ISSN 2564-7784 EISSN 2564-7040

European Journal of Therapeutics

OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

Formerly Gaziantep Medical Journal

VOLUME 23 ISSUE 3 SEPTEMBER 2017

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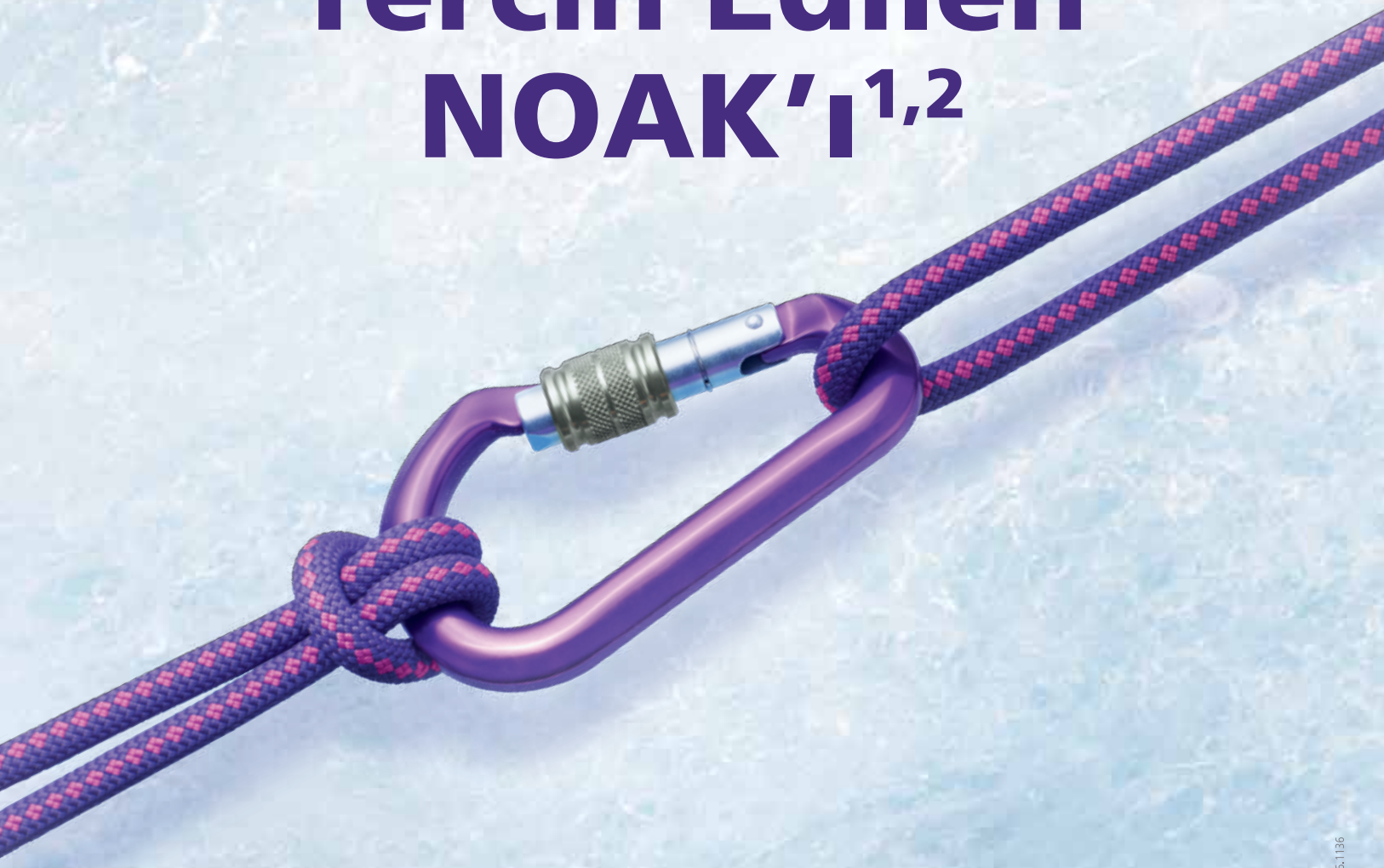

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European Journal of Therapeutics aims to contribute to the international literature by publishing original clinical and experimental research articles, case reports, review articles, technical notes, and letters to the editor in the fields of medical sciences. The journal's target audience includes researchers, physicians and healthcare professionals who are interested or working in in all medical disciplines.

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Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Technical Note	1500	No abstract	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.
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Contents

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Editorial

Dear colleagues,

The quality and the number of articles submitted to our journal are increasing. We are thankful to all of the submitting authors.

We would like to share some good news with you.

Firstly, our journal is now indexed in Turkish national indexing system, ULAKBİM TR Index. We have also applied for inclusion in international indices and waiting for a positive response.

Additionally, we have made a new agreement in place with a professional translation companies and thus, we are glad to announce that going forward accepted articles in Turkish will be translated to English and the cost will be covered by our journal.

Best wishes

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European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.24

Original Investigation / Özgün Araştırma

Contribution of left atrial volume and function in neurocardiogenic syncope

Vasovagal senkop gelişimine sol atrium fonksiyonu ve hacminin katkısı

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ABSTRACT

Objective: In this study, we aimed to investigate the presence of atrial volume and decrease in contraction force by measuring left atrial volume and contraction with the head-up tilt table (HUTT) test in patients who were diagnosed with neurocardiogenic syncope (NCS).

Methods: Overall, 45 patients (26 females/19 males, mean age: 26.4±9.2 years) who experienced vasovagal syncope in HUTT (HUTT+) and 40 healthy controls (17 females/23 males, mean age:28.8±10.5 years; HUTT-) were included in the study.

Results: When comparing the groups in terms of left atrial ejection force, there was a significant difference between the HUTT+ and HUTT−vasovagal syncope groups (p=0.05). In both groups, there was a positive correlation between atrial ejection force and left atrial volume (r=0.287, p=0.016) and left atrial volume index (r=0.261, p=0.029).

Conclusion: We showed that the left atrial ejection force and the left atrial volume index were significantly lower in positive vasovagal syncope patients than those in the negative vasovagal syncope patients.

Keywords: Syncope, echocardiography, left atrium

ÖZ

Amaç: Vasovagal Senkop (VVS) sık görülen klinik bir durum olmakla birlikte altta yatan mekanizmalar henüz tam olarak anlaşılamamıştır.Bu çalışma, eğik masa testi pozitif olan VVS'lu hastalarda, sol atrial sistolik fonksiyonun VVS gelişimindeki rolünü araştırmak amacıyla yapılmıştır.

Yöntemler: Açıklanamayan senkop nedeniyle eğik masa testi ve ekokardiyografi uygulanan toplam 95 hasta çalışmaya alındı. Eğik masa testi pozitif olan 45 hasta (n=45), eğik masa testi negatif olan 40 hasta (n=40) ile karşılaştırıldı.

Bulgular: Yaş ve cinsiyet dağılımı açısından guruplar arasında fark gözlenmedi (sırasıyla p=0,27 ve 0,11). Ekokardiyografik değerlendirmede sol atrium hacmi, sol atrium hacim indeksi ve sol atrial ejeksiyon kuvveti eğik masa testi pozitif olan gurupta anlamlı olarak daha düşük bulundu (sırasıyla p=0,03, 0,05 ve 0,05). Mitral kapak anulusünden kaydedilen Doppler akımları açısından guruplar arasında fark saptanmadı fakat E/A oranı eğik masa testi pozitif olan gurupta anlamlı olarak daha düşük bulundu (p=0,02).

Sonuç: olarak bu çalışma bazalde daha düşük atrial hacim ve kontraksiyon kuvvetine sahip bireylerin ortastatik stres esnasında ventriküler doluşun devamını sağlamada yetersiz kalabileceklerini düşündürmektedir.

Anahtar kelimeler: Vasovagal senkop, sol atrium, ekokardiografi

INTRODUCTION

Syncope is frequent among the normal population, and neurally mediated syncope is the nearly usual cause. Neurocardiogenic syncope (NCS) is clinically defined as the sudden onset and very short (usually 1 or 2 minutes) duration of loss of consciousness due to global cerebral hypoperfusion, which is quite disturbing particularly when repetitive. NCS can cause impaired quality of life and significant injury in some cases, but its exact mechanism has not been clearly understood yet (1). Several theories have been recommended to provide an explanation for the pathophysiology concerning NCS. Left atrium (LA) contraction contributes to maintaining left ventricular end-diastolic (LVED) pressure and cardiac output. We hypothesized that left atrial volume and systolic function may be a contributing component of the NCS. The present study is intended to evaluate the relation between the left atrial systolic function using left atrial ejection force (LAEF) in patients with head-up tilt test (HUTT)-induced NCS.

METHODS

We enrolled consecutive patients who had been admitted to our clinic because of unexplained syncope between January 2013 and August 2014. The selection criteria were age 18-70 years, ≥2 episodes of syncope, normal neurologic evaluations, no significant valvular heart diseases, normal ejection fraction(>50%) on echocardiography, and absence of any significant arrhythmia. We excluded patients with no technically optimal echocardiographic images, hypertension, thyroid diseases, impaired renal function, and structural heart diseases. Patients were divided

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Received/Geliş Tarihi: 10.03.2017 • **Accepted/Kabul Tarihi:** 08.05.2017

into two groups based on HUTT results: patients experiencing syncope or significant hypotension and/or bradycardia at some point of the test were assigned to HUTT-positive (+) group and those without syncope, bradycardia, and hypotension were assigned to HUTT-negative (-) group. The ethics committee approved the study protocol and informed consent was obtained from every patient.

Echocardiography: All participants underwent a detailed transthoracic echocardiographic evaluation. Transthoracic echocardiography was performed using a Vivid 7 Echocardiography machine (GE Ultrasound, Horten, Norway). Two-dimensional and tissue Doppler's images were acquired in parasternal and apical views. The values of all echocardiographic parameters from three cardiac cycles were averaged for data analysis. The two-dimensional apical four-chamber view was used to calculate left ventricular (LV) ejection fraction (LVEF) according to biplane modified Simpson's rule. LA anteroposterior dimension (LAAPD) was measured in the parasternal long axis view, and LA volume was measured using the biplane disk summation method in the apical four and two chamber views at the end of the LV systole. LA volume was indexed to the body surface area (BSA) as an LA volume index (LAVI). Mitral inflow velocities included peak early (E), peak late(A), and the E/A ratio were assessed using the pulsed wave Doppler method by putting a sample volume at the opening level of mitral valve leaflet tips in the apical four-chamber view. Tissue Doppler-derived velocities of the mitral annulus were obtained from the apical four-chamber view at the lateral and medial mitral annular corners. Peak systolic velocity (S'), early diastolic velocity (E'), and late diastolic velocity (A') were measured. The velocities were recorded at a sweep speed of 100mm/s (2). LAEF was calculated according to the method provided by Manning (3). The formula is as follows: LAEF=1/2*-MOA*A^2*q, where MOA: mitral orifice area (cm^2), A: peak late diastolic transmitral flow velocity (cm/sec), q:blood density (1.06 g/cm^3).The mitral annulus was assumed to be circular, and its diameter (d) was measured from the apical four-chamber view. MOA was calculated as ±*d^2/4. The peak velocity was obtained at the level of the mitral annulus (3). All measurements were performed by a cardiologist blinded to the study.

Head-up Tilt Table Test: The HUTT protocol began with 5 minutes in the supine position for the first phase, then the subject tilted passively to 70 degrees upright position for 20 minutes in the second period, if the second p was negative, 0.4 mg sublingual nitroglycerine spray was administered, and head-up tilt to 70 degrees was repeated for 10 minutes. During the test, subjects had electrocardiographic monitoring, and blood pressure was measured by an automatic cuff sphygmomanometer at intervals of every minute. The test was definitely positive if syncope occurs or if presyncope developed in association with an abrupt fall in systolic blood pressure to below 70 mm Hg or bradycardia (heart rate below 40 bpm) (4).

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Corp.; Armonk, NY, USA). Continuous variables were presented as mean±standard deviation (SD) and categorical variables were expressed as percentages. Patients were grouped according to the positive or negative HUTT. Differences between groups were analyzed using unpaired samples Student's t-tests and analysis of covariance for continuous variables and χ^2 analysis for discrete variables. Two-tailed p values less than 0.05 were considered significant for all tests.

RESULTS

From a total of 95 screened subjects, a positive response was induced in 45 patients (mean age: 26.4±8.8 years, 19 men, and 26 women) and negative response in 40 patients (mean age: 28.8±10.5 years, 23 men, and 17 women). Age and gender were similar between groups (p=0.27 vs p=0.11, respectively). In the echocardiographic evaluation, LVED volumes, ejection fractions, and LAAPD were found similar between groups. The statistical significance of LAVI and LAEF were p=0.05 vs p=0.05, respectively, but LAV was significantly smaller in the HUTT+ group compared to the

Table 1. The patient characteristics and intergroup comparison between HUTT+ group and HUTT− group of clinical and echocardiographic parameters

	HUTT(+) (n=45)	HUTT(−) (n=40)	p
Age	26.4±9.2	28.8±10.5	0.27
Gender (male/female)	26/19	17/23	0.11
BMI (kg/m^2)	23.1±3.1	24.6±4.5	0.08
BSA (m^2)	1.73±0.14	1.78±0.16	0.12
LVEDV (mL)	68.4±25.2	72.2±18.3	0.58
LAV (mL)	35.9±8.9	42.7±15.1	0.03
LAVI (mL/m^2)	20.1±5.1	23.7±8.0	0.05
LAEF ($kdynes/m^2$)	11.0±6.0	13.8±6.6	0.05
LAAPD (mm)	30.6±5.8	31.2±4.4	0.68
E	0.89±1.9	0.84±1.8	0.26
A	0.57±1.2	0.60±1.3	0.33
E/A	1.6±0.4	1.4±0.3	0.02
E/E'	5.6±2.1	5.3±1.7	0.47
S lateral	12.1±3.1	11.9±2.4	0.76
E' lateral	16.4±4.0	16.0±3.5	0.66
A' lateral	8.9±2.1	9.5±3.1	0.37
S septal	9.7±1.6	9.4±1.9	0.39
E' septal	13.1±3.1	12.6±3.3	0.52
A' septal	9.0±2.8	9.5±2.8	0.45

BMI: body mass index; BSA: body surface area; HUTT: head–up tilt table; LVEDV: left ventricular end–diastolic volume; LAV: left atrial volume; LAVI: left atrial volume index; LAEF: left atrial ejection force; LAAPD: left atrial anterior–posterior diameter; E: peak velocity of early diastolic filling; A: peak velocity of late diastolic filling; E/A: early mitral inflow velocity to late mitral inflow velocity ratio; S: systolic mitral annular velocity; E': early diastolic mitral annular velocity; A': late diastolic mitral annular velocity; E/E': early mitral inflow velocity to early diastolic mitral annular velocity ratio; p<0.05 indicates significance

HUTT- group (p=0.03). The Doppler flow velocities recorded from mitral annulus did not differ significantly, except for a significantly higher E/A ratio in the HUTT+ group (p=0.02). Also, (TDI) parameters were similar in the two groups. Demographic characteristics and echocardiographic findings of the HUTT+ and HUTT- groups are detailed in Table 1. A correlation analysis revealed that LAEF was significantly correlated with age (r=0.237, p=0.036), body mass index (BMI; r=0.481, p=0.001), left atrial volume (r=0.287, p=0.016), LAVI (p=0.029), and E/E (r=0.394, p=0.001), while there was a negative correlation with mitral E/A ratio (r=−519, p=0.001).

DISCUSSION

This study showed that LAEF was decreased in patients with vasovagal syncope. LAEF is defined as the force generated by the LA to expel the blood through the mitral valve during atrial systole (5). The contribution of the left atrial contraction to the LV filling becomes more significant, particularly in patients with diastolic dysfunction (6). In this study, it was associated with decreased LAEF volume and decreased LAVI in the HUTT results. Our knowledge about the NCS pathophysiology still remains unclear. The mechanism of NCS has thought to be triggered by ventricular mechanoreceptor's discharge induced by venous blood, pooling those results from orthostatic. The reflex increase in sympathetic stimulation to maintain cardiac output and peripheral vascular resistance leads to a baroreceptor-mediated sudden surge in vagal tone and retraction of the sympathetic tone, resulting in vasodilation and/or bradycardia;the consequence is a rapid decline is systolic blood pressure (7). Vaddadi et al. (8) demonstrated that efferent sympathetic activity was maintained during vasovagal syncope episodes, and they speculated that activation of vasodilator mechanisms may be responsible for vasovagal syncope. In addition, Cooke et al. (9) showed that withdrawal of muscle sympathetic activity is not mandatory for presyncope. Some studies have shown that without decrease in peripheral vascular resistance, decrease in cardiac output alone can cause presyncope (1, 10). LA systole is responsible for nearly 20% of the diastolic LV filling (11, 12). Therefore, atrial mechanical and volumetric contribution to cardiac output can be substantial in some circumstances, such as orthostatic stress. There are few studies on the contribution of LA function to the vasovagal syncope mechanism. In the present study, we used LAEF to determine atrial mechanical function and found that LAEF were moderately lower in HUTT+ group than in the HUTT- group (p=0.05). LAEF is the pressure applied by LA to drive blood through the mitral valve to the LV throughout atrial systole and has been proposed as a surrogate marker of atrial mechanical function (3). Chinali et al. (13) revealed that the left atrial systolic force was independently associated with stroke volume and cardiac output. Also, LAEF can be used as a surrogate marker for restoration of the mechanical functions of LA after successful cardioversion for atrial fibrillation (14, 15). Similar to our study, Folino et al. (16) reported that a gradual decline in LA volume due to venous pooling and brief LA hypocontractility by vagal reflexes wasknown to contribute to NCS during HUTT. In our study, tissue doppler echocardiography showed significant reductions in atrial velocities only in patients with positive HUTT test, while a decrease in early diastolic filling waves were similar and ventricular contractility remained almost unchanged in both positive and negative groups (16, 17). These findings can be explained by rich a vagal innervation of atriums, which may cause a reduction of atrial performance during vagal discharge in these patients. However, we measured echocardiographic parameters at rest just before the HUTT protocol because of technical difficulties. Therefore, we could not show atrial function changes preceding the vasovagal reaction. We also found that LAV was significantly lower in the HUTT+ group than that in HUTT− group (p=0.03). Patients with limited LA volume might be more susceptible to NCS. Moon et al showed that a small LA volume is an independent factor of HUTT-induced NCS, and patients with large LA size (LAVI >36mL/m^2) did not faint during HUTT (18). Additionally, in the present study, the E/A ratio was significantly higher in the HUTT+ group. We may speculate that despite the better early diastolic filling in the HUTT+ patients than in the HUTT- patients, the decrease of cardiac output can be attributed to the low contribution of atrial filling in these patients.

Taken together, these findings suggest that reduced active ventricular filling during atrial systole plays an important role in the pathogenesis of vasovagal syncope. This reduction is not caused by reducing ventricular filling. The finding of a similar decrease in the LAV and LAVI in the HUTT+ group further clarifies that this reduction is not caused by diminished ventricular filling and signifies deteriorated atrial mechanical function. Folino et al. (16) found similar results and hypothesized that the rich vagal innervation of the atria is responsible for diminished atrial mechanical functions. This reduced atrial function seems to be the major contributor of reduced cardiac output resulting in syncope. In the Strong Heart Study, LAEF was found to correlate with age and BMI, and we found a strong association between LAEF and age and BMI in our study (13).

Study Limitations

We did not evaluate changes in the left atrial volume and LAEF just before syncope because of technical difficulties; therefore, we could not have assessed the contribution of atrial mechanical and volumetric changes to syncope. We enrolled only patients with mixed-type NCS and thus the findings are only pertinent to this type of syncope.

CONCLUSION

We conclude that the baseline capacity of atrial volume and contractile function may determine the atrial performance during orthostatic stress. Patients with small atrial volume and contractile function may tend to fail in sufficient atrial performance to maintain ventricular filling during NCS. However, more studies investigating that the relative contribution of atrial mechanical functions to the NCS episodes are regarding the role of atrial function and NCS are needed.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - M.S., F.B., F.Y.B.; Design - F.B., F.Y.C., M.S.; Supervision - G.A., F.Y.C.; Resource - M.S., F.B.; Materials - M.S., F.B.; Data

Collection and/or Processing - F.B., F.Y.C., M.S.; Analysis and/or Interpretation - F.B., F.Y.C., M.S.; Literature Search - F.B., G.A.; Writing - F.B., F.Y.C., M.S.; Critical Reviews - G.A.

Conflict of Interest: No conflict of interest was declared by the authors

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

Etik Komite Onayı: Bu çalışma için etik komite onayı alınmıştır.

Hasta Onamı: Hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - M.S., F.B., F.Y.B.; Tasarım - F.B., F.Y.C., M.S.; Denetleme - G.A., F.Y.C.; Kaynaklar - M.S., F.B.; Malzemeler - M.S., F.B.; Veri Toplanması ve/veya İşlemesi - F.B., F.Y.C., M.S.; Analiz ve/veya Yorum - F.B., F.Y.C., M.S.; Literatür Taraması - F.B., G.A.; Yazıyı Yazan - F.B., F.Y.C., M.S.; Eleştirel İnceleme - G.A.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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How to cite:

Başanalan F, Yılmaz Coşkun F, Sucu M. Altunbaş G. Contribution of Left atrial volume and function in neurocardiogenic syncope. Eur J Ther 2017; 23: 95–8.

European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.42

Original Investigation / Özgün Araştırma

Assessment of the prevalence of obesity, stunting, and hypertension among primary school children

İlkokul çocuklarında obezite, bodurluk ve hipertansiyon yaygınlığının değerlendirilmesi

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ABSTRACT

Objective: The study aimed to investigate the prevalence of obesity, stunting, and hypertension problems among 5-14 year-old students from three primary schools.

Methods: The sample of this cross-sectional study comprised of 2930 primary school children (first-eight grade). The participants' heights, weights, and blood pressures were measured.

Results: Of the participants, 17.4% were overweight, 22.8% were obese, 1.1% stunted, and 5.9% were short. In the eight-year age group, the percentage of overweight boy students was higher than that of the overweight girl students. The proportions of the students with stage I and stage II systolic hypertension were 6.8% and 3.2%, respectively. While 1.1% of the students had stage I diastolic hypertension, 5.5% had stage II diastolic hypertension.

Conclusions: The prevalence of stunting, overweight, and stage I and II hypertension among the children aged 6-14 years was high. Thus, it is important to identify such problems early among children and take precautions by conducting routine screenings in schools.

Keywords: School children, obesity, stunting, hypertension

ÖZ

Amaç: Bu çalışmanın amacı orta sosyoekonomik düzeydeki üç ilköğretim okulunda öğrenim gören 6-14 yaş arası öğrencilerde şişmanlık, bodurluk, hipertansiyon ve görme sorunu sıklığını değerlendirmektir.

Yöntemler: Tanımlayıcı ve kesitsel tipte olan bu çalışmanın evrenini birinci sınıftan 8. Sınıfa kadar öğrenim gören 2930 öğrenci oluşturmuştur. Öğrencilere boy-kilo-tansiyon ölçümleri yapılmıştır.

Bulgular: Araştırmaya katılan öğrencilerin %17,4'ü hafif şişman, %22,8'i şişman, %1,1'i çok kısa, %83'ü kısadır. Kızlar erkeklere göre 6 yaşta şişman ve 7 yaşta hafif şişman ve şişman grubundadır. Sekiz yaşta ise şişman grubundaki erkek öğrenci oranı daha fazladır. Sistolik kan basıncı Evre I hipertansif %6,8, Evre II %3,2'dir. Diastolik kan basıncı Evre I hipertansif %5,5 ve Evre II %1,1'dir.

Sonuç: Araştırma sonuçlarına göre 6-14 yaş arası çocuklarda kısa boy uzunluğu, hafif şişmanlık/kilolu olma, Evre I ve II hipertansiyon sıklığı yüksektir. Okullarda yürütülecek rutin taramalarla çocukların sorunlarının erken belirlenmesi ve önlem alınması yönünden önem taşımaktadır.

Anahtar kelimeler: Okul çağı çocuklar, obezite, bodurluk, hipertansiyon

INTRODUCTION

School age is a special period during which children undergo changes and develop, and thus they should be provided with healthcare and be closely followed. This period is particularly important because children gain knowledge, build attitudes, and develop behaviors related to health mostly in schools. During this period, health protection and promotion measures should be undertaken and early determination of problems is likely to prevent/delay learning and will prevent further problems occurring in the future or will provide the opportunity to easily overcome these problems (1). The services to be provided for school-age children include health examinations during the registration for the school; periodic physical examinations; monitoring of growth and development; and vision, hearing, dental, and scoliosis screenings (2, 3).

Monitoring the growth and development of children is crucial among school health services. Annual height-weight measurements are simple but effective methods in the early detection of serious health problems, such as intestinal, endocrinal, and

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Received/Geliş Tarihi: 11.04.2017 • **Accepted/Kabul Tarihi:** 07.07.2017

congenital diseases (2). Within the scope of Monitoring of the Growth of School Age Children (6-10 year-age group) Project in Turkey, anthropometric measurements of 11,387 children in both rural and urban fields of 26 provinces revealed that 6.5% were obese, 14.3% were overweight, 1.3% were severely underweight, 5.0% were stunted, and 21.5% were short. In Europe, the highest prevalence of overweight and obesity among children was in Spain (35.2% among 6-9-year-olds) and Portugal (31.5% among 7-9-year-olds), whereas the lowest prevalence was in Slovakia (15% among 7-9-year-olds), France (18.1% among 7-9-year-olds), Switzerland (18.3% among 6-9-year-olds), and Iceland (18.5% among 9-year-olds) (4).

According to clinical findings, although childhood hypertension is less common than adulthood hypertension, the development of essential hypertension in adults begins within the first 10 years of life, and children who have a family history of hypertension are more prone to hypertension. Thus, detecting hypertension should be started during childhood (5). Blood pressure in children is assessed using percentile curves based on age, gender, and weight, and three consecutive measurements must be considered (6). In a Canadian study, a high positive correlation was determined between obesity and systolic blood pressure in about 2000 children and adolescents aged 6-17 years. Blood pressure in obese adolescents was determined to be 7.6 mmHg higher on an average. While the hypertension prevalence was <1%, the prehypertension prevalence was approximately 2.2% (7). In a study conducted in Tunisia, hypertension was detected in 4.7% of the adolescents (8). Regional differences in the prevalence of childhood hypertension stem from many factors, such as different cultural practices, dietary habits, environmental factors, measurement methods, and age differences (9).

School health nurses cooperate with the school administration to identify health risks earlier, to plan appropriate interventions, and to take necessary measures. Thus, they contribute not only to the protection of child health but also to the continuation of family integrity and the appropriate use of community resources with early diagnosis (1, 2). The analysis of the results of screenings conducted by nurses within the scope of the school health services revealed that such interventions provide opportunities for the early detection of many health problems in children. This study was aimed at evaluating the prevalence of obesity, stunting, and hypertension problems among 5-14-year-old students from three primary schools.

METHODS

Design and Sampling: This descriptive and cross-sectional study was conducted in 5-14-year-old students from three primary schools. All the participating students belonged to middle-class socioeconomic status. The study population comprised of 2987 children from three elementary schools. Some of the participants were from kindergartens affiliated to these elementary schools. The others were from the first-eighth grade. The study sample included 2930 children going to school.

Data Collection: Data were collected by nursing students under the supervision of the researchers. The students were trained on height, weight, and blood pressure measurements. Separate teams were assigned to each school to measure blood pressure and anthropometric parameters.

Data on the students' age and gender were recorded in a form. Then, the results were recorded in data sheets. If a student had a health problem, his/her class teacher, school counselor, and family were informed, and the student was referred to a physician. Screenings were conducted in the school's conference or meeting rooms.

Height Measurements: Before measurements, girl students were asked to take off hairpins. A measuring tape was fixed to a flat wall. Measurements were performed in accordance with height measurement standards. The results were recorded in centimeters (10, 11). Heights for age were classified as stunted (<-2 standard deviation [SD]), short (≥-2 SD-<-1 SD), normal (≥-1 SD-<+1 SD), tall (≥+1 SD<+2 SD), and very tall (≥+2 SD) (12).

Weight Measurements: Weighing scales with 100 g sensitivity were used. The scales were calibrated before each measurement. While measuring weight, the students wore a thin school uniform, took off their shoes, and did not touch anywhere (10, 11). Weights for age evaluated in accordance with the Z-score assessment recommended by the World Health Organization (WHO) were classified as severely underweight (<2 SD), underweight (≥-2 SD<-1 SD), normal (≥-1 SD-<1 SD), overweight (≥+1 SD-<+2 SD), and obese (≥+2 SD) (12). The results were recorded in kilograms (kg).

Blood Pressure Measurement: While the child rested for about 15 minutes, he/she was told how the blood pressure would be measured. All measurements were performed on the right arm at the heart level. A cuff appropriate for children's arm circumference was used. The cuff was placed just above the antecubital fossa as to cover two-thirds of the length of the upper arm (2). The stethoscope diaphragm was placed slightly on the brachial artery, the cuff was inflated to a pressure of 20 mmHg where the brachial pulse pressure was lost, and then the pressure reduced at a rate of 2-3 mm Hg/sec (13). Blood pressures measured were classified as normal (<90 P), prehypertension (90 P-<95 P), stage-I hypertension (95 P-99 P), and stage-II hypertension (>99 P) (14).

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS) 20.0 software package (IBM Corp.; Armonk, NY, USA). To analyze the data, numbers, percentage distribution, arithmetic means, and SD were used. For statistical comparisons, the chi-square analysis was used. Anthropometric parameters were measured using the WHO-2007 reference values for children aged 5-19 years (body weight for age and body height for age) (10). Assessments were classified based on the Z-score (SD) cut-off points.

Ethics Approval and Consent to Participate: Before the study was conducted, approvals were obtained from relevant institutions and from the school administrations where the study was to be conducted. The families were informed of the research and their consent to allow their children to participate in the study

Table 1. Distribution of students by gender, age, and year in school

Characteristics	n	%
Age, years	8.74±2.50 (min–max: 5–14)	
Gender		
Female	1438	49.1
Male	1492	50.9
Grade		
Preschool	276	9.4
First	442	15.1
Second	496	16.9
Third	574	19.6
Fourth	408	13.9
Fifth	195	6.7
Sixth	209	7.1
Seventh	228	7.8
Eighth	102	3.5
Total	2930	100

min: minimum; max: maximum

was obtained. Prior to the research, the children were informed regarding what measurements they would undergo.

RESULTS

Of the students surveyed, 49.1% were girls, 50.9% were boys. Their mean±SD age was 8.74±2.5 years. The majority of the students were first-, second-, third-, and fourth-grade students (Table 1).

Of them, 1.3% were severely underweight, 9% were underweight, 49.3% were normal weight, 17.4% were overweight, 22.8% were obese, 1.1% were stunted, and 5.9% were short (Table 2, 3).

The distribution of the girls' and boys' height-for-age Z scores (SD) is shown in Table 2. According to this distribution, 11-, 12-, and 13-year-old girls were very short (5.6%, 4.4%, and 4.5%, respectively). The percentage of the very short boys in the 11-year-old age group was greater than that of the very short boys in the other age groups (6.3%). The height distributions by age and gender were compared, and differences by gender were observed only between 12-year-old children. While the percentage of 12-year-old stunted and short girl students was higher than their boy counterparts, the percentage of very tall boy students was higher than their girl counterparts (χ^2 = 14.56, p=0.006).

The distribution of the girls' and boys' weight-for-age Z scores (SD) is shown in Table 3. According to this distribution, while the obesity rate (>2 SD) among the girl students aged 5-9 years ranged between 20% and 36.2%, it ranged from 18% to 34% among the boy students in the same age group. In all the age groups, except for 12 years of age, the rate of severely underweight boy and girl students was very low. The comparison of the weight distributions by age and gender revealed that while the rate of overweight girls was higher than that of the boys among the 6-year-old children (χ^2=7.97, p=0.019), the rate of overweight boys was higher than that of the girls among the 7-year-old children (χ^2=11.18, p=0.011). The comparison also demonstrated that among the 6-year-old children, the rate of overweight boys was higher than that of the girls (χ^2=8.21, p=0.016).

The distribution of blood pressure values by gender is shown in Table 4. The rate of the students with normal systolic blood pressure was 77.9% (girls, 77.3%; boys, 78.5%). While the rate of the prehypertensive students was 12.0% (girls, 12.6%; boys, 11.5%), the rate of the students with stage I hypertension was 6.8% (girls, 6.5%; boys, 7.2%) and with stage II hypertension was 3.2% (girls, 3.6%; boys, 2.8%). The rate of the students with normal diastolic blood pressure was 83.1% (girls, 83.7%; boys, 82.5%). While the percentage of the prehypertensive students was 10.4% (girls, 10.0%; boys, 10.7%), the percentage of the students with stage I hypertension was 5.5% (girls, 5.2%; boys, 5.8%) and with stage II hypertension was 1.1% (girls, 1.1%; boys, 1.1%; p>0.05).

DISCUSSION

During primary school years, children's growth and development is rapid, and they develop most of the lifetime behaviors. Measurements to be made once a year in school-age children ensure the evaluation and monitoring of growth, early identification of deviations from normal growth, and planning of appropriate initiatives (2, 3). In the present study, the results obtained from the screenings demonstrated that 17.4% of the students were slightly overweight, 22.8% were overweight, and one-half of them were normal weight according to the WHO Z-score system. Based on the Z-score distribution of the boys' and girls' weights for age, the rate of obesity ranged from 20% to 36.2% among the girls aged 5-9 years and from 18% to 34% among the boys in the same age group.

The results also indicated that the 6-8-year-old girls were more obese than were the boys in the same age group (p<0.05). According to the Monitoring of the Growth of School Age Children Project in Turkey, of those children, 6.5% were obese, 14.3% were overweight, 1.3% were severely underweight, 5.0% were stunted, and 21.5% were short. The prevalence of obesity varies from one study to another conducted in different countries and regions. The rates of slightly overweight and obesity in this study were lower than those in Spain (35.2% in 6-9-year-olds) and Portugal (31.5% in 7-9-year-olds), close to those in France (18.1% in 7-9-year-olds), Switzerland (18.3% in 6-9-year-olds), Iceland (18.5% in 9-year-olds), and Slovakia (15.2% in 7-9-year-olds) (4) and higher than those in the UK (1.7% in 4-11-year-old boys and 2.6% in girls of the same age) and Scotland (2.1% in 4-11-year-old boys and 3.2% in girls of the same age) (4). These results suggest that different cultural aspects reflect the eating and activity habits. Although it was not investigated in the present study, it would not be wrong to relate the high prevalence of obesity to the decreased physical activity in school age children resulting

Table 2. Distribution of height–for–age z scores of girl and boy students

Age, years	Female										Male									
	n	<–2 SD		≥–2 SD–<–1 SD		≤–1 SD–<1 SD		≥1 SD–<2 SD		≥2 SD		<–2 SD		–2 SD–1 SD		≥–1 SD–<1 SD		≥1 SD–<2 SD		≥2 SD	
		%	n	%	n	%	n	%	n	%	%	n	%	n	%	n	%	n	%	n	%
5	122	–	–	–	–	40	32.8	44	36.1	38	31.1	121	–	–	2	1.7	41	33.9	36	29.8	42	34.7
6	155	–	–	1	0.6	64	41.3	54	34.8	36	23.2	153	–	–	6	3.9	65	42.5	53	34.6	29	19.0
7	235	5	2.3	13	5.5	108	46.0	69	29.4	40	17.0	273	2	0.7	19	7.0	140	51.3	68	24.9	44	16.1
8	246	–	–	3	1.2	115	46.7	80	32.5	48	19.5	259	1	0.4	12	4.6	123	47.5	71	27.4	52	20.1
9	228	1	0.4	10	4.4	108	47.6	57	25.1	51	22.5	232	1	0.4	10	4.3	117	50.4	68	29.3	36	15.5
10	76	1	1.3	2	2.6	44	57.9	22	28.9	7	9.2	95	1	1.1	2	2.1	57	60.0	19	20.0	16	16.8
11	89	1	5.6	22	24.7	56	62.9	6	6.7	–	–	95	6	6.3	16	16.8	56	58.9	12	12.6	5	5.3
12	113	5	4.4	20	17.7	70	61.9	18	15.9	–	–	100	1	1.0	11	11.0	72	72.0	9	9.0	7	7.0
13	110	5	4.5	10	9.1	64	58.2	26	23.6	5	4.5	96	–	–	7	7.3	61	63.5	23	24.0	5	5.2
14	63	–	–	8	12.7	42	66.7	10	15.9	3	4.8	68	–	–	13	19.1	44	64.7	10	14.7	1	1.5
Total	1438	18	1.3	89	6.2	711	49.4	376	26.4	228	15.9	1492	12	0.8	85	5.7	776	51.0	369	24.7	237	15.9

Total (female+male): < 2 SD = 1.0%; ≥–2 SD–<–1 SD = 5.9%; ≤–1 SD–<1 SD = 50.7%; ≥1 SD–<2 SD = 25.4%; ≥1 SD–<2 SD = 15.9%

SD: standard deviation

from their excessive involvement in today's technological devices with which they spent a lot of time without physical activity.

According to the findings of the present study as in other studies, obesity is more prevalent among students aged 6-8 years. Although obesity develops in any age group, its prevalence is higher in years when rapid fat deposition occurs, and childhood obesity increases in the first years of life, in the 5-7 years of life, and during adolescence (4, 14, 15). Based on the results of the present study, it can be said that healthy eating and appropriate lifestyle habits, which are the foundation of healthy living, should be gained during childhood. Within the scope of school health, children should be encouraged to gain healthy eating habits, and programs and activities to promote physical activities should be more extensive. In literature, it has been reported that interventions targeted to school-age children's health have yielded positive results (16, 17). For instance, a meta-analysis of school-based interventions suggests that school nurses can play a key role in implementing sustainable, effective, school-based obesity interventions (18).

In the study, results on stunting, another parameter of growth and development, were evaluated. When the students were classified according to the height-for-age Z scores, it was determined that 1.1% were stunted and 5.9% were short. When the distribution of height-for-age Z scores were analyzed in the 12-year age group, the rate of the stunted and short girl students was higher than the rate of boy students of the same height; however, the rate of the very tall boy students was higher than the rate of girls of the same height (p=0.006). According to the Childhood Obesity Survey (2013), the rate of the severely stunted children was 0.1%, and the rate of the stunted children was 2.3% (19). In a study of 1018 elementary school students aged 6-14, 7.46% of the students were stunted (20). According to the Monitoring of the Growth of School Age Children Project in Turkey, 5% were stunted and 21.5% were short. The results of the same project also demonstrated that the rates of the stunted (5.2%) and short (22.3%) girls were higher than those of the boys (4.9% and 20.7%, respectively). In this study, the height Z score distributions did not differ by gender. In a study conducted in Iraq, the stunting rate among school age children aged 7-12 years is 18.7% and stunting is the most prevalent (22.4%) in the 12-year age group (21). Defects in energy balance due to early under nutrition causes increases in the central adiposity in short children, fat oxidation becomes lower, lipolysis and lipid oxidation deteriorate, and the ratio of cortisol to insulin increases due to insufficient food intake and thus insulin resistance develops. The high rate of stunted and short children in the study group is noteworthy. Therefore, in children determined to have stunted growth, early detection and monitoring of chronic diseases with a detailed physical examination is essential.

Table 3. Distribution of weight-for-age z scores of girls and boy students

Age, years	Female											Male									
	n	<–2 SD		≥–2 SD–<–1 SD		≤–1 SD–<1 SD		≥1 SD–<2 SD		≥2 SD		n	<–2 SD		–2 SD–1 SD		≥–1 SD–<1 SD		≥1 SD–<2 SD		≥2 SD	
		n	%	n	%	n	%	n	%	n	%		n	%	n	%	n	%	n	%	n	%
5	122	–	–	4	3.3	51	41.8	37	30.3	30	24.6	121	3	2.5	2	1.7	63	52.1	19	15.7	34	28.1
6	155	1	1.0	2	2.1	76	50.0	36	23.7	40	26.3	153	–	–	–	–	82	53.6	34	22.2	37	24.2
7	235	–	–	16	6.8	121	51.5	51	21.7	47	20.0	273	–	–	5	1.8	169	61.9	48	17.6	51	18.7
8	246	–	–	2	2.8	126	51.2	44	17.9	69	28.0	259	5	1.9	23	8.9	92	35.5	49	18.9	90	34.7
9	228	2	0.9	29	12.7	112	49.1	32	14.0	53	23.2	232	1	0.4	26	11.2	99	42.7	36	15.5	70	30.2
10	76	–	–	13	17.1	40	52.6	11	14.5	12	15.8	95	3	3.2	14	14.7	43	45.3	11	11.6	24	25.3
11	90	2	2.2	20	22.2	40	44.4	19	21.1	9	10.0	95	1	1.1	24	25.4	38	40.0	14	14.7	18	18.9
12	113	9	8.0	13	11.5	59	52.2	22	19.5	10	8.8	100	4	4.0	18	18.0	52	52.0	11	11.0	15	15.0
13	110	4	3.6	18	16.4	55	50.0	9	8.2	24	21.8	96	2	2.1	14	14.6	48	50.0	13	13.5	19	19.8
14	63	1	1.6	6	9.5	38	60.3	7	11.1	11	17.5	68	1	1.5	15	22.1	39	57.4	8	11.8	5	7.4
Total	1438	19	1.3	123	8.7	718	49.9	268	18.8	305	21.2	1492	20	1.3	141	9.5	725	48.6	243	16.3	363	24.3

Total (female+male): <–2 SD=1.3%; ≥–2 SD–<–1 SD=9.0%; ≤–1SD–<1 SD=49.3%; ≥1 SD–<2 SD=17.4%; ≥1 SD–<2 SD=22.8%

SD: standard deviation

According to the results of the systolic blood pressure screenings, the rate of the students with prehypertension was 12.0%, with stage I hypertension was 6.8%, and with stage II hypertension was 3.2%. According to the results of the diastolic blood pressure screenings, the rate of the students with prehypertension was 10.4%, with stage I hypertension was 5.5%, and with stage II hypertension was 1.1%. The difference between the genders was not significant (p>0.05). According to the systolic blood pressure measurements of 1411 children aged 7-11 years, 4.5% were prehypertensive and 14.3% were stage I hypertensive (>ninety-fifth percentile). According to the diastolic blood pressure measurements of those children, 4% were prehypertensive and 4.7% were hypertensive. In a study conducted with 402 students, 7.5% had stage II hypertension, 12.2% had stage I hypertension, and 21.9% had prehypertension (22). In another study, 1.30% had presystolic hypertension, 2.02% had systolic hypertension, 2.65% had prediastolic hypertension, and 2.74% had diastolic hypertension. The distribution of blood pressure at the initial screen was as follows: normal (81.1%), prehypertension (9.5%), and hypertension (9.4%) (stage I, 8.4%, stage II, 1%) (23). The total prevalence of hypertension in children aged 6-18 years in India was 6.48% (6.74% in boys and 6.13% in girls), and the prevalence of hypertension increased with age in both sexes (24). In another study, the total prevalence of hypertension in school children aged 5-15 years was 3.19% (3.16% in girls and 3.22% in boys) (25). In studies conducted in Turkey, the prevalence ranged between 3.8% and 17.8% (26). The results of the present study are lower than those of some studies and higher than those of some other studies. The wide range of prevalence of hypertension might be due to differences between measurement and assessment techniques used in the studies and eating habits and demographic characteristics of children.

CONCLUSION

The results of the present study demonstrated that the prevalence of stunting, being slightly overweight/overweight, stage I hypertension and stage II hypertension in children aged 5-14 years was high. Therefore, routine screenings in schools play an important role in the detection of problems, such as stunting, hypertension, and being slightly overweight/overweight among children. In particular, programs on the prevention and management of obesity and implementation of healthy eating habits and physical activities will contribute to the improvement of health. Implementation and supervision of nutrition-friendly programs in all schools will be effective in combating obesity and obesity-induced hypertension. School health nurses are known to have various roles and responsibilities for the implementation of health protection and promotion programs. Programs aiming to protect and promote health in the world especially in the United States are very widely implemented by school health nurses. Although laws regarding school health in Turkey have been effective since 1930, school health

Table 4. Percentile breakdown of blood pressure measurements of students by gender

Percentile values of blood pressure	Systolic						Diastolic					
	Female		Male		Total		Female		Male		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
<90	1108	77.3	1170	78.5	2278	77.9	1199	83.7	1230	82.5	2429	83.1
90–95	180	12.6	172	11.5	352	12.0	144	10.0	159	10.7	303	10.4
95.1–99	93	6.5	107	7.2	99	6.8	74	5.2	86	5.8	160	5.5
>99	52	3.6	42	2.8	12	3.2	16	1.1	16	1.1	32	1.1
Total	1433	100	1491	100	2924	100	1433	100	1491	100	2924	100

nurses are still not employed in schools. In a circular issued in 2008, emphasis was placed on school health services, but information on who will provide these services was not provided (27). Therefore, to have healthy future generations, it is important to begin with employment of health nurses in schools.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İzmir Katip Çelebi Üniversitesi (26.05.2016- 2106/118).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - M.Y., B.A., H.Y.S.; Design - M.Y., B.A., H.Y.S., F.D.; Supervision - M.Y.; Resource - M.Y., B.A., F.D., H.Y.S., G.A.K., Z.T.; Materials - M.Y., B.A., F.D., H.Y.S., G.A.K., Z.T.; Data Collection and/or Processing - M.Y., B.A., F.D., H.Y.S., G.A.K., Z.T.; Analysis and/or Interpretation -M.Y., B.A., H.Y.S.; Literature Search - M.Y., H.Y.S., G.A., F.D.; Writing - M.Y., H.Y.S., B.A., G.A.; Critical Reviews - M.Y., B.A., F.D., H.Y.S., G.A.K., Z.T.

Acknowledgements: The authors thank to all school managers, families and children.

Conflict of Interest: No conflict of interest was declared by the authors.

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

Etik Komite Onayı: Bu çalışma için etik komite onayı İzmir Katip Çelebi Üniversitesi Girişimsel Olmayan Etik Kurulu'ndan alınmıştır (26.05.2016-2106/118).

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastaların ailelerinden alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - M.Y., B.A., H.Y.S.; Tasarım - M.Y., B.A., H.Y.S., F.D.; Denetleme - M.Y.; Kaynaklar - M.Y., B.A., F.D., H.Y.S., G.A.K., Z.T.; Malzemeler - M.Y., B.A., F.D., H.Y.S., G.A.K., Z.T.; Veri Toplanması ve/veya İşlemesi - M.Y., B.A., F.D., H.Y.S., G.A.K., Z.T.; Analiz ve/veya Yorum - M.Y., B.A., H.Y.S.; Literatür Taraması - M.Y., H.Y.S., G.A., F.D.; Yazıyı Yazan - M.Y., H.Y.S., B.A., G.A.; Eleştirel İnceleme - M.Y., B.A., F.D., H.Y.S., G.A.K., Z.T.

Teşekkür: İşbirliği yapan ilköğretim okulu yöneticileri, aileler ve çocuklara teşekkür ederiz.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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How to cite:

Yılmaz M, Aktaş B, Dereli F, Sarı HY, Kundakçı GA, Tiryaki Z. Assessment of the prevalence of obesity, stunting, and hypertension among primary school children. Eur J Ther 2017; 23: 99–105.

European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.66

Original Investigation / Özgün Araştırma

Non-malignant late effects in lymphoma patients treated with autologous hematopoietic stem cell transplantation

Otolog hematopoietik kök hücre nakli yapılan lenfomalı hastalarda malign olmayan geç etkiler

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ABSTRACT

Objective: Developments in transplantation procedures have led to an increase in the number of long-term survivors after hematopoietic stem cell transplantation (HSCT). In this study, we investigated non-malignant late side effects after autologous HSCT (AHSCT) in lymphoma patients.

Methods: Patients were evaluated for immune system, eye, lung, heart, liver, kidney, and endocrine function tests.

Results: Nine (26%) patients had absolute lymphopenia. Cataract was the only eye complication. Four (11.4%) patients had obstructive- and 8 (22.9%) had restrictive-type pulmonary function abnormalities. Only one patient had symptomatic heart failure. One patient developed renal failure. Fifty-three percent of male patients described impotence. The most frequent endocrine disorder was hypothyroidism. Five (14.2%) patients had osteoporosis.

Conclusion: There is not enough data on the non-malignant late effects after AHSCT. Although the lack of a control group is a limitation of our study, our results emphasize the importance of following AHSCT patients for non-malignant late effects of transplantation.

Keywords: Lymphoma, autologous hematopoietic stem cell transplantation, non-malignant, late effect

ÖZ

Amaç: Nakil işlemlerindeki gelişmeler hematopoietik kök hücre nakli (HKHN) sonrası uzun süre yaşayan hasta sayısında artışa neden olmuştur. Biz bu çalışmada lenfomalı hastalarda otolog HKHN sonrası malign olmayan geç yan etkileri araştırdık.

Yöntemler: Hastalar immün sistem, göz, akciğer, kalp, karaciğer ve böbrek fonksiyon testleri ile değerlendirildi.

Bulgular: Dokuz (%26) hastada lenfopeni saptandı. Katarakt tek göz komplikasyonuydu. Dört (%11,4) hastada obstrüktif ve 8 (%22,9) hastada restriktif tip akciğer fonksiyon anormalliği mevcuttu. Yalnızca 1 hastada semptomatik kalp yetmezliği vardı. Bir hastada renal yetmezlik gelişmişti. Erkek hastaların %53'ü impotans tarifledi. En sık endokrin anormallik hipotiroidi idi. Beş (%14,2) hastada osteoporoz saptandı.

Sonuç: Otolog HKHN sonrası malign olmayan geç etkilere ilişkin yeterli veri yoktur. Kontrol grubunun olmaması bir kısıtlılık olmakla birlikte, sonuçlarımız otology HKHN yapılan hastaların malign olmayan nakil geç yan etkileri açısından takip edilmesinin önemini vurgulamaktadır.

Anahtar kelimeler: Lenfoma, otolog hematopoietic kök hücre nakli, malign olmayan, geç etki

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a widely used curative treatment option for various malignant and non-malignant hematological diseases. Developments in the field of transplantation procedures and supportive care have led to an increase in the number of long-term survivors after transplantation. Knowledge regarding the late side effects after transplantation is increasing due to longer post-transplantation follow-up period.

Despite the fact that post-transplant late side effects can arise after three months, they generally emerge after many years. Organ or tissue dysfunction, changes in quality of life, and delayed or abnormal immune reconstitution associated with infections, and secondary cancers are the main late side effects. Many of these events occur as a result of the accompanying chronic graft versus host disease (GVHD).

The type and risk of developing late side effects after transplantation depend on previous treatments, conditioning regimen, age at transplantation, donor type, source of stem cells, accompanying problems (especially GVHD, infection, etc.), follow-up period after transplantation, and use of steroids or other immu-

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Received/Geliş Tarihi: 27.04.2017 • **Accepted/Kabul Tarihi:** 07.07.2017

nosuppressive treatments. The actual frequency and prognostic impact of the non-malignant late effects after autologous HSCT (AHSCT) are not very well known and can be more easily overlooked. In this study, our aim was to evaluate these overlooked non-malignant effects.

METHODS

In our study, lymphoma patients who underwent transplantation between February 2004 and February 2015 were evaluated at least one year after transplantation. Thirty-five patients were included in the study. The study protocol received institutional review board approval, and the participants provided informed consent.

The diagnoses were Hodgkin lymphoma (HL) in 19 (54.3%) patients and non-Hodgkin lymphoma (NHL) in 16 (45.7%) patients. Twenty-six (74.3%) patients were males and 9 (25.7%) were females. Patients had received a median of 8 (4-11) courses of chemotherapy before transplantation. Three (8.6%) patients were treated for post-transplant recurrence. Only one (2.9%) patient received both chemotherapy and radiotherapy (RT). Thirty-one (88.5%) patients received steroids in the treatment protocol. As a pre-transplant conditioning regimen, 16 (45.7%) patients had received carmustine, etoposide, and cyclophosphamide (CBV) and 19 (54.3%) had received carmustine, melphalan, etoposide, and cytarabine (BEAM) regimens. The age of the patients at the time of transplantation was 43.5±11.7 years. Physical examination and laboratory tests were performed for the late side effects directed at the immune system, eyes, lungs, heart, liver, kidneys, endocrine system, and fertility.

Absolute lymphocyte count, CD4+ lymphocyte count, CD8+ lymphocyte count, T helper/suppressor cell ratio, total immunoglobulin (Ig) G, IgG1, IgG2, IgG3, IgG4, IgA, and IgM were evaluated for the assessment of immune reconstitution.

Microvascular retinopathy, optic disc edema, hemorrhage, infectious retinitis, cataracts, and keratoconjunctivitis sicca were investigated with regard to eye complications.

The respiratory system was evaluated through physical examination, posterior-anterior (PA) chest X-ray, and pulmonary function tests (PFT). If forced expiratory volume in 1 second (FEV_1) was ≥80%, PFT was considered normal, or FEV_1/forced vital capacity (FVC) ratio was evaluated. FEV_1/FVC <70% was considered obstructive, and FEV_1 ≥70% was considered restrictive abnormality. The patients with the ratio of FEV_1/FVC<70% and FVC≤80% were considered to have a mixed-type abnormality.

The cardiovascular system was assessed with physical examination, pro-brain natriuretic peptide (BNP), 12-lead electrocardiogram (ECG), and echocardiography (ECHO).

The renal side effects were evaluated in terms of blood-urine nitrogen (BUN), creatinine, creatinine clearance (Modification of Diet in Renal Disease [MDRD]=186×[plasma creatinine] - 1.154×[age] – 0.203 [×0.742 if female]×25), Ca, P, Na, K, Cl, urine microscopy, and spot urine protein/creatinine ratio.

The menopausal status, impotence, and fertility have been questioned in terms of endocrine late effects. Total testosterone, free testosterone, thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, adrenocorticotropic hormone (ACTH), growth hormone, and parathyroid hormone (PTH) measurements were also conducted. Bone mineral density was measured using the Dual-energy X-ray absorptiometry (DEXA) method in the Nuclear Medicine Department.

The outcomes were also compared in terms of other factors that may influence the development of late side effects (sex, primary diagnosis, stage, presence of concomitant diseases, previous therapies, RT, steroid use, conditioning regimen, stem cell count, time period between diagnosis and transplantation, time period between transplantation and assessment, smoking and alcohol use, Eastern Cooperative Oncology Group (ECOG) performance status, remission status and concomitant medications) .

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) 21 (IBM Corp. Released 2012; IBM SPSS statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The summary values of continuous variables were expressed as mean±standard deviation or median (Q1-Q3), and categorical variables were expressed as frequency and percentage. The compliance of continuous data with the normal distribution was investigated using the Shapiro-Wilk test. The groups conforming to the normal distribution were compared using independent samples t-test (2 groups), or by one-way analysis of variance (for 3 groups and above). The differences of those that do not meet the normal distribution were investigated using Mann-Whitney test (for 2 groups) or the Kruskal-Wallis test (for 3 groups and above). The relationship between categorical variables was analyzed using chi-square test. A $p<0.05$ was considered significant in the results of analysis.

RESULTS

Absolute lymphopenia was detected in 9 (26%) patients, CD4 lymphopenia was detected in 12 (34.3%), and CD8 lymphopenia was detected in one (2.9%) patient. Thelper/Tsuppressor(Th/Ts) ratio was low in 7 (20%) patients. Total IgG was low in 17.1%, IgA was low in 14.3%, and IgM was low in 51.4% patients. Total IgG reduction was detected most frequently in patients receiving cisplatin, cytarabine, dexamethasone (DHAP) followed by adriamycin (doxorubicin), bleomycin, and vinblastine (ABVD) before transplantation (p=0.024). A decrease in IgM was detected more frequently in NHL than HL (66.7% vs 33.3%; p=0.026).

The only eye complication was cataract and was detected in 6 of the 35 patients.

Chest radiography revealed interstitial involvement in 2 (5.7%) patients, bronchovascular involvement in one (2.9%) patient, and effusion and air trapping in one (2.9 %) patient. Obstructive abnormality was detected in 4 (11.4%) patients, restrictive abnormality was detected in 8 (22.9%), and mixed-type abnormality was detected in 3 (8.6%) patients through PFT.

From the viewpoint of the cardiovascular system, T-wave negativity was observed in the ECG of 2 patients. Ejection fraction (EF) was low only in one patient; pro hormone B-type Natriuretic Peptide (pro-BNP) was high (≥300 pg/mL) in 4 patients.

When the late effects associated with kidneys were evaluated, creatinine clearance was low in 6 (17.1%) patients. Spot urine protein/creatinine ratio was high in 8 (22.9%) patients.

Seven of 9 women were postmenopausal. The estradiol, progesterone, FSH, and LH levels of all women were in the normal range. Fourteen (53%) of 26 male patients described impotency. Total testosterone was low in 14 (46.2%) patients and free testosterone in 10 (38.5%) patients. Thyroid-stimulating hormone (TSH) was high (>4.2 pg/mL) in 5 (4.2%), free T3 was high in one (2.9%) patient, and free T4 was high (>1.7 ng/dL) in 2 (5.7%) patients. TSH was low (<0.27 pg/mL) in 4 (11.4%) patients and free T3 was low (<2 pg/mL) in 4 (11.4%) patients. Nine patients (25.71%) had osteopenia and 5 (14.28%) had osteoporosis.

DISCUSSION

It is well-known that allogeneic HSCT has a long-lasting effect on the immune system. Although we could not find a similar study on the late effects of AHSCT on the immune system, absolute lymphopenia, CD4 lymphopenia, CD8 lymphopenia, low Th/Ts ratio, and low Ig levels were the detected abnormalities with regard to the immune system in our study. However, there were no clinical findings suggesting immunosuppression. These findings suggest that the effects of AHSCT on the immune system may also last long but cause few clinical problems.

Majhail et al. (1) compared patients who underwent AHSCT due to HL and NHL with their healthy siblings at a median follow-up of 6 years and found an increased incidence of cataract. Cataract was observed more frequently in the group receiving total body irradiation (TBI) as a conditioning regimen. Cataract was the only eye complication detected in our study. In one patient, cataract was observed despite the absence of steroid use, and none of our patients had a history of TBI. Since our patients had no routine eye examination in the pre-transplant period, the effect of aging and/or steroid use could not be assessed.

The reduction in lung functions after HSCT is generally associated with carmustine used as a conditioning regimen and relapsed malignancy (2, 3). Carlson et al. (4) reported the interstitial pneumonitis frequency as 11% and TBI as the major risk factor at a median follow-up of 12 months in 102 patients surviving 6 months after autologous transplantation. Lane et al. (5) reported the frequency of pneumonitis as 22% in 222 patients receiving CBV as a conditioning regimen. Mediastinal radiotherapy, carmustine dose over 1000 mg, and age <54 years were reported as risk factors. Interstitial pneumonitis was present in 5.7% of patients in our study. Since all the patients received carmustine at equal doses, the effect of carmustine on pneumonitis frequency could not be evaluated in our study. TBI had not been applied to any of our patients. Thus, we concluded that caution should also be taken in terms of pneumonitis in patients not receiving TBI.

Cervera et al. (6) determined PFT as normal in 62% of 52 pediatric patients after 3-11 years of autologous and allogeneic transplantation, and they observed a restrictive loss in 23% patients. Multiple remissions, allogeneic transplantation, and pulmonary infections have been found effective on results. Although our patients consisted of only adult group and were limited with the patients undergoing autologous transplantation, obstructive and restrictive losses were found to be similar.

Clinically evident cardiac complications after HSCT are rare. Previously, age and cardiac dysfunction were accepted as more restrictive, but today, the transplantation applied to older patients may lead to an increased incidence of impaired cardiac function (7-9). Ruiz-Soto et al. (10) reported the rate of patients developing left ventricular dysfunction as 6% in their study, wherein they evaluated 493 patients with aggressive NHL who underwent AHSCT. Only 2% of these patients were reported as symptomatic. In our study, symptomatic heart failure was found to be less frequent possibly due to younger age and better cardiac performance at the pre-transplant period.

We could not find any study evaluating cardiac complications after AHSCT in terms of pro-BNP. The pro-BNP level was detected as high in 4 of our patients. All of the patients were males. Three of the patients were asymptomatic and had normal ECG and EF. The symptomatic one patient had T-wave negativity on ECG and low EF. Although the cumulative anthracycline dose, mediastinal radiotherapy, cardiac function before transplantation, and the type and intensity of conditioning regimen have been defined responsible for late cardiovascular events after HSCT (7), we could not find a relationship with these factors.

There is less information regarding the extent of late renal dysfunction after HSCT. The use of various nephrotoxic agents shows a strong relationship with renal dysfunction (11). Other risk factors reported for developing chronic renal failure (CRF) are advanced age at transplantation, post-transplant hypertension, a low glomerular filtration rate before transplantation, single-dose TBI regimen and fludarabine, and the presence of GVHD (12). In our study, only one patient met the criteria for CRF. This patient had uncontrolled hypertension as a risk factor in the pre-transplant period, but the use of nephrotoxic drugs given for post-transplant relapse may also have contributed to CRF.

Moser et al. (13) calculated the 15-year cumulative incidence of renal failure as 11% in their study, wherein they evaluated 757 NHL patients with a ≥2-year survival after AHSCT. Ruiz-Soto et al. (10) followed 439 aggressive NHL patients who underwent AHSCT for a median of 3 years after transplantation in terms of late complications. The number of the patients with late complications was 68, and renal failure was identified only in one patient. The CRF frequency in our study was found to be 2.85%. However, patient characteristics and the differences in the conditioning regimen and supportive care make the comparison difficult. Our study suggests that AHSCT does not have a significant negative effect on renal functions, but the patients with risk factors of the general population should be considered more carefully.

Mertens et al. (14) evaluated 270 pediatric and adult lymphoma patients, who underwent bone marrow transplantation and determined the rate of gonadal dysfunction as 92% in males and as 99% in females. In our study, most of our female patients (5/9) were post-menopausal in the transplantation period. Two patients became post-menopausal after transplantation. Seven patients had a history of birth in the pre-transplant period. Two patients gave birth after transplantation. Our data suggest that AHSCT has no significant negative effect on female gonadal functions but larger prospective studies are needed to make definitive results.

Schimmer et al. (15) evaluated sexual functions in 16 male patients ≤50 years of age, surviving for at least 6 months of remission in their post-transplant period and having the diagnosis of HL (n=9), acute myeloid leukemia (AML; n=4), and NHL (n=3). Four of the 16 patients described moderate sexual desire and two of them described frequent erectile dysfunction. In our study, when 26 male patients were evaluated in terms of the gonadal functions, 14 (53%) patients described impotence. Unfortunately, the results were obtained from a subjective evaluation.

Thomas et al. (16) evaluated 186 autologous and allogeneic HSCT patients remaining under complete remission for ≥1 year. The diagnosis was lymphoma in 50% of patients and the conditioning regimen was TBI. No clinical thyroid symptoms were detected in patients. Biological dysfunction was observed in 10%, hypothyroidism in 6.5%, thyroiditis in 3%, and Basedow's disease in 0.5% patients. All the patients in our study group were euthyroid before transplantation. Subclinical hypothyroidism was detected in 2 (5.8%) patients, sick euthyroid syndrome in one (2.9%) patient, overt hypothyroidism in 3 (8.7%) patients, and hyperthyroidism in 2 (5.8%) patients under Levothyroxine (LT4) in the post-transplant evaluation. The reason for different rates can be associated with a heterogeneous group of patients, the variability of evaluation methods, and the evaluation period.

Majhail et al. (17) evaluated HL (n=92) and NHL (n=184) patients in terms of the late complications compared with their siblings. Osteoporosis (4.3% vs 2.2%) and avascular necrosis (3.3 vs 0.3%) was more common in patients undergoing AHSCT at a median 6-year follow-up. Osteoporosis was more common in women. Since, our study was designed to be without a control group we were not able to make similar comparisons. The reason for higher frequencies in our study (10.5% in HL and 18.75% in NHL) is thought to be related with the lower number and the higher mean age of our patients. We could not evaluate the effect of gender to the osteoporosis due to the limited number of our female patients.

CONCLUSION

Since some of our patients received chemotherapy for recurrence after transplantation, our data may not be interpreted solely as an effect of AHSCT. However, despite other limitations of study, such as the low number of patients, heterogeneity of the patient group, and the lack of control group, our results emphasize the importance of also following AHSCT patients for non-malignant late effects of transplantation. Follow-up guidelines specific for AHSCT recipients can be useful and will probably become necessary in the future.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Eskisehir Osmangazi University (25.12.2014 - 80558721/15).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - E.G.; Design - E.G., P.S., H.Y.; Supervision - E.G., P.S.; Resource - E.G., P.S.; Materials - E.G., P.S., H.Y.; Data Collection and/or Processing - E.G., P.S., H.Y.; Analysis and/or Interpretation - E.G., P.S., H.Y.; Literature Search - E.G., P.S.; Writing - E.G., P.S.; Critical Reviews - E.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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

Etik Komite Onayı: Bu çalışma için etik komite onayı Eskişehir Osmangazi Üniversitesi Etik Kurulu'ndan alınmıştır (25.12.2014 - 80558721/15).

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - E.G.; Tasarım - E.G., P.S., H.Y.; Denetleme - E.G., P.S.; Kaynaklar - E.G., P.S.; Malzemeler - E.G., P.S., H.Y.; Veri Toplanması ve/veya İşlemesi - E.G., P.S., H.Y.; Analiz ve/veya Yorum - E.G., P.S., H.Y; Literatür Taraması - E.G., P.S.; Yazıyı Yazan - E.G., P.S.; Eleştirel İnceleme - E.G.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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How to cite:

Sırmatel P, Yılmaz H, Gündüz E. Non-malignant late effects in lymphoma patients treated with autologous hematopoietic stem cell transplantation. Eur J Ther 2017; 23: 106-10.

European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.65

Original Investigation / Özgün Araştırma

Investigation of *Brucella* and *Coxiella burnetii* antibodies among humans at risk and control groups living in southeastern Turkey

Türkiye'nin güneydoğusunda yaşayan risk ve kontrol grubundaki kişilerde *Brucella* ve *Coxiella burnetii* antikorlarının araştırılması

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ABSTRACT

Objective: *Brucella* and *Coxiella* are zoonotic pathogens with a broad geographic distribution. In this study, we investigated the prevalence of *Brucella* and *Coxiella burnetii (C. burnetii)* antibodies among at-risk and control groups living in southeastern Turkey.

Methods: Cross-sectional study. Age, gender, symptoms, and risk factors of subjects were obtained by questionnaire. The presence of *Brucella* antibodies was determined by *Brucellacapt* tests. *C. burnetii* IgM and IgG antibodies were detected by enzyme-linked immunosorbent assay. Positive and equivocal samples were confirmed with an indirect fluorescent-antibody test.

Results: The risk group was composed of farmers (27.7%), butchers (27.3%), laboratory workers (22%), slaughterhouse workers (20%), and veterinarians (3%). The control group was comprised of housewives (36.7%), tradesmen (35%), and office workers (28.3%). For *Brucella*, 22% of the risk group and 14.7% of the control group had a titer≥1:40 (p=0.020). Of the risk and control groups, 6.7% and 2.7%, respectively, had a titer ≥1:160 (p=0.020). *C. burnetii* IgM and IgG antibodies were detected in 2% and 40% of the risk group subjects and in 0.7% and 37.3% of the control group subjects, respectively (p=0.285 and p=0.502).

Conclusion: The high prevalence of brucellosis in risk groups compared to the control group and the probability of exposure to *C. burnetii,* in several sections of the community, especially the risk groups, show the importance of the control of zoonotic diseases.

Keywords: *Brucella* spp., *Coxiella burnetii*, *Brucellacapt* test, Enzyme-linked immunosorbent assay (ELİSA), Immunofluorescent assay (IFA)

ÖZ

Amaç: *Brucella* ve *Coxiella* geniş bir coğrafik dağılım gösteren zoonotik patojenlerdendir. Bu çalışmada, Türkiye'nin güneydoğusunda yaşayan risk ve kontrol grubunda bulunan kişilerde *Brucella* ve *Coxiella burnetii* antikorlarının prevalansının araştırılması amaçlanmıştır.

Yöntemler: Kesitsel bir çalışmadır. Çalışma kapsamına alınan kişilere yaş, cinsiyet, semptom ve risk faktörlerine ilişkin anket formları uygulanmıştır. *Brucella* antikorunun varlığı *Brucellacapt* testi ile araştırılmıştır. *Coxiella burnetii (C. burnetii)*, immunoglobulin M (IgM) ve immunoglobulin G (IgG) antikorları Enzyme-linked immunosorbent assay (ELİSA) ile araştırılmıştır. Pozitif ve kuşkulu saptanan örnekler Immunofluorescent assay (IFA) testi ile doğrulanmıştır.

Bulgular: Risk grubunda bulunanların %27,7'si çiftçi, %27,3'ü kasap, %22'si laboratuvar personeli, %20'si mezbaha işçisi, %3'ü veteriner, kontrol grubunda bulunanların %36,7'si ev hanımı, %35'i esnaf, %28,3'ü memurlardan oluşmuştur. *Brucella* antikor pozitifliği ≥ 1:40 titrede, risk grubunda %22, kontrol grubunda %14,7 (p=0,020), ≥1:160 titrede, risk grubunda %6,7, kontrol grubunda %2,7 oranında saptanmıştır (p=0,020). *C. burnetii* IgM pozitifliği risk grubunda %2, kontrol grubunda %0,7, IgG pozitifliği risk grubunda %40, kontrol grubunda %37,3 oranında saptanmıştır. Risk ve kontrol grubu arasında *C. burnetii* IgM ve IgG pozitifliği açısından anlamlı bulunmamıştır (p=0,285, p=0,502).

Sonuç: Risk grubunda kontrol grubuna göre yüksek oranda brucellozis prevalansı saptanması ve özellikle risk grubundakiler olmak üzere ciddi bir toplum kesiminin *C. burnetti* ile karşılaşma ihtimalinin bulunması, bize zoonotik hastalıkların kontrolünün önemini göstermektedir.

Anahtar kelimeler: *Brucella* spp., *Coxiella burnetii*, *Brucellacapt*, Enzyme-linked immunosorbent assay (ELİSA), Immunofluorescent assay (IFA)

INTRODUCTION

Brucellosis is an endemic zoonosis in some developing countries (1). *Brucella* spp. may be transmitted to humans through consumption of the meat, body fluids such as milk and urine, dairy products prepared with infected milk, or the placenta of infected animals (2). Transmission may also occur through sexual contact, through transfusion of infected blood, or in the laboratory through accidental transmission by inhalation (2). In humans, it

This study was presented as XXXV. Turkish Microbiology Congress, 3–7 November 2012, Aydın, Turkey.

Bu çalışma XXXV. Türk Mikrobiyoloji Kongresi'nde sunulmuştur. 3–7 Kasım 2012, Aydın, Türkiye.

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Received/Geliş Tarihi: 05.05.2017 • **Accepted/Kabul Tarihi:** 14.07.2017

can cause chills, undulant fever, perspiration, stomachache, arthralgia miscarriage, and orchitis and sterility in men (3). Conventional microbiological methods (culture and identification), serological tests, and enzyme-linked immunosorbent assay (ELISA) tests are mainly used to diagnose brucellosis (2). It is common as an occupational disease among veterinarians, farmers, animal breeders, herdsmen, butchers, and slaughterhouse workers, who may become infected through direct contact with animals (2).

Q fever is an infection caused by *Coxiella burnetii (C. burnetii)*. The most common sources of transmission to humans are farm animals such as sheep, goats, and cattle (4). Infected animals pass the microorganisms to the environment through their urine, feces, milk, and birthing products (5). The organism is transmitted to humans through the digestive system upon consumption of raw or unpasteurized milk and dairy products, through the skin and mucosa, or through inhalation of contaminated dust. The most common mode of transmission of *C. burnetii* to humans is inhalation (4, 6). Q fever may cause asymptomatic acute disease or a chronic infection (7). The diagnosis of Q fever is made by detecting antibodies against *C. burnetii* using complement fixation, indirect fluorescent antibody (IFA), micro-immunofluorescence, ELISA, or micro-agglutination tests. The IFA technique has been suggested as the reference method (gold standard) (8). Q fever is generally considered an occupational disease among people working with farm animals, among laboratory staff working with infected animals, and among veterinarians (9).

In this study, we aimed to investigate the seroprevalence of *Brucella* and *C. burnetii* among various occupational groups in Gaziantep and the possible risk factors.

METHODS

Ethical Approval

This study was approved (Resolution No. 05-2010/2) by the Ethics Committee of Gaziantep University School of Medicine. Informed consent was obtained from the persons involved in the study.

Risk and Control Groups

The study was carried out in Gaziantep, between October 2010 and July 2011. In this cross-sectional study, blood samples were simultaneously collected from the risk and control groups. Information about age, gender, clinical diagnosis, risk factors, and symptoms of participants were recorded. The study included 300 at-risk subjects and 300 controls.

Sample Collection

Our laboratory tests were carried out at the laboratory of the Division of Clinical Microbiology. After collection, the samples were centrifuged at 1.500 rpm for 10 minutes and the serum was stored at - 20°C until use. Hemolyzed and lipemic samples were rejected.

Laboratory Tests

Brucella antibodies were detected using the Brucellacapt test (Vircell, Spain). The results were categorized as negative, having an antibody titer ≥1:40, or having an antibody titer ≥1:160. Because blocking antibodies were detectable with the *Brucellacapt* test, all the antibody titers were determined using the *Brucellacapt* test (10, 11).

Detection of IgM and IgG antibodies against *C. burnetii* Phase II antigens was performed using an ELISA kit (Vircell, Spain). All equivocal and positive ELISA tests were evaluated with an IFA test, (Vircell, Spain) following the manufacturer's instructions. Titers of ≥1:24 and ≥1:64 with Phase I and II IgM antibodies and IgG antibodies, respectively, were considered positive. *C. burnetii* IgM and IgG antibody results given in the study showed Phase II antibody results.

Statistical Analysis

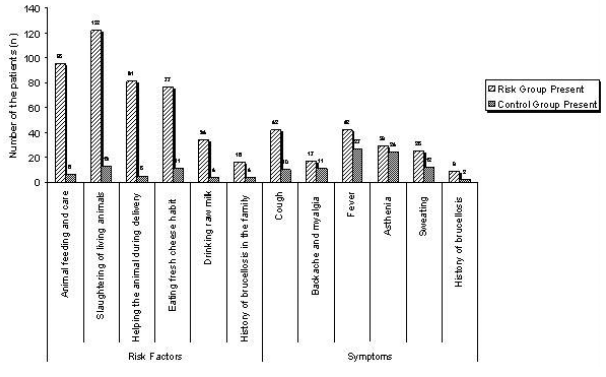
The data were analyzed using the chi-square test with Statistical Package for Social Sciences (SPSS), version 11.5 (SPSS Inc., Chicago, IL, USA).

RESULTS

Out of the 600 participants, 428 (71.3%) were male. The distribution according to age was as follows: 12.3% were 15-24 years, 38% were 25-34 years, 35.9% were 35-44 years, 11% were 45-54 years, and 2.8% were ≥55 years. In the risk group, 27.7% were farmers, 27.3% were butchers, 22% were laboratory workers, 20% were slaughterhouse workers, and 3% were veterinarians. In the control group, 36.7% were housewives, 35% were tradesmen, and 28.3% were office workers. In the risk group, 44.3% had worked more than 10 years, 28.3% 6 to 10 years, 22.7% had worked 2 to 5 years, and 4.7% had worked less than 2 years at their current occupation.

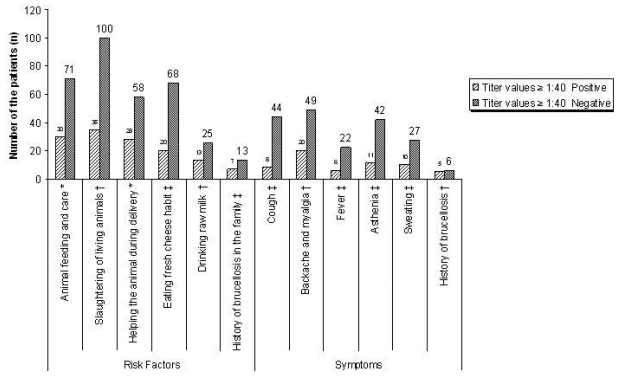
The risk factors and symptoms in the risk and control groups are shown in Figure 1. *Brucellacapt* titer results for the risk and control groups are shown in Table 1. Twenty-two percent of the risk group and 14.7% of the control group showed antibody titers (≥1:40) indicating previous exposure to *Brucella*, and the difference between the two groups was significant (p=0.02). Previous exposure was found among veterinarians (55.5%), farmers (31.3%), slaughterhouse workers (25.0%), tradesmen (17.2%), butchers (17.1%), housewives (15.4%), office workers (10.6%), and laboratory workers (9.1%). Because the number of people

Figure 1. The distribution of the risk factors and symptoms in the risk and control groups



in the various occupational groups differed, statistical comparison was not done. Previous exposure to *Brucella* determined by age groups was as follows: 13.6% among those aged 15-24 years, 20.2% among those aged 25-34 years, 18.6% among those aged 35-44 years, 19.7% among those aged 45-54 years, and 5.8% among those aged ≥55 years, and the differences were not significant (p=0.475). Previous exposure of males was 18.9% and of females was 16.8%, and the difference was not significant (p=0.554). Previous history of exposure was significantly (p=0.04) associated with the number of years worked in current occupation, and 27.1% of people who worked more than 10 years, 24.8% who worked 6 to 10 years, 11.8% who worked 2 to 5 years, and 7.1% who worked less than 2 years had elevated antibody titers. The distribution of *Brucella* antibody positivity at titers ≥1:40 among individuals according to having risk factors and symptoms (positive or negative) are shown in Figure 2.

Figure 2. The distribution of Brucella antibody positivity at titers ≥1:40 among individuals having risk factors and symptoms



Among the risk group, 6.7% had *Brucella* antibody titers ≥1:160, and among the control group 2.7% had *Brucella* antibody titers ≥1:160 (p=0.02). The distribution of participants with antibody titers ≥1:160 according to their occupation was as follows: 22.2% of veterinarians, 10.8% of farmers, 6.7% of slaughterhouse workers, 6.1% of butchers, 4.7% of tradesmen, 1.8% of housewives, and 1.2% of office workers. None of the laboratory workers had antibody titers ≥1:160. The distribution of participants with antibody titers ≥1:160 according to their age groups was as follows: 6.8% of people aged 15-24 years, 4.4% of people aged 25-34 years, 3.7% of people aged 35-44 years, and 7.5% of people aged 45-54 years. None of the subjects aged ≥55 years had titers ≥1:160 (p=0.511). Of all the participants with antibody titers ≥1:160, 5.8% were males and 1.7% were females (p=0.03). When *Brucella* antibody positivity (≥1:160) was investigated by gender, positive results were obtained in 25 (5.8%) of 428 males but in

Table 1. The results of *Brucellacapt* tests in the risk and control groups

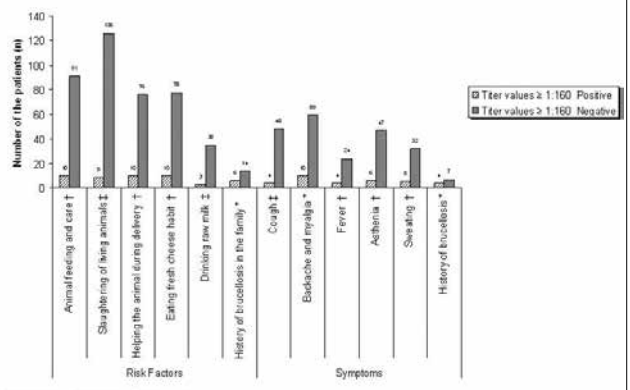
		***Brucellacapt* titer**								
		1:40	**1:80**	**1:160**	**1:320**	**1:640**	**1:1280**	**1:2560**	**1:5120**	**Total**
Risk Group n (%)	Butcher	4 (17.4)	5 (21.8)	4 (36.3)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	14 (21.2)
	Slaughterhouse worker	6 (26.1)	5 (21.8)	3 (27.3)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (22.7)
	Farmer	8 (34.8)	9 (39.1)	3 (27.3)	3 (75.0)	0 (0.0)	1 (50.0)	1 (100.0)	1 (100.0)	26 (39.4)
	Laboratory staff member	5 (21.7)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (9.1)
	Veterinarian	0 (0.0)	3 (13.0)	1 (9.1)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	5 (7.6)
	Total	23 (100.0)	23 (100.0)	11 (100.0)	4 (100.0)	1 (100.0)	2 (100.0)	1 (100.0)	1 (100.0)	66 (100.0)
Control Group n (%)	Office workers	6 (28.6)	2 (13.3)	0 (0.0)	1 (33.3)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	9 (20.5)
	Housewife	9 (42.8)	6 (40.0)	1 (33.3)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.0)	0 (0.00)	17 (38.6)
	Tradesman	6 (28.6)	7 (46.7)	2 (66.7)	2 (66.7)	0 (0.00)	1 (100.0)	0 (0.00)	0 (0.00)	18 (40.9)
	Total	21 (100.0)	15 (100.0)	3 (100.0)	3 (100.0)	0 (0.00)	1 (100.0)	1 (100.0)	0 (0.00)	44 (100.0)

Table 2. The results of *Coxiella burnetii* ELISA in the risk and control groups

	ELISA IgM				ELISA IgG			
Study group	Positive n (%)	Equivocal n (%)	Negative n (%)	Total n(%)	Positive n (%)	Equivocal n (%)	Negative n (%)	Total n (%)
Risk group	1 (0.3)	6 (2)	293 (97.7)	300 (100)	74 (24.7)	47 (15.7)	179 (59.7)	300 (100)
Control Group	1 (0.3)	1 (0.3)	298 (99.3)	300 (100)	87 (29)	31 (10.3)	182 (60.7)	300 (100)
Total	2 (0.3)	7 (1.2)	591 (98.5)	600 (100)	161 (26.8)	78 (13)	361 (60.2)	600 (100)

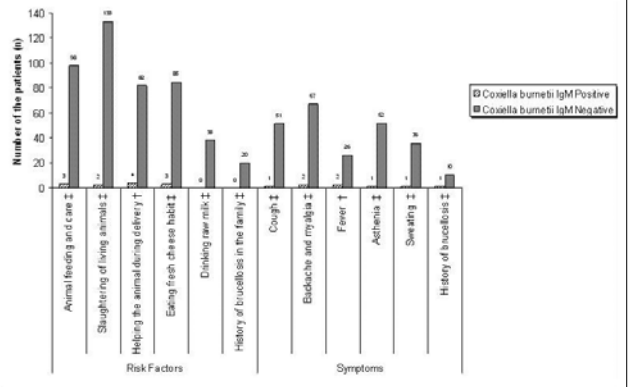
ELİSA: enzyme–linked immunosorbent assay; IgM: immunoglobulin M; IgG: immunoglobulin G

Figure 3. The distribution of *Brucella* antibody positivity at titers ≥1:160 among individuals having risk factors and symptoms



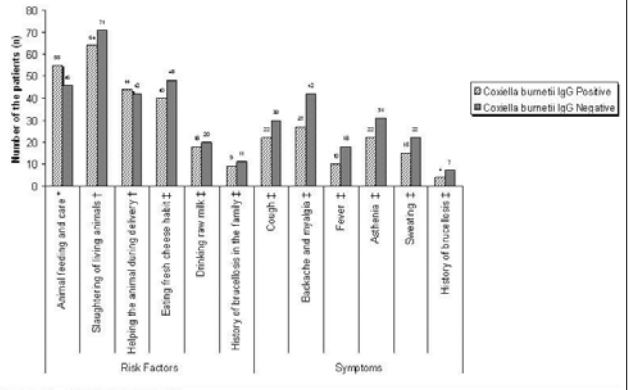
* p≤0.001, † p≤ 0.05, ‡ p>0.05

Figure 4. The distribution of *C. burnetii* IgM antibodies among individuals having risk factors and symptoms



† p≤ 0.05, ‡ p>0.05

Figure 5. The distribution of *C. burnetii* IgG antibodies among individuals having risk factors and symptoms



* p≤0.001, † p≤ 0.05, ‡ p>0.05

3 (1.7%) of 172 females. It was found statistically significantly more frequent in males (p=0.03). Brucellosis was not significantly associated with the duration of work in the current occupation (p=0.10). The distribution of *Brucella* antibody positivity at titers ≥1:160 among individuals according to having risk factors and symptoms (positive or negative) is shown in Figure 3.

Regarding *C. burnetii*, 0.3% of participants had a positive ELISA test for IgM antibodies, 1.2% had an equivocal test, and 98.5% had a negative test, whereas 26.8% had a positive ELISA test for IgG antibodies, 13% had an equivocal test, and 60.2% had a negative test (Table 2).

When ELISA and IFA antibody results for *C. burnetii* positivity were evaluated, IgM was found positive in 2% and 0.7% of the risk and control groups, respectively, whereas IgG was found positive in 40% and 37.3% of the risk and control groups, respectively. No significance was found between the risk and control groups in terms of IgM and IgG positivity (Fisher p=0.285 and p=0.502, respectively). *C. burnetii* IgM positivity was detected in 3.3% of slaughterhouse workers, 22.2% of veterinarians, 1.8% of housewives, 1.2% of farmers, and 1.5% of laboratory staff members, whereas no positivity was recorded among butchers, office workers, or tradesmen. *C. burnetii* IgG positivity was determined in 37.8% of butchers, 51.7% of slaughterhouse workers, 59% of farmers, 40% of tradesmen, 34.5% of housewives, 37.6% of office workers, 10.6% of laboratory staff members, and 22.2% of veterinarians. *C. burnetii* IgM and IgG antibodies were positive in 2.7% and 32.4% of participants aged 15-24 years, in 1.3% and 36.8% of those aged 25-34 years, and in 1.4% and 41.4% of those aged 35-44 years, respectively. While IgG antibodies were positive in 39.4% of those aged 45-54 years and in 52.9% of those aged 55 years and over, no IgM positivity was detected in those aged 45 years and over. No significant relationship was found between the age groups regarding IgM and IgG positivity (p=0.702 and p=0.450, respectively). When *C. burnetii* IgM and IgG antibodies were evaluated by gender, 2.3% and 36% of females and 0.9% and 39.7% of males were found to be positive, respectively. No significant relationship was detected between the two genders (Fisher p=0.234 and p=0.403, respectively). According to the duration of work in the risk group, no IgM positivity was determined for less than 2 years of work, whereas positivity was detected in 1.4% for 2 to 5 years, 4.7% for 6 to 10 years, and 0.8% for more than 10 years. IgG positivity was detected in 35.8% working for less than 2 years, in 30.9% working for 2 to 5 years, in 31.8% working for 6 to 10 years, and in 50.3% for working more than 10 years. Working time was not found to be significant in terms of IgM positivity (p=0.202), whereas it was significant for IgG (p=0.013). The distribution of *C. burnetii* IgM and IgG antibodies among individuals having risk factors and symptoms are shown in Figures 4 and 5.

DISCUSSION

Although brucellosis is seen in every region of the world, it is hyperendemic in the Mediterranean countries, the Arabian Peninsula, India, Mexico, and Central and South America (12). In our study, *Brucella* antibody positivity (titer≥1:40) was detected in 18.3% of 600 participants, and the titers of *Brucella* antibodies were ≥1:160 in 4.7% of the 600 participants. In this study, *Brucella* antibody positivity (titer≥1:40) in persons in the at-risk group (22%) was significantly higher than the control group (14.7%). Kılıç et al. (13)

detected 19% positivity among veterinarians and 4.7% among veterinary students and slaughterhouse workers in the province of Hatay using a micro-agglutination test. In a study carried out in the south of Iran, there was 7.8% antibody positivity (titer≥1:40) among people in the at-risk group for brucellosis with standard tube agglutination test (14). Similar to our findings, they reported that profession was the main factor for seropositivity.

Altındiş (15) reported 13.3% positivity (titer≥1:160) among fatteners, 8.6% positivity among butchers and sausage manufacturers, and 15.7% positivity among milk collectors and workers in the dairy product workshops in Afyon. In our study, the rate of *Brucella* antibodies was also high among farmers depending on these risk factors. The high prevalence among butchers and slaughterhouse workers might be accounted for by their dealing with animals with bare hands, slaughtering of animals, cuts on the skin, and inhalation of the agent.

In our study, a significant difference was found between the behaviors constituting the risk factors for the disease-such as animal feeding and care, slaughtering of living animals, helping the animal during delivery, and drinking raw milk and *Brucella* antibody positivity in terms of the indication of contact in a person (Figure 2). In their study in the province of Sivas in Central Anatolia, Alim *et al*. (16) regarded such features as direct contact with animals, the use of unhygienic meat, unpasteurized milk and their products, and occupation as the risk factors and reported 21.5% positivity among those with risk factors but 4.9% positivity among those with no risk factors using the Brucella agglutination test (Rose Bengal and Wright). The main source of transmission for brucellosis in Turkey is the consumption of unpasteurized milk and dairy products (17). In an epidemiological study carried out in Bosnia and Herzegovina, it was stated that in villages human brucellosis was transmitted mostly by contact with infected animals and their products, and in cities by consumption of dairy products made from contaminated, unpasteurized milk (18).

Q fever is an essential zoonotic infection that affects both animals and human beings. In our study, *C. burnetii* IgM positivity was found to be 2% and 0.7% in risk and control groups, while IgG positivity was found to be 40% and 37.3% in risk and control groups (Fisher p=0.285 and p=0.502, respectively). Aydın, Eyigör et al. (19) observed *C. burnetii* IgM positivity of 7.6% and IgG positivity of 42.3% in all study groups in their study with IFA and ELISA tests. Three occupational groups were included in the study (veterinarians, cattle-dealers, and butchers). In their study, they had collected serum samples from healthy people randomly in the city centers of Antalya, Diyarbakır, and Samsun, Berberoğlu *et al.* (20) reported 13.2%, 6%, and 1.8% IgG positivity, respectively, with IFA tests. Kılıç et al. (13) detected 20.6% IgG positivity against *C. burnetii* with IFA tests in their study on the at-risk groups in the province of Hatay. In the high-risk groups in eastern Turkey, Berktaş et al. (21) reported the rate of *C. burnetii* IgG seropositivity as 36.6% with ELISA tests. Sertpolat et al. (22) reported 39.3% IgG positivity using IFA tests in their study with healthy donors living in and around İzmir located in the western part of Turkey. In a study carried out in the province of Samsun in northern Turkey (23), the authors worked with 407 subjects in total, and 8.1% of them were identified as having past evidence of infection and 5.4% of them were considered to have the evoluative form of Q fever (17 acute and 5 chronic forms) by the microimmunofluorescent antibody test. They found 13.5% total seropositivity among healthy people, confirming that Q fever is prevalent in their region and is often asymptomatic. We think that the rates of *C. burnetii* seropositivity in the risk and control groups are close to each other due to its resistance to environmental conditions and due to its ability to be easily carried by air.

In our study, the highest *C. burnetii* IgG positivity (59%) was found among farmers. In Turkey, Kılıç et al. (13) reported 23.3% positivity among slaughterhouse workers, 28.6% positivity among veterinarians, and 14% positivity among veterinary students in Hatay. Berktaş et al. (21) detected the highest prevalence in the eastern region of Turkey being 65.9% among slaughterhouse workers, followed by 42.9% among butchers and 32.8% among farmers. In their study in and around İzmir, Sertpolat et al. (22) reported that the highest positivity among the occupational groups was 53.3% among farmers and butchers. In a study carried out in Southern Italy, serological testing revealed that 73.4% of subjects exposed to farm animals (cattle and sheep) were positive for anti-*C. burnetii* IgG (titer≥20) compared to 13.6% of control subjects (p<0.0001). In particular, the IgG seroprevalence for *C. burnetii* was 84% in the group of animal breeding workers, 60.6% in the group of agriculture/animal breeding, and 100% in the group of veterinarians (24).

Sertpolat et al. (22) reported that anti-*C. burnetii* IgG positivity was the highest (47.3%) in the age group of 40 years and over. They thought that this resulted from reinfection as those who were older than 40 years had been exposed to the infection for a longer period of time. *Coxiella burnetii* IgG positivity was statistically correlated to the number of years of working in the occupation (p=0.013). Karabay et al. (25) reported that the seroprevalence of *C. burnetii* was 23.8% among the participants above 18 years of age and 4.4% among those younger than 18 years of age by IFA tests (p<0.01). There was a significant relationship between *C. burnetii* seropositivity and direct contact with the birth products of farm animals (p<0.001); however, there was no significant difference between genders (25). These data show that long-term contact with animals is a real risk factor for *C. burnetii*. Human beings are often infected by the feces, milk, placenta, and body fluids of infected animals and by the inhalation of contaminated aerosols (8).

CONCLUSION

In order to prevent brucellosis in human beings in the province of Gaziantep, measures must be taken for the control and eradication of the disease in animals; unpasteurized milk and dairy products must not be consumed; and the people in the at-risk group must be informed about the need for taking protective measures while contacting animals or their waste materials. Because *C. burnetii* antibody positivity was detected at a high rate in our society in general, it was concluded that our people should be made conscious of zoonotic infections and that the epidemiological properties of the zoonotic infections should be clarified in the region.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University School Medicine (05.2010/02).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - P.A., F.E.; Design - P.A., F.E., A.B.; Supervision - P.A., F.E.; Resource - P.A., F.E.; Materials - P.A., F.E.; Data Collection and/or Processing - P.A., F.E., .A.B.; Analysis and/or Interpretation - P.A., F.E., A.B.; Literature Search - P.A., F.E.; Writing - P.A., F.E., A.B.; Critical Reviews - P.A., F.E., A.B.

Acknowledgements: The authors thank the Gaziantep University Scientific Research Projects Unit for their financial support for the study.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was supported with project number TF.11.01 by the unit of Scientific Research Projects at Gaziantep University.

Etik Komite Onayı: Bu çalışma için etik komite onayı, Gaziantep Üniversitesi Tıp Fakültesi Etik Kurulu'dan alınmıştır (05.2010/02).

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - P.A., F.E.; Tasarım - P.A., F.E., A.B.; Denetleme - P.A., F.E.; Kaynaklar - P.A., F.E.; Malzemeler - P.A., F.E.; Veri Toplanması ve/veya İşlemesi -P.A., F.E., A.B.; Analiz ve/veya Yorum - P.A., F.E., A.B.; Literatür Taraması - P.A., F.E.; Yazıyı Yazan - P.A., F.E., A.B.; Eleştirel İnceleme - P.A., F.E., A.B.

Teşekkür: Yazarlar, Gaziantep Üniversitesi Bilimsel Araştırma Projeleri Birimi'ne çalışmaya verdiği finansal destek için teşekkür eder.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Bu çalışma Gaziantep Üniversitesi Bilimsel Araştırma Projeleri Birimi tarafından TF.11.01 proje numarası ile desteklenmiştir.

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How to cite:

Arabacı P, Ekşi F, Bayram A. 90–90–90 targets: Investigation of *brucella* and *coxiella burnetii* antibodies among humans at risk and control groups living in southeastern Turkey. Eur J Ther 2017; 23: 111–6.

European Journal of Therapeutics DOI: 10.5152/ EurJTher.2017.01007

Original Investigation / Özgün Araştırma

Relation of interleukin-6 level with coronary artery disease severity in patients undergoing coronary angiography

Koroner anjiyografi yapılan hastalarda interlökin-6 düzeyi ile koroner arter hastalığının ciddiyeti arasındaki ilişki

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ABSTRACT

Objective: Atherosclerosis plays an important role in the pathogenesis of coronary artery disease (CAD). There is a closer relationship between atherosclerosis and inflammatory cytokines. Commonly used scoring systems for risk stratification in clinical practice are GENSINI and SYNergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) scores for determining disease severity and method of revascularization. The aim of this study was to investigate the relationship between interleukin (IL)-6 levels and both GENSINI and SYNTAX scores in patients with CAD.

Methods: In total, 118 patients who underwent coronary angiography were enrolled in the study. GENSINI and SYNTAX were calculated for determining disease severity. IL-6 level was measured using immunometric assay method.

Results: There were no significant differences between the groups with respect to mean age, blood pressure, heart rate, and use of alcohol. Gender and smoking status were significantly different between the groups. GENSINI and SYNTAX scores of patients were significantly higher in the CAD group than in the controls. IL-6 level was significantly higher in the CAD group than in the controls. In the correlation analysis, IL-6 level significantly correlated with GENSINI and SYNTAX scores and was an independent predictor of abnormal coronary angiography. Optimal cut-off level of IL-6 was 7.81 pg/mL to assess the ability of IL-6 to differentiate the presence of CAD (area under curve, 0.78; sensitivity, 78.3%; and specificity, 70.7%).

Conclusion: Patients with CAD have higher IL-6 levels compared with the controls. IL-6 level correlated with both GENSINI and SYNTAX scores. Moreover, IL-6 was an independent predictor of abnormal coronary angiography. An IL-6 value of ≥7.81 pg/mL predicted the presence of CAD with a sensitivity of 78.3% and a specificity of 70.7%.

Keywords: Coronary artery disease, Inflammation, IL-6, GENSINI score, SYNTAX score

ÖZ

Amaç: Ateroskleroz koroner arter hastalığının patogenezinde çok önemli rol oynamaktadır. Ateroskleroz ile enflamatuvar sitokinler arasında çok sıkı bir ilişki bulunmaktadır. GENSINI ve SYNTAX skorlaması koroner arter hastalığının şiddetinin ve uygulanacak olan revaskülarizyon yönteminin belirlenmesinde kullanılan skorlama yöntemleridir. Bu çalışmanın amacı koroner arter hastalarında interlökin-6 düzeyi ile GENSINI ve SYNTAX skorları arasındaki ilişkiyi ortaya çıkarmaktır.

Yöntemler: Koroner anjiyografi yapılan 118 hasta çalışmaya dahil edilmiştir. Hastalığın şiddeti GENSINI ve SYNTAX skorları hesaplanarak yapılmıştır. IL-6 düzeyleri kemilüminesan yöntem kullanılarak ölçülmüştür.

Bulgular: Gruplar arasında ortalama yaş, kan basıncı, nabız ve alkol kullanımı açısından bir farklılık yoktu. Cinsiyet ve sigara kullanımı açısından gruplar arasında anlamlı bir fark vardı. Koroner arter hastalarının GENSINI ve SYNTAX skorları kontrol grubundan anlamlı derecede yüksekti. Korelasyon analizlerinde IL-6 düzeyi ile GENSINI ve SYNTAX skorları arasında pozitif yönlü bir korelasyon olduğu ve IL-6'nın anormal koroner anjiyografinin bağımsız bir belirleyicisi olduğu ortaya çıkmıştır. Koroner arter hastalığını tespit edebilmek için IL-6'nın optimal cut-off değeri 7,81 pg/mL olarak tespit edildi (Area under curve=0,78, sensitivity=%78,3, specificity=%70,7).

Sonuç: Koroner arter hastaları kontrol grubuyla karşılaştırıldığında daha yüksek IL-6 düzeylerine sahiptir. IL-6 düzeyi ile GENSINI ve SYNTAX skorları arasında pozitif yönlü bir korelasyon vardır. IL-6 anormal koroner anjiyografinin bağımsız bir belirleyicisidir. 7,81 pg/mL üzerindeki IL-6 değerleri koroner arter hastalığını tespit etmede %78,3 sensitiviteye ve %70,7 spesifisiteye sahiptir.

Anahtar kelimeler: Koroner arter hastalığı, enflamasyon, IL-6, GENSINI skoru, SYNTAX skoru

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Received/Geliş Tarihi: 17.01.2016 • **Accepted/Kabul Tarihi:** 10.06.2016

INTRODUCTION

Coronary artery disease (CAD) is the most common heart disease in the world. Hypertension, obesity, smoking, diabetes, sedentary life style, hyperlipidemia, and a family history of CAD are some of the main risk factors for CAD. Although many precautions have been taken to prevent CAD, such as dietary and lifestyle modifications, optimization of blood lipid levels, and regulation of blood glucose levels, it is a very important public health problem and the most common cause of death in the world (1).

Atherosclerosis plays an important role in the pathogenesis of CAD. Inflammatory cytokines lead to endothelial cell activation and contribute to inflammatory responses in patients with CAD. Therefore, atherosclerosis is a kind of chronic immune/inflammatory disease of the vessels. Many researchers have investigated the effect of inflammation on CAD. These studies showed that inflammation plays a key role in the initiation and propagation of CAD (2, 3). There are many inflammatory markers related to CAD, including C-reactive protein (CRP), homocysteine, matrix metalloproteinases, interleukin (IL)-6, IL-8, and IL-27. IL-6 is the sign of synthesis of acute phase proteins. IL-6 levels increase with tissue injury, infections, ischemic diseases, neoplasms, and trauma (4). Recently, the clinical trials related to CAD showed that IL-6 may be an indicator of increased risk for CAD (5). In addition to these improvements, the major concern of cardiologist is the risk stratification of patients with CAD to determine prognosis, mortality, severity of disease, and appropriate revascularization methodologies. Two commonly used scoring systems for risk stratification in clinical practice are GENSINI and SYNergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) scores for determining disease severity and methods of revascularization. Even though these scoring systems have many advantages, they need invasive coronary interventions for determining risk scores. The aim of this study was to investigate the relationship between IL-6 levels and both GENSINI and SYNTAX scores in patients with CAD.

METHODS

Study Population

In total, 150 patients with suspicion of CAD who underwent coronary angiographic examination were evaluated for this study. Exclusion criteria of the study were acute and chronic infection, history of connective tissue disease, cardiomyopathy, myocarditis, previously documented CAD, congenital heart disease, pre-excitation syndromes, and impaired renal function (defined as a plasma creatinine value higher than 106.08 μmol/L or 1.2 mg/dL). After the exclusion criteria were applied, 118 patients were enrolled in the study. Demographic information, smoking and alcohol use, and blood pressures were recorded. All patients were informed about the study and written informed consent was obtained from patient who participated in this study. The local ethics committee of Marmara University approved the study.

Biochemical Assessment

Blood specimens were collected from the patients (n=118) into serum separator tubes (SST) with no additives and K_2-ethylenediaminetetraacetic acid (EDTA)-containing tubes (Becton Dickinson, NJ, USA) in a fasting state before coronary angiography. The samples in SST were allowed to clot for 20 min and centrifuged at 1300×g for 10 minutes. Serum samples were aliquoted and stored at −80°C under proper conditions until analysis of IL-6. We measured serum glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium (Na^+), potassium (K^+), creatinine, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL) using standard kits (COBAS, Integra, Roche Diagnostic Systems, Basel, Switzerland). Complete blood counts of all patients were analyzed on an LH 780 auto-analyzer (Beckman Coulter Inc., FL, USA). IL-6 was measured with a solid-phase, enzyme-labeled, chemiluminescent sequential immunometric assay (IMMULITE 2000, Siemens Health Care, UK). Within-run precision values were 4.5%-3.3% and between-run precision values were 5.3%-7.2% for 89-112 pg/mL IL-6, according to the manufacturer's claim.

Coronary Angiographic Evaluation

Coronary angiography examination was performed on all patients by the femoral approach, and high-quality cine-angiograms were used for analysis. Diameter stenosis ≥50% was accepted as significant using quantitative angiography. Fifty-eight patients had at least one significant lesion. Patients who have at least one significant lesion was accepted as patients with CAD. Sixty patients without a significant lesion were accepted as the control group. SYNTAX score was calculated by two experienced invasive cardiologist as suggested before (6) using an online calculator (http://www.SYNTAXscore.com). If any controversy was found, judgment was made by consensus. GENSINI score for determining severity of CAD (7) was calculated according to stenosis as follows: 1 point for 25% stenosis, 2 points for 26%-50% stenosis, 4 points for 51%-75% stenosis, 8 points for 76%-90% stenosis, 16 points for 91%-99% stenosis, and 32 points for totally occluded arteries. The score was then multiplied by a factor that represents the importance of the lesion in the coronary arterial tree.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 16.0 statistical package for Windows (SPSS Inc.; versiyon 16.0, Chicago, IL, USA). Continuous data were expressed as mean±standard deviation, whereas categorical data were presented as percentage. The Chi-square test was used for comparison of categorical variables, whereas the student t-test and the Mann-Whitney U test were used to compare parametric and nonparametric continuous variables, respectively. For correlation analysis, Pearson test was used. Receiver operating characteristic (ROC) analysis was used to assess the ability of IL-6 to differentiate the presence of CAD. Intra- and interobserver variability was calculated as the absolute difference between two measurements. A value of $p<0.05$ was considered statistically significant.

RESULTS

According to coronary angiographic examination, 58 patients (female/male, 18/40; mean age, 58.2±11.3 years) had significant CAD, whereas 60 patients (female/male, 36/24; mean age, 57.3±11.8 years) had no CAD (p=0.487 for age). There were no significant differences between the groups with respect to the mean ages, systolic blood pressure, diastolic blood pressure,

Table 1. Baseline characteristics and clinical data of the study population

	Patient group (n=58)	Control group (n=60)	p
Age (years)	58.2±11.3	57.3±11.8	0.487
Female gender (n)	18	36	**0.002**
Systolic blood pressure (mmHg)	136.6±20.7	140.7±19.5	0.194
Diastolic blood pressure (mmHg)	76.9±12.0	78.8±10.8	0.191
Heart rate (beat/minute)	75.7±13.1	75.4±10.1	0.518
Smoking (n)	33	17	**0.002**
Alcohol use (n)	6	7	0.819
SYNTAX score	10.7±7.3	0.1±0.2	**<0.001**
GENSINI score	47.1±30.5	2.2±3.3	**<0.001**

Data are expressed as mean ± SD or as number and percentages. Bold values indicate p<0.05.

Table 2. Comparison of laboratory findings of patient and control groups

	Patient group (n=58)	Control group (n=60)	p
Interleukin-6 levels (pg/mL)	21.0±22.6	6.6±7.8	**<0.001**
White blood cell counts	8.0±2.2	7.7±2.5	0.229
Hemoglobin (gr)	13.3±1.8	13.2±1.6	0.494
Fasting glucose (mg/dL)	128.1±55.6	121.4±47.1	0.539
Creatinine (mg/dL)	0.92±0.18	0.87±0.20	0.164
Total cholesterol (mg/dL)	205.7±50.8	219.3±57.6	0.168
Triglycerides (mg/dL)	165.1±69.6	188.8±81.6	0.120
Low density lipoprotein (mg/dL)	126.4±38.7	124.0±42.8	0.948
High density lipoprotein (mg/dL)	41.5±8.5	46.2±13.6	0.071
AST (U/L)	30.2±18.0	24.2±12.1	0.111
ALT (U/L)	26.3±14.1	23.4±13.1	0.160
Na (mmol/L)	138.9±5.3	140.3±3.0	0.127
K (mmol/L)	4.3±0.5	4.5±0.4	0.082

Data are expressed as mean±SD. Bold values indicate p<0.05.
AST: aspartate amino transferase; ALT: alanine amino transferase; Na: sodium; K: potassium

heart rates, and alcohol use. Gender and smoking status were significantly different between the two groups (p=0.002 and p=0.002, respectively). Sociodemographic and clinical data of the two groups are displayed in Table 1. GENSINI and SYNTAX scores of patients were significantly higher in the CAD group than in the control group, as expected (p<0.001, respectively). The mean values of GENSINI and SYNTAX scores were 2.2±3.3 and 0.1±0.2 for the control group and 47.1±30.5 and 10.7±7.3 for the CAD group, respectively.

Table 3. Correlation of IL-6 and WBC with severity of coronary artery disease

	Syntax score		Gensini score	
	r	p	r	p
IL-6	**0.484**	**<0.001**	**0.529**	**<0.001**
WBC	**0.167**	**0.070**	**0.104**	**0.263**

IL: interleukin; WBC: white blood cell count. Bold values indicate p<0.05

Table 4. Logistic regression analysis to determine the independent predictors of abnormal coronary angiography

	Odds Ratio (OR)	95% Confidence Interval for OR	p
Age	1.026	0.987-1.067	0.194
Gender	2.439	0.917-6.488	0.074
Interleukin-6	1.113	1.048-1.182	**0.001**
Smoking	0.417	0.156-1.113	0.081

Bold values indicate p<0.05.

Laboratory findings of the two groups are shown in Table 2. The IL-6 level was significantly higher in the CAD group compared to the control group. There was no difference in other laboratory findings. In the correlation analysis, we found that the IL-6 level significantly correlated with the GENSINI and SYNTAX scores (r=0.529, p<0.001 and r=0.484, p<0.001, respectively) in the CAD group (Table 3). The multiple logistic regression analysis showed that the IL-6 level was an independent predictor of abnormal coronary angiography [odds ratio (95% CI), 1.113 (1.048–1.182); p=0.001] (Table 4). The ROC curve analysis showed that the optimal cutoff level of IL-6 was 7.81 pg/mL to assess the ability of IL-6 to predict the presence of CAD (area under curve, 0.78; sensitivity, 78.3%; and specificity, 70.7%) (Figure 1).

DISCUSSION

In this study, we investigated the relationship between IL-6, both GENSINI and SYNTAX scores, and their association with CAD. Our results demonstrated that IL-6 levels correlated with GENSINI and SYNTAX scores in patients with CAD. Moreover, the IL-6 level was an independent predictor of abnormal coronary angiography. An IL-6 value of 7.81 pg/mL or higher predicted the presence of CAD with a sensitivity of 78.3% and a specificity of 70.7%.

It is obvious that inflammation plays a crucial role in atherosclerosis and cardiovascular disease (8). There are many inflammatory markers, such as tumor necrosis factor (TNF) alpha, IL-1, CRP, and IL-6, whose relations to the inflammatory process in CAD were shown in previous studies (9). Tanindi et al. (10) reported that IL-6 was associated with more extensive and severe CAD. They determined the sensitivity and specificity value of IL-6 for

determining CAD as 46% and 86%, respectively. In our study, the optimal cutoff value of IL-6 was 7.81 pg/mL and sensitivity and specificity were 78.3% and 70.7%, respectively.

Some studies were conducted to investigate the role of IL-6 for predicting the mortality in patients with cardiovascular diseases. In a prospective study, the relationship between IL-6 and the mortality of hospitalized patients with CAD was also examined. They reported that IL-6 was positively associated with an increased risk of all-cause and cardiovascular mortality (11). Contrary to that study, Tuomisto et al. (12) reported that CRP and TNF-α, but not IL-6, were significant independent predictors of total mortality among men. Volpato et al. reported that high IL-6 levels strongly affected the risk of mortality associated with the presence of CAD (13). In a recent study, it was found that IL-6 levels were correlated with the severity of CAD. In that study, the severity of CAD was evaluated by the GENSINI score (14). In addition to these reports, there are some studies about the therapeutic use of IL-6 inhibition. An IL-6 receptor blocking agent (tocilizumab) has been used for the treatment of rheumatoid arthritis (RA), and its use in preventing CAD is controversial. Provan et al. reported that tocilizumab treatment decreases the arterial stiffness measurements that are determined by pulse wave velocity, which is a marker of cardiovascular disease risk in patients with RA (15). It is reported that tocilizumab has antiarrhythmic potential and decreases the corrected QT interval; it may also be used to treat pericarditis associated with RA by controlling systemic inflammation (16, 17).

It is a big challenge for invasive cardiologists or cardiovascular surgeons to decide the most beneficial revascularization method. The SYNTAX score is used as a guidance system by the cardiologists. We suggested that a marker of inflammation, such as IL-6, plays a role in risk stratification, disease severity, and determining the method of revascularization. Although there are studies in the literature that investigate the relationship between IL-6 and the severity of CAD, our study is unique in its design because it combines SYNTAX and GENSINI scores in one study. In the studies by Cotsman et al. (5) and Rajpal et al. (14), plasma IL-6 levels showed positive correlation with GENSINI and SYNTAX scores, respectively. Jernbeg et al. (18) showed that the combination of N-terminal pro-brain natriuretic peptide and IL-6 is a useful tool in the identification of patients with a definite survival benefit from an early invasive strategy. Consistent with these studies, there was a positive correlation between IL-6 levels and not only GENSINI but also SYNTAX scores in our study.

Study Limitations

There are several limitations of our study. First, this was a cross-sectional study and the patients were not followed up. Therefore, we could not show the association of inflammatory markers with adverse cardiac events, and we are not able to evaluate the prognostic value of IL-6 in patients with CAD. Second, we did not investigate other inflammatory markers, such as high sensitive CRP, IL-1-beta, TNF-alpha, homocysteine, and matrix metalloproteinase. Therefore, it is not possible to compare the results with these markers. Third, we did not evaluate other cardiovascular risk factors, such as sedentary life style, body mass index, and waist circumference. Finally, we did not evaluate the medication history of the participants. These factors may also affect the inflammatory status of the patients. Future prospective and large population studies should be performed to elucidate the effectiveness of IL-6 to predict the presence, severity, and extent of CAD.

CONCLUSION

We demonstrated that patients with CAD have higher IL-6 levels compared with those in the control group. The IL-6 level positively correlated with both GENSINI and SYNTAX scores. Moreover, the IL-6 level was an independent predictor of abnormal coronary angiography. An IL-6 value of 7.81 pg/mL or higher predicted the presence of CAD with a sensitivity of 78.3% and a specificity of 70.7%.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Marmara University.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - F.G., E.D., T.K.; Design - F.G., E.D., T.K.; Supervision - M.S., İ.S.; Resource - F.G., E.D., T.K.; Materials - M.B., A.Y., E.D.; Data Collection and/or Processing - M.B., A.Y., E.D.; Analysis and/or Interpretation - F.G., E.D., T.K.; Literature Search - F.G., E.D., T.K.; Writing - F.G., E.D., T.K.; Critical Reviews - İ.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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

Etik Komite Onayı: Ethics Committee Approval: Bu çalışma için etik komite onayı Marmara Üniversitesi Etik Kurulu'ndan alınmıştır.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastadan alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - F.G., E.D., T.K.; Tasarım - F.G., E.D., T.K.; Denetleme - M.S., İ.S.; Kaynaklar - F.G., E.D., T.K.; Malzemeler - M.B., A.Y., E.D.; Veri Toplanması ve/veya işlemesi - M.B., A.Y., E.D.; Analiz ve/veya Yorum - F.G., E.D., T.K.; Literatür taraması - F.G., E.D., T.K.; Yazıyı Yazan - F.G., E.D., T.K.; Eleştirel İnceleme - İ.S.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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How to cite:

Gerin F, Durmuş E, Yaman A, Sünbül M, Mammadov C, Bozbay M, et al. Relation of interleukin-6 level with coronary artery disease severity in patients undergoing coronary angiography. Eur J Ther 2017; 23: 117–21.

European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.52

Case Report / Olgu Sunumu

Incision scar's endometriosis case that was treated with false diagnosis

Yanlış teşhis ile tedavi edilmiş, bir insizyon skari endometriozisi olgusu

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ABSTRACT

Endometriosis is defined as the placement of a functional endometrium tissue outside the uterine cavity. Abdominal-wall endometriosis is usually observed after obstetric and gynecological operations. Endometriosis masses located in incision scars can be confused with foreign body reaction, granulomas, abscess, and incisional hernia. A 45-year-old female patient, who had undergone cesarean section 14 years ago, presented to our clinic for pain on the left side of the incision for 6 months and particularly because of the painful mass that grew during menstruation in that region. The patient was misdiagnosed as reactive lymphadenopathy due to fungal and bacterial infections in her toes before presenting to our clinic, and she was treated for a long time with this false diagnosis. On the left side of the Pfannen-Stiel incision, a non-mobile, painful mass of about 2×1 cm, with moderate stiffness, was detected on the physiological examination of the patient. Superficial ultrasonography applied to the region showed lobulated contour, mild heterogeneous hypoechoic, and mild vascularized solid lesion sized 10.4×3.4×10 mm on the left side of the incision line. The patient underwent surgery with an initial diagnosis of endometriosis in the incision scar. The received tissue was sent for pathological examination, and she was diagnosed as endometriosis. Thus, if a mass is detected in the anterior wall of the abdomen in women who had undergone cesarean delivery, the possibility of endometriosis should not be overlooked after the patient's history has been cautiously taken and physical examination and radiological examinations have been performed.

Keywords: Endometriosis, abdominal-wall's masses, incision scar's endometriosis

ÖZ

Endometriosis, fonksiyonel endometrium dokusunun uterus kavitesi dışında yerleşmesi şeklinde tanımlanır. Karın duvarındaki endometriosis, genellikle, önceki geçirilmiş obstetrik ve jinekolojik ameliyatlardan sonra görülmektedir. İnsizyon skarında yerleşik olan endometriosis kitleleri, yabancı cisim reaksiyonu, granülomlar, apseler ve insizyonel hernilerle karıştırılabilirler. On dört yıl önce Sezaryen ameliyatı olan 45 yaşındaki kadın hasta, 6 aydır insizyonun sol tarafında ağrı ve özellikle, o bölgede adet döneminde büyüyen ağrılı kitle sebebiyle kliniğimize başvurdu. Hastaya, bize başvurmadan önce, ayak parmaklarında mantar ve bakteryel infeksiyona bağlı reaktif lenfadenopati olarak yanlış tanı konmuş ve bu yanlış tanıyla hasta, uzun süre tedavi edilmişti. Hastanın fizik muyenesinde, Pfannen-Stiel insizyonun sol kısmında, yaklaşık 2x1 cm'lik, orta sertlikte, mobil olmayan ağrılı kitle saptandı. Bölgeye uygulanan yüzeyel ultrasonografide insizyon hattının sol tarafında 10,4x3,4x10 milimetre boyutlarında lobule konturlu, hafif heterojen hipoekoik, hafif vaskülarize solid lezyon izlendi. İnsizyon skarında endometriosis ön tanısıyla, hasta, ameliyat edildi. Alınan doku patolojik incelemeye gönderildi ve sonuç endometriozis geldi. Sonuç olarak; sezaryen geçirmiş kadınlarda, karın ön duvarında kitle saptandığında, hastanın anamnezi dikkatli bir şekilde alınıp, muayene ve tetkikleri yapıldıktan sonra endometrisis olasılığı gözardı edilmemelidir.

Anahtar kelimeler: Endometriozis, batın duvarı kitleleri, insizyon skarı endometriozisi

INTRODUCTION

Endometriosis is defined as the placement of functional endometrium tissue outside the uterine cavity. Endometriosis is a benign disease that is estrogen dependent (1).

The most common location of endometriosis is the pelvic area, which includes the ovaries, uterine ligaments, rectovaginal septum, and peritoneum. It is observed less commonly in the bladder, bowel, appendix, kidney, spleen, stomach, bile duct, lung, extremities, and surgical scars (2, 3). Endometriosis outside the pelvis is a rare disease and its diagnosis is difficult.

Abdominal-wall endometriosis is usually seen after obstetric and gynecological operations. During menstruation, pain and swelling are experienced in the area where the endometriosis mass is present.

Endometriosis masses located in the incision scar can be confused with foreign body reaction, granulomas, abscess, and incisional hernia (3).

We present a case of a Pfannen-Stiel incision scar endometriosis that was wrongly diagnosed and treated long time as reactive

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Received/Geliş Tarihi: 22.06.2017 • **Accepted/Kabul Tarihi:** 28.06.2017

Figure 1. Superficial ultrasonography showed lobulated contour, mild heterogeneous hypoechoic, and mild vascularized solid lesion sized 10.4×3.4×10 mm

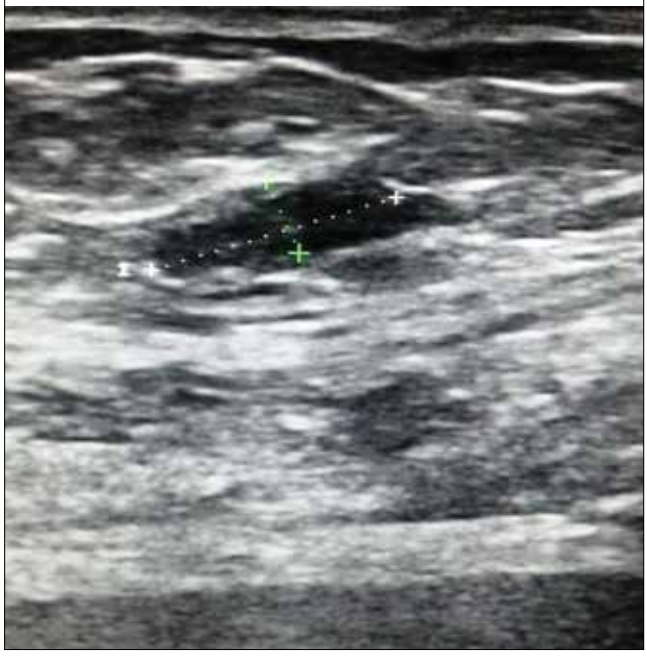
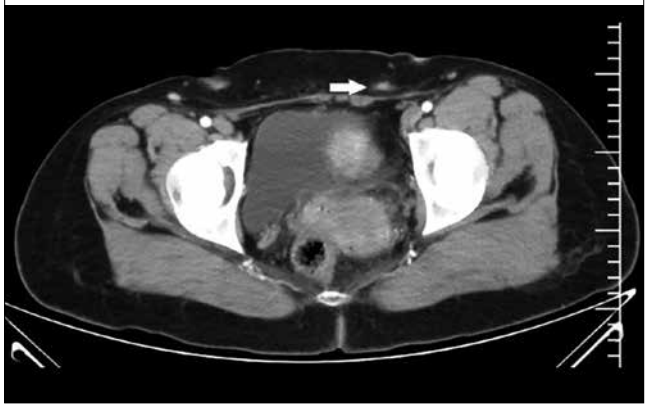


Figure 2. In the lower abdominal tomography scan, a hyperdense lesion was detected in the subcutaneous fat tissue, with a contrast enhancement sized 15×6 mm, which was not related to the abdominal cavity



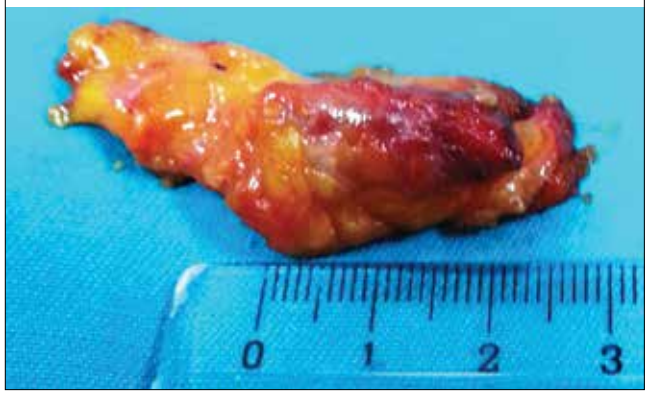
lymphadenopathy in the inguinal region due to fungal and bacterial infection for a on the toes.

CASE PRESENTATION

The patient provided consent for the case report. A 45-year-old female patient, who had undergone cesarean delivery 14 years ago, presented to our clinic for pain on the left side of the incision for 6 months and particularly because of the painful mass that grew during menstruation in that region.

The patient's first birth was through vaginal delivery and the last birth was through cesarean delivery. The patient was misdiagnosed as reactive lymphadenopathy due to fungal and bacterial infections in her toes before presenting to us, and the patient was treated for a long time with this false diagnosis.

Figure 3. Endometriosis mass of approximately 2×0.5 cm in diameter



On the left side of the Pfannen-Stiel incision, a non-mobile, painful mass of about 2×1 cm, with moderate stiffness, was detected upon physiological examination of the patient.

Radiographic examinations were performed. The abdomen and pelvic ultrasonography were normal. Superficial ultrasonography of the region showed lobulated contour, mild heterogeneous hypoechoic, and mild vascularized solid lesion sized 10.4×3.4×10 mm on the left side of the incision line (Figure 1). In the lower abdominal tomography scan, a hyperdense lesion was detected in the subcutaneous fat tissue, with a contrast enhancement of 15×6 mm in size, which was not related to the abdominal cavity (Figure 2).

Hemogram and biochemistry results were normal. Hormones, such as follicle-stimulated hormone; luteinizing hormone; estrogen; and progesterone and tumor markers, such as carcinoembryonic antigen (CEA) and CA-125 were normal.

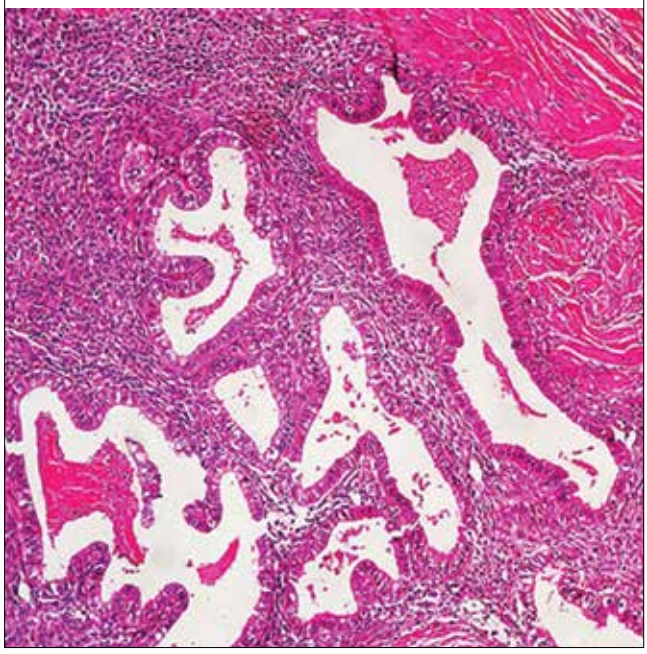
With the diagnosis of endometriosis in the incision scar, the patient was admitted to the clinic and prepared for surgery. Under local anesthesia, a mass of approximately 2×0.5 cm was removed along with a 1 cm area of surgical margin with clean tissue (Figure 3). Since the endometriosis mass is distant from the fascia and muscles, there is no defect in the fascia and muscles. After bleeding control, subcutaneous tissue and skin were closed.

The received tissue was sent for pathological examination, which confirmed endometriosis. Endometrial stroma, endometrial glands, and extravasated erythrocytes were observed in the fibrotic connective tissue in hematoxylin-eosin (H and E) -stained sections in the form of geographic areas (Figure 4).

DISCUSSION

Endometriosis is the placement of functional endometrium tissue outside the uterine cavity. This disease was first described in the ovarium by Russel in 1899 (2).

Figure 4. Endometrial stroma has endometrial glands, and fibrin is present in the lumens of the endometrial glands (10x hematoxylin-eosin stain)



This pathology is more common between the ages of 31 and 40 years (2). Our patient was 45 years old and had undergone a cesarean delivery 14 years ago.

The most common location of endometriosis is the pelvic area, which includes the ovaries, uterine ligaments, rectovaginal septum, and peritoneum. Endometriosis located outside the pelvis covers 8.9% of all cases (3).

The endometriosis tissue of our patient was placed under the skin on the left side of the Pfannen-Stiel incision scar. Scar endometriosis is a rare condition and usually occurs following uterus and fallopian tubes surgeries (4, 5).

The rate of development of endometriosis is between 0.03% and 0.4% after cesarean delivery, but it increases to 1.08% after hysterectomy (5, 6). Endometriosis in the abdominal wall often occurs with previous surgical scars, while there are also cases of spontaneously developed endometriosis in the literature (7).

There are several endometriosis case reports in the literature from a number of different regions. At the beginning, endometriosis can be confused with incisional hernia, inguinal hernia, and wall tumors (7). The reason our case is interesting is that the patient was misdiagnosed and treated for a long time for inguinal lymphadenopathy due to fungal and bacterial infection.

The endometriosis mass can be cystic, solid, or mixed and often manifests as scar mass, cyclic or non-cyclic pain. Generally, there is mass at the scar site and pain at that area during menstruation. The diagnosis can be difficult in patients without classic symptoms. This is observed in one-third of the cases (6). In our patient, there was a mass in the left inguinal region and a persistent pain problem in that region, which increased even more during menstruation. On the left side of the incision, there was a very painful mass sized approximately 2×1 cm under the skin.

Ultrasonography, color doppler ultrasonography, tomography, magnetic resonance, and needle aspiration biopsy are the recommended diagnostic methods (6, 7). Ultrasonography scar endometriosis usually appears as a hypoechoic and heterogeneous solid mass and may show internal vascularity (6). Multicolored doppler ultrasonography combined with clinical information is proposed to be more useful in the diagnosis (7). In our patient, firstly, superficial ultrasonography and abdominal ultrasound were performed. A vascularized, hypoechoic, and heterogeneous mass located on the left side of the incision line was detected.

Tomography and magnetic resonance can also be used to visualize the endometriosis mass (7). To visualize the relationship of the mass of endometriosis with the abdominal fascia, the patient underwent contrast-enhanced tomography. There was hyperdense lesion showing contrast enhancement and no relation to the abdominal fascia and abdominal cavity.

In the study performed by Emre et al. (8), biochemical tests, beta-human chorionic gonadotropin (B-hCG) and CA-125 values were determined and found to be normal . Biochemical tests of our patient, including hormones, such as follicle-stimulated hormone; luteinizing hormone; estrogen; and progesterone and tumor markers, such as CEA and CA-125 were normal.

Progesterone, oral contraceptives, and danazol, which are used to treat endometriosis, may be partially ameliorated (7). The main treatment is surgery with total removal of endometriosis with intact surgical margins.

Endometriosis tissue can be removed under local, regional, or general anesthesia, depending on its size and location. Local anesthesia was used in our patient; the mass was removed with a clean tissue margin of approximately 1 cm and sent for pathologic examination.

CONCLUSION

In conclusion, if a mass is detected in the anterior wall of the abdomen in women who had undergone cesarean delivery, the possibility of endometriosis should not be overlooked after the patient's history has been cautiously taken and physical examination and radiological examinations have been performed.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - T.K.; Design - İ.O.; Supervision - M.A.B.; Resource - T.K., M.A.B.; Materials - T.K., M.A.B.; Data Collection and/or Processing -Turgay Karataş.; Analysis and/or Interpretation - T.K., M.A.B., R.E.Ö.; Literature Search - T.K., İ.O.; Writing - T.K.; Critical Reviews - T.K., R.E.Ö.

Acknowledgements: The authors would like to thank to everyone who contributed.

Conflict of Interest: No conflict of interest was declared by the authors.

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

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastadan alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - T.K.; Tasarım - İ.O.; Denetleme - M.A.B.; Kaynaklar - T.K., M.A.B.; Malzemeler -T.K., M.A.B.; Veri Toplanması ve/veya İşlemesi - T.K.; Analiz ve/veya Yorum - T.K., M.A.B., R.E.Ö.; Literatür Taraması - T.K., İ.O.; Yazıyı Yazan - T.K.; Eleştirel İnceleme - T.K., R.E.Ö.

Teşekkür: Yazarlar katkı sağlayan herkese teşekkürlerini bildirmişlerdir.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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How to cite:

Karataş T, Altan Bitirim M, Erguvan–Önal R, Orman İ. Incision Scar's Endometriosis Case that was Treated with False Diagnosis: A Case Report. Eur J Ther 2017; 23: 122–5.

European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.10112

Case Report / Olgu Sunumu

Myocardial infarction related to coronary embolism in a patient with prosthetic mitral valve thrombosis demonstrated by three-dimensional transesophageal echocardiography

Üç boyutlu transözofageal ekokardiyografi ile gösterilmiş protez mitral kapak trombüsü olan bir hastada koroner emboliye bağlı miyokard infarktüsü

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ABSTRACT

The incidence of systemic embolization with mechanical valves is 1% per year. Bacterial endocarditis, valvular heart disease, cardiomyopathies, atrial myxoma, cardiac arrhythmias, and acute coronary syndrome are the causes of coronary embolism. Although coronary embolism due to mechanical valve thrombosis is encountered rarely, it is an important and serious complication. There is no evidence-based effective treatment and management of coronary embolism. Here we report a case of myocardial infarction caused by coronary embolism due to mechanical mitral valve thrombosis.

Keywords: Coronary embolism, myocardial infarction, prosthetic mitral valve thrombosis

ÖZ

Mekanik kapaklarla birlikte sistemik emboli insidansı yıllık %1'dir. Bakteriyel endokardit, kalp kapak hastalığı, kardiyomiyopatiler, atriyal miksoma, kardiyak aritmiler ve akut koroner sendrom koroner embolinin sebeblerindendir. Mekanik kapak trombozuna bağlı koroner emboli nadir görülmesine rağmen, önemli ve ciddi bir komplikasyondur. Koroner embolinin kanıta dayalı etkili bir tedavi ve yönetimi yoktur. Burada mekanik mitral kapak trombozuna bağlı koroner embolininin neden olduğu bir akut miyokard enfarktüsü vakası sunduk.

Anahtar kelimeler: Koroner emboli, miyokard enfarktüsü, protez mitral kapak trombozu

INTRODUCTION

The incidence of systemic embolization with mechanical valves is 1% per year (1). Most cases present with cerebrovascular events. As the incidence of mechanical valve surgery has increased, systemic thromboembolism became an important problem. Although coronary embolism due to mechanical valve thrombosis is encountered rarely, it is an important and serious complication (1). Here, we report a case of myocardial infarction caused by coronary embolism due to mechanical mitral valve thrombosis. Written informed consent was obtained from patient who participated in this study.

CASE PRESENTATION

A 54-year-old woman admitted to emergency unit (EU) with severe retrosternal chest pain radiating to inter-scapular area that had begun two hours ago. Her past medical history had hypertension for 10 years and she had undergone mitral valve replacement (MVR) 29 St. Jude and tricuspid De Vega annuloplasty for severe mitral regurgitation and moderate tricuspid regurgitation due to rheumatic heart disease 2 years ago. Coronary angiography performed before mitral valve surgery was normal. She was taking warfarin 7.5 mg/day but her international normalized ratio (INR) checked in the EU was below the therapeutic level (INR: 1.15 IU). Electrocardiogram (ECG) showed sinus rhythm, 72/min, first-degree block, left bundle branch block, ST depression, and T wave inversion in lateral and inferior leads. She was monitored and blood samples were drawn 4 hours apart for cardiac markers that showed significant increase. Physical examinations were within normal range except for blood pressure of 170/85 mmHg. Auscultation of the heart showed normal opening and closing clicks of the mitral prosthesis and 2/6 systolic murmur at apex. The lungs were clear to auscultation. High sensitive troponin (hs-troponin)

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Received/Geliş Tarihi: 30.10.2015 • **Accepted/Kabul Tarihi:** 02.05.2016

Figure 1. Coronary angiography shows normal coronary arteries except for hazy appearance in distal circumflex artery

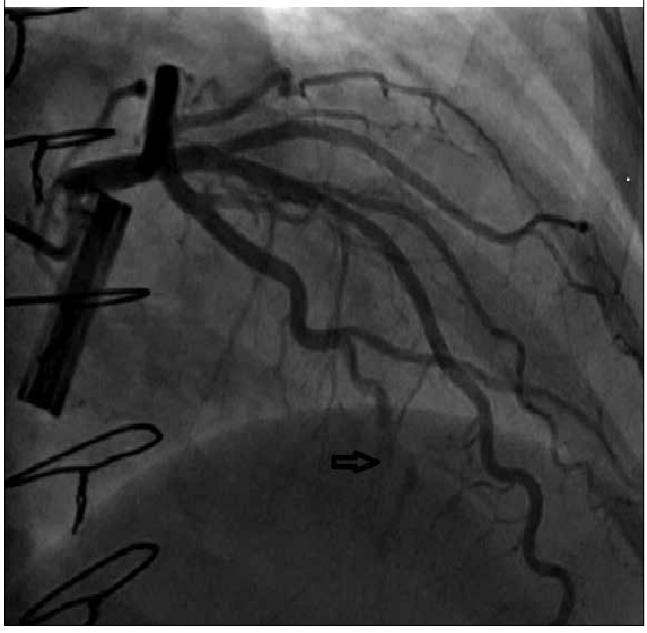
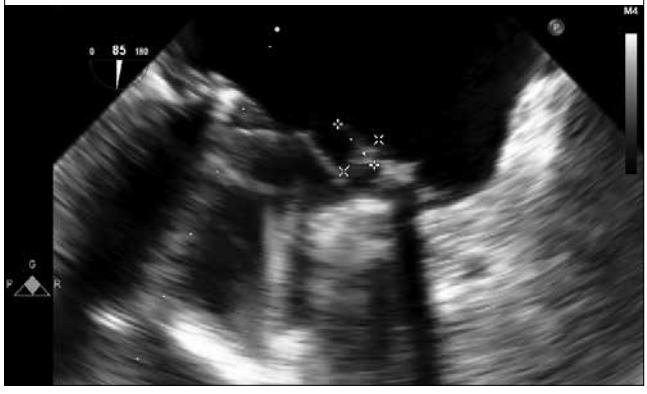
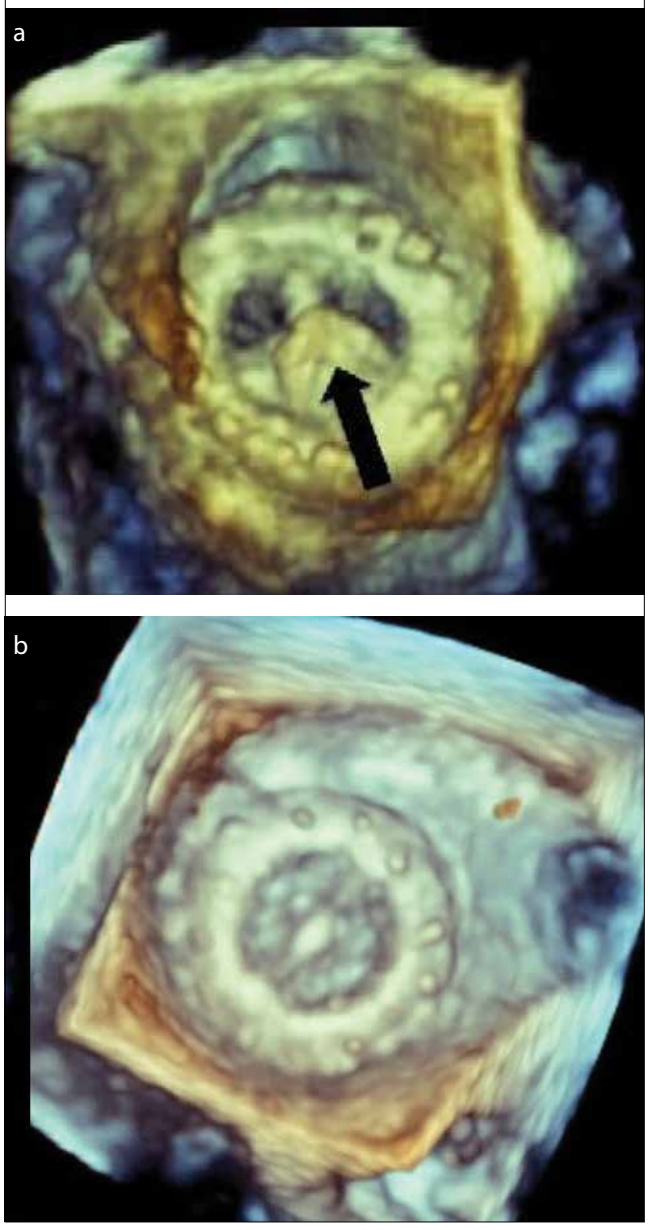


Figure 2. Two-dimensional TEE shows non-obstructing mitral annular thrombosis



and creatinine kinase myocardial band (CK-MB) levels were increased (hs-troponin: 216 ng/mL (0-15) and CK-MB: 6 ng/mL (0-5). The patient was admitted to the Coronary Care Unit with diagnosis of non-ST segment elevation myocardial infarction and treatment was started with clopidogrel, acetylsalicylic acid, beta-blocker, angiotensin-converting enzyme (ACE) inhibitor, enoxaparin, and calcium channel blocker (CCB). On the next day, coronary angiography was performed that was normal except for hazy appearance in distal circumflex artery (Figure 1). After coronary angiography, three-dimensional (3D) transesophageal echocardiography (TEE) was carried out showing normal function of prosthetic valve with normal left ventricular systolic function, mild mitral regurgitation, and non-obstructing mitral annular thrombosis (10×12 mm^2) (Figures 2 and 3a) without any paravalvular complication suggesting infective endocarditis. There were no signs and symptoms

Figure 3. a, b. a) Three-dimensional TEE shows non-obstructing mitral annular thrombosis. b) Three months later, control three-dimensional TEE shows normal prosthetic mitral valve with no thrombosis



suggesting infective endocarditis. So, we did not draw blood samples for microorganism culture. Heparin infusion was started for 48 hours, and warfarin was given 10 mg/day. Percutaneous coronary intervention was not performed, and the patient was discharged on warfarin, clopidogrel, acetylsalicylic acid, beta-blocker, ACE inhibitor, and CCB therapy after achieving INR of 2.54 IU. The patient was also educated on prophylaxis measures against infective endocarditis and rheumatic fever. Three months later, control 3D TEE was performed and it showed normal prosthetic mitral valve with no thrombosis and with normal left ventricular systolic function (Figure 3b).

DISCUSSION

Bacterial endocarditis, valvular heart disease, cardiomyopathies, atrial myxoma, cardiac arrhythmias, and acute coronary syndrome are the causes of coronary embolism. Since the introduction of prosthetic valvular surgery, another source for coronary embolism has been introduced. Bjork and Malers (2) published the first case of coronary embolism caused by the mitral prosthetic valve in 1964. Coronary embolism leads to serious problems according to size of the emboli (3). Although smaller embolic materials usually travel to the distal small arterial segments, myocardial infarction and fatal cardiac arrhythmias are less common.

There is no clear guideline for the effective treatment and management of coronary embolism. Kamishirado et al. (4) published a case report of coronary arterial embolism that was not recanalized with 960.000 IU of urokinase therapy. Glycoprotein IIb/IIIa antagonists have been investigated in many clinical studies. The findings in these studies demonstrate that patients undergoing percutaneous transluminal coronary angioplasty benefit from these agents. Coronary thrombi seen during the coronary intervention procedures are reduced or eliminated by glycoprotein IIb/IIIa antagonists. Prolonged infusion with urokinase therapy was found to be useful in eliminating thrombus from saphenous vein grafts. Recently, it has been published that a combined regimen of intracoronary urokinase and intravenous abciximab therapy was successful in achieving fully resolution of the coronary embolism in a patient with mitral and aortic valve replacement (5). Sial et al. (6) demonstrated that TIMI (thrombolysis in myocardial infarction) III coronary blood flow was obtained by extracting the thrombus with an aspiration catheter (Export XT 6F Medtronic) and continued glycoprotein IIb/IIIa antagonist for 24 hours. Yuce et al. (7) showed a similar case of coronary embolism treated with anticoagulation therapy. As in our case, the coronary vessel was not completely occluded with TIMI II antegrade flow, and the thrombus was located in distal circumflex artery with <10% myocardium at risk. So, we preferred medical management with heparin infusion to percutaneous coronary intervention or thrombolytic therapy. The infarction limited itself and hs-troponin peaked at 910 ng/mL and declined gradually. Heparin infusion did not either eliminate the thrombus on mitral valve. But after a course of anticoagulation therapy for about three months, we found that the thrombi were eliminated completely. Although most myocardial infarction in patient taking oral anticoagulation is due to inadequate anticoagulation, it is also possible that myocardial infarction may occur despite normal therapeutic range of INR (8). There is no consensus in the treatment of coronary embolism due to prosthetic valve thrombosis. A low dose (25 mg), slow infusion of tissue plasminogen activator was shown to be effective and safe in a case series of three patients with prosthetic valve thrombosis complicated with coronary embolism and causing non-ST elevation myocardial infarction (9). In another case report, Aykan et al. (10) demonstrated that low dose and prolonged infusion of tissue plasminogen activator was effective in the treatment of coronary embolism related to prosthetic mitral valve thrombosis.

CONCLUSION

Because of the lack of guidelines and the presence of many options in the management and treatment of coronary embolism due to prosthetic valve thrombosis, the decision must be made on individual basis taking into account the size of thrombus, vessel involved, presence of antegrade flow, percentage of myocardium at risk, patient hemodynamics, bleeding risk scores, and the resource available at the institution. 3D TEE is important in determining the precise location and size of prosthetic thrombosis, paravalvular complications in case of endocarditis and therefore may add up to the diagnosis and management of such cases as compared with 2D TEE.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - M.B.. A.P..; Design - M.B.. M.S.; Supervision - İ.S.; Resource - B.G.K.; Materials - B.G.K.; Data Collection and/or Processing - M.B.. İ.S.; Analysis and/or Interpretation - İ.S.. K.T.; Literature Search - M.B.. M.S.; Writing - M.B.; Critical Reviews - İ.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastadan alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - M.B.. A.P.; Tasarım - M.B.. M.S.; Denetleme - İ.S.; Kaynaklar - B.G.K.; Malzemeler - B.G.K.; Veri Toplanması ve/veya İşlemesi - M.B.. İ.S.; Analiz ve/veya Yorum - İ.S.. K.T.; Literatür Taraması - M.B.. M.S.; Yazıyı Yazan - M.B.; Eleştirel İnceleme - İ.S.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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How to cite:

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European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.22

Letter to the Editor / Editöre Mektup

Importance of neutrophil–to–lymphocyte ratio in coronary artery disease

Koroner arter hastalığında nötrofil–lenfosit oranının önemi

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With great interest, I have read the article by Coskun et al (1).

The authors report that there is a correlation between mean platelet volume (MPV) and Gensini score; however, there is no significant correlation between neutrophil-to-lymphocyte (N/L) ratio and Gensini score in myocardial infarction associated with ST elevation. They also report that there is no significant correlation between both N/L ratio and MPV and Gensini score in myocardial infarction without ST elevation. However, studies in literature have shown the relationship between cardiovascular diseases and N/L ratio.

Leukocyte counts and the ratios of leukocyte subtypes are accepted as markers of inflammation in cardiovascular diseases. In relation to this, it has been shown that the N/L ratio is a marker of prognosis in heart failure, stable angina pectoris, and acute coronary syndromes. Elevated N/L ratios may reflect an inflammatory state and may be associated with perioperative myocardial damages and long term adverse outcomes. Neutrophils have been known to play a role in influencing the progression of atherosclerotic plaques. A reduced lymphocyte count is important to reflect physiological stress. A study reports the relationship between N/L ratios and mortality in ischemic heart disease (2). Similarly, increased preoperative N/L ratio is associated with increased mortality and morbidity as an independent risk factor in coronary artery bypass graft surgery (CABG) (3). Anesthesia methods used in patients undergoing CABG are also affected by N/L ratios (4).

Considering that increased preoperative N/L ratio is associated with long-term mortality after CABG (3) and preoperative N/L ratio is an independent predictor of saphenous vein graft patency after CABG (5), it becomes important to evaluate the preoperative N/L ratio, especially in patients undergoing CABG.

Conflict of Interest: No conflict of interest was declared by the authors.

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

Çıkar Çatışması: Yazar çıkar çatışması bildirmemiştir.

Finansal Destek: Yazar bu çalışma için finansal destek almadıklarını beyan etmiştir.

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How to cite:

İnanoğlu K. Importance of neutrophil–to–lymphocyte ratio in coronary artery disease. Eur J Ther 2017; 23: 130.

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Received/Geliş Tarihi: 20.03.2017 • **Accepted/Kabul Tarihi:** 21.04.2017

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