFE graft (Fig. 2). The remainder of the arterial tree did not show any significant abnormality. The pathologic examination of the aortic wall was reported as calcific atherosclerosis. The patient's postoperative recovery was uneventful, without signs of distal ischemia 1 year after the surgery.

Fig. 1. Three dimentional computed tomography angiography (CTA) image of left external iliac artery (EIA), common femoral artery (CFA), superficial femoral artery (SFA).

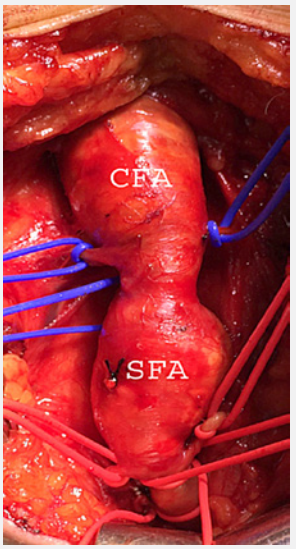

Fig. 2. Intra operative image of common femoral artery (CFA) and superficial femoral artery (SFA).

3. Discussion

Repair is indicated for symptomatic patients. Some authors stated that there is no concensus for asymptomatic patients for the appropriate intervention time however, some authors proposed that true femoral artery aneurysms which are larger than 2.5 cm in diameter should be repaired in healty patients, especially if the aneurysms are rapidly enlarging (Perini et al., 2014). Saccular aneurysms should be treated when the diagnosis is made. Femoral artery aneuryms have a more benign prognosis than popliteal artery aneurysms. Several treatment modalities have been described. The thigh incision is required for conventional surgical repair. Proximal ligation, excision of the aneurysm (aneurysmectomy), proximal and distal ligation and bypass are the surgical treatment modalities (Mohan et al., 2014). Graft interposition (with using prosthetic or saphenous vein graft), followed by exclusion are preferred for surgical treatment. Repair of the femoral artery aneuryms were reported with low rates of ischemia and limb loss. Endovascular techniques are available for treatment however, has some limitations due to crossing a flexion joint. Kinking or migration of the endovascular stent and metal fatigue can be seen after endovascular intervention (Kara et al., 2015). Soleyl proximal ligation of the aneurysm can be an option in emergency unless distal ischemia is present. We believed that aneurysms of the femoral artery greater than 2.5 cm should be repaired surgically.

In conclusion, the diameter and extent of the aneurysm are the main indicators for the surgical treatment. We believe that conventional surgery is still the gold standard treatment method.

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