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Nosocomial Burkholderia cepacia infection in a tertiary hospital; Five-year surveillance: A retrospective cross-sectional study

Bir üniversite hastanesinde nozokomiyal Burkholderia cepacia enfeksiyonu; Beş yıllık surveyans: Retrospektif kesitsel çalışma

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Abstract

Aim: Burkholderia cepacia is an aerobic, Gram-negative and multi-drug resistance bacteria that cannot ferment glucose. Burkholderia cepacia, important opportunistic bacteria in immunosuppressed patients, causes severe pulmonary infections. In this study, we aimed to evaluate Burkholderia cepacia cases detected in last five years.

Methods: The study designed as retrospectively. Forty-six cases with B. cepacia in the tertiary hospital between 2013 and 2018 were included in the study. Age, gender, clinical history of the patient, type of sample taken, and patients' final conditions (alive or dead) and duration of hospitalization were recorded.

Results: When the distribution of the samples were examined, it was found that 32.6% (n=15) in the blood culture, 32.6% (n=15) in the urine culture, 17.4% (n=8) in the tracheal aspirate culture and 17.4% (n=8). Patients' final conditions were evaluated as alive or dead. Accordingly, 65.2% (n=30) were alive and 34.8% (n=16) of the patients were dead. When the distribution of the cases according to the clinics were examined, Anesthesia with 19.6% (n=9) was the first place. The average length of stay in hospital was 24.6 ± 25.3 days (minimum-maximum: 3-122 days).

Conclusion: Burkholderia cepacia is an important nosocomial opportunistic infection and is often multi drug resistant. For this reason, the disease should be effectively treated otherwise it should not be forgotten that the disease will result in mortality.

Keywords: Burkholderia cepacia, Surveillance, Turkey

Öz

Amaç: Burkholderia cepacia, glikozu fermente edemeyen aerobik, Gram-negatif ve çok ilaca dirençli bir bakteridir. İmmunsüprese hastalarda önemli bir fırsatçı bakteri olan Burkholderia cepacia, ciddi pulmoner enfeksiyonlara neden olur. Bu çalışmada, son beş yılda tespit edilen Burkholderia cepacia vakalarını değerlendirmeyi amaçladık.

Yöntemler: Çalışma retrospektif olarak planlandı. Çalışmaya 2013-2018 yılları arasında üçüncü basamak hastanedeki 46 B. cepacia olgusu dahil edildi. Yaş, cinsiyet, klinik öykü, alınan örnek tipi, hastaların son durumu (yaşıyor veya ölü) ve hastanede yatış süresi kaydedildi.

Bulgular: Örneklerin dağılımı incelendiğinde, kan kültüründe %32,6 (n=15), idrar kültüründe %32,6 (n=15), trakeal aspiratta %17.4 (n=8) bulundu. Hastaların son durumları yaşıyor veya ölü olarak değerlendirildi. Buna göre, olguların %65,2'sinin (n=30) yaşadığı, %34,8'inin (n=16) ise öldüğü tespit edildi. Olguların kliniklere göre dağılımı incelendiğinde, anestezi %19,6 ile (n=9) ilk sıradaydı. Hastanede kalış süresi ortalama 24,6 ± 25,3 gündü (minimum-maksimum: 3-122 gün).

Sonuç: Burkholderia cepacia önemli bir nozokomiyal fırsatçı enfeksiyondur ve sıklıkla çok ilaca dirençlidir. Bu sebeple hastalık etkin bir şekilde tedavi edilmelidir aksi halde hastalığın mortalite ile sonuçlanacağı unutulmamalıdır.

Anahtar kelimeler: Burkholderia cepacia, Sürveyans, Türkiye

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Introduction

Burkholderia cepacia was first identified by Burkholder as a bacterial effect of onion rot in 1950, and this phytopathogen was named Pseudomonas cepacia. The identification of Burkholderia was made in 1992 as a result of the investigation of rRNA II belonging to P. cepacia and six other bacteria (Pseudomonas solanacearum, Pseudomonas picketii, Pseudomonas gladioli, Pseudomonas mallei, Pseudomonas pseudomallei and Pseudomonas caryophylli). Burkholderia cepacia is an aerobic, Gram-negative and multi-drug resistance bacteria that cannot ferment glucose. Burkholderia cepacia, an important opportunistic bacteria in immunosuppressed patients, causes severe pulmonary infections [1,2].

Bacteria can live in humid environments and nutrient-poor fluid. It can also cause outbreaks in hospital with contaminated intravenous solutions, disinfectants, hospital equipments, and contact person to person [3].

In this study, we aimed to evaluate Burkholderia cepacia cases detected in our hospital between 2013 and 2018.

Materials and methods

The study designed as retrospectively. Forty-six cases with Burkholderia cepacia in the tertiary hospital between 2013 and 2018 were included in the study. Ethical committee approval for the study was obtained. Patients' files were scanned. Age, gender, clinical history of the patient, type of sample taken, and patients' final conditions (alive or dead) and duration of hospitalization were recorded.

Statistical analysis

Data were statistically evaluated using the Statistical Package for the Social Sciences version 17.0 software (SPSS Inc, Chicago, Illinois, USA). Continuous data were expressed as mean and standard deviation, and categorical data were expressed as the frequency and percentage.

Results

Of the 46 cases included in the study, 30.4% (n=14) were female and 69.6% (n=32) were male. The mean age was 56.0 ± 23.7 years (minimum-maximum: 0-90 years). Of the cases, 6.6% (n=3) were under the age of 18 and 93.4% (n=43) were in the adult group.

When the distribution of the samples were examined, it was found that 32.6% (n=15) in the blood culture, 32.6% (n=15) in the urine culture, 17.4% (n=8) in the tracheal aspirate culture and 8.7% (n=4) in the sputum culture, 6.5% (n=3) in wound site culture and 2.2% (n=1) in cervical culture.

Patients' final conditions were evaluated as alive or dead. Accordingly, 65.2% (n=30) were alive and 34.8% (n=16) of the patients were dead.

When the distribution of the cases according to the clinics were examined, Anesthesia with 19.6% (n=9) was the first place. In the second place, 17.3% (n=8) of the Infectious diseases department were followed by 13% (n=6) of the Internal Medicine Intensive Care Unit (ICU) and Urology department. Sample distribution of all clinics was presented in Table 1.

When the length of stay in hospital was examined, the average length of stay in hospital was 24.6 ± 25.3 days (minimum-maximum: 3-122 days).

The antibiotic resistance status of the cases was summarized in Table 2.

Table 1: Distribution of Burkholderia cepacia according to clinics

Clinic	n (%)
Anesthesiology and Reanimation	9 (19.6)
Infectious Diseases Clinic	8 (17.3)
Internal Medicine ICU	6 (13.0)
Urology Clinic	6 (13.0)
Gynecology Clinic	3 (6.5)
Internal Medicine Clinics	3 (6.5)
Pediatrics ICU and Newborn ICU	3 (6.5)
Coronary ICU	2 (4.4)
Neurology ICU	2 (4.4)
General surgery ICU	2 (4.4)
Neurosurgery ICU and Clinic	2 (4.4)
Total	46 (100)

ICU: Intensive care unit.

Table 2: Antibiotic resistance test results of Burkholderia cepacia

Antibiotics	Resistance %
Amikacin	76.1
Ertapenem	39.1
Meropenem	34.8
Imipenem	65.2
Piperacillin tazobactam	47.8
Ceftazidime	61.5
Cefepime	65.0
Cefotaxime	66.7
Ciprofloxacin	67.4
Trimethoprim sulfametaxazole	17.4
Tigecycline	28.3

Discussion

Burkholderia cepacia is a Gram-negative rod-shape bacteria. It can be found in soil, water, fruits and vegetables. Nonfermenting, Gram-negative bacteria such as Acinetobacter baumannii, Pseudomonas aeruginosa and Stenotrophomonas maltophilia are the leading causes of hospital-acquired infections. B. cepacia can also be added to the list of these bacteria. B. cepacia, an infrequent infection, is an opportunistic bacteria. Generally, the disease is severe in patients with cystic fibrosis and chronic lung disease, and can cause lethal tabulations in immunosuppressed people [4]. In hospitalized patients, besides pulmonary infection, septic arthritis, bacteremia and sometimes outbreaks can occur [5,6]. One of the factors that facilitate intra-hospital spread is the ability of bacteria to survive in humid environment and to be non-fermentative. Thus, bacteria can multiply in tap water, nebulizers, enteral feeding containers and other contaminant hospital equipment [7,8].

The data of Burkholderia cepacia are generally presented as sporadic cases or nosocomial outbreak. In a study by Abdelfattah et al. [9], B. cepacia was detected in 14 blood cultures. It was determined that the cause of the infection was an ultrasonographic probe used in the evaluation of the central venous catheter entry site. In a study by Koruk et al. [10], eight patients who underwent urological surgery had B. cepacia in the urine culture. The investigation revealed that the outbreak was related to the DJ catheter. In a study by Dizbay et al. [4], data belong to 39 patients with B. cepacia, which is considered hospital- originated, between 2003 and 2007 has been presented. In this study, the average age was 54.4 ± 23.4 years and male / female ratio was reported as 1.29. In our study, the mean age was 56.0 ± 23.7 years and the male ratio was higher (male / female ratio 2.29). When the cases of B. cepacia in the literature are examined, it is observed that a significant part of them have

cystic fibrosis and associated lung diseases. None of the cases in this study had cystic fibrosis. In a surveillance study conducted in our country, it was determined that 64.1% of infected cases received mechanical ventilation support and 58.9% of them had pneumonia. In the same study, 61.5% of cases were followed up in ICU [4]. A patient who diagnosed as pneumonia followed up with mechanical ventilator in intensive care unit has been presented by Turan et al. [11]. In our study, 50% of the cases were intensive care patients and 26.1% were pneumonia.

In a study by Dizbay et al. [4], 58.9% of the cases were pneumonia, 25.6% were bloodstream related infection, 5.1% were urinary system infection, 7.6% were surgical site infection and 2.5% soft tissue infection. In our study, a significant part of the cases (32.6%) were bloodstream related infection and urinary system infection (32.6%) while the rate of pneumonia cases was 26.1%.

Aminoglycoside, first and second generation cephalosporins are intrinsic resistant to B. cepacia. Most are resistant to broad spectrum antibiotics. The resistance mechanisms are efflux pump activation and inducible chromosomal beta lactamase production. Ceftazidime, carbapenem, piperacillin, levofloxacin and trimethoprim / sulfamethoxazole are among the most effective antibiotics. Combination therapy is recommended, and synergy tests lead to this issue [6,12]. In many studies, carbapenem resistance was found 48-89% in cases with nosocomial Burkholderia cepacia infection with cystic fibrosis [13-15]. In a study by Dizbay et al. [4], carbapenem resistance was 46.1% for imipenem and 48.7% for meropenem. The most effective antibiotic is Piperacillin-tazobactam (38.4%). A case with bronchiectasis and pneumonia was successfully treated with imipenem [11]. In another study, patients were treated with carbapenem, co-trimoxazole, and piperacillin-tazobactam successfully in the Burkholderia cepacia outbreak [10]. In another study, the most effective antibiotic is meropenem (90%) [16]. In a study by Srinivasan et al. [17], the most sensitive antimicrobial agents were found to be colistin (93%) and Co-trimoxazole (71%).

The retrospective nature of the study is the limitation of our study.

Burkholderia cepacia is an important nosocomial opportunistic infection and is often multi drug resistant. Thus, for the control of B. cepacia infections, rational and appropriate antibiotic policies should be developed and isolation measures should be taken when colonized or infected patients are needed. Also the disease should be effectively treated otherwise it should not be forgotten that the disease will result in mortality.

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The relations of vascular endothelial growth factor–C and lymph node metastasis in breast cancer patients

Meme kanseri hastalarında vasküler endotelyal büyüme faktörü-C ve lenf nodu metastazı ilişkisi

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Abstract

Aim: Breast cancer (BC) is the 2nd most common cancer worldwide and most of the cases are sporadic. BC chooses mainly the lymphatic system and axillary lymph nodes (LN) are frequently involved. Lymph node metastasis (LNM) is driven by tumor-derived lymphangiogenic growth factors, especially vascular endothelial growth factor (VEGF) family. Higher serum levels of VEGF-C have been detected in cases of BC. In the present study, we aim to investigate the expression pattern of VEGF-C in tumor specimens and the relation of VEGF-C expression with LNM by immunohistochemistry.

Methods: In this clinical, cross-sectional study, paraffin-embedded specimens were obtained from 16 female patients who had primary invasive ductal breast cancer and received surgical treatment between April 2006 and March 2007. BC tissue sections were stained with VEGF-C antibody and evaluated according to the severity and intensity of the staining. Statistical analysis was performed using SPSS version 15.0 for Windows and in all analyses, a 'p' value less than 0.05 was considered statistically significant and comparisons were 2-tailed.

Results: The average age at the time of diagnosis was 50 years (range: 24-82 years). In the present study, on the basis of SI and SS VEGF-C expression did not show statistically significant correlation with LNM, while calculated IRS - as a variable- was correlated with LNM. The grade of the tumor correlated neither with the VEGF-C expression nor with lymph node metastasis ($p>0.05$).

Conclusions: It is interesting that the correlation with VEGF-C IRS score and axillary lymph node level was found significant statistically. In the current study, we demonstrated the VEGF-C relation with LNM via IHC staining in tumoral samples of BC patients.

Keywords: Vascular endothelial growth factor–C, Lymph node metastasis, Breast cancer

Öz

Giriş: Meme kanseri (MK) dünya çapında en sık görülen 2. kanserdir ve vakaların çoğu sporadiktir. MK yayılım için esas olarak lenfatik sistemi seçer ve aksiller lenf düğümleri (LN) sıklıkla bu yayılımda rol alır. Lenf nodu metastazı (LNM), tümör kaynaklı lenfanjiyojenik büyüme faktörleri, özellikle vasküler endotelyal büyüme faktörü (VEGF) ailesi tarafından yönlendirilir. MK vakalarında daha yüksek oranda serum VEGF-C düzeyleri tespit edilmiştir.Bu çalışmada, tümör örneklerinde VEGF-C ekspresyon paternini ve immünohistokimyasal olarak LNM ile VEGF-C ekspresyonunun ilişkisini araştırmayı amaçladık.

Yöntemler: Bu klinik çalışmada, Nisan 2006 ile Mart 2007 arasında cerrahi tedavi alan primer invaziv duktal meme kanserli 22 kadın hastadan Parafine gömülü örnekler alındı. MK doku kesitleri VEGF-C antikoru ile boyandı ve boyanma şiddeti ve yoğunluğuna göre değerlendirildi. İstatistiksel analiz, Windows için SPSS 15.0 sürümü kullanılarak gerçekleştirildi. Tüm analizlerde, 0.05'ten küçük bir 'p' değeri istatistiksel olarak anlamlı kabul edildi ve karşılaştırmalar 2 yönlü olarak yapıldı.

Bulgular: Tanı anında ortalama yaş 50 idi (dağılım: 24-82 yıl). Bu çalışmada, SI ve SS VEGF-C ekspresyonu temelinde LNM ile istatistiksel olarak anlamlı bir ilişki bulunmazken, hesaplanan IRS - değişken olarak LNM ile ilişkili gözlenmiştir. Tümör derecesi ise ne VEGF-C ekspresyonu ne de lenf nodu metastazı ile belirgin ilişkili gözlenmemiştir ($p> 0,05$).

Sonuç: VEGF-C IRS skoru ve aksiller lenf nodu düzeyi ile ilgileşiminin istatistiksel olarak anlamlı olduğu dikkati çekmektedir. Bu çalışmada, MK hastalarının tümöral örneklerinde LNM ile VEGF-C ilişkisini IHC boyaması ile gösterdik.

Anahtar kelimeler: Vasküler endotelyal büyüme faktörü –C, Lenf nodu metastazı, Meme kanseri

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Introduction

Breast cancer (BC) is the 2nd most common cancer worldwide and it is the 5th most common cause of death due to cancer in females. Its' incidence and morbidity are increasing in developed countries in spite of advances in early diagnosis and treatment modalities [1]. Most of the BC cases are sporadic and not have genetic bases. Heterogeneity and different expression level of estrogen receptor (ER), progesterone receptor and human epidermal growth factor receptor (HER-2) are characteristics of BC and it is generally classified based on immunohistochemical expression of these hormone receptors. This classification is useful not only for identification of different types of BC but also for prognosis and treatment modality assessment [2].

BC chooses mainly the lymphatic system rather than the hematologic system to spread and axillary lymph nodes (LN) are frequently involved [3]. As a surgical treatment of BC, axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB) is recommended by the guidelines. Axillary lymph nodes are classified according to their location which centering pectoralis minor muscle (PMM). LN positioning at the lateral border of PMM is level I, the posterior border is level II and the medial border is level III. ALND involves removal of the axillary LN from level I and II (and in case of apparent involvement, level III) and it is required for treatment and staging purposes [4].

It is clearly shown that lymphangiogenesis is the starting pace for LN metastases. Lymphangiogenesis, the formation of new lymphatic vessels, is approved to be driven by tumor-derived lymphangiogenic growth factors, especially vascular endothelial growth factor (VEGF) family [5]. The VEGF family is comprised of different isoforms which interact with different VEGF receptor (VEGFR) types. In this family mainly VEGF-C and VEGF-D, have been identified as lymphangiogenic growth factors and bind to the VEGF receptor (VEGFR)-3, that is expressed in lymphatic endothelial cells [6]. VEGF-C is needed for the initial migration of viviparous endothelial cells and in case of tumoral growth and lymphatic spread, VEGF-C expression increases. Higher serum levels of VEGF-C have been detected, especially in cases of breast and colon cancer. It is claimed that VEGF-C promotes tumoral growth and metastases not only by means of lymphangiogenesis but also via autocrine regulation. Besides that VEGF-C protects cancer cells against oxidative stress and immune response so increases cancer cell survival rate [7].

In the present study, we aim to investigate the expression pattern of VEGF-C in tumor specimens and the relations of VEGF-Cexpression with lymph node metastasis (LNM) by immunohistochemistry.

Materials and methods

Patient and specimens

In this clinical, cross-sectional study, Paraffin-embedded specimens were obtained from 22 female patients who had primary invasive ductal breast cancer and received surgical treatment between April 2006 and March 2007 at the Department of General Surgery, Fırat University Hospital, Elazıg, Turkey. The patients who had received radiotherapy or chemotherapy preoperatively were excluded from the study. The patients with a medical history of synchronous tumor involvement (primary origin was not breast tissue) or chronic obstructive pulmonary disease, which may increase VEGF levels, were also excluded from the study. The remaining patients were evaluated (n=16) for this study and the expression levels of VEGF-C was defined by immunohistochemistry.

All patients were undergone modified radical mastectomy with standard ALND. In all cases, BC tissue, noncancerous breast epithelial tissue, and ALND materials were collected and fixed for standard histological assessment and immunostaining. Before the initiation of the study, local Research Ethics Committee of Fırat University Hospital endorsement for the project was supplied.

Demographic data and clinicopathologic characteristics of the patients were recorded. The evaluated clinicopathologic parameters were tumor size (largest tumor diameter), histological type of tumor, grade of tumor, presence of lymphovascular invasion, presence of capsule invasion, and the statue of lymph node metastasis (which described with their localizations-levels-), estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2/neu). All of the BC patients received postoperative adjuvant chemotherapy and/or hormonotherapy consisting of combination chemotherapy. Follow- up and survival of these patients were not assessed in this study.

Immunohistochemistry

During the surgery, axillary lymph node dissection was performed and the levels were marked and sorted according to lymph node levels. These lymph nodes and BC tissue samples were fixed and stored in paraffin-embedded samples for routine histological examination and confirmation of the diagnosis. Later, new sections were obtained from paraffin blocks for immunohisto-chemical (IHC) examination.

Following the completion of the study period, the formalin-fixed and paraffin-embedded BC tissue sections were stained with the VEGF-C antibody (H-190: sc-9047; Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) for IHC examination using standard streptavidin-biotin-horseradish peroxidase (HRP) technique. Mayer's Hematoxylin was used for counterstaining the slides. The immunohistochemical staining results were interpreted by an experienced pathologist other than the first examiner.

After staining, the tissues were evaluated according to the severity and intensity of the staining. Staining strength (SS) value is described as follows;

i) If no staining has occurred, the value is '0' (Fig. 1),

ii) If it is poorly stained, the value is '1',

iii) if there is moderate staining, the value is '2',

iv) If staining is intense, the value is '3' (Figure 2).

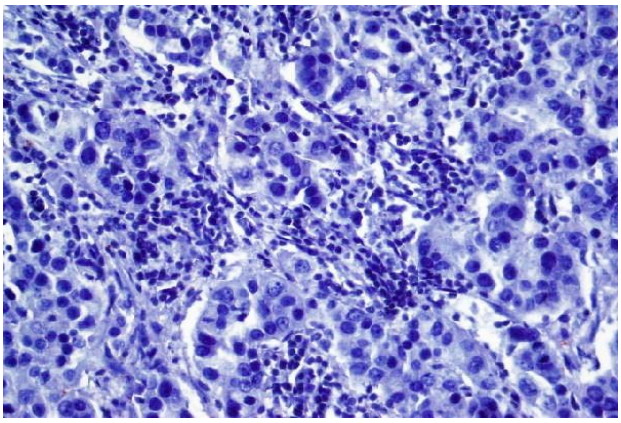

Figure 1: VEGF-C staining strength '0' (immunoperoxidase in 400 magnification)

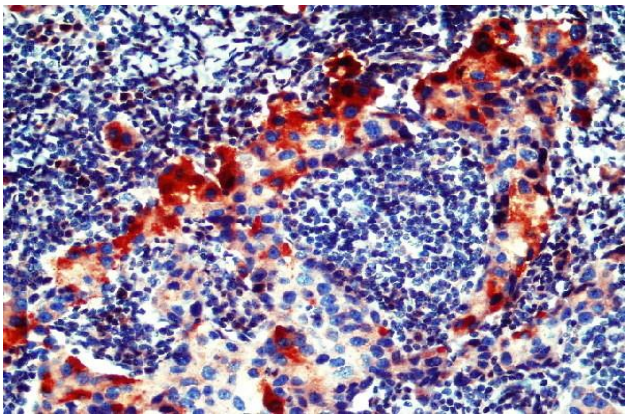

Figure 2: VEGF-C staining strength '3' (immunoperoxidase in 400 magnification)

When the staining intensity was evaluated, the ratio of the area stained positively to the entire surface of the sample was taken as the basis. According to this, staining intensity (SI);

i) If this ratio is between 0-10%, '0',

ii) If this ratio is between 10 and 25%, '1',

iii) If this ratio is between 25 and 50%,'2',

iv) If this ratio is between 50 and 75%,'3' and

v) If it is more than 75%, it is evaluated as '4'.

However, the intensity of VEGF-C staining was not considered as a parameter alone. Instead, the crude data were then transformed to an Immunoreactive Score (IRS) by adding the scores for the staining intensity and staining strength. SI, SS, IRS were considered as a variable individually.

Statistical analysis

Statistical analysis was performed using SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL., USA). Data were analyzed, and the continuous variables were reported as mean± standard deviation (SD), and nominal variables were reported as total number and percentages.

Variables were first evaluated by One-Sample Kolmogorov-Smirnov test as a normality test to choose the type of statistical tests –parametric or non-parametric test–, and the results showed that asymp. sig. (2-tailed) levels ≤ 0.05 so we decided to use non-parametric tests. For statistical analysis, correlations between variables were evaluated for significance by using the Spearman's rho test. Categorical variables were evaluated by the Mann-Whitney U test and Kruskal Wallis t-test of contingency. In all analyses, a 'p' value less than 0.05 was considered statistically significant and comparisons were 2-tailed.

Results

All 16 patients who underwent surgery for BC during the study period were evaluated. The average age at the time of diagnosis was 50 years (range: 24-82 years). All of the patients' diagnoses were confirmed as invasive ductal cancer and the clinicopathologic properties of the patients and correlations with LN metastases were outlined in Table 1.

Table 1: Demographic data and the clinicopathologic properties of the patients and correlations with LNM*

Variable	Total cases (n=16)	Lymph node metastasis (+)(n=12)	p value+
Age	50 ±15.27	50.92 ±17.53	0.716
Grade			
I/II	6 (37.5%)	2 (16.7%)	0.03
III	10 (62.5%)	10 (83.3%)	
Size			
≤5cm	9(56.3%)	8 (66.7%)	0.159
>5cm	7(43.8%)	4 (33.3%)	
SS	1.69 ±0.94	1.83± 1.11	0.056
SI	1.56 ±1.09	1.92± 0.9	0.064
IRS	3.25 ±1.94	3.75± 1.91	0.04
ER+	3 (18.8%)	0	0.01
HER-2+	6 (37.5%)	6 (50%)	0.056

* Values are either expressed as mean±standard deviation or n (%).
+p-values calculated for comparison of survivors versus non-survivors group by Mann- Whitney U test.
Abbreviations: LNM; Lymph node metastasis, SS; Staining strength, SI; staining intensity, IRS; Immunoreactive Score, ER; estrogen receptor,HER-2; human epidermal growth factor receptor

Six patients were Grade I/ II and the majority of cases were Grade III (62.5%) and it was statistically correlated with LNM ($p<0.05$). In 7 cases, tumor size was > 5cm and this variable was not related to LNM. SI and SS were not related to LNM as a variable, whereas the correlation between LNM and calculated IRS was statistically significant ($p<0.05$). In this study, the cutoff point for the IRS was chosen as 3 (the midpoint of the IRS scale) and a new category was formed with this factor to determine the relations of immunohistochemical expression of VEGF-C and clinicopathological variables(Table 2).

Table 2: The clinicopathologic properties of the patients and correlations with IRS*

Variable	Total cases (n=16)	IRS≥3(n=10)	p value+
Age	50 ±15.27	49.3 ±17.53	0.073
Size			
≤5cm	9(56.3%)	5 (50%)	0.547
>5cm	7(43.8%)	5 (50%)	
Grade			
I/II	6 (37.5%)	3(30%)	0.439
III	10 (62.5%)	7(70%)	
SS	1.69 ±0.94	2.30 ±0.48	0.006
SI	1.56 ±1.09	2.10 ±0.99	0.006
Lymphovascular invasion	6 (37.5%)	5 (50%)	0.207
ER+	3 (18.8%)	1 (10%)	0.277
HER-2+	6 (37.5%)	6 (60%)	0.014
Capsular invasion	8 (50%)	6 (60%)	0.334
Level 0	4 (25%)	1 (10%)	
Level I	6 (37.5%)	3 (30%)	0.013
Level II	3 (18.8)	3(30%)	
Level III	3 (18.8)	3 (30%)	
Lymph node metastasis (+)	12 (75%)	9(90%)	0.082

* Values are either expressed as mean±standard deviation or n (%).
+p-values calculated for comparison of survivors versus non-survivors group by Mann- Whitney U test.
Abbreviations:SS; Staining strength, SI; staining intensity, IRS; Immunoreactive Score, ER; estrogen receptor,HER-2; human epidermal growth factor receptor

Four patients showed no axillary LNM(25%), while 6 patients had LNM in level I (37.5%), and 3 patients (18.8%) in level II and level III (skipped metastases was not observed). This variable (axillary lymph node level) and IRS factor showed a statistically significant correlation (p=0.013) whereas LNM did not show a significant correlation (p=0.082). HER-2 showed significant correlation with IRS group (p=0.014) statistically and invasion –lymphovascular or capsular invasion- had no correlation with IRS of VEGF-C. The average tumor size was determined as 4.12 cm (minimum 1-maximum 10 cm) and tumor size had no relation with LNM or IRS score.

VEGF-C expression:

In 14 cases positive reaction of tumor cells to VEGF-C staining was detected (IRS scores were 2 for 4 cases and maximum score-7 was observed in 1 case). The grade of the tumor correlated neither with the VEGF-C expression nor with lymph node metastasis ($p>0.05$).

Discussion

Currently, the most frequent malignancy in the female is the Breast cancer and LNM is reported in more than one-third of the cases. One of the most substantial prognostic determinants in BC is Lymph node statue [8]. The data about LNM is crucial to establish treatment and to predict prognosis so ALND or SLNB becomes a standard process. A complicated network of growth factors, cytokines and chemokines control lymphangiogenesis which partakes to lymphatic metastasis [9,10]. VEGF-C induced lymphangiogenesis was demonstrated by Skobe et al. [11] at first and in this study, it was proposed that overexpression of VEGF-C in BC cells vigorously increased intratumoral lymphangiogenesis and augmented metastasis to the regional lymph nodes and lungs. In the present study, VEGF-C expression in 87.5% of the cases with different IRS scores correlated with LNM. It is interesting that the correlation with VEGF-C IRS score and axillary lymph node level was found significant statistically.

Vascular endothelial growth factor-C (VEGF-C) is a well-known and highly investigated member of the VEGF family and it divvies maximum homology domain with VEGF-A, which is noted to be an important angiogenic factor, among siblings [6]. The role of VEGF-C in the lymphangiogenesis process is approved by many studies, whereas the prognostic role of VEGF-C expression for LNM in BC patients is still contentious [3,10]. Previous meta-analyses showed different results about the relation of VEGF-C with prognosis and disease-free survival in breast cancer patients [12,13]. These opposite outcomes in distinct meta-analyses cause a big dilemma and in the present study, VEFG-C is related to LNM and probably with prognosis. Unfortunately, follow-up data and information about disease-free survival were missing and no conclusion can be done about VEGF-C and prognosis relation. But LNM and prognosis relation just gives us a clue about VEGF-C effect.

In some studies, the correlation between VEGF-C expression and LNM was significant, whereas in some studies this relation was not significant [8,14]. In the present study, on the basis of SI and SS VEGF-C expression did not show statistically significant correlation with LNM, while calculated IRS - as a variable- was correlated with LNM.

One of the most aggressive molecular variants of BC is the HER-2 subtype and in the present study, it was correlated with IRS score. A similar finding was detected by Schoppmann et al. [15], overexpression of VEGF-C was related with HER-2 overexpression.

Limitations

Probably the most deeply searched factor for lymphangiogenesis and tumor lymphatic metastases is VEGF-C in the literature. Our study mainly depends on data collected previously for another unpublished study years ago, but this does not depreciate the value of the findings and results. The most important limitation of this study was the small sample size which is limiting the power of the analysis. Even so, our results are parallel to other studies showing that VEGF-C plays an important role in the lymphatic metastases of BC.

Conclusion

In the current study, we demonstrated the VEGF-C relation with LNM via IHC staining in tumoral samples of BC patients. There is a need for additional studies to explore the role of VEGF-C in the augmentation and maintenance of lymphangiogenesis in BC.

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The diagnostic contribution of motor and sensory conduction studies of the wrist-palm segment in carpal tunnel syndrome

Karpal tünel sendromunda bilek-aya segmenti motor ve duysal iletim çalışmalarının tanıya katkısı

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Abstract

Aim: Sensory and motor segmental conduction studies have been performed to improve diagnostic sensitivity especially in cases with mild carpal tunnel syndrome, but there are very few studies comparing these methods. The purpose of this study was to determine the segmental conduction studies' contribution to the diagnosis of carpal tunnel syndrome (CTS), to compare the sensitivity and specificity of these methods.

Methods: Patients with suspected CTS referred to our electrophysiology laboratory and a control group was included. The data were collected prospectively. The following measurements made: median sensory conduction velocity wrist-digit 1 (W-1), median sensory conduction velocity wrist- digit 3 (W-3), median wrist-palm sensory conduction velocity (W-Ps), distoproximal ratio of velocity (D/P), median distal motor latency wrist- APB (MDML), median wrist- palm segment motor conduction velocity (W-Pm).

Results: The highest sensitivity for an electrodiagnostic CTS diagnosis were W- Pm (38%), D/P (33.3%), MDML (33.3%), W- 3 (31%), W- 1 (31%), W-Ps (24%), respectively. Seventeen out of 42 hands presented one or more abnormal results of routine electrophysiologic tests (W-1, W-3, MDML). Twenty-one patients were diagnosed CTS electrophysiologically after inclusion of D/ P and 24 patients were defined CTS after inclusion of W- Pm. Twenty-five of 42 hands with CTS were defined as an electrophysiologically proven CTS using routine electrophysiologic tests together with both D/P and W-Pm segmental studies. That is; diagnostic sensitivity increased nearly by 50%.

Conclusion: The results of this study suggested that motor or sensory segmental studies have an important contribution to the diagnosis, particularly for mild subjects.

Keywords: Carpal tunnel syndrome, Segmental conduction study

Öz

Amaç: Özellikle hafif karpal tünel sendromu olan olgularda tanı duyarlılığını artırmak için duysal ve motor segmental iletim çalışmaları yapılmıştır, ancak bu yöntemleri birbiriyle karşılaştıran çok az sayıda çalışma vardır. Bu çalışmanın amacı segmental iletim çalışmalarının karpal tünel sendromu (KTS) tanısına katkısını saptamak, bu yöntemlerin duyarlılığını ve özgüllüğünü birbiriyle karşılaştırmaktır.

Yöntemler: KTS şüphesiyle elektrofizyoloji laboratuvarına gönderilen hastalar ile bir kontrol grubu dahil edildi. Veriler prospektif olarak toplandı. Bilek- 1. parmak median duysal iletim hızı (W-1), bilek- 3. parmak median duysal iletim hızı (W-3), median bilek- aya duysal iletim hızı (W- Ps), distoproksimal hız oranı (D/P), bilek- APB median distal motor latansı (MDML), median bilek- aya segmenti motor iletim hızı (W-Pm).

Bulgular: Elektrofizyolojik KTS tanısı için sensitivitesi en yüksekler sırasıyla W- Pm (%38), D/P (%33,3), MDML (%33,3), W- 1 (%31), W- Ps (%24)' di. 42 elden 17' sinde rutin elektrofizyolojik testlerde (W-1, W-3, MDML) bir veya daha fazla anormal sonuç elde edildi. D/P eklendikten sonra 21 hasta elektrofizyolojik olarak KTS tanısı aldı ve W- Pm eklendikten sonra 24 hasta KTS olarak değerlendirildi. Rutin elektrofizyolojik testlere ek olarak hem D/P, hem W- Pm segmental çalışmalarının eklenmesiyle 25 hastaya elektrofizyolojik olarak KTS tanısı kondu. Böylece; tanısal duyarlılık yaklaşık %50 arttı.

Sonuç: Bu çalışmanın sonuçları göstermiştir ki; özellikle hafif olgularda motor ve duysal segmental çalışmalar tanıya önemli katkı sağlamaktadır.

Anahtar kelimeler: Karpal tünel sendromu, Segmental iletim çalışması

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Introduction

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy of the upper extremities, due to compression of the median nerve as it travels through the wrist at the carpal tunnel [1-5].

In patients with mild form of the carpal tunnel syndrome (CTS), electrophysiological studies may fail to detect any abnormalities [6,7-12]. False negative conduction studies may result from the masking of the slowing in the proximal segment by the normal conduction velocity in the distal part of the tunnel, since conduction abnormality is confined to the segment of the median nerve within the carpal tunnel in mild CTS cases. Therefore, wrist-palm studies are considered to provide a more sensitive means of electrophysiological diagnosis for CTS [1,5,13]. In the present study, our aim was to examine the contribution of segmental conduction studies on the electrophysiological diagnosis of CTS.

Materials and methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Forty-two symptomatic arms from 29 patients referred to our EMG laboratory with a diagnosis of CTS based on history and examination were included in this study. Patients with nocturnal numbness and tingling on the hand or hands are accepted as carpal tunnel syndrome. Exclusion criteria included suspicious co-existence of polyneuropathy, plexopathy, or radiculopathy, and presence of systemic conditions associated with polyneuropathy or mononeuritis. Of the 29 patients, 26 were female and 3 were male, with an average age of 46.4 ± 8.4 years. All 42 arms had nocturnal paresthesia, while 4 had thenar atrophy, 6 had abductor pollicis brevis (APB) motor deficit, and 2 had sensory deficit in the median nerve territory.

Control subjects were the patients referred to the EMG laboratory with a pre-diagnosis of lumbar disc herniation who had no neurological complaints of the upper extremity and healthy volunteers employed in the neurology unit (23 healthy volunteers; 19 female, 4 male; average age 42.4 ± 10.5 years).

All patients were kept in a room with a temperature of 22 to 24 C for 15 minutes prior to the electrophysiological study. Subsequently, using an infrared thermometer (Exergen Dermatemp Infrared Temperature Scanner®) the extremity temperatures were measured and were maintained at a minimum temperature of 32 C using an infrared heater when needed.

A 4-channel Keypoint Electromyograph (Medtronic-Dantec) was used for electrophysiological tests, all of which were performed by the same investigator while the patient was in the supine position and the forearm was in extension and supination. All stimulations and recordings were performed with superficial electrodes. Before placement of electrodes, the skin was cleansed using alcohol-soaked cotton balls for minimizing skin resistance and electrode gel was utilized for the study.

Two Velcro-band grounding electrodes were used, one on the wrist, the other on the metacarphophalangeal joint. Dry cotton balls were placed between the fingers to prevent contact. For recording, a Velcro-band ring electrode was used for sensory conduction and self-adhesive superficial electrodes were used for motor conduction measurements.

Sensory conduction studies

All sensory conduction measurements were performed antidromically. For the sensory conduction tests of the median nerve at the 1st finger, the active ring electrode was placed on the interphalangeal joint, while the reference ring electrode was placed on the distal phalanx, and median nerve was stimulated along its course at wrist level.

For the sensory conduction tests of the median nerve at the 3rd finger, the recorder ring electrode was placed in the middle of the middle phalanx of the third finger, while the reference ring electrode was placed in the middle of the distal phalanx. Separate stimulations were performed on the median nerve along its course at the wrist and palm.

For the sensory conduction test of the ulnar nerve at the 5th finger, the recorder ring electrode was placed on the middle of the middle phalanx of the fifth finger, while the reference ring electrode was placed on the middle of the distal phalanx. The electrical stimulation was performed along the course of the ulnar nerve in the wrist.

The amplitude of sensory action potentials were measured from peak to peak, and at least 10 measurements were averaged. The filtering frequency range was 20 to 2000 Hz.

Motor conduction studies

The superficial electrode was placed on the APB muscle at the thenar edge for median nerve motor conduction studies. The reference Velcro ring electrode was attached to the middle of the distal phalanx. Electrical stimulations were performed along the course of the median nerve in the wrist and palm. For stimulations at the palm, the anode was placed on an imaginary line connecting the cathode and the metacarpophalangeal joint of the fifth finger. This distal placement of the anode was for avoiding the stimulation of the recurrent thenar nerve beneath the anode that enters APB. The activation of the recurrent thenar nerve under the anode and cathode may lead to inaccuracy of the latency [1].

For the motor conduction tests of the ulnar nerve, the superficial electrode was placed at the hypothenar edge on the abductor digiti minimi (ADM) muscle. The reference Velcro ring electrode was placed on the middle of the middle phalanx of the fifth finger. The electrical stimulation was provided on the course of the ulnar nerve at the wrist.

The latency of the compound muscle action potentials (CMAP) were recorded as the time from the onset of stimulus artifact to the onset of the potential. The filtering frequency range was 20 to 10000 Hz.

The amplitude of CMAP was estimated from peak to peak. The sum of the negative and positive CMAP areas was recorded as the CMAP area.

Bilaterally, the following measurements and estimations were performed in all cases.

- median nerve sensory conduction velocity wrist- 1st finger (W-1)
- median nerve sensory conduction velocity wrist- 3rd finger (W-3)
- median nerve sensory conduction velocity palm- 3rd finger (P-3)
- median 1st finger sensory nerve action potential amplitude (W-1 amp)
- median 3rd finger sensory nerve action potential amplitude (W-3 amp)
- median nerve sensory conduction velocity wrist-palm (W-Ps) was calculated as follows: (wrist-palm distance)(mm)/ (W-3 latency- P-3 latency) (ms)
- distoproximal velocity ratio (D/P) was calculated as follows: (P-3)/(W-Ps) (Figure 1)
- distoproximal amplitude ratio was calculated as follows: median sensory nerve action potential amplitude (SNAP2 amp) obtained by palm stimulation divided by the median sensory nerve action potential amplitude obtained by wrist stimulation (W-3 amp).
- ulnar nerve sensory conduction velocity wrist-5th finger (W-5)
- ulnar sensory nerve action potential amplitude (UAMP)
- median distal motor latency wrist-APB (MDML)
- median wrist segment motor conduction velocity (W-Pm) was calculated as follows: the compound muscle action potential 1 (CMAP1) from wrist stimulation and the compound muscle action potential 2 (CMAP2) from palm stimulation were recorded (Wrist-palm distance) (mm)/(CMAP1 latency-CMAP2 latency) (ms) (Figure 2).
- compound muscle action potential amplitude obtained by median motor stimulation at the wrist (CMAP1 amp)
- compound muscle action potential amplitude obtained by median motor stimulation at the palm (CMAP2 amp)
- distoproximal amplitude ratio was estimated as follows: CMAP2 amp/CMAP1 amp
- compound muscle action potential area obtained by the motor stimulation of the median nerve at the wrist (CMAP1 area)
- the compound muscle action potential area obtained by the motor stimulation of the median nerve at the palm (CMAP2 area)
- distoproximal area ratio (CMAP2 area/CMAP1 area).
- ulnar nerve distal motor latency wrist – ADM (UDML)

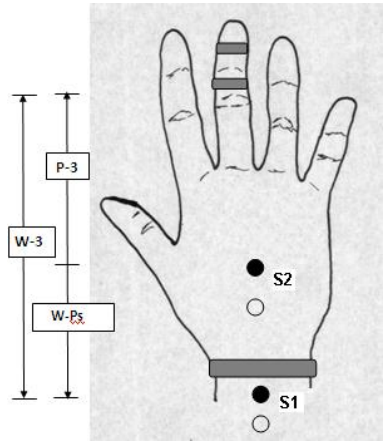

Figure 1: Mediansensory segmental nerve conduction study. Distoproximal velocity ratio=P-3/ W- P

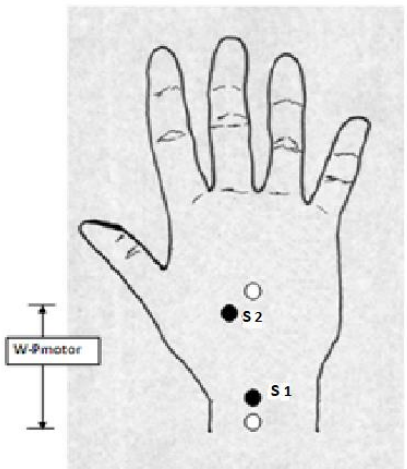

Figure 2: Median motor segmental nerve conduction study

Statistical Analysis

The patient and control groups were comparable with regard to age, as determined by the Student's t test ($p > 0.05$). The data from patients and healthy controls had normal distribution. In healthy controls, there were no significant differences between right and left sided measurements, and the normal limits were estimated using the average of the electrophysiological parameters (± 2 SD) from healthy volunteers. The patient data lying outside these limits were considered abnormal. For each electrophysiological parameter tested, a positive predictive value, a negative predictive value, specificity and sensitivity were estimated. In order to examine the multiple diagnostic performances of these electrophysiological parameters, a logistic regression analysis was performed. Odds ratio, Youden's Index and likelihood ratio were used to determine the parameters with the best positive predictive value, negative predictive value, specificity and sensitivity.

Results

Table 1 shows the comparative test results in CTS patients and controls. Table 2 shows amplitude and area results in controls and CTS subjects. Table 3 shows the sensitivity, specificity, positive predictive value and negative predictive value of the tests for CTS diagnosis.

Table 1: Conduction velocity results in CTS and control subjects

	Controls (n=46) Mean±SD	Mean±2SD	CTS (n=42) Mean±SD
W-1 (m/s)	59.40± 7.50	44.95- 74.95	50.20± 8.10
W-3 (m/s)	58.00± 6.00	46.13- 70.05	51.10± 7.70
W-Ps (m/s)	57.40± 9.70	37.88- 76.92	46.70± 12.80
D/P	1.02± 1.17	0.70- 1.34	1.20± 0.30
MDML (ms)	3.40± 0.30	2.73- 4.13	4.00± 0.70
W-Pm (m/s)	41.90± 8.00	25.84- 57.96	33.40± 11.50
W-5 (m/s)	59.30± 6.70	45.87- 72.79	59.90± 5.00
UDML (ms)	2.50± 0.50	1.60- 3.56	2.40± 0.20

W-1: Median nerve sensory conduction velocity in the 1st finger W-3: Median nerve sensory conduction velocity in the 3rd finger W-Ps: median nerve wrist-palm conduction velocity, D/P: median nerve sensory distoproximal velocity ratio; MDML: median motor distal latency, W-Pm: median wrist-palm motor velocity, W-5: ulnar nerve sensory conduction velocity, UDML: ulnar motor distal latency

Table 2: Amplitude and area results in controls and CTS subjects

	Controls (n=46) Mean±SD	Mean±2SD	CTS subjects (n=42) Mean±SD
SNAP amp	41.20± 16.00	9.09- 73.37	26.80± 12.50
SNAP2 amp/W-3Amp	1.10± 0.20	0.71- 1.59	1.20± 0.30
CMAP1 amp	11.00± 3.60	3.86-18.14	9.00± 3.00
CMAP2 amp/CMAP1 amp	1.20± 0.25	0.70- 1.70	1.20± 0.20
CMAP1 area	34.30± 10.80	9.70- 58.90	28.20± 12.10
CMAP2 AREA/ CMAP1 area	1.24± 0.34	0.56- 1.92	1.40± 0.60

Table 3: The sensitivity, specificity, positive predictive value, and negative predictive value of the tests for CTS diagnosis

Tests	Sensitivity %(n)	Specificity %	Positive predictive value %	Negative predictive value %
W-1	31.0(13)	100.0	100.0	61.3
SNAP amp	4.8(2)	100.0	100.0	53.5
MDML	33.3(14)	95.7	87.5	61.1
CMAP1 amp	2.4(1)	97.8	50.0	52.3
W-Pm	38,0(16)	100.0	100.0	55.4
W-3	31.0(13)	100.0	100.0	61.3
W-Ps	23.8(11)	100.0	100.0	59.0
W-5	0	97.8	0	51.7
D/P	33,3(14)	100.0	100.0	64
SNAP2 amp/W-3Amp	7.1(3)	100.0	100.0	54.1
CMAP2 amp/CMAP1 amp	4.8(2)	97.8	66.7	53
CMAP1 area	0	97.8	0	51.1
CMAP2 area/CMAP1 area	9.5(4)	97.8	75	53.5

Specificity: the percentage of those with normal test results within the control group; sensitivity: the percentage of patients with an abnormal test result; negative predictive value: the percentage of controls among those with a normal test result; positive predictive value: the percentage of patients within those with an abnormal test result.

The tests with highest sensitivity were median motor wrist-palm velocity (38%), median sensory distoproximal velocity ratio (33.3%), median motor distal latency (33.3%),

median sensory 3rd finger velocity (31%), median sensory 1st finger velocity (31%), and the median sensory 3rd finger wrist-palm segment velocity (24%).

The following 7 tests had a specificity and positive predictive value of 100%: median sensory 1st finger velocity, median sensory 1st finger amplitude, median motor wrist-palm velocity, median sensory 3rd finger velocity, median sensory 3rd finger wrist-palm segment velocity, median sensory 3rd finger distal to proximal velocity ratio, and median sensory 3rd finger distal amplitude to proximal amplitude ratio.

The tests with highest negative predictive value included the median sensory 3rd finger distoproximal velocity ratio (64%), median motor wrist-to palm latency (63.4%), median sensory 1st finger velocity (61%), median motor latency (61%), median sensory 3rd finger velocity (61%).

Median sensory 1st finger velocity was abnormal in 13 of the 42 hands with CTS, although it was not the sole abnormality in any of these 13 patients.

Median sensory 1st finger amplitude was abnormal in 2 patients, although it was not the sole abnormality in any of these cases. Wrist-palm segment median motor velocity was abnormal in 16 patients; in 3 of these, other electrophysiological tests revealed normal results and only the wrist-palm segment motor velocity was abnormal.

Median motor distal latency was abnormal in 14 patients, though never on its own. Median motor amplitude was abnormal in only 1 patient, and it was not the sole electrophysiological abnormality.

Median sensory 3rd finger velocity was abnormal in 13 patients, although it was not the sole abnormality in any of these cases. Median sensory 3rd finger wrist-palm segment velocity was abnormal in 10 patients. However, it was not the sole abnormality in any of these cases. Median sensory 3rd finger distoproximal velocity ratio was pathological in 14 patients. In one of these patients, it was the only abnormal electrophysiological finding. Median sensory 3rd finger distoproximal amplitude ratio was abnormal in three patients. In one of these patients, it was the only abnormal electrophysiological finding.

Median motor distoproximal amplitude ratio was abnormal in only 2 patient. In both patients, there were additional electrophysiological abnormalities. Median motor distoproximal area ratio was abnormal in 4 patients. In all these patients, there were additional electrophysiological abnormalities.

In 17 hands, at least one of the electrophysiological studies routinely used in the electrophysiology laboratory (i.e. median sensory1st finger velocity, median sensory 3rd finger velocity, median motor distal latency) was abnormal. When median sensory 3rd finger distoproximal velocity ratio was added to these tests, the number of hands with abnormality increased to 21, and when the wrist-palm velocity was added this number increased to 24. The use of these two parameters in addition to routine electrophysiological tests allowed an electrophysiological diagnosis of CTS in 25 of the 42 hands with CTS.

Discussion

CTS is a clinical diagnosis, supported by electrophysiological tests when differential diagnosis is required or when surgery is planned. Sensitivity of EMG is never close to 100% , and since in cases with mild CTS the conduction abnormality is confined within the segment of the median nerve in the carpal tunnel, the normal conduction in the distal segment may obscure the slowing in the shorter segment [14]. Therefore, in patients with normal conventional results, wrist-palm segment tests are recommended [1,3].

The tests used in the current study included the median nerve sensory conduction in the thumb and third finger, wrist-palm segment sensory conduction with 3rd finger recording, median nerve motor conduction and wrist-palm segment motor conduction, ulnar nerve fifth finger sensory conduction, and ulnar nerve motor conduction.

The median motor wrist-palm velocity emerged as the test with highest sensitivity (38.0%) followed in the decreasing order by the median sensory distoproximal velocity ratio (33.3%), distal motor latency (33.3%), median nerve 3rd finger velocity (31.0%), median sensory 1st finger velocity (31.0%), and median sensory 3r finger wrist-palm segment sensory velocity (24.0%).

In a study by Padua et al. involving 43 patients (50 hands) and 36 healthy volunteers (40 hands), the sensitivity of routine electrophysiological tests was compared with that of the distoproximal velocity ratio and found that the test with the lowest sensitivity was the median nerve distal motor latency (44%). On the other hand, the sensitivity of the median nerve 1st finger sensory velocity was 66%, and the sensitivity of the median nerve 3rd finger sensory velocity was 64%. In 38 of the hands with CTS (76%), the median nerve sensory conduction velocity was below 45 m/s. In that study the test with the highest diagnostic value was the distoproximal velocity ratio, which was below 1.0 among 40 control hands, while above 1.0 in 49 of the 50 hands with CTS (sensitivity 98%).

However, despite the high diagnostic sensitivity of the distoproximal velocity ratio for CTS, the authors pointed out to the possibility of obtaining misleading results if the tests are not performed in a standardized manner, since the area of interest spans only a short distance [6].

In a study by Chang et al. [1] involving wrist-palm segment motor conduction velocity, the results of the electrophysiological tests were compared in 160 hands with CTS. Of these 160 hands with CTS, 11 had normal electrophysiological test results (7%). In 139 (87%) and 129 (81%) hands the wrist-palm segment motor and sensory conduction velocity were abnormal, respectively. In 92% of the cases, at least one of these two tests yielded an abnormal result. They concluded that the wrist-palm segment motor conduction velocity appeared to be a more sensitive and practical technique as compared the sensory conduction velocity, and therefore the combined use of these two tests may improve the diagnostic yield.

In another study by Chang et al. [15] the sensitivity of the wrist-palm segment motor conduction velocity was compared with other sensory conduction techniques. In 32 of the 360 hands

(8.9%) electrophysiological tests were normal. The tests with highest sensitivity were as follows: median-ulnar sensory latency difference (87.2%), median-radial sensory latency difference (86.7%), wrist-palm motor conduction velocity (81.7%), wrist-palm sensory conduction time (80.8%), wrist-palm sensory conduction velocity (73.6%). Thus, although wrist-palm segment motor conduction velocity was more sensitive than the sensory conduction time, a comparison of the sensory latency differences between the median and radial or ulnar nerves provided the highest sensitivity.

Sheu et al. [16] found that the distoproximal latency ratio of the median 3rd finger sensory conduction was the most sensitive test (77.9%) in their study, followed by the median-radial sensory latency difference (74.0%) and median-ulnar sensory latency difference (70.2%). The authors proposed that segmental tests provided a more practical and more sensitive means of diagnosis vs. tests based on comparison.

In a subsequent study by Lee et al. [17] median-radial and median-ulnar sensory latency differences were the tests with highest sensitivity (84.3% and 85.7%, respectively). These authors recommended the use of these comparative tests instead of segmental studies, in patients with normal median-sensory distal latency and median motor distal latency results. In their study, the other tests and their sensitivities are as follows: the wrist-palm segment sensory conduction time (77.0%), median distal sensory latency (74.3%), wrist-palm segment motor conduction velocity (69.1%), distoproximal conduction time difference (63%), distal motor latency (61.3%), and the distoproximal conduction time ratio (46.5%).

As compared to those reported by Chang and Padua, the results of the conduction tests in CTS patients in our study are closer to normal values, which may be explained by the inclusion of milder cases of CTS. All patients in our study, i.e. 42 symptomatic hands from 29 patients, described symptoms such as paresthesia involving the whole hand or the first four fingers that awakened the patients and that relieved with moving or shaking of the hand or by suspending the hand at the bed-side. Only 6 patients had permanent physical examination findings extending into day hours. On the other hand, the addition of D/P and W-Pm to the standard three tests (i.e. W-1, W-3, and DML) improved the sensitivity of electrophysiological tests from 40% to 59.5%, implying an approximately 50% increase in diagnostic sensitivity. Considering the fact that milder cases of CTS were included in our study, it may be assumed that segmental tests may be associated with a significant diagnostic contribution, particularly in very mild cases.

Entrapment neuropathies may also lead to slowing of the conduction through segmental demyelination as well as conduction block in some patients. Since entrapment neuropathies represent chronic conditions, conduction block is significantly less frequent as compared to the slowing of the conduction. In this study, 4 patients in sensory conduction tests and 2 patients in motor conduction tests had conduction block at the wrist segment. In only one case, block was the only electrophysiological finding, and it was associated with other signs in other cases. Although it may occur as a solitary condition, presence of motor or sensory conduction block should also be examined when segmental conduction studies are carried out.

In our study, some healthy individuals had slower median nerve conduction velocity at the wrist level as compared to more distal segments. In fact, a reduction in conduction velocity from proximal to distal segments is a physiological phenomenon [18]. Despite this, the conduction velocity may also slow down due to presence of segments with anatomic narrowing even in healthy subjects, as clearly exemplified by the ulnar nerve conduction. In healthy individuals, a motor nerve conduction velocity of 63 m/s in the arm and 61 m/s in the forearm is reduced to 51 m/s at the elbow segment [19]. Studies examining the segmental conduction in the median nerve are much less in number. In some of these studies, a slowing down of motor or sensory conduction was shown in healthy individuals at the level of the wrist-palm. In our study, the sensory D/P among healthy controls was between 0.6 and 1.3. Although Padua et al. [6] suggested that these ratio should always be less than 1, some healthy individuals may also have a ratio greater than 1. With a ± 2 SD, this ratio could reach 1.3 among our healthy controls.

Limitations

Our patients are selected according to the clinical features therefore; a few normal individuals might be assessed as carpal tunnel syndrome.

Conclusions

The results of this study show that sensory and motor segmental nerve conduction studies may electrophysiologically provide significant diagnostic contributions, particularly in patients with new onset or mild disease.

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Research article
Araştırma makalesi

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The comparison of microdose flare up and flexible antagonist protocols in poor responders undergoing IVF treatment: A prospective randomized controlled trial

İVF tedavisi alan zayıf ovaryan rezervli hastalarda mikrodoz flare-up ve fleksible antagonist protokollerinin karşılaştırılması: Prospektif randomize kontrollü çalışma

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Abstract

Aim: Ovarian reserve is one of the most important prognostic factors to predict probability of pregnancy in in vitro fertilization (IVF) cycles. Poor ovarian response is associated with high cycle cancellation rate and diminished pregnancy rates. Therefore, the management of women who demonstrate an inadequate response to controlled ovarian hyperstimulation (COH) are a challenge to treat with IVF.

Methods: A hundred consecutive infertile women, defined as poor responder, were recruited to this study. It was conducted at the assisted reproductive technology (ART) unit of the Ankara Etlik Zubeyde Hanim Women's Health Teaching and Research Hospital during the period September 2009 to September 2011. All patients in Group 1(n=50) were treated by using flexible gonadotropin releasing hormone (GNRH) antagonist protocol and in Group 2 (n=50) were treated by using GnRH microdose flare-up protocol. Exogenous gonadotropin (Gonal F, Serono, Istanbul, Turkey) was initiated on the second day of menstruation in all patients in Group 1(n=50) and GnRH antagonist (0.25 mg, Cetrotide; Serono, Geneva, Switzerland) was started when the leading follicle reached 12 mm in mean diameter and were continued until the day of hCG administration.

Results: Total dosage of gonadotropins was significantly higher in group 2 (2625 IU in group 1 vs 4050 IU in group 2; p<0.001). The pregnancy rate was higher in group 2 but not statistically significant (25.7% in group 1 vs 33.3% in group 2; p=0.501).

Conclusion: There is no consensus on the best standard treatment option for assisted reproductive technology (ART) cycles of poor responders. GnRH antagonist and microdose flare-up protocols seem to have similar outcomes in poor responder patients in intracytoplasmic sperm injection (ICSI) cycles except consumption of gonadotropins. Further prospective randomized trials with large sample size are needed to assess the efficacy of the two protocols in the poor responders.

Keywords: Poor responders, Microdose flare up, Antagonist, In vitro fertilization

Öz

Amaç: Ovaryan rezerv, in vitro fertilizasyon (İVF) sikluslarında gebelik olasılığını gösteren en önemli prognostik faktörlerden birisidir. Azalmış ovaryan rezerv, azalmış gebelik oranları ve artmış siklus iptalleriyle alakalıdır. Bu nedenle kontrollü ovaryan hiperstimülasyona (KOH) zayıf yanıt veren kadınlarda İVF ile tedavi bir zorunluluktur.

Yöntemler: Bu çalışmaya, eylül 2009-2011 tarihleri arasında Ankara Etlik Zübeyde Hanım Eğitim Araştırma Hastanesi Yardımcı Üreme Teknolojileri (ART) Ünitesi' nde tedavi alan zayıf ovaryan yanıtlı 100 infertil hasta katıldı. Grup 1'deki (n=50) hastalara fleksible antagonist protokolü ve grup 2' deki (n=50) hastalara gonadotropin serbestleştirici hormon (GnRH) mikrodoz flare-up protokolü uygulandı. Ekzojen gonadotropin (Gonal F, Serono, İstanbul, Turkey) grup 1' deki (n=50) tüm hastalara menstrüasyonun 2. gününde başlandı ve folikül büyüklüğü 12 mm olunca GnRH antagonist (0,25 mg, Cetrotide; Serono, Cenevre, İsviçre) başlanarak hCG' nin uygulandığı güne kadar devam edildi.

Bulgular: Kulanılan gonadotropin total dozu grup 2' de anlamlı derecede yüksek bulundu (grup 1; 2625 IU ve grup 2; 4050 IU ; p<0,001). Gebelik oranları grup 2' de yüksek ancak istatistiksel olarak anlamlı bulunmadı (grup 1; 25,7% ve grup 2; 33,3% p=0,501).

Sonuç: Zayıf ovaryan yanıtlı hastalarda ART siklus tedavilerinde henüz standart protokol bulunamamıştır. GnRH antagonist ve mikrodoz flare-up protokolleri, zayıf ovaryan yanıtlı olup intrastoplazmik sperm enjeksiyonu (ICSI) tedavisi alan hastalarda, kullanılan gonadotropin toplam dozları haricinde benzer sonuçlar içermektedir. İleride, zayıf ovaryan yanıtlı hastalarda bu iki protokolün etkinliğini göstermek için geniş prospektif randomize çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Zayıf ovaryan rezerv, Mikrodoz flare up, Antagonist, İnvitro fertilizasyon

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Introduction

Some of variables including woman's age and ovarian reserve, embryo quality, endometrial receptivity and embryo transfer (ET) technique influences either positively or negatively pregnancy rates (PRs) in in vitro fertilization (IVF) [1-3]. Ovarian reserve is one of the most important prognostic factors to predict probability of pregnancy in IVF cycles. Poor ovarian response is associated with high cycle cancellation rate and diminishes pregnancy rates. Therefore, the management of women who demonstrates an inadequate response to controlled ovarian hyperstimulation (COH) is a challenge to treat with IVF.

There is still no consensus on the optimum COH protocol in poor responders. Several approaches have been used to manage patients who poorly respond to COH for increasing ovarian response, maximizing pregnancy rate and minimizing cancellation rate [4,5]. The microdose agonist gonadotropin releasing hormone (GnRH-a) flare-up and gonadotropin releasing hormone (GnRH) antagonist protocols are two of commonly used protocols for poor responders to improve ovarian response and clinical outcomes. The microdose agonist (GnRH-a) flare-up protocol is to stimulates follicular recruitment by the initial rise of endogenous gonadotropins in the early follicular phase and to enhances ovarian response to the subsequent administration of exogenous gonadotropins. GnRH antagonist protocols are also to reduce suppression in the early follicular phase and to potentially improve follicular recruitment and ovarian response.

Previous studies have shown that GnRH antagonist or agonist flare-up protocols might be better than the standard long protocol in these patients [6]. The aim of this prospective, randomized-controlled study was to compare the effects of gonadotropin-releasing hormone antagonist and agonist microdose flare-up protocols on cycle outcomes and pregnancy rates in poor responder patients.

Materials and methods

Participants

A hundred consecutive infertile women, defined as poor responder, were recruited to this study. It was conducted at the assisted reproductive technology (ART) unit of the Ankara Etlik Zubeyde Hanim Women's Health Teaching and Research Hospital during the period of September 2009 to September 2011. The study protocol was approved by the institutional local ethics committee and Institutional Education and Planning Committee. An informed consent was obtained from all patients. The definition of poor responders included at least one of the following: (1) a poor ovarian response in a previous stimulation protocol (<4 oocytes retrieved), (2) a prior cancelled stimulation cycle, (3) basal follicular stimulating hormone (FSH) level >10 IU/L, (4) age >38 years, (5) basal antral follicle count <6. Data were collected for cancellation rate, peak estradiol (E2) level, total dosage of FSH administered, the number of total and mature oocytes retrieved, no of pronucleus (2PN), duration of stimulation, cycle days, quality of oocytes, quality of embryos and pregnancy rate.

The sample size of the study was calculated with the G-power statistical packages. The required sample size for 95% power α=0.05 type 1 error, β=0.05 type 2 error and d=0.80, effect size was calculated as 84. To protect the study from potential loss to follow-ups, study was considered to be completed with a sample size 100.

Treatment protocols:

Patients were randomly divided into two groups. Random allocation was performed by using Random Allocation Software (Ver. 1.0.0 © Mahmood Saghaei, Isfahan University of Medical Sciences, Isfahan, Iran). All patients in Group 1 were treated by using flexible GNRH antagonist protocol and in Group 2 were treated by using GNRH microdose flare-up protocol. Exogenous gonadotropins (Gonal F, Serono, Istanbul, Turkey) was initiated on the second day of menstruation in all patients in Group 1(n=50) and GnRH antagonist (0.25 mg, Cetrotide; Serono, Geneva, Switzerland) was started when the leading follicle reached 12 mm in mean diameter and was continued until the day of human chorionic gonadotropin (hCG) administration. In all patients in group 2 (n=50) GnRH agonist (Lucrin; Abbott, Cedex, France) was started on the third day of menstruation twice daily 40 µg SC after a 21-day course of an oral contraceptive (Desolette; Organon, Istanbul, Turkey: 0.03 mg of ethinyl E2 and 0.15 mg of desogestrel). Exogenous gonadotropins (Gonal F, Serono, Istanbul, Turkey) was initiated on the fourth day of menstruation. Both of them were continued until the day of hCG administration. The starting doses of gonadotropin (range between 150 and 450 IU) was dependent on age of women, baseline serum FSH and E2 levels, body mass index and ovarian response to previous cycle (if present), with individual adjustments performed based on ovarian response via serial transvaginal scanning. Ovarian response was monitored with serum E2 measurements and transvaginal ultrasound. Cycle cancellation was recommended when not suitable endometrium for implantation, fertilization failure, no oocyte received and degenerated oosit. hCG was administered when the mean diameter of leading follicles reached ≥18 mm. Transvaginal ultrasound-guided oocyte retrieval was performed 36 hours after hCG administration. Clinical pregnancy was defined by the presence of a gestational sac or a fetus with cardiac activity on ultrasound examination.

Oocyte quality assessments

Retrieved oocytes were denuded by 80 IU/ml hyaluronidase (Vitrolife, Sweden) enzyme, and the morphology of oocytes at the time of intracytoplasmic sperm injection (ICSI) was evaluated under an inverted microscope with Hoffman modulation at 4006 magnification (Olympus IX71, Olympus Co, Japan). Morphology assessment was performed based on the previously suggested morphological features [7-9]. Basically, abnormal features were grouped as extracytoplasmic, including fragmented first polar body, abnormal first polar body, large perivitelline space, abnormal zona pellucida and abnormal oocyte shape; and cytoplasmic, including vacuoles, granularity, refractile body and brown oocytes. Morphologically evaluated oocytes were scored from best to worst as Score 7; MII oocytes with no abnormal feature, Score 6; MII oocytes with one abnormal feature, Score 5; MII oocytes with more than one abnormality, Score 4; MI oocytes with no abnormal feature, Score 3; MI oocytes with one abnormal feature, Score 2; MI

oocytes with more than one abnormality and finally Score 1 for GV with any abnormality.

Embryo quality

Inseminated oocytes were cultured in an appropriate culture medium (G5 series, Vitrolife, Sweden), and the embryo development was evaluated every day. In this study, it was focused on the scores of cleaved and blastocyst stage embryos. The embryo evaluations for

cleavage stage were performed 40–45 (day 2) and 65–70 (day 3) hours later after ICSI and scored from best (5) to worst (1) based on the previously reported embryo evaluation criteria including, the number and equality of blastomeres, the percentage of fragmentation and the existence of multinucleus [9]. On day 5, blastocyst stage embryos were scored from best (5) to worst (1) subjecting the expansion of blastocyst, the structure of inner cell mass and trophoectoderm [10].

Implantation rate was defined as the ratio of number of implanted embryos to the number of embryos transferred. Clinical pregnancy was defined as a positive intrauterine gestational sac with fetal heart beat visible by ultrasound, and ongoing pregnancy was defined as pregnancy continuing beyond 28 weeks' gestation.

Statistical Analysis

All statistical analyses were performed using SPSS for Win. Ver. 15.0 (SPSS Inc. Chicago, IL, USA). Student's t test or Mann Whitney U test was used to compare the continuous variables and the chi-square test or Fisher's exact test was used to compare categorical variables. P<0.05 was considered statistically significant.

Results

Demographic characteristics of all patients were similar between the two groups (Table 1). The clinical and laboratory outcomes related to COH are as shown in Table 1. The median age of women participating in this study was 38. Cycle cancellation rate was higher in Group 1 (2 (4%) vs 1 (2%)) than group 2 due to an impaired ovarian response. Total dosage of gonadotropins was significantly higher in group 2 (2625 IU in group 1 vs 4050 IU in group 2; p<0.001). There were no significant differences peak E2 levels, the mean number of total oocytes and mature oocytes retrieved, no of 2PN, duration of stimulations, cycle days, quality of oocytes and embryos between groups (Table 1). Thirty-five in Group 1 (72.9%) and 30 (61.2%) patients in group 2 underwent embryo transfer procedure. 13 cycles in Group 1 (one patient owing to not suitable endometrium for implantation, 9 to total fertilization failure, 3 to no oocyte retrieved) and 19 cycles in Group 2 (fifteen patients owing to total fertilization failure, 3 to no oocyte retrieved, one to degenerated oocyte) did not reach ET (Table 2).

The pregnancy rate was higher in group 2 but it was not statistically significant (25.7% in group 1 vs 33.3% in group 2; p=0.501) (Figure 1). No significant differences were observed in pregnancy parameters including 'live birth'', 'ongoing pregnancy', ''abortion'' and ''biochemical pregnancy'' (p=0.497).

Four in group 1 (44.4%) and four pregnant patients in group 2 (40%) had biochemical pregnancies and one of all pregnant patients developed abortion (in group 1, 11.1%). Furthermore two in group 1 (22.2%) and four (40%) pregnant patients in group 2 gave healthy birth and four of all pregnant patients (two patients in group 1 (22.2%), two patients in group 2 (20%)) had ongoing pregnancy when this study stopped (Figure 2). The successful pregnancies were named ''healthy birth'' and "ongoing pregnancy". Likewise the unsuccessful pregnancies were named "abortion" and "biochemical pregnancy". As a result, the successful pregnancies in group 2 were higher than group 1 but it was not statistically significant (χ^2 = 0.461; p=0.497).

Table 1: Cycle characteristics

Characteristic	Group 1	Group 2	P value
Cancellation rate	2 (4%)	1 (2%)	NS
Peak E2 level (pg/ml)	1092.0 (IQR:956.8)	983.0 (IQR:1776.5)	0.513
Total dosage of gonadotropins	2625 (IQR: 1200)	4050 (IQR: 1200)	<0.001*
No. of oocytes retrieved	6.5 (IQR:6.0)	5.0 (IQR:7.0)	0.093
No. of mature oocytes	4.5 (IQR:5.8)	3.0 (IQR:4.3)	0.194
No. of 2PN	2.0 (IQR:3.8)	1.0 (IQR:3.0)	0.079
Duration of stimulations	8(IQR: 3.0)	10 (IQR: 3.0)	0.354
Cycle days	9.0 (IQR:2.8)	11.0 (IQR:3.0)	0.816
Oocyte quality index	5.7 (IQR:0.8)	5.2 (IQR:1.2)	0.097
Day 2 embryo quality	4.6 (IQR:1.0)	4.5 (IQR:1.0)	0.984
Day 3 embryo quality	3.9 (IQR:1.3)	4.2 (IQR:1.5)	0.247
Day 5 embryo quality	2.3 (IQR:1.5)	2.1 (IQR:1.1)	0.637

*P<0.05 is considered statistically significant difference, comparison of all groups, NS: not specified

Table 2: Number of embryo transfer and causes of unachievable embryo transfer *

Transfer and causes unachievable ET	Grup I		Grup II		Total	
	n	%	n	%	n	%
ET, successful	35	72.9	30	61.2	65	67.0
Unachievable ET, endometrium is thin on the day of transfer	1	2.1	0	0.0	1	1.0
Unachievable ET, Total Fertilization Failure (TFF)	9	18.8	15	30.6	24	24.7
Unachievable ET, no oocyte	3	6.3	3	6.1	6	6.2
Unachievable ET, degenerate oocyte	0	0.0	1	2.0	1	1.0
Total	48	100.0	49	100.0	97	100.0

ET: embryo transfer, *: The numbers indicate the women who were successful or unachievable on ET

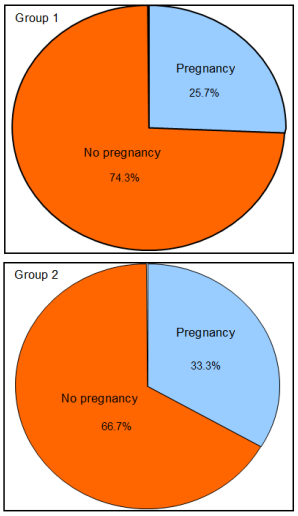

Figure 1: Group 1 and group 2 pregnancy rates after transfer

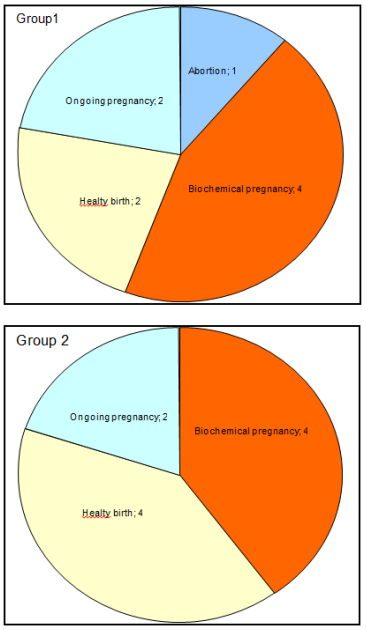

Figure 2: Group 1 and group 2 results of pregnancy

Discussion

There is no consensus on the best standard treatment option for ART cycles of poor responders. But the best stimulation protocol for the poor responder patients must be associated with the acceptable rate of minimum cancellation rate, maximum number of good quality oocyte retrieved and maximum chance of pregnancy [11]. As many stimulation protocols have been suggested for the poor responder patients,

microdose flare-up and antagonist protocols are the most popular regimes [12].

Although there is a trend toward higher pregnancy rates and lower cancellation rates in microdose GnRH-a flare-up protocol, we found that microdose GnRH-a flare-up protocol has similar IVF outcomes with flexible GnRH antagonist protocol. Moreover, maximum E2 level, total and mature oocyte number, no of 2PN were less but total dosage of gonadotropins, duration of stimulations, cycle days were higher in microdose GnRH-a microdose flare-up protocol despite that there was no significant statistical difference between two groups in terms of these parameters. In our study a clear difference was not found in both groups in terms of embryo oocyte quality on 2^{nd}, 3^{rd} and 5^{th} days. Our single center randomized prospective trial confirmed no significant differences with regards to any outcome parameters except consumption of gonadotropins. Increasing total dosage of gonadotropins, it would be considered as a disadvantage in terms of cost. Furthermore, some advantages of the present study need to be pointed currently; (1) comparable demographic features of both groups to prevent potential bias (2) adequate sample size for the power of the study.

In 1994, Scoot and Navod [13], firstly defined microdose flare-up protocol (20 μg of leuprolide acetate twice daily) for poor responders, indicated that microdose flare-up protocol improved IVF outcomes when compared with GnRH agonist protocol. They reported that it decreased cycle cancellation rate, increased peak E2 level, total number of oocyte retrieved, implantation and clinical pregnancy rates. Surrey et al. [14] assessed the effects of the microdose agonist protocol (40 μg of leuprolide acetate twice daily) in poor responders and also showed that microdose GnRH-a improves ovarian response and clinical outcome in poor responders due to enhanced release of early follicular phase endogenous FSH. Consequently, some of studies demonstrated that the microdose agonist protocol was proven to increase total mature oocyst number and maximum E2 level and decreased cancellation rates and increased both clinical and ongoing pregnancy rates in poor responders. Therefore, it was well-demonstrated that microdose flare-up protocols an important approach to improved IVF outcomes for poor responders.

GnRH antagonists for the management of poor ovarian responders have recently been an encouraging protocol and gradually gained favor [15]. A recent review evaluated role of GnRH antagonists in the treatment of poor-responder patients indicates that GnRH antagonists may offer several advantages, including a shorter duration of stimulation, a decrease in the total amount of gonadotropins, lower cost, and a shorter interval between successive treatment cycles [16]. As a meta-analysis reported that there was no difference in clinical pregnancy rates between antagonist protocol and agonist protocol in the poor responder patients [17].

In a prospective, randomized, clinical study, included 42 poor responder patients, Kahraman et al. [12] compared the efficacy of microdose GnRH agonist (GnRH-a) flare-up and multiple dose GnRH antagonist protocols and they concluded that microdose GnRH-a flare-up protocol and multiple dose GnRH antagonist protocol seem to have similar efficacy in improving treatment outcomes of poor responder patients although E2 levels of microdose GnRH agonist (GnRH-a) flare-up were higher. As well, a prospective, randomized, clinical study compared microdose GnRH agonist (GnRH-a) flare-up and multiple dose GnRH antagonist protocols demonstrated that the impact of these two regimens in ovarian stimulation of poor responders seem to be similar despite that maximum serum E2 level and number of total oocyte retrieved were higher in microdose GnRH agonist (GnRH-a) flare-up protocol [18]. In a study which compared GnRH antagonist protocol with GnRH agonist flare-up protocol in poor responders, Berin at al. [19] found excellent and comparable pregnancy and live birth rates in poor responders of advanced reproductive age with the use of either GnRH antagonist or flare protocol.

Poor ovarian response is also associated with very nominal and low quality oocyst and embryo. Some studies reported that there are similar results in terms of 2PN between micro dose flare up and antagonist protocols in poor responders [20-22]. With the effort of bettering the choice of embryos which bring about successful pregnancies and their usage, the researchers benefited from the advantages of extending the in vitro culture span before the embryo transfer. In vıtro culture span brings about usage of embryos and chooses them even after 5 days after embryo formation. While some researchers recommend the extension of culture span until 5 days, the others recommend doing the transfer in 3^{rd} day if embryos including more than 3 or 8 cells in vitro culture were determined [3,23,24].

In conclusion, GnRH antagonist and microdose flare-up protocols seem to have similar outcomes in poor responder patients in ICSI cycles except consumption of gonadotropins. Further prospective randomized trials with large sample size are needed to assess the efficacy of the two protocols in the poor responders.

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Assessment of patients presented to the emergency department with dermatological complaints: Retrospective cohort study

Dermatolojik yakınma ile acil servise başvuran hastaların değerlendirilmesi: Retrospektif kohort çalışma

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Abstract

Aim: Although dermatology is an area of expertise based largely on outpatient treatment, about 5-10% of emergency department patients are dermatological diseases. In this study, it was aimed to draw attention to management of dermatologic diseases which are frequently encountered in emergency services.

Methods: Over 18 years old 96 patients who presented with a dermatologic problem to the emergency department of Kahramanmaras Sutcu Imam University Hospital between January and June 2018 were evaluated.

Results: The mean age of the patients was 43.9 ± 17.1 years. When the gender distribution was examined, 39.6% (n=38) of the cases were male and 60.4% (n=58) were female. Pruritus and rash were the most common dermatological complaints and the most common diagnoses were urticaria (38.5%), urticaria-angioedema (13.5%), cellulitis (8.3%) and anaphylaxis (8.3%) in this study. The rate of cases without known dermatological disease was 77.1%. In 52 (54.2%) cases, there was a new drug use which may be associated with the current dermatosis, and antibiotics (22.9%) were the most frequently detected from these drugs.

Conclusion: It was seen that most of the patients who admitted with a dermatological problem had no known dermatological disease, and some adult patients with chronic dermatosis might apply to emergency services. It has been determined that not all cases are real dermatologic emergencies and most of them are relieved and discharged by intervention made at the emergency department without need of examination. The presence of a new drug use in about half of the cases revealed that drugs are an important etiologic factor in emergency dermatological diseases.

Keywords: Emergency department, Dermatological emergency, Urticaria, Drug-related rash

Öz

Amaç: Dermatoloji, büyük ölçüde ayakta tedaviye dayalı bir uzmanlık olmasına rağmen, acil servis hastalarının %5-10 kadarını dermatolojik hastalıklar oluşturmaktadır. Bu çalışmada acil serviste sık karşılaşılan dermatolojik hastalıkların yönetimine dikkat çekilmesi amaçlanmıştır.

Yöntemler: Dermatolojik bir yakınma ile Ocak ve Haziran 2018 tarihleri arasında Kahramanmaraş Sütçü İmam Üniversitesi Hastanesi acil servisine başvuran 18 yaşından büyük 96 hasta değerlendirildi.

Bulgular: Hastaların yaş ortalaması 43,9±17,1 yıl idi. %39,6'sı (n=38) erkek, %60,4'ü (n=58) kadın cinsiyette idi. En sık başvuru şikayeti kaşıntı ve kızarıklık, en sık tespit edilen tanılar ise ürtiker (%38,5), ürtiker-anjioödem (%13,5), selülit (%8,3) ve anafilaksi (%8,3) idi. Olguların %77,1'inin (n=74) bilinen dermatolojik hastalığı yoktu. Olguların %54,2'sinde (n=52) mevcut dermatoz ile ilişkisi olabilecek yeni bir ilaç kullanımı vardı ve bu ilaçlardan en sık tespit edileni antibiyotikler (%22,9) idi.

Sonuç: Dermatolojik bir problemle acile başvuran hastaların çoğunun bilinen bir dermatolojik hastalığı yokken, bazı kronik dermatozlu erişkin hastaların acil servise başvurabildiği gözlendi. Olguların tamamının gerçek dermatolojik acil olmadığı ve çoğunun tetkik ihtiyacı duyulmaksızın acil serviste yapılan müdahale ile rahatlatılıp taburcu edildiği tespit edildi. Olguların yaklaşık yarısında yeni bir ilaç kullanma öyküsünün varlığı ilaçların acil dermatolojik hastalıklarda önemli bir etiyolojik faktör olduğunu ortaya koymuştur.

Anahtar kelimeler: Acil servis, Dermatolojik acil, Ürtiker, İlaç ilişkili döküntü

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Introduction

Dermatology is an area of expertise based largely on outpatient treatment. Nevertheless, apply to the emergency department with a dermatologic problem is not uncommon [1]. Skin diseases that require urgent intervention may be caused directly by skin or by a systemic disease or external factors [2]. Due to the broad spectrum of skin diseases and various clinical findings, it presents a diagnostic challenge for emergency physicians [3]. In the literature, diseases such as toxic epidermal necrolysis, staphylococcal scalded skin syndrome, toxic shock syndrome, pustular psoriasis, erythroderma and angioedema have been defined as dermatological emergencies [4]. However, in the studies evaluating patients presenting to the emergency room with dermatological complaints, it was observed that not all patients had actual dermatological emergencies [2,5]. In this study, we aimed to draw attention to the management of frequently encountered dermatological diseases in emergency department by investigating the demographic and clinical data of emergency patients.

Materials and methods

This is a retrospective cohort study based on observation. The demographic characteristics, the complaint of the applicant, the duration of the complaint, the presence of a known systemic or dermatological disease, the history of a new drug use in the last 20 days, the type of medication used, the need for consultation, the type of emergency treatment, and the patient's latest condition were recorded. Children, trauma patients, and adult patients with dermatological problems who presented to the emergency room for another reason as a primary cause were excluded from the study.

The study was approved by the local ethics committee (decision date: 17.01.18, decision no: 2, session: 2018/02). Over 18 years old 96 patients who presented with a dermatologic problem to the emergency department of Kahramanmaras Sutcu Imam University Hospital between January and June 2018 were evaluated. The research was performed in agreement with the Helsinki Declaration. The patients were informed about the study and a voluntary consent form was filled out.

Statistical analysis

The SPSS v.17.0 package program was used for the statistical evaluation of the data obtained in the study. (SPSS Inc, Chicago, Illinois, USA). Continuous data were summarized as mean, standard deviation, while categorical data were summarized as number and percentage.

Results

The mean age of the patients was 43.9 ± 17.1 (min-max:18-80) years. 39.6% (n=38) were male and 60.4% (n=58) were female. Pruritus and rash were the most common dermatological complaints of 63 (65.6%) patients. When 4 patients with diabetic foot were excluded, the mean interval between the onset of complaint and emergency service admission was 39.8 ± 59.4 hours, ranging from 15 minutes to 1 week. Diseases with the shortest duration were anaphylaxis (2.1 ± 3.2 hours), urticaria-angioedema (5.2 ± 6.9 hours) and insect sting (11.4 ± 20.5 hours), respectively. When patients' comorbidities were questioned, 10 (10.4%) had hypertension, 8 (8.3%) had diabetes with hypertension, 7 (7.3%) had diabetes, and 5 (5.2%) had thyroid gland disease. In 5 (5.2%) cases pregnancy was present. Concomitant dermatological diseases were chronic urticaria in 15 (15.6%), eczema in 5 (5.2%) and psoriasis in 2 (2.1%) cases, while 77.1% of the cases (n=74) had no known dermatologic disease. In 54.2% of cases (n=52) there was a new drug use that could be related to the existing dermatosis. The most common drugs in the etiology were antibiotic (22.9%), nonsteroidal anti-inflammatory drug (11.5%), myorelaxan (7.3%), antiaggregant (2.1%) and iron (2.1%). Dermatology consultation was needed in 4.2% (n=4), while 21.9% (n=21) of the cases required examination for diagnosis or treatment management. The distribution according to the patients' diagnoses is given in Table 1. The most common diagnoses were urticaria (38.5%), urticaria-angioedema (13.5%), cellulitis (8.3%) and anaphylaxis (8.3%) in this study. The etiology of the diseases is considered to be drug use in 46.9% of the cases (n=45), stress in 12.5% of the cases (n=12), infection in 10.4% of the cases (n=10) and autoimmunity in 10.4% of the cases (n=10). 8.3% of the dermatoses were bacterial, 3.1% were associated with viral infection. Assessments regarding the final status of the patients showed that 80.2% of the patients' treatment was completed in emergency service and the patients were discharged, 6.2% of the patients were referred to dermatology clinic, 4.2% to intensive care and 9.4% to other clinics. Topical treatment was applied to 11.5% (n=11) of the cases and 79.2% (n=76) of the cases received systemic treatment while in 9.4% (n=9) of the cases emergency intervention was not made.

Table 1: Distribution of the diagnoses of the patients referred to the emergency department by dermatological complaint

Diagnosis	Frequency n (%)
Urticaria	37 (38.5)
Urticaria-angioedema	13 (13.5)
Cellulitis	8 (8.3)
Anaphylaxis	8 (8.3)
Pruritus	6 (6.2)
Maculopapular drug eruption	5 (5.2)
Insect bite	5 (5.2)
Ecchymosis	5 (5.2)
Diabetic foot	4 (4.2)
Eczema	3 (3.1)
Zoster	2 (2.1)

Discussion

Some dermatologic diseases may require emergency units serving throughout the day. It is estimated that dermatological complaints constitute 5-10% of all visits to emergency services [6]. Frequently identified dermatoses in studies have changed in relation to population differences, climatic and seasonal differences. In a retrospective study in Northern Cyprus, approximately 2% of emergency patients were found to have dermatologic problems and the most common disease was observed as urticaria. In addition, insect bites have been reported to be frequently detected in this study, as opposed to the literature, and this has been linked to the fact that the region has a subtropical climate [7]. In this study, the most common causes of admission to the emergency department were itching and redness, and the most common diseases were urticaria, urticaria-angioedema, anaphylaxis and cellulitis. In a study also involving pediatric cases in Singapore, eczema, urticaria, nail trauma and infections and drug eruption were

detected less frequently and at similar rates while the most frequent complications were varicella and herpes zoster. Venereal diseases were observed in 1% of cases and were reported to be rare [8]. In a study made in the summer months in Tahran, infection-associated dermatoses have been reported in 41.9% of cases [5]. In this study, the rate of infection-related dermatoses was 11.4%. We think that this low ratio is related to the fact that the study was done in the winter and spring seasons.

In a study conducted in the United States, dermatological problems and non-dermatological reasons of emergency patients were demographically compared. It has been reported that patients who present to emergency services with dermatological problems tend to be between the ages of 18-54, male and person with low-income [9]. In another study conducted in our country, the mean age of the patients with dermatological complaints was 41.7 and the female sex ratio was 56.2% [2]. Similar to the data of our country, the mean age of the patients in this study was 43.9 and the majority was female.

An immediate treatment may be required with toxic epidermal necrolysis, autoimmune bullous diseases such as pemphigus vulgaris, erythroderma, pyoderma such as cellulitis and erysipelas and with dermatological diseases such as angioedema and generalized urticaria. Nevertheless, it has been reported that a large proportion of presentations to emergency services cannot be considered a real dermatologic emergency [5]. In this study, it was observed that presentations to the emergency department were done with diseases, which are not dermatologic emergency cases such as nonspecific pruritus, ecchymosis or diabetic foot. In this study, the proportion of other diagnoses was 31.3% when urticaria, angioedema, anaphylaxis and cellulitis were excluded. The percentage of true dermatologic non-emergency cases in emergency departments was 49% in a study conducted in Spain and 82% in a study conducted in the United States [10,11]. In this study, the reason that the real dermatologic non-emergency conditions are detected at lower rates may be related to the easier access to the outpatient clinic service in our country.

In a study evaluating emergency department presentations due to adverse drug reactions, anticoagulants, antibiotics and non-steroidal anti-inflammatory drugs were reported to be determined most frequently and the most common adverse reactions to these drugs were gastrointestinal bleeding and skin rash [12]. In a study investigating the causes of anaphylaxis in all age groups, in 20% of the cases the drug was held responsible for etiology. Non-steroidal anti-inflammatory drugs were the most frequently used drugs [13]. In this study, the etiology of dermatoses with skin rash was investigated and it was seen in the history of patients that the use of antibiotics was significantly higher. This may be related to the fact that patients and physicians in our country have a high tendency to use antibiotics.

While inspection is often sufficient for the diagnosis of dermatological diseases, it may be necessary to perform an examination because it is important for diagnostic purposes or for the management of the treatment. In a study conducted in Spain, it was reported that 4 of 5 patients with urgent dermatologic complaints did not require examination [10]. The result obtained in this study is similar to literature.

In a study evaluating patients who presented to the emergency department with dermatologic problems, two most common disease groups were infectious skin diseases and eczema diseases. In the study, 64.2% of the cases were treated locally and 22.6% were treated systemically [14]. In this study, systemic treatment was applied to the majority of cases in accordance with the treatment regimens required for frequently diagnosed diseases.

Examining the rate of admission to the hospital in literature, it was seen that the rate of hospitalization due to dermatological problems changed according to the characteristics of the applied hospital [2]. In a study conducted by Wallet et al. [1] in Australia, the management of patients who applied to emergency services for skin disease was researched and it was reported that 18% of patients were admitted to the hospital. In this study, similar to literature, the admission rate was 19.8%.

Limitations of the study were that the pediatric patients were not included in the study and the number of cases in the study group was relatively low compared to the retrospective studies in literature.

Conclusion

As a result of this study, it was seen that in most of the patients, there was no known dermatological disease, and that some adult patients with chronic dermatosis might apply for emergency services. It has been determined that not all cases are real dermatologic emergencies and most of them are relieved and discharged by intervention made at the emergency department without need of examination. It was concluded that the characteristics of the present hospital, characteristics of the patient population and the season in which the patients are have an impact on dermatologic diseases in the emergency departments. This study provided information about the etiology of diseases. It has revealed the importance of keeping it in mind for rash illnesses that about half of the cases had a history of using a new drug and that drugs are an important etiological factor in urticaria, urticaria-angioedema, anaphylaxis and maculopapular eruptions.

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Effects of thiopental in cold ischemia in liver transplantation: An experimental study

Karaciğer transplantasyonunda tiyopental'in soğuk iskemi üzerine etkileri: Deneysel bir çalışma

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Abstract

Aim: The aim of this study is to use the reducing effect of thiopental on metabolic rate to reduce basal metabolic rate and thus energy requirements in organs with doses administered before organ transplantation and in this way to increase organ viability by reducing to a minimum tissue damage occurring during the cold ischemia process.

Methods: The study was started with 20 Wistar albino rats in 2 groups. In Group 1 (Control=Ketamine-Xylazine group) and Group 2 (Thiopental group), rats had a midline incision made after shaving the abdominal region under anesthesia with appropriate agents. The portal vein was entered with a cannula and organ storage solution at +4 °C was injected to the portal vein to perfuse the liver. Then hepatectomy was performed, the livers were placed in Falcon tubes containing +4°C organ storage solution and stored at +4°C. Tissue samples were taken for histopathologic and TUNEL investigation and storage solution samples were taken for biochemical analysis at 12th hour.

Results: In histopathologic evaluation, the mean for hydropic degeneration and sinusoidal dilatation was higher in Group 1 compared to Group 2, but the results weren't statistically significant. Apoptotic Index (AI) values in Group 1 were higher than Group 2; however, there was no statistically significant difference between the median values (3.50 (Min:1.00-Max:16.00) vs. 2.50 (Min:1.00-Max:20.00), respectively p=0.974). The mean values for ALT, AST and ALP were appeared to be higher in Group 1.

Conclusion: In conclusion, thiopental has a protective effect on liver tissue during the cold ischemia process via reducing the mean values of histopathological, apoptotic and biochemical assessment results, but these findings weren't statistically significant.

Keywords: Thiopental, Cold ischemia, Liver transplantation, TUNEL, Histopathology

Öz

Amaç: Bu çalışmanın amacı; tiyopentalin metabolizma hızını azaltıcı etkisinden faydalanarak, organ nakli öncesi uygulanacak olan dozlar ile, nakledilecek organın bazal metabolizma hızını düşürerek enerji ihtiyacını azaltmak ve bu sayede soğuk iskemi sürecinde meydana gelebilecek doku hasarını en aza indirerek organların viabilitesini artırmaktır.

Yöntemler: Çalışmada kullanılan 20 adet Wistar Albino cinsi sıçan iki gruba ayrılmıştır. Grup 1 (Kontrol=Ketamin-Ksilazin grubu) ve Grup 2 (Tiyopental grubu)'deki sıçanlara, kendi grupları için uygun olan ajanlarla anestezi uygulandıktan sonra karın derisi traşlanıp orta hat insizyonu yapıldı. Portal vene bir kanül ile girilerek +4 °C'deki organ saklama sıvısı enjekte edildi. Böylece karaciğer perfüzyonu sağlandı. Ardından hepatektomi yapılarak karaciğerler, içerisinde +4°C'de organ saklama sıvısı bulunan Falkon tüplere konuldu ve yine +4°C'de saklandı. 12 saat saklama süresinin sonunda histopatolojik ve TUNEL değerlendirmeler için doku örnekleri alınırken, saklama sıvısından da biyokimyasal analizler için numune alındı.

Bulgular: Histopatolojik değerlendirme sonucunda, hidropik dejenerasyon ve sinusoidal dilatasyon ortalamaları grup 1'de Grup 2'ye kıyasla yüksek bulundu ancak sonuçlar istatistiksel olarak anlamlı değildi. Apoptotik indeks (AI) değerleri Grup 1'de Grup 2'ye kıyasla yüksekti ancak ortanca değerlerinde istatistiksel olarak anlamlı bir farklılık bulunmadı(sırasıyla 3.50 (Min:1.00-Max:16.00) vs. 2.50 (Min:1.00-Max:20.00) p=0.974). Biyokimyasal ALT, AST ve ALP ortalama değerleri de Grup 1'de yüksek bulundu.

Sonuç: Sonuç olarak, tiyopentalin, soğuk iskemi sürecinde karaciğer dokusu üzerine koruyucu bir etkisi olduğu ve bu etkiyi histopatolojik, apopitotik ve biyokimyasal değerlendirme sonuçlarının ortalama değerlerini azaltmak yoluyla gerçekleştirdiği görülmüştür, ancak bu bulgular istatistiksel olarak anlamlı bulunamamıştır.

Anahtar kelimeler: Tiyopental, Soğuk iskemi, Karaciğer nakli, TUNEL, Histopatoloji

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Introduction

Liver transplantation (LT) is a life-saving treatment method for patients with end-stage liver failure [1]. The first successful LT in humans was performed in 1963 by Dr. Starzl [2]. Developments in surgical methods, in immunosuppressive medications and liver donor protection methods have advanced the topic of LT. Though there can be both deceased donors and live donor liver providers, the number of organs remain insufficient due to the increased number of patients with liver failure. Additionally, it is very important to ensure transplantation of the organ within the appropriate duration for successful transplantations. This requires developing methods of organ preservation and preserving the viability of the organ for long durations [2].

Timely transplantation of organs is one of the most important factors determining success after surgery. The duration from the time the organ is obtained to transplantation into the organ receiver is cold ischemia duration. During the cold ischemia duration, organs are left at temperatures of +1 to +4°C in standard preservation solutions [3]. During the process, hypooxygenation and hypothermia of the tissues is observed. In hypooxygenation situations, cells do not complete oxidative energy production and attempt to produce energy by oxygen-free pathways. In normal conditions the Na^+/K^+ ATPase (adenosine triphosphatase) pump using high amounts of adenosine triphosphate (ATP) is disrupted as the amount of ATP reduces and causes intracellular K^+ loss and Na^+ increases. This situation causes the cells to swell [3,4]. Hypooxygenation affects the intracellular distribution of Ca^{+2} ions. This causes disruption of enzyme activities and of the integrity of the cell membrane [5]. Additionally, the glycolysis process begins and high rates of lactate synthesis are observed accompanied by acidosis [3]. During ischemia, ATP transforms to adenosine diphosphate (ADP) and adenosine monophosphate (AMP) transforms to adenosine and progressively differentiates to reduce to adenine, inosine and hypoxanthine. Hypoxanthine accumulation catalyzes the xanthine transformation and activates xanthine oxidation. This reaction is accompanied by the production of free oxygen radicals causing injury within the cell [6].

Damage occurs to the organ for transplantation linked to these effects explained by hypooxygenation. Hypothermia slows metabolism and reduces the enzyme activities and requirements of cells. In this way, cell death is slowed; however, again energy requirements are higher than the amount of energy produced by glycolysis and oxygen-free pathways [7].

There are a variety of solutions used for organ preservation. The most common of these include University of Wisconsin (UW) solution, histidine-tryptophan-ketoglutarate (HTK), Celsior (CS), Institut Georges Lopez (IGL-1) Collins, Euro-collins, UW-PEG, Polysol, Kyoto, New Kyoto etc. [8,9].

These solutions were developed based on the principle of organ preservation by balancing the basic metabolic requirements in the process after the organ is removed. However, in spite of this, they can only preserve the viability of the organ taken from the donor for limited periods and the search for new methods to slow organ preservation and metabolism and ensure viability for long periods continues [10-19].

Thiopental is a barbituric acid sodium salt and one of the most commonly used intravenous anesthetics. Its effects are due to suppression of the reticular activating system (RAS) controlling consciousness and vital functions. The fat solubility of thiopental is excessive. As a result, the duration of effect is not related to metabolism and elimination but to redistribution. Rates of 80% of thiopental bind to plasma proteins. Due to the solubility in fat and 60% non-ionizing fraction, it reaches high concentration in the brain within 30 seconds. The elimination half-life is 3-12 hours. Thiopental transforms to water soluble inactive metabolites in the liver and metabolites are eliminated by the renal extraction [20,21].

At high anesthetic doses, thiopental reduces oxygen consumption in the brain and significantly lowers the brain's metabolic rate. The reduction in brain metabolic rate causes a reduction in the brain's blood flow requirements and this event ensures vasoconstriction of veins in the brain. The reduction in brain blood flow lowers the blood volume and intracranial pressure in the brain. This effect on brain metabolism protects both the injured and perfused healthy regions of the brain. Due to thiopental reducing brain blood flow, increasing perfusion pressure and lowering metabolic rate, it is a very beneficial agent for anesthesia of patients with increased intracranial pressure [22]. Additionally, it is used with the aim of protecting the brain during incomplete ischemia. Here, the effect is ensured by reducing the metabolic rate and lowering energy requirements to a minimum [22].

There is insufficient information in the literature about whether a similar response to this metabolic effect of thiopental in the brain develops in peripheral organs. If a similar effect to the vasoconstriction accompanying slowed brain metabolism occurs in the periphery, vasoconstriction will increase peripheral vascular resistance and reduce blood flow [23]. Slowing metabolism and reducing energy requirements in peripheral organs may be beneficial to ensure long-term preservation during transplantation.

The aim of this study is to use the reducing effect of thiopental on metabolic rate to reduce basal metabolic rate and thus energy requirements in organs for transplant with doses administered before organ transplantation and in this way to increase organ viability by reducing to a minimum tissue damage occurring during the cold ischemia process.

Materials and methods

Materials and experimental design

The study was approved by the Institutional Animal Use and Care Committee of University and performed in accordance with Turkish Law 6343/2, Veterinary Medicine Deontology Regulation 6.7.26, Guide for the Care and Use of Laboratory Animals, and with the Helsinki Declaration of World Medical Association recommendations on animal studies. Wistar albino rats were obtained from Çanakkale Onsekiz Mart University (COMU) Experimental Research Application and Research Center. Twenty female Wistar Albino rats were used in the study, with a mean age of six months and mean weight of 240–300 g. The rats were housed in stainless steel cages in an animal room maintained at a standard humidity (45%-50%) and temperature 22±2°C with 12 hour light periods (12 hours of

daylight/12 hours of dark). All animals were fed standard food and water and twelve hours before the study procedure feeding was stopped and the rats were only allowed to drink water. The entire experiment was conducted under half-sterile conditions.

Experimental procedure

The study was started with 20 Wistar albino rats in 2 groups as below;

Group 1 (Control group, n=10): Anesthetized with Ketamine (50 mg/kg, intraperitoneally) and Xylazine (15 mg/kg, intraperitoneally)

Group 2 (Thiopental group, n=10): Anesthetized with Thiopental Sodium (85 mg/kg intraperitoneally)

Liver perfusion was performed with a method previously described in the literature [10]. Rats in Group 1 had a midline incision made after shaving the abdominal region under 50 mg/kg ketamine hydrochloride (Ketalar®, Pfizer İlaçları Ltd, Şti, İstanbul, Turkey) and 15 mg/kg Xylazine (Alfazyne 2%, Ege Vet San. Tic, İzmir, Turkey) anesthesia. After observing the liver, the portal vein was entered with a cannula and tied distal of the portal pedicle. Organ storage solution (Bel-Gen Cold Storage Solution, Institut Georges Lopez, Lissieu, France, LOT: SL170190) at +4 °C was injected to the portal vein to perfuse the liver. Perfusion continued until clear fluid came from the hepatic vein. Then hepatectomy was performed. After hepatectomy rats were sacrificed with high dose anesthetic. The livers obtained from the hepatectomy procedure were placed in Falcon tubes containing +4°C organ storage solution and stored at +4°C. Tissue samples were taken for histopathologic investigation of perfused liver at 12th hour. Again, for biochemical analysis of storage solution, samples were taken at 12th hour.

Animals in Group 2 had the procedures explained above performed with intraperitoneal 85 mg/kg thiopental sodium (Pental 1 gr flacon, İ. E. Ulagay İlaç Sanayi Türk A.Ş, İstanbul, Turkey) anesthesia. Similar to Group 1, tissue samples were obtained from livers in cold ischemia at 12th hour for histopathologic investigation. Storage solutions were also sampled for biochemical analysis at 12th hour.

Histopathological examinations

To investigate histopathologic changes, liver tissue samples were consecutively numbered and placed in 10% neutral buffered formaline. Evaluation of the pathology specimens were done by a histology specialist who was blind to the two study groups.

After fixation, dehidratation and clearing processes, liver tissues were embedded in paraffin. The paraffin blocks were cut in 5 mm thickness on Rotatory Microtome (Leica RM2125 RTS) and the sections were stained with hematoxylin and eosin (H&E) method. The histopathologic sections were examined under a light microscope (Zeiss AxioScope A1) for the presence of hydropic degeneration, sinusoidal dilatation, and focal necrosis and rated on a semi-quantitative scale of 0-3 as follows;

0: no damage

1: mild damage

2: moderate damage

3: severe damage

Apoptosis assessment with TUNEL (Terminal deoxynucleotidyl transferase dUTP nick end labeling) method

Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining was used to detect apoptosis of the liver tissue. Prepared tissue was fixed with 10% neutral formaline, embedded in paraffin and 4 µm thick sections were cut from each paraffin block. After dewaxing, hydration, and serum blocking, ApopTag Peroxidase in situ Apoptosis Detection Kit (S7100, Merck Millipore, Darmstadt, Germany) was used according to the manufacturer's protocol. In order to determine the apoptotic index (AI), 5 randomly selected regions of the each section was chosen under x400 magnification. Cells, which have nucleuses stained brown, were judged TUNEL-positive apoptotic cells. The AI of hepatocytes was determined as the percentage of TUNEL positive cells with respect to the total number of cells counted using the formula:

Apoptotic index (AI) = (Number of positive cells/Total number of cells counted) x100

Biochemical Evaluation

Samples of 2 ml were taken from the storage solution that the liver tissue of each animal was stored in at 12th hour in biochemistry tubes not containing anticoagulant. The samples had aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels measured with the enzymatic colorimetric method in the Clinical Biochemistry laboratory using a biochemical autoanalyzer.

Statistical analysis

Data were analyzed with the SPSS program version 20.0. For presentation of descriptive data, mean, standard deviation, median, minimum and maximum values were used. The fit of variables to normal distribution according to numbers in the animal groups was investigated with the Shapiro-Wilk test. When sample size and normal distribution tests are investigated, non-parametric tests were chosen for the analysis methods. The chi-square test was used to compare hydropic degeneration, sinusoidal dilatation and focal necrosis degree between the groups. The Mann-Whitney U test was used to compare TUNEL score and biochemical ALT, AST and ALP values between the groups. Situations with $p<0.05$ were accepted as statistically significant.

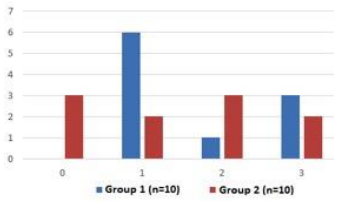
Results

Histopathologically, the hydropic degeneration, sinusoidal dilatation and focal necrosis parameters were assessed in both groups. Accordingly, the mean for hydropic degeneration (Table 1 and Graphic 1) and sinusoidal dilatation (Table 2 and Graphic 2) was higher in Group 1 compared to Group 2, but the results were not statistically significant (p=0.102 and p=0.351, respectively). Histopathologic changes are seen in Figure 1.

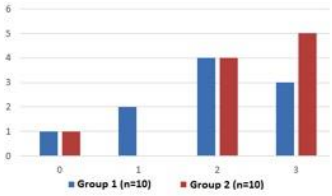
When examined in terms of focal necrosis, 4 subjects in group 1 had different levels of focal necrosis, while only 1 subject in Group 2 had grade 1 focal necrosis (Table 3). Focal necrotic areas can be seen in Figure 2.

AI values in Group 1 were higher than Group 2; however, there was no statistically significant difference between the median values (3.50 (Min:1.00-Max:16.00) vs. 2.50 (Min:1.00-Max:20.00), respectively p=0.974) (Mann-Whitney U Test) (Graphic 3). Apoptotic cells with TUNEL staining can be seen in Figure 3.

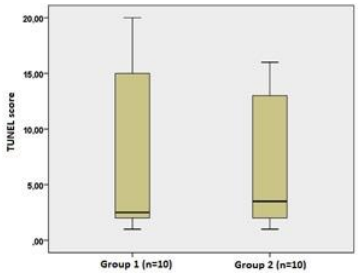
When the ALT, AST and ALP values studied in the organ preservation solutions at 12th hour are compared, the mean values for these parameters appear to be higher in Group 1. However, there was no statistically significant difference between the groups in terms of these parameters (ALT p=0.739, AST p=1.000 and ALP p=0.165) (Table 4).



Graphic 1: Distribution of hidropic degeneration grades between groups



Graphic 2: Distribution of sinusoidal dilatation grades between groups



Graphic 3: Comparison of experimental groups in terms of AI score

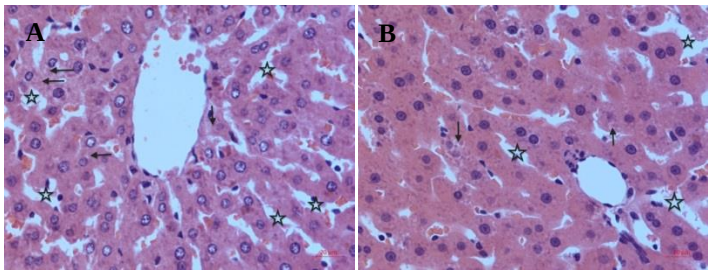


Figure 1: (A) Hematoxylin and Eosin staining of the liver tissues of Group 1 obtained after 12 hours of storage. Hydropic degenerations of hepatocytes (arrows) and sinusoidal dilatation areas (stars) are seen intensely (x400 magnification). (B) Hematoxylin and Eosin staining of the liver tissues of Group 2 obtained after 12 hours of storage. Hydropic degenerations of hepatocytes (arrows) and sinusoidal dilatation areas (stars) are seen less than Group 1 (x400 magnification).

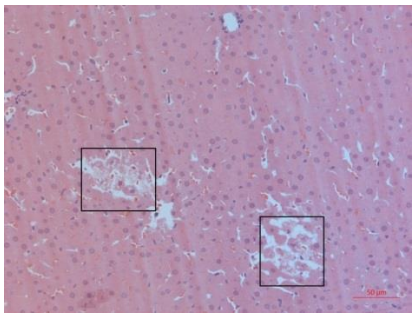


Figure 2: Hematoxylin and Eosin staining of the liver tissues of Group 1. Focal necrosis areas are seen in squares(x200 magnification).

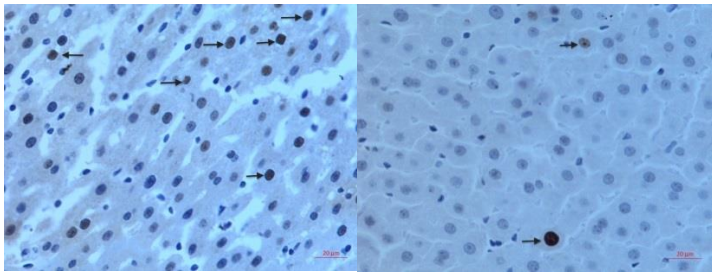


Figure 3: (A) TUNEL staining of the liver tissues of Group 1. Apoptotic hepatocytes' nucleuses are seen in brown-black color (arrow) (x400 magnification). (B) TUNEL staining of the liver tissues of Group 2. There are fewer apoptotic cells than Group 1 (x400 magnification)

Table 1: Comparison of experimental groups in terms of hydropic degeneration

Grade	Group 1 (n=10) n (%)	Group 2 (n=10) n (%)	p value*
0	0 (0.0)	3 (30.0)	
1	6 (60.0)	2 (20.0)	
2	1 (10.0)	3 (30.0)	0.102
3	3 (30.0)	2 (20.0)	

Percentage: Columnar percentage, *:chi-square test

Table 2: Comparison of experimental groups in terms of sinusoidal dilatation

Grade	Group 1 (n=10) n (%)	Group 2 (n=10) n (%)	p value*
0	1 (10.0)	1 (10.0)	
1	2 (20.0)	0 (0.0)	
2	4 (40.0)	4 (40.0)	0.351
3	3 (30.0)	5 (50.0)	

Percentage: Columnar percentage, *:chi-square test

Table 3: Comparison of experimental groups in terms of focal necrosis

Grade	Group 1 (n=10) n (%)	Group 2 (n=10) n (%)	p value*
0	6 (60.0)	9 (90.0)	
1	2 (20.0)	1 (10.0)	
2	1 (10.0)	0 (0.0)	0.402
3	1 (10.0)	0 (0.0)	

Percentage: Columnar percentage, *:chi-square test

Table 4: Comparison of biochemical parameters of 12th hours of experimental and control groups

Variables	Group 1 (n=10) Mean± sd	Median (Min-max)	Group 2 (n=10) Mean±sd	Median (Min-max)	p value
ALT	1064.75± 475.97	1120.60 (525.90-1562.90)	1014.22±374.56	870.95 (631.40-2218.00)	0.739
AST	973.33± 278.71	946.70 (629.20-1829.30)	951.49±355.46	899.15 (584.20-1386.30)	1.000
ALP	3.80± 1.14	3.00 (3.00-6.00)	3.11±0.60	3.00 (2.00-4.00)	0.165

sd: standard deviation, p: Mann-Whitney U Test

Discussion

The most important factor affecting success of organ transplantation is protecting against ischemia-reperfusion (I/R) injury and ensuring continued organ viability [8]. With the aim of reducing organ metabolism, subjecting the organ to cold ischemia is an important method to increase viability and post-transplantation success. However, in spite of this, the researches for additional methods to preserve viability continue [10-12]. The aim of this study is to use the reducing effect of thiopental on metabolic rate to ensure preservations of the liver during the cold ischemia process and to increase the post-transplantation success rates. When examined from this aspect, there was no study found in the literature related to the effect of thiopental on the cold ischemia process in the liver.

In our study, histopathologic assessment, AI and biochemical ALT, AST and ALP analyses were performed during the cold ischemia process on liver tissue after thiopental anesthesia. The results were higher in thiopental group compared to control group. However, these results were not found to be statistically significant.

Thiopental is a barbiturate group anesthetic which is highly soluble in fat [24]. There are studies revealing the antioxidant effect of thiopental by inhibiting lipid peroxidation [24,25]. Thiopental is widely known to have protective effect against cerebral ischemic injury and is routinely used for patients with ischemic attack [26]. Apart from this effect in the brain, the literature contains a variety of studies showing thiopental reduces renal ischemia reperfusion injury [27,28]. These studies biochemically measured malondialdehyde (MDA), superoxide dismutase (SOD) and catalase (CAT) values in renal tissue and additionally attempted to determine histopathological injury to renal tissue. The results of both studies revealed that thiopental had a protective effect in the kidney both in terms of biochemical enzyme activity and histopathologically. In our study, a cold ischemia model of liver tissue was studied, without reperfusion. When assessed histopathologically, the group administered thiopental had less histopathological injury compared to the control group. Additionally, lower numbers of apoptotic cells

were found in the thiopental group. However, our study did not examine antioxidant enzyme levels, different to the literature [28]. Apart from this, our study biochemically examined the ALT, AST and ALP levels in organ preservation solution samples taken at 12th hour. ALT levels have been used as a marker of liver injury for a long time [29]. AST is known to be a marker for hepatocyte integrity [30]. ALP is another marker used to assess liver function. Increase in ALP levels, along with increases in ALT and AST show hepatocellular injury, while ALP increase alone may indicate cholestatic injury [31]. In our study, samples taken from preservation solutions at 12th hour had lower ALT, AST and ALP values compared to the control group. However, these values did not reach statistical significance. This result indicates that the protective effect of thiopental which was previously demonstrated for the kidney may also be shown for liver. In our study, we left the organs in cold ischemia for 12 hours after perfusion. In situations with lengthened durations, the fall in liver enzymes may have reached statistical significance. The study duration being 12 hours is a limitation of our research.

In this study, the anesthetic agent in the experimental group was thiopental, while ketamine was used for the control group. Ketamine is a commonly chosen anesthetic agent for surgeries in rats. It is also routinely used in animal studies in our center. Ketamine, a cyclohexylamine, is used as a general anesthetic clinically and enters the dissociative anesthetic class due to some characteristics [32]. Studies have revealed that ketamine has a protective effect against ischemic injury in a variety of tissues [33,34]. Similar to thiopental, the literature shows a protective effect in incomplete cerebral ischemia [34]. In our study, though ketamine has a protective effect against ischemic injury in a variety of tissues, in the thiopental group the histopathological injury levels in the liver were lower and the biochemical ALT, AST and ALP values were lower. This indicates that thiopental may be chosen as anesthetic agent before cold ischemia in transplantation surgeries.

In the literature, two studies compared propofol and thiopental administered to different groups in a testicular I/R injury model and revealed the protective effect of propofol on testis tissue was better compared to thiopental [35,36]. In these studies, the testis was histopathologically assessed and antioxidant enzyme levels were examined, the results showed less injury in the propofol group. In our study, different to these studies, liver tissue was examined and a cold ischemia model was applied. Reperfusion was not performed so antioxidant enzyme levels were not studied. However, the lack of a third group in our study administered propofol anesthesia is a limitation of our study.

In conclusion, our study is the first study to reveal whether thiopental has a protective effect on liver tissue during the cold ischemia process and attempted to show this effect histopathologically and biochemically. The lower AI values in the group administered thiopental, especially, are important in terms of being able to show a cytoprotective effect on the liver during the cold ischemia process. In fact, during the transplantation process, the lower the number of apoptotic cells in liver tissue during cold ischemia, the better the protection of postoperative organ viability. Additionally, biochemically, the mean values of ALT, AST and ALP were low in the thiopental group, which is important for liver preservation and protection of hepatocytes. There is a need for advanced studies in order for our results to reach statistical significance.

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Depression and affecting factors in patients over 50 years of age: A cross-sectional study

50 yaş üstü bireylerde depresyon ve etkileyen faktörler: Kesitsel bir çalışma

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Abstract

Aim: The population of the elderly in the society is increasing. Old age problems and depression are over looked for various reasons. The aim of this study is to determine the level of life satisfaction of the demographically elderly living in the city or village/town and employing in work life, to determine the frequency of depression among these persons and to find the factors that may be related.

Methods: 908 individuals over the age of 50 have been reached. Type of study is cross-sectional. Sociodemographic questionnaire, Euromodule questionnaire and Geriatric Depression Scale were administered to the subjects. Mann Whitney U, Kruskal Wallis test and Spearman correlation analysis, Binary Logistic regression analysis, Chi-square test were used in the analysis of the data.

Results: The prevalence of depression was found to be 40% in people over 50 years of age. Being a woman, low income and education level, becoming a single/widow, to have a chronic illness and using regular medication increases the risk of depression($p < 0.05$). Having a hobby and a close friend, using social media decreased the risk of developing depression ($p < 0.05$). Life satisfaction was found to be low-mid-level.

Conclusion: Depression is common in people over 50 years of age. In terms of life satisfaction, urban and rural life seem to be superior to each other in some way.

Keywords: Aged, Depression, Satisfaction

Öz

Amaç: Toplumda yaşlı nüfus giderek artmaktadır. Yaşlılık dönemi sorunları ve depresyonu çeşitli nedenlerle atlanmaktadır. Bu çalışmanın amacı kentte veya köy/kasabada yaşayan demografik olarak yaşlı ve çalışan yaşamında yaşlı olan bireylerin yaşam memnuniyet düzeylerini belirlemek, bu kişiler arasında depresyon sıklığını saptamak ve ilişkili olabilecek faktörleri bulmaktır.

Yöntemler: 50 yaş üstü 908 bireye ulaşılmıştır. Çalışma kesitsel tiptedir. Kişilere sosyodemografik anket, Euromodule soru kağıdı, Geriatrik Depresyon Ölçeği uygulanmıştır. Verilerin analizinde Mann Whitney U, Kruskal Wallis testi ve Spearman korelasyon analizi, Binary Lojistik Regresyon analizi, Ki-kare testi kullanılmıştır.

Bulgular: 50 yaş üstü kişilerde depresyon prevalansı %40 olarak bulunmuştur. Kadın olmak, düşük gelir ve eğitim seviyesi, bekar/dul olmak, kronik hastalığı olmak, düzenli ilaç kullanmak depresyon riskini artırmaktadır ($p<0.05$). Hobi sahibi ve yakın arkadaş sahibi olmanın, sosyal medya kullanımının depresyon gelişim riskini azalttığı bulunmuştur ($p<0.05$). Yaşam memnuniyeti düşük-orta düzey olarak bulunmuştur.

Sonuç: 50 yaş üstü bireylerde depresyon sık görülmektedir. Yaşam memnuniyeti açısından kent ve kır yaşamının birbirine üstün yönleri olduğu görülmüştür.

Anahtar kelimeler: Yaşlı, Depresyon, Memnuniyet

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Introduction

The population living in cities is increasing day by day, and the population of Turkey is becoming older with each passing day. According to the 2013 TNSA Report, while the population over the age of 65 constituted 7.9% of the general population, 8.5% of the population consists of the elderly according to the 2017 TUIK results [1, 2]. The inadequacies that appear in old age limit the daily activities, movement areas and social relations at various levels [3].

Old age neither corresponds to a state in which people live longer and are healthier, nor to a state in which the elderly are retired and obtain more income. Together with these, it must be considered as a category in which the elderly establish relations with other groups in the society by integration, and in which the elderly have expectations about the environment, the city, and the country in which they live. When chronological age is considered, the old age period which may be defined as the third age after the first period which consists of childhood and after the second period which consists of adulthood which have heavy responsibilities of social and economic life, must be considered as a period in which the elderly develop themselves and their interests freely [4]. The number of people and the elderly population living in cities is increasing with each passing day. More than half of our population lives in cities and 20.8% of the population living in cities are at and above the age of 50 [1].

One of the most frequently observed diseases in the elderly is depression. The diagnosis of depression is ignored in the elderly due to various reasons, and the results may be negative (5). The prevalence of old age depression was reported to be different in various societies (5). It was observed that the prevalence is between 1% and 60% [6]. When the etiology of old age depression was considered it was observed that many factors are influential in this process. Among these reasons, there are the physical inadequacies due to old age, chronic diseases, psychosocial reasons, neuroendocrine and neurochemical reasons. When the people diagnosed through the scale developed in society-based studies to evaluate the depression and through psychiatric examination were considered it was seen that the frequency is lower in terms of clinical evaluations. It was seen that the frequency varied between 1-48% in the scales reported in society-based studies [7].

The purpose of the present study was to determine the life satisfaction levels of the elderly people in working life and living in cities or village/towns in demographical terms; to determine the depression frequency in these people and to find out the factors that may be associated with depression.

Materials and methods

The type, population and sampling of the study

The population of the study, which was designed in the cross-sectional manner, consisted of the elderly individuals above the age of 50 living in the city center and villages and counties of Malatya. The study was conducted between June-November 2017. Type of study is cross-sectional. The minimum number of the individuals that had to be contacted was found to be 524 when the results of the pilot study which was conducted by taking the 80% power and 95% confidence interval as reference. 908 people were contacted in clusters with the Quota Sampling Method. The inclusion criteria for the study was being above the age of 50 and being voluntary to answer the questions. Ethical approval was received from the university for the study (Decision Number: 2017/23-4).

Evaluation Tools

The questionnaire applied to the individuals consisted of three sections;

Sociodemographic information form

The first section consisted of sociodemographic questions on age, gender, education, income, living area, and average living duration in city center for those living in city center. In this section, the hunger and poverty limits on the date of the study were taken as reference values when the income groups were being formed.

Euromodule standard question paper

The second section consists of a standard question paper with the name Euromodule, which was prepared by researchers from 19 countries, who were specialists in their fields [8]. Euromodule evaluates the life satisfaction in the elderly in 5 sub-dimensions; sociodemographic and economic variables, physical health, psychological health, environmental and social relations. The factors that define the life satisfaction in old age are physical health, psychological health, the opportunity of establishing social relations, and environmental and sociodemographic and socioeconomic variables [8]. Euromodule basically consists of a basic section and subsequent another elective section. The main section is compulsory for all participant countries; and includes subjective and objective evaluations on the fields included in life. The other section consists of elective questions each of which evaluating the subjective conditions of each country. For example, the income level of the individual reflects the objective dimensions, and the satisfaction of this income reflects the subjective dimension. As a result, both sections were prepared to evaluate subjective and objective indicators at individual and social level [9].

Geriatric depression scale

The third section consists of Geriatric Depression Scale. This scale consists of yes/no questions; and excludes somatic complaints that do not have much diagnostic value in the elderly and the items that might cause reactions. The validity and reliability study of the scale, which consisted of 30 questions, was performed for Turkish. The answers given to the questions are evaluated as 0-1 in the scale. According to the Geriatric Depression Scale, 0-10 scores mean no depression, 11-13 scores mean possible depression, 14 and over scores mean absolute depression [9].

Statistical analysis

The data were analyzed with the SPSS 22.0 program. The definitive data were expressed as percentage, median, arithmetic average, and change range. The Kolmogorov Smirnov test was used as the normal distribution test. The parametric tests were used in the analysis of the data that fit normal distribution, and the Non-Parametric tests were used in the analysis of the data that did not fit normal distribution. The Chi-Square test was used in the analysis of the categorical data. The Mann Whitney U, Kruskal Wallis and Spearman Correlation Analysis, Binary

Logistic Regression Analysis, Chi-Square tests were used in the analyses of the data. The significance level was taken as $p<0.05$.

Results

The mean age of the 908 people who participated in the study was 58.06±7.24; and 49% were female, and 51% were male. 81.5% of the participants were between 50-64 ages, 18.5% were at and above the age of 65. 86.9% of the participants lived in city center, and 13.1% lived in village/town. The average life in city of the participants who lived in city was 33.84 years. The sociodemographic properties and the distribution of the answers given to the Euromodule question paper are given in Table 1.

Table 1: The distributions and values of the answers given to the EUROMODULE questions

Variables	%	X	Median	Change interval
Sociodemographic variables				
Gender; Male /female	51.0/49.0			
Marital status; married / single / widowed	80.6/6.8/12.6			
Settlement; urban / rural	86.9/13.1			
Education level				
Not literate / Literate-Elementary school	12.4/28.0			
Secondary / High School / University	15.6/17.7/26.3			
Satisfaction level of education		4.35	4.0	1-10
Household income				
0-1529/1530-4980/5000 tl and above	28.6/55.7/15.7			
Satisfaction level of household income		4.03	4.0	1-10
The social class you feel, workers / middle / upper	31.2/59.7/9.0			
Physical health				
Chronic disease present / absent	48.2/51.8			
Regular medication available / not available	52.0/48.0			
Satisfaction level from general health		4.36	4.0	1-10
Mental health				
Spiritual troubles (stress, constant fear, worry..)		1.66	1.80	0-5
Social relations				
Close friend present/absent	79.2/20.8			
Social participation (association membership) pre/abs	21.2/78.8			
Number of close friends		4.39	4.0	0-10
Interview frequency with children		9.72	10	0-14
Environment				
1- Living space: House				
Host: host / tenant	78.7/21.3			
Number of rooms		3.30	3.0	1-8
Facilities and conditions at home (separate kitchen, bathroom, hot water, heating, terrace balcony)		5.08	6.0	
2- Living space: Neighborhood				
Personal security		0.27	0.00	0-4
Close complaint (noise, air-water pollution, recreational areas)		9.60	10.0	0-16
Satisfaction level from neighbors		3.97	3.0	0-10
3- Living space: Country				
Belief in social adherence		2.36	2.33	1-4

Nearly half of the participants had chronic diseases and used continuous medication. The satisfaction from general health was low. When their social life was considered, it was determined that many people had close friends and the rate of membership in social associations was found to be low. It may be claimed that the opportunities were good in general. Complaints from close surroundings and dissatisfactions from the relations with neighbors were high. The belief in social justice was at medium level.

The sub-dimensions of the Euromodule responses of the participants were analyzed in terms of living in city or village/town. When the results were considered in terms of complaints about the physical environment, it was found that the complaints about the close surroundings were less at a significant level in the participants living in village/town (p=0.001). It was determined that the physical depression was low at a significant level in those who were living in village/town (p=0.004). When the results were considered in terms of satisfaction from general health, it was seen that the participants living in cities and the participants who were male had more satisfaction scores at a significant level (p=0.032, 0.001). When the results were considered in terms of chronic diseases, it was determined that there were no differences between the city and village (p=0.145). When the belief in social justice was considered in terms of age, gender and the area where the participant lived, no differences were determined (p=0.159, 0.879, 0.425). It was seen that the number of the participants who lived in cities had few close friends at a significant level (p=0.001). When the results were analyzed in terms of education and satisfaction from income levels, it was observed that the participants who lived in cities were satisfied at a significant level (p=0.001, 0.002). In terms of social association memberships, no differences were determined between those who lived in city and in village/town (p=0.661).

According to the scores received from the Geriatric Depression Scale, the depression frequency was found to be 40.2% in the Study Group in the analysis made about depression (Table 2). It was determined to be 47% in the group who was above the age of 65 (Table 7). The mean score received from the scale was 11.85±6.71.

Table 2: Prevalence of depression according to geriatric depression scale

Group	n	%
No depression	402	44.5
Possible depression	138	15.3
Depression	363	40.2

The scores received from the depression scale according to sociodemographic properties are given in Table 3. It was observed that the scores received from the depression scale were high at a significant level in women and in participants who were above the age of 65. In addition, it was also found that as the education and income levels decreased, the scores received from the scale increased at a significant level (Table 3).

Table 3: Average scores of depression scale according to sociodemographic characteristics

İndependent variable	Point (X±S.D.)	p
Male / Female	11.23±6.9 / 12.48±6.4	0.002
50-64 years / 65 and over	11.41±6.5 / 13.58±7.0	0.001
Not literate / Literate-Elementary school	14.44±7.4 / 12.78±6.5 /	<0.001
/ Secondary / High School / University	11.73±6.1 / 11.33±6.1 / 9.97±6.5	
0-1529/1530-4980/5000 tl and above	13.12±6.9 / 11.77±.6.5 / 9.86±6.5	<0.001
Married / single / widowed	11.45±6.4 / 12.95±7.0 / 13.92±7.7	0.005
Living in the village/ Living in the city	12.44±6.7 / 11.76±6.7	0.245

The findings on the results of the correlation among scores received from the depression scale in terms of the life in city, age, meeting children, the belief in social justice, and complaints from the close surroundings, are given in Table 4.

Table 4: Relationship between some factors and GDS

	GDS point	
Factor	r	p
Age	0.131	<0.001
Close complaint	0.174	<0.001
Interview frequency with children	-0.196	<0.001
Lifetime in the city	-0.119	0.001
Belief in the social adherence	-0.194	<0.001

According to the results of the binary logistic regression analysis, which was made to determine whether there was depression according to membership in a social club, close friends, hobby, chronic disease, it was observed that the model fitness was good (Hosmer and Lemeshow Test; p=0.449). The independent variables included in the model explained 10.1% of

the total variance in the dependent variable according to Nagelkerke R Square. The true estimation percentage of the model is 62.7%. It was observed that the coefficients of the independent variables that were included in the model were significant except for membership in a social association (Table 5).

Table 5: Logistic regression analysis results for depression

	Depression				
				95% C.I. for Exp(B)	
	B	p	Exp(B)	Lower	Upper
Not being a close friend	0.663	<0.001	1.884	1.350	2.629
Not being a hobby	0.514	<0.001	1.672	1.257	2.224
Chronic illness	0.422	0.003	1.525	1.156	2.012
Becoming a social association member	-0.096	0.571	0.909	0.653	1.265

When we considered the OR (i.e. the Odds Ratio) of the independent variables included in the model, it was observed that the risk of developing depression in the elderly who did not have close friends was 1.884-fold more; 1.672-fold more in those who did not have a hobby, and 1.525-fold more in those who had a chronic disease. According to social media use status, the average scores received in the Geriatric Depression Scale are given in Table 6.

Table 6: Average scores from the SDO by using social media

	GDS point		
Social media use	(X±S.D.)	Median	p
Yes	10.96±6.82	10.0	<0.001
No	12.80±6.47	13.0	

When considered in terms of age groups, there were statistically significant differences and the depression frequency in the individuals who were over the age of 65 was observed to be 47% (Table 7). When we considered the social media use in terms of age groups, it was determined that 74.4% of the individuals who were above the age of 65 did not use the social media (p<0.001).

Table 7: Depression frequency according to age group, chronic disease status and place of residence

	Geriatric depression scale group (n/%row)				
	No depression	Possible depression	Depression	X^2	p
Yaş grubu					
50-64	342/46.7	109/14.9	282/38.5	6.674	0.036
65 years and over	60/35.7	29/17.3	79/47.0		
Chronic disease					
Yes	167/38.5	67/15.4	200/46.1		
No	233/50.0	71/15.2	162/38.4	13.875	0.001
Living place					
City	353/45.0	124/15.8	308/39.2		
The village / town	49/41.5	14/11.9	55/46.6	2.698	0.259

Discussion

It was reported that depression symptoms were frequent in the elderly at a rate of 20% [10, 11]. It was observed that depression was more frequent in people who had long-term physical limitations. For example, the frequency of depression in diabetes patients was 30%. It was also reported that this frequency was 25% and above in COPD patients [12,13]. Depression is seen to be increased at a 7-fold in people who have two or more physical diseases [12]. In 36% of the people between 65-74 years of age, and in 47% of the individuals above the age 75, there is a chronic disease that limits life and this is a potential risk factor for depression development and causes that the mortality also increases (14). Depression is rarely detected and treated in the elderly patients. Especially in the elderly that have chronic diseases, this may be ignored [15,16]. Another delay reason in diagnosis is the labeling of the general practitioners about mental diseases in the elderly [17,18]. In addition, elderly patients want to speak rather than antidepressant treatment [18].

In a study conducted in China, it was observed that there were depression symptoms in 40.6% of the hypertension patients [19]. In the same study, a Logistic Regression Analysis was made about the factors that might be influential in depression development, and it was determined that the risk of developing depression increased in women, non-married people, people with low income, lonely people, people with chronic diseases, and in low social support (19). In another study conducted in China, the depression prevalence was found to be 5.9% in adults who were above the age of 35, 8; 8.1% in women, and 3.9% in men [20]. It was observed that income level, educational level, daily sleep duration, salt and meat consumption, and chronic disease were associated with depression symptoms [21].

In a thesis study conducted in Turkey to investigate the frequency of depression in individuals above the age of 65, the average score received from Geriatric Depression Scale was found as 14.04±7.6. It was seen that age, gender, marital status, educational status, income, chronic diseases, and continuous medication use were influential on depression development [21]. Increasing age, being woman, having deceased spouse, low educational status, low income levels, chronic diseases increased the scores received from the depression scale at a significant level [21]. It was reported that the frequency of depression in old age varied according to residential area at a rate of 0.9-42%. In our study, on the other hand, the mean score received from the Depression Scale was found to be 11.85±6.71. The depression prevalence in the group that was above the age of 50 was found to be 40.2%; and 47% at the age group above 65. Being woman, being above the age of 65, low education and income level, being single-widow or widower, having chronic disease, using continuous medication increased the risk of depression. The average scores received by the participants in this group were high at a significant level. It was observed that having close friend, having a hobby or activity and using social media were influential factors in protecting from depression. Social media use is lower in participants above the age of 65. It is considered that this age group has problems in adapting the modern age.

Being woman and low educational and income status bring disadvantages in reaching resources in social life, in participating to social life, in reaching services, and participating to activities. It is considered that this situation contributes to the development of depression. When the fact that being widow or widower cause that individuals grieve and become lonely is considered, it is possible to consider that these factors are also influential in the development of depression. Participating in social life and increased sharing with people are considered as protective factors from depression. Having close friends, having a hobby, and using social media probably facilitate integration to social life and decrease the loneliness and the feeling of insignificance brought by old age. The negative correlation between the life in city and depression supports this situation. The decrease in the number of people living in villages, and the social and economic opportunities being low in villages may help explain this relation.

The old age period is a period in which the material and spiritual dependencies of people are increased due to various reasons. If this issue is not considered in detail and no precautions are taken, we may become fully dependent on other people when we become old just like it is the case in a newborn baby [21]. While the death of friends or children in old age, residing at an old-age home after leaving one's home, the lack of social relations, falling, loss of movement, bad oral health, losing independency and similar situations cause stress, depression and similar diseases in the elderly, they also reduce life quality [22,23]. Cooking, painting, listening to music, going to the cinema, doing physical activity, spending time with peers prevent the dementia and depression in the elderly [22-24].

When we considered the sub-dimensions of life satisfaction, it was observed that the satisfaction from sub-dimensions was at low-medium level. It was observed that living in city increased satisfaction in some points. When the advantages of the city in terms of education, economy and access to healthcare services are considered, this situation may be explained. We believe that this advantageous situation increased satisfaction. When the results were analyzed in terms of complaints about physical environment, it was determined that the complaints of the people living in villages were lower at a significant level. It was observed that the people living in village/town complained less about the noise, air-water pollution, and similar physical environmental factors. The less traffic, crowd and living very close to one another in cities being also less may be the reason of this difference. It was found that the depression was low in people living in village/town at a significant level. Living close to the nature and the imprisoned home life being low in villages may be influential in this situation.

When the satisfaction from general health levels were analyzed, it was observed those males and those who lived in city were more satisfied from general health status. It is considered that benefiting more from healthcare institutions and facilitated treatment and medication for those living in city are important in explaining this situation. When considered in terms of chronic disease, no differences were detected between city-village. It is considered that living healthily and individual effort in old age and health behaviors and genetic factors are influential in this result. When the results were analyzed in terms of belief in social justice and age, gender and residential area, no differences were determined. Social justice includes several concepts like justice in the distribution of income, equal opportunities, protecting the weak one against the strong one, etc. It is clear in general that there are inequalities in the distribution of income, education, reaching healthcare services, and use of resources in our country, and it is considered that this outcome stems from general dissatisfaction. It was seen that the number of close friends was more in those who lived in the city. It is considered that the number of residents and the number of the living are explanatory in this result. It is probable that the migrating peers in village/towns or their peers being deceased may affect the low number of friends. When education and satisfaction from income are considered, it was observed that those who lived in city were more satisfied at a significant level. The majority of economic activities being in cities, and the decreased effect of agricultural life and agricultural economy triggered the migration to cities; and ensured that the people living in cities had better economic conditions when compared with those living in villages. Another advantage of city life is the availability of educational institutions and services and the increased opportunity of employment in service sector for those who receive education. When these factors are considered, the more satisfaction of education and the income, which is the result of education, is an expected outcome for people who live in cities for longer durations. In terms of membership in social associations, no differences were detected between the people living in villages and in cities. It is possible that socializing and social activities being formed as depending on various cultural factors may reduce the need for social memberships in people or does not have any difference.

In many previous studies that were conducted on the life satisfaction of the elderly it was observed that 25% of the participants were satisfied from life [25]. It was observed in the present study that the satisfaction of the elderly individuals from their performances in activities which they cared for affected their life satisfactions at a positive level; however, there was a negative relation between life satisfaction and the obstacles in the environment where the individual lives and the difficulties in reaching healthcare services, reaching information, receiving help at home and transportation [25]. In many studies in which life satisfaction was investigated according to demographical properties, it was reported that the expectations of the individuals who were married and who had low socio-cultural levels were limited, and their expectations were related with the cultural structure [25].

Our study was conducted at a single center, which limits the generalization of our findings to other institutions or populations with different resources.

As a result, the depression prevalence in the individuals who were over the age of 50 was found to be high, and even higher in the individuals who were above the age of 65. Being woman, having low income and education level, being single/widow or widower, having chronic disease and using regular medication increase the depression risk. Having close friend, having a hobby/regular activity, and use of social media decrease the depression development risk.

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Analysis of “Code Blue” events in a single center: A cohort study with 419 incidents

Tek merkezde “Mavi Kod” olaylarının analizi: 419 vakalı kohort çalışma

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Abstract

Aim: Cardiac arrest sustains a significant cause of in-hospital morbidity and mortality worldwide and “Code Blue” (emergency code) is defined as a hospital code used to indicate a patient requiring immediate resuscitation. In this study we aimed to evaluate the ‘‘code Blue’’ events retrospectively in our hospital.

Methods: Data were collected from the file book that is contained the patients’ name, protocol numbers, duration of arrivals to the arrest locale, final results of CPR and the CPR team’s names, locales of “code blue”. Patients’ gender, locales of “code blue”, false or right “code blue” situations, final results were analyzed.

Results: One hundred-nineteen “code blue” situations were analyzed, 132 of 339 true “code blue” patients died at the locale after CPR. One hundred-forty four patients were transferred to reanimation unit, 29 were to the coronary intensive care unit (ICU), 28 were to the cardio-vascular surgery ICU, four were to pediatric-ICU and two were taken to the emergency operations. Also 113 of these 207 remaining patients were died in these units in later times, 94 patients survived. Eighty of them were determined as false code blue.

Conclusions: Even the situation is in-hospital cardiac arrest and the CPR is performed by skilled team mortality rate may still be high. To prevent the false code blue situations, in-house training is indispensable for every hospital workers.

Keywords: Code Blue, In-hospital arrest, False Code Blue, Resuscitation

Öz

Amaç: Kardiyak arrest, dünya çapında hastane içi morbidite ve mortalitenin önemli bir nedenini olup “Mavi Kod” (acil durum kodu), hemen resüsitasyon gerektiren bir hastayı belirtmek için kullanılan bir hastane kodu olarak tanımlanmaktadır. Bu çalışmada, hastanemizde verilen mavi kodları retrospektif olarak değerlendirmeyi amaçladık.

Yöntemler: Çalışma verileri, hastanın adının, protokol numaralarının, olay yerine varış sürelerinin, resüsitasyon ekibinin adlarının, olay yerinin olduğu “Mavi Kod” defterinden toplandı. Hastaların cinsiyeti, “Mavi Kod” bölgelerinin yerleri, yanlış veya doğru “Mavi Kod” durumları, hastaların nihai sonuçları analiz edildi.

Bulgular: 419 “Kod mavi” durumu incelendi, 339 hastanın 132'sinin olay yerinde resüsitasyon sonrasında öldüğü görüldü. Yüz kırk dört hasta reanimasyon ünitesine, 29'u koroner yoğun bakıma, 28'i kalp-damar cerrahisi yoğun bakımına, 4'ü pediatrik yoğun bakıma ve 2'si acil operasyona alındı. Ayrıca bu 207 hastanın 113'ü bu birimlerde daha sonra öldü, 94 hasta hayatta kaldı. Seksen, mavi kod yanlış olarak belirlendi.

Sonuçlar: Kardiyak arrest durumu hastane içinde bile olsa ve resüsitasyon yetenekli bir ekip tarafından yapılsa bile ölüm oranı hala yüksektir. Yanlış mavi kod durumlarını önlemek için, tüm hastane çalışanlarına kurum içi eğitimler vazgeçilmezdir.

Anahtar kelimeler: Mavi kod, Hastane içi arrest, Yanlış mavi kod, Resüsitasyon

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Introduction

Cardiac arrest sustains a significant cause of in-hospital morbidity and mortality worldwide [1]. Considering significant therapeutic advances, survival-to-discharge rates remain in the range of 17–32% [2–6]. Numerous factors have been found to influence survival after in-hospital cardiac arrest, including age, comorbidities, the duration of arrival to the arrest locale, the duration of cardiopulmonary resuscitation (CPR) [2,6,7]. Most of these factors describe pre-existing conditions that cannot be easily controlled by the resuscitation team or hospital. Also CPR teams' skill and education are very important for the success rate of CPR [8]. "Code Blue" (emergency code) is defined as a hospital code used to indicate a patient requiring immediate resuscitation. In this study we aimed to evaluate the ''Code Blue'' events retrospectively in our hospital.

Materials and methods

The present retrospective study was conducted at Sanko University, Faculty of Medicine. The approval of the Institutional Ethics Committee of Sanko University, Gaziantep, Turkey was obtained for the study.

This study was an analysis of retrospectively collected data of all ''Code Blue'' events in one hospital from January 2012 to November 2018. The institution is a large inner-city hospital, have a surgical intensive care-reanimation unit (RU), a cardiology intensive care (C-ICU), cardiovascular surgery intensive care (CVS-ICU), and pediatric intensive care (P-ICU), an average inpatient census of 650 patients.

"Code blue" team includes two reanimation unit nurses, two anesthesia technicians and an anesthesiologist. There are two "Code blue" devices, one of these is in operating room and other is in reanimation unit. They both rings at the same time and they show the locale of the "Code blue". Reanimation nurses takes a CPR kit includes drugs, bag-valve-mask, laryngoscopy kit, intubation tubes, airways. Also there are CPR kits and defibrillators in all services. Cardiac arrest was defined as the cessation of cardiac mechanical activity as confirmed by lapse in circulation, which was determined by the absence of a palpable central pulse, unresponsiveness, and respiratory arrest defined as apnea. The resuscitation protocol begin immediately as stated in the AHA (American Heart Association) guidelines, till the blue code team arrives to the locality.

After CPR, if pulse and blood pressure is back and normal, patients are taken to the appropriate intensive care units. After CPR, patient's name, protocol number, duration of arrival to the arrest locale, final result of CPR and the CPR team's names, locales of "Code blue" are recorded to the file. Data were collected from this file book.

Patients' gender, locales of "Code blue", false or right "Code blue" situations, final results and the duration of arrival to the locale were analyzed. When we arrived to the locale, if patient is stable and was not neither respiratory nor cardiac arrested, it was accepted as false code blue.

Results

In this study, 419 "Code blue" situations were analyzed retrospectively between January 2012 and November 2018 in Sanko University, Faculty of Medicine Hospital. Eighty of these codes were noticed as false (table 1).

After minimum 45 minutes CPR duration, 132 of 339 patients couldn't be saved and died at the locale. After CPR, when pulse and blood pressure is back and normal, 207 patients were taken to the appropriate units (table 2). One hundred-forty four patients were transferred to RU, 29 were to the C-ICU, 28 were to the CVS- ICU, 4 were to P-ICU and 2 were taken to the emergency operations.

Table 1: General "Code Blue" analysis

	n	Female/Male
True code blue	339	131/208
False code blue	80	54/26

Table 2: Departments of patients that transferred to, and their outcomes

	n	Alive	Death
Total	207	94	113
RU	144	62	82
CVS-ICU	28	17	11
Coronary-ICU	29	14	15
Pediatric -ICU	4	0	4
Emergency surgery	2	1	1

RU: Reanimation unit, ICU: Intensive care unit, CVS: Cardio-Vascular Surgery

Also 113 of these 207 remaining patients were died in these units in later times, 94 patients survived. Sixty-two of 144 patients taken to the RU were survived, 17 of 28 patients taken to the CVS-ICU were survived, 14 of 29 patients taken to the C-ICU were survived and 1 of 2 patients undertaken to the emergency operation was survived.

Table 3: "Code Blue" analysis of departments

Department which is the incident occurred	n	Death/Died at the locale	Transfer to department after CPR	False "Code Blue"
CVS-ICU	32	19	13-Stayed in CVS-ICU	0
Emergency room	138	65	59-RU 2-Emergency surgery 10-coronary ICU 2-Pediatric ICU	0
Cardiology clinic	42	2	14- Coronary ICU 36-RU	0
CVS clinic	21	4	9- CVS-ICU 8-RU	0
Radiology	7	0	3-RU	4
Transplantation unit	3	2	1-RU	0
Coronary angiography and catheterization unit	9	2	4- Coronary ICU 2- CVS-ICU	1
Pediatric clinic	2	0	2- Pediatric -ICU	0
Coronary ICU	47	24	19-RU 4- CVS-ICU	0
Other clinics	33	14	16-RU	3
Out-patient clinic	77	0	2-RU 1- Coronary ICU	72

RU: Reanimation unit, ICU: Intensive care unit, CVS: Cardio-Vascular Surgery

Locales of where code blues were assigned are analyzed (table 3). One hundred-thirty eight "code blue" were assigned in emergency room, 65 died at the locale, 59 of survived patients transferred to RU, 2 of transferred to operating room, 10 of transferred to C-ICU, 2 of transferred to P-ICU. Forty-seven "code blue" were assigned in C-ICU, 24 died at the locale, 19 of survived patients transferred to RU, 4 of survived patients transferred to CVS-ICU. Thirty-two "code blue" were assigned in CVS-ICU, 19 died at the locale and 13 stayed in the ICU. Forty-two "code blue" were assigned in cardiology service, 2 died at the locale, 14 of survived patients transferred to C-ICU, 36 of transferred to RU. Twenty-one "code blue" were assigned in cardiovascular surgery service, 4 died at the locale, 9 of survived patients transferred to CVS-ICU, 8 of transferred to RU. Seven "code blue" were assigned in radiology department, 4 were determined as false code blue, 3 of transferred to RU, no one died. Three "code blue" were assigned in transplantation

department, 2 died at the locale, 1 of transferred to RU. Nine "code blue" were assigned in coronary angiography unit, 2 died at the locale, 1 of determined as false code blue, 4 of transferred to C-ICU and 2 of survived patients transferred to CVS-ICU. Two "code blue" were assigned in pediatric service, 2 of survived patients transferred to P-ICU. Thirty-three "code blue" were assigned in other services, 14 died at the locale, 3 of determined as false code blue, 16 of survived patients transferred to RU. Seventy-seven "code blue" were assigned in outpatient clinics, no one died at the locale, 72 of determined as false code blue, 2 of survived patients transferred to RU, 1 of survived patients transferred to C-ICU.

When the false code blue situations were analyzed, 72 of these were assigned by secretaries of outpatient clinics, 3 of these were assigned by nurses, 1 was assigned by coronary angiography technician, 4 were by radiology technicians.

Gender proportion of true code blues was 131/208 (female/male) but just the opposite the proportion of false code blues was 54/26 (female/male).

Discussion

Even it is in-hospital cardiac arrest mortality rate is still higher. Shin et al. studied in-hospital cardiac arrest events of 958 patients and found that %28 of these patients were survived and discharged [9]. Similarly %27.7 of our patients were survived and discharged. Also the rate of successful CPR is as low as 2.4%–18.4% [10-15] although most studies reported a successful CPR rate of 13%–59% [8]. In our study successful CPR rate at first attempt is 61%. We consider this is due to educated skills of CPR teams [anesthesiologist, anesthesia technician and reanimation unit nurse] and their level of competence in resuscitation together with the short duration of arrival to the arrest locale (38.7 second min:10 sc max:180sc).

In-hospital cardiac arrests are common and delayed treatment is associated with a lower survival rate and poor neurological outcomes. Furthermore, early recognition of "code blue" situation is important for the safety of the patients. The results of our study show that factors such as type of education, affect decision to activate code blue [16]. In our study, 72 of 80 false "code blue" situations were assigned by the secretaries of outpatient clinics and they were not educated.

Cardiac symptoms, such as chest pain, shortness of breath, tachycardia and weakness, are very common in general population. Cardiac symptoms may be related to organic heart disease or may be associated with a variety of physical or mental conditions. But in some cases the cause of cardiac symptoms remains unclear. In these situations there is a high probability that patients' symptoms (especially chest pain) are related to psychological background. Anxiety disorders such as panic disorder, depression and conversion disorders can be evaluated as urgent with non-cardiac chest pain [17]. These disorders are also associated with deterioration of oxidative metabolism as well as with psychopathological mechanisms and also conversion is associated increased neuronal damage [18,19]. Psychogenic respiratory distress is superimposed on psychogenic neurologic symptoms like these psychopathologies and misdiagnosis resulted in code blue alerts [20,21].

Sobański et al. [22] studied Neurotic personality and pseudo-cardiac symptoms, their study group consisted of 2,450 patients, and 69% of them were women, while 31% were men. Similarly in our study, in false code blue situations women were more than men. Gender proportion of true code blues was 131/208 (female/male) but just the opposite the proportion of female/male was 54/26. Most of false code blues were in outpatient clinics. Panic attacks, conversion disorders, psychiatric illnesses, neurotic behaviors were diagnosed by the CPR team, but secretaries of outpatient clinics were not able to recognize these diagnosis.

Our study has several limitations because it is a single-center, retrospective study. The results of the study are unique to our hospital. We did not study the exact reasons of arrests, but 150 of 339 true "code blue" situations were assigned from coronary and Cardio-Vascular Surgery ICU, coronary and Cardio-Vascular Surgery services. These findings gave rise to thought that causes should be cardiac problems. Also similarly, studies showed that cardiac problems are the most reason in cardiopulmonary arrests [23].

Conclusion

In conclusion, even the situation is in-hospital cardiac arrest and the CPR is performed by skilled team mortality rate may be still high. To prevent the false code blue situations, in-house trainings are indispensable for every hospital workers.

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Results of surgical treatment of ulnar nerve schwannomas arising from upper extremity: Presentation of 15 cases with review of literature

Üst ektremitede ulnar sinir schwanomlarının cerrahi tedavi sonuçlar: 15 olgu sunumu ile literatür taraması

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Abstract

Aim: Schwannomas are the most common benign tumors of upper extremities. The diagnosis of peripheral nerve lesions on clinical history, physical examination, and radiologic tests. Magnetic resonance imaging (MRI) is one of the best to use on schwannomas radiologic test. The aim of this study is to evaluate patients who are diagnosed with schwannomas on the ulnar nerve by mutual agreement between pathology and MRI.

Methods: Retrospective cohort study was designed. From January 2011 – December 2016, 15 patients who had surgery ulnar nerve mass and had been diagnosed schwannomas were included in the study. The anatomical classification was at 6 arms, 4 elbows and 5 forearms. Before surgery, all patients were diagnosed with nerve mass through by MRI. Patients were operated under regional anesthesia and microscope.

Results: All patients have diagnosed with histopathological schwannomas. All tumors were observed isointense in T1-weighted images and hyperintense in T2-weighted ones. Nerve injuries and motor deficit were not observed after surgery. All tumors were enucleated without harming any nerve fibers. The postoperative mean follow-up period was 12.4 months (9 – 29). In the early postoperative period, paresthesia, pain, and hypoesthesia were noted in 10 patients. Neurological symptoms were recovered in postoperative 5 months.

Conclusions: Schwannomas are solitary and benign tumors that are shown on the median and ulnar nerve. MRI and high-resolution ultrasonography are the big help to plan the treatment before the surgery. They are removed as intracapsular with acceptable complication ratio. Removing schwannomas can cause some sensational deficit such as pain and paresthesia but these complications are spontaneously decreased.

Keywords: Ulnar nerve, Schwannoma, Magnetic resonance imaging

Öz

Amaç: Schwannomlar üst ekstremitede en sık görülen iyi huylu tümörlerdendir. Periferik sinir kitlelerinde tanıda klinik öykü, fizik muayene ve radyolojik testler önemlidir. Schwanoma tanısında en iyi görüntüleme yöntemi manyetik rezonans görüntülemedir (MRG). Bu çalışmanın amacı ulnar sinirde schwannom tanısı konan hastaların MRG bulguları ile cerrahi eksizyon patoloji sonuçlarının karşılaştırılmasıdır.

Yöntemler: Retrospektif kohort çalışma tasarlandı. Ocak 2011 - Aralık 2016 tarihleri arasında, ulnar sinir kitlesi cerrahisi yapılan ve schwannoma tanısı alan 15 hasta çalışmaya dahil edildi. Anatomik sınıflandırma 6 kolda, 4 dirsekte ve 5 ön kolda idi. Ameliyattan önce tüm hastalara MRG ile tanı kondu. Hastalar bölgesel anestezi ve mikroskop altında ameliyat edildi.

Bulgular: Bütün hastalardan çıkarılan kitlelere histopatolojik schwannom teşhisi kondu. Tüm tümörler, T1 ağırlıklı görüntülerde izointens ve T2 ağırlıklı görüntülerde hiperintens olarak gözlendi. Ameliyat sonrası sinir yaralanmaları ve motor kayıp gözlenmedi. Tüm kitleler, herhangi bir sinir lifi zarar görmeden çıkarıldı. Postoperatif ortalama takip süresi 12,4 aydı (9 - 29). Postoperatif erken dönemde 10 hastada paraestezi, ağrı ve hipoestezi gözlendi. Tüm vakalarda postoperatif 5. ayda nörolojik semptomlarda iyileşme saptandı.

Sonuçlar: Schwannomlar median ve ulnar sinirde görülen soliter ve iyi huylu tümörlerdir. MRG ve yüksek çözünürlüklü ultrasonografi ameliyattan önce tedaviyi planlamak için büyük önem arzetmektedir. İntrakapsuler eksizyonlarda komplikasyon oranı daha düşüktür. Schwannom eksizyonu sonrası, ağrı ve parestezi gibi bazı komplikasyonlar görülsede zaman ile bu komplikasyonlar düzelmektedir.

Anahtar kelimeler: Ulnar sinir, Schwannoma, Manyetik rezonans görüntüleme

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Introduction

Schwannomas are the most common benign tumors of upper extremities and originated from Schwann cells of the myelin sheath. The symptoms are solitary, painless swelling as encapsulated mass [1]. They are located on the flexor surface of the upper limbs because upper extremities have more nerve fiber than other extremities parts. They are immobile in a longitudinal plane [2]. Schwannomas cause paresthesia or hypoesthesia and Tinnel's sign is positive [3]. They usually arise from single nerve fiber and grow circumferentially [4].

Magnetic resonance imaging (MRI) is one of the best to use on schwannomas radiological test. They are observed isointense of T1- weighted and hyperintense of T2-weighted [5]. Diagnosis is identified as microscopic for the lesions that diagnosed schwannomas on MRI [6]. Schwannomas contain histopathologically two various areas, Antoni A and Antoni B. Antoni A is an area that is formed by fusiform cell fascicule. Nucleus of cells is the shape of the elongated, and cytoplasm range is unclear. Antoni B area is the area that shows loose, edema, microcystic and hypocellular areas. Also, Antoni A area includes Verocay bodies which bizonal and bipolar array of the nucleus and homogenous pink area between them [7].

The aim of this study is to evaluate, pre and postoperative pain, paresthesia, hypoesthesia in patients who are diagnosed with schwannomas on the ulnar nerve by mutual agreement between pathology and MRI.

Materials and methods

Retrospective cohort study was designed from January 2011 – December 2016, 15 patients who had surgery ulnar nerve mass and had been diagnosed schwannomas were included in the study. Ethical approval was obtained from institutional research committee and with the 1964 Helsinki declaration and comparable ethical standards. All patients were informed about the study in detail and a signed consent form was obtained from each patient.

The average age of patients was 36.4 (19 – 61) and gender classification 6 male, 9 women. The anatomical classification was at 6 arms, 4 elbows and 5 forearms. All patients were detected an immobile mass in longitudinal line preoperatively. Tinel's signs were positive at five patients. Seven patients had paresthesia and pain, five patients had only pain and three patients had only paresthesia. Before surgery, all patients were diagnosed with nerve mass through by MRI. Patients were operated under regional anesthesia and microscope. The nerve was explored and the epineural incision was made longitudinally. The capsule was cut and reached to the tumor. Uninvolved nerve fibers were protected. The tumor was excised without harming nerve fibers (Figure 1). All skin layers were repaired after hemostasis.

Results

All patients have diagnosed with histopathological schwannomas (Figure 2). All tumors were observed isointense in T1-weighted images and hyperintense in T2-weighted ones (Figure 3). Nerve injuries and motor deficit were not observed after surgery. All tumors were enucleated without harming any nerve fibers. The postoperative mean follow-up period was 12.4 months (9 – 29).

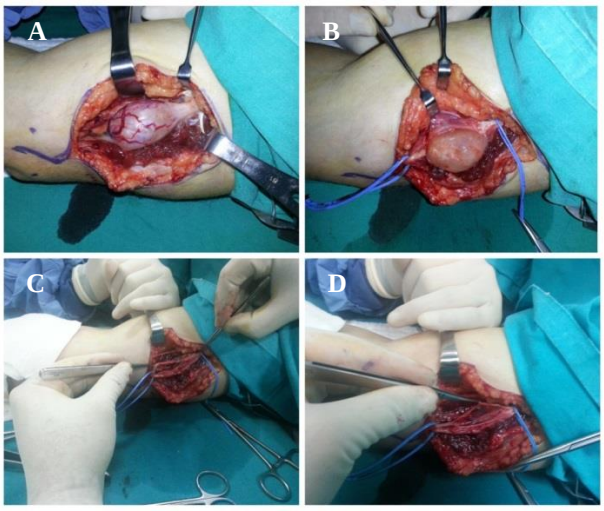

Figure 1: A: Intraoperative view of schwannoma, B: Capsule was incised. C: Schwannoma was enucleated, D: Unharmed ulnar nerve fibers

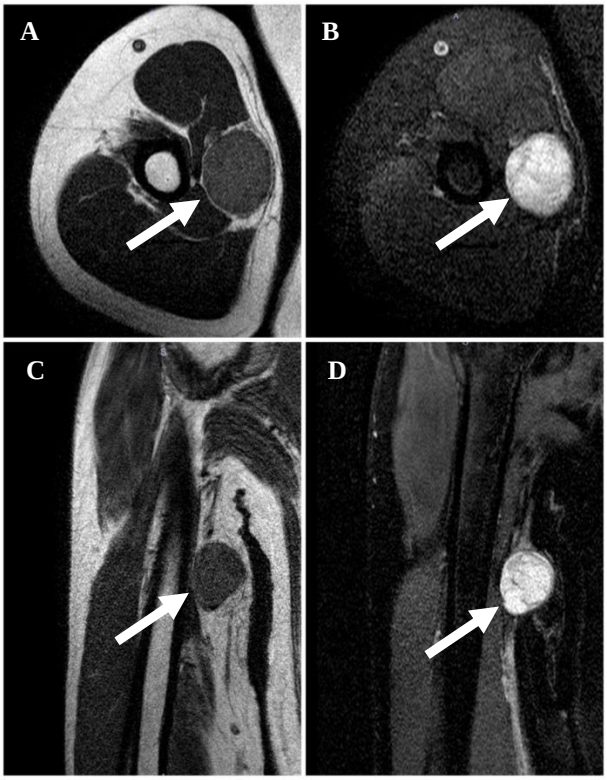

Figure 2: Magnetic resonance view of schwannoma, A,B: Axial plane, C,D: Sagittal plane, Arrow: Mass

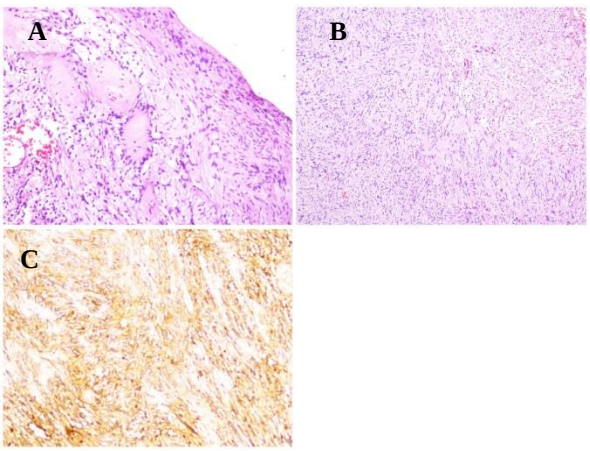

Figure 3: A: Spindle-shaped cells in a fasciculated architecture. There were also hypercellular Antoni A areas and hypocellular Antoni B areas. (H&E x100), B: Nuclear palisading around fibrillary process (Verocay bodies) were seen in cellular areas (H&E x200), C: Immunohistochemical studies revealed S100 protein positivity (x200)

In the early postoperative period, paresthesia, pain, and hypoesthesia were noted in 10 patients. Neurological symptoms were recovered in postoperative 5 months. There were only 2 patients who complained about the pain. Patients are summarized in Table 1.

Table 1: Demographic characteristics of the patients and evaluation parameters

	Age / Gender	Localization	Symptoms	Tinel's Sign	Size	Early Postoperative
1	21/M	Right Elbow	Pain and paresthesia	-	57x27x36 mm	Pain and paresthesia
2	32/F	Left Elbow	Pain	-	55 x 30x 46 mm	Hypoesthesia
3	44/M	Right arm	Pain and paresthesia	-	33.8x21.4x15.4 mm	-
4	39/F	Left Arm	Pain	+	42x31x38 mm	Pain
5	61/ M	Left forearm	Paresthesia	+	21x12x18 mm	Hypoesthesia
6	37/F	Left Elbow	Pain and paresthesia	-	58x32x41 mm	Pain and paresthesia
7	55/F	Right Arm	Pain and paresthesia	+	44x38x40 mm	-
8	28/M	Right Forearm	Pain	-	29x24x26 mm	Pain
9	33/F	Left Elbow	Pain and paresthesia	-	37x26x32 mm	Hypoesthesia
10	26/M	Left Forearm	Pain	+	41x31x34 mm	Pain
11	41/F	Right arm	Paresthesia	-	23x18x22 mm	-
12	19/F	Right arm	Pain and paresthesia	+	36x28x31 mm	Hypoesthesia
13	29/F	Left Forearm	Pain	-	45x37x39 mm	-
14	31/M	Left arm	Pain and paresthesia	-	52x36x44 mm	Pain and paresthesia
15	51/F	Right forearm	Paresthesia	-	43x35x38 mm	-

Discussion

Primary peripheral nerve tumors are rare and about 5% of them are upper extremities soft tissue tumors. Schwannomas are the most common tumors [8]. The first step of treatment is to proper diagnosis and when you face various symptoms such as slowly growing mass, pain, paresthesia and mass on the flexor surface of upper extremities, schwannomas should be kept in mind to be in charge of [9].

Open and fine needle aspiration biopsy can harm nerve even though the actual diagnosis is schwannoma in a histopathological manner. For that reason, radiologic screening needs to be evaluated and it must be applied to all patients before the surgery. It can be observed the location of tumor on nerve and relationship with surrounding tissues [10].

Treatment of schwannomas is to remove the tumor as intracapsular under the microscopically [11]. There are some studies that show minimum nerve harm [1,9]. But it has said that this surgery is difficult at a digital level and tumor should be removed completely [1]. In our study, all tumors nerve were removed intracapsular enucleation and observed paresthesia and pain were continued in a short-term but their symptoms were ended in the long term. Pulling traction of the nerve during the surgery is the reason of pain and paresthesia in a short term. We did not observe any motor nerve deficit in our patients.

Schwannomas are categorized as involved and not involved nerve fibers. Enucleation is enough on the patients not involved nerve fibers. If nerve fibers got involved, this nerve is included excision and immediately nerve should be repaired with nerve graft in order not to observe motor nerve deficit after surgery [3]. Involved nerve fibers were separated from tumor under microscopically and there was no need the use of nerve graft in our all patients.

After surgery relapse is a very rare condition of solitary and benign schwannomas. Relapse develops with the wrong diagnosis and not enough excision. This leads to secondary operation for patients [1]. Radiological images of patients should be examined well before the operation to prevent secondary surgery. Also, it must be kept in mind that some nerve can be involved in different tumors. In our study, the radiological screening of patients before the surgery ulnar nerve schwannomas has been found solitary and encapsulated mass.

Schwannomas are can be despited with some radiological tests such as ultrasonography, computerized tomography (CT) and MRI [13]. USG is a fast and easy method to access. Nerve pathology is certain diagnosed with high-resolution ultrasonography, even though MRI is the best for certain diagnosis method. Because MRI provides high resolution and three-dimensional screening but this advantages of MRI is high financial cost and not easy to reach [14]. All patients included in our study were diagnosed with histopathological schwannomas. Those patients were diagnosed the same as before surgery on MRI. Some studies show the sensitivity of MRI 91% and 51% for ultrasonography [2,9].

Possible neurological problems after schwannomas excision are between 1.5-80% [15]. Complications of high rate usually are the evaluation of postoperatively early stage [16]. 95% of problems are usually down between the first few months and a year [9]. The complications of our patients who are included in our study were gone completely in 5 months and the motor deficit was not observed. Malign transformation should be taken into consideration if the motor deficit is observed after surgery in a period of time [17].

Limitations

Main limitation of the study is the number of cases but the number was actually not less because the incidence of peripheral nerves schwannomas in adults is only 5% and upper limb schwannomas contribute 19% of them [18].

Conclusions

Schwannomas are solitary and benign tumors that are shown on the median and ulnar nerve. MRI and high-resolution ultrasonography are the help to plan the treatment before the surgery. They are removed as intracapsular with acceptable complication ratio. Removing schwannomas can cause some sensational deficit such as pain and paresthesia but these complications are spontaneously decreased.

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Effect of adrenocorticotropin hormone and cortisol on epithelial sodium channels according to delivery route

Adrenokortikotropin hormon ve kortizolün doğum şekline göre epitelyal sodyum kanalları üzerine etkisi

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Abstract

Aim: Immaturity of epithelial sodium channels (ENaC), which are affected by adrenocorticotropin hormone (ACTH) and cortisol, is believed to be the major underlying cause of transient tachypnea of the newborn. The aim of this study is to investigate the differences in ACTH and cortisol levels and the expression of lung ENaC α subunit of the babies in relation to mode of delivery.

Methods: The study was planned as prospective cohort study. Eighteen women who underwent elective caesarean section (C/S) and fifteen women who admitted to hospital for normal spontaneous delivery (NSD) and their term 33 newborn infants were included in the study. Blood samples for ACTH and cortisol levels were collected from the mothers prior to birth and the newborn infants 1 hour after birth. Nasal mucosa species of the infants were performed to assess ENaC α subunit levels.

Results: The ACTH and cortisol levels of mothers of C/S group were lower than the ACTH and cortisol levels of mothers of NSD group ($p<0.001$). Although the ACTH levels of infants delivered by C/S were significantly higher than the ACTH levels of infants delivered by NSD ($p=0.001$), no significant difference was identified between them with regards to the levels of cortisol ($p=0.078$) and ENaC α subunits ($p=0.671$).

Conclusion: Our results suggest that hormonal mechanisms in newborn infants function independently from their mothers. In term babies mode of delivery is not the major factor affecting the expression of ENaC α subunit.

Keywords: Adrenocorticotropin hormone, Cortisol, Epithelial sodium channels, Delivery route

Öz

Amaç: Adrenokortikotropin hormon ACTH ve kortizolün etkilediği epitelyal sodium kanalı (ENAC) immatüritesinin Yenidoğanın takipnesinin altta yatan başlıca nedeni olduğuna inanılmaktadır. Bu çalışmanın amacı doğum şekline göre ACTH, kortizol düzeylerinin ve bebeklerin akciğer ENaC alfa subünit ekspresyonunun ilişkisinin araştırılmasıdır.

Yöntemler: Çalışmamız prospektif kohort çalışma olarak planlandı. Hastanemizde elektif sezaryen(C/S) planlanan 18 gebe ve normal spontan doğum (NSD) için başvuran 15 gebe ve onların miat 33 yenidoğan bebekleri çalışmaya dahil edildi. ACTH ve kortizol için kan örnekleri annelerden doğumdan önce ve bebeklerinden doğumdan 1 saat sonra alındı. Bebeklerin ENaC α subunit değerlendirmesi için burun mukoza örnekleri alındı.

Bulgular: Sezaryen olan annelerin ACTH ve kortizol düzeyleri NSD yapan annelerin ACTH ve kortizol düzeylerinde daha düşüktü ($p<0,001$). Sezaryen ile doğan bebeklerin ACTH düzeyleri NSD ile doğan bebeklerin ACTH düzeylerinden anlamlı derecede yüksek ($p<0,001$) olmasına rağmen kortizol ($p=0,078$) ve ENaC α subunit düzeyleri arasında fark saptanmadı ($p=0,671$).

Sonuç: Çalışmamızın sonuçları yenidoğan bebeklerde hormonal mekanizmaların annelerinden bağımsız olduğunu göstermektedir. Miat bebeklerde doğum şeklinin ENaC α subünit ekspresyonunu etkileyen ana faktör olmadığını göstermektedir.

Anahtar kelimeler: Adrenokortikotropin hormon, Kortizol, Epitelyal sodium kanalı, Doğum yolu

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Introduction

It is believed that the underlying cause of transient tachypnea of the newborn is the lack of maturation of epithelial sodium channels (ENaC), which play an important role in controlling sodium movements and in the absorption of fluids in the alveoli [1-3]. ENaC in the airway epithelium is constituted of 3 sub units, which are α, β and γ. The α subunit is responsible for the channel functions of ENaC [4].

During pregnancy, the release of CRH (corticotrophin releasing hormone) from placental and fetal membranes increases progressively. By increasing both fetal adrenocorticotropin hormone (ACTH) and adrenal gland cortisol release, placental CRH initiates the process of delivery and enables the maturation of the fetus lung for postnatal adaptation [5]. As this mechanism is not involved in elective caesarean section, sufficient lung maturation and fetal lung fluid reabsorption does not take place. This factor along with iatrogenic prematurity contributes to a greater frequency of respiratory morbidity. Furthermore, it is known that these respiratory diseases' progression is also different in elective caesarean sections performed prior to the initiation of the delivery process, that these newborn infants require oxygen for longer periods, and that there is an increased need for CPAP and mechanical ventilation for these newborn infants [6]. It has been clinically demonstrated that the administration of antenatal corticosteroids in pregnant women with elective caesarean section planned in or near their term increases the clearance of fluids in the lung of their newborn [7].

The aim of this study is to evaluate the effects of ACTH and cortisol levels on the expression of neonate lung ENaC α subunit in mothers giving birth by spontaneous delivery and caesarean section delivery and their newborn infants. The study also aims to investigate the changes observed in hormone release according to the method of delivery.

Materials and methods

The study was planned as prospective cohort study. Eighteen pregnant women giving birth by elective caesarean section delivery and fifteen normal spontaneous vaginal delivery were included into this study along with their 33 newborn infants between January 2011 - September 2011 at the Akdeniz University Medical Faculty, Department of Gynecology and Obstetrics. Approval from the Akdeniz University Medical Faculty Ethics Committee was obtained prior to the study commencement (Ethics Committee approval no.: B.30.2.AKD.0.20.05.05/249). For pregnant women participating to the study, consent for blood sampling was also obtained.

Pregnant women with the prenatal risk factors of hypertension, eclampsia, early membrane rupture, diabetes or symptoms of infection were excluded from the study. Newborn infants born prior to 37 weeks of gestation, with perinatal asphyxia, or with meconium aspiration syndrome were also excluded from the study, as were the newborn of mothers who received antenatal steroids. In addition, cases which underwent urgent caesarean section for various reasons, such as fetal distress or labor in which normal spontaneous delivery commenced but did continue, were also not included into the study.

Pregnant women

From the eighteen mothers who have completed thirty seven weeks of gestation and underwent elective caesarean section, blood samples for ACTH and cortisol tests were obtained before epidural and/or general anesthesia was performed. From fifteen pregnant women admitted to hospital for normal spontaneous vaginal delivery (NSD), blood samples were obtained for ACTH and cortisol tests when their cervical opening was 4-6 cm and before spinal anesthesia was performed.

Newborn infants

Postnatal routine care and examinations were performed on the 33 newborn of mothers who gave birth by elective caesarean section or normal vaginal delivery. Twelve of the children were males (36.3 %) and twenty one were females (63.7 %). The newborn infants were also weighted. Their weight, gender, hour of birth, whether they had respiratory problems and whether they need intensive care was recorded. Their arterial blood pressure was measured in the first hour, before the blood samples were taken. One hour after birth, blood samples for ACTH and cortisol were obtained, and nasal mucosa sample from the frontal 1/3rd section of the nasal septum was collected with a rhinoprobe (Martin, Germany) in order to determine ENaC α subunit mRNA expression.

Clinical chemistry tests

Venous blood was collected for clinical chemistry assessments. Blood sugar was determined from the venous blood for each patient by using glucometer (GlucoLeader Yasee, LOTHA no 17082).

Blood samples for ACTH measurement were collected in tubes with EDTA and shipped in ice, while blood samples for cortisol measurement were collected in tubes without anticoagulants and shipped at room temperature to the laboratory. Plasma and serum in the samples were separated by centrifuging for 15 minutes. The separated plasma and serum were kept at -80°C until the assessment were performed.

Measurement of serum cortisol

By using the electrochemiluminescence immunoassay (ECLIA) procedure (Roche Modular Analytics E170), serum samples were measured in the immunoassay analyzer. The kit's intra-assay CV was 1.1% (control value: 15.1 µg/dL), inter-assay CV was %1.7 (control value: 14.8 µg/dL)

Serum ACTH measurement

Plasma samples with EDTA were measured by using the ECLIA procedure with the Cobas e 602 immunoassay analyzer within the Cobas 8000 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The kit's intra-assay CV was %1.5 (control value: 115 pg/mL), inter-assay CV was %1.7 (control value: 115 pg/mL) and the minimum level of insulin that could be measured was 1.0 pg/mL.

Quantification of the α-ENaC subunit mRNA in the nasal mucosa sample of newborn infants

The nasal mucosa samples obtained from the newborn infants were kept in RNAlater solution (RNA Stabilization Reagent for stabilization of RNA; QIAGEN Cat. No. 76104) at -20ºC until RNA isolation was to be performed. Approval from the Akdeniz University Medical Faculty Ethics Committee was

obtained prior to the procedure. (Ethics Committee approval no.: B.30.2.AKD.0.20.05.05/249)

Once all samples were collected, RNA was extracted by using High Pure RNA Isolation Kit (Roche Cat. No. 11 828 665 001). The qualitative and quantitative analysis of the obtained RNA samples was performed by a spectrophotometer (Beckman Coulter DU Series 700 Spectrophotometers Item No. A49421). A certain quantity of RNA was separated to prepare cDNA, and the remaining RNA samples were kept at -80ºC.

To obtain cDNA from RNA, Transcriptor High Fidelity cDNA Synthesis Kit (Roche Cat. No.05 081 955 001) was used. To test the cDNA that was obtained, PCR was performed using GADPH primers according to the procedure recommended by the kit. The results were controlled in 2% agarose gel.

After the PCR result was obtained, RealTime-PCR (RT-PCR) was performed for the α-ENaC subunit. The obtained results were quantified in proportion to the GAPDH gene.

RT-PCR protocol (LC480)

The solutions to be used (water, probes master, primer) were removed from -20°C storage and thawed. Prior to opening their lids, samples were centrifuged in a microcentrifuge. Solutions were kept in ice during this procedure. The solution mixes were prepared according to the number of samples. The mixes were stirred with the use of a pipette. Of this mix, 8 µl were added to each cuvette of the LightCycler 480 Multiwell Plate. Following this, 2 µl of cDNA was added to each cuvette. Plate Lightcycler 480 was closed using the Sealing Foil (Lightcycler 480 Sealing Foil: Cat. No. 04 729 757 001). The Plate was centrifuged at 1500g for 2 minutes. LightCycler 480 (LightCycler 480 Instrument: Cat. No. 05 015 278 001) was placed in its device, and measurements were performed according to the protocol recommended by the kit (LightCycler 480 Probes Master: Cat. No. 04 707 494 001 and Real Time ready Assay: Cat. No. 05 532 957 001).

Statistical analysis

The data were analyzed using SPSS (version 20). To define the sample, statistics such as the frequency distribution, mean, standard deviation and median were used. In the comparison of continuous variables based on groups, the difference test between two means according to distribution assumptions or the Mann-Whitney U test were employed. The relation between continuous variables was assessed using the Spearmen Correlation analysis. In addition, the Chi-squared test was employed in the analysis of categorical variables. To be able to identify differences in the analysis, a 95% level of significance was used.

Results

Eighteen pregnant women giving birth by elective C/S (54.5% of cases) and fifteen pregnant women giving birth by NSD (45.5% of cases) were included into this study along with their newborn infants between January 2011 - September 2011 at the Akdeniz University Medical Faculty Department of Gynecology and Obstetrics. Informed consent was obtained from all pregnant women. Spinal anesthesia was used in all 18 (100%) of the mothers giving birth by elective C/S and in 1 (6.6%) of the mothers giving birth by NSD. TTN developed in 2 (11.1%) of the newborn infants delivered by elective C/S and in 1 (6.6%) of the newborn infants delivered by NSD. Oxygen support was provided to these newborn infants.

Evaluation of the data for the mothers

ACTH levels in mothers giving birth by elective C/S [39.89 pg/mL [7.90-96.13] were found to be significantly lower compared to the levels in mothers giving birth by NSD [118.80 pg/mL [30.90-354] (p<0.001). Similarly, cortisol levels in mothers giving birth by elective C/S [31.28 µg/dL [17.41-48.97] were found to be significantly lower compared to the levels in mothers giving birth by NSD [52.68 µg/dL (25.33-138.30)] (p<0.001) (Table 1).

Evaluation of the data for the newborn infants

Of the infants born by elective C/S, 5 were male (27.8%) and 13 were female (72.2%), while of the infants born by NSD, 7 were male (46.7%) and 8 were female (53.3%).

Gestation age was determined as 38 weeks (38-39) for infants born by elective C/S and 39 weeks (38-40) for infants born by NSD. A statistically significant difference was identified between these two groups (p=0.001). Of the infants born by elective C/S, 13 (72.2%) were delivered in 38th week of gestation, and 5 (27.8%) were delivered in the 39th week of gestation or later; of the infants born by NSD, 3 (20%) were delivered in the 38th week of gestation, and 12 (80%) in the 39th week of gestation or later. The birth weight of the infants delivered by elective C/S was determined as 3200 gr (2568-4150), and for the infants delivered by NSD it was determined as 3305 gr (2735-3790). No statistically significant difference was identified between these two groups (Table 2).

ACTH levels of infants born by elective C/S [141.4 pg/mL (19.39-447.40)] were found to be significantly higher (p=0.001) than the ACTH levels of infants born by NSD [47.56 pg/mL (15.64-119.70)]. On the other hand, no significant difference was identified (p=0.078) between the levels of cortisol of infants born by elective C/S [20.56 µg/dL (8.67-33.85)] and the levels of cortisol for infants born by NSD [27.56 µg/dL (6.97-48.75)].

Table 1: Comparison of laboratory data according to method of delivery

Parameters Evaluated	Method of Birth	Median (Minimum-Maximum)	p
ACTH (pg/mL)	C/S* (n:18)	39.89 (7.90-96.13)	<0.001
	NSD** (n:15)	118.80 (30.90-354)	
Cortisol (µg/dL)	C/S (n:18)	31.28 (17.41-48.97)	<0.001
	NSD (n:15)	52.68 (25.33-138.30)	

* Mother giving birth by caesarean section, ** Mother giving birth by normal spontaneous vaginal birth

Table 2: General data for newborn infants born by C/S and by NSD

General Characteristics	Group	Number of Cases	Median (Minimum-Maximum)	p
Gestation Week	C/S*	18	38.2 (38-39)	0.001
	NSD**	15	39 (38-40)	
Birth Weight (gram)	C/S	18	3200 (2568-4150)	0.874
	NSD	15	3305 (2735-3790)	
Blood Sugar (mg/dL)	C/S	18	76.50 (56-111)	0.856
	NSD	15	79.00 (59-11)	
Systolic Blood Pressure (mmHg)	C/S	18	69.50 (57-81)	0.542
	NSD	15	69.00 (53-103)	
Diastolic Blood Pressure (mmHg)	C/S	18	38.00 (23-59)	0.741
	NSD	15	34.00 (21-60)	

* Newborn infants born by caesarean section, **Newborn infants born by normal spontaneous vaginal delivery

The ENaC α subunit level in newborn infants delivered by elective C/S was determined as 2.729 relative to the expression of GADPH (1.0-4.98), and for newborn infants

delivered by NSD it was determined as 3.39 relative to the expression of GADPH (0.445-5.769). No statistically significant difference was identified between the two groups (p=0.671) (Table 3, 4).

Evaluation of the data for the newborn according to the gestation periods

When the data of the newborn infants were evaluated according to their gestation ages, it was determined that the birth weight of infants born in the 38th week was 2990 gr (2568-4150), while the birth weight of infants born in the 39th week or later was 3390 gr (3015-3900). No statistically significant difference was identified between the two groups based on their birth weight according to gestation weeks (p=0.671) (Table 3, 4).

Similarly, no statistically significant difference was identified (p=0.140) between the ACTH levels for infants born in the 38th week [114.2 pg/mL (19.39-447.40)] and the ACTH levels for infants born in the 39th week or later [59.47 pg/mL (15.64-209.50)].

Table 3: ACTH, cortisol and ENaC α subunit levels for newborn infants

Parameters Evaluated	Method of Delivery	Median (minimum-maximum)	p
ACTH (pg/mL)	C/S* (n:18)	141.40 (19.39-447.40)	0.001
	NSD** (n:15)	47.56 (15.64-119.70)	
Cortisol (µg/dL)	C/S (n:18)	20.56 (8.67-33.85)	0.078
	NSD (n:15)	27.56 6.97-48.75	
ENaC α subunit	C/S (n:18)	2.729 (1.0-4.98)	0.671
	NSD (n:15)	3.39 (0.445-5.76)	

* Newborn infants born by caesarean section, * Newborn infants born by spontaneous vaginal delivery

Table 4: Comparison of the ACTH, cortisol and ENaC α subunit levels according to gestation age of newborn infants

Evaluated Parameters	Infants born in 38th week of gestation (n:16) Median (Minimum-Maximum)	Infants born in 39th week of gestation or later (n:16) Median (Minimum-Maximum)	p
ACTH (pg/mL)	114.2 (19.39-447.40)	59.47 (15.64-209.50)	0.140
Cortisol (µg/dL)	20.48 (8.67-48.75)	27.48 (6.97-39.52)	0.293
ENaC α subunit	2.955 (1.0-5.76)	2.675 (0.445-4.79)	0.295

With regards to cortisol, no statistically significant difference was identified (p=0293) between the levels for infants born in the 38th week [20.48 µg/dL (8.67-48.75)] and the levels for infants born in the 39th week of gestation or later [59.47 pg/mL (15.64-209.50)].

The ENaC α subunit level in newborn infants delivered in the 38th week was determined as 2.955 relative to the expression of GADPH (1.0-5.76), and for newborn infants delivered in the 39th week or later it was determined as 2.675 relative to the expression of GADPH (0.445-5.769). No statistically significant difference could be identified between the gestation period for the newborn infants and the ENaC α subunit levels (p=0.295).

Discussion

As is also the case worldwide, the frequency of elective caesarean section has risen significantly in our country over the last years based on the expectation that it will decrease the risk birth asphyxia, trauma and meconium aspiration encountered during delivery. However, as this method of delivery is often performed in the 37-38th weeks of gestation, which are accepted as being close to the end of term, infants are born before lung maturation is complete and transient tachypnea of newborn (TTN) is becoming an increasingly more frequent respiratory problem. It has been shown in the literature that elective caesarean section deliveries lead to iatrogenic prematurity, which causes an increase in respiratory morbidity in association with the insufficiency of surfactant production and TTN [8,9]. For this reason, ACOG and the European RDS have decided that elective caesarean sections should not be performed before the end of the 38th week of gestation as long as there are no problems necessitating an early delivery [10,11]. Taking this recommendation into consideration, efforts are now being made in our hospital's Obstetrics Clinic to avoid performing elective caesarean section prior to the 38th week of gestation. Despite these efforts, it was nevertheless found that the gestation week of infants born by elective C/S was significantly lower than the gestation week of infants born by NSD.

The process of delivery leads to a stress response by stimulating both the fetal and maternal systems. While pain, uterine contractions and the mother's anxiety during delivery stimulates stress hormones in the mother, the mechanical stress and hypoxia, associated with the infant's passage through the birth canal constitutes the fetal stress response. The stress experienced during the passage through the birth canal is essential for the adaptation of the newborn infant to postnatal life, and this stress stimulates stress hormones such as cortisol in infants born through NSD. It has been demonstrated in various studies that uterine contractions, pain and stress of delivery in the mother initiates this cycle during normal delivery and that, for this reason, ACTH levels are higher in mothers giving birth by NSD [12,13]. It was found in our study that ACTH levels were also significantly higher in mothers giving birth by NSD compared to the levels in mothers giving birth by caesarean section. Similarly, the level of cortisol in mothers giving birth by NSD was significantly higher compared to the levels in mothers giving birth by caesarean section.

It is known that during delivery, placental CRH increases cortisol release from the adrenal in the fetus by stimulating fetal ACTH secretion. For this reason, it is assumed that both the ACTH and the cortisol levels are higher in newborn infants that undergo normal spontaneous vaginal delivery and experience this trauma. However, contrary to what might be expected, our study's results have shown that ACTH levels in infants born by NSD is lower compared to the ACTH levels observed in infants born by caesarean section. Although no statistically significant difference was identified between the two groups of newborn infants with regards to the levels of cortisol, the level of cortisol in infants born by NSD was found to be slightly higher in comparison to the level of cortisol in infants born by caesarean section. Several differences are observed in the results of studies conducted on ACTH and cortisol level in newborn infants depending on the method of delivery [14-17]. In Ocheldalski's study [13], no difference was identified in the umbilical cord ACTH levels in infants born by caesarean section and NSD. On the other hand Zenciroğlu et al. [14] determined that while umbilical cord ACTH levels were higher in newborn infants born by NSD, no difference was found in the 1st hour venous blood samples.

In our study, depending on the method of delivery, both the ACTH and cortisol levels of mothers giving birth by NSD was higher than the ACTH and cortisol levels observed in mothers giving birth by caesarean section. On the other hand, ACTH levels in infants born by NSD were found to be lower compared to the levels in infants born by caesarean section, while the cortisol level in both groups was determined to be close to one another. These results appear to indicate that it is necessary for a certain level of cortisol to be attained by the newborn for postnatal life, and that in order to achieve this, the newborn infant can modify its own levels of ACTH, regardless of the method of delivery or maternal influence. In addition, the independence of the newborn infant's ACTH and cortisol levels from their mother suggest that the underlying causes of fetal and maternal stress might be different.

The higher frequency of TTN in infants that are born by elective caesarean section has led to an increase in the number of studies conducted on the endogenous factors that are involved in the regulation of ENaC expression during delivery. Our results demonstrate that ENaC α subunit expression does not vary according to the method of delivery or gestation week (p: 0.671 according to the method of delivery, and p: 0.295 according to gestation week). We are of the opinion that the lack of difference in the level of expression of ENaC α subunit between the two groups is due to the importance of the role of cortisol in ENaC expression and the fact that cortisol levels in both groups of newborn infants were very close to one another. The results regarding the relation between ENaC subunit expression and the method of delivery in the previously conducted studies are also contradictory. Baines et al. [18] have concluded that day 1 ENaC α subunit expression in newborn guinea pigs undergoing term C/S delivery is higher than in term normal newborn infants born by vaginal delivery, and that ENaC α subunit expression is independent of the process of delivery and that expression increases postnatally. In their study, Helve et al. [19] have assessed postnatal ENaC α subunit expression at 1-5 hours and 22-28 hours after birth in term newborn infants, and determined that there were no differences based on method of delivery at 1-5 hours. However, while the ENaC α subunit expression of infants born by term vaginal delivery decreased at 22-28 hours, this decrease was not observed in infants born by caesarean section. The high level of ENaC α subunit level observed for a longer period in infants born by caesarean section was explained by the fluid absorption potential being possibly higher in infants born by vaginal delivery. In the study conducted by Janer et al. [20], while ENaC α subunit expression in the first 3 hours was higher in infants born by elective caesarean section than in infants born by vaginal delivery, no difference in levels of expression was identified at the 24th and 48th hours after birth. While the gestation week of the newborn from both groups in the study of Helve et al. [19] were similar, the gestation weeks of newborn infants born by caesarean section was found to be lower, which was also the case in our study. In Janer et al.'s study [20], a positive correlation was identified between the ENaC α subunit expression in nasal mucosa collected in the first 30 minutes following caesarean section delivery and the plasma cortisol in the umbilical cord blood, and when all cases included to the study were evaluated together, saliva cortisol and ENaC α subunit mRNA expression were also found to be correlated in the first 2 hours after birth. In our study, no correlation was identified between the ACTH and cortisol levels and the levels of ENaC α subunit in infants born by either elective caesarean section or NSD.

The limitation of our study is that the number of cases is low and the blood is taken in a single hour for hormone levels which is a dynamic process.

In conclusion, our study's results have demonstrated that although ACTH and cortisol levels in mothers giving birth by NSD is higher than the ACTH and cortisol levels in mothers giving birth by caesarean section, the levels observed in the infants are not in accord with the values observed in their mothers. In parallel with the cortisol levels in the newborn infants, no differences were identified between the groups with regards to ENaC α subunit expression. Our results suggest that hormonal mechanisms in newborn infants function independently of their mothers, and that infants might regulate their own ACTH levels in order to maintain their cortisol level at a certain level. However, as the ACTH and cortisol hormones that were assessed are very dynamic substances, capable of significantly changing within a few hours, we consider that it might be beneficial to assess ACTH, cortisol levels and ENaC α subunit expression at birth and also 1, 2, 6, 12, 24, 36 and 48 hours after birth, in order to clarify the relationship between them more apparent.

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Percutaneous transhepatic biliary drainage related infectious complications after living donor liver transplantation

Canlı vericili karaciğer nakli sonrası perkütan biliyer drenaja bağlı enfeksiyöz komplikasyonlar

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Abstract

Aim: Biliary complications were the most common cause of morbidity after living donor liver transplantation. Percutaneous transhepatic biliary drainage (PTBD) is performed in this patients. The purpose of our study was to determine the rate of PTBD related infection (cholangitis and sepsis) after living donor liver transplantation.

Methods: This is a retrospective cohort study. Fifty two patients PTBD procedures were performed after living donor liver transplantation. Two main groups were established; Post PTBD infection group and non-infection group. Demographic characteristics, infectious complications and mortality rates were compared.

Results: PTBD procedure related infection (cholangitis and sepsis) rate was 52% (28 patients) and early (thirty days) mortality rate was 17.9% (5 patients).

Conclusion: PTBD related infectious complication and mortality rates are high. In these patients we need to be very careful after PTBD.

Keywords: Living donor liver transplantation, Percutaneous transhepatic biliary drainage, Infectious complications

Öz

Amaç: Biliyer komplikasyonlar canlı vericili karaciğer nakli sonrası en sık görülen morbidite nedenidir. Bu hastalarda perkütan transhepatik biliyer drenaj (PTBD) yapılır. Çalışmamızın amacı canlı vericili karaciğer nakli sonrası PTBD'ye bağlı enfeksiyon (kolanjit ve sepsis) oranını belirlemekti.

Yöntemler: Bu retrospektif kohort bir çalışmadır. Elli iki hastaya canlı vericili karaciğer nakli sonrası PTBD işlemi uygulandı. Hastalar iki gruba ayrıldı. PTBD sonrası enfeksiyon gelişen ve gelişmeyen grup. Bu iki grubun demografik özellikleri, enfeksiyöz komplikasyonları ve mortalite oranları karşılaştırıldı.

Bulgular: PTBD prosedürüne bağlı enfeksiyon (kolanjit ve sepsis) oranı %52 (28 hasta) ve erken (otuz gün) mortalite oranı %17,9 (5 hasta) idi.

Sonuç: PTBD ile ilişkili infeksiyöz komplikasyon ve mortalite oranları yüksektir. Bu hastalarda PTBD'den sonra çok dikkatli olmak gerekir.

Anahtar kelimeler: Canlı vericili karaciğer nakli, Perkütan transhepatik biliyer drenaj, Enfeksiyöz komplikasyonlar

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Introduction

The only definitive treatment of end stage liver disease is liver transplantation. In countries where cadaveric liver transplantations are limited, living donor liver transplantation is performed. Percutaneous transhepatic biliary drainage (PTBD) is an effective management of biliary leakage and strıcture after lıvıng donor liver transplantation and it involves sterile cannulation of a peripheral bile duct, cholangiography, determining the location of bile issues, catheter positioning above the bile anastomosis and allowing decompression of the biliary system [1-3]. PTBD is effective at relieving biliary leakage and stricture; however, it has been associated with complications including sepsis, cholangitis and pancreatitis [4].

The aim of the present study was to review PTBDs related infectious complications and mortality rate after living donor liver transplantation.

Materials and methods

Between December 2014 and December 2018 at Medipol University Medical Faculty Hospital Organ Transplantation Department, Istanbul, Turkey, 220 patients with living donor liver transplantation were studied retrospectively. PTBD procedures were performed in 52 (24%) patients.

Two main groups were established; Post PTBD infection group and non-infection group. For each of these groups, the age, sex, etiology, CHILD scores, Model for End-Stage Liver Disease (MELD) scores, rationale of PTBD, infectious complications and early (first thirty days) mortality rates were compared. Also, bacterial and fungal infectious agents and using antibiotic and antifungal types were evaluated.

Patients

For all patients, informed consent was obtained before the procedure. All patients were given pre-PTBD prophylactic antibiotic coverage with 4.5 g of intravenous piperacillin/tazobactam. Patients who were allergic to penicillin or cephalosporin were administered 400 mg of intravenous ciprofloxacin at before 1 hour the procedure.

New developed cholangitis was defined as fever (>38.5°C) that arises within 24 hours after the PTBD. After taking blood for hemoculture (two sets-4 bottles- 40 milliliters blood) and bileculture (10 milliliters bile) at the tıme of fever, the treatment was continued with prophylactic antibiotics (piperacillin/tazobactam or ciprofloxacin).

New developed sepsis includes the criteria for cholangitis as well as the development of hemodynamic instability (heart rate ≥90 beats/minute, respirations ≥ 20/minute) such as a drop in blood pressure requiring intravenous fluid resuscitation, administration of vasopressors within 24 hours of the PTBD. All patients with sepsis were routinely transferred to intensive care unit. Antibiotic treatment was changed according to the hemoculture and bileculture.

Statistical Analysis

SPSS 22.0 (SPSS for Windows, 2007, Chicago) was used for statistical analysis. Continuous variables which have normal distribution were presented as mean ± Standard deviation. Statistical analysis for the parametric variables was performed by the Student's T-test. The qualitative variables were given as percent and the correlation between categorical variables was investigated by the chi-square test and Fisher's exact test. Statistical significance level was defined as $p<0.05$.

Results

Mean age of the infection group was 53.5 (19-71) years; non-infection group was 57.5 (26-69) years, 36 (70 %) of the 52 patients PTBD procedures were male.

Mean CHILD scores of the infection group was 8.5 (6-15); non-infection group was 9 (6-12) respectively. Mean MELD scores of the infection group was 16.5 (8-40); non-infection group was 16.5 (10-30), respectively.

The common etiologic factors of transplantation were HBV in 10 (71.4%) patients (in the infection group), non-alcoholic steatohepatitis in six (46.2%) patients and cryptogenic in six (66.7%) patients (in the non-infection group).

Table 1 shows the comparison of demographic and clinical findings of the infection and non-infection groups. PTBD procedure related infectious complications (cholangitis and sepsis) rate was 52% (28 patients) and early (first thirty days) mortality rate was 17.9% (5 patients). The cause of death in all cases was post-PTBD sepsis.

Table 1: Demographic and clinical data of the groups

		Infection (n=28)	Non-Infection (n=24)	p
Age (Years)		53.5 (19-71)	57.5 (26-69)	0.291
Sex (M/F)		22 (78.6%) / 6 (21.4%)	14 (58.3%) / 10 (41.7%)	0.141
CHILD		8.5 (6-15)	9 (6-12)	0.268
MELD		16.5 (8-40)	16.5 (10-30)	0.847
Etiology		n (%)	n (%)	
	HBV	10 (71.4)	4 (28.65)	0.185
	NASH	7 (53.8)	6 (46.2)	
	Cryptogenic	3 (33.3)	6 (66.7)	
	Autoimmune	2 (50)	2 (50)	
	SBC	3 (100)	-	
	PSC	-	3 (100)	
	HCV	2 (66.7)	1 (33.3)	
	Ethanol	1 (33.3)	2 (66.7)	
Requirement for PTBD				0.022
	Stricture	11 (39.3)	17 (70.8)	
	Leak	17 (60.7)	7 (29.2)	
Early Mortality		5 (17.9)	-	0.038

M: Male, F: Female, HBV: Hepatitis B Vırus, NASH: Non-alcoholic Steatohepatitis, SBC: Secondary biliary cirrhosis, PSC: Primary Sclerosing Cholangitis, HCV: Hepatitis C Vırus, PTBD: Percutaneous Transhepatic Biliary Drainage

Table 2 shows the comparison of bacterial and fungal infectious agents of the two patient groups. The most common cause of bacterial infectious agents was Klebsiella in 15 (53.6%) patients detected in the blood, the most common fungal infectious agents was Candida in 6 (21.4%) patients detected in the blood. All patients were using tacrolimus and mycophenolate mofetil as immunosuppressive therapy after liver transplantation. Table 3 shows the comparison of used antibiotic or antifungal medications. The most commonly used antibiotic was meropenem (42.3%), and the antifungal was anidulafungin (28.8%).

Table 2: Bacterial and fungal agents data of the groups

		Infection	Non-Infection
Klebsiella	Bile	17 (60.7%)	1 (4.2%)
	Blood	15 (53.6%)	-
Enterococcus	Bile	18 (64.3%)	8 (33.3%)
	Blood	9 (32.1%)	-
Pseudomonas	Bile	12 (42.9%)	2 (8.3%)
	Blood	7 (25%)	-
E.coli	Bile	22 (78.6%)	1 (4.2%)
	Blood	7 (25%)	-
Candida	Bile	13 46.4%)	4 (16.7%)
	Blood	6 (21.4%)	-
Acinetobacter	Bile	3 (10.7%)	-
	Blood	5 (17.9%)	-

Table 3: Antibiotics and antifungals used for infection

Antibiotics and Antifungals	n	%
Meropenem	22	42.3
Teicoplanin	18	34.6
Piperacillin/tazobactam	17	32.7
Anidulafungin	15	28.8
Tygacil	7	13.5
Colistin	2	3.8
Imipenem	2	3.8

Discussion

The only definitive treatment of end stage liver disease is liver transplantation. In countries where cadaveric liver transplantations are limited, living donor liver transplantation is performed. In our clinic, 220 patients performed living donor liver transplantation in four years. Patients with living donor liver transplantation carry a higher risk of biliary system complications [5,6] and this complication rate is 20 to 40 % [7-9]. Biliary complications were the most common cause of morbidity after living donor liver transplantation. In addition to biliary complications were shortening graft and recipient survival [10]. In our clinic, there are 52 (24 %) patients with biliary complications (leakage and stricture) in four years.

PTBD is an effective management of biliary complications after living donor liver transplantation [3]. PTBD is performed in patients with biliary leakage and stricture at the earliest. In our clinic, PTBD procedures were performed in all biliary complication patients. PTBD success rate was >95%, but first thirty days significant infectious complications [11]. PTBD related infectious complications (sepsis and cholangitis) have an incidence rate of 34% [12,13]. In our study PTBD procedure related infectious complications (cholangitis and sepsis) rate was 28 (52%) patients.

Pre-PTBD prophylactic antibiotics reduce the incidence of sepsis and cholangitis [14-16]. Making pre-PTBD prophylactic antibiotics to living donor liver transplantation group is more important. Prophylactic antibiotics including coverage for Klebsiella, Escherichia Coli, Enterococcus and Pseudomonas Aeruginosa, decrease risk of potential septic complications [17]. In our study, all patients took pre-PTBD prophylactic antibiotic coverage with 4.5g of intravenous piperacillin/tazobactam. Patients who were allergic to penicillin or cephalosporins were administered 400 mg of intravenous ciprofloxacin. The detected blood culture overgrowth bacteria were Klebsiella 53.6%, Enterecoccus 32.1%, Psodomonas 25%, Escherichia Coli 25%, Acinetobacter 17.9% and fungus was Candida 21.4% in the infection group.

PTBD related infectious complications (sepsis and cholangitis) have an early mortality rate of approximately 20% [18,19]. In our study PTBD procedure related early mortality rate was 17.9 % (5 patients). The cause of death in all cases was post-PTBD sepsis. In our study, the commonly used drugs are meropenem 42.3%, teicoplanin 34.6%, piperacillin/tazobactam 32.7%, anidulafungin 28.8%, tygacil 13.5%, colistin 3.8%, imipenem 3.8%.

Our study has several limitations. First, this study was retrospective. Second, the number of cases in PTBD performed and infectious complications were small.

In conclusion, PTBD is an effective management of biliary complications but infectious complications and mortality rates are high. In these patients we need to be very careful after PTBD.

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Outcomes of intravenous thrombolytic and adjuvant surgery in acute limb ischemia: Review of 23 patients

Akut bacak iskemisinde intravenöz trombolitik ve adjuvan cerrahi tedavi sonuçları: 23 olgunun değerlendirilmesi

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Abstract

Aim: Today, combined thrombolytic and surgical adjuvant embolectomy is known to have positive results in acute limb ischemia (ALI) treatment. In thrombolytic therapy, the intra-arterial method is generally used. In our study, we performed an intravenous thrombolytic and / or adjuvant surgical embolectomy in patients with failed bypass or diffuse aorta vascular disease who were unable to perform catheter directed thrombolytic therapy (CDT) due to technical difficulties. We evaluated the mortality and morbidity results of the patients.

Methods: Retrospective cohort study was planned. This study consists of patients treated for ALI between January 2014 and September 2018. First, the intravenous thrombolytic treatment was performed. The patients who failed this treatment were additionally treated with surgical embolectomy. The patients were in Rutherford Class IIa and IIb.

Results: A total of 23 ALI patients were included in the study. Thrombolytic treatment was performed on all of the patients. Twelve (52%) patients who failed thrombolytic treatment were also treated with surgical adjuvant embolectomy. In the first month, two patients (8.7%) required major amputation. In follow-up period of one year, a total three patients (13%) required major amputation and one patient (4.3%) had intracranial hemorrhage.

Conclusions: ALI, despite all the developments in its treatment, is still a life threatening disease. This study suggests that our rate of amputation, hemorrhage and extremity rescue are similar or a little lower than the large series of intra-arterial thrombolytic treatments in the literature. Today, the thrombolytic treatment methods have one thing in common which is the use of intra-arterial route. Yet we reckon that as in our study; the patients who cannot be treated with intra-arterial catheterization the intravenous thrombolytic therapy and/or surgical adjuvant embolectomy can be helpful in rescuing those patient's life and extremity.

Keywords: Acute limb ischemia, Intravenous thrombolytic, Adjuvant surgery

Öz

Amaç: Günümüzde ALI tedavisinde trombolitik ve kombine advujan cerrahi embolektominin iyi sonuçlar verdiği bilinmektedir. Trombolitik tedavi de genellikle intra-arteryel yolla yapılmaktadır. Başarısız bypass ya da diffüz aortailyak damar hastalarında teknik zorluktan dolayı intravenöz trombolitik ve/veya adjuvan cerrahi embolektomi yaptığımız hastaların mortalite ve morbidite sonuçlarını değerlendirdik.

Yöntemler: Bu çalışma Ocak 2014 ile Eylül 2018 yılları arasında ALI sebebiyle tedavi edilen hastalardan oluşmaktadır. Çalışma tek merkezli ve retrospektif olarak yapılmıştır. Tedavide öncelikle venöz trombolitik tedavi uygulandı. Bu tedavinin başarısız olduğu hastalarda ise ek olarak cerrahi embolektomi yapıldı. Hastalar Rutherford class IIa and IIb sınıfından oluşmaktadır.

Bulgular: Toplam 23 ALI hastası çalışmaya dahil edildi. Bütün hastalara trombolitik tedavi uygulandı. Trombolitik tedavinin yetersiz kaldığı 12 (52%) hastaya advujan cerrahi embolektomi yapıldı. İlk bir ayda 2(8,7%) hastada major amputasyon tespit edildi. Bir yıllık takip süresinde ise toplam 3(13%) hastada major amputasyon tespit edildi. 1 hastada (4,3%) oranında intrakranial hemoraji görüldü.

Sonuç: ALI tedavisinde günümüzdeki bütün gelişmelere rağmen hastaların ekstremite ve hayatlarını tehdit etmektedir. Bizim hasta grubumuzdaki amputasyon, kanama ve ekstremite kurtarma oranlarımız, literatürdeki intra-arteryel trombolitik tedavinin kullanıldığı geniş serilere benzer ya da biraz daha kötü olduğunu tespit ettik. Günümüzde trombolitik tedavi yöntemlerinde ortak nokta intra-arteryel yolun kullanımı şeklindedir. Ancak bizim çalışmamızda olduğu intra-arteryel kateterizasyonun kullanılamadığı hastalarda venöz trombolitik ve/veya kombine adjuvan cerrahi girişimlerin bu hastaların hayatını ve ekstremitesini kurtarmada faydalı olabileceğini düşünmekteyiz.

Anahtar kelimeler: Akut bacak iskemisi, Intravenöz trombolitik, Adjuvan cerrahi

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Introduction

The arterial embolization and the thrombus of native and graft vessels are the causes of acute limb ischemia. Acute limp ischemia (ALI) is a serious, life-threatening condition. The treatment is usually thrombolytic therapy with an intra-arterial catheterization. Intra-arterial thrombolytic therapy can be performed under local anesthesia and by this means, patients with comorbidities are treated more safely [1].

ALI patients are treated with surgical adjuvant embolectomy when catheter directed thrombolytic therapy (CDT) is not effective. There are also other new treatment choices like revascularization and endovascular treatment. Additionally, another treatment called percutaneous aspiration thrombectomy can also be performed [2]. Yet, in case of complex conditions like failed bypass graft or diffuse aorto-iliac arterial disease; CDT therapy would be difficult to perform due to arterial catheterization complexity. The purpose of this study is to present the results of ALI patients treated with intravenous thrombolytic therapy or surgical adjuvant embolectomy.

Materials and methods

This study consists of patients treated for ALI in our hospital between January 2014 and September 2018. This is a single center, retrospective cohort study. A written informed consent was obtained from each patient. The study protocol was approved by the Bursa Yüksek İhtisas Hospital Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki. The patient records were taken from the hospital's medical record system. All patients received physical examination, EKG, Echocardiography and routine blood tests. In the physical examination, the patient ALI was accepted in the presence of extremity coldness, pallor, cyanosis, pain, inability to palpate peripheral pulses and/or hand Doppler flow. Vascular scanning was performed with ultrasonography, computed tomography, angiography or conventional angiography (Figure 1). First, the patients were treated with intravenous thrombolytic therapy with Actilyse® (Boehringer Ingelheim, Ingelheim, Germany) which is a recombinant tissue plasminogen activator (rtPA). Patients with unhealed ischemia received surgical adjuvant embolectomy.

The inclusion criteria: Patients with diffuse arterial disease having intravenous thrombolytic therapy, ALI patients with failed bypass graft, patients with symptoms of less than 14 days duration, patients with arterial run-off detected by angiography and/or ultrasonography, ALI of class IIa and IIb according to the Rutherford classification [3].

Exclusion criteria: Patients with active bleeding, recent history of a major surgical operation, recent cerebral trauma, active cancer or recent history (last two months) of neurovascular disease were not included in the case study. Due to the risk of bleeding, patients with anemia (Hemoglobin <8gr/dl), thrombocytopenia (Platelet <80000), with an INR above 1.5 and with serious renal insufficiency are not able to have thrombolytic therapy, for this reason, they are excluded from the study.

The thrombolytic treatment procedure started with Actilyse® bolus dose of 4-5 mg, followed by 0.5-1 mg/h/kg. Total dose was 50 mg. Patients were given 5000 units unfractionated heparin before the thrombolytic treatment. During the procedure, the patients' vital signs were constantly monitored in intensive care unit. Patients with a blood pressure 120/80 mmHg were constantly given nitroglycerine infusion and blood pressure regulation was provided before thrombolytic treatment.

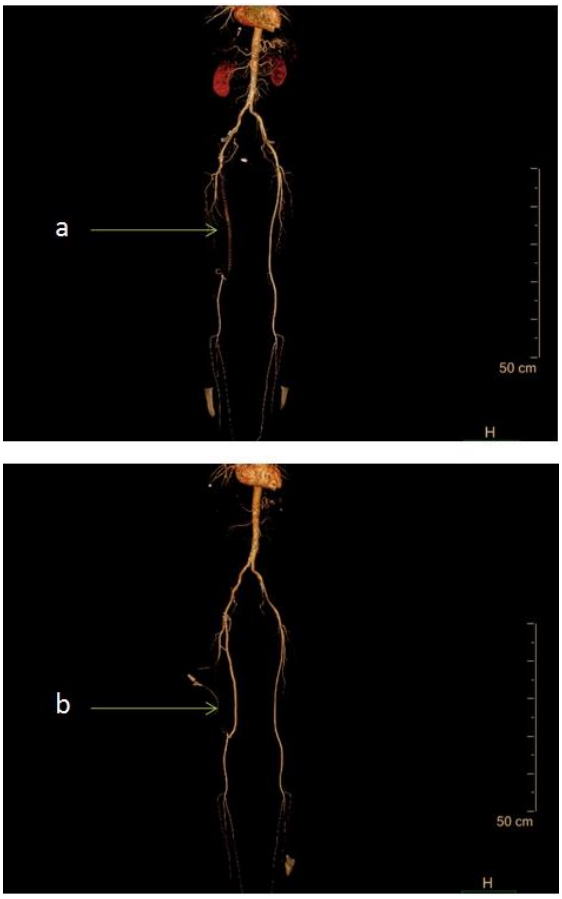

Figure 1: a: before treatment CT angiography of an ALI patient, the arrow shows the graft thrombosis, b: after treatment CT angiography of the same patient, arrow shows the open graft (Combined thrombolytic and surgical adjuvant embolectomy procedures are performed in this patient.)

After the thrombolytic treatment, symptoms like warming of feet, healing of pain, palpable distal pulse or palpable distal pulse measured by a hand-held Doppler were counted as the indications of a successful treatment. In case of a failure in thrombolytic treatment, surgical adjuvant embolectomy was performed after 4-6 hours' time. Embolectomy procedure was performed under local anesthesia in sterilized operating room. Patients were given 5000 UI standard heparin before the operation. After that, thrombectomy was performed with appropriate Fogarty embolectomy catheter inserted with transverse section of the femoral artery. Arteriotomy then closed with 6/0 or 7/0 polypropylene suture. Patients then treated with appropriate antibiotic therapy. After the procedure, the patients' follow-up in 1-month and 1-year periods were examined with regard to bleeding complications, amputation, (Major/minor amputation was defined as amputation above/lower foot-level) and limb rescue. Patients developing extremity gangrene in spite of medical and surgical treatment were referred to orthopedics for amputation. Other patients were discharged after their further treatment in our clinic.

Statistical analysis

SPSS 15.0 (SPSS, Chicago, IL, USA) was used in the evaluation of the results. All the data were presented as mean ± standard deviation or proportions as appropriate.

Results

Twenty three patients with ALI which were treated with thrombolytic and surgical adjuvant embolectomy were included in this study. 14 (60%) patients were male and the average age of the patients was 62.56±16.60. Number of patients with hypertension was 20 (86%). Number of patients with a history of diabetes mellitus was 9 (39%). Number of smokers was 19 (82%). Number of patients with a history of failed bypass was 13(56%). Patient's average duration of ALI symptoms was 7.82±3.45 days. Six (26%) patients were in Rutherford Class IIa and 17 (73%) of them were in Rutherford class IIb according to their symptom levels (Table 1).

In the first place, all of the patients were treated with intravenous thrombolytic therapy. 12 patients (52%) with unhealed symptoms of ALI despite of thrombolytic therapy were also treated with surgical adjuvant embolectomy. Two patients (8.7%) were reported need major amputations in the first month. In the follow-up period of one year, a total number of 3 patients (13%) were reported need major amputation. Patients with amputations were previously treated with both thrombolytic and surgical methods. 30-day survival was observed in 22 patients (95.7%). One patient (4.3%) developed intracranial hemorrhage on the first day after the treatment (Table 2). This patient died during the follow-up in intensive care unit due to multi-organ failure. One patient (4.3%), previously treated with thrombolytic and surgical methods, was reported with foot drop in postoperative period. Extremity-rescuing number in the first month was reported as 21 patients (91%). Other patients were not reported with any minor amputations or bleeding complications.

Table 1: Demographic data and preoperative risk factors

	Value
Age mean ± SD	62.56±16.60
Gender male n (%)	14 (61)
Hypertension n (%)	20 (86)
Diabetes Mellitus n (%)	9 (39)
Smoke n (%)	19 (82)
Coronary artery disease n (%)	14 (60)
Peripheral surgical story n (%)	13 (56)
Atrial fibrillation n (%)	4 (17)
Symptom duration (Day) mean ± SD	7.82±3.45
Rutherford classification 2a n (%)	6 (26)
Rutherford classification 2b n (%)	17(73)

SD: Standard deviation

Table 2: Postoperative data and complications

	n (%)
Extremity rescue	21 (91)
Minor amputation	0 (0)
Major amputation 30 day	2 (8.7)
Major amputation 1 year (total)	3 (13)
Intracranial bleeding	1 (4.3)
Additional surgical procedure (embolectomy)	12 (52)
30 Day survival	22 (95.7)
1 year survival	22 (95.7)
Deceased	1 (4.3)

Discussion

ALI is described as a sudden decrease in extremity perfusion and it threatens the vitality of the extremity. The incidence of ALI is 9-16 cases per 100.000 persons per year for the lower extremity. Etiology includes embolism, thrombosis with coexisting peripheral arterial disease, graft/stent thrombosis or peripheral aneurysm with embolism or thrombosis [4]. With the onset of ALI symptoms, both the patient's extremity and life are under threat. 30-day amputation rate is examined in many early and recent studies of ALI. The amputation rate in the 90s was reported as 6-16 percent. Yet again in the same era, the 30-day mortality rate was reported as 16-22 percent [5,6]. In a wider study made on ALI patients in 2000s showed that amputation rates were 13-14 percent and mortality rates were 9-12 percent [7]. Today's studies, 30-day mortality rate are 5.2 percent. The overall rate of major amputation is 15.0% [8].

These studies show that more effective surgical procedures or newer medical therapies lead to a partial decrease in mortality and amputation rates in ALI treatment. In spite of all the new developments, early 30-day mortality and amputation rates are still high. Thus, ALI still continues to be a health problem in today's world threatening patient's extremities and lives.

Thrombolysis and open surgical revascularization are current options for the treatment of ALI. Despite the several randomized controlled trials comparing the two options, no single treatment is recommended in the ALI treatment. CDT is preferred in medical treatment. Thrombectomy and perioperative endovascular aspiration and mechanical thrombectomy are used as surgical treatments. Fast revascularization in ALI is achievable with combined thrombolytic therapy [9,10]. Today, commonly-accepted use of thrombolytic agents is in case of an extremity threatening ischemia. When directly applied into thrombus, thrombolytic agents are more effective. Systemic intravenous thrombolysis is less effective than intra-arterial thrombolysis but can have higher risk of bleeding complications [11].

In ALI treatment, CDT therapy when compared to open surgery has become a routine clinical therapy in the last thirty years following three published randomized controlled studies that showed similar findings. The main advantages of intra-arterial thrombolysis are the avoidance of anesthesia and its being a safer way of treatment in elderly patients and patients with comorbidities. Thrombolysis, with lower risk of endothelial dysfunction and re thrombosis, was observed locally dissolve the thrombus even in the divisions of main artery. Furthermore, the underlying stenosis becomes detectable through imaging methods after the dissolution of thrombus with thrombolytic therapy. By this means, following treatment decisions can be simplified and the potential long-term results can be improved [12]. Today, CDT therapy being more effective with fewer side effects compared to the intravenous therapy is the general consent. Yet outside of this consent, there are other researches showing ALI treatments with intravenous thrombolytic therapies and the results' similarities with CDT therapy results. Saroukhani et al. [13] evaluated the results of intravenous thrombolytic therapy and CTD therapy. According to this research, the complication rates along with the clinical results are comparable. There was no significant difference between two study groups regarding the incidence of limb amputations. At the end of the study, it was also indicated that both therapy methods are safe and effective. The incidents of bleeding complications indicated in Grip et all's 689 disease studies were high with a rate of 29.8%. Yet most of them were minor and controllable without a cut-off in thrombolysis. Intracranial hemorrhage was reported with a rate of 0.4% in Grip et al.'s patient group [12].

Berridge et al [14] indicated hemorrhagic complications in a meta-analysis of five randomized controlled study that

included a comparison of intra-arterial thrombolysis and operations in ALI treatment including a total 1283 patients. In this study, rate of the stroke incidents was reported as 1.2% while the major bleeding rate was 8.8% [14]. Byrne et al [8] gave alteplase as an intra-arterial thrombolytic agent to his 147 ALI case study patients. This patient group was reported with Rutherford class IIa with 70.1% and class IIb with 20.1%. Technical success was achieved in 83.8% of cases, with a 30-day mortality rate of 5.2%. Procedural complications including systemic bleeding were seen in 5.2%, access site hematoma 4.5%, acute renal failure 1.9%, and distal embolization 9.7%. The overall rate of major amputation was 15.0% [8].

In our patient group, a total of 23 patients are performed intravenous thrombolytic therapy due to ALI. All of the cases were either having a failed bypass graft or with diffuse vascular disease. The patients could not be treated with CDT due to the difficulty of arterial intervention. 17 patients (73%) were in Rutherford class IIb. 12 (52%) patient had to have surgical embolectomy in addition to thrombolytic therapy. Extremity rescue ratio of our patients was 91% with 21 patients. Extremity rescue rate in literature is indicated between 84-94 percent [5,6]. In our patient group, only 2 patients 8.7% were reported with major amputation in the first month. In one-year follow up period 3 patients 13% were reported with major amputation. Minor amputation was not reported. In literature, the major amputation rate was 6.4% in 30 days which increased 13% in 12 months' time [8]. According to the total evaluation of these results, it is seen that the extremity rescue and major amputation rates we have are similar or a little lower than the ones in literature [6,8].

Major hemorrhage was indicated between 5.2% and 13.9% in various series [8,15]. Within our patient group, one patient 4.3% developed major hemorrhage. The type of the major bleeding was intracranial hemorrhage and this patient died. One patient developed foot drop. Other patients did not develop any kind of bleeding or other complications. The two main precautions we took could be effective in our patient group not developing many hemorrhagic complications even if we had not had a control group. First one is the analysis of a probable thrombolytic contraindicated condition on patients we treated with thrombolytic therapy. Second one is the close follow-up of blood pressure of the patients during and after their treatment. In our patient group 30-day survival rate was 22 patients 95.7%. In literature, the 30-day survival in various patient groups is reported rates 93% to 97% [12].

When examined, we reckon there are similarities between our patient group and the patient groups in literature with regard to major bleeding and 30-day survival. Patients in the literature that we are comparing to our patient have also been treated with intra-arterial thrombolytic therapy. CDT is known to have positive effects on patients with ALI symptoms. Yet the patients with inapplicable CDT due to diffuse vascular disease or failed bypass graft as in patients in our group can be treated with intravenous thrombolytic therapy.

30-day survival and bleeding complications are similar to the ones in the literature and amputation rates are generally similar or lower than the literature. In conclusion, we support CDT therapy in ALI patients if possible. Yet ALI patients with inapplicable or failed arterial catheterization may not be treated with CDT therapy, in this case intravenous thrombolytic therapy and necessary combined surgical interventions can become extremity rescuing and life-saving procedures.

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Research article
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The association of mean platelet volume and platecrit and bone marrow fibrosis in patients with essential thrombocythemia: A cohort study

Esansiyel trombositemi hastalarında kemik iliği fibrozisi ile ortalama trombosit hacmi ve plateletkritin ilişkisi: Bir kohort çalışma

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Abstract

Aim: Essential thrombocythemia (ET) patients exhibit higher mean platelet volume (MPV) values compared to the healthy individuals. However, the association of degree of bone marrow fibrosis with either MPV or platecrit (PCT) has not been evaluated previously. The aim of this study was to investigate MPV and PCT values as predictive markers for evaluating bone marrow fibrosis (BMF) in ET patients.

Methods: We conducted a retrospective cohort study to analyze the data of ET patients, who were followed in out-patient clinic of our hematology department, between January 2015 and December 2016. Patients older than 18 years, who had bone marrow biopsy, CBC, biochemistry tests and an abdominal sonography performed at the time of diagnosis, JAK2 test ordered and were BCR-ABL negative were included in the study. The patients were divided into two groups according to the presence of BMF as "the BMF group" and "the non-BMF group". The cut-off value for MPV and PCT was determined according to the median value. Fisher's exact test and χ^2 were used for comparative statistical analysis.

Results: There were 22 males and 26 females with a median age of 56 years (range, 28–81). The BMF group included 35 (73%) patients while the non-BMF group included 13 (27%) patients. The median MPV was 8.8 fL (6.6-11.5) and median PCT was 0.69% (0.42-2.26), which was considered as the cut-off values for these parameters. There was no significant difference between the groups in patients with MPV ≤8.8 fL and MPV >8.8 fL (p=0.104) and also in patients with PCT ≤0.69% and PCT >0.69% (p=0.616).

Conclusion: There is no association between the BMF and MPV and PCT in ET patients. However this is the first study investigating the role of both MPV and PCT in BMF in ET patients.

Keywords: Essential thrombocythemia, Mean platelet volume, Platecrit, Bone marrow fibrosis

Öz

Amaç: Esansiyel trombositemi (ET) hastalarında ortalama trombosit hacmi (MPV) değerleri sağlıklı bireylere göre daha yüksek seyretmektedir. Ancak, ET'da MPV veya plateletkritin (PCT) kemik iliği fibrozisi (KİF) derecesi ile ilişkisi henüz araştırılmamıştır. Amacımız MPV ve PCT değerlerinin ET hastalarında kemik iliği fibrozisini değerlendirmede prediktif bir belirteç olarak rolünü araştırmaktır.

Yöntemler: Retrospektif bir kohort çalışması yaparak Ocak 2015 ile Aralık 2016 arasında hematoloji polikliniğimizden takip edilen ET hastalarının verilerini inceledik. 18 yaşından büyük, tanı anında kemik iliği biyopsisi, hemogram, biyokimya ve batın ultrasonu olan, JAK2 istenmiş olan ve BCR-ABL negatif hastalar çalışmaya dâhil edildi. Hastalar KİF varlığına göre "KİF grubu" ve "KİF olmayan grup" olarak iki gruba ayrıldı. MPV ve PCT için eşik değer için ortanca değer alındı. Karşılaştırmalı istatistiksel analizler için Fisher exact ve ki kare testi kullanıldı.

Bulgular: Hastaların 22'si erkek 26'sı kadın olup ortanca yaş 56 yaştı (Aralık 28-81). KİF grubunda 35 (%73) hasta varken KİF olmayan grupta 13 (%27) hasta mevcuttu. Medyan MPV 8,8 fL (6,6-11,5) iken medyan PCT %0,69 (0,42-2,26) idi ve bunlar iki parametre için eşik değer olarak kullanıldı. KİF varlığı ile MPV ≤8,8 fL ve MPV >8,8 fL olan hastalar arasında, PCT ≤%0,69 ve PCT >%0,69 olanlardaki gibi anlamlı fark bulunmamaktaydı (p=0,104 ve 0,616).

Sonuç: Çalışmamızda ET hastalarında KİF ile MPV veya PCT arasında ilişki bulamadık. Bununla birlikte çalışmamız ET hastalarında KİF'ni öngörmede MPV ve PCT'nin rolünü araştıran ilk çalışmadır.

Anahtar kelimeler: Esansiyel trombositemi, Ortalama trombosit hacmi, Plateletkrit, Kemik iliği fibrozisi

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Introduction

Essential thrombocythemia (ET), one of the Philadelphia-negative classical myeloproliferative neoplasms, is a stem cell disorder and characterized by the proliferation of exclusively megakaryocytes, leading to excessive platelet production without any abnormalities in erythroid and myeloid lineages in the bone marrow [1]. Although ET might be complicated particularly by thrombosis, it can also progress to fibrotic phase (post-ET myelofibrosis) and leukemia in long term, during the course of the disease [2-3].

Platelets, which are anucleated small cells with a volume of about 7 to 11 fL, play a crucial role in vascular homeostasis, furthermore in inflammation and atherogenesis. Platelets contain various granules, a microtubular system and an active membrane. Among them, granules contribute to the generation of inflammation and thrombosis by releasing their ingredients upon activation [4-6]. During those events, larger platelets are more potent in terms of thrombotic potential compared to the smaller ones [7]. Herein, mean platelet volume (MPV), representing the average platelet volume, has emerged as an indicator of platelet function and activation in various proinflammatory and prothrombotic clinical states [8]. Another MPV-related platelet index, which can be easily attained from complete blood count (CBC), is platecrit (PCT). It is the product of MPV multiplied by the platelet count and is stated as a percentage [9].It was demonstrated that ET patients exhibited higher MPV values compared to healthy individuals [10,11] and patients with reactive thrombocytosis [11]. However, the association of degree of bone marrow fibrosis with either MPV or PCT has not been previously evaluated. Therefore, the aim of this study is to investigate MPV and PCT values as predictive markers for evaluating bone marrow fibrosis in ET patients.

Materials and methods

We conducted a retrospective cohort study to analyze the data of ET patients, who were followed in out-patient clinic of our hematology department, between January 2015 and December 2016. Patients older than 18 years, who had bone marrow biopsy, CBC, biochemistry tests and an abdominal sonography performed at the time of diagnosis, JAK2 test ordered and were BCR-ABL negative were included in the study. All eligible patients with a diagnosis of ET were included in the study and thus no sample size analysis was performed.

The diagnosis of ET was based on 2008 World Health Organization criteria [12]. The data included gender, age, white blood cell count (WBC), hemoglobin (hb) level, platelet (plt) count, lactate dehydrogenase (LDH) level, disease age, MPV, PCT, splenomegaly status, Janus kinase 2 (JAK-2) mutation status and the degree of reticulin fibrosis. Thrombotic complications were evaluated at the time of entering the study. MPV and PCT values were gathered from the CBC measured on an EDTA tube at the time of diagnosis, on the same day with the bone marrow biopsy procedure.

Bone marrow fibrosis (BMF) degree was determined according to the reticulin and trichrome staining applied to the specimens and grading was done as follows [13]:

- Grade 0: Scattered linear reticulin with no intersections (cross-overs) corresponding to normal bone marrow
- Grade 1: Loose network of reticulin with many intersections, especially in perivascular areas
- Grade 2: Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
- Grade 3: Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis

The patients were divided into two groups according to the presence of BMF as “the BMF group” and “the non-BMF group”. The cut-off value for MPV and PCT was determined according to the median value. This study protocol was approved by the institutional review board of the University of Health Sciences, Istanbul Training and Research Hospital (Number 939/2017).

Statistical analysis

The data were analyzed by using SPSS version 17.0 program. Data were presented as numbers and percentage or median and range, when appropriate. χ^2 and Fisher’s exact test was used for evaluating categorical values. All p-values were 2-sided with statistical significance at 0.05 alpha levels.

Results

The data of 48 ET patients are summarized in Table 1. There were 22 males and 26 females with the median age of 56 years (range, 28–81) at the time of diagnosis. The median WBC was 10110/mm^3 (3580-32520), hb was 13.6 g/dl (7.6-16.9), plt was 844500/mm^3 (484000-2637000), and LDH was 212 U/L (131-642). The median disease age was 22 months (5-105). Nine (18.8%) patients had splenomegaly. There were 26 (54.2%) patients who had JAK-2 mutation.

Table 1: Patient characteristics

Characteristic	n = 48
Gender, n, (%)	
Female	26 (54.2)
Male	22 (45.8)
Age, years, median, (range)	56 (28-81)
WBC, /10^3/mm^3, median (range)	10110 (3580-32520)
Hgb, /g/dl, median (range)	13.6 (7.6-16.9)
Plt, /10^3/mm^3, median (range)	844500 (484000-2637000)
PCT, %, median (range)	0.69 (0.42-2.26)
MPV, fL, median (range)	8.8 (6.6-11.5)
LDH, U/L, median (range)	212 (131-642)
Disease age, months, median (range)	22 (5-105)
Splenomegaly, n, (%)	
Present	9 (18.8)
Absent	39 (81.2)
JAK-2 mutation, n, (%)	
Present	26 (54.2)
Absent	22 (45.8)
Reticulin fiber, n, (%)	
Present	35 (73)
Absent	13 (27)

WBC: white blood cell count, Hgb: hemoglobin, Plt: platelet, PCT: Platecrit, MPV: mean platelet volume, LDH: lactate dehydrogenase

The BMF group included 35 (73%) patients while the non-BMF group included 13 (27%) patients. The median MPV was 8.8 fL (6.6-11.5) and median PCT was 0.69% (0.42-2.26), which was considered as the cut-off values for these parameters. There was no significant difference between the groups in patients with MPV ≤8.8 fL and MPV >8.8 fL (p=0.104) and also in patients with PCT ≤0.69% and PCT >0.69% (p=0.616) (Table 2).

Table 2: The association of the reticulin fiber with MPV and PCT

	BMF	Non-BMF	p
Gender, n, (%)			
Female	8 (61%)	18 (51%)	0.746
Male	5 (39%)	17 (49%)	
Age, years, median, (range)	57 (40-81)	55 (28-80)	0.076
MPV			
≤ 8.8	4 (31%)	20 (57%)	0.104
> 8.8	9 (69%)	15 (43%)	
PCT			
≤ 0.69	7 (54%)	16 (46%)	0.616
> 0.69	6 (46%)	19 (54%)	
WBC, /10^3/mm^3, median (range)	11010 (8710-27780)	9470 (3580-32520)	0.214
Hgb, /g/dl, median (range)	13.6 (9.8-16.6)	13.6 (7.6-16.9)	0.141
Plt, /10^3/mm^3, median (range)	731000 (506000-2172000)	879000 (484000-2637000)	0.171
LDH, U/L, median (range)	203 (131-320)	218 (162-642)	0.113
Splenomegaly, n, (%)			
Present	1 (8%)	8 (23%)	0.418
Absent	12 (92%)	27 (77%)	
JAK-2 mutation, n, (%)			
Present	7 (54%)	19 (54%)	1.000
Absent	6 (46%)	16 (46%)	

MPV: mean platelet volume, PCT: Platecrit, Hgb: hemoglobin, LDH: lactate dehydrogenase, lym: lymphocyte, MPV: mean platelet volume, neu: neutrophil, plt: platelet, WBC: white blood cell count, BMF: bone marrow fibrosis

Discussion

Fibrotic transformation is a rare complication of ET, but it can lead to considerable morbidity and mortality in ET patients [3,14]. The diagnosis of fibrotic transformation requires the demonstration of bone marrow fibrosis ≥ grade 2 [15], which require performing a bone marrow biopsy, a procedure with a substantial discomfort. Although various risk factors such as anemia and advanced age were defined for the occurrence of fibrotic transformation in ET patients [16], a predictor, which notifies about the bone marrow fibrosis, has not yet been described. Accordingly, in the current study we evaluated the predictive role of MPV and PCT on BMF in ET patients, and did not find an association of BMF with MPV and PCT.

Mean platelet volume, a readily available parameter from CBC, provides significant clues about the megakaryocytic activity and platelet activation [8,17]. Mean platelet volume has been found to be increased in a number of diseases like heart disease [6,18-20], type 2 diabetes mellitus [21], nonalcoholic fatty liver disease [22], pancreatitis [23] and malignancies [24]. More importantly, higher MPV values were demonstrated to be associated with higher mortality in coronary artery disease [6,18,20], and increased risk of stroke in atrial fibrillation patients [19]. Another remarkable finding regarding the role of MPV is its decline with treatment in malignancies, which allows it to be a valuable parameter in the follow-up of malignancy patients [24]. Similar to MPV, PCT was also evaluated in heart diseases and shown to be an indicator of no-reflow [25] and adverse outcomes [26] in patients with myocardial infarction.

The role of both MPV and PCT has not been yet investigated comprehensively in hematological diseases. In a study including patients with the diagnosis of either immune thrombocytopenia (ITP) or acute myeloid leukemia (AML), MPV values were found to be higher in ITP patients compared to the AML patients and healthy subjects. Thus, MPV denotes the status of thrombopoiesis in the bone marrow, and higher MPV values are associated with increased bone marrow activity [27]. Mean platelet value was also increased in patients with heterozygous beta thalassemia, who had mild ineffective hematopoiesis and hemolysis [28]. Similar to the previous studies, MPV was increased in patients with the diagnosis of ET compared to the patients with reactive thrombocytosis [11] and healthy individuals [10,11]. Also MPV was higher in ET patients with a history of thrombosis [29]. Different from these issues, we evaluated the role of MPV together with PCT in estimating the BMF in ET patients; however, we were not able to demonstrate such an association.

The retrospective nature of the study, relatively low number of patients and also lack of a control group including patients with the diagnosis of myelofibrosis might have concealed the genuine association of BMF with MPV and PCT in ET patients, leading to limitation in this study. However, this is the first study investigating the role of both MPV and PCT in predicting BMF in ET patients.

Conclusion

Although MPV has been demonstrated to be high and a sign of hypercoagulability in ET, it seems that there is no association between BMF and MPV and PCT in ET. Further studies with larger sample sizes are warranted to verify this observation.

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Prophylaxis for latent tuberculosis infection in liver transplant recipients

Karaciğer nakli alıcılarında latent tüberküloz enfeksiyonu proflaksisi

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Abstract

Aim: Immunosuppressive drugs predispose the liver transplant recipient to reactivation of latent tuberculosis infections. Prophylactic therapies given to these patients are very important for prevention of reactivation. The aim of this study was to evaluate the prophylaxis of latent tuberculosis infections in liver transplant recipients.

Methods: We designed a retrospective cohort study. We examined liver transplant recipients Between December 2014 and December 2017 with results of T Spot and prophylactic treatment.

Results: Among 143 recipients, positive T Spot results were detected in 21 (14.7%) cases. Twenty one patients received Isoniazid prophylaxis and no reactivation of tuberculosis was detected during follow-up of 48 months.

Conclusion: Isoniazid appears to be successful in prophylactic treatment of latent tuberculosis infection in liver transplant recipients.

Keywords: Liver transplantation, Latent tuberculosis infections, Prophylaxis

Öz

Amaç: İmmünsüpresif ilaçlar karaciğer nakli alıcısını latent tüberküloz enfeksiyonlarının reaktivasyonuna yatkınlaştırır. Bu hastalara verilen profilaktik tedaviler, reaktivasyonun önlenmesi için çok önemlidir. Bu çalışmanın amacı, karaciğer nakli alıcılarında latent tüberküloz enfeksiyonlarının profilaksisini değerlendirmektir.

Yöntemler: Retrospektif bir kohort çalışması tasarladık. Karaciğer nakli alıcılarını Aralık 2014 - Aralık 2017 tarihleri arasında T Spot ve profilaktik tedavi sonuçları ile inceledik.

Bulgular: 143 alıcı arasında, 21 (%14,7) vakada pozitif T Spot sonucu tespit edildi. Yirmi bir hastaya İsoniazid profilaksisi yapıldı ve 48 aylık takipte tüberkülozun herhangi bir reaktivasyonu tespit edilmedi.

Sonuç: Isoniazid, karaciğer nakli alıcılarında latent tüberküloz enfeksiyonunun profilaktik tedavisinde başarılı görünmektedir.

Anahtar kelimeler: Karaciğer nakli, Latent tüberküloz enfeksiyonu, Proflaksi

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Introduction

Tuberculosis is a serious opportunistic infection for liver transplant recipients [1–4]. Tuberculosis incidence estimated as 0.7% to 2.3% in liver transplant recipients [5,6].

Mycobacterium tuberculosis specific interferon gamma release assays; QuantiFERON ® (QI-AGEN, Gaithersburg, USA, and Australia) and T-SPOT® (Oxford Immunotec, Oxford, UK) are methods for diagnosing latent tuberculosis infections [7,8].

Isoniazid prophylaxis are used for avoid to reactivation of latent tuberculosis infection in the post-transplant period [9]. The risk of Isoniazid hepatotoxicity is higher for liver transplant recipients [6].

The aim of this study was to evaluate the prophylaxis for latent tuberculosis infections in liver transplant recipients.

Materials and methods

Between December 2014 and December 2018, liver transplant recipients at Medipol University Medical Faculty Hospital Organ Transplantation Department, Istanbul, Turkey were studied retrospectively.

Two main groups were established; positive T Spot group (Isoniazid prophylaxis) and negative T Spot group (No Isoniazid prophylaxis) group. For each of these groups the age, sex, CHILD scores, Model for End-Stage Liver Disease (MELD) scores, prophylaxis for latent tuberculosis infections, reactivation of latent tuberculosis infections and mortality due to tuberculosis were evaluated.

All patients were examined by Department of Thoracic Medicine before liver transplantation and pulmonary function test, chest graph, computed tomography of thorax and T Spot test were performed.

In our clinic, Isoniazid prophylaxis was given only in patients with latent tuberculosis infection risk factors (3 patients was diabetes mellitus, 3 patients was elderly recipient (>65 years old), 2 patients history of recent contact with a person who was diagnosed with active tuberculosis) and positive T Spot (none clinical and radiological findings in patients). Patients received 300 mg Isoniazid daily and 50 mg Pyridoxine daily, and duration of treatment was 6 months. Patients were examined by Department of Thoracic Medicine every month. We investigated Isoniazid hepatotoxicity. Alanine aminotransferase, aspartate aminotransferase and bilirubin were performed every day of the admission period, and once per fifteen days after discharge.

Statistical Analysis

Continuous variables with normal distribution presented as mean ± Standard deviation. The categorical variables were given as percent and number.

Results

Among 143 recipients, T spot test was positive in 21 cases (14.7%). All these patients were treated with Isoniazid prophylaxis. Mean age of the positive T Spot group was 56.5 (25-72) years; negative T Spot group was 58.5 (26-69) years, 17 (70%) of the 21 positive T Spot group patients were male.

Mean CHILD scores of the positive T Spot group was 9 (6 -12); negative T Spot group was 8.5 (6-15) respectively. Mean MELD scores of the positive T Spot group was 15 (9-24); negative T Spot group was 16.5 (10-30) respectively.

Sixteen (76.2%) patients underwent right lobe living donor liver transplantation and 5 (23.8%) patients underwent cadaveric liver transplantation.

In study, no reactivation of latent tuberculosis infections was detected, no hepatotoxicity occurred due to Isoniazid, and no patient died due to tuberculosis in follow up period of 48 months.

Discussion

The definitive treatment of end stage liver disease is liver transplantation. The standard immunosuppressive treatment starts immediately after liver transplantation.

The immunosuppressive drugs used of transplantation patients the reactivation of latent tuberculosis infections to increases. Immunosuppressive agents greatly enhance the risk of tuberculosis reactivation in patients with latent tuberculosis infections [10-12]. In our center, Immunosuppression regimens were based on calcineurin inhibitor (tacrolimus or cyclosporine), mycophenolate mofetil and corticosteroids in liver transplant recipient.

Latent tuberculosis infection risk factors were a history of recent contact with a person who was diagnosed with active tuberculosis, human immunodeficiency virus infection, country of origin, higher intensity immunosuppression, Diabetes mellitus, and increased recipient age [13]. Liver transplant recipients have an 18 fold increased risk of latent tuberculosis infection reactivation in comparison with the general population [13-14].

Current guidelines for transplantation recommend that all recipients be routinely screened for latent tuberculosis infection with a tuberculin skin test or Interferon-gamma release assay [15-17]. In our study, among 143 recipients, 21 cases of positive T Spot were detected (14.7 %) but not clinical and radiological findings in these patients.

Isoniazid is known to be effective for tuberculosis prevention in liver transplant recipient as well as in the general population [18]. However, Isoniazid for liver transplant recipients remains controversial be¬cause of concerns about ısoniazid hepatotoxicity [19]. The rate of Isoniazid toxicity was 29% and 42.8 % in liver transplant patients [6,13]. In our clinic, Isoniazid prophylaxis (Daily 300 mg Isoniazid and daily 50 mg Pyridoxine with duration of 6 months) was given only in patients with latent tuberculosis infection risk factors and positive T Spot. All our patients were not reactivation of latent tuberculosis infections and isoniazid hepatotoxicity.

Tuberculosis in liver transplant recipients is associated with mortality rates as high as 30% to 40% [20]. In our study none of the cases died due to tuberculosis.

Our study has several limitations. First, this study was retrospective. Second, the number of cases was small.

Conclusion

Despite the limitations, Isoniazid appears to be successful prophylactic treatment of latent tuberculosis infection in liver transplant recipients.

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Factors affecting complications of transrectal ultrasound-guided prostate biopsy: A cohort study with 403 patients in a single center

Transrektal ultrason eşliğinde prostat biyopsisinin komplikasyonlarını etkileyen faktörler: Tek merkezde 403 hasta ile yapılan kohort çalışma

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Abstract

Aim: Prostate cancer is among the common cancer types in male population. Transrectal ultrasound (TRUS) guided prostate biopsy is considered the gold standard for diagnosis of prostate cancer. Complications in this tissue sampling method were analyzed in the present study.

Methods: A descriptive study with retrospective design was planned. A total of 403 patients who had 12 core TRUS guided prostate biopsy for the first time in December 2016 -November 2018 period were evaluated. Age of the patients, digital rectal examination finding, prostate specific antigen (PSA) levels, prostate volumes and complications were analyzed.

Results: Average age, serum total PSA level and prostate volume of patients were 63.2±8.53 years, 21.6±18.19 ng/mL and 65.63±20.19 cc, respectively. Genitourinary system infection was observed in 7.2% of the patients after the procedure. In terms of non-infection complications, 23.1% of patients had hematuria, 16.1% hematospermia and 2.2% rectal bleeding. On the other hand, 4.2% of the patients had vasovagal episodes and 0.7% had acute urinary retention. Of all patients, 8.9% were hospitalized due to observed complications.

Conclusion: We conclude that TRUS-guided prostate biopsy is a reliable diagnostic tool with low complication rates in patients with prostate cancer pre-diagnosis.

Keywords: Biopsy, Complications, Prostate, Transrectal ultrasound

Öz

Amaç: Prostat kanseri erkek populasyonda yaygın izlenen kanser türleri arasında yer almaktadır. Prostat kanseri tanısında transrektal ultrasonografi (TRUS) eşliğinde prostat biyopsi altın standart olarak gösterilmektedir. Çalışmamızda bu doku örnekleme metodunun komplikasyonları analiz edilmiştir.

Yöntemler: Çalışmada Aralık 2016 ile Kasım 2018 tarihleri arasında ilk defa TRUS eşliğinde 12 kor prostat biyopsisi yapılan 403 olgu değerlendirildi. Hastaların yaşları, parmakla rektal muayene bulguları, prostat spesifik antijen (PSA) düzeyleri, prostat hacimleri ve komplikasyonları değerlendirilmiştir.

Bulgular: Hastaların ortalama yaşı, serum total PSA düzeyi ve prostat hacmi sırasıyla 63,2 ± 8,53 yıl, 21,6 ± 18,19 ng/mL ve 65,63 ± 20,19 cc idi. İşlem sonrası hastaların %7,2'sinde genitoüriner sistem enfeksiyonu izlendi. Enfektif olmayan komplikasyonlara bakıldığında ise hastaların %23,1'inde hematüri, %16,1'inde hematospermi, %2,2'sinde rektal kanama gözlemlendi. Öte yandan hastaların %4,2'sinde vazovagal epizodlar ve %0,7'sinde ise akut üriner retansiyon ile karşılaşıldı. Çalışmaya alınan hastaların %8,9'u komplikasyonlara bağlı hospitalize edildi.

Sonuç: Prostat kanseri ön tanısı olan hastalarda TRUS eşliğinde prostat biyopsisinin düşük komplikasyon oranları ile güvenle kullanılabilecek bir tanı aracı olduğu düşüncesindeyiz.

Anahtar kelimeler: Biyopsi, Komplikasyon, Prostat, Transrektal ultrason

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Introduction

Prostate cancer is among the most prominent health problems in aging male population. It ranks second after pulmonary malignancies in cancer-linked deaths [1]. Mortality rate due to prostate cancer in the United States for 2006-2010 periods was 23% [2]. It has been reported that 382,000 prostate cancer diagnoses were made in EU countries in 2008, and about 89,000 people lost their lives as a result of this disease [3]. Epidemiology studies in Turkey, on the other hand, showed an incidence rate of 36.3 per 100,000 people for prostate cancer in 2008 [1].

Methods used for diagnostic evaluation of prostate cancer include digital rectal examination, prostate specific antigen (PSA), transrectal ultrasound (TRUS) guided prostate biopsy and recently popular multi-parametric magnetic resonance as well as medical history of patient [4]. However, as in other cancer types, diagnosis is made based on histopathological examination. Today, TRUS guided prostate biopsy is considered diagnostic tool of gold standard by urologists [5]. Along with the increasing awareness for prostate cancer in the society, common use of PSA and aging populations of countries, prostate biopsies have been increasingly used [1]. Based on scientific data in the United States, about 7% of males who are 65 years of age and over take prostate biopsy every year [6].

In parallel to increasing use of prostate biopsies, frequency of undesired side effects from this invasive uro-radiological procedure are also on increase. In this retrospective study, patients who had 12 core TRUS guided prostate biopsy in our center were analyzed and complication frequencies were evaluated.

Materials and methods

A total of 403 patients who had 12 core TRUS guided prostate biopsy first time in December 2016 – November 2018 period and who had complete information in hospital record files were analyzed retrospectively in the present study. Abnormal digital rectal examination findings and/or an elevated serum total PSA levels were considered main biopsy indications. All cases had prophylactic antibiotherapy. Starting from one day before the procedure, twice daily doses of 500 mg ciprofloxacin was administered orally for three days. Before the biopsy procedure, rectum cleaning was carried out through routine enema procedure. After prostate examination in left lateral decubitus position, intrarectal 5% lidocaine pomade application and periprostatic nerve block using 5 cc 2% lidocaine solution guided with ultrasound were applied to all patients. Then, 12-core biopsy specimens were obtained from the base of the right, and left prostate lobes, lateral, and far remote lateral to the midline, medial, and lateral parts of the apex. All these procedures were carried out using 18 Gauge 30 cm biopsy needle and automatic biopsy gun (Angiotech Tru-Core I, Florida, USA) guided by a Diagnostic Ultrasound System 3535 (B&K Medical, Herlev, Denmark) with 7.5 MHz rectal probe. Specimens taken were sent to pathology department in tubes containing 10% formaldehyde solution. Patients were informed about all possible complications and discharged after being kept under observation for two hours. Patients with neurological disorders, patients who previously underwent prostatic surgery, patients who had pathology in anal region or who were on antithrombotic or anticoagulant medication were excluded.

Age of the patients, digital rectal examination findings, PSA levels, prostate volumes and complications of included patients were evaluated.

Informed consent was taken from all patients and all steps of the study were carried out according to the basic principles of Helsinki declaration. The study was approved by Local Ethics Committee.

Statistical analysis

All statistical analysis was performed using SPSS 21.0 program for Windows (SPSS, Inc., Chicago, IL, USA). Student T test was used to test whether there was any difference between the two groups. $p < 0.05$ was considered statistically significant. The values obtained in the study were given as mean ± standard deviation (minimum – maximum).

Results

Average age of 403 patients who underwent TRUS guided prostate biopsy examination in the present study was 63.2±8.53 years, and average total PSA level was 21.6±18.19 ng/mL. Average prostate volume of the patients was 65.63±20.19 cm^3. In terms of indications for prostate biopsy, 87 patients had only abnormal digital rectal examination findings such as nodule in prostate, asymmetry and irregularities while 204 cases had only high PSA levels. On the other hand, 112 patients had both high PSA levels and abnormal digital rectal examination findings. Histopathological diagnosis of 141 (35%) cases was prostate adenocarcinoma.

With regard the biopsy complications, 93 patients (23.1%) complained of hematuria. Average duration of the complaint was 3.6±3.1 days. Hematuria complaint healed itself in 82 cases without any medical intervention. Remaining 11 patients were hospitalized and bladder irrigation was performed for these patients. Five of these patients had blood transfusion. Hematospermia was observed in a total of 65 patients (16.1%). No treatment protocol was applied for any patients monitored for hematospermia, and symptoms healed within 4-16 days. Rectal bleeding was observed in nine patients (2.2%). All of them lasted for less than two days and no surgical or medical intervention was needed other than intrarectal compression rectal bleeding points by finger. A total of 17 cases (4.2%) had vasovagal symptoms such as sweating, nausea, paleness, head swimming and hypotension. All of these cases were remedied clinically by Trendelenburg position and intravenous liquid support. No patients had myocardial infarction or cerebrovascular disorder due to vasovagal stimulus. Urinary retention, another complication observed after the procedure, was detected in three patients (0.7%). Emergency suprapubic cystostomy catheter was placed in three patients under local anesthesia. After alpha blocker, analgesic and antimicrobial treatment, cystostomy of all patients were taken, which showed that all cases improved without needing surgical intervention.

Infective pathology was observed in 29 patients (7.2%) after TRUS guided prostate biopsy procedure. Six of these cases had orchitis, two had epididymitis and 21 had prostatitis. A total

of 23 patients had fever over 38.5 °C at least once. In 16 of the patients who had infective complication, urine culture was positive. Cultures of nine patients were positive for Escherichia coli, four for Enterococcus, two for Klebsiella and one for Pseudomonas. Urosepsis developed in only one patient. All complications taken together, 36 patients (8.9%) were treated by hospitalization.

Hematuria and hematospermia were positively associated with high PSA and prostate volume (p<0.001). On the other hand, hematospermia was more common in young patients and hematuria was found more frequently in older patients (p<0.001). No association was found between rectal bleeding and age, PSA, prostate volume (p=0.892, p=0.874, p=0.647, respectively). Increased incidence of vasovagal symptoms with decreasing age was observed (p=0.035). On the other hand, no correlation was found between PSA and prostate volume of these patients (p=0.836, p=0.706, respectively). In addition, acute urinary retention was positively associated with increased age, PSA and prostate volume (p<0.001). When the infectious pathologies were examined, it was determined that only the high PSA values were correlated (p=0.034) (Table 1).

Table 1: Overview of complications following prostate biopsy

Complications	Variable	Complication mean±SD	No-complication mean±SD	p
	Number	93	310	
	Cancer diagnose after biopsy	38	103	
Hematuria	Age(y)	66.26±6.47	62.28±8.86	<0.001
	PSA(ng/mL)	32.03±21.13	18.59±15.99	<0.001
	Prostate volume (cm^3)	82.25±25.62	60.64±15.05	<0.001
	Number	65	338	
	Cancer diagnose after biopsy	26	115	
Hematospermia	Age(y)	61.12±7.25	63.60±8.71	<0.001
	PSA(ng/mL)	34.90±23.45	19.14±15.80	<0.001
	Prostate volume (cm^3)	90.15±26.60	60.90±14.59	<0.001
	Number	9	394	
	Cancer diagnose after biopsy	4	137	
Rectal bleeding	Age(y)	63.33±2.54	63,20±8.62	0.892
	PSA(ng/mL)	21.88±2.47	21.69±18.39	0.874
	Prostate volume (cm^3)	65.01±2.50	65.64±20.41	0.647
	Number	17	386	
Vasovagal	Cancer diagnose after biopsy	6	135	
symptoms	Age(y)	58.94±8.42	63.39±8.50	0.035
	PSA(ng/mL)	22.55±6.39	21.65±18.54	0.836
	Prostate volume (cm^3)	63.82±7.40	65.71±20.57	0.706
	Number	3	400	
Acute urinary	Cancer diagnose after biopsy	1	140	
retention	Age(y)	76.01±6.92	63.10±8.48	<0.001
	PSA(ng/mL)	52.33±44.45	21.46±17.87	<0.001
	Prostate volume (cm3)	88.33±20.21	65.46±20.12	<0.001
	Number	29	374	
Infective	Cancer diagnose after biopsy	12	129	
pathology	Age(y)	61.58±5.87	63.32±8.70	0.291
	PSA(ng/mL)	27.72±22.06	21.22±17.80	0.034
	Prostate volume (cm^3)	69.13±21.01	65.36±20.13	0.332

SD: standard deviation, PSA: prostate specific antigen

Discussion

A detailed analysis of medical literature shows that the first prostate needle biopsy was performed in 1930 by Fergusan. This first attempt was carried out using transperineal approach with an 18-gauge needle. However, longer distance traversed difficulty of manipulations, patients' disturbances due to perineal susceptibility and longer procedures in transperineal biopsies directed clinicians to find different approaches. With subsequent multicenter, large cohort studies, many superior aspects of transrectal prostate biopsies have been shown and this biopsy procedure has been a common practice in modern clinics. Among the mentioned superior features of transrectal biopsies are shorted distance to sampling area, ease of manipulation, less susceptibility of rectum and shorter time needed for the procedure [7,8].

In post-World War II period, Sonar (Sound Navigation and Ranging) machines that function using data obtained from advancing of sound energy in a medium, its refraction, reflection and absorption have been started to be used in health practice. Parallel to scientific advancements, there were groundbreaking developments in uro-radiology area. In terms of use of sonographic evaluation in prostate tissue, Wild and Reid used TRUS the first time in 1957, and Watanabe et al. [9] put this method in clinical practice in 1974. TRUS allows clinicians to take specimens appropriate for zonal anatomy of prostate. With specific design of machines for pelvic organs using emerging technologies, both prostate gland and seminal vesicles could be visualized with high resolution in transverse and sagittal planes [10].

Before these revolutionary developments in scientific world, prostate biopsies were performed physically with the guidance of a finger in many centers. With TRUS going into practice, extremely significant changes took place in data about prostate cancer. Scientific analyses revealed that even in patients for whom abnormal digital rectal examination findings, about half of the patients with negative outcomes in biopsies carried out by the guidance of a finger in fact was found to have cancer based on TRUS guided prostate biopsies [11]. An extremely critical historical procedure seems to have started in prostate cancer diagnosis with the introduction of systemic sextant prostate biopsy (6-core) with the guidance of TRUS by Hodge et al. in 1989 [12]. However, there was no standardization for taking specimen in TRUS guided prostate biopsies. Studies conducted revealed that 6-core prostate biopsy was extremely inadequate in the diagnosis of prostate cancer [1]. Clinical studies showed that prostate cancer could be missed in 15-34% of patients who had sextant biopsy [13,14]. Subsequent studies showed that increasing the number of TRUS guided biopsy specimens to 12 markedly increased the success rate in finding malignant tissues [15]. In recent approaches of TRUS guided prostate biopsies, specimens are taken from peripheric zone and lateral regions where 70% of malignancies arise, whereas routine sampling is not carried out in transitional zone in which cancer rate is as low as 1.9-2.1%. Besides, it is clear that no biopsy method is 100% successful in making prostate cancer diagnosis. In patients who had prostate cancer diagnosis clinically which could not be verified by tissue sampling, on the other hand, repeating prostate biopsies and increasing the number of specimens are quite common approaches adopted by many clinics [1,15].

Although TRUS guided prostate biopsies are commonly used in medicine, different preparation procedures have been used. This invasive procedure causes complications varying from hematuria to urosepsis with different frequencies. These complications are caused by many factors such as position given to patient, physical contact of probe to anal region and damage as a result of making hole in rectum mucosa for the purpose of sampling. However, complication frequencies have been considerably decreased in recent years as a result of great care observed during preparation stage before biopsy, introduction of automatic biopsy guns, routine use of antibiotic prophylaxis and increasing knowledge of clinicians. Based on recent reports, 64-78% of cases have minor post-operative complications such as hematuria, urinary retention, hematospermia and vasovagal

reaction while 0.3-3.0% have major complications such as urosepsis and Fournier gangrene [16].

Hematuria and hematospermia are most common post-operation complications of TRUS guided prostate biopsy. In their studies covering 2049 cases, Efesoy et al. [1] found that hematuria and hematospermia complication rates in TRUS guided prostate biopsy were 66.3 and 38.8%, respectively. On the other hand, Rietbergen et al. [17] examined 1687 prostate biopsies and reported that 23.6% of the patients had hematuria and 45.3% had hematospermia after the procedure. Hematuria and hematospermia observed after TRUS guided prostate biopsies generally heal themselves without needing a treatment. However, in 0.25–0.7% of the cases hematuria leading to clot retention and/or requiring transfusion can be seen [1]. In the present study, 23.1% of the patients had hematuria and 16.1% had hematospermia. Hematuria healed itself in 82 cases without needing any intervention, while 11 cases (2.7%) needed hospitalization. On the other hand, no treatment was performed for any patients who had hematospermia complication, and symptoms regressed within 4-16 days. Dede et al. [18] reported a rectal bleeding rate of 8% for TRUS guided prostate biopsy. Similarly, frequency of this complication was reported as 10% by Naughton et al. [19]. On the other hand, a lower incidence rate of 2.3% was reported for rectal bleeding by Berger et al. [20] in a large patient series including 5957 patients. Among the treatment modalities for rectal bleeding is intrarectal compression is applied on rectal bleeding points by finger, ultrasound probe or anoscope. Nevertheless, endoscopic sclerotherapy is another treatment option in cases for which hemostatic control cannot be achieved. In the present study, rectal bleeding was observed in 2.2% of the patients. Bleeding did not last longer than two days in any patient and no patients needed blood transfusion.

Infective pathologies are other complications that could develop after prostate biopsies. All clinicians today have a consensus over the use of prophylaxis for TRUS guided prostate biopsies. However, there is no agreement on type, dose and duration of antibiotic treatment and on combined approaches [21,22]. In cases without prophylaxis administration, incidence rates of infective pathologies range from 20 to 50%, and some of these clinic cases could lead to mortality [23]. With the introduction of antibiotic prophylaxis these rates decreased to 0.1-10.0% [18]. After TRUS guided prostate biopsy, very different infective pathologies such as pyuria, prostatitis, epididymitis, orchitis, asymptomatic bacteriuria and urosepsis could develop. Of all these pathologies of prostate biopsy, urosepsis is the most serious complication [1,22]. Erkoç et al. [24] studied 1280 cases for complications after TRUS guided prostate biopsy and observed a 6.5% infective complication rate. Similarly, Wu et al. [25] found 8.23% incidence rate for this complication. Infective pathology rate was 7.2% in the present study.

Vasovagal episodes are other complications observed after TRUS guided prostate biopsy. Most of them are considered to develop as a result of anxiety. However, they could also develop as a result of decrease in blood supply to brain due to vasodilation which develops in gastrointestinal veins as secondary to distension in rectum. For affected cases, Trendelenburg position and intravenously applied liquid hydration are sufficient treatment modalities for most patients [22]. It is estimated to be 8% after the procedure [26]. This rate was 4.2% in our series. All cases recovered clinically using Trendelenburg position and intravenous liquid support. Another complication of TRUS guided prostate biopsy is lower urinary system symptoms. These complaints arise due to trauma and edema caused by the procedure. An average of 0.8-40% of cases who had TRUS guided prostate biopsy were reported to have lower urinary system symptoms and 0.2-9.1% were reported to have acute urinary retention [1]. In the present study, 0.7% of the cases had acute urinary retention. Suprapubic cystostomy was performed in these patients.

Retrospective nature and limited number of cases were the main limitations of the present study.

In conclusion, based on the findings of the present study, it could be stated that with its low complication rates, TRUS guided prostate biopsy is a reliable diagnostic tool for prostate cancer.

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Neck pain and dysphagia secondary to diffuse idiopathic skeletal hyperostosis of the cervical spine: A case report

Diffüz idiyopatik iskelet hiperostozuna ikincil gelişen boyun ağrısı ve yutma güçlüğü: Olgu sunumu

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Abstract

Diffuse idiopathic skeletal hyperostosis (DISH), also known as Forestier disease is characterized by calcification and ossification of the soft tissues, mainly ligaments and entheses. DISH is a systemic non inflammatory disease of unknown cause and is considered an underdiagnosed and mostly asymptomatic nonprimary osteoarthritis. This condition is recognized radiologically only. Rarely, large projecting anterior osteophytes result in esophageal impingement and distortion leading to dysphagia. We report the case of dysphagia and neck pain due to DISH of the cervical spine in a 60 year old female. The patient came to the emergency department with neck pain and dysphagia after falling.

Keywords: Neck pain, Dysphagia, Osteophyte, Diffuse idiopathic skeletal hyperostosis

Öz

Forestier hastalığı olarak da adlandırılan diffüz idiyopatik iskelet hiperostozu (DISH), yumuşak dokuların ve ligamentlerin kalsifikasyonu ve ossifikasyonu ile karekterize klinik tablodur. DISH; etyolojisi tam olarak bilinmeyen, inflamatuvar olmayan, çoğunlukla asemptomatik olup az tanı alan primer osteoartrit olarak düşünülür. Tanı radyolojik incelemelerle konur. Nadiren osteofitler özafagusa bası yaparak disfajiye neden olur. Biz olgu sunumumuzda düşme sonrası yutma güçlüğü ve boyun ağrısı yakınmalarıyla acil servise başvuran, DISH tanısı konan 60 yaşında kadın hastayı sunmayı amaçladık.

Anahtar kelimeler: Boyun ağrısı, Yutma güçlüğü, Osteofit, Diffüz idiyopatik iskelet hiperostozu

Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is a non-inflammatory disease of unknown cause, characterized by ossification of spinal ligaments and entheses. The diagnosis of the disease is made by anatomical, clinical and radiological data. [1]. The criteria for spinal involvement in DISH, all three of which must be met; 1) presence of flowing calcification and ossification along the anterolateral aspect of at least four contiguous vertebral bodies, with or without associated localized pointed excrescences at the intervening vertebral body intervertebral disc junctions; 2) presence of relative preservation of intervertebral disc height in the involved vertebral segment and the absence of extensive radiographic changes of “degenerative” disc disease; and 3) absence of apophyseal joint bony ankylosis and sacroiliac joint erosion, sclerosis, or intra-articular osseous fusion [2]. Clinical signs of the disease depend on the location of involvement. Literature have shown that 17- 28 % of patients with DISH manifested symptoms of dysphagia due to cervical osteophytes [3]. We present a case report of a female patient seen in the emergency department with neck pain and dysphagia secondary to DISH.

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Case presentation

A 60-year-old woman was admitted to the emergency service with neck pain and swallowing difficulty after falling down. According to the patient's story the neck pain was dull and progressive but generally tolerated by the patient, swallowing difficulty solid food for 4 years and increased after falling down. She was diagnosed with diabetes mellitus and hypertension and was taking oral antidiabetic and antihypertensive drugs. There was no trauma and operation from the neck region. On physical examination, the patient was alert, afebrile, and well oriented, with stable vital signs. The systemic and neurological exam and the patient's reflexes were normal. Cervical range of motion reduced. The patient did not show clinical, radiological, or serological evidence of rheumatoid arthritis or of ankylosing spondylitis. CK in laboratory tests was 493 u / l and other laboratory were normal. No pathology was detected in superficial tissue ultrasonography. Chest X-ray was normal. The lateral radiograph of her cervical spine showed characteristic flowing ossification along the anterior aspect of the cervical vertebrae from C5-7 and the facet joints and spinous processes did not appear ankylosed (Figure 1). The computed tomography scan of the cervical showed degenerative changes and osteophytes. Sagittal T2-weighted magnetic resonance imaging showed bone marrow signal abnormality in C5–C7 as well as in the outgrowth hyperostosis. Magnetic resonance imaging did not show cord compression and spinal stenosis. Symptoms were considered to be the diffuse idiopathic skeletal hyperostosis affecting the cervical spine and were treated with conservative approaches. We advised the patient to change the food pattern to semisolid diet, taking plenty of water with food, taking frequent meal with small quantity at a time and taking time to complete the meal. Swallow therapy was applied. Medical treatment was regulated as anti-inflammatory medication, muscle relaxants and antireflux medication. After 3 month, the symptoms of the patient decreased significantly. Neurological deficit was not detected. Informed consent was obtained from patient.

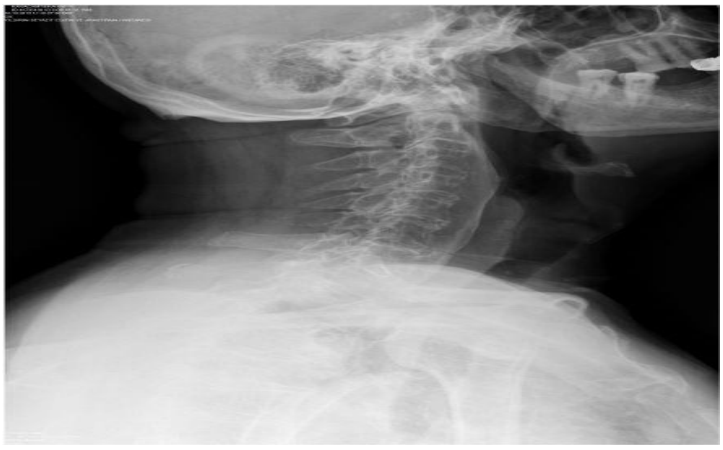

Figure 1: Lateral radiograph of cervical spine

Discussion

Forestier's disease, also known as DISH, is a non-inflammatory disease of unknown cause and is an ossifying diasthesis characterized by spinal and peripheral enthesopathy. It was first described as senile ankylosing hyperostosis of the spine by Forestier and Rothe-Querol in 1950 [4]. The prevalence of DISH is between races ranging from2.9% to 25% [5,6]. There is a male predominance of Forestier's disease, mainly affecting elder individuals in their fifth or sixth decades [7,8]. The incidence of metabolic disorders, such as metabolic syndrome, diabetes and obesity, has been reported to be increased in patients with DISH [9].

Clinical signs of the disease depend on the location of involvement. DISH is considered an underdiagnosed and mostly asymptomatic nonprimary osteoarthritis. Symptomatic degenerative changes of the cervical spine affect 75% of the population above 60 years of age [10]. Dysphagia from hyperostosis is most commonly associated with anterior osteophyte formation of C3–C6, likely due to the fact that the normal epiglottic tilt lies over the laryngeal inlet at this level [11]. Evaluation of dysphagia involves imaging studies such as X-ray, CT, and/or magnetic resonance imaging. Invasive diagnostic tests such as barium swallow, nasal endoscopy, esophagram and videofluoroscopic studies are also useful for visualizing potential mechanical obstruction; but the literature does not set standard for diagnosis [12]. Nonsurgical methods such as dietary restrictions, speech and swallow therapy, anti-inflammatory medication, steroids, muscle relaxants, and antireflux medication are most effective for treatment of dysphagia. The literature suggests that osteophyte resection is considered to be highly successful when conservative methods fail [13].

We presented a case report of a female patient seen in the emergency department with neck pain and dysphagia secondary to DISH. Our patient was a female and had onset of symptoms at >50 years of age, associated diabetes mellitus, arterial hypertension.

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Case report
Olgu sunumu

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Novel usage of superficial liposuction in hidradenitis suppurativa

Hidradenitis suppurativa'da yüzeysel liposuctionın yeni kullanımı

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Abstract

Hidradenitis suppurativa otherwise known as acne inversa is a common skin disease that presents as recurrent painful nodules, which form in characteristic sites of the body and often progress to chronic purulent discharge, scarring, and sinus formation. Currently there is no gold standard treatment to combat this recurring disease. Here we describe a novel usage of superficial liposuction in treatment of hidradenitis suppurativa.

Keywords: Superficial liposuction, Subdermal liposuction, Hidradenitis suppurativa, Acne inversa

Öz

Akne inversa olarak bilinen hidradenitis suppurativa, vücudun karakteristik bölgelerinde oluşan ve sıklıkla kronik pürülan akıntı, skarlaşma ve sinüs oluşumuna kadar ilerleyen ağrılı nodüller olarak ortaya çıkan yaygın bir deri hastalığıdır. Şu anda bu yinelenen hastalıklarla mücadele etmek için altın standart tedavi yoktur. Burada hidradenitis suppurativa tedavisinde yeni bir yüzeyel liposuction kullanımı tarif ediyoruz.

Anahtar kelimeler: Yüzeysel liposuction, Subdermal liposuction, Hidradenitis suppurativa, Akne inversa

Introduction

Hidradenitis suppurativa (HS) is related with the apocrine sweat glands and is sometimes referred to as acne inversa or apocrine acne. In HS, it is believed that the apocrine ducts become blocked. The secretions and bacteria entrapped within and then abscess developed. These inflamed boil-like nodules either slowly disappear or erupt as painful suppurative abscesses [1-3].

Although healing follows, the affected skin is left with deep scarring. There are periods of remission, as the disease progresses, the condition becomes chronic. More diffuse multiple abscesses occur with the formation of a network of sinus tracks accompanied by pockets of induration. Hurley in 1989 first described staging of HS based on severity (Table 1). This classification had been evolved to be more acceptable and widely used from time to time. This classification is important to determine the course of treatment planned for the patient either medically or surgically [4].

Liposuction was first introduced by fisher in 1976, it underwent several modification in the technique and the instruments used. Back than liposuction was used exclusively in the deep layer of subcutaneous tissue and not to suck superficial fat layer to avoid skin irregularities [5,6]. With better anatomical understanding of superficial fascia system, Gasperoni [7] described superficial liposuction technique. He further described subcutaneous layer which is dived into 2 by superficial fascia: superficial fat-areolar and deep fat layer-lamilla (Figure 1). With superficial liposuction it is possible to reach sweat glands located at hypodermis and to break deep seated abscess in subcutaneous layer in HS.

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Table 1: Severity based classification of Hidradenitis suppurativa

Stage	Characteristics
I	Abscess formation, single, or multiple, without sinus tracts and cicatrisation.
II	Recurrent abscesses with tract formation and cicatrisation, single or multiple, widely separated lesions
III	Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.

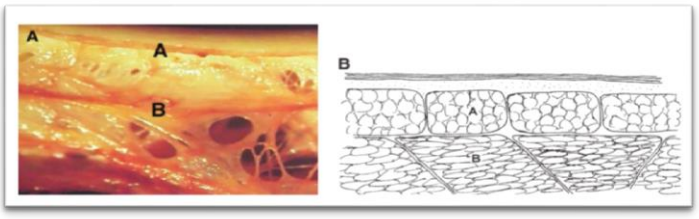

Figure 1: A: cross section of subcutaneous tissue A.A: skin, A.B: superficial fascia. B: schematic diagram of subcutaneous tissue B.A: superficial areolar fat layer densely contained in fibrous septa, B.B: deep lamellar fat layer loosely arranged. Adapted from [6]

Case presentation

Case 1

A 37 years old lady with underlying diabetes mellitus presented with small multiple pustule lesions at bilateral axilla for 6 years. The lesions were increasing in size with intermittent flare up manifested by fever, skin erythema and foul pus discharge. Initially she was treated with multiple courses of antibiotics which partially resolved her flare symptoms (Figure 2). This illness had caused her to take frequent work leave due to her symptoms, pain and social embarrassment.

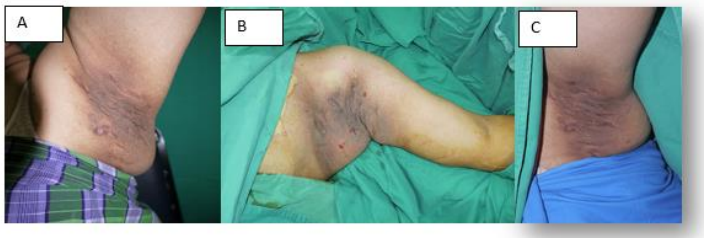

Figure 2: A: preoperative left axilla, B: immediate post liposuction, C: four months post superficial liposuction

She underwent superficial liposuction (subdermal liposuction) over bilateral axillae under general anesthesia. The procedure was uneventful. She was well and discharged two days after the surgery. Six months after surgery, on her clinic follow up. She has only complaint of slight discomfort probably due to skin tightness at her bilateral axillae. Otherwise there were no signs of inflammation, no hematoma, no discharge. She has not noticed any recurring symptoms after 1 year.

Case 2

A 46 years old policeman, ex-smoker presented with history of recurrent right gluteal abscess, scarred and puckered skin with intermittent flare up symptom with fever and secondary bacterial infection requiring hospital admission and IV antibiotics. Magnetic Resonance imaging showed right gluteal abscess with multiple tract. Colonoscopy was performed to rule out anorectal fistula. Subsequently this patient was referred to our center for further management. Tissue from right gluteal region was obtained for histopathological examination: No malignancy, feature of HS.

We proceeded with superficial liposuction on the right gluteal region under spinal anesthesia. Six months post operation patient was highly satisfied with marked improvement of his symptom especially on lateral gluteal area. He still has occasional discharge located at medial gluteal fold but he never required hospitalization again for secondary bacterial infection. He was offered another session of superficial liposuction however patient not keen for another operative procedure.

Discussion

FHS disease is a burdensome to healthcare economy, prevalence of HS is as high as 1–4% in population [1] and most patients are young to middle-aged adults where women are more affected than men [8]. Currently there is no one gold standard treatment to combat HS [2].

In 1989, Gasperoni [7] discovered a new path of liposuction when he presented superficial liposuction, which is the suction of superficial fat layer (subdermal). This technique permits treatment at the thin adipose layer so that better result can be achieved than traditional liposuction. Knowing that sweat gland is located at hypodermis area, we used superficial liposuction to destroy these glands and the chronic sinuses formed in hypodermis area.

Superficial liposuction is not just a simple and safe procedure, postoperative care is swift and patient does not require prolong hospital stay. Both our patients could be safely discharge on day 2 post liposuction. Patient in case one showed no signs of relapsed on her 1 year following surgery. She had tightness over her bilateral axilla, this is a known effect of superficial liposuction where skin retraction occurred by defatting immediately under the skin.

In our second case, the patient has never turned back. In my opinion he had near total recovery which hinders him from coming back to received further treatment. To my best knowledge this is the first report of liposuction usage for HS treatment. More series needed to ascertain the efficacy of this treatment. This may add additional armamentarium for plastic surgeon to combat a chronic recurrent HS.

Superficial liposuction is a simple and safe treatment for HS. However, more study is needed to verify the effectiveness of liposuction in treatment.

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Synchronous association of gastrointestinal stromal tumors of the jejunum and sigmoidal adenocarcinoma: A case report

Jejunum ve sigmoidal adenokarsinomun gastrointestinal stromal tümörlerinin senkron ilişkisi: Olgu sunumu

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Abstract
The association of a gastrointestinal stromal tumor (GIST) with an epithelial tumor of the digestive tract is very rare and frequently discovered by chance during the surgical treatment of digestive carcinoma. These tumors developed from the mesenchyme are known to have a good prognosis given their low malignancy potential. The possibility of a genetic mutation or an oncogenic agent capable of inducing tumors of different histotypes seems less plausible but it is not to be discarded. We report the case of a 74-year-old patient, operated for a sigmoid adenocarcinoma, with incidental discovery of a small bowel tumor whose histology confirmed the diagnosis of a GIST.
Keywords: Synchronous tumors, Gastrointestinal stromal tumor, Adenocarcinoma, Digestive tract

Öz
Sindirim kanalının epitelyal tümörü ile gastrointestinal stromal tümörün (GIST) birlikteliği çok nadirdir ve sindirim karsinomunun cerrahi tedavisi sırasında sıklıkla tesadüfen keşfedilmiştir. Mezenşimden gelişen bu tümörlerin, düşük malignite potansiyelleri göz önüne alındığında iyi bir prognoza sahip oldukları bilinmektedir. Bir genetik mutasyonun veya farklı histotiplerin tümörlerini indükleyebilen onkojenik bir maddenin olasılığı daha az akla yatkın görünmektedir, ancak yadsınamaz. Biz histolojisi bir GIST tanısı doğrulayan ince bağırsak tümörünün tesadüfen keşfiyle, sigmoid adenokarsinom için ameliyat edilen 74 yaşında bir hastayı sunuyoruz.
Anahtar kelimeler: Senkron tümörler, Gastrointestinal stromal tümör, Adenokarsinom, Sindirim sistemi

Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. Their metachronous or synchronous association with digestive carcinoma has been rarely reported in the literature [1-3]. We report the synchronous association of a jejunum's GIST with a sigmoid adenocarcinoma.

Case presentation

A 74-year-old patient, diabetic and hypertensive on treatment, who presented two months before her admission defecatory rectorrhagia of low abundance. An abdominal CT scan revealed a tumor process of the partially stenotic sigmoid loop (figure 1), without metastases found during the extension assessment.

A colonoscopy showed a lesion 25 cm from the anal margin, stenosing and impassable. A biopsy was made and revealed well differentiated and infiltrating lieberkhunal adenocarcinoma. The patient has undergone a sigmoidal resection, the surgical exploration discovered a jejunal tumor, and the surgical procedure was completed by a cuneiform jejunal resection removing the tumor. Anatomopathological study confirmed the diagnosis of lieberkhunal adenocarcinoma with clean margins classified stage pT2 N1b M0. The histological analysis of the jejunal tumor concluded to the diagnosis of GIST (figure 2, 3) (CD117 and the strongly positive DOG1) with low risk of recurrence. The postoperative thoracoabdominopelvic CT scann and tumor markers were normal. The patient received adjuvant chemotherapy: oxaliplatin and capecitabine (Xelox).

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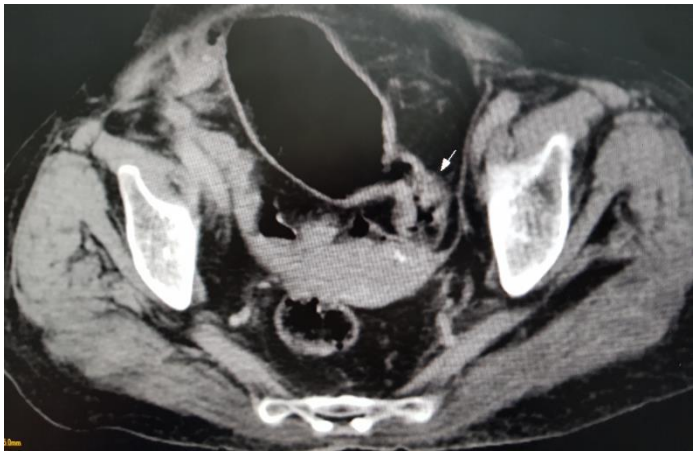

Figure 1: A computed tomography scan showing a sigmoidal wall mass

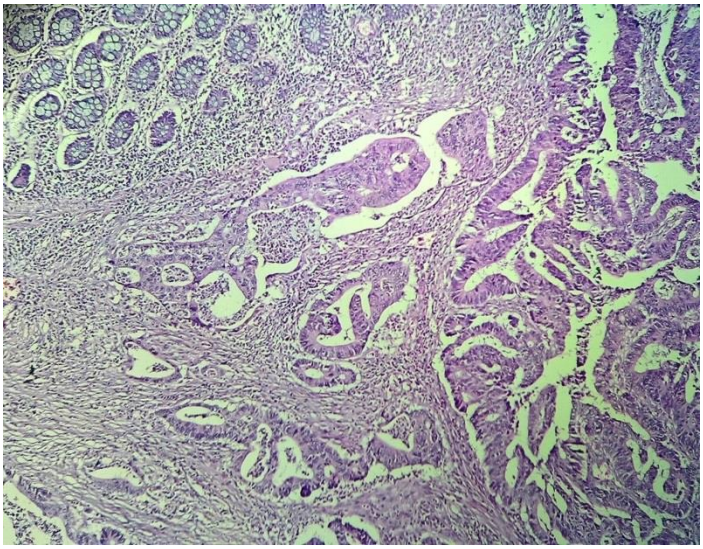

Figure 2: Colon adeno-carcinomatous proliferation

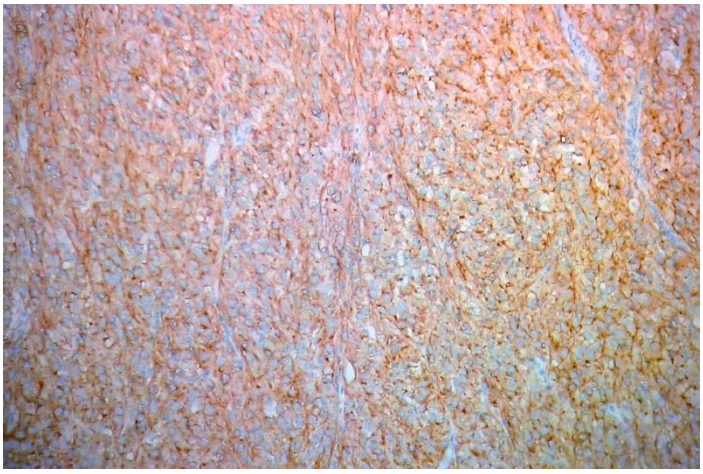

Figure 3: Tumor cells express CD117

Discussion

GISTs are the most common mesenchymal tumors of the digestive tract. Often isolated, they can rarely come into association. They can be observed in the context of family syndromes. The Carney Triad associates multiple gastric stromal tumors, a pulmonary chondroma, and an extra-adrenal paraganglioma [1].

Of the 1765 gastric GISTs studied by Miettinen and Lasota [2], only four cases of Carney's triad were found. GISTs can also be seen in 5 to 25% of cases in type 1 neurofibromatosis. There are familial forms of GIST associated with hyperpigmentation, urticaria pigmentosa and / or systemic mastocytosis [1]. An oncogenetic consultation is recommended in these cases after information and agreement of the patient. Apart from these associations, the synchronous or metachronous development of GISTs and digestive epithelial tumors is very rare. These GISTs are often of low malignancy potential.

About 30 cases of mesenchymal tumors including synchronous GIST with other gastrointestinal tumors have been reported [3], including adenocarcinomas, lymphomas and carcinoid tumors [3,4] but also hemopathies, melanomas, breast, kidney, prostate and female genital cancers [5,6]. In a study involving 783 patients, Pandurengan et al. [7] showed that about 20% of cases with GIST developed other types of digestive cancers. The association of GIST with colorectal adenocarcinoma is the most frequently reported [8]. In most cases, the discovery of GISTs is fortuitous during laparotomy for primary adenocarcinoma [6].

Maiorana et al. [3], by examining 2035 carcinomas, showed six cases of stromal and epithelial synchrone tumors including five adenocarcinomas and one carcinoid tumor (a frequency of 0.29%). Chacon et al. [9] evaluated the incidence of tumors associated with GIST and reported two cases of colonic adenocarcinoma in a series of 86 patients (a frequency of 2.32%). Thirty isolated cases of GIST associated with gastrointestinal adenocarcinoma have been reported mainly in Japanese literature. GISTs can also be associated with other digestive mesenchymal tumors such as lipomas. Exceptionally, triple associations have been reported.

Two etiopathogenic hypotheses have been advanced to explain the association of GIST with digestive carcinoma. Maiorana et al. [3], noting that most of the cases reported come from Japan, have suggested the hypothesis of a simple accidental association, especially in countries with a high incidence of digestive cancer especially gastric cancer. As for Cohen et al. [10], they evoke the possibility of a genetic mutation or an oncogenic agent capable of inducing tumors which are histologically different.

Agaimy and Wunsch [5] analyzed 97 GIST cases, of which 18 (18.6%) were associated with other tumors. This study involved 12 women and six men aged 43 to 87 years. Twelve GISTs were present in the stomach, four in the small intestine, one in the duodenum and one in the appendix. The tumors associated with these GISTs were carcinomas of gastrointestinal and pancreatic origin in nine cases, gynecological in three cases, mammary in two cases, pulmonary in two cases, prostatic in one case, and renal in one case and a lymphomatous proliferation in two cases.

The rather limited number of cases of this association does not allow defining its exact pathogenesis which requires further studies. Given the low risk of recurrence of GISTs in association with digestive carcinomas, the treatment should aim the epithelial lesion, since it is the surveillance that is adopted for low-risk GISTs.

Conclusion

The reported case is about a synchronous development of a sigmoid adenocarcinoma and a jejunal GIST with a low risk of recurrence. Their association is very rare and the hypothesis of a pathogenic relationship between these different histological

types resulting from a common genetic disorder is not yet confirmed but remains plausible for better management.

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Left persistent superior vena cava with large coronary sinus: A case report

Sol persistant vena kavaya bağlı geniş koroner sinus: Olgu sunumu

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Abstract

Persistent left superior vena cava (LPSVC) is a rare and important congenital venous anomaly. It is caused by a defect in the closure of the left anterior cardinal vein during cardiac development. The LPSVC drains into the right atrium via the coronary sinus (CS) in 90% of cases, connects to the left atrium in 10 % of them. When cardiac anomalies are present, LPSVC is usually linked directly to left atrium. Thus, LPSVC which drains in the CS is generally isolated and asymptomatic. In our case, patient presented a heavy respiratory symptomatology without any diagnosis since all of the respiratory tests were normal. After realization of a computed tomography (CT), LPSVC had been discovered inducing a huge dilatation of CS, which its diameter was three times more than reported in literature and without any associated congenital heart disease. LPSVC seems to be a complex anatomic variation with different clinic and anatomic shapes. CS dilatation can be found in association with LPSVC in CT. As a result, it is important to use non-invasive cardiovascular examinations to make an optimal diagnosis of congenital cardiovascular variations and in order to avoid further interventional complications.

Keywords: Superior vena cava, Left persistent vena cava, Thorax radiology

Öz

Kalıcı sol superior vena kava (LPSVC) nadir ve önemli bir konjenital venöz anomalidir. Bu anomali, kardiyak gelişim sırasında sol anterior kardinal venin regresyonunda bir defektten kaynaklanır. LPSVC, % 90 oranında koroner sinüs (CS) yoluyla sağ atriyuma akar, % 10'unda sol atriyuma bağlanır. Kardiyak anomaliler mevcut olduğunda, LPSVC genellikle doğrudan sol atriyuma bağlanır. CS'ye drene olan LPSVC genellikle izole ve asemptomatiktir (4). Bizim olgumuzda, solunum testlerinin tümü normaldi ancak hasta herhangi bir tanı olmaksızın ağır bir solunum semptomatolojisi sundu. Bilgisayarlı tomografi (BT)'de LPSVC'nin, CS dilatasyonunu indülendiği saptanmıştır; CS literatürde belirtilen normal boyutun 3 kat üzerinde izlenmekteydi, herhangi bir konjenital anamali saptanmadı. LPSVC, farklı klinik ve anatomik şekillerle kompleks bir anatomik varyasyon gibi görünmektedir. CS dilatasyonu BT'de LPSVC ile ilişkili olarak bulunabilir. Sonuç olarak, konjenital kardiyovasküler varyasyonların optimal tanısını koymak ve girişimsel komplikasyonları önlemek için non-invaziv kardiyovasküler muayenelerin kullanılması önemlidir.

Anahtar kelimeler: Superior vena cava, Sol persistan vena kava, Toraks radyolojisi

Introduction

Persistent left superior vena cava (LPSVC) is a rare and important congenital venous anomaly and it is caused by a defect in the closure of the left anterior cardinal vein during cardiac development [1]. It can lead to coronary sinus (CS) dilatation when it drains to right atrium. In another perspective, this dilatation is very important to understand the way of drainage of LPSVC. Additionally, knowledge of LPSVC's physiopathology is also important before some interventional and surgery procedures [2,3]. We will put the light in our case report on LPSVC with a huge CS dilatation.

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Case presentation

We report the case of 56-years-old woman admitted to hospital with respiratory complains. Pulmonary functional tests were normal. There was a second line adjacent to the shadow of the descendant aorta in chest x-ray image. Bilateral lung parenchyma was normal. The ascending aorta was slightly tortoise and elongate. Trachea was in midline and borders were regular. No hilar pathology was noticed (Figure 1c). In computed tomography (CT) imaging, the patient had double superior vena cava. There was a normal formed right superior vena cava but LPSVC was detected at the anterior left side of the aorta. Left jugular and left subclavian veins merged and formed the LPSVC. Two of the vena cava had approximately the same diameter (Figure 1d). There was no contrast enhancement in left vena cava, because of right atrial communication (Figure 1a). In addition, long diameter of coronary sinus was 2.5 cm which was very large according to normal ranges (Figure 1b). In the report of echocardiography, no congenital anomaly was detected. Only they found a large coronary sinus connected with the right atrium and its roof was intact. In colored reconstruction images, LPSVC is connected with the coronary sinus. It goes between aortic arch and the vascular structures of the left pulmonary hilum and finally curves right and anteriorly to end in the right atrium. Atriums, ventricles and aorta were normal (Figure 2). The patient consent was taken before writing this case report.

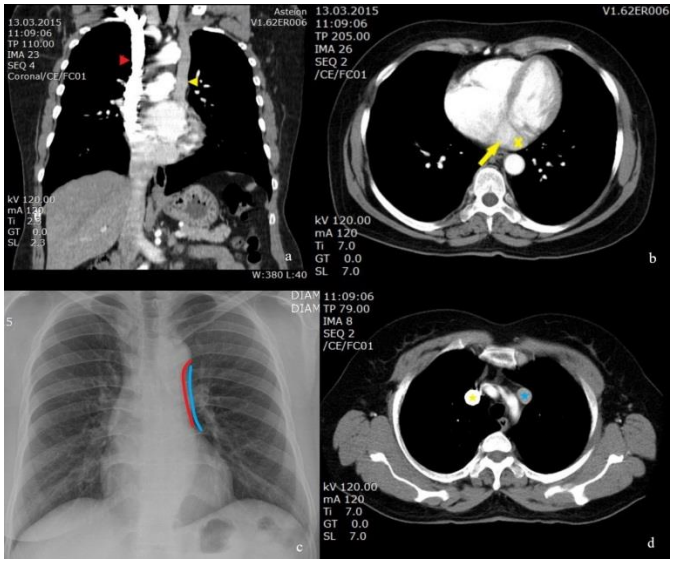

Figure 1: a: Right vena cava (red arrow head) LPVCS (yellow arrow head), b: Coronary sinus (yellow arrow) PLVCS connection with coronary sinus (yellow cross), c: Border of descendant aorta (red line) PLVCS (blue line), d: Enhanced contrast of normal Vena cava (yellow star) unenhanced contrast of PLVCS (blue star)

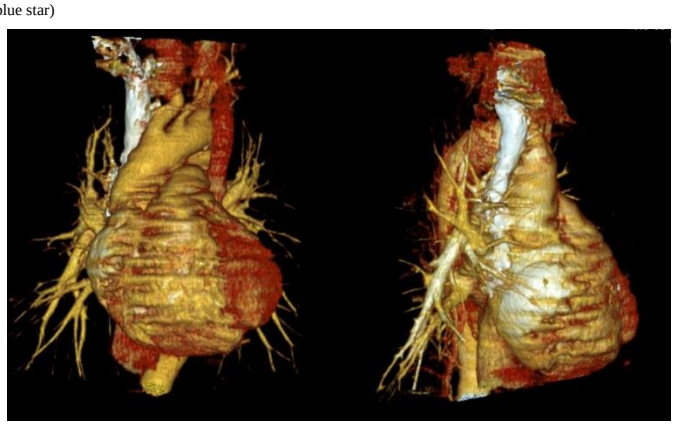

Figure 2: Double vena cava and normal configuration of heart, Right: Antero-posterior view of the heart, Left: Lateral view of heart

Discussion

LPSVC is a rare organogenesis abnormality [4]. The ratio of LPSVC is 0.3-0.5% in the general population [5]. It is due to the persistence of the terminal part of the left anterior cardinal vein, which normally involutes in the sixth month of uterine life [4]. The major venous drainage system of the embryo is constituted by the cardinal veins. The oblique anastomotic branch joins to the anterior cardinal veins and two of them forms left brachiocephalic vein. Normally the right anterior cardinal vein and the right common cardinal vein merge to form the SVC while the left anterior cardinal vein and the left common cardinal vein must undergo atrophy. Patency of embryonic veins lead to multiple variations for example double SVC, double inferior vena cava (IVC) or other venous connections which don't normally exist [6]. The PLSVC represents failure of obliteration of the left anterior cardinal vein in early embryological development [7].

In 90% of cases the persistent left-sided SVC connects to the right atrium via the coronary sinus, 10% the left SVC connects to the left atrium causing a right-to-left shunt. The variant linked with left atrium has potential hazard of systemic embolization of thrombus or air [7]. Cardiac anomalies accompanying LPSVC usually are a shunt type. The most commonly associated cardiac abnormality is an atrial septal defect (ASD). Others include Fallot's tetralogy, coarctation of the aorta, pulmonary stenosis and interventricular septal defect (VSD). If a double SVC is not associated with other congenital cardiac abnormalities, it is usually asymptomatic and hemodynamically insignificant [7]. LPSVC is the most common congenital venous anomaly of the thorax that causes a dilated CS [2]. As mentioned above, in the absence of congenital heart disease, LPSVC drains into the right atrium through the coronary sinus which expands because of hemodynamically overload [3].

Enlargement of the CS can be part of an anatomical variation like LPSVC or congenital anomaly like total anomalous pulmonary venous return, coronary atrioventricular fistula and anomalous hepatic venous drainage causing anomalous venous overload into the coronary sinus. It can also result from a wide spectrum of conditions causing right atrial dilatation, including tricuspid stenosis, tricuspid regurgitation, right ventricular dysfunction, and pulmonary hypertension [6,8]. Rare causes of dilated CS include postoperative obstruction, thrombosis and unroofing of the sinus [8].

In our paper we described the incidental discovery of a dilated CS due to a PLSVC in 56 years old female during CT screening for respiratory failure, in purpose to highlight the importance and usefulness of combining non-invasive cardiovascular examinations to make an optimal diagnosis and illustration of congenital cardiovascular variations.

PLSVC is often present in asymptomatic individuals and is discovered incidentally during cardiovascular imaging, device implantation, or surgery [3]. Although it is a benign condition, PLSVC has important clinical implications. From one hand, it can be associated with a variety of congenital malformations of the heart and great vessels, and in the other hand it may technically complicate some endovascular and surgery procedures.

Knowing the anatomy of the coronary sinus (CS) and cardiac venous drainage is important because of its relevance in electrophysiologic procedures and cardiac surgeries. Several procedures make use of the CS, such as left ventricular pacing, mapping and ablation of arrhythmias, retrograde cardioplegia for coronary artery bypass, targeted drug delivery, and stem cell therapy therefore it is primordial to detect the dilatation of CS before the intervention [6,8].

Otherwise, when the left subclavian vein is used as access, serious complications such as arrhythmias, shock and coronary sinus thrombosis may occur. Furthermore, pacemaker (PM) or implantable cardioverter defibrillator (ICD) placement can be difficult and dangerous [3]. Consequently, it is beneficial for physicians to interpret the results of cardiac CT examinations in order to identify normal variants and congenital anomalies and to understand their clinical importance [6].

In our case, the patient presented a heavy respiratory symptomatology without any diagnosis since all of the respiratory tests were normal. After realization of a CT, PLSCV had been discovered inducing a huge dilatation of CS. In the literature, using contrast-enhanced non ECG-gated chest CT, the mean diameter of the CS was reported as 7.05 mm ± 1.90 [6]. In our patient it was tree time more and this, in the absence of any congenital heart disease. It seems obvious that noninvasive investigation like CT make a considerable contribution for showing cardiovascular variations when other tests have failed to put a diagnosis.

Conclusion

PLSVC is a rare congenital variation. If not associated with congenital heart disease, it is benign condition without any clinical manifestation. The originality of our case resides in the fact that our patient presented with respiratory insufficiency when all of the tests were normal. The realization of a CT made the diagnosis of a PLSVC with a much dilated CS and in the absence of a congenital heart disease. This finding was highly important since it is necessary to take some precautions before risky interventions.

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Case report
Olgu sunumu

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Contribution of radiation therapy of head and neck paragangliomas: About 6 cases presentation

Baş ve boyun paragangliomalarında radyasyon tedavisinin katkısı: 6 vaka sunumu

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Abstract

The neck's paraganglions are bilateral nodular structures, with the same embryological origin which is the cephalic neural crest. They have a branchiomeric distribution. They have an important secreting function during the embryonic life, and then regress when the adrenal medulla starts functioning. Then only carotid and aortic paraganglions have chemoreceptor, baroreceptor and endocrine proved functions. The paragangliomas are tumors developed at the expense of paraganglions by proliferations of the chief cells (of type I) most of the time. Generally these tumors exhibit a slow growth rate, most often presenting asymptomatically as a space occupying mass lesion witnessed clinically or radiographically. The secreting tumors are very rare (5%). The benignity is the rule but the localization near noble structures makes it a highly risky tumor. This disease is often monofocal but it may also be part of a multifocal disease (6%). Advances in imaging have facilitated the diagnosis and the assessment of this disease. Diagnosis is generally made through a combination of clinical findings and radiographic studies. Surgery is the treatment of choice through total subadventitial resection, and rebuilding of the carotid axis when necessary. Surgery may lead to significant morbidity, resulting from major cranial nerve injury and especially at a late stage in the evolution of the disease. The preoperative embolization can facilitate ablation and reduce morbidity. Precisely, external radiotherapy can de indicated for recurrences, tumoral operating residues, and counter indications.

Keywords: Paraganglioma, Radiotherapy, Head and neck, Pheochromocytoma

Öz

Boynun paraganglionları, sefalik sinir kreti olan aynı embriyolojik kökene sahip iki taraflı nodüler yapılardır. Branşmerik dağılımları var. Embriyonik yaşam boyunca önemli bir salgılama fonksiyonuna sahiptirler ve adrenal medulla çalışmaya başladığında gerilerler. O zaman sadece karotis ve aort paraganglionları kemoreseptör, baroreseptör ve endokrin kanıtlanmış fonksiyonlara sahiptir. Paragangliomalar, çoğu zaman baş hücrelerin çoğalmasıyla (tip I) paraganglionlar pahasına geliştirilen tümörlerdir. Genellikle bu tümörler, klinik veya radyografik olarak tanık olan bir yer kaplayan kitle lezyonu olarak asemptomatik olarak ortaya çıkan yavaş bir büyüme hızı gösterir. Salgılanan tümörler çok nadirdir (%5). Benign olması kuraldır ama asil yapılara yakın lokalizasyon onu oldukça riskli bir tümör yapar. Bu hastalık genellikle monofokaldir, fakat aynı zamanda multifokal bir hastalığın parçası olabilir (%6). Görüntüleme alanındaki ilerlemeler, bu hastalığın teşhis ve değerlendirmesini kolaylaştırmıştır. Tanı genellikle klinik bulgular ve radyografik incelemelerin bir kombinasyonu ile yapılır. Cerrahi, total subadventitial rezeksiyon ve gerektiğinde karotis ekseninin yeniden inşası ile tercih edilen tedavi yöntemidir. Cerrahi, önemli kranial sinir yaralanmasından kaynaklanan ve özellikle hastalığın evriminde geç bir aşamada ciddi morbiditeye yol açabilir. Preoperatif embolizasyon ablasyonu kolaylaştırabilir ve morbiditeyi azaltabilir. Kesin olarak, dış radyoterapi nüks, tümörlü çalışma artıkları ve karşı endikasyonlar için gösterilebilir.

Anahtar kelimeler: Paraganglioma, Radyoterapi, Baş ve boyun, Feokromositoma

Introduction

Paragangliomas (PGL) of the head and neck are rare, slow-growing, generally benign tumors of neuroendocrine cells associated with the peripheral nervous system that commonly involve the carotid body, jugular bulb, vagal ganglia, and temporal bone. Treatment options include surgery, radiotherapy (RT), stereotactic radiosurgery (SRS), and observation. This article briefly reviews our 45-year institutional experience treating this neoplasm with RT.

Paraganglia cells originate from the neural crest but differentiate into sympathetic and parasympathetic subtypes that can give rise to paraganglioma [1]. Sympathetic PGL secrete norepinephrine, parasympathetic PGL are non-secretory and typically occur in head and neck region like carotid body PGL and jugulotympanic PGL. In fact PGL can occur from the base of skull to the pelvic, anywhere there are paraganglia. Unlike other types of cancer, there is no test that determines benign from malignant tumors.

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The diagnosis is focused on clinical signs and imaging. The reference treatment is surgery, but radiotherapy is an excellent therapeutic alternative for inextirpable tumors and can be indicated in case of recurrence for these tumors which are readily recurrent. Approximately 50% of patients with recurrent disease experience distant metastasis and the five years survival in the setting of metastatic disease is 40% to 45%. Long term follow up is therefore recommended for all individuals with PGL [2-5].

Genetic aspect

The genetic predisposition to HNPGLs and adrenal/extra-adrenal PGLs caused by heterozygous mutations by SDHD, SDHC, and SDHB is transmitted in an autosomal dominant fashion with age-dependent and incomplete penetrance [6-8]. Mutations in the SDHD gene show a parent-of-origin effect (transmitted mostly from the father) [4,5]. Despite this pattern of inheritance, SDHD shows bi-allelic expression in normal tissues and neural crest derived cancers with no promoter hyper-methylation in neuroendocrine tissues and related tumors [9]. In 2009, Hao et al. [8] evaluated a previously reported large Dutch family with an autosomal-dominant pattern of PGLs; they identified a mutation (G- to A- transition at nucleotide 232 of exon 2) in the SDHAF2 gene. The pattern of inheritance seen in this family was suggestive of an SDHD-like inheritance. However, more studies are needed to elucidate the mechanism. More recently, mutations in SDHA were reported in a limited number of kindred with PGL and/or PCC (figure 1).

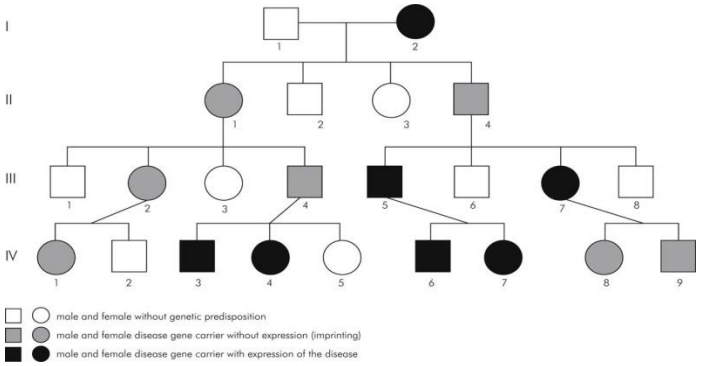

Figure 1: Imaginary example of a family with hereditary paragangliomas and genomic imprinting. The pedigree has four generations (I-IV). Expression of the disease skips one or two generations. In these generations, the genetic predisposition is present. In the first generation (I) the mother (I 2) is a carrier of the paraganglioma disease gene and has expression of the disease. Her daughter (II 1) inherited the mutated paraganglioma gene, but will not develop paragangliomas. She will transfer the mutated paraganglioma gene to two of her children (daughter III 2 and son III 4). These children will not develop the disease, but pass the predisposition to the next generation. The granddaughter of (II 1) IV 1 has the predisposition but no expression, whereas the grandson IV 3 and granddaughter IV 4 have both the predisposition and expression of the disease. The son (II 4) of I 2 has also inherited the disease gene from his mother, but will not have symptoms. His son (III 5) is a paraganglioma carrier and will have complaints just the same as his sister III 7. His children (IV 6 and 7) have predisposition for paragangliomas and will have the disease. The son and daughter (IV 8 and 9) of III 7 do inherit the mutated paraganglioma gene from their mother, but will not have symptoms (10)

Case presentation

Case 1

A 41 year-old female complained of a right hearing loss since 2 months, her past medical history was unremarkable and no similar cases were found in her family. Her physical examination did not reveal any others abnormalities. The CT scan and the MRI of the head and neck were performed and showed a tumor process of the middle and outer ear (figure 2). A biopsy was performed showing a paraganglioma (figure 3-5).

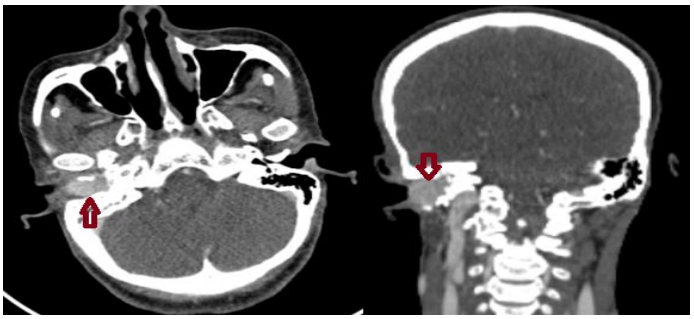

Figure 2: Axial scan images showing a paraganglioma of the right ear

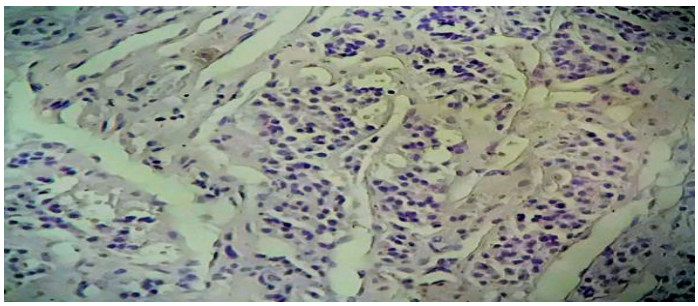

Figure 3: Histological aspect typical of a paraganglioma of the patient N°1 showing a tumor proliferation arranged in nests (HESX200)

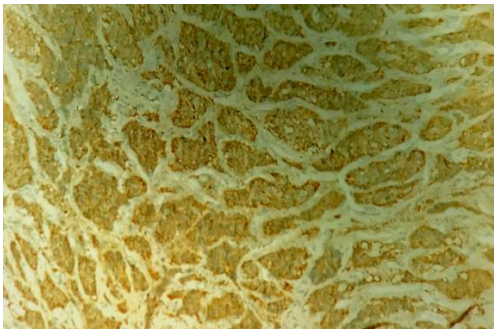

Figure 4: Immunohistochemical aspect expressing synaptophysin by tumor cells

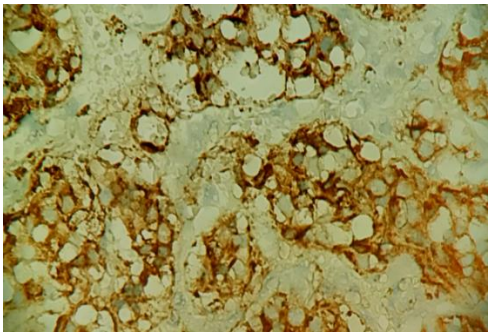

Figure 5: Immunohistochemical aspect expressing chromogranin by tumor cells

View of the difficult location of the tumor an exclusive IMRT radiotherapy has been at a dose of 50.4 Gy (28 fraction of 1.8Gy) (figure 6). After a follow up of 14 months, the case was stable and the patient did not complain of obvious discomfort.

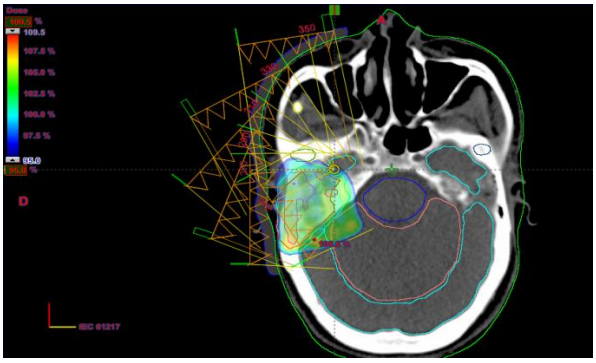

Figure 6: Radiotherapy IMRT of the right ear paraganglioma

Case 2

A 58 year-old female complained of a right otorrhagia. The past medical history and the family's history were negative and the clinical examination eliminated other primary lesion. The CT scan and the MRI of the head and neck showed a paraganglioma of the apex petrous with cavernous extension (figure 7). Given the location and the tumor volume, an exclusive IMRT have been realized at a dose of 60 Gy (figure 8). After a follow up of 15 months, the case was stable with clinical improvement.

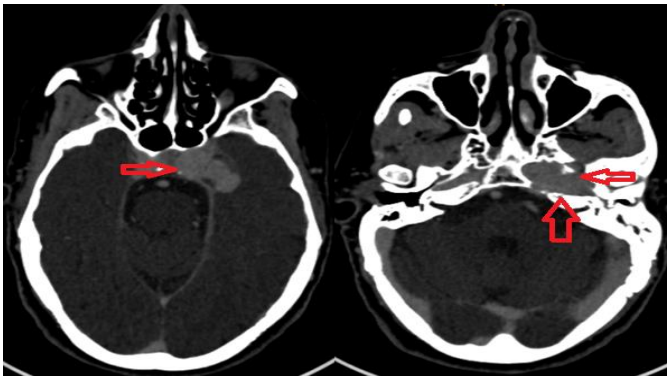

Figure 7: Axial scan images showing a paraganglioma of the left apex petrous with cavernous extension

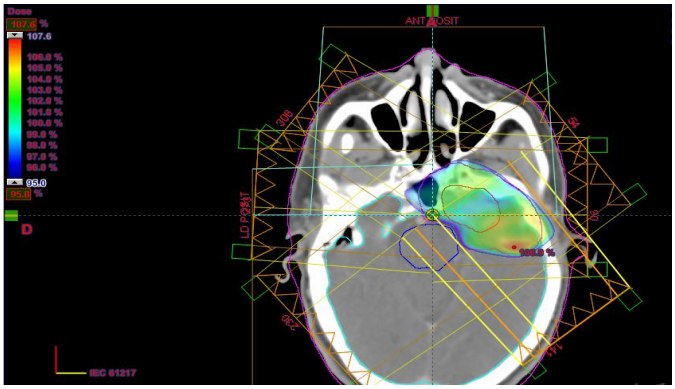

Figure 8: Radiotherapy IMRT of the apex petrous paraganglioma

Case 3

A 59 year-old female complained of a non-painful right lateral cervical mass progressively increasing in volume for the last month. The past medical history and the patient's family history were negative. Physical examination did not reveal any serious abnormalities except the right lateral cervical mass.

The cervical CT scan and the MRI showed an adherent mass to 160 the right carotid, very extensive locally in favor of a carotid paraganglioma. Account of the extent of the lesion, the patient received an external radiotherapy IMRT at a dose of 50 Gy in 25 fractions (figure 9), allowing a local control maintained with a 14 month follow-up.

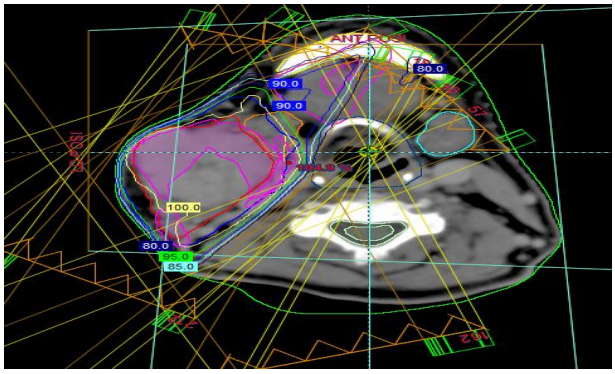

Figure 9: Radiotherapy IMRT of the big carotid paraganglioma

Case 4

A 69 year-old female was treated for a carotid paraganglioma, four years ago, and complained, for the second time, of a lateral cervical mass. The feature in the CT scan and the MRI of the head and neck confirmed recurrent homolateral carotid paraganglioma (figure 10). The patient received a 3D conformational radiotherapy at a dose of 50 Gy (figure 11). After the end of the treatment the patient was followed for 16 months and we noticed a clinical improvement and the tumor did not recrudesce.

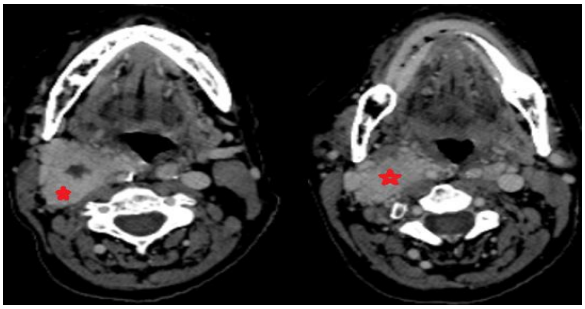

Figure 10: Axial scan images showing a left cervical paraganglioma

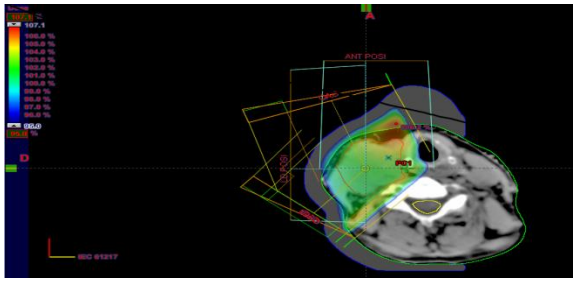

Figure 11: 3D conformational radiotherapy of the carotid paraganglioma

Case 5

A 47 year-old female complained of a lateral cervical mass for the last months. The past medical history was negative.

The CT scan and the MRI of the head and neck showed a huge mass in favor of a carotid paraganglioma (figure 12). An exclusive 3D conformational radiotherapy was delivered at a dose of 50 Gy (figure 13). After 6 months, the patient presented a tumor progression.

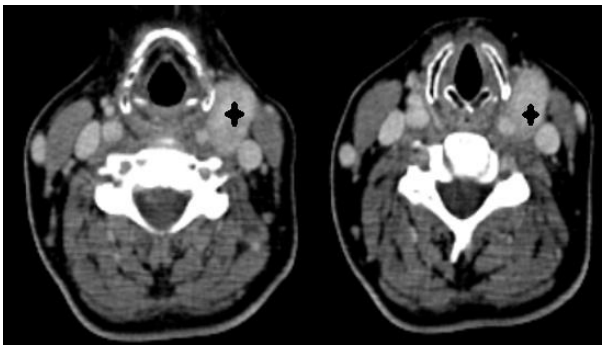

Figure 12: Axial scan images showing cervical paraganglioma

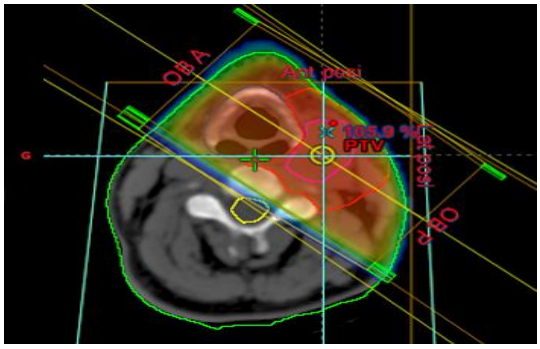

Figure 13: 3D conformational radiotherapy of the carotid paraganglioma

Case 6

A 45 year-old female complained of a left non painful lateral cervical swelling for the last year, the past medical history was negative. The cervical CT scan showed a well-limited left laterocervical mass of 8x7 cm, hypervascularized rapidly enhancing after injection of contrast product (figure 14).

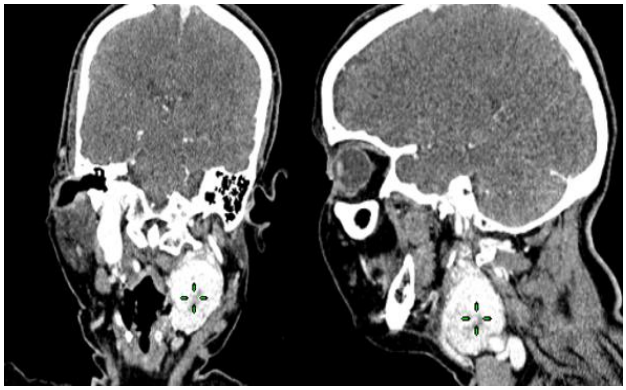

Figure 14: Two CT scans of the patient. Coronal to left and axial to a new carotid paraganglioma left (green sign) raised after injection

A biopsy was performed and confirmed a carotid paraganglioma. Faced with the impossibility of surgery, the patient received a 3D conformational radiotherapy at a dose of 54Gy (figure 15). After a follow up of 14 months we noticed a stability and clinical improvement.

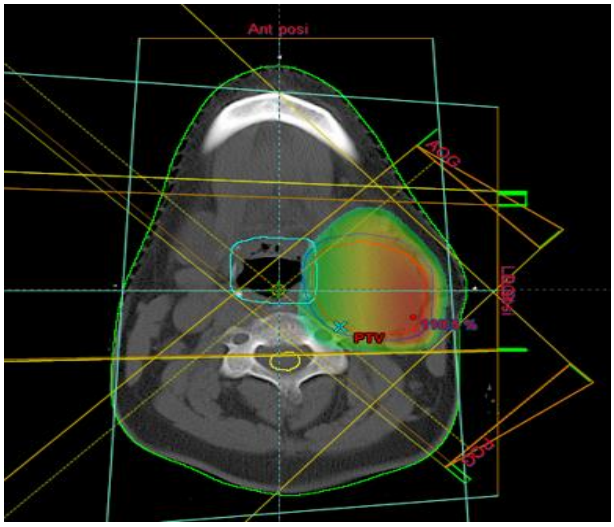

Figure 15: 3D conformational radiotherapy of the carotid paraganglioma

Features common

The six patients followed for head and neck paragangliomas; they are all female, the median age was 45.5 years (between 33-69 years).

The first symptom of consultation was a latero-cervical mass in 4 patients; the others are diagnosed with hearing loss and otorrhagia. All patients received scan imaging with MRI in 4 patients. The diagnosis was made in front of the clinical and radiological assessment in 4 patients and before the histological examination in the 2 others. All the tumors were considered unresectable, hence the indication of exclusive radiotherapy, at the dose between 50 and 60 Gy, 3 patients received intensity-modulated radiotherapy and the three others received conformational 3D radiotherapy. Median follow-up was one year, tumor stability was observed in 5 patients, and tumor progression was observed in a patient with carotid paraganglioma.

Discussion

PGL are rare, affecting 2 to 5 people per million per year. PGL are slowly growing tumors, presented as painless masses and have a culture doubling time of approximatively 42 years. Up to 30% of PGL appear to present in a hereditary manner and to date current research has stressed the increased importance of genetic predisposition in the development of PGL.

The diagnosis of PGL remains a challenge because patient do not present with characteristic signs and symptoms and, if untreated, PGL can have a devastating outcome even the tumors are potentially low grade malignant; however invasive biological behavior have been reported. Patients can be asymptomatic or symptomatic depends on their location, so clinical suspicion for PGL often begins with the patient history and is confirmed with biochemical testing [11], for this measurement of plasma and urinary metanephrine levels has long been used effectively in the diagnosis of PGL; also is bases on imaging finding [12] although there is no consensus on the order in with radiologic test should be performed for patients with suspected neural crest tumors; in fact locating and staging these tumors requires a combination of anatomic imaging with computing tomography or magnetic resonance imaging and functional imaging [13].

Thus, patients with PGL ultimately require follow-up because metastatic disease or recurrence can appear even after decades free of disease, the follow-up of these patients remains clinical, radiological and biological. And the best prognostic is that of carotid topographies [14].

The HNPs incidence is estimated to be at around 0,001%.Carotid body tumor represents the most common type, other PGL that are frequently detected in the head and neck include jugular PGL and tympanic PGL [15].

HNP surgery is a challenge to the surgeon because of the tumor's location in the vicinity of important blood vessels and cranial nerves. As well as pre-operative impairment of nerve function, surgery may result in deficits of cranial nerves VII, VIII, IX, X, XI, and XII [16].

From a retrospective study of Gilbo et al. [17] From 131 patients with 156 benign paragangliomas of the temporal bone, carotid body, jugular bulb, or glomus vagale were treated with RT at the University of Florida; a median dose of 45 Gy in 25 fractions. The mean and median follow-up times were 11.5 years and 8.7 years, respectively. Conventional RT, 86 patients (55%); non-coplanar stereotactic RT (SRT), 14 patients (9%); and intensity-modulated RT (IMRT), 56 patients (36%); in our study there are three patients treated with conventional RT and the three others with IMRT [17]. The treatment options for patients with head and neck paragangliomas include surgery, fractionated RT, and observation. The choice of treatment depends on tumor size and location. Five of 156 (3.2%) tumors recurred locally at 1.3 years, 4.4 years, 4.9 years, 8.1 years, and 8.4 years after RT [17].

A recent systematic review from Suarez et al focused on the management of jugular and vagal paragangliomas and found that the likelihood of local control was better after RT (P=0.002) and that the probability of a major complication was lower (p =0.003) compared with surgery. Although there are fewer data pertaining to SRS, which is suitable for skull base tumors; the

advantage of SRS compared with RT is convenience; the disadvantage is that the risk of hearing loss is 50% [18-20].

A fourth management option is observation, which is a reasonable approach for asymptomatic patients with a limited life expectancy.68 However, physicians taking this approach should recognize that cranial nerve deficits that may result from tumor progression are typically permanent, and should be weighed against the relatively low morbidity of RT [17].

Conclusion

The diagnosis of the neck paraganglioma is often late. The surgical treatment of the advanced forms is technically difficult and is a source of peripheral neurological after-effects. The tumors operated at an advanced stage are the most incriminated by far. The radiotherapy remains a complementary (additional) treatment to the surgery and can even represent an alternative with convincing result.

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