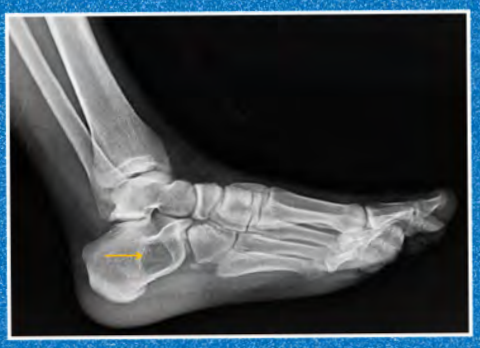
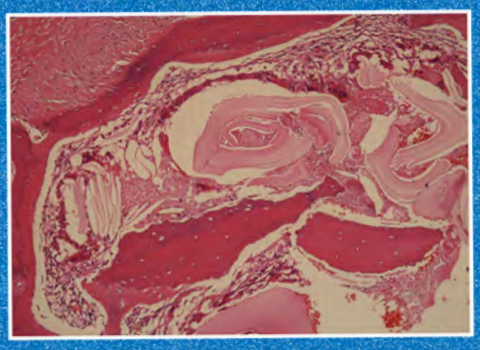
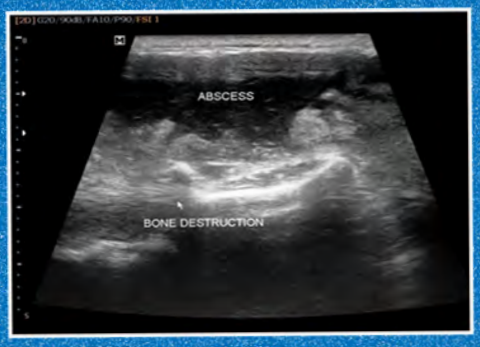
Volume 4 Issue 4 October 2018

e-ISSN: 2149-3189

EuRJ The European Research Journal







The Association of Health Research & Strategy I www.dergipark.gov.tr/eurj

The European Research Journal

Focus and Scope

The European Research Journal (EuRJ) is an international, independent, peer reviewed, open access and online publishing journal, which aims to publish papers on all the related areas of basic and clinical medicine. Manuscripts must describe original data that has not been published previously nor submitted for publication elsewhere. Manuscripts that adhere to the EuRJ submission guidelines and are deemed appropriate for the scope of the journal are sent to two reviewers who are specialists in the field. The reviewers' comments are then considered by the members of the EuRJ Executive Editorial Board who discuss the suitability of each submission. The final decision for all submitted manuscripts rests with the Editor- in-Chief.

The journal publishes in the field of original research, case report, reviews and letters to the editor are published only in English.

Editorial Board of the European Research Journal complies with the criteria of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME) , and Committee on Publication Ethics (COPE).

The journal is published three times in a year (March, July and November).No fee is required for publishing the manuscipt. No copyright fee is paid to the authors. All articles are detected for similarity.

Journal Contact/ Principal Contact

Mailing Address: The European Research Journal (EuRJ)
The Association of Health Research & Strategy
Kırcaali Mh. Fevziçakmak Cd. Göktaş İş Mrk. Kat:3 No:62/12
Osmangazi/BURSA-TURKEY
Phone: +90(224) 2734545
Email: info@eurj.org

Publisher

The European Research Journal (EuRJ)
The Association of Health Research & Strategy
Kırcaali Mah. Fevziçakmak Cd. Göktaş İş Mrk. Kat:3 No:62/12 Osmangazi/BURSA-TURKEY
www.dergipark.gov.tr/eurj/
http://dergipark.ulakbim.gov.tr/eurj/index

e-ISSN: 2149-3189

Editorial Board

INTERNATIONAL EDITORIAL BOARD MEMBERS

Table of Contents

Original Articles

MiR-33a and statins collaboratively reduce the proliferative capacity of prostate cancer cells 266-274
Ömer Faruk Karataş, Michael Ittmann

Toxoplasma gondii seropositivity in pregnancies with normal delivery and complicated with abortion 275-279
Burcu Dinçgez Çakmak, Betül Dündar, Feyza Bayram, Gülten Özgen

Investigation of the relationship between alexithymia and eating attitude, self-esteem and anger in women who applied to psychological counseling center 280-288
Hüseyin Ünübol, Feride Gökben Hızlı Sayar, Sinem Kanbolat

Isolated scapular tuberculosis: an uncommon presentation of skeletal tuberculosis 289-293
Ghanshyam Dev, Shwait Sharma, Mohd Ilyas

Associations of glycated hemoglobin (HbA1c) level with central corneal and macular thickness in diabetic patients without macular edema 294-299
Kuddusi Teberik, Mehmet Tahir Eski, Murat Kaya

The experience of anesthesia during kidney transplantation with robot assisted laparoscopic surgery 300-307
Yasemin Tekdöş Şeker, Nalan Saygı Emir, Oya Hergünsel, Evrim Tülübaş, Figen Öztürk, Derya Mandacı

Sternal cable wires for sternal closure in moderately or extremely obese patients undergoing cardiac surgery 308-313
Yusuf Ata, Ufuk Aydın, Ahmet Kağan As, Kadir Kaan Özsin, Orhan Fındık, Tamer Türk

Motor performance, functional status and quality of life in children with dyslexia 314-319
Sebahat Yaprak Çetin, Ali Kitiş, Figen Şen Kösem

Effects of a single dose 20 mg tadalafil on resistive index value of prostate zones 320-325
Tayfun Şahinkanat, Erkan Efe, Hasan Çetin Ekerbiçer, Faruk Küçükdurmaz

Impact of low-pressure pneumoperitoneum and local anesthetic combination on postoperative pain in patients undergoing laparoscopic cholecystectomy 326-332
Oğuz Uğur Aydın, Lütfi Soylu

Pathological analysis of cystic lesions of the bones: a retrospective single-center 10-year overview 333-342
Gonca Özgün, Ulviye Yalçınkaya, Zeynep Yazıcı, Bartu Sarısözen

Therapeutic plasmapheresis: an eleven-year clinical experience 343-348
Yasemin Tekdöş Şeker, Gülsüm Oya Hergünsel, Deniz Özel Bilgi

Liver functions in patients with obstructive sleep apnea syndrome 349-355
Seda Beyhan Sağmen, Elif Torun Parmaksız, Sevda Şener Cömert, Ali Fidan, Banu Salepçi

The use of doppler ultrasound in evaluation and follow-up of arteriovenous fistula patients 356-361
Nail Kahraman, Kadir Kaan Özsin

Changes in cerebral blood flow in rheumatology patients treated with rituximab 362-365
Uygar Utku, Gözde Çetin, Nurhan Atilla

Three-dimensional turbo spin-echo sequence versus conventional two-dimensional turbo spin-echo sequences in the evaluation of lumbar intervertebral discs 366-373
Volkan Kızılgöz, Ali Kemal Sivrioğlu, Hasan Aydın, Sunay Sibel Karayol, Can Hakan Yıldırım, Utku Menderes

The impact of cigarette dependence severity on disease outcomes and depression in ankylosing spondylitis 374-380
Seyhan Dülger, İlknur Aykurt Karlıbel, Tekin Yıldız, Lale Altan, Özlem Şengören Dikiş, Meliha Kasapoğlu Aksoy

An investigation of the prevalence of depression and related factors in pregnant women living in the province of Erzurum 381-389
Elif Okşan Çalıkoğlu, Banu Bedir, Ayşegül Aydın, Sinan Yılmaz

Nausea and vomiting in pregnant adolescents: impact on health-related quality of life 390-398
Elif Yılmaz, Betül Tokgöz, Çağanay Soysal, Seda Şahin Aker, Tuncay Küçüközkan

The effect of Enterobius vermicularis infection (oxyuriasis) on eosinophil and IgE levels in allergic rhinitis 399-404
Fevzi Solmaz, Oğuzhan Dikici, Davut Akduman, Mehmet Haksever, İsmail Necati Hakyemez, Muhammed Yanılmaz

Review

Hip disorders in cerebral palsy patients: diagnostic and therapeutic approaches 405-410
Bülent Karslıoğlu, Ali Çagrı Tekin, Ersin Taşatan, Fatih Mehmet Erkin

Case Report

Early detection of brain damage in emergency department and the organ donation process: a case series 411-415
İskender Aksoy, Mehtap Pehlivanlar Küçük, Çağatay Erman Öztürk, Ahmet Baydın

A challenging palliation via novel therapeutic approach for unusual presenting with gingival metastasis from renal cell carcinoma relapsed eight years after nephrectomy 416-420
Asım Armağan Aydın, Ahmet Şükrü Alparslan, Hülya Ayık, Erkan Kayıkçıoğlu, Banu Öztürk

Treating daytime blindness with eye movement desensitization and reprocessing: a case report 421-424
Fatma Dilara Altunbaş

Acute myocardial infarction associated with the induction of general anesthesia 425-428
Murathan Küçük, Necmettin Korucuk, Veysel Tosun, Fatma Ertuğrul, Aytül Belgi Yıldırım

Complicated acute appendicitis presenting as a necrotizing fasciitis of the abdominal wall: a case report 429-431
Betül Tiryaki Baştuğ, Berkay Subaşı, Emre Emekli, Kübra Parpucu, Mahmut Kebapçı

An unusual intraosseous calcaneal lipoma: case report 432-435
Ender Alkan, Hasan Erdoğan, Turgay Kara

Intrathoracic extramedullary hematopoiesis as a posterior mediastinal tumor: a case report 436-438
Elçin Ersöz Köse, Gökay Reyhan, Serda Kanbur Metin, Serdar Evman, Çağatay Tezel, İrfan Yalçınkaya

Idiopathic ileoileal intussusception without lead point in a 4-year-old child 439-443
Ayşe Selcan Koç, Zerrin Özçelik, Feride Fatma Görgülü

Metastatic gastric adenocarcinoma in a pregnant woman 444-447
Raikan Büyükavcı, Hakan Apaydın, Semra Aktürk

Fatty necrosis of falciform ligament due to torsion mimics falciform ligament cyst on MRI 448-451
İlknur Özdeniz, Ali Önder Devay, Ediz Tevfik Özgan

Bilateral obstetric brachial plexus paralysis: a case report 452-454
Canan Çelik, Fazıl Kulaklı, Asiye Mukaddes Erol, Şeniz Akçay Yalbuzdağ, Kadir Hacıoğlu

he appearance of pulmonary alveolar microlithiasis on dual-energy X-ray absorptiometry 455-459
Ahmed Fathala, Alaa Alduraibi

The European Research Journal 2018;4(4):266-274 ORIGINAL ARTICLE

MiR-33a and statins collaboratively reduce the proliferative capacity of prostate cancer cells

Ömer Faruk Karataş[1, 2], Michael Ittmann[1]

[1]*Department of Pathology & Immunology, Michael E. DeBakey Dept. of Veterans Affairs Medical Center, Houston, TX, United States*
[2]*Department of Molecular Biology and Genetics, Erzurum Technical University, Erzurum, Turkey*

DOI: 10.18621/eurj.380619

ABSTRACT

Objective: Prostate cancer (PCa) is one of the leading causes of cancer deaths among men in the developed countries. Accumulating data suggests a high-cholesterol Western diet as an important risk factor for PCa. Besides,significant evidencesassociate increased serum cholesterol levels with PCa development and progression.In this study, we aimed at investigating the collaborative roles of cholesterol analogs, cholesterol-lowering drugs, and miR-33a, which is an important microRNA involved in regulation of cholesterol metabolism,on the cellular phenotypes associated with PCa progression.

Methods: We evaluated the effects of low-density lipoprotein (LDL) cholesterol, 25-hydroxycholesterol (25-HC), mevastatin and simvastatin on their ownand together with miR-33a on the proliferation, invasion and anchorage independent growthcapacity of PCa cells using Cell Counting Kit-8, Matrigel invasion, and soft agar assays, respectively.

Results: We show that cholesterol analogs significantly promoted proliferative, invasive, and clonogenic potential of PCa cells, while cholesterol loweringstatins demonstrated opposite effects. Moreover, LDL and 25-HC reversed the tumor suppressive potential of miR-33a and statin treatment promoted the proliferation inhibitory effect of miR-33a on PCa cells.

Conclusions: We demonstrated that statins inhibited the cellular phenotypes associated with PCa progression and miR-33a treatment strengthens the impacts of statins on cellular proliferation. These findings suggest that statins alone and together with miR-33a might be a useful tool for effective and successful eradication of PCa cells.

Keywords: Prostate cancer, microRNA, miR-33a, cholesterol, statins

Received: January 18, 2018; Accepted: March 14, 2018; Published Online: March 20, 2018

Prostate cancer (PCa) is one of the most frequently diagnosed malignanciesin men in the developed countries [1]. Hormone ablation therapy, radical prostatectomy, and radiotherapy are considered as the first line treatment options for clinically localized PCa,however, they do not necessarily provide improved survival rates and almost one third of the patients develop clinical recurrence [2, 3]. For advanced tumors, chemotherapy, the only therapeutic alternative, is not curative [4]. Therefore, a comprehensive understanding of the molecular contributors to the prostate carcinogenesis is necessary to develop novel therapeutic modalities.

Accumulating data suggest a high-cholesterol Western diet as a critical risk factor for many solid tumors including PCa [5]. Although conflicting

Address for correspondence: *Ömer Faruk Karataş, PhD., Assistant Professor, Erzurum Technical University, Department of Molecular Biology and Genetics, Ömer Nasuhi Bilmen Mah. Havaalani Yolu Cad. No:53 Yakutiye, Erzurum, Turkey*
E-mail: faruk.karatas@erzurum.edu.tr, Tel: +90 444 5 388 - 2390, Fax: +90 442 230 00 39

e-ISSN: 2149-3189

findings are present in terms of association of serum cholesterol levels with PCa risk, significant evidences support an important role for high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol in PCa development and progression [6-9]. Prostate tumor cells might acquire castration-resistance through activating intrinsic androgen biosynthesis pathway, which might be via acquisition of capability to synthesize androgens from its precursors including cholesterol [10]. Statins, as cholesterol-lowering drugs, might be considered as effective adjuvant therapeutic agents against PCa [5]. Interestingly, several epidemiological studies reported a significant association between statin use and overall reduced cancer risk and mortality, including PCa [11-13].

Furthermore, an intronic microRNA, miR-33a, together with its host sterol-response-element-binding protein gene *(SREBF2)*, play important roles in the control of lipid and cholesterol metabolism [14]. It has been reported to be predominantly coexpressed with its host gene both in human and mouse tissues [15] and has been recently demonstratedto act as a tumor suppressor in PCa along with several other tumor types [16-23]. MiR-33a is involved in regulation of cholesterol metabolism through targeting 3' untranslated regions of genes like *ABCA1,CPT1A* and *HADHB* [24].

In this study, we aimed at investigating the roles of LDL, 25-hydroxycholesterol (25-HC), mevastatin, and simvastatin on the cellular phenotypes associated with PCa progression, and evaluating their collaborative actions with increased miR-33a expression on the proliferative potential of PCa cells. We found that cholesterol analogs significantly promoted proliferative, invasive, and clonogenic potential of PCa cells, while statins inhibited those features. Besides, LDL and 25-HC reversed the tumor inhibitory potential of miR-33a and statin treatment increased the inhibitory effects of miR-33a on PCa cells. These findings suggest that miR-33a and statins might be useful tools for effective and successful eradication of PCa cells.

METHODS

Chemicals and Reagents

Fetal bovine serum (FBS, Gibco, Gaithersburg, MD, USA), penicillin/streptomycin (Invitrogen, Waltham, MA, USA), RPMI-1640 medium (GenDepot, Barker, TX, USA), Dulbecco's Modified Eagle Medium (DMEM, Invitrogen, Waltham, MA, USA), and lipoprotein deficient serum (LPDS, Kalen Biomedical, Germantown, MD, USA) was used for cell culture experiments. LDL, 25-HC, and simvastatin were purchased from Sigma and Mevastatin was purchased from MedChemExpress.

Cell Culture

LNCaP and VCaP cells with miR-33a expression reduced by more than 50% compared toimmortalized benign prostate epithelial cell line PNT1a were utilized in this study [16]. Cell lines were acquired from American Type Culture Collection (ATCC, Manassas, VA, USA) and their authentication was performed with STR analysis at MD Anderson Cancer Center Characterized Cell Line Core Facility. LNCaP cells were grown within RPMI-1640 medium containing 10% FBS and 1% penicillin/streptomycin. VCaP cells were cultured in DMEM containing 10% FBS and 1% penicillin/streptomycin. Cells treated with cholesterol analogs and statins were grown in medium supplemented with 10% LPDS. Cells were maintained at 37 °C in a humidified 5% CO2 incubator.

MicroRNA Transfection

Transfection of miR-33a and non-targeting control microRNA (Invitrogen) was performed with Lipofectamine RNAiMAX Transfection Reagent (Invitrogen, Waltham, MA, USA) according to the manufacturer's instructions.Briefly, appropriate number ofLNCaP or VCAP cells were seeded in 96 well plates to be 60-80% confluent at the time of transfection. Lipofectamine® RNAiMAX Reagent (Invitrogen, Waltham, MA, USA)and 60 pmol miR-33a mimic were diluted in Opti-MEM® Medium(Gibco, Gaithersburg, MD, USA). Diluted miR-33a mimic and Lipofectamine® RNAiMAX Reagent were mixed in 1:1 ratio and incubated for 5 minutes at room temperature. Then, microRNA-lipid complex was added to the medium of cells.

RNA Isolation, cDNA Synthesis and Quantitative Real-Time PCR

Total RNA from reagent treated and/or

microRNA-transfected samples were isolated using TRIzol (Invitrogen, Waltham, MA, USA) reagent. The concentrations and purities of RNA samples were evaluated spectrophotometrically with NanoDrop ND-2000c (Thermo Fisher Scientific, Wilmington, DE, USA).

MicroRNA first strand DNA (cDNA) synthesis from equal amounts of total RNA was carried out with microRNA specific primers (Applied Biosystems, Foster City, CA, USA) and "TaqMan MicroRNA reverse transcription Kit (Applied Biosystems, Foster City, CA, USA) following the manufacturer's instructions. TaqMan Fast Advanced Master Mix (Applied Biosystems, Foster City, CA, USA) and microRNA probes (Applied Biosystems, Foster City, CA, USA) were used for microRNA expression analysis. Each experiment was performed in triplicates and microRNA expression data were normalized to RNU43.

For gene expression analysis, equal amounts of total RNA samples were reverse transcribed using "amfiRivert cDNA Synthesis Platinum Master Mix" (GenDepot, Barker, TX, USA) following the manufacturers' protocol. SYBR Green PCR Master Mix (Applied Biosystems, Foster City, CA, USA) was used for quantitative real time PCR (qRT-PCR). Each experiment was performed in triplicates andnormalization of gene expression was done comparingß-actin expression.

Primer sequences used to evaluate gene expressions are listed in Table 1. qRT-PCR was performed in a StepOnePlus™ real-time thermal cycler (Applied Biosystems, Foster City, CA, USA) with standard parameters. 2- $^{\Delta\Delta CT}$ method was utilized to calculate the alterations in expression levels.

Cell Proliferation Test

The proliferation capacities of LNCaP and VCaP cells in the presence of the reagents alone (LDL in 50 µg/ml [25], 25-HC in 1 µg/ml [25], Mevastatin in 10 µM [26], and Simvastatin in 10 µM [26] final concentration) or in combination with miR-33a mimic (60 pmol final concentration) were evaluated as follows. Cells were seeded in 96 well plates and after 24 hours, cells were transfected with miR-33a mimic or non-targeting control. Then 3 hours later, cells were treated with reagents to assess their effects on cell proliferation alone or in combination with miR-33a.

Proliferation capacities were evaluatedat the end of each day for 4 days with the Cell Counting Kit-8 (Dojindo, Rockville, MD, USA) according the manufacturer's protocol and the absorbances were measured with a VERSAmax Tunable microplate reader (Conquer Scientific, San Diego, CA, USA).

Table 1. qRT-PCR primer sequences

Gene	Sequence
Beta-actin-F	5'-GCCTCGCCTTTGCCGATC-3'
Beta-actin-R	5'-CCCACGATGGAGGGGAAG-3'
CPT1A-F	5'-GGCAAGTTTTGCCTCACATACG-3'
CPT1A-R	5'-GAACAACTTCAGCCTCTGTTCC-3'
HADHB-F	5'-AAACCAAGGTTGGATTGCCTC-3'
HADHB-R	5'-CACTATCATAGCATGGCCCTG-3'

Matrigel Invasion Test

Invasion capacities of cells were evaluated with BD BioCoat Matrigel invasion chambers (Becton Dickinson, Franklin Lakes, NJ, USA). After treated with reagents alone (LDL in 50 µg/ml, 25-HC in 1 µg/ml, Mevastatin in 10 µM, and Simvastatin in 10 µM final concentration) or in combination with overexpression of miR-33a mimic or non-targeting control (60 pmol final concentration) for 48 hours, LNCaP cells were harvested and plated into invasion chambers in triplicates. After 24 hours, cells on the upper surface of the chamber were removed and the cells on the lower side of the filter were initially fixed inmethanol and stained with 0.3% crystal violet and 2% ethanol containing solution for 20 min. Then, relative invasion ratios were calculated through counting cells.

Soft Agar Colony Formation Test

LNCaP cells were suspended in 0.3% agar diluted in RPMI at a density of 3x103 cells/ml and seeded on a 0.6% base agar in 6-well culture plates in triplicates. Then cells were cultured in the presence or absence of reagents (LDL in 50 µg/ml, 25-HC in 1 µg/ml, Mevastatin in 10 µM, and Simvastatin in 10 µM final concentration) at 37°C incubator for 2 to 3 weeks.

Cells were fixed and stained with 0.01% crystal violet and 10% ethanolcontaining solution. Relative colony numbers were calculated through counting colonies with a dissecting microscope.

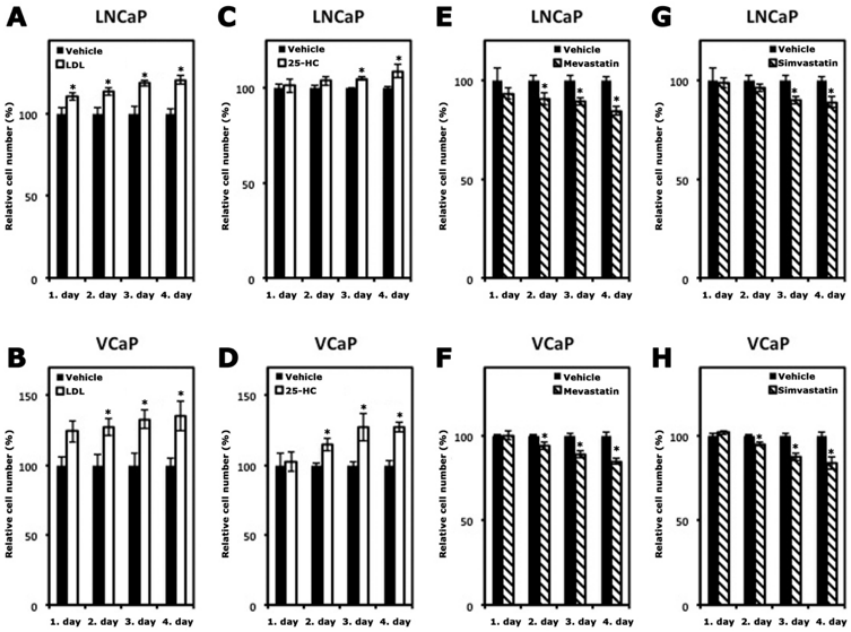


Figure 1. Impacts of cholesterol analogs and statins on the proliferative potential of PCa cells. Proliferation of LNCaP cells treated with LDL (a), 25-HC (c), Mevastatin (e), Simvastatin (G). Proliferation of VCaP cells treated with LDL (b), 25-HC (d), Mevastatin (f), Simvastatin (h). Mean +/- SEM is shown *p <0.05; t-test

Statistical Analysis

Data were plotted as ± mean standard error of mean (SEM) and the statistical significances were tested using Student's t test. A p value of 0.05 or below was accepted as statistically significant.

RESULTS

LDL and 25-HC promoted and Statins inhibited the proliferation, invasion, and clonogenic capacity of PCa cells

To explore the biological relevance of cholesterol analogs and statins in PCa, we initially evaluated their effects on the proliferative capacity of PCa cells. Treatment of LNCaP and VCaP cells with LDL significantly promoted proliferation by up to 20% (Figure 1a) and 35% (Figure 1b), respectively. 25-HC treatment also resulted in increased proliferation in both cell lines (Figures 1c and 1d). On the contrary, cholesterol-lowering drugs, Mevastatin and Simvastatin, reduced proliferation by up to 16% (Figure 1e) and 12% (Figure 1g) in LNCaP cells, respectively. Similarly, statin treatment caused significant decrease in proliferation of VCaP cells (Figures 1f and 1h).

Moreover, LDL significantly increased the invasive and clonogenic potential of LNCaP cells, while statins demonstrated opposite effects (Figures 2a and 2b). 25-HC treatment also resulted in enhanced invasive potential (Figure 2b), however, it did not result in a significant change in colony formation ability of LNCaP cells (Figure 2b). This might be due to accumulation of 25-HC within the cells during soft agar assays, which could make the concentration of 25-HC reach the toxic levels for LNCaP cells. These overall findings point the potential of statins to inhibit cellular phenotypes associated with PCa progression.

MiR-33a reverses the effects of cholesterol analogs and strengthens the impacts of statins on cellular proliferation

To evaluate the collaborative action of miR-33a with cholesterol analogs and statins on the proliferative potential of PCa cells, we treated cells that are overexpressing miR-33a with LDL, 25-HC, mevastatin, and simvastatin and evaluated their dual impact on the proliferation of both LNCaP and VCaP cells. We initially investigated the efficiency of miR-33a transfection in cells, which showed that miR-33a was overexpressed up to ~40 and ~130 fold in LNCaP and VCaP cells, respectively, relative tocells

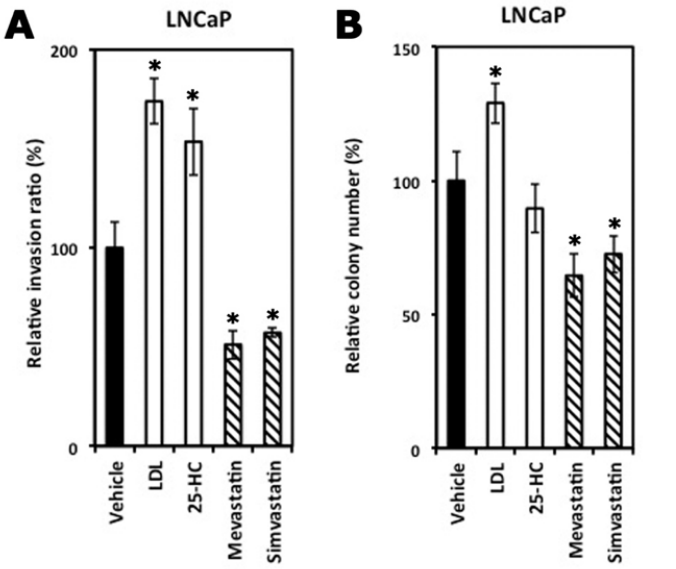


Figure 2. Impacts of cholesterol analogs and statins on the invasive and clonogenic potential of PCa cells. Invasion (a) and anchorage independent growth (b) of LNCaP cells treated with LDL, 25-HC, Mevastatin, Simvastatin. Mean +/- SEM is shown **p* <0.05; t-test

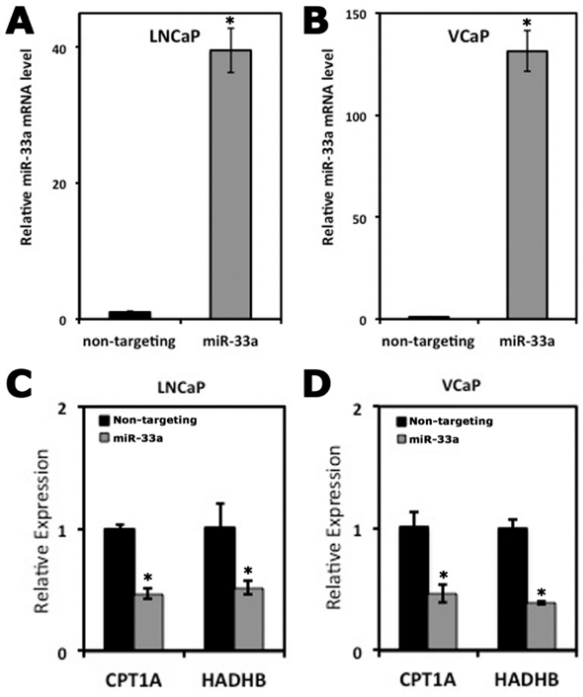


Figure 3. Overexpression of miR-33a. Relative miR-33a level in miR-33a transfected LNCaP (a) and VCaP (b) cells. qRT-PCR validation of CPT1A and HADHB as direct targets of miR-33a involved in cholesterol metabolism in miR-33a transfected LNCaP (c) and VCaP (d) cells. MiRNA levels are demonstrated as fold change and were normalized to RNU43, mRNA levels are demonstrated as fold change and were normalized to ß-actin. Mean +/- SEM is shown **p* < 0.05; t-test

overexpressing non-targeting controls (Figures 3a and 3b).

We then validated the downregulation of CPT1A and HADHB, which are direct targets of miR-33a as implicated in cholesterol metabolism, at the mRNA level upon ectopic miR-33a overexpression (Figures 3c and 3d), and confirmed the inhibitory role of miR-33a on the proliferative capacity of both LNCaP and VCaP cells (Figure 4).

Furthermore, treatment of LNCaP and VCaP cells ectopically overexpressing miR-33a with LDL and 25-HC reversed the inhibitory potential of miR-33a and resulted in increased proliferation (Figures 4a, 4b, 4c and 4d). To explore the collaborative action of miR-33a and statins on PCa cell inhibition, we also treated PCa cells ectopically overexpressing miR-33a with statins and demonstrated that treatment of cells with either Mevastatin or Simvastatin along with miR-33a overexpression significantly enhanced the proliferation inhibitory potential of miR-33a.This points the power of utilization of miR-33a and statins together as a tool for effective and successful eradication of PCa cells.

DISCUSSION

High cholesterol, also known as hypercholesterolemia, is a worldwide problem with a global prevalence of about 39% among adults [27]. Adults with high cholesterol are considered as at higher risk for cardiovascular diseases as well as several cancers, and recent data suggest that hypercholesterolemia might be implicated with the risk of PCa development [7, 8, 28, 29].

3-Hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, commonly referred as statins, are effective lipid-lowering drugs, which are generally administered in Western countries [27]. Accumulating evidences like (i) significant reduction of PSA levels, which is in parallel with the amount of LDL decline, in PCa-free men after starting a statin [30], (ii) profound inhibition of cellular growth upon combinatorial therapy with atorvastatin and celecoxib, but not upon their individual use, in PCa xenograft models [31, 32], and (iii) associations between statin use and a decline in the advanced PCa incidence and recurrence risk after treatment compared to controls

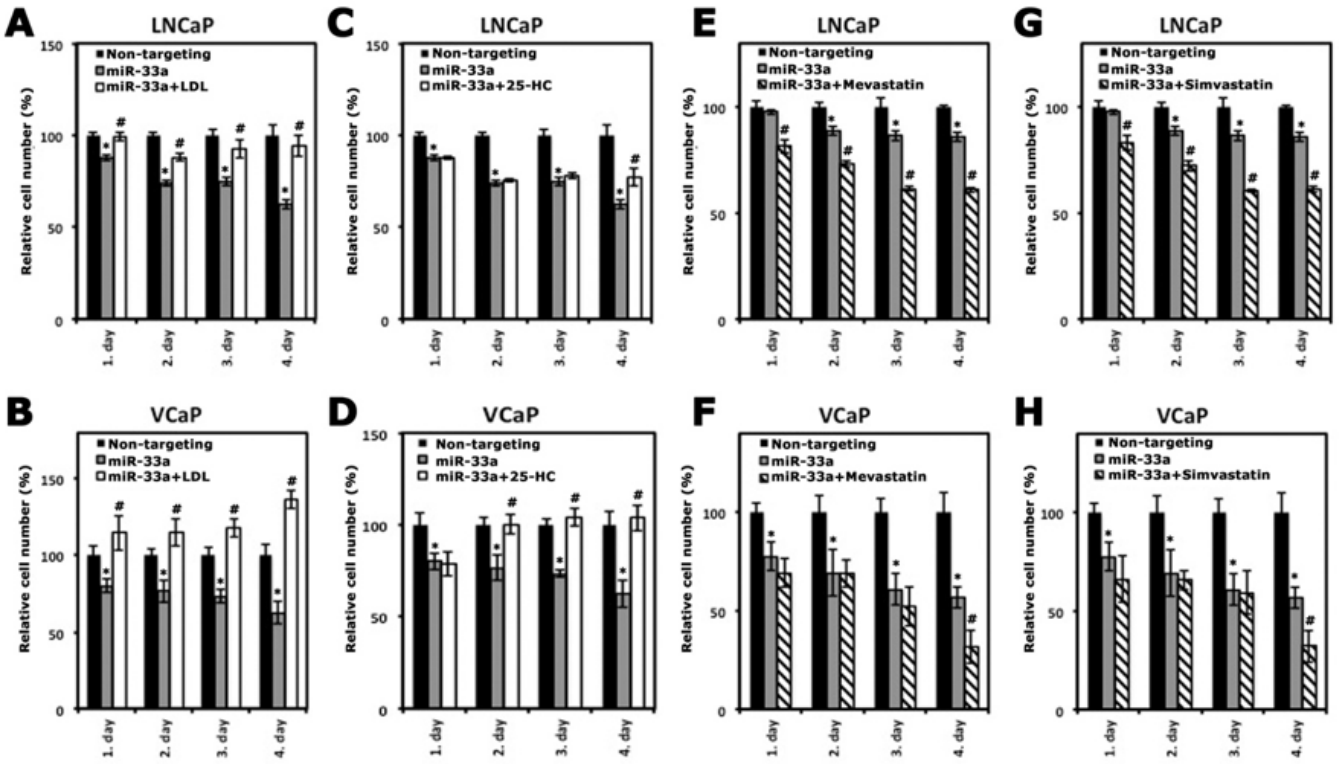


Figure 4. Collaborative effects of miR-33a with cholesterol analogs and statins on cellular proliferation. Proliferation of LNCaP cells overexpressing miR-33a treated with LDL (a), 25-HC (b), Mevastatin (c), Simvastatin (d). Proliferation of VCaP cells overexpressing miR-33a treated with LDL (e), 25-HC (f), Mevastatin (g), Simvastatin (h). Mean +/- SEM is shown *$p < 0.05$; t-test

[27], suggest that development of cholesterol-dependent therapeutic approaches may be key to enhance the fight against PCa.

Our results demonstrated that introduction of cholesterol analogs significantly promoted proliferation, invasion, and clonogenic capacity of PCa cells, whereas, statins inhibited their proliferation, invasion, and anchorage independent growth, which is in line with previous findings [25, 33]. Interestingly, in those studies, both Mevastatin and Simvastatin have been shown to display toxic effects to RWPE-1 to some extent, however, they were found to have selective inhibition against PCa cells and reduced potency against benign epithelial RWPE-1 cells compared to PCa cells [26, 34].

Statins are thought to eradicate PCa cells through (i) regulation of cholesterol levels required for signal transduction, and (ii) modulation of signaling pathways associated with several cellular phenotypes independent of cholesterol lowering, like cell proliferation, invasion, and migration [30, 35-37]. Moreover, statins inhibit proliferation via regulation of androgen receptor expression and activity [26,38]. Androgens are implicated in PCa progression and androgen deprivation therapies have been an effective means of treatment for disseminated PCa [39]. However, cancer cells are able to endure the androgen-depleted environment and develop castration resistant tumors through several androgen receptor related adaptive mechanisms like reactivation of androgen receptor and *de novo* intratumoral production of androgens [34, 40]. Considering the synthesis of androgens via multi-enzymatic conversion of cholesterol, use of statins might be useful for treating castration resistant PCa patients [41]. Besides, Simvastatin, as an FDA approved cholesterol-lowering drug, display well tolerated side-effect profiles, which proposes statins as an ideal combinatorial therapy option with chemotherapeutic agents with minimal additional risk to the patients [34, 42]. However, further studies are needed to determine the class and optimal *in vivo* doses of statins with minimum toxic effects to normal cells.

In this study, we also investigated the potential

collaborative inhibitory function of miR-33a and statins on the proliferative potential of PCa cells. In normal tissues, miR-33a, along with its host gene *SREBF2*, modulate regulation of cholesterol levels [43]. Downregulation of miR-33a allows upregulation of oncogenic genes such as PIM1 and causes increase of β-oxidation of fatty acids through upregulation of genes like HADHB and CPT1A [16, 24]. Such elevated β-oxidation might contribute to providing of energy to PCa cells. Another potential association of miR-33a to cholesterol metabolism is its targets that are involved in cholesterol transport such as *ABCA1, ABCG1,* and *NPC1* [24].

Several studies demonstrated that overexpression of miR-33a *in vitro* profoundly suppressed cholesterol export in various cell culture models [15, 44-46]. Further in vivo studies also demonstrated significant elevation in serum HDL cholesterol in miR-33a -/- mice [45].

Until now, there are numerous microRNAs that are proposed as putative therapeutic agents against PCa. Unraveling the mechanism of actions, finding their true targets, and determining accurate expression data are required to develop effective and practical therapies. For example, recently overexpression of the lethal-7 (let-7) was suggested as a therapeutic tool for PCa through utilization of either lenti- or adenoviruses to inhibit the survival and proliferation of tumor cells [47, 48]. In another study, a natural product, 3,3'-diindolylmethane (DIM), was given to patients prior to radical prostatectomy to evaluate its therapeutic role. The phase II clinical trial demonstrated that DIM intervention lead to increased levels of let-7 and reduced expression of its target, EZH2, in PCa cells, which resulted low self-renewal and clonogenic capacity [49]. This findings point the potential of treatment options targeting deregulated microRNAs in PCa.

The Limitations of the Study

Certain limitations should be considered when interpreting the results of our study. Analysis of the impacts of cholesterol analogs and statins along with miR-33a overexpression were performed only with two PCa cell lines, which does not effectively reflect the heterogeneity of the PCa. Moreover, utilization of only cancer cells but not a healthy prostate epithelial cell line restricts to foresee potential side effects of miR-33a overexpression and statin treatment. Lack of in vivo experiments prevents drawing a clear conclusion about the collaborative function of miR-33a and statins against PCa. Lastly, not utilization of control cell lines that are not associated with cholesterol would effect the specificity of the proposed mechanism. Therefore, further detailed in vitro research should be performed to reveal the possible mechanisms of differential expression of miR-33a and the role of deregulated cholesterol homeostasis in PCa as well as to show the importance of targeting these deregulations to eradicate PCa cells. Also, further in vivo and clinical researches are needed to clarify the potential of miR-33a and statins against PCa.

CONCLUSION

In conclusion, we demonstrated that LDL and 25-HC promoted and statins decreased the proliferation, invasion, and clonogenic features of PCa cells and miR-33a reverses the effects of cholesterol analogs and strengthens the affects of statins on the phenotypes related to PCa progression, which suggests that miR-33a and statins might be useful tools for effective and successful eradication of PCa cells. However, more evidences on the curative or preventive impacts of statins against PCa both *in vitro* and *in vivo* still needs to be provided.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Acknowledgements

The research conducted in this study was partially supported by grants from the Prostate Cancer Foundation (MI), the Dept. of Veterans Affairs Merit Review program (MI) and partially by the National Cancer Institute to the Dan L. Duncan Cancer (P30 CA125123) supporting the Human Tissue Acquisition and Pathology Shared Resource and experiments were carried out using the facilities of the Michael E. DeBakey VAMC.

REFERENCES

[1] Yang B, Liao GQ, Wen XF, Chen WH, Cheng S, Stolzenburg JU, et al. Nuclear magnetic resonance spectroscopy as a new approach for improvement of early diagnosis and risk stratification of prostate cancer. J Zhejiang Univ Sci B 2017;18:921-33.
[2] Brookman-Amissah N, Nariculam J, Freeman A, Willamson M, Kirby RS, Masters JR, et al. Allelic imbalance at 13q14.2 approximately q14.3 in localized prostate cancer is associated with early biochemical relapse. Cancer Genet Cytogenet 2007;179:118-26.
[3] Barron N, Keenan J, Gammell P, Martinez VG, Freeman A, Masters JR, et al. Biochemical relapse following radical prostatectomy and miR-200a levels in prostate cancer. Prostate 2012;72:1193-9.
[4] Bhatnagar N, Li X, Padi SK, Zhang Q, Tang MS, Guo B. Downregulation of miR-205 and miR-31 confers resistance to chemotherapy-induced apoptosis in prostate cancer cells. Cell Death Dis 2010;1:e105.
[5] Masko EM, Alfaqih MA, Solomon KR, Barry WT, Newgard CB, Muehlbauer MJ, et al. Evidence for feedback regulation following cholesterol lowering therapy in a prostate cancer xenograft model. Prostate 2017;77:446-57.
[6] Van Hemelrijck M, Walldius G, Jungner I, Hammar N, Garmo H, Binda E, et al. Low levels of apolipoprotein A-I and HDL are associated with risk of prostate cancer in the Swedish AMORIS study. Cancer Causes Control 2011;22:1011-9.
[7] Farwell WR, D'Avolio LW, Scranton RE, Lawler EV, Gaziano JM. Statins and prostate cancer diagnosis and grade in a veterans population. J Natl Cancer Inst 2011;103:885-92.
[8] Mondul A, Weinstein S, Virtamo J, Albanes D. Serum total and HDL cholesterol and risk of prostate cancer. Cancer Causes Control 2011;22:1545-52.
[9] Allott EH, Howard LE, Cooperberg MR, Kane CJ, Aronson WJ, Terris MK, et al. Postoperative statin use and risk of biochemical recurrence following radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. BJU Int 2014;114:661-6.
[10] Dillard PR, Lin MF, Khan SA. Androgen-independent prostate cancer cells acquire the complete steroidogenic potential of synthesizing testosterone from cholesterol. Mol Cell Endocrinol 2008;295:115-20.
[11] Murtola TJ, Tammela TL, Lahtela J, Auvinen A. Cholesterol-lowering drugs and prostate cancer risk: a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2007;16:2226-32.
[12] Graaf MR, Beiderbeck AB, Egberts AC, Richel DJ, Guchelaar HJ. The risk of cancer in users of statins. J Clin Oncol 2004;22:2388-94.
[13] Platz EA, Leitzmann MF, Visvanathan K, Rimm EB, Stampfer MJ, Willett WC, et al. Statin drugs and risk of advanced prostate cancer. J Natl Cancer Inst 2006;98:1819-25.
[14] Ono K. Functions of microRNA-33a/b and microRNA therapeutics. J Cardiol 2016;67:28-33.
[15] Najafi-Shoushtari SH, Kristo F, Li Y, Shioda T, Cohen DE, Gerszten RE, et al. MicroRNA-33 and the SREBP host genes cooperate to control cholesterol homeostasis. Science 2010;328:1566-9.
[16] Karatas O, Wang J, Shao L, Ozen M, Zhang Y, Creighton C, Ittmann M. miR-33a is a tumor suppressor microRNA that is decreased in prostate cancer. Oncotarget 2017;8:60243-56.
[17] Kuo PL, Liao SH, Hung JY, Huang MS, Hsu YL. MicroRNA-33a functions as a bone metastasis suppressor in lung cancer by targeting parathyroid hormone related protein. Biochim Biophys Acta 2013;1830:3756-66.
[18] Zhang C, Zhang Y, Ding W, Lin Y, Huang Z, Luo Q. MiR-33a suppresses breast cancer cell proliferation and metastasis by targeting ADAM9 and ROS1. Protein Cell 2015;6:881-9.
[19] Liang C, Yu XJ, Guo XZ, Sun MH, Wang Z, Song Y, et al. MicroRNA-33a-mediated downregulation of Pim-3 kinase expression renders human pancreatic cancer cells sensitivity to gemcitabine. Oncotarget 2015;6:14440-55.
[20] Zhang J, Wang D, Xiong J, Chen L, Huang J. MicroRNA-33a-5p suppresses growth of osteosarcoma cells and is downregulated in human osteosarcoma. Oncol Lett 2015;10:2135-41.
[21] Zhou J, Xu D, Xie H, Tang J, Liu R, Li J, et al. miR-33a functions as a tumor suppressor in melanoma by targeting HIF-1α. Cancer Biol Ther 2015;16:846-55.
[22] Kang J, Kim W, Lee S, Kwon D, Chun J, Son B, et al. TFAP2C promotes lung tumorigenesis and aggressiveness through miR-183- and miR-33a-mediated cell cycle regulation. Oncogene 2017;36:1585-96.
[23] Yang L, Yang J, Li J, Shen X, Le Y, Zhou C, et al. MircoRNA-33a inhibits epithelial-to-mesenchymal transition and metastasis and could be a prognostic marker in non-small cell lung cancer. Sci Rep 2015;5:13677.
[24] Bommer GT, MacDougald OA. Regulation of lipid homeostasis by the bifunctional SREBF2-miR33a locus. Cell Metab 2011;13:241-7.
[25] Krycer JR, Kristiana I, Brown AJ. Cholesterol homeostasis in two commonly used human prostate cancer cell-lines, LNCaP and PC-3. PLoS One 2009;4:e8496.
[26] Yokomizo A, Shiota M, Kashiwagi E, Kuroiwa K, Tatsugami K, Inokuchi J, et al. Statins reduce the androgen sensitivity and cell proliferation by decreasing the androgen receptor protein in prostate cancer cells. Prostate 2011;71:298-304.
[27] Schnoeller TJ, Jentzmik F, Schrader AJ, Steinestel J. Influence of serum cholesterol level and statin treatment on prostate cancer aggressiveness. Oncotarget 2017;8:47110-20.
[28] Almutairi F, Peterson TC, Molinari M, Walsh MJ, Alwayn I, Peltekian KM. Safety and effectiveness of ezetimibe in liver transplant recipients with hypercholesterolemia. Liver Transpl 2009;15:504-8.
[29] Kitahara CM, Berrington de González A, Freedman ND, Huxley R, Mok Y, Jee SH, et al. Total cholesterol and cancer risk in a large prospective study in Korea. J Clin Oncol 2011;29:1592-8.
[30] Hamilton RJ, Goldberg KC, Platz EA, Freedland SJ. The influence of statin medications on prostate-specific antigen levels. J Natl Cancer Inst 2008;100:1511-8.
[31] Zheng X, Cui XX, Avila GE, Huang MT, Liu Y, Patel J, et al. Atorvastatin and celecoxib inhibit prostate PC-3 tumors in immunodeficient mice. Clin Cancer Res 2007;13(18 Pt 1):5480-7.
[32] Zheng X, Cui XX, Gao Z, Zhao Y, Lin Y, Shih WJ, et al. Atorvastatin and celecoxib in combination inhibits the progression of androgen-dependent LNCaP xenograft prostate tumors to androgen independence. Cancer Prev Res (Phila) 2010;3:114-24.
[33] Murtola TJ, Syvälä H, Pennanen P, Bläuer M, Solakivi T, Ylikomi T, et al. The importance of LDL and cholesterol metabolism for prostate epithelial cell growth. PLoS One 2012;7:e39445.
[34] Ingersoll MA, Miller DR, Martinez O, Wakefield CB, Hsieh KC, et al. Statin derivatives as therapeutic agents for castration-resistant prostate cancer. Cancer Lett 2016;383:94-105.
[35] Gonçalves I, Cherfan P, Söderberg I, Nordin Fredrikson G, Jonasson L. Effects of simvastatin on circulating autoantibodies to oxidized LDL antigens: relation with immune stimulation markers. Autoimmunity 2009;42:203-8.
[36] Kusama T, Mukai M, Iwasaki T, Tatsuta M, Matsumoto Y, Akedo H, et al. Inhibition of epidermal growth factor-induced RhoA translocation and invasion of human pancreatic cancer cells by 3-hydroxy-3-methylglutaryl-coenzyme a reductase inhibitors. Cancer Res 2001;61:4885-91.
[37] Nübel T, Dippold W, Kleinert H, Kaina B, Fritz G. Lovastatin inhibits Rho-regulated expression of E-selectin by TNFalpha and attenuates tumor cell adhesion. FASEB J 2004;18:140-2.
[38] Yang L, Egger M, Plattner R, Klocker H, Eder IE. Lovastatin causes diminished PSA secretion by inhibiting AR expression and function in

LNCaP prostate cancer cells. Urology 2011;77:1508.e1501-1507.
[39] Wong YN, Ferraldeschi R, Attard G, de Bono J. Evolution of androgen receptor targeted therapy for advanced prostate cancer. Nat Rev Clin Oncol 2014;11:365-76.
[40] Gordon JA, Midha A, Szeitz A, Ghaffari M, Adomat HH, Guo Y, et al. Oral simvastatin administration delays castration-resistant progression and reduces intratumoral steroidogenesis of LNCaP prostate cancer xenografts. Prostate Cancer Prostatic Dis 2016;19:21-7.
[41] Locke JA, Guns ES, Lubik AA, Adomat HH, Hendy SC, Wood CA, et al. Androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant prostate cancer. Cancer Res 2008;68:6407-15.
[42] Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al.; Collaboration CTTC. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.
[43] Najafi-Shoushtari SH, Kristo F, Li Y, Shioda T, Cohen DE, Gerszten RE, et al. MicroRNA-33 and the SREBP host genes cooperate to control cholesterol homeostasis. Science 2010;328:1566-9.
[44] Gerin I, Clerbaux LA, Haumont O, Lanthier N, Das AK, Burant CF, et al. Expression of miR-33 from an SREBP2 intron inhibits cholesterol export and fatty acid oxidation. J Biol Chem 2010;285:33652-61.
[45] Horie T, Ono K, Horiguchi M, Nishi H, Nakamura T, Nagao K, et al. MicroRNA-33 encoded by an intron of sterol regulatory element-binding protein 2 (Srebp2) regulates HDL in vivo. Proc Natl Acad Sci U S A 2010;107:17321-6.
[46] Marquart TJ, Allen RM, Ory DS, Baldán A. miR-33 links SREBP-2 induction to repression of sterol transporters. Proc Natl Acad Sci U S A 2010;107:12228-32.
[47] Nadiminty N, Tummala R, Lou W, Zhu Y, Shi XB, Zou JX, et al. MicroRNA let-7c is downregulated in prostate cancer and suppresses prostate cancer growth. PLoS One 2012;7:e32832.
[48] Barh D, Malhotra R, Ravi B, Sindhurani P. MicroRNA let-7: an emerging next-generation cancer therapeutic. Curr Oncol 2010;17:70-80.
[49] Kong D, Heath E, Chen W, Cher ML, Powell I, Heilbrun L, et al. Loss of let-7 up-regulates EZH2 in prostate cancer consistent with the acquisition of cancer stem cell signatures that are attenuated by BR-DIM. PLoS One 2012;7:e33729.

The European Research Journal 2018;4(4):275-279 ORIGINAL ARTICLE

Toxoplasma gondii seropositivity in pregnancies with normal delivery and complicated with abortion

Burcu Dinçgez Çakmak, Betül Dündar, Feyza Bayram, Gülten Özgen

Department of Obstetrics and Gynecology, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

DOI: 10.18621/eurj.339882

ABSTRACT

Objective: *Toxoplasma* infection during pregnancy may cause remarkable mortality and morbidityin fetus due to transplacental transmission. It has fetal consequences such as abortion, stillbirth and congenital malformations. In the Turkish literature, there is limited investigations evaluating the prevalence of *Toxoplasma gondii* among pregnancies complicated with abortion. The aim of this study is to compare the *Toxoplasma* seropositivity between pregnancies with normal delivery and complicated with abortion.

Methods: This is a retrospective, single center study conducted between May 2015 and June 2016. We included 412 patients in the study group and 828 patients in the control group. The study group (Group 1) was compromised of pregnants whose pregnancies were complicated with abortion and the control group (Group 2) was pregnants with normal delivery. *Toxoplasma* IgM and IgG seropositivity were compared between two groups.

Results: There was no difference between two groups in terms of sociodemographic features ($p > 0.05$). *Toxoplasma* IgM was positive in 62 (5%) patients and IgG was positive in 282 (22.9%) patients in all groups. In subgroup analysis *Toxoplasma* IgM was found to be positive in 27 (6.6%) patients in Group 1 and 35 (4.2%) patients in Group 2. Moreover, *Toxoplasma* IgG was positive in 125 (30.6%) patients in Group 1 and in 157 (19.2%) patients in Group 2. *Toxoplasma* IgM and *Toxoplasma* IgG were significantly higher in Group 1 ($p = 0.023$ and $p = 0.016$, respectively).

Conclusion: We concluded that *Toxoplasma* seropositivity is high in our country and routine screening is essential for pregnancies. Toxoplasmosis may play a role in the etiology of abortion.

Keywords: Abortus, pregnancy, *toxoplasmosis*, *toxoplasma* immunglobuline

Received: September 26, 2017; Accepted: December 6, 2017; Published Online: February 14, 2018

Toxoplasma gondii, which belongs to TORCH (*Toxoplasma gondii, Rubella, Cytomegalovirus and Herpes simplex*) group, is an intracelullar obligate parasite with a complex life cycle [1]. Infection is transmitted to humans by ingestion of uncooked meat containing live organisms or by vegetables, fruits and water that are contaminated by oocytes [2, 3]. Although serologic positivity of *toxoplasma* is generally asymptomatic, during pregnancy this infection may cause remarkable mortality and morbidity in fetus due to transplacental transmission. While congenital transmission is most common during last trimester with a ratio of 70-80 %, it is 10-15% in the first trimester. However the risk of severe

Address for correspondence: *Burcu Dinçgez Çakmak, MD., University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Obstetrics and Gynecology, Emniyet Caddesi No:35, Yıldırım, Bursa, Turkey*
E-mail: burcumavis@gmail.com

e-ISSN: 2149-3189

congenital sequela is much higher in the first trimester [4]. It is a preventable cause of severe fetal consequences such as abortion, still-birth and congenital malformations. It can result in central nervous system anomalies, mental and physical retardation, blindness, cerebral calcifications, pneumonia, hepatitis, myocarditis, hydrocephalus, microcephalus and chorioretinitis [5-8]. Fortunately, spiramycin treatment following confirmation of maternal infection is known to prevent the fetal transmission and congenital infection [9]. However, it is still controversial whether screening of *T. gondii* is essential. Since, the seropositivity ratios are high in our country screening is currently being suggested.

T. gondii canbe determined in as high as 1/3 of world population. This frequency can change according to geographical regions, dietary habitutes, socioeconomic status and age [1]. In previous studies, the seropositivity of toxoplasmosis in women isreported to be 43.8% for Spain, 11% for USA and 63.7% for Iran [10]. In our country, this ratio is reported to be between 25.2 % to 69.5 % [11, 12]. Among pregnant women the prevalence of T. gondii is stated as 9.1% for England, 6.1% for Mexico, 43.8% for France, 35% for Switzerland and 33.9-60.4% for Turkey [6, 10, 13, 14]. Worldwide prevalence of *T. gondii* among pregnancies complicated with abortion is given to be between 17.5% and 79.03% [15-17]. In the Turkish literature, there is limited investigations evaluating the prevalence of *T. gondii* seropositivity among pregnancies complicated with abortion and the relevant data is quite limited.

The aim of this study is to compare the *T. gondii* seropositivity between pregnancies with normal delivery and the ones complicated with abortion.

METHODS

This is a retrospective, single center study which was conducted in a university affiliated research and training hospital between May 2015 and June 2016. A total of 1240 pregnancies,between 18-40 years of age were included in this study.There were 412 patients in the study group and 828 patients in the control group. The study group was compromised of pregnant women whose pregnancies were complicated with first trimester abortion and the control group was pregnants with normal delivery. We excluded patients whose *Toxoplasma* seropositivity and pregnancy outcomes were unavailable.

Demographic, clinical and laboratory parameters of patients were obtained from the systemic medical records of the study center. Also, *Toxoplasma* Immunglobuline (Ig) M and G values were obtained from patients' files. *Toxoplasma* specific IgM and IgG values were analyzed by micro-ELISA (Roche, cobalt E601). The positive value for anti-*Toxoplasma* IgM index was accepted as >1.0 IU/ml, the borderlinevalue was ≥ 0.8 and ≤ 1.0 IU/ml and the negative value was < 0.8 IU/ml. Also anti-*Toxoplasma* IgG index was accepted as positive for values > 3.0 IU/ml, as borderline for values ≥ 1.0 and ≤ 3.0 IU/ml and as negative for values < 1.0 IU/ml. The ratios of seropositivity of *Toxoplasma* IgM and IgG were calculated.

Table 1. Socio-demographic characteristics of the patients

	Abortus (n = 412)	Normal Delivery (n = 828)	*p value*
Age (years)	27.6 ± 11.4	29.1 ± 9.87	0.921
Gravida (n)	3 (1:5)	3 (1:6)	0.708
Parity (n)	2 (1:4)	2 (1:5)	0.632
Residence			0.443
Urban	229 (55.6%)	418 (50.5%)	
Rural	183 (44.4%)	410 (49.5%)	
Education			0.826
Illiterate	52 (12.6%)	97 (11.7%)	
Primary	116 (28.2%)	25.3 (30.6%)	
Secondary	187 (45.4%)	365 (44.2%)	
High School	57 (13.8%)	112 (13.5%)	

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. For retrospective studies, ethics committee approval is not required.

Statistical Analysis

Statistical analyses were performed with SPSS software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). For group comparisons, independent samples t test or Mann Whitney U test were used according to normality test results. Variables were demonstrated as mean ± standard deviation or median values. A p value < 0.05 was considered as statistically significant. Also, categorical variables were shown as percentages and were compared by Chi-square or Fisher's exact test.

RESULTS

The mean age of all participants was 28.4 ± 10.3 years. Mean gravida was 3 (1:5) and mean parity was 2 (1:4). The patients were divided into two subgroups: pregnancies complicated with abortus (Group 1) and pregnancies with normal delivery (Group 2). Demographic characteristics of the study (n = 412) and control (n = 828) group were presented in Table 1. There was no difference between two groups in terms of age, gravida, parity, education status and residency (p > 0.05).

According to the *T. gondii* seropositivity, *Toxoplasma* IgM was positive in 62 (5%) patients and *Toxoplasma* IgG was positive in 282 (22.9%) patients in all groups. A total of 47 patients were anti-*Toxoplasma* IgG positive and anti-*Toxoplasma* IgM positive group. The distribution of both anti-*Toxoplasma* IgG and anti-*Toxoplasma* IgM was demonstrated in Table 2. In subgroup analysis *Toxoplasma* IgM was found to be positive in 27 (6.6%) patients in Group 1 and 35 (4.2%) patients in Group 2. The seropositivity of *Toxoplasma* IgM was statistically significantly higher in pregnancies complicated with abortus (p = 0.023). Moreover, *Toxoplasma* IgG was positive in 125 (30.6%) patients in Group 1 and in 157 (19.2%) patients in Group 2 (Table 3). In addition, the seropositivity of *Toxoplasma* IgG was statistically significantly higher in pregnancies complicated with abortus (p = 0.016).

Table 2. The distribution of anti-*Toxoplasma*IgM and anti-*Toxoplasma* IgG

	Anti-*Toxoplasma* IgM Positive (n=62)	**Anti-*Toxoplasma* IgM Negative (n=1178)**
Anti-*Toxoplasma* IgG Positive (n=282)	47 (3.8%)	235 (19%)
Anti-*Toxoplasma* IgG Negative (n=958)	15 (1.2%)	943 (76%)

DISCUSSION

Prevention, detection and management of congenital toxoplasmosis is a crucial issue for fetal well-being in daily obstetric practice. It has catastrophic consequences such as cephalic abnormalities, retinochoroiditis, blindness, epilepsy, retardation of psychomotor and mental functions, trombocytopenia and anemia [18, 19]. Although *T.*

Table 3. *Toxoplasma* seropositivity of the patients

	Total (n = 1240)	**Abortus (n = 412)**	**Normal Delivery (n = 828)**	***p value***
Anti-*Toxoplasma* IgM				
-Positive	62 (5%)	27 (6.6%)	35 (4.2%)	0.023
-Negative	1178 (95%)	385 (93.4%)	793 (95.8%)	
Anti-*Toxoplasma* IgG				
-Positive	282(22.9%)	125 (30.6%)	157 (19.2%)	0.016
-Negative	958 (77.1%)	287 (69.4%)	671 (80.8%)	

gondii infection which occurs up to 3 months before conception have nearly no risk for fetus, the rate of transmission varies between 60-81% in the third trimester [20]. Therefore, the confirmation of primary infection is critical to evaluate the risk of transmission and provide appropriate therapy and counseling. It is controversial whether routine screening for *T. gondii* is essential among pregnant women all over the world. Generally, decision on routine screening depends on the prevalence of infection, testing costs, sensitivity of screening tests and limitations of treatment effectiveness [21].

The seroprevalence of toxoplasmosis shows a widespread distribution all over the world depending on age, geographical regions, dietary habits and socioeconomic status [5]. Recent studies have demonstrated that *Toxoplasma* IgG positivity was 48.7% in Argentina, 9.1% in England, 61.6% in Brasil, 35% in Switzerland, 6.1% in Mexico, 50.6% in Morocco, 43.8% in France and 10.6% in China [10, 13, 22, 23]. In our country, Saracoglu *et al*. [24] reported *Toxoplasma* IgG positivity as 38.1% in Ankara. Moreover, it has been reported to be 60.4% in a city of southeastern region, 36% in a city of eastern region, 30.1% in a city of western region [14, 25, 26]. In our study *Toxoplasma* IgG positivity was found to be 22.9%. Our prevalence seems to be lower as compared to our country data. We suggest that the age of our patients was younger than the other studies and our trial center was in the northwestern part of our country which had a better socioeconomic status than the other regions.

Another interesting data of our study is that *Toxoplasma* IgM positivity was 5% among our study group. Similarly, in a study of Aynalı *et al*. [27] they found *Toxoplasma* IgM positivity as 5.2% among reproductive women. Also, other studies evaluating *Toxoplasma* IgM positivity in Turkey showed a prevalence between 0.3%-9.9% [26-28].

In the literature, there is a few data about the prevalence of *T. gondii* in pregnancies complicated with abortion. Ghasemi *et al*. [29] reported *Toxoplasma* IgG prevalence as 25.5% in abortion and stilbirth group, and as 26.4% in control group. Also they reported that *Toxoplasma* IgM was detected in 6.4% of the case group and 1.8% in control group and they concluded that toxoplasmosis might play a role in the etiology of abortion and stillbirth [29]. Tammam *et al*. [30] demonstrated that *Toxoplasma* spesific IgG seropositivity was 46.1% and IgM was 18.4% in spontaneous abortus group. They suggested that *Toxoplasma* seroprevalence is high and antenatal screening is needed in Egypt [30]. In Iran, *Toxoplasma* IgG seropositivity was 17.5% in repeated abortion, in Sari 34.21% and in South Iran 79.03% [15, 16, 31]. In those studies *Toxoplasma* IgM prevalence was reported to be 7.89-15.32%. In the study of Anubhuti *et al*. [32] *Toxoplasma* IgG was found to be positive in 20% of women with history of spontaneous abortion and 5% of women with no bad obstetric history while none of the women were reported to be *Toxoplasma* IgM positive. The seroprevalence of *Toxoplasma* IgM was investigated in women with recurrent abortion and it was found as 49.47%. This was much more higher than the seroprevalence in normal delivery group, which was reported as 8.88% [33]. The cases of abnormal pregnancies, including spontaneous abortions, premature deliveries, embryo damage and birth defects, were shown to have significantly higher seropositivity rates of *Toxoplasma* IgM and IgG as compared to normal pregnancies (7.94% vs 1.90% and 19.84% vs 8.75%, respectively) [34]. In our study, *Toxoplasma* IgG positivity was 30.6% in abortus group and 19.2% in control group. Also, *Toxoplasma* IgM was positive in 6.6% of abortus group and in 4.2% of control group. Consequently, the seropositivity of IgM and IgG were significatly higher in pregnancies complicated with abortus as compared to pregnancies with normal delivery and the *Toxoplasma* seroprevalence was observed to be similar with other countries. Moreover, as it was suggested by the authors of those researches, we suggest that toxoplasmosis is related with first trimester abortus.

CONCLUSION

In conclusion, *Toxoplasma* seropositivity is high in our country and routine screening is essential for pregnancies to provide fetal well-being. Toxoplasmosis may play a role in the etiology of abortion and this can be prevented by routine screening and appropriate management.

Conflict of interest

The authors disclosed no conflict of interest during

the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] Jones JL, Kruszon-Moran D, Wilson M, McQuillan G, Navin T, McAuley JB. Toxoplasma gondii infection in the United States: seroprevalence and risk factors. Am J Epidemiol 2001;154:357-65.
[2] Yang N, Wang D, Xing M, Li C, Li J, Wu A, et al. Seroepidemiology and risk factors of Toxoplasma gondii infection among the newly enrolled undergraduates and postgraduate students in China. Front Microbiol 2017;8:2092.
[3] Miller MA, Gardner IA, Kreuder C, Paradies DM, Worcester KR, Jessup DA, et al. Coastal freshwater runoff is a risk factor for T. Gondii infection of southern sea otters (Enhydralutrisnereis). Int J Parasitol 2002;32:997-1006.
[4] Anonymous. UK Standards for Microbiology Investigation. Investigation of Toxoplasma Infection in Pregnancy. UK: Health Protection Agency, Standards Unit, Microbiology Services Division. 2012.
[5] Kayman T, Kayman M. Seroprevalence of toxoplasmosis among pregnant women in Kayseri. Perinatoloji Dergisi 2010;18:92-6.
[6] Elsheikha HM. Congenital toxoplasmosis: priorities forfurther health promotion action. Public Health 2008;122:335-53.
[7] Abamecha F, Awel H. Seroprevalence and risk factors of Toxoplasma gondii infection in pregnant women following antenatal care at Mizan Aman General Hospital, Bench Maji Zone (BMZ), Ethiopia. BMC Infect Dis 2016;16:460.
[8] Montoya JG, Liesenfeld O. Toxoplasmosis. Lancet 2004;363:1965-76.
[9] Singh S. Congenital toxoplasmosis: clinical features, outcomes, treatment, and prevention. Trop Parasitol 2016;6:113-22.
[10] Pappas G, Roussos N, Falagas ME. Toxoplasmosis snapshots: global status of Toxoplasma gondii. Int J Parasitol 2009;39:1385-94.
[11] Tekay F, Ozbek E. [The Seroprevalence of Toxoplasma gondii in women from Sanliurfa, a province with a high raw meatball consumption]. Turkiye Parazitol Derg 2007;31:176-9. [Article in Turkish]
[12] Güneş H, Kaya S, Çetin ES, Taş T, Demirci M. [Seroprevalance of Toxoplasmosis in reproductive women]. SDU Tıp Fak Derg 2008;15:21-4. [Article in Turkish]
[13] Alvarado-Esquivel C, Sifuentes-Alvarez A, Narro-DuarteSG. Seroepidemiology of Toxoplasma gondiiinfectionin pregnant women in a public hospital in northern Mexico. BMC Infect Dis 2006;6:113.
[14] Harma M, Harma M, Gungen N, Demir N. Toxoplasmosis in pregnant women in Sanliurfa, SouthEastern Anatolia City, Turkey. J Egypt Soc Parasitol 2004;34:519-25.
[15] Ebadi P, Solhjoo K, Bagheri K, Eftekhar F. Seroprevalence of toxoplasmosis among the women with recurrent spontaneous abortion in comparison with the women with uncomplicated delivery. J Jahrom Univ Med Sci 2011;9:32-6.
[16] Jahromi AS. Anti-toxoplasma antibodies in women with abortion or still birth. J Jahrom Univ Med Sci 2007;4:47-52.
[17] Saki J, Mohammadpour N, Moramezi F, Khademvatan S. Seroprevalence of Toxoplasma gondii in women who have aborted in comparison with the women with normal delivery in Ahvaz, Southwest of Iran. Sci World J 2015;2015:764369.
18] Flatt A, Shetty N. Sero-prevalence and risk factors for toxoplasmosis among antenatal women in London: a re-examination of risk in an ethnically diverse population. Eur J Public Health 2013;23:648-52.
[19] Torgerson PR, Macpherson CNL. The socioeconomic burden of parasitic zoonoses: global trends. Vet Parasitol 2011;182:79-95.
[20] Alavi SM, Alavi L. Toxoplasmosis in Iran: A guide for general physicians working in the Iranian health network setting: A systematic review. Caspian J Intern Med 2016;7: 233-41.
[21] Chaudhry SA, Gad N, Koren G. Toxoplasmosis and pregnancy. Can Fam Physician 2014;60: 334-6.
[22] Berger F, Goulet V, Le Strat Y, Desenclos JC. Toxoplasmosis among pregnant women in France: risk factors and change of prevalence between 1995 and 2003. Rev Epidemiol Sante Publique 2009;57:241-8.
[23] Liu Q, Wei F, Gao S, Jiang L, Lian H, Yuan B, et al. Toxoplasma gondii infection in pregnant women in China. Trans R Soc Trop Med Hyg 2009;103:162-6.
[24] Saracoglu F, Sahin I. [Prevalence of Toxoplasmosis in a pregnant population and seroconversion rate of seronegative pregnants]. T Klin Jinekol Obst 2001;11:326-8. [Article in Turkish]
[25] Ertug S, Okyay P, Turmen M, Yuksel H. Seroprevalence and risk factors for Toxoplasma infection among pregnant women in Aydin province, Turkey. BMC Public Health 2005;5:66.
[26] Efe Ş, Kurdoğlu Z, Korkmaz G. [Seroprevalance of Cytomegalovirus, Rubella and Toxoplasma antibodies in pregnant women of Van Region]. Van Tıp Derg 2009;16:6-9. [Article in Turkish]
[27] Aynalı A, Cicioglu, Arıdogan B, Tola E, Onalı S, Sesli Çetin E. [Evaluation of anti-Toxoplasma IgM and IgG seropositivity among women in reproductive period, who admitted to Suleyman Demirel University Hospital]. Turk Hij Den Biyol Derg 2016;73:33-8. [Articie in Turkish]
[28] Bakıcı MZ, Nefesoglu N, Erandac M. Results of screening for Torch of blood samples collected in a microbiology laboratory. CÜ Tıp Fak Derg 2002;24:5-8. [Articie in Turkish]
[29] Ghasemi FS, Rasti S, Piroozmand A, Bandehpour M, Kazemi B, Mousavi SG, et al. Toxoplasmosis-associated abortion and stillbirth in Tehran, Iran J Matern Fetal Neonatal Med 2016;29:248-51.
[30] Tammam AE, Haridy MAM, Abdellah AH, Ahmed SR, Fayed HM, Alsammani MA. Seroepidemiology of Toxoplasma gondii infection in women with first trimester spontaneous miscarriage in Qena Governorate, Egypt. J Clin Diagn Res 2013;7:2870-3.
[31] Sharif M, Ajami A. Serological survey of toxoplasmosis in women with abortion or still birth referring to women clinic in Sari, 1997-1998. J Mazandaran Univ Med Sci 1999;26:13-8.
[32] Anubhuti, Roy RR, Mittra JP, Begum SJ. Seroprevalence of Toxoplasma gondii in spontaneous abortions in pregnant women. J Evol Med Dental Sci 2015;4:6763-8.
[33] Zargar AH, Masoodi SR, Laway BA, Sofi BA, Wani AI. Seroprevalence of toxoplasmosis in women with repeated abortions in Kashmir. J Epidemiol Community Health 1998;52:135-6.
[34] Zhang SF, Song RH. Toxoplasma gondii infection status in abnormal pregnancy women. Zhongguo Xue Xi Chong Bing Fang Zhi Za Zhi 2014;26:437-8, 452. [Articie in Chinese]

The European Research Journal 2018;4(4):280-288 ORIGINAL ARTICLE

Investigation of the relationship between alexithymia and eating attitude, self-esteem and anger in women who applied to psychological counseling center

Hüseyin Ünübol, Feride Gökben Hızlı Sayar, Sinem Kanpolat

Department of Psychology, Üsküdar University, Faculty of Humanities and Social Sciences, İstanbul, Turkey

DOI: 10.18621/eurj.350423

ABSTRACT

Objectives: The main purpose of this study was to examine self-esteem, anger and eating attitude with alexithymia in people who consult to the psychological counseling center. The sample of the study consist of 100 women who were located in Istanbul and applied to the psychological consulting center.

Methods: Consent form, demographic form, State-Trait Anger Expression Inventory, Rosenberg Self-Esteem Inventory, Toronto Alexithymia Scale and Eating Attitude Test have been used to collect the data in this study. In this research, the relationship between sociodemographic features, alexithymia, self-esteem, anger, eating attitude of women who consult to the psychological counseling center had been examined. Data obtained have been analyzed statistically by using SPSS 15.0 for Windows.

Results: The findings of this research supported our hypothesizes. Regarding the relationship between eating attitude and alexithymia, there is a positive relationship between difficulties in identifying and describing feelings with eating attitudes ($p < 0.05$). Regarding the relationship between alexithymia and self-esteem, there is a positive relation between sub-dimensions of alexithymia scale with subscales of self-esteem ($p < 0.05$). There is a positive relationship between identifying feelings with trait anger and anger-out scores ($p < 0.05$).

Conclusions: According to these results, it appears that alexithymia has a serious relationship with anger, eating attitude and self-esteem. We suggest that alexithymia may be at the center of other features relations with each other.

Keywords: Alexithymia, eating attitude, anger, self-esteem

Received: November 11, 2017; Accepted: December 23, 2017; Published Online: March 14, 2018

Alexithymia is a personality trait that is associated with a difficulty identifying and describing one's feelings, with difficulty in distinguishing between feelings and bodily sensations and with an externally focused, logical, thinking style [1]. Also, alexithymia is suggested to result in chronic sympathetic hyperarousal, physiological response, somatosensory amplification, and complaints of physical symptoms [2]. When one can not distinguish the emotional tension experienced, this emotion can feel like anger. The relationship between alexithymia and anger has been evaluated by few studies providing evidence of a complex association between them. Compared to individuals in the low-alexithymia group, subjects in the high-alexithymia group exhibited more non-verbal anger [3]. Anger trait, as defined by Forgays *et al*. [4] is a tendency to experience angry feelings and is thought to be a relatively stable personality character-

Address for correspondence: *Hüseyin Ünübol, MD., Assistant Professor, Üsküdar University, Faculty of Humanities and Social Sciences, Department of Psychology, İstanbul, Turkey*
E-mail: huseyin.unubol@uskudar.edu.tr

e-ISSN: 2149-3189

istic. A wider range of situations is easier to be perceived by individuals high in anger trait as anger eliciting. These people tend to experience more persistent anger during these situations than do individuals with low anger trait. The maladaptive form of aggression can be caused by poor awareness of emotions, alexithymia which is a diminished ability to think and talk about feelings [5], emotion dysregulation, and impulsivity. Those who do not know their emotions have difficulties in mitigating emotional awakening, especially under stress.

People may feel a sense of tension when they see a potential danger in their relational environment, and they may be deprived of appropriate strategies (e.g., to adopt appropriate communication and negotiating skills) to resolve possible interpersonal conflicts without recognizing the source and nature of this feeling. One of the most widely accepted conceptualizations is the lack of awareness of emotions and lack of comprehension, lack of understanding, acceptance of emotional reactions, difficulty in being in goal-oriented behavior when adversity, ability to avoid impulse responses while experiencing negative emotions, and limited effective emotional regulation strategies [6]. Research in recent years has shown that the challenges in these areas may increase the individual's tendency to react with aggression-perceived threats or crimes [7]. Indeed, even among people who fully realize their emotions, there is a certain variability in how they handle and organize them (e.g., rethinking the situation or thinking about different problem-solving strategies). For this reason, dysregulation of emotions, and especially anger, is considered a possible mechanism underlying aggression [8]. Emotional regulation processes and negative mood in particular play an important role in the development [9] and maintenance of binge eating disorder [10], although in children and adolescents findings are somewhat contradictory [11]. It was assumed that the negative impact came before and disappeared from inappropriate eating behavior, which could be understood as an attempt to deal with them or to distract them [12]. Heatherton and Baumeister [13] suggested a model, in which binge eating is seen as the result of an escape from unpleasant states, especially from "the awareness of the self's shortcomings, creating negative affects such as anxiety and depression" and represents a maladaptive way of coping. Fox and Power [10] also assume that emotions play a central role in all eating disorders. In their model, an eating disorder has the function of inhibiting emotions, in particular, negative emotions like anger and disgust. Only a few studies examined a broad range of emotional states in subjects with binge eating disorder and its relation to eating, although a more differentiated understanding of the term negative emotion is necessary to use research findings in everyday work with these patients. Arnow *et al*. [14] described anger and frustration preceding an urge to eat more often than sadness and depression. In their study, anger/frustration, anxiety and sadness/depression accounted for 95% of the antecedent moods preceding a binge. The Emotional Eating Scale (EES), which was subsequently developed [15] asks subjects to report on the intensity of an urge to eat under a range of possible negative emotional states (summarized to the three factors mentioned above). To our knowledge, there are no further studies. In people with alexithymia, negative emotions in the body-esteem seem to be associated with abnormal eating behaviors. Both self-esteem and body-esteem play a role in the pathogenesis of eating disorders. Abnormal eating behaviors may worsen self-esteem and the feelings about one's body [16].
The aims of the present study were to examine the central effect of alexithymia on anger, eating attitudes and self-esteem, which are closely related with emotional awareness and with each other, to determine the correlations of self-esteem, eating attitudes, anger and alexithymia with each-other, in the women who applied to the psychological counseling center.

METHODS

Participants

This study was conducted with 100 women counselors who applied to Counseling Center and were randomly selected. Our inclusion criterias are the absence of psychological and medical condition that could prevent them from responding to the questionnaires, and older than 18 years old. In the study, the average age of the group is 35.7 years and the age range is between 18-71 years.

Research Design

The researcher introduced himself/herself before starting the data collection process and explained the

purpose and content of the research. The respondents who agreed to participate in the survey explained how to fill the questionnaire. In the demographic form, participants were asked to respond to research questions, and participation in the survey was based on volunteerism. The survey participants were informed that this study was conducted to examine the relationship between alexithymia, eating attitude, self-esteem, and anger in adult individuals referred to Psychological Counseling Centers. All the answers given to the questions were kept confidential, and the scales were filled out, expressing that they could not be used except for scientific purposes. Each questionnaire was completed within 15-25 minutes. The study was approved by ethics committee from Üsküdar University.

Measures

Demographic Information Form

It was designed by the researcher to determine the participants' characteristics such as age, gender, education, marital status and economic level. In the last six months, there are also questions about whether treatment is due to a psychiatric/psychological problem.

Toronto Alexithymia Scale (TAS-20)

The five-point Likert-type scale consists of 20 items. There are subscales of difficulty in defining feelings (TAS-1), difficulty in identifying feelings (TAS-2) and outward thinking (TAS-3). High scores indicate high alexithymic level. Bagby *et al*. [17] developed the scale. Turkish adaptation was made by Güleç *et al*. [18]. The total scale was found to be 0.78 for Cronbach alpha and 0.57-0.80 for subscales. According to confirmatory factor analysis results, the alexithymia structure has been shown to provide 3 factors.

State-Trait Anger Expression Inventory (STAXI)

Trait anger and anger expression style scale developed by Spielberger [19] was adapted into Turkish by Özer [20]. It is a self-assessment scale composed of thirty-four items. Ten items of this 34-item scale determine trait anger and 24 items determine anger expression style (Anger-in, Anger-out and Anger control). High scores received from trait anger indicate high levels of anger; high scores from anger-in scale indicate suppressed anger; high scores from anger-out scale indicate easy expression of anger and high scores from anger control scale indicate controllability of anger. Internal consistency coefficients measured for the scale in its Turkish adaptation are 0.79 for trait anger dimension, 0.84 for control anger, 0.78 for anger out and 0.62 for anger suppression [20].

Rosenberg Self-Esteem Scale (RSES)

It consists of 63 items and 12 subscales of multiple choice [21]. Subjects are a measure of their filling. The validity and reliability study in our country was carried out by Çuhardaroğlu [22]. D4-Criticism, D5-Depressive affect, D6-Dream establishment, D7-Psychosomatic manifestations, Self-esteem, D8-Personal threat, D9-Discussion participation level, D10-Parent interest, D11-Parent relationship, D12-Psychic isolation. Items belonging to other sub-scales other than the self-esteem sub-scale are evaluated according to the response key, and each score is given a '1' score. If self-esteem is sub-scale, the answers are evaluated between 0-6 points. A zero-one point is high, 2-4 points moderate, 5-6 points low self-esteem level.

Eating Attitude Test (EAT)

By Garner and Garfinkel [23]; is a self-reporting scale developed to evaluate possible eating disorders in both eating disorders and non-eating disorders. The scale consists of forty items, and the measurement is applied to sixty Likert types. Savaşır and Erol [24] conducted validity and realibility, but no cut-off score was calculated for Turkish form. The scale was used to evaluate eating attitudes in both groups of patients.

Statistical Analysis

The data were analyzed using the SPSS 15.00 Windows package program. After applying the Kolmogorov-Smirnov Normality Test, the Independent Sample T-Test, Independent Sample One-way ANOVA, and Tukey Test were applied to the data showing normal distribution. Mann-Whitney U Test and Kruskal-Wallis T Test were applied to the data without normal distribution. Also, the Spearman Correlation Test was used to measure the severity of relations between variables.

RESULTS

Of the 100 women who participated in the research; 23 women between the ages of 18-24, 22 women between the ages of 25-34, 38 women between the ages of 35-44, and 17 women over the age of 45. Twenty-seven women weighed 55 kilograms or less, 31 women between 56 and 65 kilograms, 19 women between 66 and 75 kilograms, and 23 women over 76 kilograms. There were 31 female primary school graduates, six female secondary school graduates, 27 high school graduates, nine female university students, 27 female college or university graduates (Table 1).

Table 1. Distributions related to socio-demographic characteristics

n = 100		n	%
Age (years)	18-24	23	23
	25-34	22	22
	35-44	38	38
	Over 45	17	17
Weight (kg)	Less than 55	27	27
	56-65	31	31
	66-75	19	19
	Over76	23	23
Education	Primary school	31	31
	Secondary school	6	6
	High shool	27	27
	College student	9	9
	Graduated form university	27	27
Marital status	Maried	63	63
	Single	29	29
	Engaged	2	2
	Divorced/Widow	6	6
Monthly income (Turkish Liras)	0-500	1	1
	501-1000	0	0
	1001-1500	5	5
	1501-2000	16	16
	2001-2500	35	35
	2501- 3000	27	27
	3001-3500	12	12
	Over 3501	4	4
Diagnosis from psychologist or psychiatrist in last 6 months	No	61	61
	Yes	39	39
Drug usage status	No	65	65
	Yes	35	35

Correlation between Toronto Alexithymia Scale Sub-dimensions and Eating Attitude

A Pearson correlation analysis revealed a weak positive correlation between difficulty in identifying feelings and eating attitude ($r = 0.21$; $p < 0.05$); it was observed that there was a weak positive relationship between difficulty in describing feelings and eating attitude ($r = 0.21$; $p < 0.05$), while the correlation between externally-oriented thinking and eating attitude were not significant ($r = 0.14$; $p > 0.05$) (Table 2).

Correlation between Toronto Alexithymia Scale Sub-dimensions with Rosenberg Self-esteem Subscales

A positive moderate relationship ($r = 0.34$; $p < 0.01$) between difficulty in identifying feelings and self-esteem; there is a moderate relationship ($r = 0.35$; $p < 0.01$) between the continuity of the self concept; a moderate relationship between Sensitivity to criticism ($r = 0.31$; $p < 0.01$); a moderate relationship ($r = 0.29$; $p < 0.01$) between the depressive mood and; a moderate relationship ($r = 0.29$; $p < 0.01$) between Visionary; a moderate relationship between psychosomatic symptoms ($r = 0.35$; $p < 0.01$); a weak relationship ($r = 0.23$; $p < 0.05$) between feeling threatened in interpersonal relationships; psychic isolation ($r = 0.38$; $p < 0.01$) correlations were found to be significant. Also relying on people ($r = -0,03$; $p > 0.05$); the Degree of participating in discussions ($r = -0.06$; $p > 0.05$); Interest of parents ($r = 0.18$, $p < 0.01$); Relationship with father ($r = 0.09$; $p > 0.05$) were not significant (Table 2).

A moderate relationship ($r = 0.27$; $p < 0.01$) between difficulty in describing feelings and Sensitivity to criticism; a moderate relationship between psychosomatic symptoms ($r = 0.29$; $p < 0.01$); a weak relationship between parental interest ($r = 0.22$; $p < 0.05$) and correlations were found to be significant. Also, self-esteem ($r = 0.17$; $p < 0.05$); continuity of the self-concept ($r = 0.20$; $p > 0.05$); relying on people ($r = 0.02$; $p > 0.05$); depressive mood ($r = 0.11$; $p > 0.05$); visionary ($r = 0.16$; $p > 0.05$); feeling threatened in interpersonal relationships ($r = 0.16$; $p > 0.05$); the degree of participating in discussions ($r = -0,13$; $p > 0.05$); relationship with the father ($r = -0,04$; $p > 0.05$); relationship between psychic isolation ($r = 0.18$; $p > 0.05$) were not significant (Table 2).

Table 2. Correlations of TAS-20 sub-scales with EAT, RSES, STAXI scores

		Toronto Alexithymia Scale		
		Difficulties in identifying Feelings	**Difficulties in Describing Feelings**	**Externally Oriented Thinking**
Eating Attitude Test	Eating Attitude	r = 0.21	r = 0.21	r = 0.14
		***p* = 0.04**	***p* = 0.04**	*p* = 0.17
Rosenberg Self-Esteem Scale	Self-Esteem	r = 0.34	r = 0.17	r = 0.00
		***p* < 0.01**	*p* = 0.08	*p* = 0.99
	Continuity of self-concept	r = 0.35	r = 0.20	r = 0.15
		***p* < 0.01**	*p* = 0.051	*p* = 0.14
	Relying on people	r = -0.03	r = 0.02	r = -0.11
		p = 0.73	*p* = 0.84	*p* = 0.26
	Sensitivity to criticism	r = 0.31	r = 0.27	r = 0.23
		***p* < 0.01**	***p* = 0.008**	***p* = 0.02**
	Depressive mood	r = 0.29	r = 0.11	r = -0.01
		***p* < 0.01**	*p* = 0.28	*p* = 0.90
	Visionary	r = 0.29	r = 0.16	r = -0.02
		***p* < 0.01**	*p* = 0.10	*p* = 0.85
	Psychosomatic symptoms	r = 0.35	r = 0.29	r = 0.24
		***p* < 0.01**	***p* < 0.01**	***p* = 0.02**
	Feeling threatened in interpersonal relationships	r = 0.23	r = 0.16	r = 0.12
		***p* = 0.02**	*p* = 0.10	*p* = 0.23
	Degree of participating in discussions	r = -0.06	r = -0.13	r = -0.16
		p = 0.58	*p* = 0.18	*p* = 0.11
	Interest of parents	r = 0.18	r = 0.22	r = 0.30
		p = 0.08	***p* = 0.03**	***p* < 0.01**
	Relationship with father	r = 0.09	r = -0.04	r = -0.04
		p = 0.36	*p* = 0.71	*p* = 0.72
	Psychic isolation	r = 0.38	r = 0.18	r = 0.32
		***p* < 0.01**	*p* = 0.07	***p* < 0.01**
Trait Anger Scale	Trait Anger	r = 0.30	r = 0.30	r = 0.05
		***p* < 0.01**	***p* < 0.01**	*p* = 0.60
Anger Expression Styles	Anger-Control	r = -0.04	r = -0.12	r = -0.13
		p = 0.70	*p* = 0.24	*p* = 0.19
	Anger-Out	r = 0.22	r = 0.34	r = 0.04
		***p* = 0.02**	***p* < 0.01**	*p* = 0.68
	Anger-In	r = 0.16	r = 0.10	r = -0.08
		p = 0.11	*p* = 0.32	*p* = 0.46

EAT = Eating Attitudes Test, STAXI = State-Trait Anger Expression Inventory, RSES = Rosenberg Self-Esteem Scale, TAS = Toronto Alexithymia Scale

A weak relationship (r = 0.23; $p < 0.05$) between externally oriented thinking and sensitivity to criticism; a weak relationship (r = 0.24; $p < 0.05$) between psychosomatic symptoms; a moderate relationship (r = 0.30; $p < 0.01$) between the interest of parents; a moderate relationship (r = 0.32; $p < 0.01$) between psychic isolation were found to be significant. Also self-esteem (r = 0; $p > 0.05$); continuity of the self-concept (r = 0.15; $p > 0.05$); relying on people (r =-0.11; $p > 0.05$); depressive mood (r =-0.01; $p > 0.05$); visionary (r = -0,02; $p > 0.05$); feeling threatened in interpersonal relationships (r = 0.12; $p > 0.05$); the degree of participating in discussions (r = -0,16; $p > 0.05$); relationship with father (r = -0.04; $p > 0.05$) were not significant (Table 2).

Correlation between the Toronto Alexithymia Scale Sub-dimensions with State-Trait Anger Expression Inventory Sub-dimensions

A moderate relationship between the difficulty in identifying feelings and the trait anger (r = 0.30; $p < .01$); A weak relationship between anger-out (r = 0.22, $p < 0.05$) were observed and the correlations

Table 3. Correlations of EAT with RSES and STAXI Scores

		Eating Attitude Test
Rosenberg Self-Esteem Scale	Self-Esteem	r = 0.18 *p* = 0.08
	Continuity of self-concept	r = 0.20 ***p* = 0.049**
	Relying on people	r = -0.14 *p* = 0.17
	Sensitivity to criticism	r = 0.16 *p* = 0.12
	Depressive mood	r = 0.09 *p* = 0.39
	Visionary	r = 0.20 ***p* = 0.045**
	Psychosomatic symptoms	r = 0.11 *p* = 0.28
	Feeling threatened in interpersonal relationships	r = 0.23 ***p* = 0.02**
	Degree of participating in discussions	r = -0.13 *p* = 0.21
	Interest of parents	r = 0.01 *p* = 0.93
	Relationship with father	r = -0.10 *p* = 0.35
	Psychic isolation	r = 0.09 *p* = 0.37
Trait Anger Scale	Trait Anger	r = 0.24 ***p* = 0.02**
Anger Expression Styles	Anger-Control	r = 0.00 *p* = 0.97
	Anger-Out	r = 0.05 *p* = 0.61
	Anger-In	r = 0.16 *p* = 0.11

EAT = Eating Attitudes Test, STAXI = State-Trait Anger Expression Inventory, RSES = Rosenberg Self-Esteem Scale

were found to be significant. Furthermore, correlations with anger-control (r = -0,04; $p > 0.05$); and anger-in (r = 0.16; $p > 0.05$) were not significant (Table 2).

A moderate relationship between the difficulty in describing feelings and trait anger (r = 0.30; $p < 0.01$); anger-out (r = 0.34, $p < 0.01$) were observed and the correlations were found significant. Furthermore, relationships wiht anger-control (r = -0,12; $p > 0.05$); anger-in (r = 0.10; $p > 0.05$) were not significant (Table 2).

Relationships between externally oriented thinking with trait anger (r = 0.05; p > 0.05); anger-control (r = -0,13; $p > 0.05$); anger-out (r = 0.04; $p > 0.05$); anger-in (r =-0.08; $p > 0.05$) were not significant (Table 2).

Correlation between Eating Attitude with Rosenberg Self-esteem Subscales

A weak relationship (r = 0.20; $p < 0.05$) was found between the eating attitude and the continuity of the self-concept; a weak relationship (r = 0.20; $p < 0.05$) between visionary; a weak relationship (r = 0,23; $p < 0.05$) between feelings threatened in interpersonal relationships and correlations were found to be significant. Also, self-esteem (r = 0.18, $p > 0.05$); relying on people (r =-0.14; $p > 0.05$); sensitivity to criticism (r = 0.16; $p > 0.05$); depressive mood (r = 0.09; $p > 0.05$); psychosomatic symptoms (r = 0.11; $p > 0.05$); the degree of participating in discussion (r = -0,13; $p > 0.05$); interest of parents (r = 0.01; $p > 0.05$); relationship with father (r = -0,10; $p > 0.05$); psychic isolation (r = 0.09; $p > 0.05$) were not significant (Table 3).

Correlation between Eating Attitude and State-Trait Anger Expression Inventory Sub-dimensions

It was observed that there was a weak relationship between eating attitude and trait anger (r = 0.24, $p < 0.05$) and the correlation was found to be significant. In addition, correlations with anger-control (r = 0; $p > 0.05$); anger-out (r = 0.05, $p > 0.05$) and anger-in (r = 0.16; $p > 0.05$) were not significant (Table 3).

DISCUSSION

Alexithymia is a personality construct that involves difficulties in identifying feelings, in describing feelings, and an externally oriented thinking style [17]. This construct was initially introduced to describe clinical patients with so-called psychosomatic diseases who experienced difficulties describing their emotions and who presented impoverished mental representations of their emotional states. This may explain the high prevalence of alexithymia in somatic and mental disorders [25]. The association of alexithymia with somatic symptoms in all aspects may also be considered in accordance with the literature.

When we look at the research done in this matter; individuals with higher alexithymia scores seem to have lower self-esteem. As scores of alexithymia increase, self-esteem scores decrease [26, 27]. The social interactions that develop together with low self

esteem are threatening and the process of deterioration in social relations becomes more prominent [28]. It is known that alexithymic people apparently live in harmony with the environment, but they are in fact known to have little relation to their spiritual realities. The alexithymic person has a structure that can not express itself in society [29, 30]. Individuals with alexithymic structure were more likely to have insecure attachment style [31], which is a way of expressing themselves in society. In line with these results; it is thought that shyness causes the person to be distressed by the anxiety to be in a difficult situation against the people and supports the formation of an alexithymic structure.

Alexithymia was also thought to be related to lack of confidence and self-esteem [26]. A study of adolescents by Sayar *et al*. [27] found that depression and anxiety levels were significantly higher than those without alexithymic adolescents, but that self-esteem was significantly lower.

When the relationship between alexithymia and anger is examined; it was observed that there was a meaningful relationship between difficulty in expressing difficulties and describing feelings between trait anger and anger-out. Individuals with a high score of alexithymia are more likely to feel anger; introspection and irrelevant reactions tend to be more frequent in interpersonal relationships [3, 32, 33].

In the literature search; it is possible to say that all of these findings with anger are related to the alexithymia with high levels. Berenbaum and Irvin [3] reported that alexithymic individuals experienced more anger than non-alexithymic individuals, even so they use non-verbal expressions, because of difficulty in expressing feelings. And also; they point out that these persons have escaped from conflict. Similarly, there are also different studies that show the relationship between alexithymia and introverted anger [34], as well as the relationship between alexithymia and aggression [33].

One of the behaviors associated with anger is aggression. Fossati *et al*. [33] argue that insecure attachment and alexithymia together are significantly associated with impulsive aggression. Bekker *et al*. [35] found that antisocial behavior, a component of alexithymia, is negatively related to antisocial behavior. As we have already pointed out, in a study, alexithymic individuals showed more anger and aggression as well as more psychological symptoms such as anxiety, depression, negative self, somatization [3]. It is also consistent with the literature that our results, especially difficulties in describing and identifying feelings, are related to persistent angry and outrage.

Not defining or expressing a feeling does not cause it to disappear. As a solution to these people, the emotions are turned into anger. The first level solution becomes a second level problem. In our research; it was seen that there was a meaningful relationship between anger with eating attitudes as well as difficulties in identifying and describing feelings.

Recent anger-related studies have shown that anger and aggression are associated with eating disorders. It is also stated that it is one of the basic features of psychopathology [36]. It is reported that patients with eating disorders are less aware of their anger, and have difficulty in describing and expression of feelings [37]. Interesting part of our study, difficulty in describing and identifying of feelings was related to continuous anger and outrage feelings, as well as with eating disorders, but eating attitudes was associated only with persistent anger. It is consistent with literature, because lack of expression of anger is the other source of problematic eating attitudes. Studies of eating disorders seem to focus specifically on women. It is reported that these patients have more anger attacks compared to normals, that their anger is mostly state anger, and that women who have an eating disorder have high-suppressed anger [38]. And also; there is a view that the anger influences women's excessive eating habits [39]. Thompson *et al*. [40] argue that the anorexic or bulimic attitudes of adolescents are an expression of unexpressed anger towards their parents. Adolescents view the amount of food as the only thing their parents can not control. As has been pointed out in previous studies, the frequency of eating disorders in recent years has also increased in eastern countries [41, 42].

In general, the most basic step in one's life is the awareness of its feelings [43, 44]. The level of emotional awareness and ability to cope with these emotions determines their subsequent cognitive and behavioral attitudes [45]. When feelings are not identified and expressed, the tension we are experiencing can turn into anger. Anger then begins to shape our own cognitive and behavioral attitudes. If it

can be expressed, it can turn into an aggressive behavior and pave the way for the formation of some cognitive attitudes. We can evaluate the results of our work from this perspective. The low awareness of emotions can also shape our need to avoid encountering it as it causes it to turn into anger [46]. We can also evaluate the relevance of the sensitivity to criticism in our self-respect to all the alexithymia subscales from this perspective. Our unexpressed feelings find a way to express themselves in a way. One of the most concrete signs of this is somatic complaints [47]. Another finding in our study is consistent with studies in the literature related to alexithymia and somatic complaints. Anger results in two ways in the person; “to express" or “not to express." According to our results, unexpressed feelings are related to eating attitudes, as well as both trait anger and anger-out. However, while eating attitudes were related to trait anger, there were not associated with anger-out. It was also emphasized that the studies were related to the relationship of eating disorders with anger that is repressed and unexpressed and eating attitudes act as an expression of the indefinable anger [48]. In this sense, results are compatible with the studies in the literature.

The Limitations of the Study

Our work was conducted among women in psychological counseling centers provided free counseling by the municipality. Because the socioeconomic level is limited to a low population, it caused a shortage of interpretation of the data. It can also be applied in subsequent studies, with emotion regulation related scales and with larger populations. Further prospective studies are needed the highlight the role of emotional awareness in understanding the cause-and-effect relationship.

CONCLUSION

Our study has dealt with many known associations in a single study. We can use a wide variety of scales to understand patients. But sometimes when we are dealing with parts, we can not see the whole thing. Self-esteem, anger and eating attitudes are cognitive, emotional, and behavioral aspects of a person. We can separate these features or interpret them as a reflection of a problem in different layers. We wanted to evaluate the results of this work by opening a different window for future work. According to these results, we can interpret that the relations of alexithymia with anger, with the eating attitudes of the anger, with the self-esteem of the eating attitudes and with the alexithymia of the self-esteem are not spontaneous relations, they are all parts of a continuum and a general structure. We can interpret it as the establishment of cause-effect relations in more different layers than these relations occur in local interactions. The results of the study suggest that alexithymia, which is the most fundamental layer, can indirectly change many cognitive, emotional and behavioral outcomes that related to anger, eating attitudes and self-esteem in the struggle with problems.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] Levenson H. Time-Limited Dynamic Psychotherapy: A Guide to Clinical Practice. New York: Basic Books, 1995.
[2] Taylor GJ, Bagby RM, Parker JD. The alexithymia construct. A potential paradigm for psychosomatic medicine. Psychosomatics 1991;32:153-64.
[3] Berenbaum H, Irvin S. Alexithymia, anger, and interpersonal behavior. Psychother Psychosom 1996;65:203-8.
[4] Forgays DG, Forgays DK, Spielberger CD. Factor Structure of the State-Trait Anger Expression Inventory. J Pers Assess 1997;69:497-507.
[5] Loas G, Fremaux D, Otmani O, Lecercle C, Delahousse J. Is alexithymia a negative factor for maintaining abstinence? A follow-up study. Compr Psychiatry 1997;38:296-9.
[6] Gratz KL, Roemer L. The relationship between emotion dysregulation and deliberate self-harm among female undergraduate students at an urban commuter university. Cogn Behav Ther 2008;37:14-25.
[7] Velotti P, Garofalo C, Petrocchi C, Cavallo F, Popolo R, Dimaggio G. Alexithymia, emotion dysregulation, impulsivity and aggression: A multiple mediation model. Psychiatry Res 2016;237:296-303.
[8] Wahlstrom LC, Scott JP, Tuliao AP, DiLillo D, McChargue DE. Posttraumatic stress disorder symptoms, emotion dysregulation, and aggressive behavior among incarcerated methamphetamine users. J Dual Diagn 2015;11:118-27.
[9] Stice E. Risk and maintenance factors for eating pathology: a meta-analytic review. Psychol Bull 2002;128:825-48.
[10] Fox JRE, Power MJ. Eating disorders and multi-level models of

emotion: an integrated model. Clin Psychol Psychother 2009;16:240-67.
[11] Zeeck A, Stelzer N, Linster HW, Joos A, Hartmann A. Emotion and eating in binge eating disorder and obesity. Eur Eat Disord Rev 2011;19:426-37.
[12] Stice E. Interactive and mediational etiologic models of eating disorder onset: evidence from prospective studies. Annu Rev Clin Psychol 2016;12:359-81.
[13] Heatherton TF, Baumeister RF. Binge eating as escape from self-awareness. Psychol Bull 1991;110:86-108.
[14] Arnow B, Kenardy J, Agras WS. Binge eating among the obese: a descriptive study. J Behav Med 1992;15:155-70.
[15] Arnow B, Kenardy J, Agras WS. The emotional eating scale: the development of a measure to assess coping with negative affect by eating. Int J Eat Disord 1995;18:79-90.
[16] Sasai K, Tanaka K, Hishimoto A. Alexithymia and its relationships with eating behavior, self esteem, and body esteem in college women. Kobe J Med Sci 2011;56:E231-8.
[17] Bagby RM, Taylor GJ, Parker JDA. The twenty-item Toronto Alexithymia scale-II. Convergent, discriminant, and concurrent validity. J Psychosom Res 1994;38:33-40.
[18] Güleç H, Köse S, Güleç MY, Çitak S, Evren C, Borckardt J, et al. Reliability and factorial validity of the Turkish version of the 20-item Toronto alexithymia scale (TAS-20) Klinik Psikofarmakoloji Bulteni 2009;19:213-9.
[19] Spielberger CD. State-Trait Anger Expression Inventory. Hoboken, NJ, USA: John Wiley & Sons, Inc; 2010. p1.
[20] Özer AK. Öfke, kaygı ve depresyon eğilimlerinin bilişsel alt yapısıyla ilgili bir çalışma. Turk Psikolojisi Dergisi 1994;9:15-25. [Article in Turkish]
[21] Rosenberg M. Society and the Adolescent Self-Image. NJ: Princeton University Pres, Princeton; 1965.
[22] Çuhadaroğlu F. [Self-esteem in adolescence]. Unpublished doctoral dissertation, Hacettepe University, Ankara, Turkey. [Article in Turkish]
[23] Garner DM, Garfinkel PE. The Eating Attitudes Test: an index of the symptoms of anorexia nervosa. Psychol Med 1979;9:273-9.
[24] Savaşır I, Erol N. Yeme Tutum Testi: Anoreksiye nervoza belirtiler endeksi. Turk Psikoloji Dergisi 1989;7:19-25. [Article in Turkish]
[25] Lumley MA, Neely LC, Burger AJ. The assessment of alexithymia in medical settings: implications for understanding and treating health problems. J Pers Assess 2007;89:230-46.
[26] Zimmermann G, Rossier J, De Stadelhofen FM, Gaillard F. Alexithymia assessment and relations with dimensions of personality. Eur J Psychol Assess 2005;21:23-33.
[27] Sayar K, Kose S, Grabe HJ, Topbas M. Alexithymia and dissociative tendencies in an adolescent sample from Eastern Turkey. Psychiatry Clin Neurosci 2005;59:127-34.
[28] Dreessen L, Arntz A, Hendriks T, Keune N, van den Hout M. Avoidant personality disorder and implicit schema-congruent information processing bias: a pilot study with a pragmatic inference task. Behav Res Ther 1999;37:619-32.
[29] Evren EC, Can S, Evren B, Çakmak D. The relationship between alexithymia and depression, anxiety and erectile dysfunction in a sample of male alcoholic inpatients: A controlled study. Klinik Psikofarmakoloji Bulteni 2002;12:165-73.
[30] Graugaard PK, Holgersen K, Finset A. Communicating with alexithymic and non-alexithymic patients: an experimental study of the effect of psychosocial communication and empathy on patient satisfaction. Psychother Psychosom 2004;73:92-100.
[31] Oskis A, Clow A, Hucklebridge F, Bifulco A, Jacobs C, Loveday C. Understanding alexithymia in female adolescents: The role of attachment style. Pers Individ Dif 2013;54:97-102.
[32] Teten AL, Miller LA, Bailey SD, Dunn NJ, Kent TA. Empathic deficits and alexithymia in trauma-related impulsive aggression. Behav Sci Law 2008;26:823-32.
[33] Fossati A, Acquarini E, Feeney JA, Borroni S, Grazioli F, Giarolli LE, et al. Alexithymia and attachment insecurities in impulsive aggression. Attach Hum Dev 2009;11:165-82.
[34] Sayar K, Gulec H, Topbas M. Alexithymia and anger in patients with fibromyalgia. Clin Rheumatol 2004;23:441-8.
[35] Bekker MHJ, Bachrach N, Croon MA. The relationships of antisocial behavior with attachment styles, autonomy-connectedness, and alexithymia. J Clin Psychol 2007;63:507-27.
[36] Krug I, Bulik CM, Vall-Llovera ON, Granero R, Agüera Z, Villarejo C, et al. Anger expression in eating disorders: Clinical, psychopathological and personality correlates. Psychiatry Res 2008;161:195-205.
[37] Miotto P, Pollini B, Restaneo A, Favaretto G, Preti A. Aggressiveness, anger, and hostility in eating disorders. Compr Psychiatry 2008;49:364-73.
[38] Geller J, Cockell SJ, Hewitt PL, Goldner EM, Flett GL. Inhibited expression of negative emotions and interpersonal orientation in anorexia nervosa. Int J Eat Disord 2000;28:8-19.
[39] Feinson MC, Hornik-Lurie T. Binge eating & childhood emotional abuse: The mediating role of anger. Appetite 2016;105:487-93.
[40] Thompson KA, Kelly NR, Schvey NA, Brady SM, Courville AB, Tanofsky-Kraff M, et al. Internalization of appearance ideals mediates the relationship between appearance-related pressures from peers and emotional eating among adolescent boys and girls. Eat Behav 2017;24:66-73.
[41] Nasser M. Eating disorders across cultures. Psychiatry 2009;8:347-50.
[42] Bilali A, Galanis P, Velonakis E, Katostaras T. Factors associated with abnormal eating attitudes among Greek adolescents. J Nutr Educ Beha 2010;42:292-8.
[43] Heck A, Hock A, White H, Jubran R, Bhatt RS. Further evidence of early development of attention to dynamic facial emotions: Reply to Grossmann and Jessen. J Exp Child Psychol 2017;153:155-62.
[44] Lyons M, Hughes S. Feeling me, feeling you? Links between the Dark Triad and internal body awareness. Pers Individ Dif 2015;86:308-11.
[45] Sharpe E, Wallis DJ. Attitudes towards emotional expression, emotion regulation and eating psychopathology. Appetite 2014;83:354.
[46] Shin M-K, Eom JY. Study on the alexithymia and anger in the Korean college students. Advanced Science and Technology Letters (Healtcare and Nursing) 2015;116:189-95.
[47] Erkic M, Bailer J, Fenske SC, Schmidt SNL, Trojan J, Schröder A, et al. Impaired emotion processing and a reduction in trust in patients with somatic symptom disorder. Clin Psychol Psychother 2018;25:163-72.
[48] Eom JY, Shin M-K. Relation of alexithymia, anger and binge eating behavior. Int J Bio-Sci Bio-Technol 2016;8:63-70.

Isolated scapular tuberculosis: an uncommon presentation of skeletal tuberculosis

Ghanshyam Dev[1], Shwait Sharma[1], Mohd Ilyas[2]

[1]*Department of Radiodiagnosis, Government. Medical College, Jammu, India*
[2]*Department of Radiodiagnosis, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India*

DOI: 10.18621/eurj.387051

ABSTRACT

Objective: The main objective of the study was to evaluate the radiological manifestations of isolated scapular tuberculosis.

Methods: A prospective study was performed wherein 50 patients with the complaint of swelling in the scapular region were evaluated using various imaging modalities for scapular tuberculosis. Patients having features of scapular tuberculosis were subjected to fine needle aspiration cytology (FNAC) and histopathology for confirmation of diagnosis.

Results: Four patients were diagnosed as having isolated scapular tuberculosis. All the four patients presented with lytic lesions in scapula with associated collections in adjacent muscles. All were subjected to anti-tuberculosis therapy (ATT). In two patients drainage of abscess was done. All patients showed excellent response to treatment at 6 months follow-up.

Conclusion: Radiological investigations play a key role in early diagnosis of isolated scapular tuberculosis with excellent outcome with ATT and drainage of collection.

Keywords: Tuberculosis, lytic lesion, scapula, anti-tuberculosis therapy, musculoskeletal infections

Received: January 31, 2018; Accepted: February 23, 2018; Published Online: March 20, 2018

Scapula is a broad flat, triangular bone lying obliquely over the posterior aspect of chest wall at the first seven ribs. Like any other bone scapula is also affected by congenital, traumatic, neoplastic and infectious process [1]. Infectious process of the scapula is represented by osteomyelitis of the scapula and is a rare diagnosis. Most of the cases of lytic lesion of the scapula with associated swelling are due to benign or malignant pathology affecting the scapula. Only few reports of tubercular involvement of the scapula are available. Tuberculosis continues to be a major cause of morbidity and mortality from infectious diseases worldwide more so in endemic areas. Musculoskeletal infection may account for 10-30% of cases of extrapulmonary tuberculosis and overall for almost 2% of all cases of tuberculosis [2]. The spine is involved in approximately half of patients with musculoskeletal infections. The next most common is tuberculous arthritis followed by extra-spinal tuberculous osteomyelitis. Occurrence of tuberculosis in flat bones without any other foci is very rare. Less than 1% of skeletal tuberculosis occurs in the shoulder. Isolated scapular involvement in tuberculosis is very rare [3]. The aim of this study was to evaluate the radiological manifestations of isolated scapular tuberculosis.

Address for correspondence: *Ghanshyam Dev, Professor and Head, Govt. Medical College, Department of Radiodiagnosis, Jammu, 180001 India, E-mail: ilyasmir40@gmail.com, Tel: +91 941 9183783*

e-ISSN: 2149-3189

METHODS

This prospective study was performed over a period of two years (August 2015 to July 2017). Fifty patients with lytic lesion of the scapula along with associated swelling and pain in the shoulder and scapular region were evaluated with various radiological modalities including computed tomograhy (CT) scan, magnetic resonance imaging (MRI), and ultrasonography. After careful clinical history, physical examination and laboratory investigations, the patients were subjected to various radiological modalities for diagnosis of lytic lesion of the scapula. Out of the 50 patients, four patients were diagnosed with isolated tuberculosis of the scapula. The diagnosis was confirmed on histopathology. In all the patients a detailed clinical history, complete local and systemic examination was done followed by laboratory investigations. Informed consent was obtained from all the patients included in the study. Laboratory investigations included hemogram, total and differential counts, sputum exam, erythrocyte sedimentation rate (ESR) and Mantoux test. Radiological investigations included CT scan, MRI and ultrasonography. CT scan included contrast scan where required. MRI sequences included T1, T2, STIR and post-contrast sequences. All the patients were subjected to FNAC for confirmation of diagnosis on ZN staining & histopathology. After confirmation of diagnosis, all the four patients were given anti-tuberculosis therapy (ATT). In two out of four drainage of abscess was done for treatment. All the four patients showed excellent response to treatment at 6 months follow-up.

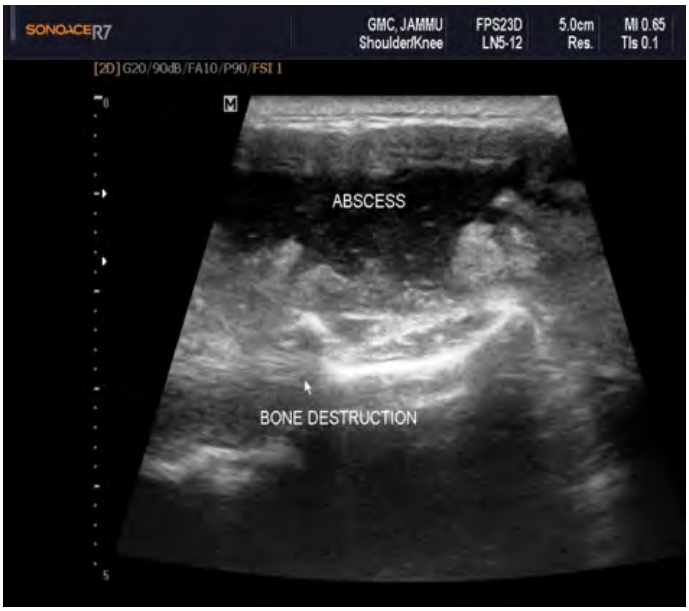


Figure 1. Linear ultrasound image of a patient with scapular tuberculosis showing scapular bone destruction with adjacent abscess in muscle.

RESULTS

All the four patients diagnosed with isolated scapular tuberculosis presented with swelling in the scapular region gradually increasing in size. In two patients it was associated with deep dull aching pain while in other two it was painless. One patient reported history of fever on & off. No history of weight loss, fatigue, loss of appetite or cough was present in all the four patients. One out of four patients was diabetic. On physical examination, all patients presented with a lobulated swelling over left scapular region. The swelling was non tender with firm

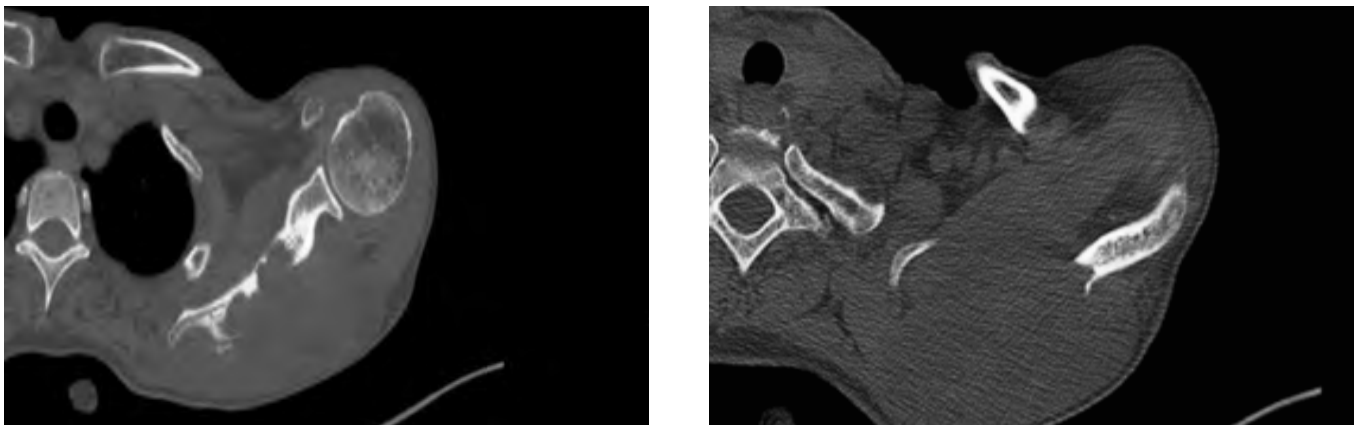


Figure 2. Non-contrast CT scan in axial plane in two patients showing lytic lesions with associated soft tissue collections.

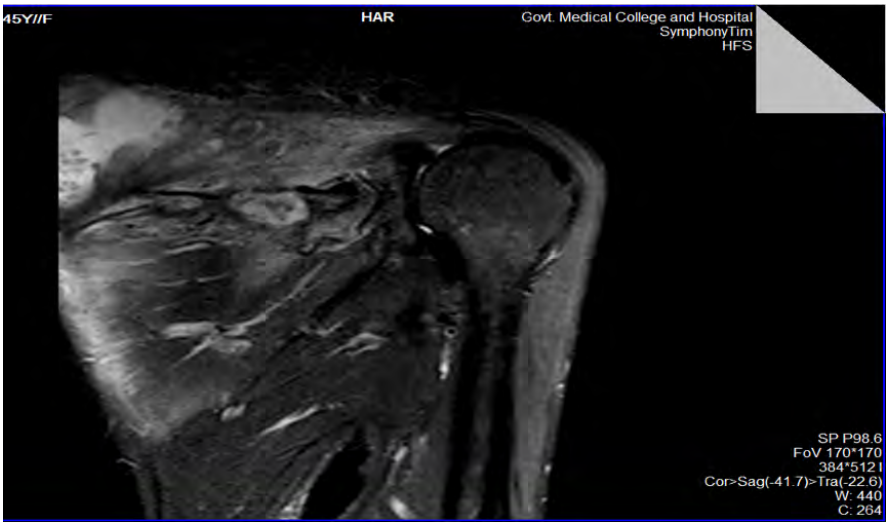


Figure 3. STIR weighted oblique coronal image of scapula showing scapular spine lytic lesion with associated edema in supra-spinatous and infra-spinatous muscle and adjacent collection.

consistency. Laboratory investigations revealed raised ESR and positive qualitative C-reactive protein (CRP) in all the four patients.

X ray of the shoulder region revealed lytic lesion involving the scapula with associated soft tissue swelling. Scapular blade was involved in two patients, one showed involvement of inferior angle while in fourth one spine and blade was involved. Glenoid was not involved in any case. Shoulder joint was normal in all the four cases. No lesion was evident in humerus in all cases.

Ultrasonography of the swelling in all four patients revealed an echoic collection in soft tissues around the scapula with no internal vascularity on colour Doppler. Associated bony destruction was evident (Figure 1).

CT scan was done in two out of the four patients. Both patients revealed lytic lesion involving the scapula (Figure 2). One patient showed involvement of scapular blade while in other both scapular spine and

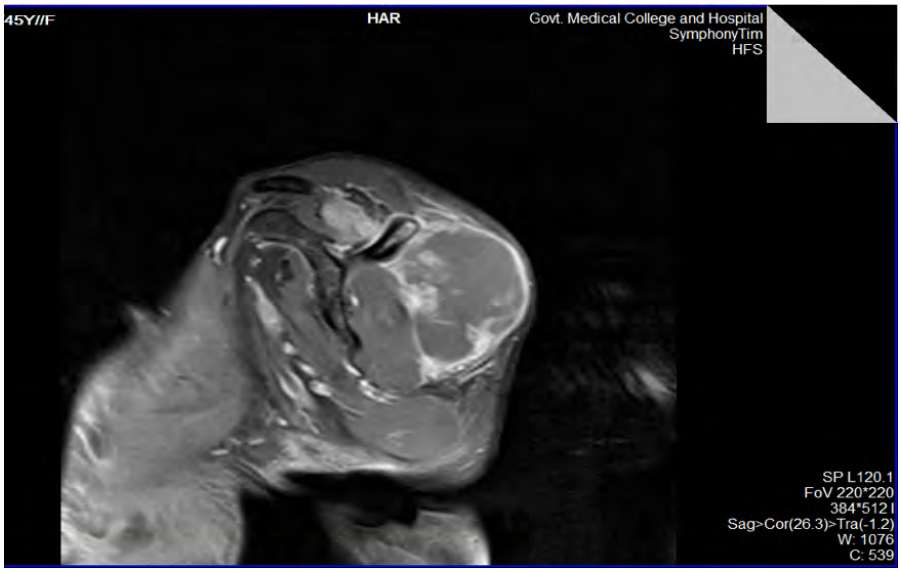


Figure 4. Post-contrast T1FS sagittal oblique MRI scan of the patients showing destruction of scapular blade and spine with associated collections in soft tissue.

blade were involved. In both the patients, glenoid was not involved. Shoulder joint was normal. Upper end of the humerus was normal. Associated collections in adjacent soft tissue were noted in both patients.

Contrast enhanced MRI was done in one out of four patients. T1, T2, STIR and post-contrast sequences were taken in axial, sagittal and coronal planes (Figures 3 and 4). MRI revealed destruction of the scapular spine with associated collections in supra-spinous fossa and in the axilla. Adjacent vertebral spine was normal.

The scapular tuberculosis is one of the rarest pathologies affecting the scapula and in the present study it accounted for only 8% patients. Three of these patients were males and one was female. The diabetic patient was female. The patients aged 34, 36, 50, and 48 years. None of these patients had any history of any pulmonary or extra-pulmonary tuberculosis.Three of these patients were living in the rural areas and one was from urban residence. All the investigations were effective in evaluation of the lesion.

DISCUSSION

Tuberculosis is an infection involving virtually every organ including skeletal system and is known since ages. Typical features of spinal tuberculosis have been seen in Egyptian mummies dating back to almost 4000 BC [4]. Musculoskeletal infection constitutes about 10-35% cases of extra-pulmonary tuberculosis and about 2% of all cases of tuberculosis. In the majority of patients, the spine is involved constituting about 50% cases. The next most common is tuberculous arthritis followed by extra-spinal tuberculous osteomyelitis [5]. Skeletal tuberculosis, especially isolated scapular tuberculosis, simulates a malignant lesion clinically and high suspicion is key to diagnosis [6]. Solitary tuberculous osteomyelitis involving flat membranous bones is a rare described entity. Very few cases of isolated scapular tuberculosis has been reported till date [7].

Clinically, scapular tuberculosis presents with pain and swelling in the scapular region. Restriction of movements of the shoulder may be present. Discharging sinus and constitutional symptoms are uncommon, making a diagnostic dilemma. Skeletal tuberculosis can appear as joint space narrowing, sub-chondral erosions, lytic lesions or articular osteopenia on plain radiographs [8]. Laboratory investigations reveal elevated ESR and CRP with lymphocytosis in few cases [2].

In our case series all the cases of scapular tuberculosis presented with pain and swelling in the scapular region. X-ray of the scapular region revealed lytic lesion of the scapula. Ultrasonography showed collection around the scapula. CT revealed lytic lesion of the scapula with adjacent collection in deep muscles around the scapula. MRI study revealed lysis of the scapula with adjacent peripherally enhancing collection.

Multimodality imaging approach play a key role in diagnosis of the scapular tuberculosis. High index of suspicion in appropriate clinical setting leads to early diagnosis in many cases enabling the timely initiation of therapy for better outcome. Surgical treatment of scapular tuberculosis involves drainage of collection. Sequestra of tuberculosis resolve with adequate ATT and surgical removal is not warranted [9]. Surgical removal is required in patients with giant sequestra or where the response to conservative treatment of 4 to 6 weeks is not satisfactory [10]. In our three out of four cases drainage of collection was done. However, surgical removal of sequestra was not required as all the four cases showed excellent response to drainage of collection and ATT. Differential diagnosis include other chronic skeletal infections such as brucellosis, actinomycosis, etc., and malignant pathologies including metastasis.

Tubercular osteomyelitis of the scapula is an extremely rare manifestation and atypical presentation at unusual site like the scapula, many a times may lead to misdiagnosis or delay in diagnosis [11]. The indolent nature of the disease and lack of constitutional symptoms often causes late presentation. Raised ESR and positive Monteux test are though consistent findings; these are not diagnostic of tuberculosis in endemic areas. Radiographic findings in tubercular osteomylitis include radiolucent lesion with irregular margin and surrounding sclerosis [12]. The cystic cavitary lesions on radiograph are highly nonspecific and simulate with pyogenic osteomylitis, fungal infection, metastasis, telengiectactic osteosarcoma, aneurysmal cyst, sarcoidosis, eosinophilic granuloma or chordoma. Differentiation of tuberculosis from all these

differentials may not be possible without tissue biopsy. MRI scan may be sometime deceptive [2]. In the present study, the MR showed peripheral enhancement of the collection in the scapula which was higly reflective of an infective pathology but final diagnosis was formulated only on histopathological analysis.

CONCLUSION

To conclude, isolated scapular tuberculosis is a rare entity. Very few cases are reported earlier. Radiological investigations play a key role in early diagnosis of isolated scapular tuberculosis with excellent outcome with ATT and drainage of collection. High index of suspicion in cases of destructive scapular mass with associated collections in adjacent muscles in appropriate clinical setting can lead to early diagnosis supported by appropriate radiological investigations and confirmed on biopsy and histopathology.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

REFERENCES

[1] Alvarez de Sierra Garcia B, Exposito Jimenez D, Bueno Horcajadas A, Olmedilla P, Sanz-Merino A, Martel Villagran J. Radiologic assessment of scapular region: US, MDCT and MR features. ECR 2012: C-1080, Madrid, Spain.
[2] Singh A, Chatterjee P, Pai MC, Chacko RT. Tuberculous osteomyelitis of the scapula masquerading as metastasis. J Radiol Case 2009;3:27-31.
[3] Mohan V, Danielsson L, Hosni G, Gupta RP. A case of tuberculosis of the scapula. Acta Orthop Scand 1991;62:79-80.
[4] Arriaza BT, Salo W, Aufderheide AC, Holcomb TA. Pre-Columbian tuberculosis in northern Chile: molecular and skeletal evidence. Am J Phys Anthropol 1995;98:37-45.
[5] Tuli SM. Tuberculosis of the Skeletal System (bones, joints, spine and bursal sheaths). 1st edn. Jaypee Brothers Medical Publishers (P) Ltd: New Delhi (India), 1993., p.121.
[6] Tsay MH, Chen MC, Jaung GY, Pang KK, Chen BF. Atypical skeletal tuberculosis mimicking tumor metastasis: report of a case. J Formos Med Assoc 1995; 94:428-31.
[7] Balaji G, Arockiaraj J, Roy AC, Ashok A. Isolated tubercular osteomyelitis of scapula – A report of two cases and review of literature. J Orthop Case Rep 2013;3:7-11.
[8] Teo HE, Peh WC. Skeletal tuberculosis in children. Pediatr Radiol 2004;34:853-60.
[9] Martini M, Adjrad A, Boudjemaa A. Tuberculous osteomyelitis. A review of 125 cases. Int Orthop 1986;10:201-7.
[10] Khan SA, Zahid M, Sharma B, Hasan AS. Tuberculosis of frontal bone: a case report. Indian J Tub 2001;48:95-6.
[11] Tripathy SK, Sen RK, Sharma A, Tamuk T. Isolated cystic tuberculosis of scapula: case report and review of literature. J Orthop Surg Res 2010;5:72.
[12] Kam WL, Leung YF, Chung OM, Wai YL. Tuberculous osteomyelitis of the scapula. Int Orthop 2000;24:301-2.

The European Research Journal 2018;4(4):294-299 ORIGINAL ARTICLE

Associations of glycated hemoglobin (HbA1c) level with central corneal and macular thickness in diabetic patients without macular edema

Kuddusi Teberik, Mehmet Tahir Eski, Murat Kaya

Department of Ophthalmology, Düzce University School of Medicine, Düzce, Turkey

DOI: 10.18621/eurj.362263

ABSTRACT

Objectives: To determine the correlation between central corneal thickness (CCT) and central macular thickness (CMT), and fasting plasma glucose levels and HbA1c levels before diabetic macular edema (DME) in type 2 diabetes mellitus (DM) patients without diabetic retinopathy.

Methods: Forty-four eyes of subjects diagnosed with type 2 DM, and 45 healthy control subjects participated in this study. Detailed ophthalmologic examination was performed with all participants. CMT was measured in both groups by Spectral-domain optical coherence tomography. CCT measurements were made with an Echoscan US-500 ultrasonic pachymeter. Blood biochemical tests for glycated hemoglobin (HbA1c) and fasting plasma glucose levels were run on all patients.

Results: The results of the study showed that the mean CCT was significantly thicker in type 2 DM patients 563.84 ± 33.25 µm than in the controls 550.13 ± 28.41 µm ($p = 0.039$). The mean of CMT was 231.27 ± 37.74 µm in the study group and 225.38 ± 38.33 µm in the control group ($p > 0.05$). No relationship was found between CCT and CMT and HbA1c level in the study and control groups.

Conclusions: The mean CCT was significantly thicker in type 2 DM patients without diabetic retinopathy than in the controls. The mean CMT is thicker in type 2 DM patients without diabetic retinopathy patients than in the controls, but this difference was not statistically significant. Optical coherence tomography can be a perfect detector for early detection of DME.

Keywords: Diabetic macular edema, HbA1c, fasting plasma glucose levels, central corneal thickness, central macular thickness

Received: December 5, 2017; Accepted: December 24, 2018; Published Online: March 31, 2018

Diabetic retinopathy is defined as a particular microvascular complication of diabetes and is the major reason of vision loss within the preferred populace in many nations, together with the employed adult population and the old aged [1-4]. It was estimated that diabetic retinopathy would spread to more than 200 million people around the world by 2012 [5]. It was estimated that in 2000, the spread rate of diabetes for all age groups worldwide would be 2.8% and 4.4% in 2030. It is thought that the number of patients with diabetes all over the world will increase from 171 million in 2000 to 366 million in 2030 [6].

Diabetes is associated with alterations in multiple layers of the retina. For example, it is observed that vascular leak [7, 8] and therefore diabetic retinopathy

Address for correspondence: *Kuddusi Teberik, MD., Assistant Professor Düzce University School of Medicine, Department of Ophthalmology, Düzce, Turkey*
E-mail: kuddusiteberik@yahoo.com, Phone: +90 505 636 13 15, Fax: +90 380 542 13 87

e-ISSN: 2149-3189

are caused by pericyte loss [9] and vascular endothelial damage [10].

Diabetic macular edema (DME) is the leading reason for visual acuity impairment in diabetic patients. DME is characterised by increased vascular permeability and accumulation of hard exudate in the central retina. DME can be seen at any phase of diabetic retinopathy [11]. DME has been noted to be seen in 10% of cases and is more common in type 2 diabetes mellitus (DM) than in type 1 [12]. DME affects the whole body adversely by prolonging the duration of diabetes, worsening glycemic control, increasing systolic blood pressure and serum lipids [13]. One way in which diabetic retinopathy can be prevented is through the systemic control of glycemia and tension in diabetic patients [2, 14]. The Diabetes Control and Complications Trial (DCCT) [15] and the United Kingdom Prospective Diabetes Study (UKPDS) [16] asserted that a tighter control of glycemia (intended glycated hemoglobin [HbA1c] level of < 7%) decrease the risk of growth and evolution of diabetic retinopathy and DME in type 1 DM and type 2 DM.

In diabetic cases, neovascular glaucoma, optical neuropathy, and front segment complications can also be observed besides retinopathy. 47-64% of diabetic patients show indications of corneal epitheliopathy even if it is not clinically a top priority [17]. Diabetes-related ocular surface and tear changes including corneal epitheliopathy are defined as "diabetic keratopathy" [17, 18]. There are corneal epithelial defects, recurrent corneal erosions, delayed epithelial recovery, corneal ulcer and dry eye disease in this range. Many studies point out that neurotrophic keratopathy is the main reason for corneal epithelial changes [19-21]. Despite the evidence of corneal epithelium and ocular surface changes in diabetic keratopathy, there are also wrinkles in the Descemet membrane and malformation and malfunction of the corneal endothelium [17, 18]. Increase in corneal stromal edema and central corneal thickness are observed more frequently in diabetic cases [22-24]. The increase in CCT has been claimed by some studies to be one of the earliest symptoms of the diabetic eye [25].

The aim of this study is to determine the correlation between CMT and CCT, and fasting plasma glucose levels and HbA1c levels before DME becomes clinically apparent in type 2 diabetic patients.

METHODS

Forty-four eyes of subjects diagnosed with type 2 DM, who were being followed by the endocrinology clinic, and 45 healthy control subjects participated in this study between January 2017 to June 2017. According to the principle of the declaration of Helsinki, the study was explained to the subjects and they were asked to sign a written informed consent. The research was approved by the local ethics committee. Information about the duration of diabetes was by self-report based on the date of detection by a medical practitioner. On each patient's first visit, a detailed systemic and ophthalmological medical history was taken, visual acuity was measured with the chart at 4 meters, a slit-lamp examination was performed, intraocular pressure was measured with Goldmann applanation tonometry, and a dilated fundus examination with a 90D lens was undertaken.

The central macular thickness (CMT) was measured in both groups by Spectral-domain optical coherence tomography (Heidelberg Engineering, Heidelberg, Germany). The CMT was measured after providing pupil dilation with tropicamide drops 2 times, 10 minutes before measurements (Tropicamide 1%, Alcon Lab. Inc., USA). After receiving measurements with spectral-domain optical coherence tomography, 0.5% proparacaine hydrochloride (Alcaine, Alcon Laboratories Inc., Fort Worth, TX, ABD) was applied for topical anesthesia. Approximately 5 minutes later, CCT measurements were made with an Echoscan US-500 ultrasonic pachymeter (Nidek Co. Ltd, Aichi, Japan). Participants were asked to fix their gaze on a target during contact measurements, and the pachymetry probe was placed in the central cornea as steeply and gently as possible. During contact process, the probe tips and the double prism were disinfected with 3% hydrogen peroxide. Measurements were taken in the morning (between the hours of 9:00 am and 11:00 am). All procedures were performed by the same physician. Blood biochemical tests for HbA1c and fasting plasma glucose levels were run on all patients. All cases were subjected to HbA1c testing on the day of the ophthalmic examination.

Exclusion criteria included patients who received intraocular surgery (cataract surgery, pars plana vitrectomy, intravitreal injection of triamcinolone or Bevacizumab), keratoconus, contact lens use, glaucoma, dry eye, pseudoexfoliation syndrome, previous anterior segment surgery, rubeosis iridis, subtenon injection, photocoagulation therapy within 1 year of evaluation and severe vitreous hemorrhage or vitreous opacity that would interfere with the optical coherence tomography examination. Inclusion criteria for the study group included no visible findings of diabetic retinopathy (hard-soft exudate, microaneurysms) on retina at slit-lamp fundus examination with a +90D lens, type 2 DM, no other problems (such as hypertension, uveitis), and no history of ocular trauma, and high refractive errors (spherical equivalent between +1.00D and −1.00 D). Inclusion criteria for the control group patients included no ophthalmologic or systemic problems, no history of intraocular surgery or treatment of the retina, and no high refractive errors (spherical equivalent: between −1.0D and +1.0D).

Statistical Analysis

Statistical analyses were performed with SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). Gender distribution between the groups was investigated by a chi-square test. The distribution of age and HbA1c values were evaluated by one-way ANOVA. Independent sample tests were used to compare the means between the diabetic and control groups. Pearson's correlationanalyses were conducted to evaluate the relationship between the parameters showing normal distribution, and Spearman's rho correlation analyses have been used to evaluate the correlation between the parameters not showing normal distribution. The level of significance was set at $p < 0.05$.

RESULTS

Of the 44 Type 2 DM patients included in the study, 24 were male (54.5%) and 20 (45.5%) were female and the mean age was 60.11 ± 8.17 (47-76). Twenty-one (46.7%) of the control group were male and 24 (53.3%) were female and the mean age was 59.40 ± 5.1 years (range, 50-70 years). There were no differences in sex, age and best corrected visual acuity (BCVA) between the groups ($p > 0.05$).

The results of the study showed that the mean CCT was significantly thicker in type 2 DM patients 563.84 ± 33.25 µm than in the controls 550.13 ± 28.41 µm ($p = 0.039$). The mean of CMT was 231.27 ± 37.74 µm in the study group and 225.38 ± 38.33 µm in the control group ($p > 0.05$).

The mean HbA1c level was 7.92 ± 1.69% in the study group and 5.18 ± 0.51% in the control group. The mean level of HbA1c was statistically higher in the study group than in the control group ($p = 0.001$). Fasting plasma glucose level was statistically higher in the study group than in the control group ($p = 0.001$). The duration of diabetes mellitus was 13.45 ± 5.5 years (range, 3-27 years) (Table 1).

No correlation was found between CCT and fasting plasma glucose level in the study ($p = 0.415$) and control ($p = 0.342$) groups. No relationship was found between CCT and HbA1c level in the study (*p*

Table 1. Demographic characteristics, values for CCT, CMT, and biochemical analysis in patients with type 2 diabetes without clinical retinopathy

Parameters	Study group ($n = 44$)	Control group ($n = 45$)	*p* value
BCVA (logMAR)	0	0	NS
IOP (mmHg)	15.0 ± 2.7	15.8 ± 2.1	NS
Age (years)	60.11 ± 8.17	59.40 ± 5.1	NS
Male/ Female	24/20	21/24	NS
CCT (µm)	563.84 ± 33.25	550.13 ± 28.41	**0.039**
CMT (µm)	231.27 ± 37.74	225.38 ± 38.33	NS
HbA1c (%)	7.92 ± 1.69	5.18 ± 0.51	**0.001**
Fasting blood glucose level (mg/100 ml)	213.09 ± 81.28	89.46 ± 13.92	**0.001**

Data are shown as mean±standard deviation or number. BCVA = best corrected visual acuity, CCT = central corneal thickness, CMT = central macular thickness, Control group = healthy subjects, HbA1c = glycated hemoglobin, IOP = Intraocular pressure, logMAR = logarithm of the minimum angle of resolution, NS = nonsignificant, Study group = patients with type 2 diabetes without clinical retinopathy

Table 2. Relationship between CCT, CMT, HbA1c, fasting blood glucose levels, and duration of DM in patients with type 2 diabetes without clinical retinopathy

Parameters	Study group		Control group	
	r	*p value*	r	*p value*
CCT-HbA1c	0.284	0.062	0.122	0.424
CCT-fasting plasma glucose level	0.126	0.415	0.145	0.342
CCT-duration of DM	0.077	0.617	-	-
CMT-HbA1c	-0.031	0.841	0.025	0.870
CMT-fasting plasma glucose level	-0,07	0.649	0.111	0.469
CMT-duration of DM	0.074	0.634	-	-

CCT = central corneal thickness, CMT = central macular thickness, Control group = healthy subjects, DM = diabetes mellitus, HbA1c = glycated hemoglobin, *r* = relation between two variables, Study group = patients with type 2 diabetes without clinical retinopathy,

= 0.062) and control groups (p = 0.424). No relationship was found between CMT and fasting plasma glucose level in the study (p = 0.649) and control (p = 0.469) groups. No relationship was found between CMT and HbA1c level in the study (p = 0.841) and control groups (p = 0.870; Table 2).

DISCUSSION

DM can affect almost all ocular structure. DM does not only lead to an ocular complication, diabetic retinopathy, but it is also believed to lead to some changes in the anterior segment of the eye [26, 27]. Examples of these abnormalities are a decrease in endothelial cell density and hexagonality, and an increase in polymegathism, pleomorphism and CCT [23, 28]. In this study, ultrasonic pachymeter examinations were performed in type 2 diabetic patients without DME. The mean CCT was significantly thicker in type 2 DM patients than in the controls. Additionally, no statistically significant relationship was found between CCT, HbA1c, and fasting plasma glucose level in either group.

Many studies have used specular microscopy and shown that DM-diagnosed patients have many structural changes in the corneal endothelium compared to healthy individuals [29, 30]. It is stated that hyperglycemia affects the corneal thickness in diabetic patients by impairing corneal hydration, thereby destroying the corneal structure by McNamara *et al*. [32]. Schultz *et al*. [29] examined the barrier and pump function of corneal endothelium using a fluorometric method and found that there were some deficiencies as a result. Consequently, it has been claimed that change in corneal thickness is common in patients with DM. As reported by the results of Herse's experimental study [32], the evaluated fall in Na+/K+ ATPase activity of diabetic rabbits proves that abnormal corneal hydration system of the diabetic rabbits which are not controlled is managed by a functional disorder of endothelial fluid pump. The biological basis of corneal changes in the eyes of diabetic patients is not yet found and the underlying mechanisms are still unknown. Su *et al*. [33] studied the association of diabetes and hyperglycemia with CCT in 3239 eyes where 748 diabetic patients participated and showed a 6.5 μm thicker CCT than the healthy group in non-diabetic patients. Lee *et al*. [23] found that CCT was higher in patients with DM than in the control group, as a result of studying the CCT of diabetic patients with normal fundus and DR history. Inoue *et al*. [24] and Choo *et al*. [11] reported that diabetic group CCT data did not show any significant difference from control groups. According to the results of the study conducted by Ozdamar *et al*. [34], CCT values in diabetic group were significantly higher than the control group. The same study shows no correlation between HbA1c and CCT. Although HbA1c is a marker of long-term DM control, we assume that high glucose levels may lead to corneal thickening than at any other time in the life of a diabetic patient.

The relationship between CMT, HbA1c and fasting plasma glucose levels was also observed in patients with type 2 diabetes who did not have clinical diabetic retinopathy in our study. Although the mean CMT was thicker in type 2 DM patients without diabetic retinopathy compared to healthy subjects, this difference was not statistically significant. There was no positive correlation between fasting plasma glucose level and CMT in patients with diabetes mellitus and

without retinopathy. CMT was not increased by mild or high levels of HbA1c (7.92 ± 1.69%). CCT and CMT were not affected by the duration of diabetes mellitus in patients with diabetes type 2 without retinopathy.

Browning *et al*. [35] reported in their study that in patients without clinically macular edema in spite of being diagnosed with diabetic retinopathy, especially the variations in central subfield macular thickness and total macular volume (TMV) in optical coherence tomography were not greater than the measurement variation in eyes with or without DME. It was stated that the changes, which are more than 10% compared to the initial macular thickness, should be considered as a real change, whereas the remaining values could be due to measurement variations, diurnal variations, or variations of the long-lasting scale. Sugimoto *et al*. [36] found that the retinal thickness increased and the retinal nerve fiber layer thickness decreased in the superior quadrant in the eyes of patients with non-diabetic retinopathy in the study they tried to confirm early diabetic injury and evaluate optical coherence tomography as a clinical test. They also reported that it is possible to detect early signs and structural changes with optical coherence tomography at a much earlier stage and that optical coherence tomography can be used in early treatment planning. Bressler *et al*. [37] determined in their studies evaluating macular thickness with optical coherence tomography in type 1 and type 2 diabetic patients without retinopathy or with very mild retinopathy and no macular thickening on clinical examination that the macular thickness values of these diabetic patients without retinopathy or with very mild retinopathy were similar to those of normal individuals but found that the average central subfield thickness in males was statistically significantly higher than that of females (209 ± 18 μm vs. 194 ± 23 μm).

Glycemic control is critical for DM treatment and can be assessed periodically by HbA1c measurement. Chou *et al*. [11] demonstrated that 8% or more of HbA1c in diabetic retinopathy-diagnosed diabetic patients is associated with an increase in macular thickness. Moreira *et al*. [38] demonstrated that no other variables other than HbA1c were associated significantly with macular edema. According to the findings of the Los Angeles Latino Eye Study (LALES), there is a 22% increase in the spread of diabetic retinopathy and a 1% increase in HbA1c level [39]. The Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR) reported that the presence of high levels of HbA1c increased the risk of developing DME within a 10-year period [40]. The most widely accepted pathophysiological model for diabetic retinopathy development involves microvascular dysfunction. Abnormalities in glucose metabolism lead to changes in the capillary vessels of the retina and deterioration of the blood/retinal barrier, resulting in microaneurysms, hemorrhages, and retinal exudate. These retinal changes cause retinal thickening that can be detected with 0ptical coherence tomography. Since HbA1c levels were recorded for only 3 months, it is difficult for this study to determine whether the positive correlation between chronic HbA1c level and macular thickness is more harmful to microvasculature caused by high chronic hyperglycemia.

The Limitations of the Study

There are limitations to the study. One of these is the small sample size in both groups and another is that none of the patients had diabetes mellitus for longer than 20 years.

CONCLUSION

In this study, the mean CCT was significantly thicker in type 2 DM patients without diabetic retinopathy than in the controls. The mean CMT is thicker in type 2 DM patients without diabetic retinopathy than in the controls, but this difference was not statistically significant. No correlation between HbA1c, fasting plasma glucose levels and duration of DM was found with both CCT and CMT. Optical coherence tomography can be a perfect detector for early detection of DME.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. N Engl J Med 2012;366:1227-39.
[2] Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010;376: 24-36.
[3] Klein R, Lee KE, Gangnon RE, Klein BE. The 25-year incidence of visual impairment in type 1 diabetes mellitus. the wisconsin epidemiologic study of diabetic retinopathy. Ophthalmology 2010;117 63-70.
[4] Moss SE, Klein R, Klein BE. The 14-year incidence of visual loss in a diabetic population. Ophthalmology 1998;105:998-1003.
[5] Chu J, Ali Y. Diabetic retinopathy. Drug Deve Res 2008;69:1-14.
[6] Wild S, Roglic G, Greene A. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-53.
[7] Matsuura H, Setogawa T, Tamai A. Electron microscopic studies on retinal capillaries in human diabetic retinopathy. Yonago Acta Med 1976;20:7-10.
[8] Antonetti DA, Lieth E, Barber AJ, Gardner TW. Molecular mechanisms of vascular permeability in diabetic retinopathy. Semin Ophthalmol 1999;14:240-8.
[9] de Oliveira F. Pericytes in diabetic retinopathy. Br J Ophthalmol 1966;50:134-43.
[10] Craitoiu S, Mocanu C, Olaru C, Rodica M. Retinal vascular lesions in diabetic retinopathy. Oftalmologia 2005;49:82-7.
[11] Chou TH, Wu PC, Kuo JZ, Lai CH, Kuo CN. Relationship of diabetic macular oedema with glycosylated haemoglobin. Eye (Lond) 2009;23:1360-3.
[12] GirachA, Lund-Andersen H. Diabetic macular oedema: a clinical overview. Int J Clin Pract 2007;61:88-97.
[13] Wat N, Wong RL, Wong IY. Associations between diabetic retinopathy and systemic risk factors. Hong Kong Med J 2016;22:589-99.
[14] Frank RN. Diabetic retinopathy. N Engl J Med 2004;350:48-58.
[15] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
[16] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 1998;352:837-53.
[17] Schultz RO, Van Horn DL, Peters MA, Klewin KM, Schutten WH. Diabetic keratopathy. Trans Am Ophthalmol Soc 1981;79:180-99.
[18] Kaji Y. Prevention of diabetic keratopathy. Br J Ophthalmol 2005;89:254-5.
[19] Saito J, Enoki M, Hara M, Morishige N, Chikama T, Nishida T. Correlation of corneal sensation, but not of basal or reflex tear secretion, with the stage of diabetic retinopathy. Cornea 2003;22:15-8.
[20] Zhivov A, Winter K, Hovakimyan M, Peschel S, Harder V, Schober HC, et al. Imaging and quantification of subbasal nerve plexus in healthy volunteers and diabetic patients with or without retinopathy. PLoS One 2013;8:e52157.
[21] Chang PY, Carrel H, Huang JS,Wang IJ, Hou YC, Chen WL, et al. Decreased density of corneal basal epithelium and subbasal corneal nerve bundle changes in patients with diabetic retinopathy. Am Ophthalmol 2006;142:488-90.
[22] Siribunkum J, Kosrirukvongs P, Singalavanija A. Corneal abnormalities in diabetes. J Med Assoc Thai 2001;84:1075-83.
[23] Lee JS, Oum BS, Choi HY, Lee JE, Cho BM. Differences in corneal thickness and corneal endothelium related to duration in diabetes. Eye 2006;20:315-8.
[24] Inoue K, Kato S, Inoue Y, Amano S, Oshika T. The corneal endothelium and thickness in type II diabetes mellitus. Jpn J Ophthalmol 2002;46:65-9.
[25] Busted N, Olsen T, Schmitz O. Clinical observations on the corneal thickness and the corneal endothelium in diabetes mellitus. Br J Ophthalmol 1981;65:687-90.
[26] Wiemer NG, Dubbelman M, Kostense PJ, Ringens PJ, Polak BC. The influence of chronic diabetes mellitus on the thickness and the shape of the anterior and posterior surface of the cornea. Cornea 2007;26:1165-70.
[27] Wiemer NG, Dubbelman M, Hermans EA, Ringens PJ, Polak BC. Changes in the internal structure of the human crystalline lens with diabetes mellitus type 1 and type 2. Ophthalmology 2008;115:2017-23.
[28] Shenoy R, Khandekar R, Bialasiewicz A, Al Muniri A. Corneal endothelium in patients with diabetes mellitus: a historical cohort study. Eur J Ophthalmol 2009;19:369-75.
[29] Schultz RO, Matsuda M, Yee R, Edelhauser HF, Schultz KJ. Corneal endothelial changes in type 1 and 2 diabetes mellitus. Am J Ophthalmol 1984;98:401-10.
[30] Torun B, Ülkü G, Yılmaz T. [Evaluation of central corneal thickness in patients with diabetes mellitus]. Fırat Tıp Dergisi 2010;15:128-30. [Article in Turkish]
[31] McNamara NA, Brand RJ, Polse KA, Bourne WM. Corneal function during normal and high serum glucose levels in diabetes. Invest Ophthalmol Vis Sci 1998;39:3-17.
[32] Herse PR. Corneal hydration control in normal and alloxan induced diabetic rabbits. Invest Ophthalmol Vis Sci 1990;31:2205-13.
[33] Su DH, Wong TY, Wong WL, Saw SM, Tan DT, Shen SY, et al. Singapore Malay Eye Study Group. Diabetes, hyperglycemia, and central corneal thickness: the Singapore Malay Eye Study. Ophthalmology 2008;115:964-8.
[34] Ozdamar Y, Cankaya B, Ozalp S, Acaroglu G, Karakaya J, Ozkan SS. Is there a correlation between diabetes mellitus and central corneal thickness? J Glaucoma 2010;19:613-6.
[35] Browning DJ, Fraser CM, Propst BW. The variation in optical coherence tomography-measured macular thickness in diabetic eyes without clinical macular edema. Am J Ophthalmol 2008;145:889-93.
[36] Sugimoto M, Sasoh M, Ido M, Wakitani Y, Takahashi C, Uji Y. Detection of early diabetic change with optical coherence tomography in type 2 diabetes mellitus patients without retinopathy. Ophthalmologica 2005;219:379-85.
[37] Bressler NM, Edwards AR, Antoszyk AN, Beck RW, Browning DJ, Ciardella AP, et al. Diabetic Retinopathy Clinical Research Network. Retinal thickness on Stratus optical coherence tomography in people with diabetes and minimal or no diabetic retinopathy. Am J Ophthalmol 2008;145:894-901.
[38] Moreira RO, Trujillo FR, Meirelles RM, Ellinger VC, Zagury L. Use of optical coherence tomography (OCT) and indirect ophthalmoscopy in the diagnosis of macular edema in diabetic patients. Int Ophthalmol 2001;24:331-6.
[39] Varma R, Macias GL, Torres M, Klein R, Klein R, Peña FY, et al.; Los Angeles Latino Eye Study Group. Biologic risk factors associated with diabetic retinopathy: the Los Angeles Latino Eye Study. Ophthalmology 2007;114:1332-40.
[40] Klein R, Klein BEK, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. Ophthalmology 1995;102:7-16.

The European Research Journal 2018;4(4):300-307 ORIGINAL ARTICLE

The experience of anesthesia during kidney transplantation with robot assisted laparoscopic surgery

Yasemin Tekdöş Şeker, Nalan Saygı Emir, Oya Hergünsel, Evrim Tülübaş, Figen Öztürk, Derya Mandacı

Department of Anesthesia and Reanimation, University of Health Sciences, Bakırköy Dr. Sadi KonukTraining and Research Hospital, İstanbul, Turkey

DOI: 10.18621/eurj.356547

ABSTRACT

Objective: Renal transplantation is the most commonly used method to improve the quality of life of patients with end-stage renal failure. Kidney transplantation began in our hospital in 2016 with robot-assisted laparoscopic surgery (RALS). Here, we retrospectively compared the RALS technique and open surgery with respect to anesthesia management during kidney transplant operations done in our clinic.

Methods: Anesthesia management, the duration of the operation and of vascular anastomosis, the amount of fluid delivered perioperatively, amount of urine, and diuretic requirements were investigated retrospectively in cases of renal transplantation (Group O, open surgical technique, n = 22; Group R, RALS technique, n = 14). Blood gas values, and lactate, bicarbonate, glucose, and electrolyte levels, were examined preoperatively after extubation.

Results: The durations of surgery and vascular anastomosis were significantly longer in Group R than in Group O ($p < 0.05$). Perioperative liquid volume was not significantly different between Groups R and A. Postoperative systolic arterial pressure was significantly higher in Group R than in Group O. As venous blood samples were obtained in Group O and arterial blood samples were obtained in Group R, blood gas parameters were evaluated within, but not between, groups. The pH and HCO_3 values at the end of the operation were significantly lower, while the lactate level was significantly higher, in Group O compared to Group R ($p < 0.001$). There was a significant decrease in calcium level at the end of the operation versus pre-anesthesia induction in Group O, but no significant increase in the glucose level was found. There were no significant differences in sodium or potassium levels within or between the groups ($p > 0.05$).

Conclusions: The surgical superiority of RALS technique is known. However, anesthesia management in this patient group is difficult due to the risk of the Trendelenburg position and pneumoperitoneum

Keywords: robotic surgical procedures, kidney transplantation anesthesia, pneumoperitoneum, head-down tilt

Received: November 20, 2017; Accepted: February 4, 2018 ; Published Online: February 28, 2018

Chronic kidney disease (CKD) is defined as kidney damage in which the glomerular filtration rate (GFR) is < 60 mL/min for ≥3 months. A GFR of <1 5 mL/min is defined as end-stage renal disease (ESRD) [1]. Today's most effective treatment for ESRD is known as renal transplantation in eligible patients. Cadaveric donor kidney transplantation has been implemented with increasing success rates since

Address for correspondence: *Yasemin Tekdöş Şeker, MD., University of Health Sciences, Bakırköy Dr. Sadi KonukTraining and Research Hospital, Department of Anesthesia and Reanimation, İstanbul, Turkey*
E-mail: yasemintekdos@gmail.com

e-ISSN: 2149-3189

1945, and live donor kidney transplantation has been increasing since 1954 [2, 3]. Renal transplantation with classic open surgery for many years has been successfully accomplished with laparoscopic and robotic assisted laparoscopic surgery (RALS) methods with the help of developing technology and increasing laparoscopy experience [4]. Laparoscopic donor nephrectomy has significant advantages such as less pain, premature mobilization and reduction in hospital stay [4, 5].

The first robot-assisted laparoscopic kidney transplant was performed successfully in 2002, in a 26-year-old man, by Hoznek *et al.* [6]. Kidney transplantation has been carried out in our hospital since 2011. The first RALS was performed in our hospital in December 2015, and kidney transplantation with the RALS procedure has since entered into our daily practice.

Experience with nephrectomy and renal transplantation is new with RALS, which is becoming widespread with the use of laparoscopic robot assisted addition with advancing technology. Anesthesia management of patients with RALS shows various differences from open surgery [7].

Open surgical management of renal transplantation, laparoscopic and RALS techniques shows some differences. For this reason, evaluation of the characteristics of anesthesia methods applied for open surgery and RALS method is preliminary.

There are many studies related to anesthesia management of RALS and open surgical procedures. However, there are no similar studies evaluating the management of anesthesia in patients undergoing nephrectomy and renal transplantation. Here, we compared the anesthesia management of 22 open renal transplant surgeries and 14 RALS in cases of ESRD.

METHODS

After obtaining approval from our ethics committee, we performed a retrospective comparison of 22 renal transplantation cases using open surgical techniques (Group O) and 14 robot-assisted laparoscopic surgical cases (Group R) in 2016. Demographic data, total duration of the operation, duration of vascular anastomosis, perioperative fluid volume, perioperative urine output, and diuretic requirements were evaluated. Blood gas values, and lactate, bicarbonate, glucose, sodium, potassium, and calcium levels, were examined before and after induction of anesthesia. Both groups were subject to standard electrocardiography (ECG) and peripheral O_2 saturation monitoring. Noninvasive blood pressure monitoring was used at Group O, invasive blood pressure monitoring was used at Group R. In Group O, four vessels were open intravenously with an 18 Gauge (G) silicone cannula (BICAKCILAR B-CAT2 18 G). The cannula at the distal end was always closed for venous blood gas monitoring. Isotonic infusion into the third vessel was started and the other vessels received anti-human thymocyte globulin (ATG-Fresenius S® 20 mgr/5mL; Fresenius Kabi, Richmond Hill, ON, Canada) and remifentanil infusion. Arterial blood pressure was measured noninvasively. In Group R, two vascular accesses were opened with an 18 G cannula. In Group R both arms were closed. In both groups, 1.5 mg Midazolam (Dormicum®, Roche, Germany), 50 mcg Fentanyl (Fentanyl 50 mcg/mL solution®, Mercury, Ireland), 1 g Acetaminophen, and 100 mg tramadol were administered as premedication. Radial artery cannulation was performed with an 18 G cannula (Seldicath, 1.2 mm; Plastimed, Saint-Leu-La-Forêt, France) with local anesthesia. The arm where fistula is found did not use for monitorization. Blood gases were determined before anesthesia induction in both groups.

Subsequently, induction with 0.05 mg/kg Midazolam, 1 mg/kg Propofol (Diprivan® 10 mg/mL, Fresenius Kabi, USA,), 1.5 mcgr/kg Fentanyl, and 0.5 mg/kg Atracurium besylate (Tracrium® 10 mg/mL, GlaxoSmithKline, Australia) was performed, followed after 120 s by orotracheal intubation. Ventilation was performed with a ventilator (Maquet™©, Germany) in pressure-regulated volume control (PRVC) mode with FiO_2 < 40%, respiratory frequency of 14/min, a positive end-expiratory pressure (PEEP) of 5, and 7 kg/mL vidal volume. Group O were placed in a slightly supine Trendelenburg position, while Group R had a Trendelenburg position ~45° deep. Anesthesia was administered with remifentanil hydrochloride (Ultiva® 5 mg/10 mL, Glaxo Smith Kline, Australia) at 0.1-0.5 mcgr/kg/min and sevoflurane (Sevoflurane® 250 mL, Baxter, Australia). Infusion of ATG was performed, and 500 mg methylprednisolone was administered. After completion of venous

anastomoses, all patients were resuscitated by crystalloid-based fluid replacement. Blood gases were determined at the end of the operation after extubation.

Statistical Analysis

In the statistical assessment and the analysis of the study, SPSS (ver. 22.0; IBM Corp., Armonk, NY, USA) and PAST 3 software (Hammer *et al*. [8], 2001) programs were used. The conformity of the data with a single variety to the normal distribution was assessed with Shapiro-Wilk and of the data with multiple variables with Mardia (Dornik and Hansen Omnibus), and for the homogeneity of the variety the Levene test was made. In the comparison of the two independent groups with each other based on the quantitative data, the Independent-Sample *t* test was used together with the results of Bootstrap, and the Mann-Whitney U test with those of Monte Carlo. In order to investigate the interaction of the dependent variables with those of the repetitive quantitative measurements according to the groups, the general linear model-repeated anova test was used with the results of the Bootstrap. In the comparison of the categoric variables together with each other, the Fisher exact was also tested with the results of the exact. The quantitative variables were shown in the tables as mean ± standard deviation (SD.) and median range (minimum-maximum) and the categoric ones as n (%). The variables were investigated as being 95% correct, and the *p* value less than 0.05 was taken meaningful statistically.

RESULTS

Group O consisted of 22 patients including 14 (63.6%) men and 8 (36.7%) women, Group R consisted of 14 patients including 7 (50%) men and 7 (50%) women. The mean age of the 22 patients in Group O was 44.59 ± 12.32 years, and that of the 14 patients in Group R was 37.58 ± 10.2 years. There were no statistically significant differences between the two groups for age ($p = 0.085$) and gender ($p = 0.418$) (Table 1).

The mean duration of operation was 351.82 ± 67.52 min in Group O and 412.86 ± 88.85 min in Group R (Table 2). The difference in the mean duration of operation between the two groups was statistically significant ($p = 0.048$). The mean duration of vascular anastomosis was significantly longer in Group R than in Group O (34 min vs. 25 min, respectively; $p = 0.004$) (Table 2).

Group O received total 4500 cc fluid and Group R received total 2700 cc fluid during the perioperative period. The difference between the total fluid volumes of the groups was significant and the volume of fluid given during the operation period of Group R was found to be very low ($p < 0.001$). The total liquid usage of the groups is shown in Table 2.

Duration time of operations and anastomosis, total fluid, diuretic requirement of the groups are shown in Table 2. There were not found statistically significant difference about need to use perioperative diuretics

Table 1. Demographic data for groups.

	Group A (n = 22)	Group R (n = 14)	*p* value
Age (year)	44.59 ± 12.32	37.58 ± 10.20	0.085
Gender			0.418
Female	8 (36%)	7 (50%)	
Male	14 (64%)	7 (50%)	

Data are shown as mean ± standard deviation or n (%) or median.

Table 2. Operation time of groups, duration of anastomosis, fluid management.

	Group A (n = 22)	Group R (n = 14)	*p* value
Operation time (min)	351.82 ± 67.52	412.86 ± 88.85	**0.048**
Vascular anastomosis time (min)	5 (53-13)	34 (50-21)	**0.004**
Total fluid replacement (ml)	4500 (10000-2600)	2700 (3800-1650)	**< 0.001**
Urine output (ml)	300 (3300-0)	250 (1300-0)	0.067
Diuretic requirement			
No	18 (81.8%)	12 (85.7%)	1.000
Yes	4 (18.2%)	2 (14.3%)	

Data are shown as mean ± standard deviation or n (%) or median (minimum-maximum).

and urine output in the both groups (p = 1.000 and p = 0.067, respectively) (Table 2).

The difference between pre-induction and post-operative blood gas pH values of Group O patients was statistically significant. (p = 0.01) (Table 3). In Group R, however, the pH showed a significant decrease at the end of the operation (pre-induction pH = 7.41 ± 0.09, postoperative pH = 7.31 ± 0.05; p = 0.004) (Table 3).

The PCO_2 and PO_2 values of both groups are shown in Tables 3 and 4. In Group O, there was no significant difference between the preinduction and postoperative PCO_2 (38.67 ± 5.479 mmHg and 41.19 ± 6.06 mmHg, respectively; p = 0.053), while PO_2 decreased significantly from a preinduction value of 106±0.5 mmHg to a postoperative value of 85.95 ± 45.57 mmHg (p=0.03) (Table 3). Group R showed no significant changes in PCO_2 (p > 0.05) or PO_2 (p >

Table 3. Blood gases, lactate, sodium, calcium, red blood cells, hemodynamic parametres

	Time	Group O (n= 22)	Group R (n= 14)	p^1
	1	1.05 ± 0.08	1.02 ± 0.09	0.279
Calcium	3	0.96 ± 0.09	1.01 ± 0.09	0.091
	(1-3)	0.09 ± 0.09	0.01 ± 0.10	**0.010**
p^2		**0.003**	**0.785**	
	1	10.61 ± 1.33	10.25 ± 2.03	0.519
Hemoglobin	3	9.61 ± 1.75	9.59 ± 1.82	0.970
	(1-3)	1.00 ± 1.29	0.66 ± 1.25	0.447
p^2		**0.003**	**0.80**	
	1	21.84 ± 3.75	22.81 ± 2.87	0.415
HCO_3	3	17.76 ± 2.71	19.55 ± 2.49	**0.048**
	(1-3)	4.08 ± 2.69	3.26 ± 3.34	0.465
p^2		**0.001**	**0.002**	
	1	31.27 ± 3.99	30.43 ± 5.98	0.614
Hematocrit (Hct) %	3	28.18±5.16	28.07 ± 5.36	0.951
	(1-3)	3.09 ± 3.79	2.36 ± 3.95	0.581
p^2		**0.001**	**0.046**	
	1	135.20 ± 3.39	135.64 ± 2.56	0.679
Sodium	3	136.32 ± 4.55	136.22 ± 3.11	0.947
	(1-3)	-1.12 ± 3.02	-0.58 ± 2.94	0.589
p^2		**0.098**	0.479	
	1	7.36 ± 0.07	7.41 ± 0.09	**0.128**
pH	3	7.25 ± 0.06	7.31 ± 0.05	**0.003**
	(1-3)	0.11 ± 0.07	0.10 ± 0.11	0.691
p^2		**0.001**	**0.004**	
	1	106.05 ± 57.98	154.02 ± 50.29	**0.015**
PO_2	3	85.95 ± 45.57	146.62 ± 64.61	**0.005**
	(1-3)	20.10 ± 38.55	7.40 ± 83.93	0.574
p^2		**0.030**	**0.751**	
	1	136.68 ± 30.04	158.21 ± 23.99	**0.034**
Sistolic blood pressure	3	138.86 ± 19.81	156.29 ± 26.60	**0.041**
	(1-3)	-2.18 ± 29.58	1.93 ± 29.04	0.685
p^2		**0.721**	0.818	
	1	82.73 ± 17.71	93.21 ± 15.01	0.076
Diastolic blood pressure	3	83.73 ± 15.18	91.14 ± 10.11	0.106
	(1-3)	-1.00 ± 18.16	2.07 ± 17.63	0.620
p^2		**0.800**	0.672	
	1	84.32 ± 18.79	87.64 ± 21.28	0.624
Heart Rate	3	86.82 ± 14.82	88.07 ± 21.30	0.842
	(1-3)	-2.50 ± 22.32	-0.43 ± 19.06	0.776
p^2		**0.600**	0.941	

Data are shown as mean ± standard deviation. General Linear Model Repeated Anova (Wilks' Lambda). p^1 = value for comparison between groups, p^2 = value for intra-group comparisons, 1 = before induction, 3 = after extubation.

0.05). Preinduction HCO_3 in Group O was 21.84 ± 3.75 mmol/L, which decreased significantly to a postoperative HCO_3 value of 17.76 ± 2.71 mmol/L (p = 0.001). In Group R, there was a significant decrease in HCO_3 from a preinduction value of 22.81 ± 2.87 mmol/L to a postoperative value of 19.55 ± 2.49 mmol/L (p = 0.002). There were no statistically significant differences between the two groups at either time point (p = 0.465) (Table 3).

Lactate levels increased significantly after the operation in both Group O (preinduction: 0.9 mmol/L, postoperative value: 1.385 mmol/L; $p < 0.01$) and Group R (preinduction: 0.65 mmol/L, postoperative value: 1.385 mmol/L; p = 0.001) (Table 4). There was no statistically significant difference between the two groups in terms of changes in perioperative bicarbonate level (p = 0.465) (Table 3).

The hemoglobin and hematocrit (Hct) levels of the two groups are shown in Table 3. The Hct levels decreased significantly in both groups after the operation compared to the respective preinduction value (Group O, 31.27 ± 3.99 vs. 28.15 ± 5.16, respectively; p = 0.001; Group R, 30.43 ± 5.93 vs. 28.07 ± 5.36, respectively; p = 0.046). There was no statistically significant difference in the postoperative decrease in Hct level between the two groups (p = 0.581). The preinduction and postoperative hemoglobin level decrease in the O group was statistically significant, but this was not significant in the R group (p = 0.003 and p = 0.080, respectively). Similarly, there was no statistically significant difference between hemoglobin declines in both groups (p = 0.447) (Table 3).

The hemodynamic parameters of the groups are shown in Table 3. The arterial systolic blood pressure in Group R was significantly higher than that in Group O (158.21 ± 23.09 mmHg vs 136.68 ± 30.04 mmHg respectively; p = 0.034). There was no statistically significant change in mean arterial systolic blood pressure after the operation versus pre-anesthesia induction within either group ($p > 0.05$) (Table 3). There were also no statistically significant differences in arterial diastolic blood pressure or heart rate, either between or within groups.

There were no statistically significant differences in the sodium and potassium levels between groups, either before anesthesia induction or after the operation ($p < 0.05$) (Tables 3 and 4). Preinduction and postoperative decrease of calcium levels were statistically significant in group O compared to group R (p = 0.010) (Table 3). The mean glucose level in Group O was 102 g/L before induction and 136.5 g/L postoperatively ($p < 0.001$), while there was no significant change in Group R. There was no statistically significant group difference in the mean electrolyte or glucose level (Tables 3 and 4).

Table 4. Blood gas parameters

			Group O (n = 22)	Group R (n = 14)	p^1
Glucose		1	102 (197-87)	104.5 (264-64)	**0.795**
		3	136.5 (238-105)	137.5 (219-92)	**0.555**
		(1-3)	-45 [92–(-116)]	-31 [61-(-96)]	**0.418**
	p^2		**< 0.001**	0.094	
Potassium		1	4.055 (7.32-3.1)	4.25 (6.09-3.19)	**0.548**
		3	4.355 (5.44-2.62)	4.43 (5.24-3.4)	**0.752**
		(1-3)	0.03 [2.92 -(-1.07)]	0.01 (0.85 - (-0.8)]	**0.632**
	p^2		0.902	0.612	
Lactate		1	0.9 (1.99-0.23)	0.655 (1.94-0.34)	**0.174**
		3	1.385 (4.88-0.66)	1.49 (2.5-0.49)	**0.667**
		(1-3)	-0.39 [0.53-(-4)]	-0.62[0.08-(-2.04)]	**0.727**
	p^2		**< 0.001**	**0.001**	
PCO_2		1	38 (53.5-27.3)	36.5 (64.6-27)	**0.258**
		3	42 (51-30.5)	39.15 (46.5-32)	**0.233**
		(1-3)	-5 [12-(-13)]	-3 [28.3-(-17)]	**0.942**
	p^2		0.053	0.266	

Data are shown as median (minimum-maximum). Mann-Whitney U test (Monte Carlo), Wilcoxon signed ranks test (Monte Carlo). p^1 = value for comparison between groups, p^2 = value for intra-group comparisons, 1 = before induction, 3 = after extubation.

DISCUSSION

RALS with the Da Vinci Surgical System (Intuitive Surgical®, Sunnyvale, CA, USA), which uses advanced technology and provides a 3D view, has improved with increasing surgical experience. In RALS, CO_2 pneumoperitoneum is used in the steep Trendelenburg position to remove abdominal viscera from the surgical site [9, 10]. As the increase in intraabdominal pressure continues in the steep Trendelenburg position, the left ventricle effects a decrease in diastolic end-volume and cardiac output, resulting in tachycardia and hypotension [11]. The effects of the supine position during open surgery on pulmonary and cardiovascular system perfusion are less marked than those of the trendelenburg position [12]. Meininger *et al.* [9] reported that, for prostatectomy with RALS, pneumoperitoneum and use of the steep Trendelenburg position resulted in increases in all hemodynamic parameters except heart rate and cardiac index, but these parameters returned to baseline values at the end of pneumoperitoneum. Heart rate and cardiac index increased when the patient was placed in the supine position. Pneumoperitoneum results in an increase in systemic vascular resistance, mean arterial pressure, heart rate, and catecholamine release. Kalmar *et al.* [10] and Pandey *et al*. [13] reported that mean arterial pressure increased in the steep trendelenburg position and with pneumoperitoneum, respectively.

In the present study, hemodynamic parameters before anesthesia induction remained at normal levels during open surgery, while high systolic arterial pressure was observed pre- and after induction of anesthesia in patients undergoing the RALS procedure. This was taken as a clinical indicator of CKD. While systolic arterial pressure was high in the RALS group, diastolic arterial pressure and heart rate values were both similar to those of the open surgery group. Unlike the studies of Kalmar *et al.* [10] and Pandey *et al*. [13], the expected peaks in mean arterial pressure and heart rate while in the steep Trendelenburg position were not observed in our cases. Hemodynamic parameters in both groups returned to baseline values at the end of the operation, and position during surgery showed no effect on hemodynamic parameters.

In our study, the initial hemoglobin levels of both groups were around 10 g/dL, and did not decrease significantly at the end of the operation. Horgan *et al*. [14] reported that bleeding control in RALS was as reliable as in open surgery. In the present study, the hemoglobin and hematocrit levels did not change significantly in either group, pre-versus postoperatively. While RALS technique is considered better for a hemostasis control without any anaemia, there is also no such anaemia in the open surgical one of our study. In this regard, our findings were consistent with those in the literature [15-17]. Functional residual capacity (FRC), vital capacity (FVC), peak airway pressure and ventilation/perfusion (V/Q) mismatch increase when the compliance is reduced in the deep Trendelenburg position in RALS With the diaphragm elevation, the small airline closes. In pneumoperitoneum, decreased compliance, increased V/Q mismatch is observed. In RALS technique, both the deep Trendelenburg position and CO_2 insufficiency cause hypercarbia, pH decrease [10, 12, 13, 15]. In our study, hypoxemia was not detected with significant increase in PCO_2 values at the end of operation of the groups. The RALS group was protected from mechanical ventilation (MV) maneuvers and the effects of position and pneumoperitoneum on the respiratory system. In our study, changes in pH and bicarbonate values independent of each other in both groups were thought to be due to chronic renal failure. Low pH and bicarbonate values are expected in CKD [18-21]. Blood gas monitorizations of patients showed an increase in lactate levels at the end of operation compared to baseline values in both groups. In the presence of hypoxia, tissue hypoperfusion and anaerobic glycolysis lead to elevated lactate levels [21]. There was no statistically significant difference between groups in terms of lactate levels. It was observed that the position used in the surgical technique was not effective at lactic acid levels. Studies of Kalmar *et al.* [10] and Pandey *et al*. [13] found high lactate levels in the cases. The hyperlactatemia observed in the study in both groups is consistent with the literature. Liquid restriction in the perioperative period helps to reduce the airway edema during the deep Trendelenburg position. In general, 2 liter fluid is recommended for the prostatectomy operations performed by the RALS technique [16, 17]. In our study, an average of 2700

cc crystalloid replacement was performed peroperatively in the RALS group. With this application, it was aimed to provide partial protection from position-dependent fluid overload in the events [22]. In the experience gained from RALS prostatectomy operations, which we have been doing for a long time, liquid restriction in the RALS kidney transplant group in liquid management was deemed appropriate. The need for fluid in RALS is less with open surgery. In our study, less fluid was used for the RALS group than for the open surgery group; The applied liquid management complies with the literature [7, 13, 23]. The most commonly used infusion fluid during kidney transplantation (0.9%) is NaCl [11]. In our study, 0.9% NaCl was used for fluid treatment. In our study, diuretic and urine removal were not targeted. For this reason, diuretic use is not discussed.

Horgan *et al.* [14] reported a mean surgical duration of 166 minutes, Giacomonni *et al.* [5] reported a mean follow-up of 311 minutes and, in the first case of RALS kidney transplantation reported by Hoznek *et al.* [6], the operation time was 178 minutes [8, 10, 21]. In our study, RALS group's operation time average is 412 minutes. In line with the longer duration of donor operations, in this study the operation times for the RALS group exceeded those reported in the literature. While the mean duration of vascular anastomosis was 57 minutes in the report by Hoznek *et al*. [6]. Horgan *et al*. [14] did not provide information on the operation time. The mean duration of vascular anastomosis in our study was 34 minutes, which was shorter than that reported by Hoznek *et al.* [6]. Modi *et al*. [4] have subsequently demonstrated effectiveness of laparoscopic kidney transplantation when the kidney was procured by retroperitoneoscopic living donor nephrectomy. The anastomosis time was longer in the laparoscopic group compared to the open surgery group. We have received a laparoscopic kidney transplantation when the kidney was procured by retroperitoneoscopic living donor nephrectomy. The anastomosis time was longer in the laparoscopic group compared to the open surgery Group O. In the review of all robotic kidney transplantations done in Europe over a 1-year period revealed an average vascular anastomosis operation time of 42 minutes [24]. The mean duration of vascular anastomosis in the RALS group in the present study was those reported in the literature, by an average of 34 minutes. Only 3 of 36 patients included in our study had peritoneal potassium levels >5.5 mEq/ L, and increased potassium levels returned to normal on intravenous glucose-insulin administration. Sodium and potassium levels remained within their respective normal limits at the end of the operation. Calcium levels were lower than expected in the open surgery group during the postoperative period. No information was found in the English language literature on electrolyte levels in RALS.

CONCLUSION

RALS is being used with increasing frequency due to its minimally invasive nature, reduced surgical stress response, and rapid postoperative recovery. In kidney transplantation operations, the risk of infection due to lymphocele, which is observed frequently with the open surgical technique, is less common in RALS, which is also associated with a shorter hospital stay. However, pneumoperitoneum and use of the steep Trendelenburg position can lead to hemodynamic and respiratory changes, which may result in serious complications. Concomitant comorbidities, such as renal dysfunction, limited systemic reserves, and electrolyte imbalance increase the risk of mortality and morbidity. In this report, we shared our experience of using kidney transplantation with RALS in daily practice.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] Parmar MS. Chronic renal disease. BMJ 2012;325:85-90.
[2] Margreiter R. Renal Medicine: History of Renal Transplantation [Online]. Available: http://www.renalmed.co.uk/history-of/renal-transplant.
[3] Erek E, Suleymanlar G, Serdengecti K. Nephrology, dialysis and transplantation in Turkey. Nephrol Dial Transplant 2002;17:2087-93.

[4] Modi P, Rizvi J, Pal B, Bharadwaj R, Trivedi P, Trivedi A, et al. Laparoscopic kidney transplantation: an initial experience. Am J Transplant 2011;11:1320-4.
[5] Giacomoni A, Di Sandro S, Lauterio A, Concone G, Buscemi V, Rossetti O, et al. Robotic nephrectomy for living donation: surgical technique and literature systematic review. Am J Surg 2016;211:1135-42.
[6] Hoznek A, Zaki SK, Samadi DB, Salomon L, Lobontiu A, Lang P, et al. Robotic assisted kidney transplantation: an initial experience. J Urol 2002;167:1604-6.
[7] Herling SF, Dreijer B, Wrist Lam G, Thomsen T, Moller AM. Total intravenous anaesthesia versus inhalational anaesthesia for adults undergoing transabdominal robotic assisted laparoscopic surgery. Cochrane Database Syst. Rev 2017;4:CD011387.
[8] Hammer Ø, Harper DAT, Ryan PD. PAST: Paleontological Statistics Software Package for Education and Data Analysis. Palaeontol Electron 2001;4:1-9.
[9] Meininger D, Westphal K, Bremerich DH, Runkel H, Probst M, Zwissler B, et al. Effects of posture and prolonged pneumoperitoneum on hemodynamic parameters during laparoscopy. World J Surg 2008;32:1400-5.
[10] Kalmar AF, Foubert L, Hendrickx JFA, Mottrie A, Absalom A, Mortier EP, et al. Influence of steep Trendelenburg position and CO(2) pneumoperitoneum on cardiovascular, cerebrovascular, and respiratory homeostasis during robotic prostatectomy. Br J Anaesth 2010;104:433-9.
[11] Rosendal C, Markin S, Hien MD, Motsch J, Roggenbach J. Cardiac and hemodynamic consequences during capnoperitoneum and steep Trendelenburg positioning: lessons learned from robot-assisted laparoscopic prostatectomy. J Clin Anesth 2014;26:383-9.
[12] O'Brien TJ, Ebert TJ. Physiologic changes associated with the supine position. In Martin JT, Warner MA (ed.): Positioning in Anesthesia and Surgery, 3rd ed. Philadelphia: WB Saunders. 1997.
[13] Pandey R, Garg R, Roy K, Darlong V, Punj J, Kumar A. Perianesthetic management of the first robotic partial cystectomy in bladder pheochromocytoma. A case report. Minerva Anestesiol 2010;76;294-7.
[14] Horgan S, Vanuno D, Sileri P, Cicalese L, Benedetti E. Robotic-assisted laparoscopic donor nephrectomy for kidney transplantation. Transplantation 2002;73:1474-9.
[15] Fracalanza S, Ficarra V, Cavalleri S, Galfano A, Novara G, Mangano A, et al. Is robotically assisted laparoscopic radical prostatectomy less invasive than retropubic radical prostatectomy? Results from a prospective, unrandomized, comparative study. BJU Int 2008;101:1145-9.
[16] Phong SVN, Koh LKD. Anaesthesia for robotic-assisted radical prostatectomy: considerations for laparoscopy in the Trendelenburg position. Anaesth Intensive Care 2007;35:281-5.
[17] Danic MJ, Chow M, Alexander G, Bhandari A, Menon M, Brown M. Anesthesia considerations for robotic-assisted laparoscopic prostatectomy: a review of 1,500 cases. J Robot Surg 2007;1:119-23.
[18] Rebholz CM, Coresh J, Grams ME, Steffen LM, Anderson CAM, Appel LJ, et al. Dietary acid load and incident chronic kidney disease: Results from the ARIC Study. Am J Nephrol 2015;42:427-35.
[19] Murray CJL, Richards MA, Newton JN, Fenton KA, Anderson HR, Atkinson C, et al. UK health performance: findings of the Global Burden of Disease Study 2010. Lancet 2013;381:997-1020.
[20] Lentine KL, Kasiske BL, Levey AS, Adams PL, Alberú J, Bakr MA, et al. KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors. Transplantation 2017;101(8 Suppl 1);S7-S105.
[21] Streja E, Nicholas SB, Norris KC. Controversies in timing of dialysis initiation and the role of race and demographics. Semin Dial 2013;26:658-66.
[22] Hsu RL, Kaye AD, Urman RD. Anesthetic challenges in robotic-assisted urologic surgery. Rev Urol 2013;15:178-84.
[23] Lee JR. Anesthetic considerations for robotic surgery. Korean J Anesthesiol 2014;66:3-11.
[24] Breda A, Territo A, Gausa L, Decaestecker K, Stöckle M, Fornara P, et al. Robotic kidney transplantation: European one-year data. Eur Urol 2018;16 Suppl;e1977-8.

The European Research Journal 2018;4(4):308-313

ORIGINAL ARTICLE

Sternal cable wires for sternal closure in moderately or extremely obese patients undergoing cardiac surgery

Yusuf Ata[1], Ufuk Aydın[1], Ahmet Kağan As[1], Kadir Kaan Özsin[1], Orhan Fındık[2], Tamer Türk[1]

[1]Department of Cardiovascular Surgery, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey
[2]Department of Cardiovascular Surgery, Derince Training and Research Hospital, Kocaeli, Turkey

DOI: 10.18621/eurj.429502

ABSTRACT

Objectives: Sternal dehiscence is a frequent complication after cardiac surgery. Our study focused on the efficiency of a sternal cable system combined with conventional steel wires for sternal fixation in patients suffering from moderate or extreme obesity and undergoing cardiac surgery.

Methods: Prospectively collected data from 22 male and 41 female patients (a mean body mass index [BMI] of 37.9 ± 2.5 kg/m^2) who underwent major cardiac surgery via median sternotomy and sternal closure using a multifilament sternal cable system were retrospectively reviewed and analyzed.

Results: All patients were closed with a conjunction of two sternal cables and two traditional steel wires. There were two mortalities. There were no occurrences of sternal dehiscence or deep mediastinitis. Three patients suffered superficial sternal wound infections. The mean hospitalization time was 8.4 ± 2.5 days.

Conclusion: Our study showed that our surgical technique using a sternal cable system in combination with conventional wires decreased the incidence of sternal dehiscence in moderately and extremely obese patients.

Keywords: Sternal dehiscence, cardiac surgery, obesity

Received: June 1, 2018; Accepted: June 14, 2018; Published Online: September 24, 2018

Median sternotomy is the most commonly used incision and provides excellent access to the heart and surrounding structures for the performance of cardiopulmonary bypass in cardiac surgery. However, the proper closure of the incision is difficult.

Although rare, sternal dehiscence occurs in 0.5-5% of patients, requires reoperation and carries significant mortality and morbidity risk at 10-40% [1, 2]. In addition to causing significant pain for the patient, sternal dehiscence also predisposes patients to developing deep sternal wound infections and mediastinitis, resulting in a high mortality rate up to 25% [3-5]. Furthermore, prolonged hospitalization results in higher costs. Previously, obesity has been shown to be the single most important risk factor for postoperative sternal dehiscence [6, 7]. Therefore, effective primary closures of median sternotomies are important for preventing high-risk complications and patient discomfort especially in obese patients.

Although many different sternal closure devices have been introduced in past decades, none have been able to fully replace traditional steel wires in terms of practicability and costs. Sternal dehiscence remains an unsolved problem after cardiac surgery especially in

Address for correspondence: *Tamer Türk, MD., Professor, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Cardiovascular Surgery, Mimar Sinan Mah., Emniyet Cad., No: 35, 16310 Bursa, Turkey*
E-mail: tturkon@yahoo.com

e-ISSN: 2149-3189

obese patients. This article reports on promising results for sternal closure in moderately (i.e., a body mass index [BMI] ranging from 35 to 39.9) and extremely obese (BMI ≥ 40) patients with a combination of traditional steel wires and a new sternal cable system (Pioneer Surgical Technology, Inc., Marquette, Michigan, USA).

METHODS

Prospectively collected data from 63 patients (22 males and 41 females with a mean age of 64.3 ± 7.6 years) who underwent major cardiac surgery via median sternotomy and sternal closure using a multifilament sternal cable system between January 2014 and February 2016 were retrospectively reviewed and analyzed. Study protocol was approved by the local ethics committee. Informed consent was obtained before operation (24 hours) from each patient.

The BMI is calculated as weight (kg)/height squared (m^2). The weight classification for this study was performed using the American National Institutes of Health guidelines with normal BMIs ranging from 18.5 to 24.9, mildly obese BMIs from 25 to 34.9, moderately obese BMIs from 35 to 39.9, and extremely obese BMIs > 40 [8]. The mean BMI of our study population was 37.9 ± 2.5 kg/m2 (ranging from 35 to 47.6). Fifty-four patients were classified as moderately obese, and nine patients were classified as extremely obese.

All patients received the same prophylactic antibiotic protocol, i.e., cephazolin. Perioperative risk factors were noted. The patient demographics are presented in Table 1.

Surgical Technique

The Pioneer® Sternal Cable System is an improved alternative to the traditional monofilament sternal wire. This system consists of multi-strand stainless steel 1.0-mm diameter cables tensioned and secured using Pioneer's patented tensioner/crimper instrument. The insertion and removal of the cable is safe and easy due to its smoothness and flexibility. The tensioner assures adequate tension is applied, whereas a tension scale ensures each cable is tensioned to the same degree before crimping. Multiple figure-eight constructs work as one unit to provide optimal stabilization.

Sternal cables were deployed in a figure-eight fashion around the sternum in all patients, and conventional stainless steel wires were added around the manubrium and the lower part of the sternal body. Two multifilament cable wires were used for sternal closure, and two conventional stainless steel wires were used in the procedure. First, two simple interrupted conventional steel wires were placed separately in the proximal part of the manubrium and the distal part of the sternal body. Then, two sternal cables were deployed in a figure-eight pattern in the distal part of the manubrium and around the sternal body (Figure 1). If required, another conventional steel wire was added in the distal part of the sternal body. The conventional steel wires helped in maintaining sternal closure as the sternal cables were crimped. By

Table 1. Characteristics of patients

Characteristics	n	%	Mean ± SD (range)
Age (years)			64.3 ± 7.6 (46-83)
BMI (kg/m^2)			37.9 ± 2.5 (35-47.6)
BMI>40	9	14.3	
Sex (female)	42	66.7	
DM	24	38.1	
COPD	19	30.2	
Renal insufficiency	4	6.3	
Smoking	27	44.3	
X clamp (min)			64. 3 ± 15.3 (32-109)
Perfusion (min)			91.4 ± 19.4 (54-149)

BMI = body mass index, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, X clamp = aortic cross clamp

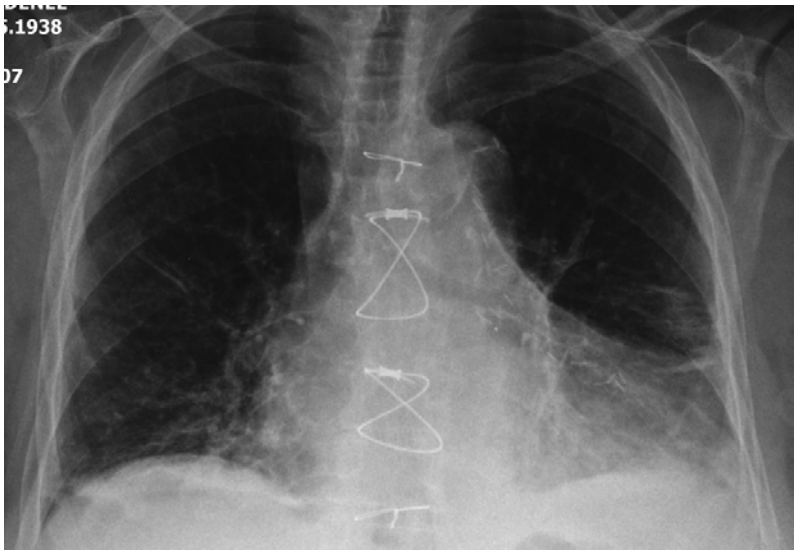


Figure 1. X-Ray of a patient closed with sternal cable system.

using this technique, the crimping of the cables was proper and easily executed. Only five patients required additional conventional steel wires for approximation due to the length of the sternal body.

RESULTS

All patients were closed with a conjunction of two Pioneer Cable System wires and two conventional steel wires. A majority of the patients underwent isolated CABG (54/63) with the use of left internal thoracic artery (LITA). Nine patients underwent open cardiac surgery other than CABG. The surgical interventions of the patients are shown in Table 2.

In five patients, a third conventional steel wire was added in the distal part of the sternal body due to length of the sternum. There were 2 (3.2%) mortalities. Both patients died due to low cardiac output and multiple organ failure, one on the 12th and the other on the 19th postoperative day. There were no sternal dehiscence or deep mediastinitis in the whole group. Three (4.8%) patients suffered superficial sternal wound infections. The mean postoperative drainage was 490 ± 142.6 ml, and the mean hospitalization time was 8.4 ± 2.5 days. The operative and postoperative variables are presented in Table 3.

Table 2. Surgical procedures

Variables	n	%
CABG	54	85.7
AAR	3	4.8
CABG+MVR	2	3.2
DVR	2	3.2
MVR	1	1.6
AVR	1	1.6

AAR = ascendant aorta replacement, AVR = aortic valve replacement, CABG = coronary artery bypass grafting, DVR = double valve replacement, MVR = mitral valve replacement

Table 3. Postoperative variables

Variables	n	%	Mean ± SD (range)
Drainage, ml			490 ± 142.6 (150-750)
Hospitalization, days			8.4 ± 2.5 (6-19)
Sternal dehiscence	0	0	
Superficial wound infection	3	4.8	

DISCUSSION

Sternal dehiscence is a serious complication after cardiac surgery. The instability of the chest wall and the higher risk for infection leads to high mortality and morbidity rates. Our study focused on the efficiency and mechanical fatigue performance of a sternal cable system combined with conventional steel wires for sternal fixation in patients suffering from moderate or

extreme obesity, i.e., major risk factors for sternal dehiscence after cardiac surgery.

The loosening and failure of a sternal closure is associated with compromised wound healing and may lead to sternal wound dehiscence and infection [9]. Complications due to median sternotomy have been reported to occur in 0.3% to 5.0% of patients and are associated with significant morbidity and mortality rates of 14% to 47% with a high risk of mortality especially in cases of mediastinitis [3, 10].

Sternal dehiscence has been shown to be of major concern by Molina *et al*. [6]. When the BMI is greater than 30, sternal dehiscence occurs at an incidence of 6.46%, whereas the occurrence of sternal dehiscence is 1.63% in non-obese patients. Kiessling *et al*. [11] reported that when sternal closures were performed with conventional steel wires, there was a 12% incidence of sternal dehiscence in obese patients with a mean BMI of 34.6 ±1.7 kg/m2, whereas the incidence of dehiscence of the whole study group of 100 patients was 7%. In our study group consisting of 61 patients with a mean BMI of 37.9 ± 2.5 kg/m^2 there were no sternal dehiscences.

A variety of sternum closure techniques have been developed. The primary aim in selecting the appropriate closure technique should be in its effectiveness to ensure a rigid closure of the sternum to restore stability to the sternum. A variety of sternal closure techniques using different closure materials have been reported to prevent sternal dehiscence. However, no ideal, standardized method has been adopted. In a meta-analysis by Khasati *et al*. [12] comparing simple wire and figure-eight closure techniques found that the figure-eight method had no significant benefit over the simple wire method. Grapow *et al*. [13] used a new material named ZipFix, which showed promising results. Wangsgard *et al*. [14] reported that the figure-eight stainless steel cable system and the dynamic sternal fixation plate system were expected to show lower failure rates when compared with the figure-eight stainless-steel wire system. Our findings with no sternal dehiscence and only three superficial wound infections supported the experimental findings of Wangsgard *et al*. [14].

The sternal cables of the Pioneer sternal cable system have been reported to have fatigue strengths approximately ten times stronger than standard steel wires [15]. The sternal cables are wrapped around the sternum in a figure-eight pattern, uniformly hugging the sternal bone to minimize micro-motion and wire loosening, which would otherwise result in lower postoperative non-union potential and compromised wound healing.

Oh *et al*. [10] used sternal cables in 781 patients and conventional steel wires in 573 patients and did not find any clear clinical advantages of sternal cables over conventional steel wires. However, the mean BMI values of the cable group and the conventional wire group were 24.1 ± 3.2 kg/m^2 and 23.9 ± 3.1 kg/m^2, respectively, i.e., the moderately or severely obese patient population was very low in the whole study group especially compared with the mean 37.9 ± 2.5 kg/m^2 BMI of our study group.

In a recent study by Ozen *et al*. [16], the authors compared 24 obese patients (mean BMI 34.4 ± 3.1 kg/m^2) on whom they used the sternal cable system with 32 obese patients (mean BMI 34.2 ± 2.7 kg/m^2) on whom they used conventional wires for sternal closures. Ozen *et al*. [16] did not observe any sternal dehiscence in the cable group and observed 3 incidences (9.4%) of sternal dehiscence in the conventional wire group (a non-significant difference). However, the study group was too small to reach a definitive conclusion. The main difference between the cable groups in the Ozen *et al*. [16] study and in our study was that our group consisted of moderately or severely obese patients. Furthermore, our surgical technique was of lower cost due to the utilization of two sternal cables on each patient compared with the use of three sternal cables in the Ozen *et al*. [16] study. The sternal cable group of 24 patients in the study by Ozen *et al*. revealed a satisfactory result with no postoperative sternal dehiscence. Similarly, none of the 63 patients in our study suffered postoperative sternal dehiscence when compared with the obese patient groups in the studies conducted by Molina *et al*. [6] and Kiessling *et al*. [11] (with 6.46% and 12% incidence rates of sternal dehiscence, respectively). The patients in the latter two studies utilized conventional steel wires in a traditional way for sternal closure. Additionally, our study group consisted of more obese patients with a mean BMI of 37.9 ± 2.5 kg/m^2.

Oh *et al*. [10] and Ozen *et al*. [16] also reported decreased postoperative bleeding. Total postoperative drainage was 499.0 ± 218.3 ml in the cable group and

741.9 ± 243.3 ml ($p < 0.001$) in the steel wire group in the study of Ozen et al. In the study by Oh et al. [10], 17 patients in the cable group and 29 patients in the conventional wire group underwent reoperation for bleeding ($p = 0.068$). Although this comparison was not significant, the results indicate a tendency for decreased sternal bleeding. This tendency may be attributed to the ability for the sternal cable wires to hold the sternum at a higher tension around the bone more than conventional steel wires. This would allow for a tighter and more stable fixation of the sternum and lead to decreased bleeding from bone marrow and nearby structures. In our study, one reoperation was required for bleeding, and the mean drainage was 490 ± 142.6 ml.

Generally, sternal dehiscence occurs when sternal steel wires cut through the bone or in rare cases, when the suture material breaks. As conventional sternal closure techniques and conventional wires find continued use in obese patients, the incidence of sternal dehiscence will continue to occur at high rates. If the rate of obesity continues to increase, higher incidences of sternal dehiscence will result in increased mortality and morbidity rates and higher hospital costs.

The sternal cables are easy to handle and may decrease the time required for sternum closure. The cables are more flexible than the traditional steel wires. This enables a surgeon to more easily complete a figure-eight suture and allows the cable to more uniformly hug the sternum to decrease the chance for the cable to cut into the sternal bone. Additionally, the flexibility of the cable wires allows for active motion of the chest and the sternal bone. Additionally, the multifilament cables are stronger than traditional wires; this minimizes wire breakage concerns for larger patients. These advantages allow for a more rigid closure and apposition of the sternal bone and likely results in increased resistance to infection. However, despite these advantages, surgeons should avoid over-tensioning sternal cables due to the likelihood of breaking or cutting through unprotected or non-immobilized soft bone tissue.

Limitations

This study has several limitations. Our study group was small and encompassed 63 moderately or extremely obese patients. While limited in number, our study population seemed to have more obese patients treated with sternal cable wires compared with other reports in the literature. Another limitation was the retrospective design of our study. Other than these limitations, our study is the first study in English literature that concerns multifilament cable wire sternal closures for a group consisting of only moderately or extremely obese patients.

CONCLUSION

Our study showed that our surgical technique using a sternal cable system in combination with conventional wires decreased the incidence of sternal dehiscence in moderately and extremely obese patients when compared with other similarly reported studies in the literature.

Author's Contributions

YA: data interpretation, manuscript revision; UA: data collection, analysis, manuscript revision; AKA: data collection, manuscript revision; KKÖ: data interpretation, manuscript revision; OF: data interpretation, manuscript revision; TT: study conception, correspondence, data collection, analysis.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] Voss B, Bauernschmitt R, Will A, Krane M, Kröss R, Brockmann G, et al. Sternal reconstruction with titanium plates in complicated sternal dehiscence. Eur J Cardiothorac Surg 2008;34:139-45.

[2] John LCH. Modified closure technique for reducing sternal dehiscence; a clinical and in vitro assessment. Eur J Cardiothorac Surg 2008;33:769-73.

[3] El Oakley RM, Wright JE. Postoperative mediastinitis: classification and management. Ann Thorac Surg 1996;61:1030-6.

[4] Baskett RJ, MacDougall CE, Ross DB. Is mediastinitis apreventablecomplication? A 10-year review. Ann Thorac Surg

1999;67:462-5.
[5] Bryan AJ, Lamarra M, Angelini GD, West RR, Breckenridge IM. Mediansternotomy wound dehiscence: a retrospective case control study of risk factors and outcome. J R Coll Surg Edinb 1992;37:305-8.
[6] Molina JE, Lew RSL, Hyland KJ. Postoperative sternal dehiscence in obese patients: incidence and prevention. Ann Thorac Surg 2004;78:912-7.
[7] Prabhakar G, Haan CK, Peterson ED, Coombs LP, Cruzzavala JL, Murray GF. The risks of moderate and extreme obesity for coronary artery bypass grafting outcomes: a study from the Society of Thoracic Surgeons' database. Ann Thorac Surg 2002;74:1125-31.
[8] National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. National Heart, Lung and Blood Institute. June 1998.
[9] Schimmer C, Reents W, Berneder S, Eigel P, Sezer O, Scheld H, et al. Prevention of sternal dehiscence and infection in high-risk patients: a prospective randomized multicenter trial. Ann Thorac Surg 2008;86:1897-904.
[10] Oh YN, Ha KJ, Kim JB, Jung SH, Choo SJ, Chung CH, et al. Multifilament cable wire versus conventional wire for sternal closure in patients undergoing major cardiac surgery. Korean J Thorac Cardiovasc Surg 2015;48:265-71.
[11] Kiessling AH, Isgro F, Weisse U, Möltner A, Saggau W, Boldt J. Advanced sternal closure to prevent dehiscence in obese patients. Ann Thorac Surg 2005;80:1537-9.
[12] Khasati N, Sivaprakasam R, Dunning J. Is the figure-of-eight superior to the simple wire technique for closure of the sternum? Interact Cardiovasc Thorac Surg 2004;3:191-4.
[13] Grapow MT, Melly LF, Eckstein FS, Reuthebuch OT. A new cable-tie based sternal closure system: description of the device, technique of implantation and first clinical evaluation. J Cardiothorac Surg 2012;7:59.
[14] Wangsgard C, Cohen DJ, Griffin LV. Fatigue testing of three peristernal median sternotomy closure techniques. J Cardiothorac Surg 2008;3:52.
[15] Pioneer Surgical Technology Inc. Pioneer sternal cable system: cardiothoracic: cable system [Internet]. Marquette (MI): Pioneer Surgical Technology Inc.; c2015 [cited 2014 Dec 27]. Available from: http://www.pioneersurgical.com/cardiothoracic/Cable-System/Pioneer-Sternal-Cable-System/
[16] Özen Y, Sarıkaya S, Rabuş MB, Günay D, Aksoy E, Dedemoğlu M, et al. Comparison of the sternal wires and sternal cable in closure of the sternum during cardiac surgery. Cardiovasc Surg Interven 2014;1:41-4.

The European Research Journal 2018;4(4):314-319 ORIGINAL ARTICLE

Motor performance, functional status and quality of life in children with dyslexia

Sebahat Yaprak Çetin[1], Ali Kitiş[2], Figen Şen Kösem[3]

[1]1Department of Physical Therapy and Rehabilitation, Cyprus International University Faculty of Health Sciences, Nicosia, North Cyprus
[2]Department of Physical Therapy and Rehabilitation Pamukkale University School of Medicine, Denizli, Turkey
[3]Child and Adolescent Psychiatrist, Dr. Figen Şen Kösem Private Clinic, Denizli, Turkey

DOI: 10.18621/eurj.365934

ABSTRACT

Objectives: The purpose of this study was to assess motor performance, functional status and quality of life in children with dyslexia by the Diagnostic and Statistical Manual of Mental Disorders Turkish version (DSM-IV-TR), and compare the outcome with typically developing children.

Methods: This study includes 28 dyslexic and 28 typically developing children at the age of 7 to 12 years. Motor abilities and proficiencies were evaluated with the short form of the second version of the Bruininks Oseretsky Test of Motor Proficiency (BOTMP 2-SF). The Functional Independence Measure for Children (WeeFIM) was used to measure functional status. Quality of life in the children evaluated with the Pediatric Quality of Life Inventory (PedsQL).

Results: There was a significant difference found between the results of the two groups on motor abilities, functional status and quality of life ($p < 0.05$).

Conclusions: We think that, according to the obtained results, it is important to assess in detail and plan rehabilitation programs such as education at daily living activities in order to increase the quality of life in dyslexic children who were diagnosed in terms of motor performance.

Keywords: dyslexia, motor performance dysfunction, activities of daily living, quality of life

Received: December 14, 2017; Accepted: January 10, 2018; Published Online: February 10, 2018

Dyslexia is a neurobiological origin of learning disability called developmental dysfunction defined by Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [1]. Even though children with dylexia have difficulties in reading, writing and spelling, the intelligence levels are normal or above. Prevalence of dyslexia in schools of the western world is reported to be 5% to 10%; it also occurs four to five times more often in boys than girls [2, 3]. Learning disabilities which contain dyslexia have various negative effects on a person's life, especially when it comes to students since it leads to deficiencies in their academic learning, a low self-esteem, physical and psychological problems, and behavioral problems [4]. Literature's main focus has been on the school-related problems such as deficiency in reading skills and academic performance because there is a relationship between dyslexia and academic performance. However, recent studies have shown that this population also suffers deficits in motor performance, including bilateral hand coordination, general hand dexterity, and fine motor dexterity [5-7]. The

Address for correspondence: *Sebahat Yaprak Çetin, MD., Cyprus International University Faculty of Health Sciences, Department of Physical Therapy and Rehabilitation Nicosia, North Cyprus*
E-mail: fzt_s.yaprakulgen@hotmail.com

e-ISSN: 2149-3189

relationship between dyslexia and alterations in motor coordination is important during assessment and diagnosis [8, 9].

Specific learning disorders including dyslexia children are faced with many limitations when it comes to physical activities including personal care, their schoolwork, and social activities they do with friends because they have deficiencies in motor skills [4]. However, early identification of these problems and using different measures to improve the dyslexic child's level of participation may help to solve the physical and psychological problems.

Children with specific learning disorders who have difficulty in motor skills may also encounter difficulties in their daily living activities [1]. Though there were studies on motor skills and quality of life in children with dylexia in the literature [4, 5, 7], there were no studies evaluating the activities of daily living in this children. Studies generally examined children with specific learning disorders and not only children with dylexia. Furthermore, there has not yet been any of these kind of studies done in Turkey. The purpose of this study was to assess motor performance, functional status, and quality of life in children with dyslexia who have diagnosed by using Turkish version of DSM IV and compare the outcomes with typically developing children.

METHODS

This study includes 28 dyslexic and 28 typically developing children with ages ranging from 7 to 12 years. Inclusion criteria for children with dyslexia: diagnosis of dyslexia, to attend elementary school together with a full scale Wechsler Intelligence Scale for Children-Revised (WISC-R) IQ of at least 85 at diagnosis; children whose visual, hearing, physical and mental handicap with the diagnosis of dyslexia were excluded [10]. The dyslexic children who were included in the study have been studying at an elementary school affiliated with the Denizli Provincial Directorate of National Education and also have been getting special education and rehabilitation in a center affiliated with the Denizli Provincial Directorate of National Education. The typically developing children were in the same age range as dyslexic children included in the study with no visual, hearing, physical, mental and special learning disabilities. The typically developing children were randomly chosen among the students studying at elementary school, which is affiliated to the Denizli Provincial Directorate of National Education. The study protocol was approved by The Ethics Committee of Pamukkale University (number 60116787-020/54981). An informed consent form has been signed to the parents of the children.

Motor abilities and proficiencies were evaluated using The short form of the second version of the Bruininks Oseretsky Test of Motor Proficiency (BOTMP 2-SF). This scale was developed by Dr. Robert H. Bruininks [11]. BOTMP 2-SF is able to measure the motor abilities of children from 4 years old until 14.5 years old. The scale was tested for validity and reliability, and its validity and reliability were found to be sufficient. It can be used a screening tool to identify children with motor deficits who may benefit from intervention activities and takes less time to administer. BOTMP 2-SF comprises 8 subtests: Fine motor precision, fine motor integration, manual dexterity, bilateral coordination, balance running speed and agility, upper limb coordination, and strength [11].

The Functional Independence Measure for Children (WeeFIM) was used to measure functional status. This scale contains 18 items, taking minimum amount of time, and has minimum number of questions and provides information about selfcare, sphincter control, mobility, locomotion, communication, and social cognition. Each sub-item of the WeeFIM is scored using a scale that ranges from 1 to 7; 7: fully independent (timely, safety), 6: modified independent (device), 5: supervision, 4: minimal assistance (subject = 75% +), 3: moderate assistance (subject = 50% +), 2: maximal assistance (subject = 25% +), and 1: total assistance (subject = 0% +). The total score is calculated as minimum being 18 and maximum 126 points [12]. WeeFIM was first used to determine the functional status of congenital malformations between 6 months and 7 years of age, and validity and reliability of these disease groups have been demonstrated [13]. For individuals with neurodevelopmental impairment such as special learning disorders, it is used between 6 months and 21

years [14].

Quality of life of the children was evaluated with the Pediatric Quality of Life Inventory (PedsQL). PedsQL was developed by Varni et al. [15] to measure the health-related quality of life for children ages between 2 and 18 years and adolescents. This scale uses a Likert-type scale and asks questions for a child or adolescent of what has happened in the last month. The items are scored between 0 and 100. The answers were never marked as 100 and rarely marked 75; sometimes it was marked 50, at times marked 25, and almost always 0. The total score was calculated by dividing the number of items by the sum of the points received from all items.

Statistical Analysis

The statistical analysis was done by using 16.0 version of Statistical Package for Social Sciences (SPSS) which uses Windows operating system. For the descriptive data average of standard deviation, frequency, and percentage was used. Since the parameters did not show a normal distribution, nonparametric analysis (Mann-Whitney U) was used for compare the groups. In statistics p value was accepted as 0.05 significance level.

RESULTS

The dyslexic children consisted of 21 boys and 7 girls; and the typically developing children were 11 girls and 17 boys. The average age of the dyslexic children was 9.14 ± 1.48 years; the average age of the typically developing children was 9.50 ± 1.26 years (Table 1).

When dyslexic children were compared with typically developing children, there was a significant difference between the two groups in all subtests of BOT 2-SF and the total score ($p < 0.05$) (Table 2). According to WeeFIM test results, there was a significant difference between the two groups in self-care, social cognition, and total score ($p < 0.05$) (Table 2). There was a significant difference between the two groups in all parts of the PedsQL test and in the total score ($p < 0.05$) (Table 3).

Table 1. Demografic data in dyslexic and typically developing children

	Dyslexic children (n = 28)	**Typically developing children (n = 28)**
Age (years)	9.14 ± 1.48	9.50 ± 1.26
Gender		
Boys, n (%)	21 (75)	17 (60.7)
Girls, n (%)	7 (25)	11 (39.3)

Data are shown as mean ± standard deviation or number (percent)

Table 2. Comparison of motor abilities and proficiencies in dyslexic and typically developing children

BOTMP 2-SF subtests	**Dyslexic children**	**Typically developing children**	***p***
Fine motor precision	6.89 ± 4.54	10.92 ± 2.12	0.00*
Fine motor integration	6.85 ± 2.22	8.64 ± 1.76	0.00*
Manual dexterity	5.55 ± 1.46	5.50 ± 1.47	0.00*
Bilateral coordination	0.92 ± 0.89	7.00 ± 0.00	0.00*
Balance	1.50 ± 0.74	8.00 ± 0.00	0.00*
Running speed and agility	7.14 ± 6.81	9.64 ± 1.06	0.03*
Upper-Limb coordination	1.21 ± 0.73	10.82 ±2.07	0.00*
Strength	7.32 ± 4.65	13.17 ± 3.78	0.00*
Total	38.96 ± 15.35	73.35 ± 3.87	0.00*

Data are shown as mean ± standard deviation. BOTMP-2 SF = Short Form of the second version of the Bruininks Oseretsky Test of Motor Proficiency, *Mann Whitney U test ($p < 0.05$)

Table 3. Comparison of functional status and quality of life of dyslexic and typically developing children

	Dyslexic children	Typically developing children	*p*
Self-care	41.00 ± 1.69	42.00 ± 0.00	0.00*
Sphincter control	14.00 ± 0.00	14.00 ± 0.00	1.00
Transfers	21.00 ± 0.00	21.00 ± 0.00	1.00
Locomotion	14.00 ± 0.00	14.00 ± 0.00	1.00
Communication	14.00 ± 0.00	14.00 ± 0.00	1.00
Social cognition	13.14±3.75	20.42 ± 2.11	0.00*
WeeFIM total	117.28 ± 3.83	125.32 ± 2.58	0.00*
Physical	85.71 ± 5.60	91.96 ± 3.84	0.00*
Emotional	81.96 ± 7.85	88.21 ± 11.15	0.01*
Social	36.60 ± 24.11	96.25 ± 4.43	0.00*
School	30.00 ± 16.44	72.40 ± 11.71	0.00*
PedsQL total	61.46 ± 7.48	87.80 ± 6.20	0.00*

Data are shown as mean ± standard deviation. WeeFIM = Functional Independence Measure for Children, PedsQL = Pediatric Quality of Life Inventory, *Mann Whitney U test ($p < 0.05$)

DISCUSSION

The conclusion of this study is that the motor performance consisting of fine motor precision and integration, manual dexterity, bilateral coordination, balance, running speed and agility, and upper limb coordination in dyslexic children was found to be at lower levels than the motor performance of typically developing children. Also, the functional status (self-care and social cognition subsections) and quality of life of dyslexic children was found to be worse than in the typically developing children.

Many studies comparing the motor performance of dyslexic children with typically developing children could be found in the literature. In Miyahara's study [16] the gross motor skills of children with learning disorders and typically developing children were compared, by using the subtests running speed and agility, balance, bilateral coordination, strength, and upper limb coordination of the BOTMP. On the subtests running speed and agility, bilateral coordination and strength significant differences were found between the two groups. In another study dyslexic children were compared with children with good academic performance at school in motor skills by using all subtests of the BOTMP. The result of this study showed a lower performance for dyslexic children in all subtests when compared to other children. Although there is no significant statistical difference found between the two groups in the motor skills subtests, there is a significant difference that is seen in gripping, cutting, drawing, and writing especially in the area of accuracy and hand dexterity [7]. Several studies have compared dyslexic children with typically developing children in terms of balance skills and dyslexic children were worse than typically developing children [5, 17, 18].

In our study, we found that children with dyslexia had lower scores than typically developing children in all subtests of BOTMP 2-SF. The conclusion that was drawn regarding the upper extremity coordination suggests that the difference between the two groups is a clinically significant difference. The evidence of deficiencies in motor skills cannot be interpreted only with the BOTMP 2-SF test because the difficulties in motor skills are heterogeneous and these difficulties include balance, coordination, and motion control and all are related to poor cerebellar function [19]. Nicolson *et al.* [20] suggest that reading and writing problems that come from motor control may not alone be only caused by impaired functioning of the cerebellum in dyslexia. They think that cerebellar dysfunction limits motor control and coordination as well as cognitive skills such as reading. Besides, Berninger *et al.* [21] stated that reading and writing require proper muscle activation for sound production, control of tongue, sensory motor tasks, and hand skills. In this case, dyslexia is closely related to sensory integration [21]. Sensory integration training should be given to dyslexic whose weaknesses is in

academic skills such as reading and writing and for motor problems in the occupational therapy.

According to the additional criteria specified in the DSM IV, motor difficulties have a negative impact on academic achievement and daily living activities [22]. The daily life of individuals with learning disabilities might be affected by neurobiological problems like poor memory, lack of judgment, and problem-solving potential [23]. Accordingly, in their childhood they show poor performance at school, and as adults they face problems when it comes to being able to function professionally [24]. In our study, children with dyslexia received lower scores in self-care and social cognition subscales, and the total scores in the assessment of functional status were also lower than in typically developing children. The fine motor skills and upper extremity coordination are important when it comes to self-care and in performing everyday activities. Dyslexia is also part of the sensorymotor integration that occurs in the majority of our daily life. In this context, our study found that the inadequacies of children with dyslexia in daily activities and in motor skills were perceived by parents, but they were not interviewed and asked about whether they were getting training in daily living activities. According to our findings, we believe that occupational therapy for the difficulties in daily living activities that students meet in school and at home should be supported by legal and standardized educational programs. In addition, individual and group activities may be useful in getting rid of social communication difficulties that they experience in school. Future studies will contribute to the literature by assessing the daily living activity difficulties that are caused by the insufficient motor performance of children with dyslexia such as dyslexia by various methods.

A learning disorder is a lifelong condition. The impact on society is quite meaningful. Children with special learning disorders, like dyslexia, are negatively affected in school, social interaction, and relationships with their family and peers. The social relationships and emotional functionality of an individual might become affected because of cognitive function deficits. Karande *et al.* [25] have stated a lower quality of life status in children with newly diagnosed specific learning disorders. The quality of life of children studying in primary education in Austria wasevaluated by PedsQL, and the result showed a lower quality of life for children who were diagnosed with a disorder as dyslexia [26]. In recent years, there was no difference between the groups in a study that evaluated the quality of life in children with reading disorders and non-reading disorders [27]. In our study, PedsQL was used to assess quality of life and children with dyslexia and those children were found to have lower scores. Insufficient motor performance causes dependence in activities of daily living and poor quality of life status in children with dyslexia.

There is a need for many more studies in order to identify possible causes and underlying mechanisms of dyslexia. As Stoodley and Stein think, the dyslexia sensorymotor relationship can shed some light on these issues [28].

The Limitations of the Study

One of the main limitations of this study is that insufficient number of children with dyslexia participate in this study. Additionally, comparing different age groups that have dyslexia could help the research to achieve a more detailed picture of the effects on motor skills. Another limitation of this study is the use of cross-sectional data.

CONCLUSION

We think that the obtained results need to be assessed in detail in order to help plan occupational therapy and sensorimotor integration training programs for daily living activities in order to increase the quality of life for dyslexic children who were diagnosed in terms of motor performance. In addition to this literature, there is a need for more studies in order to evaluate the motor performance, functional status and quality of life of dyslexic children.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

Acknowledgements

This article was presented as a poster at I.

International Participated Ergotherapy and Rehabilitation Congress, on May 30th - June 1st, 2013, Ankara, Turkey

REFERENCES

[1] American Psychiatric Association, Diagnostic and statistical manual of mental disorders Criteria DSM-4, American Psychiatric Association Washington, DC, 2005.
[2] Badian NA. Reading disability in an epidemiological context: incidence and enviromental correlates. J Learn Disabil 1984;17:129-36.
[3] Siegel LS. Perspectives on dyslexia. Peadiatr 2006;11:581-7.
[4] Kheyroddin B. The comparison of motor skills of dyslexic and nondyslexic students. Med J Tabriz University of Med Sci 2007;28:7-10.
[5] Getchell N, Pabreja P, Neeld K, Carrio V. Comparing children with and without dylexia on the movement assessment battery for children and the test of gross motor development. Percep Motor Skill 2007;105:207-14.
[6] Wolff PH, Michel GF, Ovrut MR. Rate and timing precision of motor coordination in developmental dyslexia. Dev Psychol 1990;26:82-9.
[7] Okudo PMM, Ramos FG, Santos LCA, Padula NAMR, Kirby A, Capellini SA. Motor profile of students with dyslexia. Psychol Res 2014;4:31-39.
[8] Nicolson R, Fawcett A. Dyslexia, dysgraphia, procedural learning and the cerebellum. Cortex 2011;47:117-27.
[9] Pieters S, Desoete A, Van Waelvelde H, Vanderwalsmen R, Roeyers H. Mathematical problems in children with developmental coordination disorder. Res Dev Disabil 2012;13:1128-35.
[10] Savaşır I, Şahin N. Wechsler çocuklar için zeka ölcegi (WISC-R) uygulama kitapçığı. Türk Psikologlar Dernegi, Ankara, 1995.
[11] Bruininks R, Bruininks B. Bruininks-Oseretsky test of motor proficiency (2nd ed.). Minneapolis, MN: NCS Pearson; 2005.
[12] Msall ME, DiGaudio K, Rogers BT, LaForest S, Catanzaro NL, Campbell J, et al. The Functional Independence Measure for Children (WeeFIM). Conceptual basis and pilot use in children with developmental disabilities. Clin Pediatr (Phila) 1994;33:421-30.
[13] Msall ME, DiGaudio KM, Duffy LC. Use of functional assessment in children with developmental disabilities. Phys Med Rehabil Clin North Am 1993;4:517-27.
[14] Gurucharri L. Measuring developmental and functional status in children with disabilities. Pediatr Phys Ther 2003;15:43-5.
[15] Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care 1999;37:126-39.
[16] Miyahara M. Subtypes of students with learning disabilities based upon gross motor functions. Adapt Phys Activ Q 1994;11:368-82.
[17] Chaix Y, Albaret JM, Brassarda C, Cheureta E, Castelnaua P, Benesteaua J, et al. Motor impairment in dyslexia: the influence of attention disorders. Eur J Peadiatr Neurol 2007;11:368-74.
[18] Nicolson RI, Fawcett AJ. Comparison of deficits in cognitive and motor skills among children with dyslexia. Ann Dyslexia 1994;44:147-64.
[19] O'Hare A, Khalid S. The association of abnormal cerebellar function in children with developmental coordination disorder and reading difficulties. Dyslexia 2002;8:234-48.
[20] Nicolson RI, Fawcett AJ, Dean P. Developmental dyslexia: the cerebellar deficit hypothesis. Trends Neurosci 2001;24:508-11.
[21] Berninger VW, Nielsen KH, Abbott RD, Vinjsman E, Raskind W. Writing problems in developmental dyslexia: under-recognized and under-treated. J Sch Psychol 2008;46:1-21.
[22] Visser, J. Developmental coordination disorder: a review of research on subtypes and comorbidities. Human Mov Sci 2003;22:479-93.
[23] Tsatsanis KD, Fuerst DR, Rourke BP. Psychosocial dimensions of learning disabilities: External validation and relationship with age and academic functioning. J Learn Disabil 1997;30:490-502.
[24] Silver CH, Ruff RM, Iverson GL, Barth JT, Broshek DK, Bush SS, et al. Learning disabilities: the need for neuropsychological evaluation. Arch Clin Neuropsychol 2008;23:217-9.
[25] Karande S, Bhosrekar K, Kulkarni M, Thakker A. Health-related quality of life of children with newly diagnosed specific learning disability. J Tropic Pediatr 2008;55:161-9.
[26] Felder-Puig R, Baumgartner M, Topf R, Gadner H, Formann AK. Health related quality of life in Austrian elementary school children. Med Care 2008;46:432-9.
[27] Balazs J, Miklosi M, Toro KT, Nagy-Varga D. Reading disabilities and quality of life based on both self- and parent- reports: importance of gender differences. Front Psychol 2016;15:1942.
[28] Stoodley CJ, Stein JF. The cerebellum and dyslexia. Cortex 2011;47:101-16

The European Research Journal 2018;4(4):320-325 ORIGINAL ARTICLE

Effects of a single dose 20 mg tadalafil on resistive index value of prostate zones

Tayfun Şahinkanat[1], Erkan Efe[1], Hasan Çetin Ekerbiçer[2], Faruk Küçükdurmaz[1]

[1]Department of Urology, Kahramanmaraş Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey
[2]Department of Public Health, Sakarya University School of Medicine, Sakarya, Turkey

DOI: 10.18621/eurj.349721

ABSTRACT

Objectives: Although there are several studies addressing the efficacy of phosphodiesterase type 5 inhibitors for the management of benign prostatic hyperplasia-lower urinary tract symptoms (BPH-LUTS), unfortunately, there is a lack of high evidence data to support their effect at the prostate level. The existing studies suggested that resistive index (RI) could be used as a hemodynamic parameter to measure the severity of benign prostatic hyperplasia and intraprostatic pressure or bladder outlet obstruction. The aim of this study was to evaluate the effect of a single dose 20 mg tadalafil on resistive index value in prostate zones to evaluate the mechanism of action of phosphodiesterase type 5-inhibitors at the prostate level.

Methods: Twenty consecutive patients aged between 54-67 years with BPH-LUTS [International Prostate Symptom Score ≥ 12] and erectile dysfunction [five-item International Index of Erectile Function (IIEF) questionnaire < 22] underwent RI measurement in prostate transitional zone (TZ) and peripheral zone (PZ) using transrectal power Doppler ultrasonography baseline and within 16 hours after the administration of 20 mg tadalafil. The primary study end point is the change in prostate TZ RI values.

Results: The mean baseline total prostate scores and peak urinary flow were 16.2 ± 4.34 (range: 12-26) and 10.45 ml/s (range: 7-13 ml/s), respectively. The mean baseline total IIEF was 12.8 ± 4.22 (range: 6-20). The mean TZ RI at baseline and after tadalafil administration were 0.4985 and 0.5497, respectively (p = 0.232). No statistically significant differences for RI changes between baseline and after the administration of a single dose 20 mg tadalafil were observed in the prostatic zones.

Conclusion: A single dose 20 mg tadalafil showed no impact on prostate TZ RI.

Keywords: tadalafil, prostate, phosphodiesterase type 5 inhibitors, resistive index, erectile dysfunction

Received: November 7, 2017; Accepted: January 2, 2018; Published Online: March 21, 2018

The incidence of lower urinary tract symptoms (LUTS) secondary to clinical benign prostatic hyperplasia (BPH) increases with aging and is often a comorbid condition with erectile dysfunction [1]. Given the multiple pathways by which nitric oxide influences and mediates male prostatic function by increasing the blood perfusion, there has been substantial interest in the potential of phosphodiesterase type 5 inhibitors (PDE5i) in the treatment of LUTS [2, 3].

Tadalafil is an oral selective inhibitor of the enzyme phosphodiesterase type 5 (PDE5) that is currently used for the management of erectile dysfunction and LUTS associated with BPH. Many studies in men with benign prostatic hyperplasia-lower urinary tract symptoms (BPH-LUTS) have

Address for correspondence: *Faruk Küçükdurmaz MD, FECSM, MD., Kahramanmaraş Sütçü İmam University School of Medicine, Department of Urology, Kahramanmaraş, Turkey*
E-mail: fkucukdurmaz@gmail.com, Tel: +90 344 3003800

e-ISSN: 2149-3189

consistently demonstrated statistically significant improvements in International Prostate Symtom Score (IPSS) with tadalafil [1, 3].

In the literature, several clinical studies of tadalafil and other PDE5i have reported significant symptom reduction as assessed by IPSS in patients with BPH compared to placebo [1-4]. It is not completely clear what role PDE5 inhibition plays in the treatment of LUTS since most of those studies failed to demonstrate a significant effect on the urinary flow [1, 2, 4, 5]. Roehrborn *et al*. [5] reported that improvements in LUTS occurred without a significant increase in overall peak urinary flow (Qmax) and different doses of tadalafil provided similar results. In a recent dose-finding study in more than 1000 men with moderate to severe BPH-LUTS, while tadalafil was associated with significant improvements in multiple measures of LUTS and quality of life compared to placebo, no statistically significant effect of treatment compared to placebo was noted for Qmax at any tadalafil dose [1].

Although all those studies reported limited Qmax improvement, the precise mechanism of action of PDE5i at the prostate level remains unclear. The most widely accepted hypothesis, based on studies conducted on prostate tissue specimens [6, 7], is that those agents act by reducing the smooth muscle tone, but this effect could produce vascular changes as well [8]. However, this effect has not been adequately shown in vivo until now.

On the other hand, recent studies have demonstrated the potential value of resistive index (RI = maximum velocity-minimum velocity/maximum velocity) measurement (by using transrectal pulsed-wave spectral Doppler imaging) of prostate in the evaluation of the severity of BPH and the degree of intraprostatic pressure or bladder outlet obstruction [9-11]. In a series examining 214 men with BPH, power Doppler imaging revealed that RI was discriminative between normal patients and patients with BPH [12]. Thus, if PDE5i showed their effect on LUTS by reducing the smooth muscle tone of the prostate, it is reasonable to expect a relationship between mechanism of action of PDE5i at the prostatic level and RI of prostate.

Therefore, the aim of this study was to assess whether a single dose 20 mg tadalafil administration induces changes in prostatic vasculature as a marker of the smooth muscle tone of the prostate that can be detected with RI.

METHODS

Men aged over 45 years and who were diagnosed as erectile dysfunction determined by a score of less than 22 in International Index of Erectile Function (IIEF) questionnaire and BPH-LUTS, as clinically diagnosed more than 6 months before screening, with IPSS > 13 were enrolled in the study. All patients underwent uroflowmetry and a peak urinary flow rate (Qmax) of less than 15 mL/s (from an ultrasonography-assessed prevoid total bladder volume of > 150 to < 550 mL and a minimum voided volume of 125 mL) were included.

Men were excluded from the study if they met any of the criteria such as being nitrate or nitric oxide donors, use of α-blockers, anti androgens, 5α-reductase inhibitors within the previous 6 months; a history of pelvic surgery, radiotherapy and prostate biopsy. In addition, men with an evidence on baseline transrectal ultrasound (TRUS) of any conditions that could interfere with ultrasonographic blood flow measurement such as lower urinary tract malignancy, trauma or recent instrumentation; urinary retention; urethral obstruction due to stricture, sclerosis or tumor; bladder calculi; neurogenic bladder; detrusor-sphincter dyssynergia; urinary tract inflammation or infection; prostate cancer; any drug administration or neurologic diseases affecting the lower urinary system and a post-voiding residual volume of ≥ 350 ml at the screening visit were also excluded from the study.

The study was approved by local-ethics committee (Protocol no:188/29-2015). An informed consent before the study was obtained from each participant. The effect of tadalafil on the smooth muscle tone of the prostate was assessed by RI measurement. By using this approach, it was able to demonstrate that prostatic blood flow was altered following tadalafil administration and this change could be detected in a reproducible and noninvasive manner with transrectal power Doppler ultrasonography (PDUS).

TRUS Procedures and Measurement of Blood Flow Parameters

All TRUS examinations were performed using the

Table 1. RI values of various prostate zones before and after the administration of 20 mg tadalafil

Prostate zones	RI		*p* value
	Mean ± SD	Median (min-max)	
Left side PZ			< 0.001
Baseline	0.51 ± 0.05	0.52 (0.42-0.65)	
After tadalafil	0.57 ± 0.03	0.56 (0.50-0.66)	
Right side PZ			0.001
Baseline	0.54 ± 0.04	0.54 (0.47-0.60)	
After tadalafil	0.56 ± 0.03	0.56 (0.49-0.61)	
Left side TZ			0.007
Baseline	0.49 ± 0.06	0.49 (0.37-0.59)	
After tadalafil	0.54 ± 0.06	0.53 (0.42-0.71)	
Right side TZ			0.298
Baseline	0.49 ± 0.04	0.50 (0.40-0.57)	
After tadalafil	0.55 ± 0.03	0.54 (0.48-0.61)	

RI = resistive index, PZ = peripheral zone, TZ = transition zone

same patient position throughout the study that is left decubitus and on men with an empty or nearly-empty bladder to avoid extrinsic compression affecting intraprostatic vessels. TRUS examinations were performed using a SSI-8000 ultrasound machine equipped with ultrasound-angio for power Doppler imaging with a 5.0 MHz end-fire probe. Blood flow samples were obtained and followed by spectral waveform analysis. When pulsatile waveforms of a given Doppler spectrum became stable, RI (maximum velocity-minimum velocity/maximum velocity) was measured from each blood flow sample using on-board software and the mean value was recorded. Power Doppler imaging of both right and left lobes of the prostate was performed and prostate transitional zone (TZ) RI and peripheral zone (PZ) RI were measured. Mean RI values were calculated by dividing the sum of right and left lobe RI results into two. All patients underwent RI measurement in prostate TZ and PZ using transrectal PDUS at baseline and within 16 hours after administration of single dose 20 mg tadalafil. The primary end point was the change in prostate TZ RI values. All measurements were performed by the same examiner (EE), who was blinded to the symptom scores of the patients at the time of the sonographic studies.

Statistical Analysis

Data were expressed as mean ± standard deviations or as medians and ranges. Post-hoc power analysis were conducted using RI values of four prostate zones before and after the administration of 20 mg tadalafil and the minimum power was calculated as 97.5%. A related-samples Wilcoxon Signed Rank test was performed to compare RI values. Calculations were performed using G*Power version 3.1.9.2 (Franz Faul, Universitat Kiel, Germany) and SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

The mean baseline IPSS and Qmax were 16.2 ± 4.34 (range: 12-26) and 10.45 ml/s (range: 7-13 ml/s), respectively. Fifteen (75%) patients had moderate BPH-LUTS (total IPSS = 8-19) at baseline. The mean baseline total IIEF was 12.8 ± 4.22 (range: 6-20). Mild to moderate erectile dysfunction (total IIEF = 12-16) was 60% (n =12) in the study population.

The mean TZ RI at baseline and after tadalafil administration were 0.4985 and 0.5497, respectively ($p = 0.232$). According to the prostate zones, statistically significant differences for changes between baseline and after the administration of a single dose 20 mg tadalafil were observed in RI of the left side TZ, and both sides of PZ appeared in the form of increasing while no statistically significant difference was observed in RI of the right side TZ. RI values in different prostate zones at baseline and after tadalafil administration are shown in Table 1.

DISCUSSION

The available studies on the use of PDE5i for the treatment of LUTS are promising. Criticism of the use of PDE5i in LUTS has centered over the lack of precise understanding of the mechanism of action of these agents at the prostate level [13-15]. There are some studies to explain the effect of PDE5i at prostatic level. Bertolotto *et al*. [14] reported that after single dose tadalafil administration, the enhancement peak and area under curve (AUC) increased significantly ($p < 0.01$), reflecting changes in prostatic vasculature which can be detected with contrast-enhanced US. Haaga *et al*. [15] showed that sildenafil increased the enhancement and blood flow of the normal prostate on contrast-enhanced magnetic resonance imaging.

Clinical data on the effect of PDE5i on smooth muscle tone of the prostate are limited [13, 14]. RI, which is emerging as a new and promising parameter, measures the intraprostatic pressure changes and blood flow and, thereby, can be used to explain the mechanism of action of PDE5i on the prostate. Prior observational studies have suggested that RI in the prostate TZ of men with BPH is higher than that measured in healthy controls, suggesting decreased prostate blood flow in those men [12].

In the present study, we assessed whether a single dose 20 mg tadalafil administration induces changes in prostatic tone that can be detected with RI measurement in the patients with erectile dysfunction and LUTS. The primary analysis of our results did not reveal an effect of single dose 20 mg tadalafil on the RI measured in the prostate TZ. This may be due to the high rate of patients (75%) with moderate LUTS and the mean TZ RI (0.4985) at baseline was lower than expected range of mean arterial RI in the prostate of men with BPH (0.70 to 0.80) [10, 16-20]. Moreover, the role of the effect of PDE5i on prostate may be more pronounced in men with true obstruction (Qmax < 10 ml/s) than the men with a Qmax of > 10 ml/s. Roehrborn *et al*. [1] reported that tadalafil treatment resulted in larger numeric improvements in Qmax, bladder capacity and voiding efficiency compared with placebo in men with uroflowmetrically verified obstruction at baseline. In our study, the mean baseline Qmax was 10.45 ml/s (range: 7-13 ml/s).

In a randomized placebo-controlled study, Pinggera *et al*. [13] reported that tadalafil 5 mg once daily for 8 weeks did not provide detectable decreases in arterial RI in the prostate or bladder neck in men with BPH-LUTS. Our results are consistent with that study. According to that study, detection of changes may not be possible because of already low baseline, insufficient sensitivity of techniques used, or may have been confounded by methodologic variability across sites.

One possibility is that the lack of effect of PDE5i on flow rate in some patients with LUTS suggests that smooth muscle relaxation of the prostate and/or urinary outlet are only a partial mechanistic contributor to PDE5i-related improvements in BPH-LUTS. A randomized, double-blind, placebo-controlled study investigated the effects of a twice-daily treatment with vardenafil 10 mg in 222 patients (IPSS ≥ 12, mean age of 56 yr) on irritative and obstructive LUTS secondary to BPH with or without erectile dysfunction [2]. After 8 weeks of treatment, there was a significant improvement in the IPSS scores in the vardenafil group compared with placebo (-5.9 vs. -3.6, $p < 0.0013$) as well as in irritative and obstructive IPSS sub-scores and in a quality-of-life questionnaire. The authors also reported that the effects of PDE5i on storage symptoms are more marked than on the voiding symptoms, and maximal flow rate and post-void residual volume did not change. Besides, the superiority of combination of alpha-blocker and PDE5i over either single agent in the treatment of LUTS also suggests that alternative mechanisms may be involved [21]. In addition to aforementioned studies, the present study provided evidence that the effects of PDE5i on urinary symptoms are not predominantly mediated through its effects on prostate.

The Limitations of the Study

It should be mentioned that our study had several major limitations. First, it was conducted on a small patient series, so our findings require validation on larger populations. Second, the imaging techniques used were technically complex and are not part of routine clinical management for BPH. Third, the mean TZ RI at baseline was lower than expected range of mean arterial RI in the prostate of men with BPH. This limitation could potentially be addressed by only enrolling patients with a prostatic RI confirmed to be at least 0.70 or higher at baseline. In addition, since

peripheral zone of the prostate was not thought to be involved in the development of LUTS, we did not discuss the significant PZ RI differences and mean prostate RI values in the study.

Moreover the mean Qmax at baseline was 10.45 ml/s (range: 7-13 ml/s). Lack of measurement of prostate sizes is another limitation of the study. Further clinical trials into account the RI measurement of prostate in the men with Qmax ≤ 10 ml/s will better clarify the mechanism of action of PDE5i at the prostate level. Lastly, our results based on a single dose of 20 mg tadalafil which is not indicated for daily use.

CONCLUSION

The available studies on the use of PDE5i for the treatment of LUTS are promising. However, clinical data on the effect of PDE5i on the prostate level are limited. Resistive index measurement allows objectively evaluation of tone of the smooth muscle of the prostatic stroma (the dynamic component of bladder outlet obstruction) and can therefore help to explain the mechanism of action of PDE5i at the prostate level. In the present study, single dose 20 mg tadalafil in men with BPH-LUTS and erectile dysfunction did not result in decreases in arterial RI in prostate. The missing effect on RI may be due to the fact that we included predominantly men without obstruction or smooth muscle relaxation of the prostate and/or urinary outlet tract are only a partial mechanistic contributor to PDE5i-related improvements in BPH-LUTS. A bigger sample size consist with men with true obstruction (Qmax < 10 ml/s) is required in order to confirm our results.

Author contributions

TŞ = Project development, conception and design, data collection and management, manuscript writing. EE = Conception and design, data collection, manuscript writing. HCE = Data analysis, statistical analysis, manuscript editing. FK = Data collection and management, data analysis, manuscript writing and editing.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] Roehrborn CG, McVary KT, Elion-Mboussa A, Viktrup L. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study. J Urol 2008;180:1228-34.
[2] Stief CG, Porst H, Neuser D, Beneke M, Ulbrich E. A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Eur Urol 2008;53:1236-44.
[3] McVary KT, Roehrborn CG, Kaminetsky JC, Auerbach SM, Wachs B, Young JM, et al. Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia. J Urol 2007;177:1401-7.
[4] McVary KT, Monnig W, Camps JL Jr, Young JM, Tseng LJ, van den Ende G. Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: A randomized, double-blind trial. J Urol 2007;177:1071-7.
[5] Roehrborn CG, Kaminetsky JC, Auerbach SM, Montelongo RM, Elion-Mboussa A, Viktrup L. Changes in peak urinary flow and voiding efficiency in men with signs and symptoms of benign prostatic hyperplasia during once daily tadalafil treatment. BJU Int 2010;105:502-7.
[6] Tinel H, Stelte-Ludwig B, Hutter J, Sandner P. Pre-clinical evidence for the use of phosphodiesterase-5 inhibitors for treating benign prostatic hyperplasia and lower urinary tract symptoms. BJU Int 2006;98:1259-63.
[7] Waldkirch ES, Uckert S, Langnase K Richter K, Jonas U, Wolf G, et al. Immunohistochemical distribution of cyclic GMP-dependent protein kinase-1 in human prostate tissue. Eur Urol 2007;52:495-501.
[8] Grimsley SJ, Khan MH, Jones GE. Mechanism of phosphodiesterase 5 inhibitor relief of prostatitis symptoms. Med Hypotheses 2007;69:25-6.
[9] Yencilek E, Koyuncu H, Arslan D, Bastug Y. The measurement of the prostatic resistive index is a reliable ultrasonographic tool to stratify symptoms of patients with benign prosthatic hyperplasia. Med Ultrason 2014;16:208-13.
[10] Zhang X, Li G, Wei X, Mo X, Hu L, Zha Y, et al. Resistive index of prostate capsular arteries: a newly identified parameter to diagnose and assess bladder outlet obstruction in patients with benign prostatic hyperplasia. J Urol 2012;188:881-7.
[11] Kojima M, Ochiai A, Naya Y, Okihara K, Ukimura O, Miki T. Doppler resistive index in benign prostatic hyperplasia: correlation with ultrasonic appearance of the prostate and infravesical obstruction. Eur Urol 2000;37:436-42.
[12] Tsuru N, Kurita Y, Masuda H, Suzuki K, Fujita K. Role of Doppler ultrasound and resistive index in benign prostatic hypertrophy. Int J Urol 2002;9:427-30.
[13] Pinggera GM, Frauscher F, Paduch DA, Bolyakov A, Efros M, Kaminetsky J, et al. Effect of tadalafil once daily on prostate blood flow and perfusion in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia: a randomized, double-blind, multicenter, placebo-controlled trial. Urology 2014;84: 412-20.
[14] Bertolotto M, Trincia E, Zappetti R, Bernich R, Savoca G, Cova

MA. Effect of tadalafil on prostate haemodynamics: preliminary evaluation with contrastenhanced US. Radiol Med 2009;114:1106-14.
[15] Haaga JR, Exner A, Fei B, Seftel A. Semiquantitative imaging measurement of baseline and vasomodulated normal prostatic blood flow using sildenafil. Int J Impot Res 2007;19:110-3.
[16] Berger AP, Deibl M, Leonhartsberger N, Bektic J, Horninger W, Fritsche G, et al. Vascular damage as a risk factor for benign prostatic hyperplasia and erectile dysfunction. BJU Int 2005;96:1073-8.
[17] Kojima M, Watanabe H, Watanabe M, Okihara K, Naya Y, Ukimura O. Preliminary results of power Doppler imaging in benign prostatic hyperplasia. Ultrasound Med Biol 1997;23:1305-9.
[18] Abdelwahab O, El-Barky E, Khalil MM, Kamar A. Evaluation of the resistive index of prostatic blood flow in benign prostatic hyperplasia. Int Braz J Urol 2012;38:250-5.
[19] Özden C, Günay I, Deren T, Bulut S, Koparal S, Memiş A. Effect of doxazosin on prostatic resistive index in patients with benign prostatic hyperplasia. Fırat Tıp Dergisi 2009;14:171-4.
[20] Ozden C, Gunay I, Deren T, Bulut S, Ozdal OL, Koparal S, et al. Effect of transurethral resection of prostate on prostatic resistive index. Urol Int 2010;84:191-3.
[21] Gacci M, Corona G, Salvi M, Vignozzi L, McVary KT, Kaplan SA, et al. A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combinationwith α-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol 2012;61:994-1003.

The European Research Journal 2018;4(4):326-332 ORIGINAL ARTICLE

Impact of low-pressure pneumoperitoneum and local anesthetic combination on postoperative pain in patients undergoing laparoscopic cholecystectomy

Oğuz Uğur Aydın, Lütfi Soylu

Department of General Surgery, Güven Hospital, Ankara, Turkey

DOI: 10.18621/eurj.345129

ABSTRACT

Objectives: Despite the advantages of laparoscopic cholecystectomy (LC), postoperative pain remains a major complaint for many patients. In this study, in patients undergoing LC, the application of LC via incisional bupivacaine and low inflation pressure, alone or combined, and a comparison of the effects on postoperative pain has been purposed.

Methods: Patients were randomly assigned into the following 4 groups: the standard pressure (SP) group (n = 30); patients with an intraabdominal insufflation pressure of 12 mmHg, where bupivacaine application was not performed at the trocar locations. The SP+local anesthetic (LA) (SP+LA) group (n = 30); patients with an intraabdominal insufflation pressure of 12 mmHg, where bupivacaine application was performed at the trocar locations. The low pressure (LP) group (n = 30); patients with an intraabdominal insufflation pressure of 8 mmHg, where bupivacaine application was not performed at the trocar locations. The (LP+LA) group (n = 30); patients with an intraabdominal insufflation pressure of 8 mmHg, where bupivacaine application was performed at the trocar locations. Postoperative pain was evaluated using the visual analogous scale (VAS).

Results: When the relationships between the VAS scores, gender, age, and American Society of Anesthesiologists classification were evaluated, no significant relationships between the groups were observed ($p > 0.05$). A significant relationship between the groups was detected with regards to the VAS scores, 1st analgesic application, 2nd analgesic application, and patients' satisfaction ($p < 0.05$).

Conclusions: The combination of low insufflation pressure with intrafacial preincisional local anesthetic infiltration in post-LC pain palliation is thought to be more effective and applicable.

Keywords: Laparoscopic cholecystectomy, local anesthetic, low pressure

Received: October 19, 2017; Accepted: January 8, 2018; Published Online: February 16, 2018

Laparoscopic cholecystectomy (LC) has been the gold standard method of treatment since the 1990s for symptomatic gallbladder stones [1]. Studies in the literature comparing it with open surgery have revealed that LC leads to a decrease in postoperative pain, analgesic consumption, and hospital stay.

Despite the advantages of laparoscopic surgery, postoperative pain is a significant complaint factor for many patients. Pain reaches its peak value within several hours postoperatively and disappears within an average of 48-72 h. Postoperative pain may lead to tachycardia, an increase in the cardiac load, nausea, vomiting, and deceleration of the bowel passage. This situation is strongly related with a long hospital stay

Address for correspondence: *Oğuz Uğur Aydın, MD., Güven Hospital, Department of General Surgery, 06540 Ankara, Turkey*
E-mail: oguzuguraydin71@gmail.com
Fax: +90 312 4572894

e-ISSN: 2149-3189

and morbidities, such as pulmonary complications, which is especially important in centers where this operation is executed on a daily basis [2].

In most cases, postoperative pain after LC is encountered on the abdominal wall at the incision site, with the systemic and local affect at abdominal region that pneumoperitoneum leads and at liver on the bed where gall bladder is located.

Based on carbon dioxide insufflation, an increase in intraabdominal pressure leads to a change of function in many organs in the body, which then also leads to postoperative pain. The degree of intraabdominal pressure is directly related to these changes. LC can be performed through pneumoperitoneum that was formed via low pressure, but the obtained operational area will be more limited than the area obtained via high pressure. There are studies in the literature indicating that, with low-pressure pneumoperitoneum, it is possible to reduce postoperative pain [3, 4].

Local anesthetic infiltration at the trocar site is effective postoperatively within the first 24-48 h of pain palliation and a decrease in pain occurs after 24 h. It has be seen that the application is simple, secure, and low-cost, but when its effectiveness is researched, there are many studies that indicate results with opposite opinions [5, 6].

The pain visual analogous scale (VAS) is a valid tool for measuring pain at one point in time. After LC, regarding pain palliation, studies regarding the use of various local anesthetics (tenoxicam [7], non-steroidal anti-inflammatory medications [8], tramadol [9], morphine [10], beta blockers [11], and fentanyl [12]) do exist in the literature, but they do not offer much hope.

Within this study, in patients undergoing LC, the application of LC via incisional bupivacaine and low inflation pressure, alone or combined, and a comparison of the effects on postoperative pain has been purposed.

METHODS

Before beginning this study, approval was granted by the Research Ethical Committee of Guven Hospital, Ankara, Turkey. Included in this randomized, placebo-controlled study were 120 patients above the age of 18, who gave written and oral approval, and were due to have elective LC. LC were performed for symptomatic gallbladder stones. Exclusion criteria for the study included the following: patients with defined psychiatric diseases stories, alcohol addiction, or pregnant women; patients who use psychotropic and opioid medications, defined chronic pain not related to gall bladder stones, use steroids, are sensitive to local anesthetics, or have had operations because of acute cholecystitis, due to the risk of bleeding or surgery-related risks after drainage. Patients were categorized according to the American Society of Anesthesiologists (ASA) classification I or II, and operated on between June 2016 and June 2017.

The patients were randomly assigned into 4 groups using the closed envelope method as follows: The standard pressure (SP) group (n = 30); patients with an intraabdominal insufflation pressure of 12 mmHg, where bupivacaine (Marcaine®) application was not performed at the trocar locations. The SP+local anesthetic (LA) (SP+LA) group (n = 30); patients with an intraabdominal insufflation pressure of 12 mmHg, where bupivacaine application was performed at the trocar locations. The low pressure (LP) group (n = 30); patients with an intraabdominal insufflation pressure of 8 mmHg, where bupivacaine application was not performed at the trocar locations. The (LP+LA) group (n = 30); patients with an intraabdominal insufflation pressure of 8 mmHg, where bupivacaine application was performed at the trocar locations. In a preoperative meeting with the patients, detailed information regarding the VAS was provided and the patients were instructed with regards to how to evaluate themselves postoperatively, as follows: 0 indicates no pain and 10 represents the highest level of pain. The postoperative pain levels were inquired about and collected by responsible nurses, who were not provided with any information regarding the intraoperative local anesthetic applications and insufflation pressure. With regard to the nurses collecting the VAS pain scores, both questioning and analgesic requirement application training was provided. In cases where a VAS pain score of ≥4 was attained, intravenous (iv) dexketoprofen (Arveles® 50 mg) was administered. In cases requiring an analgesic, iv dexketoprofen was administered.. None of the patients received a preemptive analgesic application. Anesthetic induction

was executed through Fentanyl (Talinad®) (1-2 mg/Kg/min iv infusion) and Propofol (Propofol®) (2mg/kg, iv). Every patient received tracheal intubation. Sustainability of the anesthetics was provided via Sevoflurane 1%-1.5% at intervals with Fentanyl, oxygen/air. The end tidal CO2 pressure was sustained at 35-45 mmHg via mechanical ventilation. Metoclopramide (Metpamide®) iv 10 mg was administered to all of the patients, either during the operation or after, in order to prevent nausea and vomiting before they woke up.

All of the LC applications were executed by surgeons who had performed at least 200 LC operations. In order to avoid pneumoperitoneum, and avoid a vasovagal reaction, an initial slow current (3 L/min) was administered followed by a fast current (15 L/min) afterwards in the LP group, whereas in the SP group, the value was fixed. After which, the patients were placed into the reverse-Trendelenburg position. All of the LCs were performed with 4 trocars. At both the 10-mm infraumbilical and 10-mm subxiphoid incision locations and again at the 5-mm frontal axis, and 5-mm midclavicular incision locations, the incision was performed on the left-side of the abdomen. After which, the cystic artery and cystic ductus were clipped with non-absorbable clips and the gall bladder was separated from the liver bed, and placed inside of an endobag, which was then taken out through the subxiphoid at the 10-mm trocar incision and removed via the abdomen. At the infraumbilical and subxiphoid incision locations, the fascia was closed with number 0 non-absorbable sutures. The skin was closed subcutaneously with 3-0 absorbable suture material. Bupivacaine of 0.5% (50 mg) (each 10 mL, containing bupivacaine hydrochloride 52.8 mg equivalent to anhydrous bupivacaine hydrochloride 50 mg) was then diluted with 10 mL of physiological saline solution until a solution of 20 mL was reached. Next, 6 cc infraumbilical, 6 cc subxiphoid, if 4 cc to lateral incision trocar locations just before the incision was injected intrafascially. At 8 h postoperatively, all of the patients were offered something to eat and drink.

Zero-hour was considered to be when the patients were returned to their rooms for recovery. From this point onward, the requirement for analgesics within the first 24 h (0 min, 30 min, 1 h, 2 h, 6 h, 12 h, and 24 h) and the pain scores were recorded. Patients with VAS pain scores of ≥ 4 were administered iv dexketoprofen (50 mg).

Statistical Analysis

Significant differences in the various categorical variables, such as gender, ASA, patient satisfaction, etc., were analyzed via chi square analysis, whereas significant differences in the quantitative variables, such as age, operation duration, and VAS values were analyzed via 1-way analysis of variance (ANOVA) analysis. As a result of the 1-way ANOVA analysis, in cases where differences were observed within the groups, the Tukey test was used in order to identify which group represented that distinction. Analysis was applied using the Statistical Package for the Social Sciences 20.0 software at a 95% significance level.

Table 1. Demographic characteristics of the patients, time of first dose of analgesic, and operation duration details.

		Groups								
		SP		SP+LA		LP		LP+LA		*p*
		n	%	n	%	n	%	n	%	
Gender	Male	18	32.10%	11	19.60%	12	21.40%	15	26.80%	0.260
	Female	12	18.80%	19	29.70%	18	28.10%	15	23.40%	
ASA	I	9	22.50%	6	15.00%	12	30.00%	13	32.50%	0.212
	II	21	26.30%	24	30.00%	18	22.50%	17	21.30%	
Age		47.1±11.6		50.7±2.2		51.3±12.1		52.2±14.7		0.437
First analgesic time		5.1±12.7		91.4±117.5		44.2±72.9		193±208,9		**0.000**
Surgery time		32.3±9.6		30.4±9.5		42.8±10.8		40.4±11.3		**0.000**

ASA = American Society of Anesthesiologists classification, LA = local anesthetic, LP = low pressure, SP = standard pressure

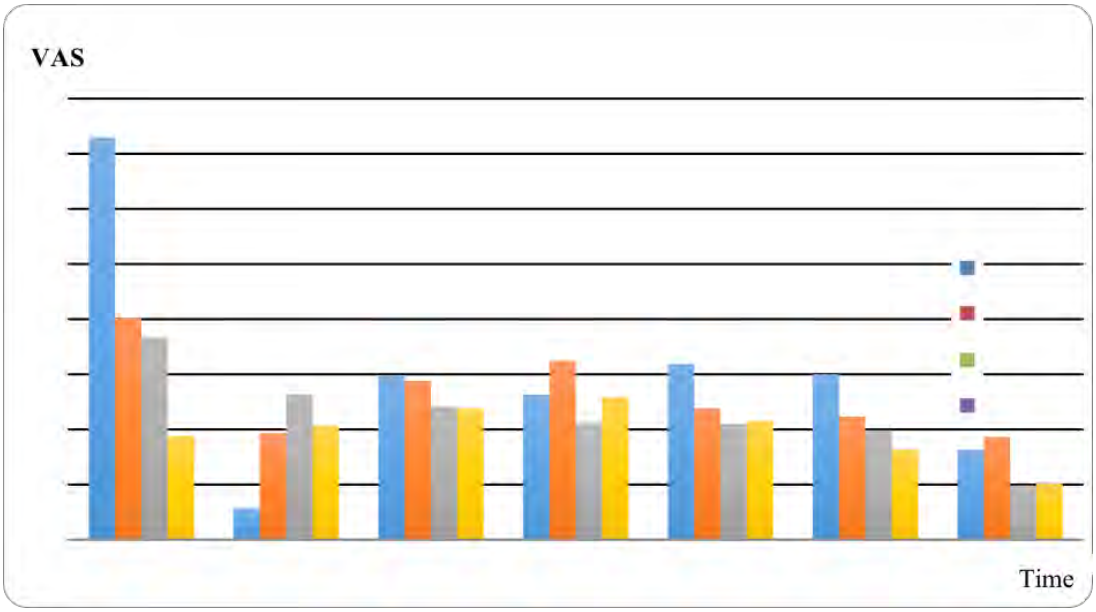


Figure 1. Pain scores according to hours. VAS = visual analogous scale

RESULTS

The demographic characteristics of the patients, average time of the 1st dose of analgesic, and operation duration details, as well as distinctions among the groups can be seen in Table 1.

When the relationship between the VAS scores and gender was evaluated, it was observed that there was no significant relationship between the groups and gender ($p > 0.05$). When the relationship between the ASA and VAS scores was evaluated, no significant relationship was detected ($p > 0.05$). When we evaluated whether the distinction was significant between the VAS scores and gender averages, and the differences between these averages, among the groups regarding age, it was determined that there was no significant distinction ($p > 0.05$).

When we examined the groups with regards to the average time of the 1st dose of analgesic and whether the distinctions between those averages were significant or not, a significant difference among the groups was observed ($p < 0.05$). That average time in the LP+LA group was detected as significantly higher than that of the average values in the other groups ($p < 0.001$). Additionally, in the SP+LA group, the average time of the 1st dose of analgesic was found to be only slightly higher than that of the standard group average ($p < 0.001$). The other groups were identified as having no significant distinction.

According to the group results, when the operation durations were analyzed, a significant distinction was also detected. In the LP group, the average operation was observed to be significantly longer than that in the SP group ($p < 0.05$). Different times of the analysis results, in cases of coughing and at rest, in order to identify whether or not there was a significant difference between the group VAS scores, are shown in Table 2 ($p < 0.05$). At 0 min, the rest and coughing VAS scores were identified as significantly high in the SP group ($p < 0.001$). At 30 min, the VAS scores in the SP group were detected as significantly low ($p < 0.001$). When the LP+LA group average was compared with that of the standard treatment group, it was observed to be significantly low at 12 and 24 h ($p < 0.05$). Moreover, in the SP group, the pain scores at 12 and 24 h were significantly higher than those in the SP+LA group. A graphical representation of the pain scores according to the hour can be seen in Figure 1.

According to the relationship between the group and patient satisfaction; in the SP group, 40% of the patients had negative opinions and feedback, 43.3% were averagely satisfied, and 16.7% were satisfied; in the SP+LA group, 20% had negative feedback, 60% were averagely satisfied, and 20% were satisfied; in the LP group, 16.7% had negative feedback, 50% were averagely satisfied, and 33.3% were satisfied, and in the LP+LA group, 10% had negative feedback, 26.7% were averagely satisfied, and 63.3% were satisfied. It

Table 2. VAS scores in cases of coughing and at rest.

Time		SP	SP+LA	LP	LP+LA	*p*
0 min	Rest	6.73±1.89	3.67±1.3	3.37±1.38	1.5±1.36	**0.000**
	Coughing	7.87±1.91	4.37±1.81	3.97±1.69	2.27±1.2	**0.000**
30 min	Rest	0.53±1.72	1.93±1.64	2.47±2.03	1.83±1.29	**0.000**
	Coughing	0.6±1.96	1.93±1.74	2.8±2.4	2.3±1.26	**0.000**
1 h	Rest	2.63±1.16	2.63±1.63	2.17±1.64	2.13±1.14	0.323
	Coughing	3.3±1.64	3.13±1.74	2.67±2.09	2.63±1.16	0.323
2 h	Rest	2.5±1.2	2.97±1.94	1.9±1.4	2.37±1.07	**0.044**
	Coughing	2.77±1.57	3.53±2.34	2.33±1.52	2.8±1.19	0.059
6 h	Rest	2.73±2.02	2.2±2.06	1.8±1	1.87±1.57	0.141
	Coughing	3.63±2.44	2.57±2.56	2.4±1.19	2.43±1.92	0.076
12 h	Rest	2.77±2.56	1.9±1.37	1.77±1.1	1.37±1.35	**0.015**
	Coughing	3.23±2.84	2.57±1.55	2.2±1.1	1.9±1.42	**0.038**
24 h	Rest	1.4±1.07	1.73±0.83	1.07±0.87	0.73±0.78	**0.000**
	Coughing	1.87±1.25	2±1.05	0.9±0.84	1.3±0.88	**0.000**

LA = local anesthetic, LP = low pressure, SP = standard pressure, VAS = visual analogous scale

was also detected that there is significant relationship between the group and patient satisfaction ($p = 0.001$) (Table 3).

Within the groups, when the requirement for a 2nd dose of analgesic was reviewed, it was found that 76.7% of the SP group, 23.3% of the SP+LA group, 13.3% of the LP group, and 3.3% of the LP+LA group received the 2nd dose. Hence, a significant relationship between the groups and the 2nd dose of analgesic was observed ($p = 0.001$) (Table 3).

DISCUSSION

In 1993, the first published study of laparoscopic surgery with regards to pain palliation and local anesthetics was conducted [13], and many more such studies have been conducted since then. The most important component of postoperative pain is incision-sourced pain, as incisional pain is much stronger, especially within the first 48 h when compared to visceral pain [14]. In many studies, with regards to the effectiveness of a local anesthetic injection at the trocar entry locations in pain palliation, it has been indicated that an intrafacial injection was very effective for pain control [15, 16]. Within the literature, there are many publications regarding the prevention of post-LC pain in subcutaneous or intraperitoneal infiltration, using such local anesthetics as bupivacaine, ropivacaine, and levobupivacaine [17]. Bupivacaine is a local analgesic with a half-life of 2.7 to 3.5 h, which controls pain for an average of 6 h [18]. In small incisions, bupivacaine's security margins are quite broad. At the upper limit of 2.5 mg

Table 3. Requirement for a 2nd dose of analgesic and patient satisfaction results.

		SP		SP+LA		LP		LP+LA		
		n	%	n	%	n	%	n	%	
Patient satisfaction	Poor	12	40.00%	6	20.00%	5	16.70%	3	10.00%	**0.001**
	Mild	13	43.30%	18	60.00%	15	50.00%	8	26.70%	
	Good	5	16.70%	6	20.00%	10	33.30%	19	63.30%	
2nd dose analgesic	No	7	23.30%	23	76.70%	26	86.70%	29	96.70%	**0.001**
	Yes	23	76.70%	7	23.30%	4	13.30%	1	3.30%	

LA = local anesthetic, LP = low pressure, SP = standard pressure

of bupivacaine per kg of body weight, 100 mg of the drug can be used safely in a patient with a lean body mass of 40 kg (total body weight, 70 kg). In our study, we used bupivacaine as an intrafacial local anesthetic agent. Despite the fact that there are studies in the literature indicating the fact that the usage of local anesthetics postoperatively is effective in pain palliation [19], it is thought that local anesthetics decrease postoperative pain via the prevention of transmission of nociceptive stimulus in the central nervous system when applied immediately before the incision [20, 21]. In the LA group, we administered a bupivacaine intrafacial injection immediately before making an incision like a study by Cantore *et al.* [22] and others [23, 24]. Pain scores after LC in the SP group were significantly high, despite the fact that an intrafacial bupivacaine injection was administered (in both the SP and SP+LA groups) when compared to those in the LP group, and this effect was obvious, especially at 2 and 24 h. This means that in the SP group, the sole application of local anesthetic did not provide sufficient analgesic when compared to the LP group.

According to Ingelmo *et al.* [25], after laparoscopic surgery, pain is primarily connected to the parietal peritoneal distention generated by carbon dioxide or damage that is caused by electrocauterization. Carbon dioxide, due to its fast diffusion characteristics, is used frequently to generate pneumoperitoneum [26]. Carbon dioxide insufflation and an increase in intraabdominal pressure leads to changes in organ physiology and hence, postoperative pain occurs. The degree of intraabdominal pressure is strongly and directly related to these changes. Thus, within the LC procedure, intraabdominal insufflation pressure is directly related to postoperative pain. Studies in which it has been foreseen that low pressure pneumoperitoneum leads to less postoperative pain do exist in the literature [3, 4]. In our study, when the pain scores of the LP group were compared to those of the SP and SP+LA groups, postoperative pain was observed at 2 and 24 h at significantly low levels. However, concerning patient satisfaction and the requirement for a 2nd dose of analgesic, no significant distinctions were detected. LC can be successfully applied via low-pressure carbon dioxide; however, the obtained operational area will be more limited than the area obtained via high pressure. However, pneumoperitoneum that is generated by low pressure has been indicated to form a satisfying surgery zone for the surgeon in many studies [27]. Since we did not question to the surgeons about their satisfaction postoperatively, we could not identify whether or not low pressure LC provides the patient with a sufficient surgery zone. In LP+LA group, early postoperative (0 min) pain scores were significantly low when compared to the other groups. At 30 min, in the SP group, where no treatment was applied, the fact that the pain scores were significantly low is that we think to the most of this group at 0 min, since their pain scores were high analgesic application has been done. In the LP+LA group, immediately before the patients were discharged from the hospital (24 h), the VAS scores were detected as significantly low. While having a rest and while coughing, the pain scores were observed as significantly low, and this was also obvious at 0 min, 12 h and 24 h during rest. Within the LP+LA group, the fact that the requirement for a 2nd dose of analgesic was extremely low, the patient satisfaction rate was rather high when compared to the other groups, and the time of the 1st dose of analgesic was significantly late when compared to other groups leads us to believe that this application is more effective with regards to pain palliation. In addition, the operation duration was also quite a bit longer than in the other groups.

The Limitation of the Study

We did not question to the surgeons about their satisfaction postoperatively, we could not identify whether or not low pressure LC provides the patient with a sufficient surgery zone.

CONCLUSION

In cases of symptomatic cholelithiasis, LC can be used effectively and safely in selected patients with severe pulmonary and cardiac co-morbidities in centers with intraabdominal low-head and local anesthetic infiltration and advanced laparoscopy experience.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] Soper NJ, Stockmann PT, Dunnegan DL, Ashley SW. Laparoscopic cholecystectomy. The new "gold standard"? Arch Surg 1992;127:917-21.
[2] Boddy AP, Mehta S, Rhodes M. The effect of intraperitoneal local anesthesia in laparoscopic cholecystectomy: a systematic review and meta-analysis. Anesth Analg 2006;103:682-8.
[3] Joshipura VP, Haribhakti SP, Patel NR, Naik RP, Sani HN, Patel B, et al. A prospective randomized, controlled study comparing low pressure versus high pressure pneumoperitoneum during laparoscopic cholecystectomy. Surg Laparosc Endosc Percutan Tech 2009;19:234-40.
[4] Viyaraghavan N, Sistla SC, Kundra P, Ananthanarayan PH, Karthikeyan VS, Ali SM, et al. Comparison of standard-pressure and low-pressure pneumoperitoneum in laparoscopic cholecystectomy: a double-blind randomized controlled study. Surg Laparosc Endosc Percutan Tech 2014;24:127-33.
[5] Bisgaard T, Klarskow B, Kristiansen VB, Callesen T, Shulze S, Kehelet H, et al. Multiregional local anesthetic infiltration during laparoscopic cholecystectomy in patients receiving prophylactic multimodal analgesia: a randomized double blinded placebo controlled study. Anesth Analg 1999;89:1017-24.
[6] Lewis DL, Thompson WA. Reduction of post operative pain. BMJ 1953;1:973-4.
[7] Pirbudak L, Balat Ö, Karadali H, Ugur MG, Öner Ü. Intraperitoneal and abdominal wall infiltration with bupivacaine plus tramadol and tenoxicam after total abdominal hysterectomy provides analgesia. Pain Clin 2004;16:77-81.
[8] Tiippana E, Bachmann M, Kalso E, Pere P. Effect of paracetamol and coxib with or without dexamethasone after laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2008;52:673-80.
[9] Akinci SB, Ayhan B, Aycan IO, Tirnaksiz B, Basgul E, Abbasoglu O, et al. The postoperative analgesic efficacy of intraperitoneal tramadol compared to normal saline or intravenous tramadol in laparoscopic cholecystectomy. Eur J Anaesthesiol 2008;25:375-81.
[10] Schulte-Steinberg H, Weninger E, Jokisch D, Hofstetter B, Misera A, Lange V, et al. Intraperitoneal versus interpleural morphine or bupivacaine for pain after laparoscopic cholecystectomy. Anesthesiology 1995;82:634-40.
[11] Collard V, Mistraletti G, Taqi A, Asenjo JF, Feldman LS, Fried GM, et al. Intraoperative esmolol infusion in the absence of opioids spares postoperative fentanyl in patients undergoing ambulatory laparoscopic cholecystectomy. Anesth Analg 2007;105:1255-62.
[12] Gupta R, Bogra J, Kothari N, Kohli M. Postoperative analgesia with intraperitoneal fentanyl and bupivacaine: A randomized control trial. Can J Med 2010;1:1-11.
[13] Chundrigar T, Hedges AR, Morris R, Stamatakis JD. Intraperitoneal bupivacaine for effective pain relief after laparoscopic cholecystectomy. Ann R Coll Surg Engl 1993;75:437-9.
[14] Louizos AA, Hadzilia SJ, Leandros E, Kouroukli IK, Georgiou LG, Bramis JP. Postoperative pain relief after laparoscopic cholecystectomy: a placebo-controlled double-blind randomized trial of preincisional infiltration and intraperitoneal instillation of levobupivacaine 0.25%. Surg Endosc 2005;19:1503-6.
[15] Papadima A, Lagoudianakis EE, Antonakis P, Filis K, Makri I, Markogiannakis H, et al. Repeated intra-peritoneal instillation of levobupivacaine for the management of pain after laparoscopic cholecystectomy. Surgery 2009;146:475-82.
[16] Lee IO, Kim SH, Kong MH, Lee MK, Kim NS, Choi YS, et al. Pain after laparoscopic cholecystectomy: the effect and timing of incisional and intraperitoneal bupivacaine. Can J Anesth 2001;48:545-50.
[17] Inan A, Sen M, Dener C. Local anaesthesia use for laparoscopic cholecystectomy. World J Surg 2004;28:741-4.
[18] American Society of Hospital Pharmacists, Committee on Pharmacy and Pharmaceuticals. American hospital formulary service: a collection of drug monographs and other information. Hamilton (IL): Hamilton Press, 1996.
[19] Lin S, Hua J, Xu B, Yang T, He Z, Xu C, et al. Comparison of bupivacaine and parecoxib for postoperative pain relief after laparoscopic cholecystectomy: a randomized controlled trial. Int J Clin Exp Med 2015;8:13824-9.
[20] Papagiannapoulou P, Argiriadou H, Georgiou M, Papaziagos B, Sfyra E, Kanakoudis F. Preincisional local infiltration of levobupivacaine vs. ropivacaine for pain control after laparoscopic cholecystectomy. Surg Endosc 2003;17:1961-4.
[21] Uzunkoy A, Coskun A, Akinci. The value of pre-emptive analgesia in the treatment of postoperative pain after laparoscopic cholecystectomy. Eur Surg Res 2001;33:39-41.
[22] Cantore F, Boni L, Di Giuseppe M, Giavarini L, Rovera F, Dionigi G. Pre-incision local infiltration with levobupivacaine reduces pain and analgesic consumption after laparoscopic cholecystectomy: a new device for day-case procedure. Int J Surg. 2008;6;89-92.
[23] Effectiveness of local anesthetics in laparoscopic cholecystectomy: a randomized clinical trial. Surg Laparosc Endosc Percutan Tech 2015;25:317-20.
[24] Hilvering B, Draaisma WA, vander Bilt JD, Valk RM, Kofman KE, Consten EC. Randomized clinical trial of combined preincional infiltration and intrperitoneal instillation of levobupivacaine for postoperative pain after laparoscopic cholcystectomy. Br J Surg 2011;98:784-9.
[25] Ingelmo PM, Bucciero M, Somaini M, Sahillioglu E, Garbagnati A, Charton A, et al. Intraperitoneal nebulization of ropivacaine for pain control after laparoscopic cholecystectomy: A double− blind, randomized, placebo−controlled trial. Br J Anaesth 2013;110:800-6.
[26] Montroni I, Sabattini E, Ramadori E, Koprivica V, Ugolini G, Locatelli F, et al. Small bowel obstruction caused by a large B-cell lymphoma in a patient with multicentric Castleman's disease: an unusual occurrence. Int J Surg Pathol 2014;22:434-7.
[27]. Neudecker J, Sauerland S, Neugebauer E, Bergamaschi R, Bonjer HJ, Cuschieri A, et al. The European Association for Endoscopic Surgery clinical practice guideline on the pneumoperitoneum for laparoscopic surgery. Surg Endosc 2002;16:1121-43.

The European Research Journal 2018;4(4):333-342 ORIGINAL ARTICLE

Pathological analysis of cystic lesions of the bones: a retrospective single-center 10-year overview

Gonca Özgün[1], Ulviye Yalçınkaya[2], Zeynep Yazıcı[3], Bartu Sarısözen[4]

[1]Department of Pathology, Başkent University School of Medicine, Ankara, Turkey
[2]Department of Pathology, Uludağ University School of Medicine, Bursa, Turkey
[3]Department of Radiology, Uludağ University School of Medicine, Bursa, Turkey
[4]Department of Orthopaedics and Traumatology, Uludağ University School of Medicine, Bursa, Turkey

DOI: 10.18621/eurj.345991

ABSTRACT

Objective: Many different neoplastic and non-neoplastic lesions involve the skeletal system. Clinical and radiological tools primarily assess the nature of these lesions. The aim of this study was to analyze the cystic bone lesions in a pathologic point of view.

Methods: All bone cysts between 2002 and 2013 retrospectively evaluated under the guidance of clinical information and radiological images. Descriptive data such as age, gender, tumor site, symptoms, and clinical and radiological findings obtained from the hospital's database system.

Results: There were 96 cystic bone lesions; 47 were aneurysmal bone cysts (ABCs), 37 were simple bone cysts (SBCs), one was a lesion with features of both ABC and SBC, four were intraosseous ganglia, four were epidermoid cysts, and three were hydatid cysts. The mean ages of the patients with ABCs and SBCs were 18.7 ± 12.8 years (range, 3-75 years) and 23.8 ± 13.3 years (range, 3-62 years), respectively. Most of the lesions located in the long bones.

Conclusions: Cystic lesions of the bone rarely encountered in daily pathology routine. As with all conditions affecting the skeletal system, one of the most important steps towards an accurate pathological diagnosis is to perform with clinical and radiological information while evaluating the patients.

Keywords: Aneurysmal bone cyst, simple bone cyst, intraosseous ganglion, hydatid cyst, epidermoid cyst

Received: October 23, 2017; Accepted: January 25, 2018; Published Online: March 1, 2018

Aneurysmal bone cyst (ABC), simple bone cyst (SBC), and their combinations, usually considered non-neoplastic cystic lesions. Other cystic lesions that may encounter in bone tissue include intraosseous ganglion cysts of undetermined origin, epidermoid cysts, and hydatid cysts of infectious origin [1]. Bone cysts may develop as solitary or multiple lesions. Cystic bone lesions may mimic and behave similarly to a bone tumor [2].

The aim of this study was to analyze the cystic bone lesions in a pathologic point of view.

METHODS

All bone cysts diagnosed between 2002 and 2013 were retrospectively evaluatedfrom the archives. The samples sent to the pathology department various surgical methods: bone curettage, excision, and biopsy. Macroscopically, the samples were hemorrhagic, irregular tissues containing areas having the hardness of bone as well. All material routinely fixed in 10% buffered formalin and embedded in paraffin. The pathological evaluation based on routine

Address for correspondence: *Gonca Özgün, MD., Assistant Professor, Başkent University School of Medicine, Department of Pathology, 79. Cadde, No:7/4, Bahçelievler, 06490 Ankara, Turkey*
E-mail: gbarit@gmail.com, Phone: +90 312 2126591, Fax: +90 312 2127572

e-ISSN: 2149-3189

hematoxylin-eosin stained slidesunder the guidance of clinical information and radiological images. The age of the patients, gender, localization, symptoms, and clinical and radiological findings obtainedfrom the hospital's database system. The collected information has transferred to the preformed forms to do the statistical analysis. The institutional Ethical committee guidelines conducted the study.

Statistical Analysis

The statistical analysiswas performed with SPSS statistical software for Windows, version 20.0 (SPSS Inc, Chicago, IL, USA). Descriptive analysis such as frequency, percentage, mean ± standard deviation, and range (min-max)was used for the patient groups.

RESULTS

Of the 96 cystic bone lesions in the overview, 47 were ABCs, 37 were SBCs, one was a cystic lesion with features of both aneurysmal and simple bone cyst, four were intraosseous ganglia, four were epidermoid cysts, and three were hydatid cysts.

The mean age of the patients with ABCs was 18.7 ± 12.8 (range, 3-75 years). Of these 47 patients, 23 were female, and 24 were male. The lesions located in the lower extremities in 27 patients, the upper extremities in 6 patients, the sacrum in 5 patients, the vertebrae in 3 patients, the skull in 3 patients, the ribs in 2 patients, and the clavicula in 1 patient. There were concurrent lesions with the ABCs in 6 patients (Table

Table 1. Characteristics of the aneurysmal bone cysts.

Characteristics	Data (n = 47)
Age at diagnosis (years)	18.7 ± 12.8 (range, 3-75 years)
Male/Female	24/23
Localization	
Lower extremities	27
(Femur/tibia/fibula/bones of the feet)	(12/9/3/3)
Pelvis	5
Vertebra	3
Upper extremities	6
(Humerus/radius/bones of the hands)	(2/2/2)
Others	6
Concurrent lesions	
Giant cell tumor	2
Intraosseous lipoma	1
Ossifying fibroma	1
Fibrous dysplasia	1
Reparative granuloma	1
Recurrence	5

Table 2. Characteristics of the simple bone cysts.

Characteristics	Data (n = 37)
Age at diagnosis (years)	23.8 ± 13.3 (range, 6-62 years)
Male/Female	23/14
Localization	
Humerus	13
Femur	9
Tibia	4
Pelvis	3
Bones of the feet and hands)	5
Others	3
Concurrent lesions	
Callus	1
Fracture recovery	3
Recurrence	2

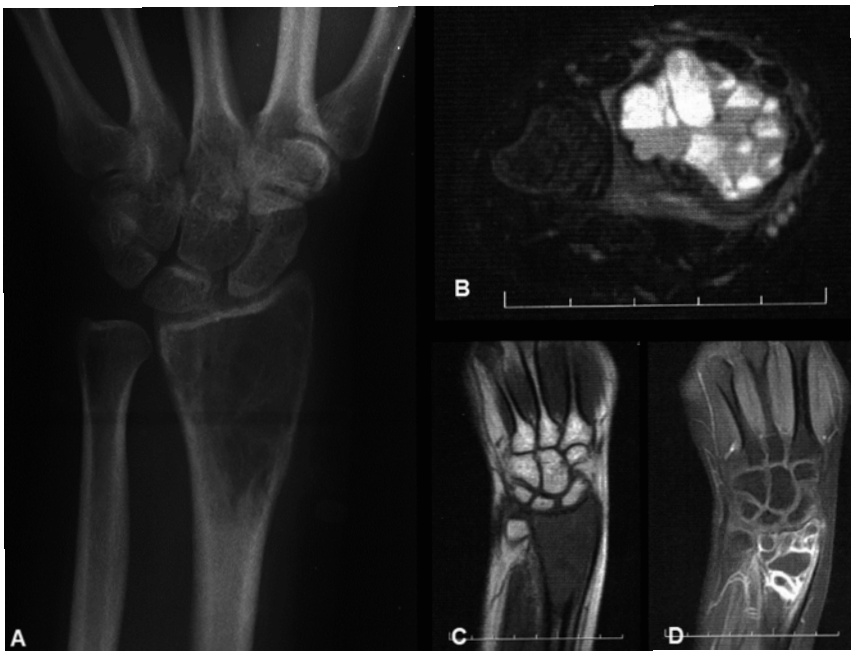


Figure 1. Aneurysmal bone cyst of a 20-year-old woman. A. The anteroposterior radiographshowed an osteolytic, moderately expansile lesion in the distal radial metaphysis. B. Axial T2-weighted MR image showed multiple fluid-fluid levels within the lesion. C. Coronal T1-weighted MR image of the lesion. D. On contrast-enhanced coronal T1-weighted MR image,there was an enhancement of the cyst wall and internal septations.

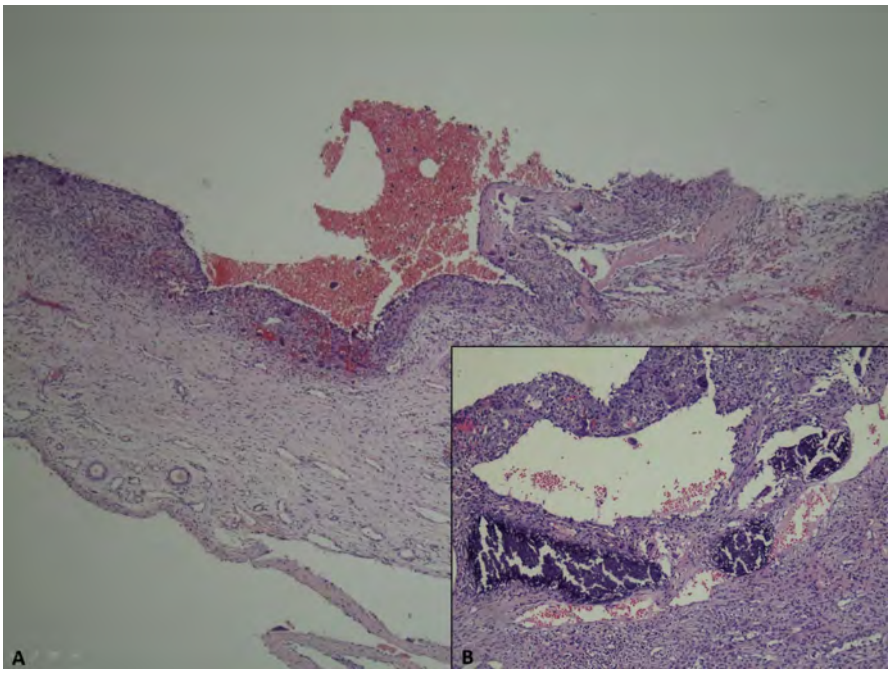


Figure 2. Aneurysmal bone cyst. A. Fibrous cyst wall and a blood-filled cavernous spacewithout endothelial lining were seen. The fibrous wall contained multiple multinuclear giant cells andspindle fibroblasts (Hematoxylin-eosin ×40). B. Patchy areas of the basophilic bone formationcalled “blue bone” were noted (Hematoxylin-eosin ×100).

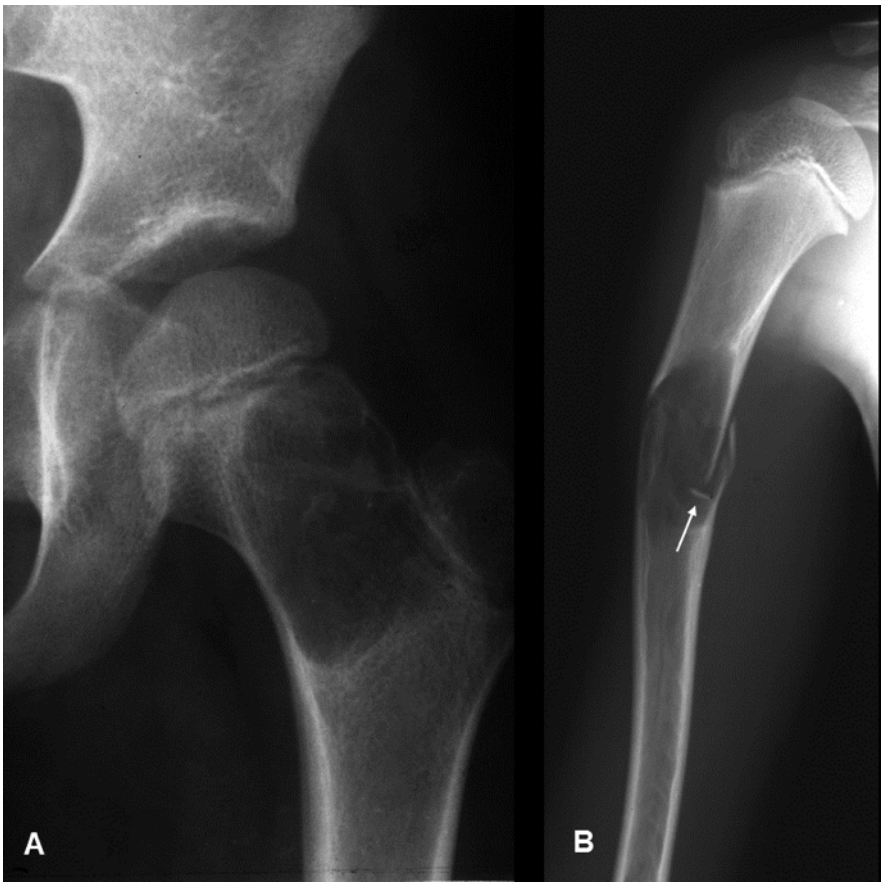


Figure 3. Simple bone cyst. A. A child with a simple bone cyst in the femoral neck.The anteroposterior radiograph showed a well-defined medullary lytic lesion with moderatecortical thinning. B. A child patient with a simple bone cyst in the humerus. The antero-posteriorradiograph revealed the cyst complicated by a pathologic fracture. A fragment of the cortex(arrow) was lying medially within the cyst (fallen fragment sign).

1). In 2 patients the cystic bone lesions reported as solid ABC. There were five patients with a recurrence, however, none of them underwent malignant transformation in the clinical follow-up time. Microscopic examination revealed blood-filled cavernous spaces without an endothelial lining surrounded by a fibrous wall. The fibrous wall contained multiple multinuclear giant cells, spindle fibroblasts with mitotic figures, and patchy areas of new bone production (Figure 1). No cytologic atypia or atypical mitotic figures observed.

The majority of cases with an SBC were male (23 males, 14 females). The mean age of these patients was 23.8 ±13.3 years (range, 3-62 years). The lesions located in the lower extremities in 18 patients, the upper extremity in 16 patients, and the pelvis in 3 patients (Table 2). SBCs co-occurred with another lesion in four of these patients. The lesions recurred after excision in 2 patients. There was not any malignant transformation. Microscopically, a thin fibrous cystic wall with interspersed benign giant cells was observed. Patchy areas of hemosiderin-laden macrophages and cell aggregates consisting of mononuclear inflammatory cells were also noted (Figure 2). In cases with accompanying fracture healing and callus formation, proliferating fibroblasts and callus formation were present on the cyst wall and inside the cyst lumen. The patient in whom had a mixed cystic lesion consisting of an ABC, and an SBC was a 12-year-old boy. The lesion located in the distal part of the right tibia.

Comparing the two most common cystic bone lesions, ABCs and SBCs, the male-female distribution was equal in the cases with ABCs, whereas in SBCs there was a male predominance. The mean age of the patients with SBCs was higher than those with ABCs. The recurrence rate was higher in ABCs than for SBCs.

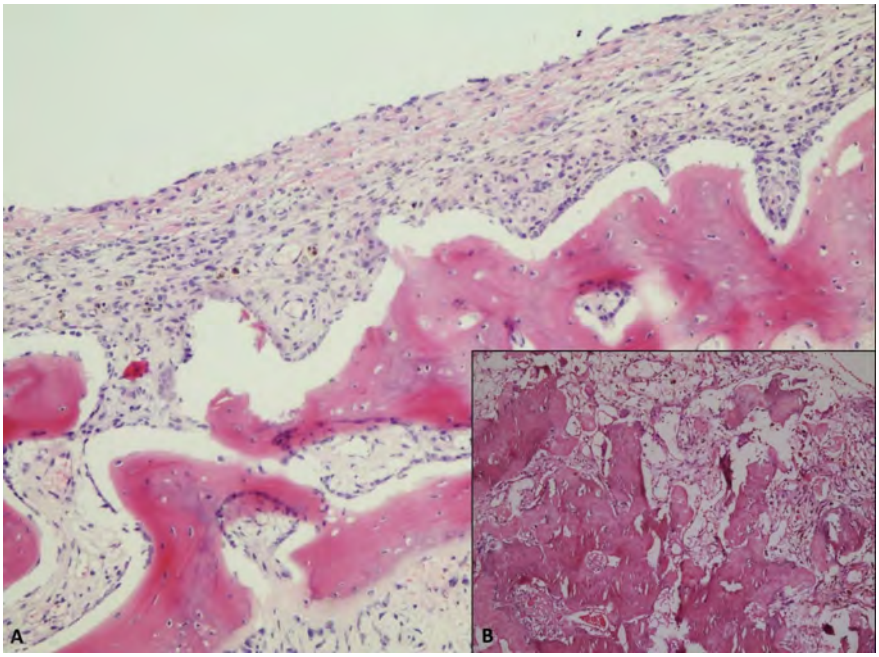


Figure 4. Simple bone cyst. A. cyst wall composed of collagen and thin fibrous tissue, which contained giant cells and hemosiderin-laden macrophages (Hematoxylin-eosin ×100). B. The cystwall contained abundant and irregular fibrin deposits (Hematoxylin-eosin ×100)

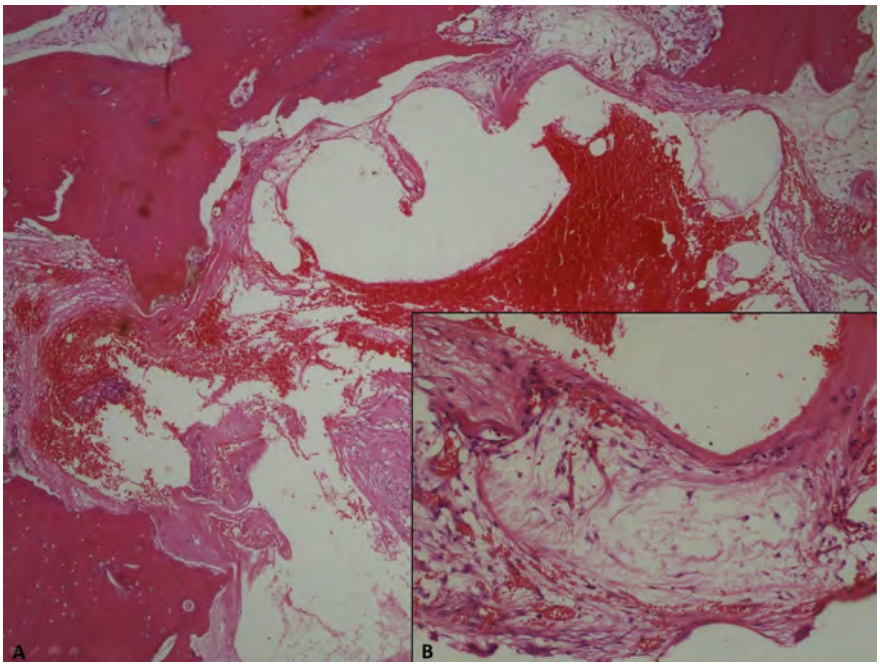


Figure 5. Intraosseous ganglion cyst. A. Thin fibrous cyst walls without an endothelial liningbetween the bony trabeculas were seen (Hematoxylin-eosin ×40). B. Myxoid changes werepresent in the cyst wall (Hematoxylin-eosin ×200)

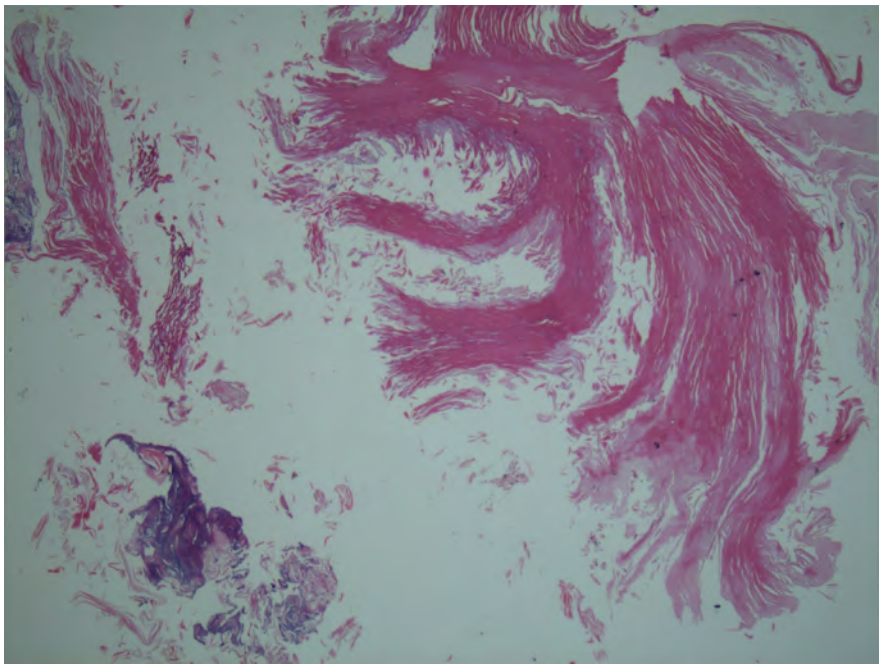


Figure 6. Epidermoid cyst. Keratinous material intermingled with the bone fragments (Hematoxylin-eosin ×40)

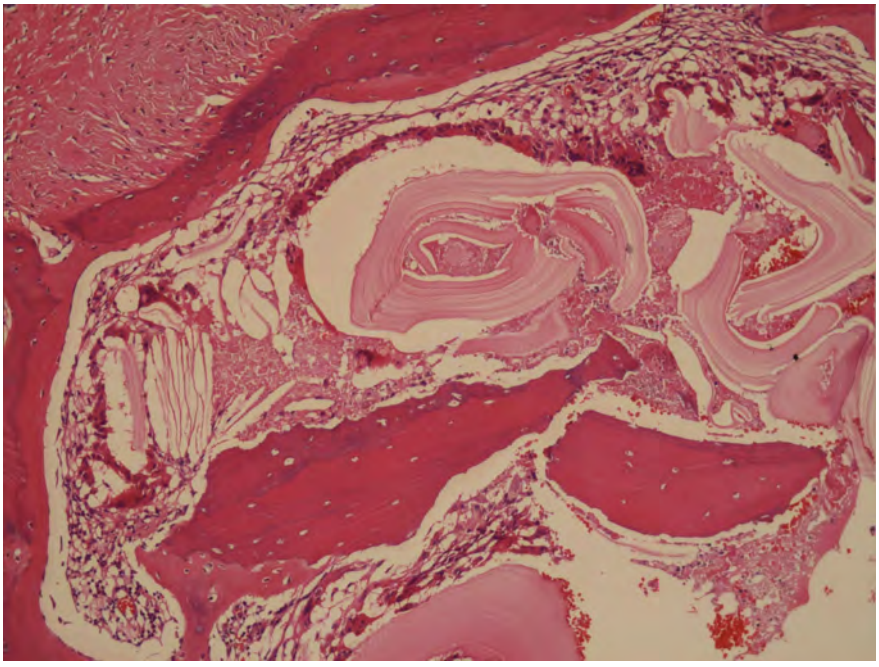


Figure 7. Hydatid cyst. Germinative membranous structures are seen between the fibrouscyst wall and the bone fragments (Hematoxylin-eosin ×100)

Intraosseous ganglion cysts and epidermoid cysts were also present in our 10-year bone cyst archive. There were four intraosseous ganglion cyst patients. The mean age of the patients was 42 ± 12.1 years (range, 30-58 years). Three of them were female, and one of them was male. The lesions located in the acetabulum in three of these patients and the foot lateral in one patient. Microscopic examination demonstrated a thin fibrous cyst wall with mucinous content. Myxoid changes were present on the cyst wall between areas of loose fibroblastic proliferation (Figure 3). Three of the patients with epidermoid cysts were female, and one was male. Their mean age was 17.7 ± 12.4 years (range, 1-31 years). The location was distal phalanx in three patients and the orbital bone in one patient. The microscopic evaluation showed cystic spaces lined with keratinized squamous epithelium (Figure 4). Our case series included three intraosseous hydatid cysts located in the femur in two patients and the vertebrae in one patient. Two of these patients were male, and one was female; their mean age was 44.6 ± 21.7 years (range, 25-68 years). Microscopically, these lesions characterized by a fibrous cyst wall, a germinative membranous structure on the internal surface, and a few scolices (Figure 5).

DISCUSSION

Aneurysmal bone cysts

ABCs are not considered neoplastic lesions because they may show signs of regression, even after incomplete resection [3]. However, cytogenetic and molecular studies showing karyotypic anomalies on the short arm of chromosome 17 have suggested that the primary ABCs are neoplastic lesions rather than reactive lesions [4-6]. This cyst may be encountered in all age groups although they have been most commonly reported during the first two decades of life, with a slightly higher prevalence in women compared to men [7]. Pain and swelling are the main symptoms, although compressive symptoms are also sometimes present when the lesions are located in the vertebrae [1]. Our case series also showed that 34 (72.3%) patients were in their first two decades. The female-to-male ratio was 0.95 (23/24). Our case series also revealed that pain and swelling were the most prevalent symptoms.

ABCs, which are composed of blood-filled spaces separated by fibroblasts, osteoclast-type giant cells, and septae consisting of reactive woven bone, may develop either de novo or secondary to hemorrhagic cystic changes due to benign or malignant bone tumors [1]. They may grow in all types of bone although they tend to be located in the metaphysis of long bones, mainly the femur, tibia, and humerus, as well as the posterior portions of the vertebral bodies; 70-80% of all aneurysmal bone cysts are found in these two localizations [7]. In our case series, 29 (61.7%) of the aneurysmal bone cysts were found in the long bones and the vertebrae (Table 1).

Radiological images vary depending on the stage of the lesion and its relationship with the adjacent bone. Eccentric localization is common in long tubular bones, whereas central and parosteal lesions are less common [7, 8]. In earlier stages, lesions appear as small, typically eccentric, and infiltrative masses that do not widen the bone. During the growth phase, they are characterized by marked cortical lysis and destruction. In their stable phase, they may have the classic appearance of an ABC marked by a widened lesion with multiple internal trabeculations and an osseous periphery, which distorts the pattern of host bone. In the healing phase, on the other hand, they appear as irregular, coarsely trabecular, osseous lesions as a result of progressive ossification of the lesion [9].

ABCs may be primary, or they may co-occur with or develop secondary to another lesion. Most ABCs are labeled primary, although development secondary to a preexisting lesion that described in 20-30% of cases [10]. Many secondary ABCs reported in the literature [11-14]. It indicated that ABCs accompany, in descending order, giant cell tumors of the bone, chondroblastoma, chondromyxoid fibroma, and fibrous dysplasia [6]. In our case series, six patients had accompanying lesions to ABCs: two of them secondary to giant cell tumors, one of them to ossifying fibroma, one of them to fibrous dysplasia, one of them to intraosseous lipoma, and one of them to giant cell reparative granuloma.

Microscopically, ABCs consist of multiple blood-filled cavernous spaces without a muscular layer or an endothelial lining. There are also fibrous walls that separate these areas. Fibroblasts, histiocytes, giant cells, inflammatory cell infiltration, osteoid, and

chondroid can be found on the fibrous walls [5]. The osteoid usually has a trabecular pattern. It is entirely composed of fibrous septa-like cellular components and contains no or focally distributed widened vascular spaces in its solid variant [15]. It has been reported that solid variant of ABCs usually located in the posterior segments of the vertebral bones [16, 17]. However, two patients in our series (age; 20 and 22 years) had femoral and calcaneal locations.

Differential diagnosis must include giant cell tumors of the bone, low-grade osteosarcoma, and telangiectatic osteosarcoma. The fibrous septa of ABCs also contain multiple giant cells; however, the age of the patient and the metaphyseal location of the lesion are helpful hints in the differential diagnosis. Low-grade osteosarcomas contain fewer mitoses and low cellularity compared to a typical ABC [3].

Many mitotic figures may be observed, especially in the osteoid-containing areas, which creates a challenge in the differential diagnosis from telangiectatic osteosarcoma [5]. Radiologically, a smooth border, an irregular appearance, and a thin calcific line in the cortical bone indicate aneurysmal bone cysts. Microscopically, the absence of anaplastic cells and atypical mitotic figures in the fibrous trabeculae, as well as an osteoid pattern that is parallel and linear to the septae, favor the diagnosis [18, 19]. In approximately 1/3 of the cases, a basophilic bone formation called “blue bone” may be noted, albeit non-diagnostic [1].

The prognosis of aneurysmal bone cysts is quite favorable. There are case reports in the literature suggesting malignant transformation although this is not an expected finding in general [3, 20-22]. We detected recurrence in five (10%) cases with age range of 8 to25 years. Recurrent lesions located in the lower extremity and the pelvis in four patients and the maxilla in one patient. In one patient, there was a solid component seen microscopically, which recurred later. None of the cases in our series had a malignant transformation.

Simple bone cysts

SBCs of undetermined origin are considered reactive or developmental lesions. They constitute roughly 3% of cases biopsied from bone tissue. These lesions create an irregularity in the epiphysis plaque. They are usually observed in the second decade with a prevalence three times higher in men [3]. In our case series, 20 (54%) patients were in their 2nd decade. The number of males and females were 23 and 14, respectively, with a ratio of 1.6. The majority of these lesions is found in the humerus, femur, and tibia [1, 6]. We similarly found that 26 (70.2%) of the SBCs in our case series located in the humerus, femur, and tibia (Table 2). Patients may present with pain. The SBCs could locate adjacent to a pathological fracture or present as an incidental radiological finding [8]. Likewise, four cases in our case series presented with pathological fractures, whereas the other patients were admitted with pain and swelling.

SBCs appear as lesions that may be trabeculated or multiloculated and appear as cystic masses located at the metaphysis in relation with the epiphysis plaque. Cortical thinning, erosion and widening may be present; however, the cortical bone is not destroyed. The growth rate of cystic lesions that are about the epiphysis plaque is slower than that of bone. Therefore, they may appear as metaphyseal cystic lesions in patients of advanced age [7, 23].

Histologically, there is a cyst wall composed of collagen and thin fibrous tissue, which contains giant cells, hemosiderin-laden macrophages, and lymphocytes. The cyst wall may contain abundant, irregular, and sometimes calcific fibrin deposits [7]. Because SBCs may have a giant cell component, the differential diagnosis must include giant cell tumors of the bone. The presence of septae in the lesion should raise the suspicion of an ABC [24]. In SBCs, the presence of a fracture is an indication for surgery. Spontaneous regression takes place in 15% of cases; however, the majority of these lesions do not regress, and they even progress.

Ganglion cysts

An intraosseous ganglion resembles a ‘ganglion' that is located in a tendon sheath, and it is composed of spaces filled with mucoid fluid. Patients are asymptomatic, and these cysts are incidentally detected in radiological studies. Patients may present with pain in the presence of a fracture [3]. In a study of 88 patients, the intraosseous ganglion was most commonly located in the hip and adjacent structures [25]. In our case series, three cases were found in the acetabulum and one in the ankle. Cases with metacarpal and vertebral locations have also reported

[26, 27]. These cysts have usually been reported in young and middle-aged adults [27]; the age range in our study was between 30 and 58 years (mean: 42 years). Three of these patients were female, and one was male. In our series, the presenting symptom of all the patients was a pain.

Radiologically, these cysts are lytic masses with well-defined borders which widen the joint cartilage. A sclerotic margin is evident at the periphery of the lesion [28]. Histopathological examination shows a fibrous cyst wall and mucinous material within the cyst. Differential diagnosis must include degenerative joint disease. The absence of any degenerative lesion in the adjacent joint may suggest the diagnosis [3, 29].

Epidermoid cysts

Epidermoid cysts with intraosseous location are rare non-neoplastic lesions in the jaw bone, distal phalanges, or the skull [30]. They are frequently located in the skull and distal phalanges. Location in the skull is thought to occur as a result of developmental defects, whereas distal phalangeal locations are considered secondary to traumatic implantations of squamous epithelium. The most common complaint is swelling of the bone [7]. These cysts have a low growth rate, leading to a marked widening in the host bone. They may also extend to the soft tissues nearby, altering the clinical picture. Cases in which the lesion is located in the skull and extends intracranially may present with a clinical picture resembling that of a brain tumor [31]. Three patients in our case series had a distal phalangeal location, and one had a maxillary location with extension to the orbital soft tissue. Case series in literature have reported an age range of 21 to 69 years, with the majority of cases being male (87.5%) [30]. In our series, three female and one male case were present with an age range of 1 to 31 years (mean: 17.7 years). They presented with pain and swelling.

Radiologic studies have shown that these lesions have a considerably well-defined border with a sclerotic ring. The cortical bone is usually thinned and widened. Histopathological diagnosis is made by noting the cyst wall lined by a squamous epithelium that produces keratin, even if in a focal area [3, 32].

Hydatid cysts

Echinococcosis is a common parasitic infection in countries where livestock farming is practiced. It tends to be localized, in particular, in the liver, lung, and brain. Approximately 3% of all hydatidosis cases are localized in bone, with a predilection for vertebral bones, long bones, and pelvic bones [33]. Patients may present with symptoms of spinal compression when lesions are localized to the vertebral column [34-36]. Two of our cases located in the femur, while one located in vertebra. One of the cases in the femur extended to the soft tissue of the thigh. The pain was the primary symptom in both the femoral and vertebral lesions. Two of our patients were male, and one was female; their ages ranged between 25 and 68 years (mean: 44.6 years). Radiologically, the pathognomonic appearance of these lesions is the presence of sister vesicles in the cyst lumen [36].

CONCLUSION

Cystic lesions of the bone are not frequently encountered. Differential diagnoses must also include malignant bone tumors. As in all conditions affecting the skeletal system, clinicopathologic meetings where clinical, radiological, and pathological assessments made together, are one of the most important steps towards a correct diagnosis.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] Rosenberg AE, Nielsen GP, Fletcher JA, Kalil RK, Araujo. Aneurysmal bone cyst, Simple bone cyst. In: Fletcher CDM, Unni KK, Mertens F, eds. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone. Lyon: IARC Press, 2002.

[2] Doğanavşargil B, Ayhan E, Argin M, Pehlivanoğlu B, Keçeci B, Sezak M, et al. Cystic bone lesions: histopathological spectrum and diagnostic challenges. Turk Patoloji Derg 2015;31:95-103.

[3] Unni KK, Inwards CY. Miscellaneous unusual tumors of bone. In: Dahlin's Bone Tumors. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2010.

[4] Oliveira AM, Perez-Atayde AR, Inwards CY, Medeiros F, Derr V, Hsi BL, et al. USP6 and CDH11 oncogenes identify the neoplastic cell

in primary aneurysmal bone cysts and are absent in so-called secondary aneurysmal bone cysts. Am J Pathol 2004;165:1773-80.
[5] Remotti F, Feldman F. Nonneoplastic lesions that simulate primary tumors of bone. Arch Pathol Lab Med 2012;136:772-88.
[6] Szuhai K, Cleton-Jansen A, Hogendoom PCW, Bovée JVMG. Molecular pathology and its diagnostic use in bone tumors. Cancer Genet 2012;205:193-204.
[7] Unni KK, Inwards CY, Bridge JA, Kindblom L, Wold LE. In: Tumors of The Bones and Joints. AFIP Atlas of Tumor Pathology. Washington, D.C.: American Registry of Pathology, Armed Forces Institute of Pathology, 2005.
[8] Mirra JM, Picci P, Gold RH. In: Bone tumors: clinical, radiologic, and pathologic correlation. Philadelphia: Lea & Febiger, 1989.
[9] Rapp TB, Ward JP, Alaia MJ. Aneurysmal bone cyst. J Am Acad Orthop Surg 2012;20:233-41.
[10] Martinez V, Sissons HA. Aneurysmal bone cyst. A review of 123 cases including primary lesions and those secondary to other bone pathology. Cancer 1988;61:2291-304.
[11] Lee JW, Kim JH, Han SH, Kang HI. Fibrous dysplasia with aneurysmal bone cyst presenting as painful solitary skull lesion. J Korean Neurosurg Soc 2010;48:551-4.
[12] Yazici B, Yazici Z, Yalcinkaya U. Aneurysmal bone cyst secondary to ossifying fibroma in the orbit. Ophthal Plast Reconstr Surg 2011;27:84-5.
[13] Ozan F, Toker G. Secondary aneurysmal bone cyst of the patella. Acta Orthop Traumatol Turc 2010;44:246-9.
[14] Guedes A, Barreto B, Soares Barreto LG, Athanazio DA, Athanazio PR. Calcaneal chondroblastoma with secondary aneurysmal bone cyst: a case report. J Foot Ankle Surg 2010;49:298.e5-8.
[15] Sanerkin NG, Mott MG, Roylance J. An unusual intraosseous lesion with fibroblastic, osteoclastic, osteoblastic, aneurysmal and fibromyxoid elements. "Solid" variant of aneurysmal bone cyst. Cancer 1983;51:2278-86.
[16] Karampalis C, Lenthall R, Boszczyk B. Solid variant of aneurysmal bone cyst on the cervical spine of a child: case report, differential diagnosis and treatment rationale. Eur Spine J 2013;22:523-31.
[17] Gothner M, Citak M, Schildhauer TA, Roetman B. Aneurysmal bone cyst of the spine in an adolescent: a case report. Acta Orthop Belg 2011;77:853-7.
[18] Lee HM, Cho KS, Choi KU, Roh HJ. Aggressive aneurysmal bone cyst of the maxilla confused with telangiectatic osteosarcoma. Auris Nasus Larynx 2012;39:337-40.
[19] Sangle NA, Layfield LJ. Telangiectatic osteosarcoma. Arch Pathol Lab Med 2012;136:572-6.
[20] Mei J, Gao YS, Wang SQ, Cai XS. Malignant transformation of aneurysmal bone cysts: a case report. Chin Med J (Engl) 2009;122:110-2.
[21] Brindley GW, Greene JF Jr, Frankel LS. Case reports: malignant transformation of aneurysmal bone cysts. Clin Orthop Relat Res 2005;438:282-7.
[22] Cottalorda J, Bourelle S. Modern concepts of primary aneurysmal bone cyst. Arch Orthop Trauma Surg 2007;127:105-14.
[23] Weinman J, Servaes S, Anupindi SA. Treated unicameral bone cysts. Clin Radiol 2013;68:636-42.
[24] Baumhoer D, Smida J, Nathrath M, Jundt G. The nature of the characteristic cementum-like matrix deposits in the walls of simple bone cysts. Histopathology 2011;59:390-6.
[25] Schajowicz F, Clavel Sainz M, Slullitel JA. Juxta-articular bone cysts (intra-osseous ganglia): a clinicopathological study of eighty-eight cases. J Bone Joint Surg Br 1979;61:107-16.
[26] Kural C, Sungur I, Cetinus E. Bilateral lunate intraosseous ganglia. Orthopedics 2010;33:514.
[27] Lin JD, Koehler SM, Garcia RA, Qureshi SA, Hecht AC. Intraosseous ganglion cyst within the L4 lamina causing spinal stenosis. Spine J 2012;12:9-12.
[28] Bauer TW, Dorfman HD. Intraosseous ganglion: a clinicopathologic study of 11 cases. Am J Surg Pathol 1982;6:207-13.
[29] Gould CF, Ly JQ, Lattin GE Jr, Beall DP, Sutcliffe JB 3rd. Bone tumor mimics: avoiding misdiagnosis. Curr Probl Diagn Radiol 2007;36:124-41.
[30] Simon K, Leithner A, Bodo K, Windhager R. Intraosseous epidermoid cysts of the hand skeleton: a series of eight patients. J Hand Surg Eur 2011;36:376-8.
[31] Kalfas F, Ramanathan D, Mai J, Schwartz S, Sekhar LN. Petrous bone epidermoid cyst caused by penetrating injury to the external ear: case report and review of literature. Asian J Neurosurg 2012;7:93-7.
[32] Nakajo M, Ohkubo K, Nandate T, Nagano Y, Shirahama H, Nakajo M. Intraosseous epidermal cyst of the distal phalanx of the thumb: radiographic and magnetic resonance imaging findings. Radiat Med 2005;23:128-32.
[33] Kural C, Ugras AA, Sungur I, Ozturk H, Erturk AH, Unsaldi T. Hydatid bone disease of the femur. Orthopedics 2008;31:712.
[34] Guney M, Tekeli H, Kendirli MT, Kaya S, Turhan V, Sonmez G, et al. Intramedullary hydatid cyst of the cervical spine. Indian J Med Microbiol 2012;30:480-1.
[35] Ahmad M, Ekramullah, Ahmad I, Ali SA. A rare case of intradural spinal hydatid cyst in a paediatric patient. JBR-BTR 2012;95:87-8.
[36] Kapoor SK, Kataria H, Patra SR, Bharadwaj M, Vijay V, Kapoor S. Multi-organ hydatidosis with extensive involvement of the hemi-pelvis and ipsilateral femur. Parasitol Int 2013;62:82-5.

The European Research Journal 2018;4(4):343-348 ORIGINAL ARTICLE

Therapeutic plasmapheresis: an eleven-year clinical experience

Yasemin Tekdöş Şeker, Gülsüm Oya Hergünsel, Deniz Özel Bilgi

Department of Anesthesia and Reanimation, University of Health Sciences, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Turkey

DOI: 10.18621/eurj.356552

ABSTRACT

Objective: Therapeutic plasma exchange (TPE) is currently indicated as an alternative treatment regimen in a number of guidelines for various medical conditions. In this article we retrospectively reviewed cases who underwent TPE in Bakırköy Dr. Sadi Konuk Training and Research Hospital intensive care unit between 2007 and 2016 and compared the findings to the current reports in the literature.

Methods: A total of 80 cases were treated with TPE between 2007 and 2016 in our intensive care unit. Information on demographic variables, therapeutic indications, catheterized veins, complications during the procedure, number of sessions, replacement products used and survival data was collected. In addition, pre- and post-procedure serum triglyceride, cholesterol and amylase levels were also collected in acute pancreatitis cases associated with hypertriglyceridemia.

Results: A total of 501 TPE sessions were performed on 80 cases comprising 35 neurology, 18 hematology, 12 hypertriglycemic acute pancreatitis and 7 acute hepatic insufficiency patients, along with 8 cases with less common indications including sepsis, hyperthyroidism resistant to medical therapy and toxic epidermal necrolysis. The age of the subjects ranged between 12 and 82 years (mean; 45.08 ± 14.67 years). Sixteen (23.19%) cases died before the completion of the planned sessions. Pre- and post-procedure serum triglyceride, cholesterol and amylase levels were significantly different in acute pancreatitis cases ($p < 0.05$).

Conclusion: Timely implementation of TPE in applicable indications may be helpful in preventing morbidity and mortality in a wide spectrum of disorders.

Keywords: plasmapheresis, plasma exchange, pancreatitis, Guillain barre syndrome, intensive care unit

Received: November 20, 2017; Accepted: January 29, 2018; Published Online: March 30, 2018

In therapeutic plasma exchange (TPE), blood is separated into components outside the body and cellular elements are reinfused into the body. TPE and double filtration plasmapheresis is a technique in which blood is removed extracorporeally by a method in which the plasma is separated from the rest of the blood. This process is usually performed to remove increased toxins or autoantibodies in the plasma [1]. Blood is broken down into components with the help of a filter or pump and the separated plasma is cleansed by absorbent surfaces. The depleted volume is corrected with replacement fluids composition of which is akin to plasma. A main goal in the broad clinical spectrum is to remove large molecular weight substances from the plasma, including lipoproteins containing pathological autoantibodies, immunocomplexes, cryoglobulins, endotoxin or cholesterol. TPE indications were identified and revised by the American Apheresis Community in 2010 and are divided into four categories, from 1 to 4, based on available literature [2]. Diseases in Category 1 are diseases that are considered as primary treatment

Address for correspondence: *Yasemin Tekdöş Şeker, MD., University of Health Sciences, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Anesthesia and Reanimation, İstanbul, Turkey*
E-mail: yasemintekdos@gmail.com

e-ISSN: 2149-3189

for plasma exchange or in combination with other treatment modalities. The main ones of these diseases are; Guillain-Barre syndrome (GBS), myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, thrombotic diseases thrombocytopenic purpura, Goodpasture syndrome and atypical hemolytic uremic syndrome (aHUS) [3-5].

Removal of proinflammatory and inflammatory mediators enhances the reticuloendothelial functions as well as immune regulation. Rapid reduction of specific autoantibodies on the surface can sometimes cause excessive production of similar antibodies. It is thought that rebound production of antibodies in this way leaves the multiplied pathogenic cells more vulnerable to cytotoxic drugs. For this reason, it can usually be applied to increase the efficacy of cytotoxic drugs (eg, cyclophosphamide). The number of treatments varies greatly depending on the severity of the disease and the general condition of the patient [4, 6, 7].

Plasmapheresis is an extracorporeal procedure requiring special filters and equipment. A central venous line through jugular, subclavian or femoral vein is necessary to achieve the required blood flow rate but hemodynamic balance should not be disturbed during the removal of the blood out of the body. Hemodynamic instability or hypersensitivity reactions may develop during the procedure. Acute pulmonary edema, thromboembolism, anaphylaxis, bleeding diathesis and mechanical complications of the venous catheter may be associated with mortality [8, 9]. Therapeutic plasmapheresis, generally used in the treatment of autoimmune disorders and those affecting neurologic, hematologic or immunologic systems with or without known etiologies, has recently been utilized in the treatment of sepsis cases to reduce mortality and morbidity [1, 4, 10, 11]. TPE is performed at our intensive unit since 2007 for a wide spectrum of disorders. In this article we aim to review our plasmapheresis experience in the light of the current articles in the literature.

METHODS

Records of the cases who underwent TPE in Bakırköy Dr. Sadi Konuk Training and Research Hospital Training and Research Hospital intensive care unit between 2007 and 2016 have been reviewed retrospectively. Data on demographic variables including age and sex, indication for plasmapheresis, method and site of venous access, complications developed during or following the procedure, total number of sessions, replacement fluids used (albumin, fresh frozen plasma, etc.), survival and the serum triglyceride, cholesterol and amylase levels of the acute pancreatitis cases before and after the procedure were collected. The hospital Institutional Ethics Committee approved the study.

Complete blood count, coagulation panel and serum electrolyte levels were run for all cases transferred from their primary clinics with different etiologies. Hemodynamic and pulmonary status were monitored with Nihon-Kohden BSM 4113 K® bedside monitor (Nihon-Kohden Corporation, Tokyo, Japan). The most convenient central vein was accessed using a double lumen 12F dialysis catheter under sterile conditions. Following the catheterization plasmapheresis was initiated with Prismaflex® (Gambro Lundia AB, Branding & Market Com, Sweden) system using Prismaflex TPE 2000® filters (Gambro Lundia AB, Branding & Market Com, Sweden). There were 2 or 3 day intervals between the sessions. Total plasma volume to be processed was calculated with the formula (1-hematocrit %) × total blood volume (weight in kg × coefficient). Minimum and maximum blood flow rates, 100 and 400 ml/hr, respectively, were determined regarding the hemodynamic parameters of the subject and the technical specifications of the filter. Total plasma volume was processed 1 to 1.5 times in each session. Fresh frozen plasma was used as the preferred replacement fluid. Heparine sodium was infused at 10 U/kg/hr through the plasmapheresis system in order to prevent the activation of the coagulation cascade in the extracorporeal circuit and anticoagulation activity was monitored with activated partial thromboplastin time (aPTT). Number of plasmapheresis sessions was determined by the progress of the subject in light of the reported similar cases in the literature.

Statistical Analysis

SPSS® version 13.0 was used for the statistical analysis of the data. Data on demographics, indications for plasmapheresis and survival were

analyzed using descriptive statistics. Pre- and post-procedure serum triglyceride, cholesterol and amylase levels in acute pancreatitis subjects were evaluated with paired t-test. A p value of < 0.05 was considered significant.

RESULTS

A total of 80 patients, 38 (47.5%) female and 42 (52.5%) male, aged between 12 and 82 years (mean: 45.08 ± 14.68 years) received 501 TPE sessions between 2007 and 2016. Most common site for catheterization was internal jugular vein (n = 44, 55%), followed by femoral vein (n = 33, 41.25%) and subclavian vein (n = 2, 2.5%). A pre-existing brachial arteriovenous fistula was used in one (1.25%) subject for plasmapheresis. Total number of plasmapheresis sessions varied between 4 and 14 (median: 6). Demographic variables and technical information the plasmapheresis procedure are summarized in Table1. Underlying etiologies necessitating plasmapheresis constitute five major groups which are neurologic, hematologic, pancreatic, hepatic and other disorders. Neurologic disorders are the most common pathologies requiring TPE in the study group with 35 subjects (43.75% of all subjects) which include Guillain-Barre syndrome (n = 13, 16.25 %), myasthenia gravis (n = 6, 7.5%), neuromyelitis optica (n = 4, 5%), transverse myelitis (n = 3, 3.75%), multiple sclerosis (n = 2, 2.5%), acute disseminated encephalomyelitis (ADEM) syndrome (n = 1, 1.25%), stiff person syndrome (n = 1, 1.25%), resistant epilepsy (n = 3, 3.75%), Isaac syndrome (n = 1, 1.25%) and Eaton-Lambert syndrome (n = 1, 1.25%). Hematologic disorders are the second most common group with 18 subjects (22.5% of all subjects) including the diagnoses of hyperviscosity syndrome (n = 10, 12.5 %), disseminated intravascular coagulopathy (DIC) (n = 3, 3.75%), microscopic polyarteritis nodosa (PAN) (n = 1, 1.25%) and thrombotic thrombocytopenic purpura (TTP) (n = 4, 5 %). Acute pancreatitis associated with hypertriglyceridemia constituted the third group with 12 (15%) subjects. Fourth most common disorder was hepatic insufficiency with 7 subjects (8.75% of all subjects) consisting of Wilson's disease (n = 1, 1.25%), autoimmune hepatitis (n = 2, 2.5%) and toxic hepatitis due to mushroom (n = 3, 3.75 %) and drug (n = 1, 1.25%) intoxication. There were seven complications that occurred during or following the total 501 TPE sessions. Three cases complained of dyspnea following plasmapheresis and displayed infiltrations on chest X-rays. All three cases responded

Table 1. Demographics, technichal properties of plasma exchange, complications (n = 80)

Characteristics	Data
Sex (female/male) (n)	38/42
Age (year)	45.08 ± 14.67
Localisation of catheterisation (n)	
Vena Jugularis Interna	44
Vena Femoralis	33
Vena Subclavia	2
Fistula	1
Complications (n)	
Dispnea	3
Rush	2
Pulmoner emboli	1
Labile hemodynamics	1

Table 2. Therapeutic plasma exchange indications

Indications	Data (n = 80)
Neurologic, n(%)	**35 (43.75%)**
Guillain-Barre syndrome	13 (16.25%)
Myasthenia gravis	6 (7.5%)
Neuromyelitis optica	4 (5%)
Transverse myelitis	3 (3.75%)
Multiple sclerosis	2 (2.5%)
Syndromes[+]	7 (8.75%)
Haematologic	**18 (22.5%)**
Hyperviscosity	10 (12.5%)
TTP	4 (5%)
DIC	3 (3.75%)
Microscopic PAN	1 (1.25%)
Pancreatitis	**12 (15%)**
Liver	**7 (8.75%)**
Toxic hepatitis	4 (5%)
Wilson	1 (1.25%)
Autoimmune hepatitis	2 (2.5%)
Others	**8 (10%)**
Sepsis	4 (5%)
Goodpasture syndrome	2 (2.5%)
Toxic epidermal necrolysis	1 (1.25%)
Resistant hyperthyroidism	1 (1.25%)

DIC = disseminated intravascular coagulopathy, PAN = polyarteritis nodosa, TTP = thrombotic thrombocytopenic purpura, Syndromes[+] = Adem's syndrome, Stiff-Person's syndrome, resistant epilepsy, Isaac's syndrome, Eaton-Lambert's syndrome

Table 3. Survival data (n = 80)

	Healed n = 40 (50%)	No benefit n= 16 (20%)	Exitus n = 24 (30%)
Neurologic	14	16	5
Haematologic	8	-	10
Liver	4	-	3
Pancreatitis	12	-	-
Others	2	-	6

Others = Toxic epidermal necrolysis, Goodpasture syndrome, hyperthyroidism resistant to medical treatment, sepsis

Table 4. Evaluation of pancreatitis cases due to hypertriglisemia

	Before PE	After PE	*p* value
Triglyceride (mg/dl)	3223 ± 1974.094	612 ± 239.513	**< 0.001**
Cholestrol (mg/dl)	365.83 ± 114.638	182.2 ± 52.174	**< 0.001**
Amylase (U/L)	203.42 ± 82.656	70.33 ± 50.68	**0.001**

PE = Plasma exchange

to noninvasive mechanical ventilations. One subject who developed dyspnea and hypotension during the third plasmapheresis session and required orotracheal intubation for mechanical ventilation was diagnosed with pulmonary embolism. This patient was discharged with full recovery after seven plasmapheresis sessions. In two patients, plasmapheresis was stopped due to widespread rash developing on the subjects. The lesions resolved with antihistaminic agents and plasmapheresis therapy was continued with the addition of antihistaminics to the treatment regimen. Fourty (50%) of the cases were discharged with full recovery after plasmapheresis. Sixteen (20%) cases were transferred back to their primary clinics after the acute exacerbation requiring plasmapheresis was resolved. Remaining 24 (30%) cases died due to complications related to the primary disorder. Medical indications for TPE and survival data are summarized in Tables 2 and 3. Twelve subjects with acute pancreatitis due to hypertriglyceridemia had TPE in order to normalize the serum lipid levels. Baseline mean serum triglyceride level of 3223 mg/dl was reduced to 612 mg/dl and mean serum cholesterol was reduced from the baseline level of 286.7 mg/dl to 135.4 mg/dl after TPE ($p < 0.05$ for both parameters). Baseline mean serum amylase level was reduced from 203.42 U/l to 70.33 U/L after the procedure ($p < 0.001$). Changes in serum lipid and amylase levels are summarized in

DISCUSSION

TPE is currently accepted as a treatment option for a wide variety of medical disorders [3, 4, 12]. Still, there are no clear cut guidelines for the number and frequency of TPE sessions recommended for given disorders and the treatment is planned according to the medical progress of the subject. The ASFA guideline recommends that neurological diseases can be performed daily for 5 days, daily for 3 days, non-neurological disease for 3 days, or longer and more frequent than the clinical severity of the disease [2]. Plasma exchange is considered to be a symptomatic treatment. Because it does not remove the basic source of pathogenic factors. For this reason, the success of TPE is dependent on whether the pathogens can be accessed by circulation and whether the transfer rate of production and transfer to the plasma component can be adequately addressed by the TPE.

McLeod 2012 compared the alternative replacement solutions for TPE and reported albumin as the replacement product of choice [1]. Among these two solutions, both recommended in the previous reports [1, 4, 13], we preferred fresh frozen plasma due to excessive financial burden associated with albumin.

Central veins or arteriovenous fistulas may be used for catheterization in plasmapheresis. Subclavian veins were used for vascular access in only two subjects and the last one was performed in 2009, as it is not a preferred site for catheterization due to higher risk of thrombosis [9]. No mechanical complications or infections related to catheterization were reported in our case series. For the 501 plasmapheresis sessions over 9 years, the complication rate in our clinic was 8.75% (mostly minor). Most common reason for mortality during plasmapheresis is cardiac arrhythmias and none of the cases in our series had arrhythmias during the sessions [12, 14]. Neutrophils located at the pulmonary endothelium play a major role in transfusion related acute lung injury (TRALI). When used as a replacement fluid, fresh frozen plasma may trigger neutrophil activation in pulmonary endothelium and lead to TRALI [11, 12]. Noninvasive mechanical ventilator support was necessary because of the development of respiratory distress only in three of our cases. Following the resolution of respiratory distress, TPE was completed without any other

problems.

Following the 2012 review of Cortese and Cornblath [15] covering 2263 reports, neurology guidelines began including plasmapheresis as a therapeutic alternative for various disorders. The most common neurologic disorder requiring TPE is Guillain-Barre syndrome (GBS). GBS is an autoimmune subacute polyneuropathic demyelinating disorder with unknown etiology that is associated with acute inflammation. Recent studies support the use of plasmapheresis for the recovery of muscle strength in GBS [4, 16, 17]. Of the 13 GBS subjects in our study group, 11 had full recovery of the muscle strength after plasmapheresis and only one subject did not benefit from this procedure. Our study results are similar to the study of 63 patients with neurological disease by Tombak *et al*. [18]. Myasthenia gravis is another common neurologic disorder requiring plasmapheresis. It presents with a neuromuscular transmission defect due to autoantibody mediated damage to the acetylcholine receptors. TPE is thought to be beneficial by reducing circulating humoral factors (i.e., anti-ACHR antibodies and immunocomplexes) in the circulation. It can be used as part of other immuno-regulatory treatments or in crisis management [19, 20]. Similar to intravenous immunoglobulin treatment, plasmapheresis is often reserved for myasthenic crises and refractory cases. Recovery is usually expected within a few days, but not more than 2 months [21]. Of the 6 myasthenic crises cases in our study group, four responded very well to treatment and were mostly relieved of their symptoms during the crisis. Our success rate in myasthenic crises is similar to another case series. In the acute attacks of the demyelinating disorders of the central nervous system, high dose corticosteroid therapy is indicated. For patients who do not respond to corticosteroid therapy, suggested next step is plasmapheresis. Hematologic disorders formed another major group in our study group. Removal of autoantibodies may improve survival in autoimmune based hematologic disorders [3, 22, 23]. TPE administration has been observed to reduce serum triglyceride levels rapidly and in retrospective studies, hypertriglyceridemia-induced pancreatitis (HIP) has been considered as a potential therapeutic treatment [24]. The potential role of TPE in HIP has not been adequately confirmed by large prospective studies. The 2013 Guidelines for the Use of Therapeutic Apheresis discussed the potential role of plasma exchange for HIP and found 2C (poor evidence). However, there are many cases of hepatitis infusion in HIP with severe pancreatitis, which is the clinical benefit of TPE as well as heparin infusion [25]. There were 12 cases, including 2 pregnant women, with acute pancreatitis due to hypertriglyceridemia undergoing plasmapheresis in order to normalize the high lipid levels. We were able to decrease the mean triglyceride levels by 80%, cholesterol levels by 50% and amylase levels by 65% and discharged all pancreatitis cases with full recovery. Our pancreatitis results are comparable to previous reports. There were 6 cases, including one with drug intoxication and 3 others with mushroom poisoning, undergoing plasmapheresis for acute hepatitis. It has been reported that initiating plasmapheresis within 36-48 hours from the onset of intoxication symptoms is associated with higher survival rates. All four intoxication cases in our study had plasmapheresis within 48 hours of admission and all had achieved full recovery. In toxic hepatitis, plasmapheresis is as effective as hemoperfusion, another extracorporeal treatment method [26]. Unfortunately, the remaining 3 hepatitis cases who had Wilson's disease and acute hepatic insufficiency on an autoimmune basis did not improve after plasmapheresis and both cases died shortly thereafter.

CONCLUSION

Between 2007 and 2016, 80 subjects in our clinic received a total of 501 plasmapheresis sessions. Our results suggest that timely initiation of plasmapheresis for the proper indications may reduce the morbidity and mortality rates in various disorders associated with unfavorable prognosis.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] McLeod BC. Plasma and plasma derivatives in therapeutic plasmapheresis. Transfusion 2012;52(Suppl 1):38S-44S.
[2] Schwartz J, Padmanabhan A, Aqui N, Balogun RA, Connelly-Smith L, Delaney M, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. J Clin Apher 2016;31:149-62.
[3] Wozniak K, Urbanowska E, Snarski E. [Plasmapheresis in haematology]. Wiad Lek 2015;68:173-8. [Article in Polish]
[4] Lainez-Andres JM, Gascon-Gimenez F, Coret-Ferrer F, Casanova-Estruch B, Santonja JM. [Therapeutic plasma exchange: applications in neurology]. Rev Neurol 2015;60:120-31. [Article in Spanish]
[5] Matsumoto M. New developments in treatment modalities of thrombotic thrombocytopenic purpura. Rinsho Ketsueki 2017;58:2081-6.
[6] Stefanutti C, Morozzi C, Petta A. Lipid and low-density-lipoprotein apheresis. Effects on plasma inflammatory profile and on cytokine pattern in patients with severe dyslipidemia. Cytokine 2011;56:842-9.
[7] Saito A. Current progress in blood purification methods used in critical care medicine. Contrib Nephrol 2010;166:100-11.
[8] Golestaneh L, Mokrzycki MH. Vascular access in therapeutic apheresis: update 2013. J Clin Apher 2013;28:64-72.
[9] Stegmayr B, Wikdahl AM. Access in therapeutic apheresis. Ther Apher Dial 2003;7:209-14.
[10] Nguyen TC, Han YY. Plasma exchange therapy for thrombotic microangiopathies. Organogenesis 2011;7:28-31.
[11] Rimmer E, Houston BL, Kumar A, Abou-Setta AM, Friesen C, Marshall JC, et al. The efficacy and safety of plasma exchange in patients with sepsis and septic shock: a systematic review and meta-analysis. Crit Care 2014;18:699.
[12] Pruijm MT, Cherpillod A, Vogt B, Burnier M. [Plasmapheresis: technique, complications and indications]. Rev Med Suisse 2008;4:581-2, 584-6, 588. [Article in French]
[13] Stevenson ME, Leung N, Winters JL. What are the newer applications for therapeutic apheresis in Nephrology?: Current Indications for Therapeutic Plasma Exchange in Nephrology. Semin Dial 2016;29:350-3.
[14] Sutton DM, Nair RC, Rock G. Complications of plasma exchange. Transfusion 1989;29:124-7.
[15] Cortese I, Cornblath DR. Therapeutic plasma exchange in neurology: 2012. J Clin Apher 2013;28:16-9.
[16] Nomura K. [Treatment of Guillain-Barre Syndrome]. Brain Nerve 2015;67:1397-410. [Article in Japanese]
[17] Kulkantrakorn K, Sukphulloprat P. Outcome of Guillain-Barre Syndrome in tertiary care centers in Thailand. J Clin Neuromuscul Dis 2017;19:51-6.
[18] Tombak A, Ucar MA, Akdeniz A, Yilmaz A, Kaleagasi H, Sungur MA, et al. Therapeutic plasma exchange in patients with neurologic disorders: review of 63 cases. Indian J Hematol Blood Transfus 2017;3397-105.
[19] Hassan A, Yasawy ZM. Myasthaenia Gravis: clinical management issues before, during and after pregnancy. Sultan Qaboos Univ Med J 2017;17:e259-67.
[20] Deguchi K, Matsuzono K, Nakano Y, Kono S, Sato K, Deguchi S, et al. A case of anti-MuSK antibody-positive myasthenia gravis successfully treated with outpatient periodic weekly blood purification therapy. Intern Med. 2018. doi: 10.2169/internalmedicine.9466-17.
[21] Prakash S, Hans R, Sharma RR, Lal V, Marwaha N. Therapeutic plasma exchange in a patient of myasthenic crisis, refractory to intravenous immunoglobulin and immunosuppressive therapy. Neurol India 2017;65:1409-12.
[22] Niewold TB, Bundrick JB. Disseminated intravascular coagulation due to cytomegalovirus infection in an immunocompetent adult treated with plasma exchange. Am J Hematol 2016;81:454-7.
[23] Winters JL. Plasma exchange in thrombotic microangiopathies (TMAs) other than thrombotic thrombocytopenic purpura (TTP). Hematology Am Soc Hematol Educ Program 2017;2017:632-8.
[24] Click B, Ketchum AM, Turner R, Whitcomb DC, Papachristou GI, Yadav D. The role of apheresis in hypertriglyceridemia-induced acute pancreatitis: a systematic review. Pancreatology 2015;15:313-20.
[25] Uyar S, Harmandar F, Kok M, Tas Z, Dolu S, Tokuc A, et al. Management of hypertriglyceridemia induced acute pancreatitis and therapeutic plasmapheresis : report of nine cases and review of literature. Acta Gastroenterol Belg 2017;80:71-4.
[26] Disel NR, Akpinar AA, Sebe A, Karakoc E, Surer S, Turhan FT, et al. Therapeutic plasma exchange in poisoning: 8 years' experience of a university hospital. Am J Emerg Med 2015;33:1391-5.

The European Research Journal 2018;4(4):349-355 ORIGINAL ARTICLE

Liver functions in patients with obstructive sleep apnea syndrome

Seda Beyhan Sağmen[1], Elif Torun Parmaksız[1], Sevda Şener Çömert[1], Ali Fidan[1], Banu Salepçi[2]

[1]Department of Pulmonary Diseases, University of Health Sciences, Kartal Dr. Lütfi Kırdar Training and Research Hospital, İstanbul, Turkey
[2]Department of Pulmonary Diseases, Yeditepe University School of Medicine, İstanbul, Turkey

DOI: 10.18621/eurj.381906

ABSTRACT

Objectives: Objective. Previous studies showed that obstructive sleep apnea syndrome (OSAS) was associated with liver diseases such as elevated liver enzyme levels and hepatic steatosis. The aim of this study was to assess the relationship between serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and OSAS and its severity.

Methods: A total of 617 patients who underwent PSG (polysomnography) between January 2016 and May 2017 were evaluated in this study. AST, ALT, total cholesterol, triglyceride levels and body mass index were analyzed. The data were analyzed using the Student's t-test, ANOVA, Chi-square test, and Pearson's correlation coefficient.

Results: Five hundreds and thirty patients with OSAS and 60 healthy controls were included in the study. Of the patients in the OSAS group, 17.7% had an elevated ALT level and 7.9% had an elevated AST level. There was a statistically significant difference in ALT and AST levels between the OSAS and control groups ($p < 0.001$ and $p < 0.001$, respectively). In the OSAS group, there was a statistically significant positive relationship between serum ALT and AST levels and apnea-hypopnea index (AHI), apnea index, oxygen desaturation index. Both AST and ALT levels were statistically significantly higher in obese patients than in non-obese patients ($p < 0.001$ and $p < 0.001$, respectively). ALT level was statistically significantly higher in patients without hypertension than in patients with hypertension ($p < 0.001$). In OSAS patients without hypertension, there was a statistically significant relationship between serum ALT and AST levels and AHI (r =0.223, $p < 0.001$ and r =0.142, $p = 0.007$; respectively).

Conclusion: OSAS is a risk factor for elevated liver enzyme levels. Hypoxia plays an important role on liver enzymes in OSAS patients.

Keywords: Liver enzymes, obstructive sleep apnea syndrome, hypertension

Received: January 20, 2018; Accepted: February 26, 2018; Published Online: March 15, 2018

Obstructive sleep apnea syndrome (OSAS) is a clinical condition that occurs when the upper airway collapses during sleep and repeatedly stops breathing for brief moments. Breathing is fully and partially blocked [1]. The prevalence of OSAS is estimated to be 3-7% among males and 2-5% among females [2]. OSAS is accompanied by a variety of metabolic abnormalities such as insulin resistance, hypertension, obesity, and liver diseases [3]. The sympathetic nervous system activation and hypoxia

Address for correspondence: *Seda Beyhan Sağmen, MD., University of Health Sciences, Kartal Dr. Lütfi Kırdar Training and Research Hospital, Department of Pulmonary Diseases, İstanbul, Turkey*
E-mail: sedabeyhansagmen@gmail.com

e-ISSN: 2149-3189

due to apnea/hypopnea and the oxidative stress due to reoxygenation are the main causes of cardiovascular and metabolic events for OSAS [4]. Hepatic steatosis can manifest itself with asymptomatic elevation of liver enzymes, although liver biopsy is required for the diagnosis of liver diseases. Although the pathogenesis of hepatic steatosis is not clear, obesity and insulin resistance have been found to be associated with hyperlipidemia and hypertension [5].

A previous study found that high body mass index (BMI) and presence of OSAS were independently associated with an elevation in serum aminotransferase levels [6]. A study conducted in mice demonstrated the effect of chronic intermittent hypoxia-induced oxidative stress on the liver [7]. In studies, it was found that OSAS was associated with some liver diseases such as elevated liver enzyme levels and hepatic steatosis. However, it is debatable whether OSAS is an independent risk factor for liver damage [8]. Serum AST and ALT levels are the most commonly used markers for screening fatty liver disease. Some studies found that serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were elevated in patients with OSAS. The aim of this study was to evaluate serum ALT and AST levels in OSAS patients and to determine the relationship between OSAS severity and liver enzymes.

METHODS

A total of 617 patients who underwent polysomnography (PSG) between January 2016 and May 2017 were evaluated in this study. Patients who had chronic pulmonary disease, renal disease, liver disease and who drank more than 20 g of alcohol per day and who received hepatotoxic drugs were excluded. Seven patients were excluded because they had COPD and liver disease. Twenty patients were excluded because their liver enzyme levels could not be reached. Finally, 590 patients were included in the study. Additional diseases (Diabetes mellitus, hypertension), age, gender, and BMI were recorded from patient files. AST, ALT, glucose, total cholesterol, and triglyceride levels were evaluated by analyzing routine blood samples. The upper limit was taken as 38 for AST and 41 for ALT.

Overnight polysomnographic recordings were taken from the patients using a video camera. Sleep and physiological variables were monitored with a Grass PSG device. 10-channel electroencephalography, submental electromyography (EMG), right and left eye electrooculography, electrocardiography, oronasal airflow (thermal sensor and nasal pressure transducer), body position, thoracic and abdominal motion sensor (inductance plethysmography), measurement of arterial blood oxygen saturation using finger pulse oximetry, and left and right leg motion sensors (EMG) were used. Apnea was defined as a ≥ 90% decrease in airflow signal for ≥ 10 sec. At least 90% of the event's duration must meet the amplitude reduction criteria for apnea. Obstructive apnea was defined as the absence of breathing for 10 seconds or more, despite an effort to breathe. Central apnea was defined as the absence of airflow and respiratory effort lasting for at least 10 seconds. Mixed apnea was defined as a lack of respiratory effort during the initial apneic period followed by gradually increasing effort against an occluded upper airway. Hypopnea was defined as an airflow decrease of ≥ 30% compared with the baseline for at least 10 s plus oxygen desaturation ≥ 3. At least 90% of the event's duration must meet the amplitude reduction criteria for hypopnea. OSAS was categorized into severity levels of mild (apnea-hypopnea index [AHI]: 5-14.9 events/h), moderate (AHI: 15-29.9 events/h), and severe (AHI: ≥ 30 events/h). The patients were divided into mild-moderate OSAS group (Group 1) and severe OSAS group (Group 2). The patients with AHI < 5 were considered as a control group.

Statistical Analysis

The SPSS 20.0 statistical software package was used for the statistical analysis of data. The Kolmogorov-Smirnov test was used to determine whether continuous variables were normally distributed. For normally distributed continuous variables, the Independent t-test was used for comparing the means of two groups, and the one-way ANOVA was used for comparing the means of multiple groups. If the ANOVA result was significant, the Dunnett's and Tukey's multiple comparison tests were used to determine which group caused the difference. While the Dunnett's test was used in paired

Table 1. Demographic, clinical, and polysomnographic parameters of obstructive sleep apnea syndrome and control groups

	OSAS	Control	*p* value
Age (years)	49 ± 12	48 ± 10	> 0.05
Male (gender)	64%	51.7%	> 0.05
BMI (kg/m2)	31.63 ± 5.5	30.76 ± 5.3	> 0.05
AHI (events/h)	32.6 ± 25.8	2.4 ± 1.4	< 0.0001
AI (events/h)	20.1 ± 25	3.5 ± 1.5	< 0.0001
ODI	27.6 ± 24.1	4.6 ±3.1	< 0.0001
TS90%	16.9 ± 24.5	4.5 ± 3.1	< 0.0001
Minimum saturation (%)	80.5 ± 9.4	89 ± 3.7	< 0.0001
SO2 (%)	92.5 ± 3.9	94.7 ± 2.1	< 0.0001
Glicose (mg/dl)	113 ± 35.2	102 ± 22.4	< 0.001
Total cholesterol (mg/dl)	217.4 ± 45.1	205.9 ± 40.1	> 0.05
Triglyceride (mg/dl)	162.6 ± 85.7	141.3 ± 76.4	> 0.05
LDL (mg/dl)	140 ± 38.3	132.3 ± 35.2	> 0.05
HDL (mg/dl)	45.4 ± 11	45.2 ± 12.2	> 0.05
AST level	25.1 ± 11.9	20.4 ± 5.8	< 0.0001
ALT level	30 ± 20.2	21.1 ± 10.3	< 0.0001

AI = apnea index, AHI = apnea-hypopnea index, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, HDL = high density lipopretein, LDL = low density lipoprotein, ODI = oxygen desaturation index, OSAS = obstructive sleep apnea syndrome, SO_2= oxygene saturation, TS90% = percent of total time with oxygen saturation level < 90%

comparisons according to the control group, the Tukey's test was used in the comparison of other groups with each other. The relationship between two continuous variables was assessed by the Pearson's test. The Chi-square test was used for the statistical evaluation of categorical variables. While categorical variables were expressed as frequency and percentage, continuous variables were expressed as mean±standard deviation. The risk factors (age, sex, BMI) were analyzed by using lineer regression analysis. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Five hundreds and thirty patients with OSAS and 60 healthy controls were included in the study. The mean age of the OSAS group was 49 ± 12 years, and the mean age of the control group was 48 ± 10 years. Demographic data are given in Table 1.

Of the patients in the OSAS group, 17.7% had an elevated ALT level and 7.9% had an elevated AST level. Of the patients in Group 1, 15.8% had an elevated ALT level and 6.3% had an elevated AST level. Of the patients in Group 2, 20.7% had an elevated ALT level and 10.3% had an elevated AST level ($p < 0.05$).

ALT and AST levels were statistically significantly higher in the OSAS group compared to the control group ($p < 0.001$ and $p < 0.001$, respectively). There was a statistically significant difference in AST and ALT levels in Groups 1 and 2 ($p = 0.028$ and $p = 0.006$, respectively) (Table 2).

Table 2. The level of liver enzymes according to obstructive sleep apnea syndrome severity

	Mild-moderate OSAS (Group 1 = 317)	Severe OSAS (Group 2 = 213)	*p* value
AST	24.1 ± 11.7	26.5 ± 12.2	0.028
ALT	28 ± 19.3	33 ± 21.1	0.006

ALT = alanine aminotransferase, ALT = alanine aminotransferase, AST = aspartate aminotransferase

Table 3. Correlation of liver enzymes with polysomnographic parameters, age, and body mass index

	AST		ALT	
	r	***p* value**	**r**	***p* value**
Age	-0.136	0.002	-0.240	<0.0001
BMI	0.116	0.008	0.125	0.004
AHI	0.114	0.009	0.165	<0.0001
AI	0.098	0.023	0.156	<0.0001
ODI	0.117	0.007	0.172	<0.0001

AI = apnea index, AHI = apnea-hypopnea index, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, ODI = oxygen desaturation index

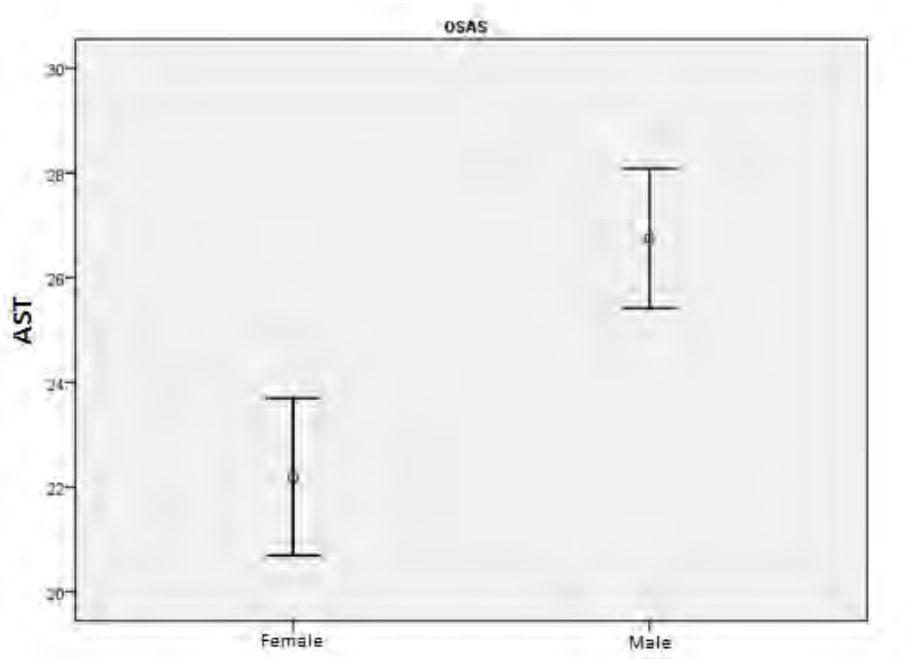


Figure 1. The difference of AST levels between male and female (AST = aspartate aminotransferase).

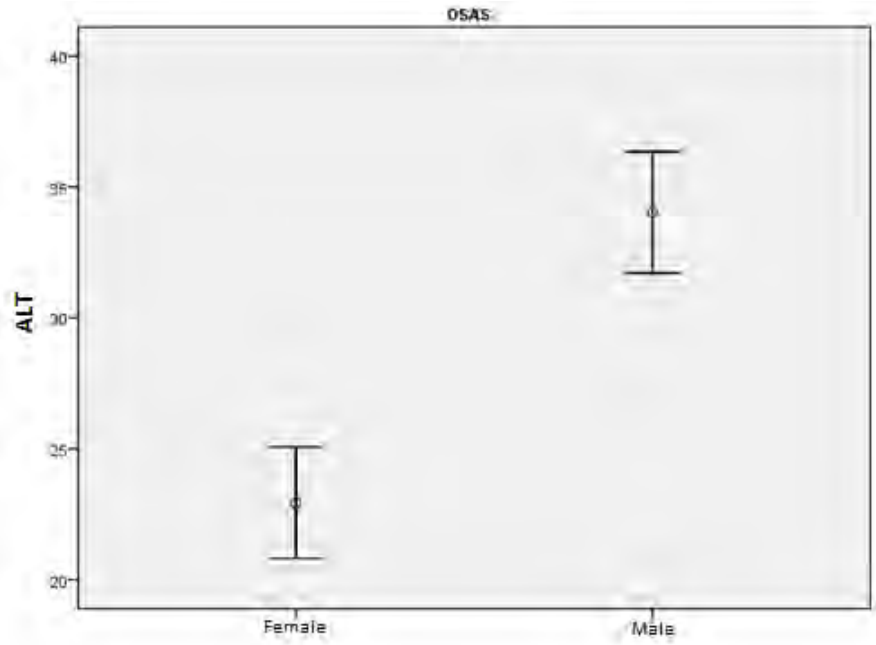


Figure 2. The difference of ALT levels between male and female (ALT = alanine aminotransferase).

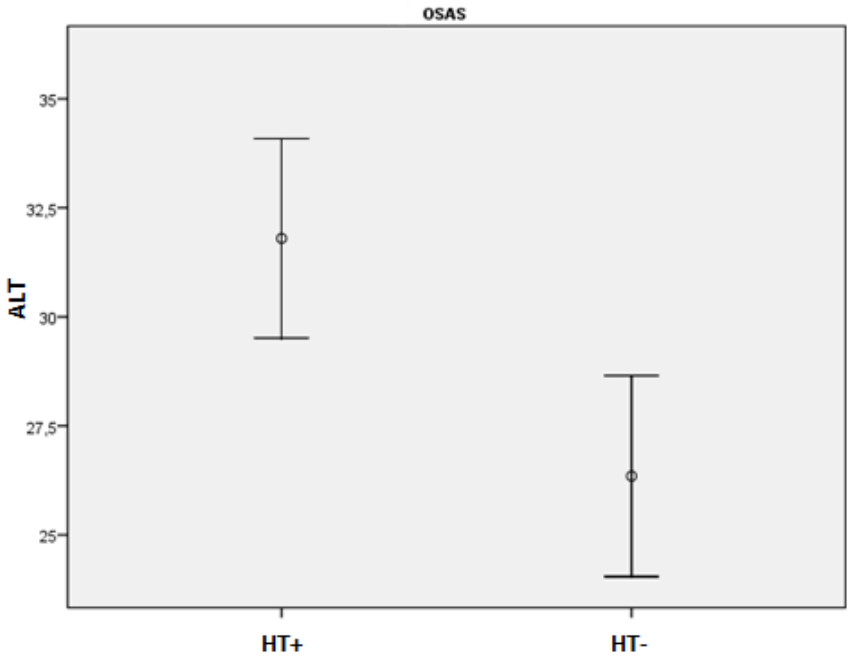


Figure 3.The difference of ALT levels in OSAS patients with hypertension and without hypertension (ALT = alanine aminotransferase, HT = hypertension, OSAS = obstructive sleep apnea syndrome).

In the OSAS group, there was a statistically significant difference in AST and ALT levels between genders. Both AST and ALT levels were statistically significantly higher in male patients than in female patients ($p < 0.001$ and $p < 0.001$, respectively) (Figures 1 and 2).

In the OSAS group, there was a statistically significant positive relationship between serum ALT and AST levels and AHI, apnea index, oxygen desaturation index. In the OSAS group, serum ALT and AST levels showed a statistically significant negative relationship with age and a statistically significant positive relationship with BMI (Table 3).

In the OSAS group, there was a statistically significant difference between those with ALT ≤ 41 and those with ALT > 41 in terms of age, BMI, and AHI ($p < 0.05$). In the OSAS group, there was a statistically significant difference in AST and ALT levels between non-obese and obese patients (according to body mass index). Both AST and ALT levels were statistically significantly higher in obese patients than in non-obese patients ($p < 0.001$and $p < 0.001$, respectively).

Hypertension was detected in 32.4% of OSAS patients. In the OSAS group, there was a statistically significant difference in ALT level between patients with and without hypertension. ALT level was statistically significantly higher in patients without hypertension than in patients with hypertension ($p < 0.001$) (Figure 3). In the control group, there was no statistically difference in AST and ALT levels and AHI value between patients with and without hypertension. In OSAS patients without hypertension, there was a statistically significant relationship between serum ALT and AST levels and AHI (r = 0.223, $p < 0.001$ and r = 0.142, p =0.007, resspectively).

In 143 patients having normal cholesterol and triglyceride levels in the OSAS group, serum ALT level had a statistically significant but weak positive correlation with AHI, apnea index, oxygen desaturation index and a statistically significant but weak negative correlation with age (r = 0.242, p =0.004; r = 0.180, p =0.032; r = 0.241, p = 0.004 and r = -0.234, p = 0.005; respectively). When 143 patients having normal cholesterol and triglyceride levels in the OSAS group were examined, serum AST level had a statistically significant but weak negative correlation with only age (r = -0.243, p = 0.003).

An adjusted linear regression analysis was conducted for AST and ALT variables as dependent variables. Age, sex and BMI adjusted regression equations were given. OSAS was an independent risk factor for abnormal liver enzymes.

For OSAS and control group AST = 8.097 +

3.615×control - 0.090×age + 4.824×sex + 0.353×BMI; ALT = 7.807×control – 0.291×age + 10.767×sex + 0.710×BMI.

For OSAS (mild-moderate and severe group) AST = 15.405 – 0.099×age + 4.90×sex + 0.363×BMI; ALT = 15.953 – 0.318×age + 11.019×sex + 0.721×BMI.

DISCUSSION

In our study, there was a statistically significant difference in ALT and AST levels between the OSAS and control groups. In the OSAS group, both AST and ALT levels were statistically significantly higher in male patients than in female patients. Of the patients in the OSAS group, 17.7% had an elevated ALT level and 7.9% had an elevated AST level.

In a study conducted by Jouet *et al*. [9] in obese patients, serum ALT, AST, and GGT levels were found to be increased (25%, 42.9%, and 52.8%; respectively). In another study examining OSAS and serum AST, ALT, and GGT levels, elevated liver enzyme levels were present in 42.3% of OSAS patients. A meta-analysis showed that 4.4% of OSAS patients had an elevated ALT level and 13.3% of OSAS patients had an elevated AST level [10]. There was a relationship between elevated liver enzyme level and OSAS severity (respectively, 51% for severe group and 32.4% for mild-moderate group) [11]. In our study, elevated ALT and AST levels were statistically significantly higher in severe OSAS group (Group 2) (20.7% and 10.3%, respectively) than in mild-moderate OSAS group (15.8% and 6.3%, respectively). In a study involving 163 patients, elevated liver enzyme levels were present in 20% of OSAS patients. This was identified as a strong predictor of elevated liver enzymes in OSAS patients with AHI > 50 [6].

In a study in which OSAS patients were classified according to severity, ALT level was statistically significantly higher in severe OSAS group than in mild-moderate OSAS group [11]. In our study, AST and ALT levels were statistically significantly higher in severe OSAS group than in mild-moderate OSAS group.

Chin *et al*. [12] found that abnormal liver enzyme levels were present in 35% of obese patients with OSAS. Of the obese patients with OSAS in our study, 21.3% had an elevated ALT level and 10.6% had an elevated AST level. In our study, both AST and ALT levels were statistically significantly higher in obese patients than in non-obese patients.

In our study, no relationship was found between serum AST and ALT levels and minimum oxygen saturation level. Unlike our study, a study involving 109 patients demonstrated that there was a significant relationship between serum AST and ALT levels and minimum oxygen saturation level and percent of total time with oxygen saturation level <90% (TS90%). Moreover, there was a significant correlation between serum ALT level and age [13]. In our study, there was a significant relationship between serum AST and ALT levels and age.

Daltro *et al*. [14] found that serum AST and ALT levels were elevated independently of AHI, minimum oxygen saturation, and TS90%). In our study BMI, age and sex were included in the regression equation. Our study showed that OSAS is a risk factor for abnormal liver enzymes compared to control group independent of BMI, sex and age but we did not find an association related to severity. Mishra *et al*. [15] showed that nocturnal intermittent hypoxia was a risk factor for the development of hepatic steatosis and liver fibrosis in morbidly obese patients with OSAS.

In a study conducted in OSAS patients, it was found that total cholesterol and triglyceride levels were statistically significantly higher in group with elevated ALT and AST levels than in group with normal ALT and AST levels. In this study, cholesterol and triglyceride levels were not categorized as normal or elevated [11]. In our study, there were significant correlations between ALT and AHI, apnea index, oxygen desaturation index in 143 patients with normal cholesterol and triglyceride levels in the OSAS group. In another study conducted in OSAS patients, serum AST and ALT levels were measured before continuous positive airway pressure (CPAP) therapy and after one-night of CPAP therapy and then were compared to each other. However, no significant difference was detected. That study had some limitations such as the fact that it included a very small number of patients and the control group did not exist [16].

Liver hypoxia, reoxygenation, and catecholamine-mediated metabolic changes cause metabolic changes in the liver, for example, mitochondrial anaerobic breath. Liver biopsies in nonalcoholic fatty liver

patients indicating mitochondrial changes showed this speculation. A past report has demonstrated that hypoxia goes about as a noteworthy of angiogenesis and fibrogenesis, especially by the actuation of hypoxia-inducible factor-1α and vascular endothelial growth factor flagging pathways or by initiating movement of activated hepatic stellate cells [17, 18]. In the light of these data, OSAS is a risk factor for elevated liver enzyme levels. Liver damage occurs after hypoxia. AST, ALT are nonspesific to define liver disease but it can be guide for detecting liver diseases.

The Limitations of the Study

This study has a few limitations. The research was retrospective, liver histology was not evaluated and also liver enzyme levels were not evaluated after CPAP therapy.

CONCLUSION

Evaluating liver enzymes in our routine tests plays an important role in clinical practice. The fact that how liver enzyme levels are affected by CPAP therapy should be examined with large-scale studies.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] Lindberg E, Gislason T. Epidemiology of sleep-related obstructive breathing. Sleep Med Rev 2000;4:411-33.
[2] Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008;5:136-43.
[3] Lam JC, Lam B, Lam CL, Fong D, Wang JK, Tse HF, et al. Obstructive sleep apnea and the metabolic syndrome in community-based Chinese adults in Hong Kong. Respir Med 2006;100:980-7.
[4] Somers VK, Dyken ME, Clary MP, Abbod FM Symphathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995;96:1897-904.
[5] Oh SY, Cho YK, Kang MS, Yoo TW, Park JH, Kim HJ, et al. The association between increased alanine aminotransferase activity and metabolic factors in nonalcoholic fatty liver disease. Metab Clin Exp 2006;55:1604-9.
[6] Tanne, F, Gagnadoux, F, Chazouilleres O, Fleury B, Wendum D, Lasnier E, et al. Chronic liver injury during obstructive sleep apnea. Hepatology 2005;41:1290-6.
[7] Savransky V, Bevans S, Nanayakkara A, Li J, Smith PL, Torbenson MS, et al. Chronic intermittent hypoxia causes hepatitis in a mouse model of diet-induced fatty liver. Am J Physiol Gastrointest Liver Physiol 2007;293:G871-7.
[8] Byrne TJ, Parish JM, Somers V, Aqel BA, Rakela J. Evidence for liver injury in the setting of obstructive sleep apnea. Ann Hepatol 2012;11:228-31.
[9] Jouët P, Sabaté JM, Maillard D, Msika S, Mechler C, Ledoux S, et al. Relationship between obstructive sleep apnea and liver abnormalities in morbidly obese patients: A prospective study. Obes Surg 2007;17:478-85.
[10] Sookoian S, Pirola CJ. Obstructive sleep apnea is associated with fatty liver and abnormal liver enzymes: A meta-analysis. Obes Surg 2013;23:1815-25.
[11] Li J, Zhang YL, Chen R, Wang Y, Xiong KP, Huang JY, et al. Elevated serum liver enzymes in patients with obstructive sleep apnea-hypopnea syndrome. Chin Med J (Engl) 2015;128: 2983-7.
[12] Chin K, Nakamura T, Takahashi K, Sumi K, Ogawa Y, Masuzaki H, et al. Effects of obstructive sleep apnea syndrome on serum aminotransferase levels in obese patients. Am J Med 2003;114:370-6.
[13] Norman N, Bardwell WA, Arosemena F, Nelesen R, Mills PJ, Loredo JS, et al. Serum aminotransferase levels are associated with markers of hypoxia in patients with obstructive sleep apnea. Sleep 2008;31:121-6.
[14] Daltro C, Cotrim HP, Alves E, de Freitas LA, Araújo L, Boente L, et al. Nonalcoholic fatty liver disease associated with obstructive sleep apnea: Just a coincidence? Obes Surg 2010;20:1536-43.
[15] Mishra P, Nugent C, Afendy A, Bai C, Bhatia P, Afendy M, et al. Apnoeic-hypopnoeic episodes during obstructive sleep apnoea are associated with histological nonalcoholic steatohepatitis. Liver Int 2008;28:1080-6.
[16] Sadasivam K, Patial K, Ravi K, Aiyyavo S. Liver enzymes in obstructive sleep apnoea syndrome. Natl J of Physiol, Pharm Pharmacol 2017;7:865-9.
[17] Sookoian S, Rosselli MS, Gemma C, Burgueño AL, Fernández Gianotti T, Castaño GO, et al. Epigenetic regulation of insulin resistance in nonalcoholic fatty liver disease: impact of liver methylation of the peroxisome proliferator-activated receptor γ coactivator 1α promoter. Hepatology 2010;52:1992-2000.
[18] Rosmorduc O, Housset C. Hypoxia: a link between fibrogenesis, angiogenesis, and carcinogenesis in liver disease. Semin Liver Dis 2010;30:258-70.

The European Research Journal 2018;4(4):356-361 ORIGINAL ARTICLE

The use of doppler ultrasound in evaluation and follow-up of arteriovenous fistula patients

Nail Kahraman, Kadir Kaan Özsin

Department of Cardiovascular Surgery, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

DOI: 10.18621/eurj.376240

ABSTRACT

Objectives: The The aim of the present study was to search the effect of preoperative Doppler ultrasonography (DUS) of the concerning limb on AVF patency for arteriovenous fistula (AVF) to be performed on the patients with end-stage renal disease.

Methods. One hundred and three patients were enrolled into the study. The exclusion criteria were previous central catheter procedure, history of thrombophlebitis on the upper limb and previous surgery on the upper limb. Among the remaining patients, those who fulfilled the physical examination criteria were included. The patients were divided into two groups as the control, DUS (-) group and the study group, DUS (+). The patients in the control group were taken into the procedure after a physical examination only. Brescio-Cimino method was preferred for all patients. Function of the AVF was controlled on the procedure day, at day 10, months 1, 3 and 6 as well as year 1 after the procedure. The results in both groups were statistically evaluated.

Results: Twenty patients in the DUS (+) group (50% male, mean age: 57.25 ± 13.34 years) and 20 patients in the DUS (-) group (45% male, mean age: 56.10 ± 12.35) were recorded in the study. Cumulative primary patency rates between DUS (+) group and DUS(-) group for 12 months were 95% and 65%, respectively (log-rank, $p = 0.022$).

Conclusion: We believe that the DUS performed before AVF procedure would increase the primary patency rates of AVF created between the most convenient vessels and reduce the procedure failure.

Keywords: Hemodialysis, arteriovenous fistula, doppler ultrasonography, primary patency

Received: January 8, 2018; Accepted: February 19, 2018; Published Online: March 15, 2018

The patient population with end-stage renal disease (ESRF) consistently increases worldwide. The number of the patients who need dialysis treatment increases about 10% of current patients every year [1]. Arteriovenous fistula (AVF) procedures are the most common methods implemented to facilitate the hemodialysis process and increase the life standards of the patient [2]. The blood flow required for hemodialysis depends on the venous blood flow of the arteriovenous anastomosis to be created. The success of the procedure is dependent to the anastomosis technique and the formation of the vessel selected for surgical procedure. The AVFs were first suggested by Cimino-Brescia in 1966; although such technique was modified by technical developments up to date, the target always remained the same [3].

Doppler Ultrasonography (DUS) is the most applicable and complication-free diagnostic method. Other advantages of this method include not

Address for correspondence: *Nail Kahraman, MD., University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey*
E-mail: nailkahraman1979@gmail.com, Fax: +90 224 2955497

e-ISSN: 2149-3189

administration of any contrast agent, availability and dynamic approach. Vascular system mapping may be performed before the procedure. It was shown that unnecessary graft placement decreased, autogenous fistula formation increased and the rates of complications detected on the fistula decreased [4-9]. Early failures may be detected by implementing a routine follow-up program after the fistula procedure and required interventions may be performed timely. Furthermore, this method may be used for diagnosis of possible complications such as thrombus, pseudo-aneurysm steal syndrome and venous hypertension.

The aim of the present prospective, randomized controlled study was to search the effect of preoperative evaluation of the AVF performed on the patients with ESRF by DUS on AVF patency.

METHODS

Patients

One hundred and three patients who referred to our clinic for AVF procedure was evaluated. A detailed informed consent form was signed by all the participants. The present study was carried out in accordance with Helsinki standards and good clinical practice standards. The group whom AVF would be created according to physical examination findings only was defined as the control group or DUS (-) group whereas the group whom limb assessment was performed by preoperative DUS was determined as the study group or DUS (+) group. The physical examination criteria on the limb that AVF would be created for hemodialysis were presented in Table 1. Twenty patients who met the physical examination criteria were included into the control group. Only one upper extremity was used in each patient. Non dominant arm was preferred for fistula formation.

The patients with a radial artery and cephalic vein diameters below 1.5 cm; any stenosis, sclerosis, thrombus and occlusion on the cephalic vein and subclavian vein; lack of triphasic flow form on the radial artery and a significant stenosis in the radial artery all which were detected by preoperative DUS were excluded from the study. Twenty patients who met the DUS criteria were included into the control group.

Functionality of the AVFs created in both groups, presence of any thrill and whether the patient was taken into hemodialysis from the fistula created were controlled for 12 months. All the patients in both groups completed the study.

Preoperative DUS Assessment

In the present study, the requirement that the diameters of the radial artery and cephalic vein should be larger than 1.5 mm for the AVF created was determined. The patients were positioned at supine position following DUS; and the arms were fixed at 60 degrees on a comfortable position adjacent to the body to limit potential changes of some measurement such as internal lumen diameter and flow angle. A high-resolution DUS (Sonosite Micromaxx Ultrasound System model,USA) with a 10 to 12 MHz linear alignment probe was used to take records. Each DUS scan lasted about 30 minutes. Colored Doppler and gray scale examinations were used for evaluation of spaces and anatomic variations of the radial artery

Table 1. Physical examination criteria for AVF

1.	The visible vein length should be longer than 5 cm and may be compressed by superficial palpation.
2.	The palpable strength of the arterial pulse should be over 2 (at a subjective scale determined between 0 and 2; 0: no pulse; 1: weak pulse; 2: normal pulse) [10].
3.	No catheter should be inserted from the limb where the fistula procedure is planned.
4.	No previous fistula procedure should be performed from the limb which was planned for fistula procedure
5.	No venous collaterals should exist on the shoulder area
6.	No lymphedema should exist
7.	Allen test should be negative
8.	No history of thrombophlebitis on the upper limb
9.	No history of surgical procedure on the upper limb

Table 2. Demographic features of the patients

	Control Group DUS (-) (n = 20)	Study Group DUS (+) (n = 20)	*p* value
Age(years)	56.10 ± 12.35	57.25 ± 13.34	> 0.05*
Male gender	9 (45%)	10 (50%)	0.750#
Hypertension	3 (15%)	6 (30%)	0.451a
Diabetes mellitus	5 (25%)	6 (30%)	0.720#

DUS = Doppler ultrasonography. *Student's t test, #Pearson Chi- Suquare test, aFisher's Exact test

and cephalic vein bilaterally, of which suitability for AVF was searched. When stenosis was suspected via colored DUS, waveforms were reviewed through the gray scale. The diameter of the radial artery at anteroposterior dimension and transverse plane through gray-scale ultrasonography on the wrist (1a). Diameter of the cephalic vein was measured individually on the wrist, elbow and mid-arm (Figure 1b). Venous measurements were also repeated by a tourniquet placed on the middle of the arm (Figure 2a). All cephalic vein and subclavian vein were examined. Sclerosis, stenosis and occlusion states were recorded. Any thrombus was controlled by slightly compressing on each vein (Figure 2b).

Surgical Technique

Brescio-Cimino procedure was implemented by preferring the non-dominant arm if both limbs are suitable. A parallel incision was done onto the forearm on the wrist area and the vessels were dissected from the surrounding tissues, liberated and hung by a ruler. The patients were heparinized (5,000 IU) before vascular occlusion; an approximately 5-7 mm longitudinal arteriotomy and venotomy were performed on the revealed vessels. Proximal end of the vein was closed; and end to side arteroivenous anastomosis was performed by 7/0 polypropylen suture.

Postoperative Assessment of Arteriovenous Fistula

Detection of murmur by auscultation and existence of thrill by palpation were assessed as a successful AVF procedure just after the procedure and at day 1. Thrill was controlled in the patients during the control visits at day 10, months 1, 3, 6 and 12. The patients were taken into hemodialysis sessions at day 2. A successful AVF procedure was considered as implementation of a 4-hour hemodialysis through a 16

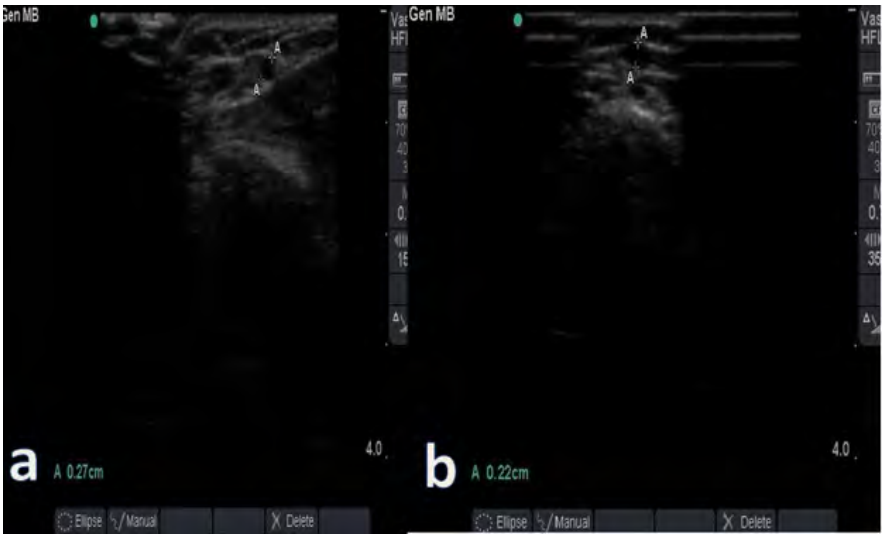


Figure 1. Measurement diameter of vessels by DUS. Radial artery (a) and cephalic vein (b). DUS = Doppler ultrasonography

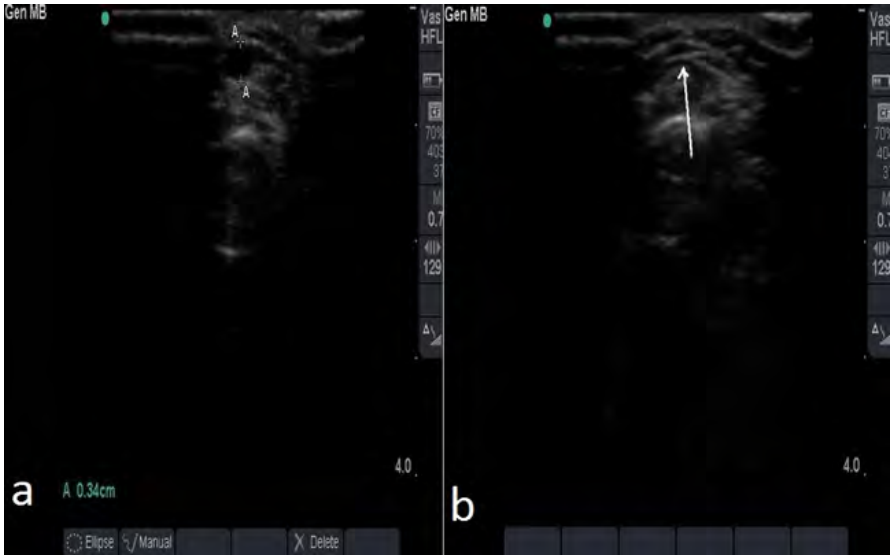


Figure 2. Cephalic vein image; (a) measurement diameter of cephalic vein with upper arm compression, (b) demonstration of cephalic vein compression with DUS (arrow). DUS = Doppler ultrasonography

gauge branule at 400 ml/min blood flow rate, three times a week. Primary patency of AVF was determined as the time interval between fistula creation day and the day that trreatment is required because of dysfunction.

Statistical Analysis

In such single-sided design with a significance level of 0.05, the total number of the patients required for the sample size was 40; and these were divided into two equal parts as the control and the study groups including 20 patients each. We concluded that 40 patients would be sufficient for this study. Chi-square analysis was used for evaluation of categorical variables. Primary patency was analysed through Kaplan Mayer method. The t-test or corresponding non-parametric test was used for analysis of continuous variables. A $p < 0.05$ value was accepted as statistically significant for all analyses. The SPSS 15.0 program was used for statistical evaluation.

RESULTS

No Twenty patients in the DUS (+) group (50% male, mean age: 57.25 ± 13.34 years) and 20 patients in the DUS (-) group (45% male, mean age: 56.10 ± 12.35) were recorded in the study. Demographic and clinical properties of the subjects were summarized in Table 2. Both DUS (+) group and DUS (-) group were similar in terms of demographic properties.

Kaplan-Meier curves; cumulative primary patency rates DUS (+) group at days 1, 10, months 1, 3, 6 and 12 were 100 %, 100%, 100%, 100%, 95% and 95%; respectively. DUS (-) groups at days 1, 10, months 1, 3, 6 and 12 were were 80 %, 75 %, 75%, 70%, 65% and 65%; respectively. Cumulative primary patency rates between DUS (+) group and DUS (-) group for 12 months were 95% and 65%, respectively. In the DUS (+) group, primary patency rates were superiority during follow-up periods.

There were 7 patients with AVF failure whom thrill could not be palpated during follow-up period in DUS (-) group. DUS was performed to reveal causes of AVF failure in these patients. Four unsuccessful AVFs were detected at postoperative day one. Chronic thrombotic modifications were detected in 3 patients whereas 1 patient presented an anastomosis defect. An insufficient radial artery flow existed in the unsuccessful fistula at postoperative day 10. A hyperplasia of the intima which causes stenosis in the juxta-anastomosis zone was detected in 2 fistulas which were considered as failure during the follow-ups at months 3 and 6. In the DUS (+) group, intimal hyperplasia was detected on the anastomosis line in 1 fistula which was considered as failure at month 6.

None of the patients presented hemorrhage, edema, minor neural damage and wound site infection.

DISCUSSION

This iA detailed physical examination is essential for a patient with chronic renal failure whom vascular procedure is planned. However, a preoperative radiological assessment of arterial and venous formations of the limb of which a vascular procedure is planned would have a positive contribution on the surgical plan [3-8].

Patency of Brescio-Cimino fistula is around 80% despite developments of surgical techniques, training of the hemodialysis staff and novel medical methods [2]. A wide range of the patients with AVF, different surgical techniques and different anatomic sites for AVF make the randomization difficult. Same problem exists in the studies performed with DUS. Therefore, we assessed the patients whose overall status is well, who did not have any fistula procedure and catheter insertion.

Many studies focused on use of preoperative DUS before AVF creation [5-8, 11, 12]. An analysis showed that AVF remains unsuccesful during short-term when subclavian vein flow rate is below 400 ml/min detected by preoperative DUS. Some authors associated the arterial flow rate over 400 ml/min with high fistula flow rate; another study reported that an arterial or venous diameter below 1.6 mm is a reliable indicator for a possible AVF failure. However, increase in AVF patency as well as decrease in AVF failure within short-term were reported as preoperative DUS using criteria in case of minimal arterial diameter of 2 mm and minimal venous diameter of 2.5 mm [13].

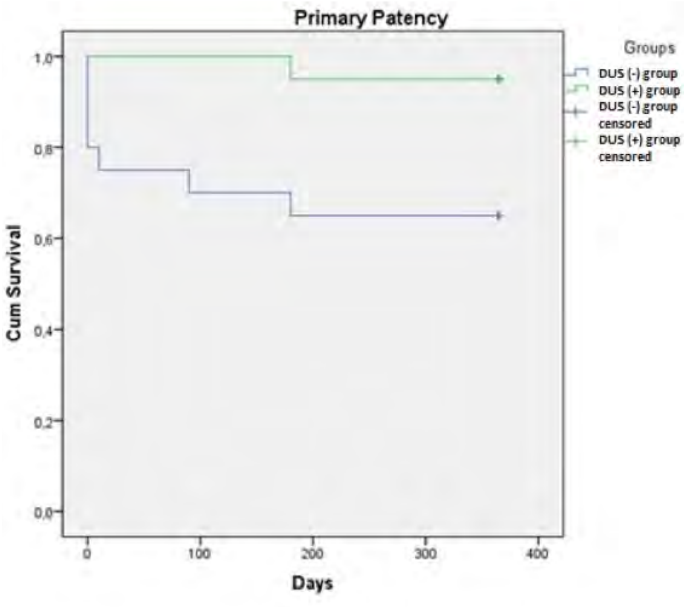


Figure 3. Kaplan-Meier curves; cumulative primary patency rates for twelve months. DUS = Doppler ultrasonography

A similar and interesting study demonstrated that preoperative use of the DUS increase the achievement rate in AVF surgery and the surgical procedure was modified in 31% of 52 patients in terms of AVF site. The findings of the present study support use of preoperative DUS for AVF procedure. A tourniquet placed on the proximal side may enable measurement of maximum or real diameters of venous formations for evaluation of venous diameters. The venous congestion pressure should be > 40 mmHg for an ideal measurement. In addditon to the venous diameter, a non-defective venous length above 10 cm detected by DUS is determinative at AVF function [14]. Venous diameters were measured without and with a tourniquet placed on the mid-arm and inflated by 40 mm Hg (Figure 2a).

A previous study assessed AVF patency at 3-month following mapping by preoperative DUS and detected a direct proportion between venous diameter and patency. The veins with a diameter between 1.5 and 3.9 mm revealed an average patency rate of 71.08% at one-year whereas patency of smaller veins (1.5 to 2 mm) was detected as 20% [15]. In another study, upon dysfunction of the fistula created on the forearm following venous mapping on the forearm and arm by preoperative DUS, same mapping process was used and a fistula was opened on the arm and a total achievement by 95% was reached [16]. It was reported in a study that preoperative assessment would be useful before AVF procedure; however, universal parameters were not determined yet [14]. In line with the literature, primary patency rates were found significantly higher in the AVF created through preoperative coloured DUS in the DUS (+) group and such higher rates were statistically significant (p = 0.022) (Figure 3). There was not any difference detected in terms of thrill palpation between the DUS (+) and DUS (-) groups just after the AVF procedure and early postoperative period (early success of AVF). However, regular dialysis, AVF patency rates were found significantly higher in the DUS (+) group.

The difference of the present study was carrying out the study on the most eligible patient group for AVF procedure. These patients who had AVF

procedure first were selected by the aforesaid exclusion criteria and only 40 of 103 patients met the inclusion criteria. A statistically significant higher patency rates in the DUS (+) group than the DUS (-) group during 12-month follow-up period reveals that such easily applicable imaging method, the DUS should be used routinely before AVF procedure.

The Limitations of the Study

Our study has one limitation. The small sample size may be to considered as the one limitation of this study, but the excess of exclusion criteria has minimized the risk factors for patency. Further prospective studies with a larger number of patients are required.

CONCLUSION

In Consequently, although the operative strategy is usually considered sufficient according to the physical examination of the surgeon before creation of AVF in practice, the DUS performed before AVF procedure would increase the primary patency rates of AVF created between the most convenient vessels and reduce the procedure failure. Accurate patient selection, accurate patient preparation seems to be a preliminary condition for high rate of primary patency and we believe that DUS assessment is valid and necessary.

Authorship contributions

Consept-Design: NK, KKÖ; Data collection : NK, KKÖ; Analysis: KKÖ, NK; Literature search: KKÖ, NK; Writing: KKÖ, NK; Critical review:NK, KKÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] Rooijens PP, Burgmans JP, Yo TI, Hop WC, de Smet AA, van den Dorpel MA, et al. Autogenous radial-cephalic or prosthetic brachial-antecubital forearm loop AVF in patients with compromised vessels? A randomized, multicenter study of the patency of primary hemodialysis access. J Vasc Surg 2005;42:481-6.
[2] Rahman A, Özsin KK. Upper extremity otogen arteriovenous fistulas for hemodialysis. Turkish J Vasc Surg 2007;16:19-24.
[3] Brescia MI, Cimino JC, Appel K. Chronic hemodialysis using venipuncture and surgically created arteriovenous fistulas. N Eng J Med 1966;275:1089-92.
[4] Guedes Marques M, Ibeas J, Botelho C, Maia P, Ponce P. Doppler ultrasound: a powerful tool for vascular access surveillance. Semin Dial 2015;28:206-210.
[5] Wong CS, McNicholas N, Healy D, Clarke-Moloney M, Coffey JC, Grace PA, et al. A systematic review of preoperative duplex ultrasonography and arteriovenous fistula formation. J Vasc Surg 2013;57:1129-33.
[6] Ko SH, Bandyk DF, Hodgkiss-Harlow KD, Barleben A, Lane J 3rd. Estimation of brachial artery volume flow by duplex ultrasound imaging predicts dialysis access maturation. J Vasc Surg 2015;61:1521-7.
[7] Lomonte C, Meola M, Petrucci I, Casucci F, Basile C. The key role of color Doppler ultrasound in the work-up of hemodialysis vascular access. Semin Dial 2015;28:211-5.
[8] Matsui S, Nakai K, Taniguchi T, Nagai T, Yokomatsu T, Kono Y, et al. Systematic evaluation of vascular access by color-Doppler ultrasound decreased the incidence of emergent vascular access intervention therapy and X-ray exposure time: a single-center observational study. Ther Apher Dial 2012;16:169-72.
[9] Older RA, Gizienski TA, Wilkowski MJ, Angle JF, Cote DA. Hemodialysis access stenosis: early detection with color DUS. Radiology 1998;207:161-4.
[10] Sidawy AN1, Spergel LM, Besarab A, Allon M, Jennings WC, Padberg FT Jr, et al. The Society for Vascular Surgery: clinical practice guidelines for the surgical placement and maintenance of arteriovenous hemodialysis access. J Vasc Surg 2008;48:2S-25S.
[11] Bay WH, Henry ML, Lazarus JM, Lew NL, Ling J, Lowrie EG. Predicting hemodialysis access failure with color flow Doppler ultrasound. Am J Nephrol 1998;18:296-304.
[12] Dossabhoy NR, Ram SJ, Nassar R, Work J, Eason JM, Paulson WD. Stenosis surveillance of hemodialysis grafts by duplex ultrasound reduces hospitalizations and cost of care. Semin Dial 2005;18:550-7.
[13] Schanzer H, Skladany M. Vascular access for dialysis. In: Haimovici H. Editor. Haimovici's Vascular Surgery: Principles and Techniques. 4th ed. Cambridge: Black Science, 1996. pp.1028-41.
[14] Planken RN, Tordoir JHM, Duijm LEM, de Haan MW, Leiner T. Current techniques for assessment of upper extremity vasculature prior to hemodialysis vascular access creation. Eur Radiol 2007:17:3001-11.
[15] Hamish M, Geddoa E, Reda A, Kambal A, Zarka A, Altayar A, et al. Relationship between vessel size and vascular access patency based on preoperatively ultrasound Doppler. Int Surg 2008;93:6-14.
[16] Nguyen VD, Treat L, Griffith C, Robinson K. Creation of secondary AV fistulas from failed hemodialysis grafts: the role of routine vein mapping. J Vasc Access 2007;8:91-6.

The European Research Journal 2018;4(4):362-365 ORIGINAL ARTICLE

Changes in cerebral blood flow in rheumatology patients treated with rituximab

Uygar Utku[1], Gözde Çetin[2], Nurhan Atilla[3]

[1]Department of Neurology, Kahramanmaraş Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey
[2]Department of Rheumatology, Kahramanmaraş Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey
[3]Department of Pulmonology, Kahramanmaraş Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey

DOI: 10.18621/eurj.346321

ABSTRACT

Objectives: We aimed to assess the effects of rituximab therapy on cerebral hemodynamics in rheumatic patients with transcranial Doppler (TCD) ultrasonography.

Methods: The study included seven patients aged 20-65 years (2 patients with secondary interstitial lung involvement to rheumatoid arthritis, 3 patients with systemic lupus erythematosus and lupus nephritis, 2 patients with scleroderma and secondary interstitial lung disease) who received rituximab treatment due to rheumatic diseases. Healthy control group (non-rheumatic group) consisted of seven age and sex-matched, randomly selected persons did not have risk factors for atherosclerosis. Bilateral middle cerebral artery peak-systolic, end-diastolic, and mean blood flow velocities, Gosling's pulsatility index values, and Pourcelot's resistance index values were recorded with TCD by a neurosonologist before rituximab administration. Control TCD performed to the rheumatic group after six months from the last rituximab dosage.

Results: One patient was male and six patients were female. Peak-systolic, end-diastolic and mean blood flow velocities of rheumatic patients were significantly higher than healthy group ($p < 0.001$). Peak-systolic, end-diastolic and mean blood flow velocities of rheumatic patients were significantly decreased after rituximab therapy ($p < 0.001$).

Conclusions: This study highlights that the increased cerebral blood flow is indirectly associated with atherosclerosis regarding persistent inflammation in patients with rheumatic diseases. It was thought that treatment with rituximab could reverse this situation.

Keywords: Rituximab, inflammation, atherosclerosis, cerebral blood flow

Received: October 24, 2017; Accepted: January 22, 2018; Published Online: March 8, 2018

Inflammation has an important role in the pathogenesis and prognosis of atherosclerosis [1, 2]. Rituximab is a monoclonal antibody drug used for improving the symptoms and preventing from the rheumatologic diseases [3]. Apart from traditional vasculo-protective agents, biologics such as rituximab, infliximab and etanercept may also exert favorable effects on the atherosclerosis and arterial stiffness. Furthermore, none of the existing studies examined with transcranial Doppler (TCD) ultrasonography whether increased arterial stiffness can be reversed by anti-inflammatory therapy. The technique of TCD ultrasonography enables assessment of hemodynamic parameters, including flow velocity in intracranial

Address for correspondence: *Uygar Utku, MD., Assistant Professor, Kahramanmaraş Sütçü İmam University School of Medicine, Department of Neurology, 46100 Kahramanmaraş, Turkey*
E-mail: utkuzar@gmail.com

e-ISSN: 2149-3189

arteries. A milder or more generalized increased flow velocity could reflect intracerebral atherosclerosis. Here, we aimed to assess the effects of rituximab treatment on inflammation regarding atherosclerosis in rheumatic patients with TCD ultrasonography.

METHODS

Seven patients aged 20-65 years (2 patients with secondary interstitial lung involvement to rheumatoid arthritis, 3 patients with systemic lupus erythematosus and lupus nephritis, 2 patients with scleroderma and secondary interstitial lung disease) were eligible for enrolment. Patients were treated with rituximab according to medical practitioners' opinion. They received two intra-venous infusions of rituximab (1000 mg each) 2 weeks apart. They have not any risk factors for atherosclerosis, such as diabetes, hypertension, and coronary artery disease. Seven healthy persons were included to the study for control group.

Firstly, TCD performed before rituximab administration (baseline). Results of rheumatic group compared with the results of healthy control group. After six months from the last rituximab dosage control, TCD performed to the rheumatic group (one year period). Values of bilaterally middle cerebral artery (MCA) peak-systolic, end-diastolic and mean blood flow velocities, Gosling pulsatility index and Pourcelot's resistance index were recorded with TCD by a neurosonologist. The obtained values were compared with each other. The study was approved by the local research ethics committee and all participants gave written informed consent.

of TCD ultrasonography was performed with Multi-Dop X DWL, TCD machine after the subjects rested in a supine position for 10 min. The right and the left MCA were insonated from the temporal windows at 50-65 mm depth with 2 MHz pulsed Doppler probes. Bilateral MCA peak-systolic, end-diastolic, and mean blood flow velocities; pulsatility index values, and resistance index values were recorded.

Statistical Analysis

The data was analyzed using the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA) 15.0 program. Paired t-test, cross-tabs tests were used for statistical analysis. In the analysis, p value < 0.05 was considered significant.

RESULTS

One patient was male and six patients were female. The mean age was found 52.3 years (Table 1). TCD values were compared with rheumatic patients and healthy group (sex and age matched). Then, TCD values of before and after treatment with rituximab compared in each other. Peak-systolic, end-diastolic and mean blood flow velocities of rheumatic patients were significantly higher than healthy group (p < 0.001) (Table 2). Peak-systolic, end-diastolic and mean blood flow velocities of rheumatic patients were significantly decreased after rituximab therapy (p < 0.001) (Table 3).

DISCUSSION

Recently there is a considerable attention

Table 1. Demographics and biochemical and hemodynamic characteristics of patients

	Rheumatic group (n = 7)	Control group (n = 7)	*p* value
Gender (male/female)	1/6	1/6	-
Age (years)	52	50	-
BMI (kg/m ^{2})	22	22	-
Systolic Blood Pressure (mmHg)	130	125	0.22
Diastolic Blood Pressure (mmHg)	80	80	0.33
CRP (mg/L)	6.8	1.47	< 0.001

BMI = body mass index, CRP = C-reactive protein

Table 2. Transcranial Doppler data of rheumatic group compared with healthy control group

	Rheumatic group (n = 7)	Control group (n = 7)	*p* value
L-peak systolic BFV	168.7 ± 6.8	104.5 ± 13	< 0.001
L-end diastolic BFV	62.4 ± 11.6	38.4 ± 6.2	< 0.001
L-mean BFV	106 ± 13.8	61.8 ± 8.2	< 0.001
L-PI	0.87 ± 0.09	0.9 ± 0.09	0.78
L-RI	0.61 ± 0.03	0.6 ± 0.05	0.57
R-peak systolic BFV	157 ± 7.2	103.5 ± 17.05	< 0.001
R-end diastolic BFV	65.7 ± 13	36.7 ± 12.36	< 0.001
R-mean BFV	97.7 ± 15.47	63.2 ± 10.5	< 0.001
R-PI	0.9 ± 0.08	0.85 ± 0.09	0.89
R-RI	0.6 ± 0.04	0.63 ± 0.06	0.63

BFV = blood flow velocity, L = left, PI = pulsatility index, R = right, RI = resistance index

concerning the possible causal role of systemic inflammation in the development of endothelial dysfunction and accelerated atherosclerosis in rheumatic patients [4, 5]. In these patients, inflammatory markers such as particularly interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) are found in high levels. Currently, apart from traditional vasculo-protective agents, biologics such as rituximab, infliximab and etanercept may also exert favorable effects on the vasculature but there are conflicting data regarding the effects of these agents on atherosclerosis and arterial stiffness. We aimed to assess the effects of rituximab treatment on inflammation regarding atherosclerosis, a predictor of cerebrovascular diseases, in rheumatic patients.

There may be differences in the effects of TNF blockers on dyslipidemia, as long-term infliximab therapy may be proatherogenic, while some studies suggest that etanercept and adalimumab may exert beneficial effects on lipids. Infliximab stimulates the number and differentiation of endothelial progenitor cells that lead to vascular repair. Preliminary data suggest that rituximab may also improve endothelial function and dyslipidemia [6, 7]. In a study of Provan *et al*. [8], changes in cardiovascular disease risk markers over the 12-month follow-up in patients receiving rituximab were assessed by mixed models repeated analyses. And they showed significant reductions in these markers [8]. But in another study arterial stiffness did not improve after 6 and 12 months of rituximab therapy. The treatment had a beneficial effect on biologic inflammation and disease activity, but caused a pro-atherogenic lipid profile [9]. Further studies are needed to determine the net effects of biologics on the vasculature.

We found peak-systolic, end-diastolic and mean blood flow velocities were significantly higher in

Table 3. Comparison of TCD data before and after rituximab administration

	Before Rtx treatment	After 6 months from last Rtx treatment	*p* value
L-peak systolic BFV	168.7 ± 6.8	96.57 ± 4.89	< 0.001
L-end diastolic BFV	62.4 ± 11.6	35.85 ± 4.33	< 0.001
L-mean BFV	106 ± 8.83	58.7 ± 6.89	< 0.001
L-PI	0.87 ± 0.09	0.81 ± 0.06	0.22
L-RI	0.61 ± 0.03	0.6 ± 0.04	0.33
R-peak systolic BFV	157 ± 7.2	97.42 ± 11.2	< 0.001
R-end diastolic BFV	65.7 ± 14.6	34.8 ± 13.8	< 0.002
R-mean BFV	97.7 ± 16.45	62.8 ± 10.9	< 0.001
R-PI	0.9 ± 0.08	0.8 ± 0.08	0.06
R-RI	0.6 ± 0.04	0.6 ± 0.05	0.06

BFV = blood flow velocity, L = left, PI = pulsatility index, R = right, RI = resistance index, Rtx = rituximab, TCD = Transcranial Doppler

rheumatic group than in the healthy control group. But the pulsatility index and resistance index values were not significantly different in each group. However, correct interpretation of the pulsatility index is complex, because it depends not only on cerebrovascular resistance, but also on several systemic and cerebral variables [10]. The Rotterdam study reported that increased mild-to-moderate cerebral blood flow velocity is due to diffuse atherosclerosis or vasoconstriction [11]. Therefore, mechanisms that underlie this condition (increased velocities but normal PI values) are most likely to be due to mild diffuse subclinical atherosclerosis.

The Limitations of the Study

Our study had methodological limitations, including inadequate sample size and non-blinding of those involved in the measurements.

CONCLUSION

Increased cerebral blood flow velocities were observed in patients with rheumatologic diseases. The normalization of increased blood flow velocity with rituximab treatment suggests a reversible condition.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

Acknowledgement

The paper has been presented as a poster at Annual European Congress of Rheumatology, 10-13 June 2015, EULAR 2015 Roma, Italy.

REFERENCES

[1] Ross R. Atherosclerosis -- an inflammatory disease. N Engl J Med 1999;340:115-26.
[2] Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135-43.
[3] Selmi C, Generali E, Massarotti M, Bianchi G, Sciré CA. New treatments for inflammatory rheumatic disease. Immunol Res 2014;60:277-88.
[4] Yüksel S, Ayvazyan L, Gasparyan AY. Familial mediterranean fever as an emerging clinical model of atherogenesis associated with low-grade inflammation. Open Cardiovasc Med J 2010;23:4:51-6.
[5] Lin CW, Huang YP, Chiu YH, Ho YT, Pan SL. Increased risk of ischemic stroke in young patients with ankylosing spondylitis: a population-based longitudinal follow-up study. PloS One 2014;9:e94027.
[6] Kerekes G, Soltesz P, Der H, Veres K, Szabo Z, Vegvari A, et al. Effects of biologics on vascular function and atherosclerosis associated with rheumatoid arthritis. Ann N Y Acad Sci 2009;1173:814-21.
[7] Szekanecz Z, Kerekes G, Soltesz P. Vascular effects of biologic agents in RA and spondyloarthropathies. Nat Rev Rheumatol 2009;5:677-84.
[8] Provan SA, Berg IJ, Hammer HB, Mathiessen A, Kvien TK, Semb AG. The impact of newer biological disease modifying anti-rheumatic drugs on cardiovascular risk factors: a 12-month longitudinal study in rheumatoid arthritis patients treated with rituximab, abatacept and tociliziumab. PloS One 2015;10:e0130709.
[9] Mathieu S, Pereira B, Dubost JJ, Lusson JR, Soubrier M. No significant changes in arterial stiffness in RA after 6 months and 1 year of rituximab treatment. Rheumatology (Oxford) 2012;51:1107-11.
[10] de Riva N., Budohoski KP, Smielewski P, Kasprowicz M, Zweifel C, Steiner LA, et al. Transcranial Doppler pulsatility index: what it is and what it isn't. Neurocrit Care 2012;17:58-66.
[11] Bos MJ, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM. Transcranial Doppler hemodynamic parameters and risk of stroke: the Rotterdam study. Stroke 2007;38:2453-8.

The European Research Journal 2018;4(4):366-373 ORIGINAL ARTICLE

Three-dimensional turbo spin-echo sequence versus conventional two-dimensional turbo spin-echo sequences in the evaluation of lumbar intervertebral discs

Volkan Kızılgöz[1], Ali Kemal Sivrioğlu[2], Hasan Aydın[3], Sunay Sibel Karayol[1], Can Hakan Yıldırım[4], Utku Menderes[5]

[1]Department of Radiology, Kafkas University School of Medicine, Kars, Turkey
[2]Department of Radiology, Okmeydanı Training and Research Hospital, İstanbul, Turkey
[3]Department of Radiology, Abdurrahman Yurtaslan Oncology Research and Training Hospital, Ankara, Turkey
[4]Department of Neurosurgery, Kafkas University School of Medicine, Kars, Turkey
[5]Department of Radiology, Eskişehir State Hospital, Eskişehir, Turkey

DOI: 10.18621/eurj.354357

ABSTRACT

Objectives: The aim of this study was to evaluate the efficacy of a three-dimensional (3D) turbo spin-echo (TSE) sequence for determining lumbar disc protrusions, and to compare the findings with those of conventional two-dimensional (2D) TSE sequences and reveal the interobserver and intermethod agreements of both sequences.

Methods: A total of 127 discs from 84 patients were evaluated by three radiologists. Conventional 2D TSE images and 3D TSE images were independently interpreted with regard to disc pathology and herniation zones and were scored for the degree of spinal stenosis and lumbar neural foraminal stenosis by the three reviewers. To evaluate the lumbar discs, areas of protrusion or extrusion were classified. Interobserver and intermethod reliabilities were calculated using Krippendorff's alpha (Kα) test.

Results: Lumbar disc pathology identification was similar between the 2D TSE and 3D TSE sequences. Interobserver agreements were better for 3D TSE than 2D TSE in the evaluation of disc hernias (Kα ratio; 0.965 vs. 0.944), herniation zones (Kα ratio; 0.894 vs. 0.847), and foraminal narrowing (Kα ratio; 0.965 vs. 0.924). Both 2D and 3D TSE had 100% sensitivity for disc pathologies and spinal stenosis, 81% sensitivity for herniation zones, and 92.5% sensitivity for foraminal stenosis in only operated patients.

Conclusions: The 3D TSE sequence was comparable to conventional magnetic resonance imaging (MRI) sequences in the evaluation of lumbar disc herniation. This approach can be used in radiology departments either alone or combined with routine MRI for lumbar disc hernias as a diagnostic sequence and an approach to overcome problems.

Keywords: Magnetic resonance imaging, spin echo imaging, intervertebral disc, spine

Received: November 16, 2017; Accepted: February 15, 2018; Published Online: March 23, 2018

The lumbar spinal magnetic resonance imaging (MRI) protocol in the evaluation of intervertebral disc pathologies often involves T1-weighted (T1W) and T2-weighted (T2W) sequences in the sagittal and axial planes. Axial spinal images can be obtained as either "stack" images or "through

Address for correspondence: *Volkan Kızılgöz, MD, FECSM, MD., Kafkas University School of Medicine, Department of Kafkas University School of Medicine, Kars, Turkey*
E-mail: volkankizilgoz@gmail.com

e-ISSN: 2149-3189

disc" sequence images. Stack images are obtained in axial planes with respect to the scanner table, and variable disc angulations owing to natural lordosis of the lumbar spine are not taken into consideration. On the other hand, "through disc" sequence images are obtained by imaging slabs parallel to intervertebral disc spaces,which are set by a radiology technician with a reset of the axial axis at each disk levelfor proper assessment of intervertebral discs [1].

Some radiology departments use three-dimensional (3D) T2W sequences in the evaluation of lumbar intervertebral discs, and a number of them use axial plane images of this MR sequence [2-4]. With variable flip angles, 3D turbo spin-echo (TSE) maintains constant signals by utilizing refocusing radiofrequency pulses and enables very long echo train lengths.Therefore, 3D TSE might allow the acquisition of thin section images within acceptable examination times [5]. It is known that specific 3D TSE and 3D gradient echo sequences, such as constructive interference in steady state (CISS), are very successful in the assessment of nerves. The 3D steady-state refocused gradient echo sequence is a flow-compensated MRI sequence with high contrast and high spatial resolution, enabling detailed visualization of nerve roots and neural structures surrounded by cerebrospinal fluid [6-9]. These sequences are significant examination approaches, which enable visualization of normal nerves in their course, and they are assumed to be adequate imaging approaches for the detection of even small lesions at the initial stage of a disease [6].

In the literature, some papers have indicated the extent of success with the 3D TSE approach. However, the present study attempted to reveal most of the aspects of disc herniation and assess herniation zone by zone using 3D TSE. The aim of this study was to evaluate the efficacy of a 3D TSE sequence for determining lumbar disc protrusions, and to compare the findings with those of conventional 2D TSE sequences and reveal the interobserver and intermethod agreements of both sequences.

METHODS

Patients

After receiving approval from the local ethics committee, 84 patients (35 male and 49 female patients) and 127 intervertebral discs were included in this study. Between March 2016 and January 2017, 96 patients, who accepted and signed an informed consent form, underwent MRI with conventional MR sequences and a 3D TSE sequence. The patients were aged between 17 and 79 years (mean age: 42.62 years). Twelve patients who signed the informed consent form but had normal MRI results (after evaluation and consensus of the interpreters) were excluded from the investigation. Three radiologists (a musculoskeletal radiologist with 11 years of experience, a general radiologist with 15 years of experience, and a neuroradiologist with 16 years of experience) interpreted the MR images. At the time of analysis, the radiologists were blinded to the clinical history of the patients, and they were not provided with any information by clinicians and did not have access to previous reports. The conventional TSE and 3D TSE sequences of a patient were interpreted at different times (at least a 1-week interval) by each researcher. Only the lumbar intervertebral levels of pathologic discs were included in the study for evaluation of the areas of disc protrusion, spinal stenosis, and foraminal stenosis.

Image Analysis

Alterations of intervertebral disc morphology were classified as disc bulging, protrusion, and extrusion. Circumferential symmetric extension of the disk beyond the intervertebral space border was considered as bulging. Focal or asymmetric extension of the intervertebral disc beyond the intervertebral space border was considered as protrusion. Extreme extension of the disc beyond the interspace border with a herniation base, which was wider than the disk of origin or had no connection between the herniated disc material and disk of origin was considered as extrusion [10]. Disc herniation was evaluated in seven areas (central zone and bilateral paracentral, foraminal, and extraforaminal zones). The central zone was considered as the middle region located behind the intervertebral disc that included the anterior aspect of the dural sac. The paracentral zone was considered as the region just adjacent to the central region, and it was at the beginning of the neural foramina. The foraminal zone was considered as the region that included the neural foramen, and the extraforaminal

Table 1. MRI parameters for both conventional 2D TSE and 3D TSE sequences

Parameters	2D TSE sequences			3D TSE sequence	
	Sagittal T1	Sagittal T2	Axial T2	Sagittal	Axial
TR	571	4000	5562	842	842
TE	11	87	88	110	110
Slice thickness (mm)	4	4	4	0.8	0.8
Slice spacing (mm)	0.8	0.8	0.4	0.1	0.1
Number of slices	12	12	6	-	-
Voxel size	1.1×0.7×4.0	1.0×0.7×4.0	1.0×0.7×4.0	0.9×0.9×0.8	0.9×0.9×0.8
Band width	157	181	198	190	190
Flip angle	150	150	150	150	150
Matrix size	260×384	288×384	234×320	220×256	220x256
Field of view	280×280	280×280	230×230	220×220	220×220
Acquisition time (m:sc)	3:05	3:18	4:00	3:08	3:24

MRI = magnetic resonance imaging, 3D TSE = three-dimensional turbo spin-echo, 2D TSE = two-dimensional turbo spin-echo, TE = echo time, TR = repetition time

zone was considered as the region far from the neural foramen, just outside the foraminal zone. If a disc herniation was observed in multiple zones, the interpreters marked all these zones in the worksheet used in the study.

Spinal canal stenosis was evaluated as no stenosis, mild stenosis (0-33% narrowing of the spinal canal space), moderate stenosis (33-66% narrowing of spinal canal space), or severe stenosis (> 66% stenosis of the spinal canal space). The percentages of these measurements were based on the total anteroposterior diameter of the spinal canal.

Foraminal stenosis was evaluated using the grading system proposed by Lee *et al*. [11]. Grade 0 represents normal neural foramina, without any foramen obliteration or neural compression. Grade 1 stenosis represents a mild degree of foraminal stenosis (perineural fat obliteration by a thickened ligamentum flavum or by disc osteophytic protrusion in the foraminal zone). Grade 1 foraminal stenosis shows no evidence of a morphologic change in the nerve root. Grade 2 stenosis represents a moderate degree of foraminal stenosis (perineural fat obliteration in four directions, with obliteration of the vertical and transverse axes). Grade 2 stenosis involves narrowing of the foraminal width and height owing to ligamentum flavum thickening, facet arthropathy, disc protrusion, or osteophytic protrusion, without a morphologic change in the nerve root. Grade 3 stenosis represents a severe degree of neural foraminal stenosis, witha morphologic change in the nerve root and nerve root collapse due to disc protrusions, facet arthropathy, ligamentum flavum thickening, or osteophytic protrusion [11].

MRI Procedures

A Magnetom Essenza 1.5T system (Siemens, Erlangen, Germany) was used to obtain images. Lumbar spinal MRI examinations were performed with an 8-channel spinal coil. The time intervals for each 2D TSE sequence were as follows; T1 sequence in sagittal plane: 3 minutes and 5 seconds; T2 sequence in sagittal plane: 3 minutes and 18 seconds; T2 sequence in axial plane: 4 minutes. The time intervals of 3D TSE sequence for each plane were as follows; Sagittal 3D TSE: 3 minutes and 8 seconds, axial 3D TSE: 3 minutes and 24 seconds. The parameters of MRI for both conventional 2D TSE and 3D TSE sequences are presented in Table 1.

Statistical Analysis

After image acquisition and collection of data from the interpreters, all statistical analyses were performed using a commercially available software (Statistical Package for Social Sciences, version 24.0, IBM Corp., Armonk, NY, USA), with the exception of Krippendorff's alpha ratio for which the Recal 0.2/0.3 Alpha program was used (http://dfreelon.org/recal/recal3.php).

For assessing intraobserver agreements, 2D TSE and 3D TSE results were compared using Krippendorff's alpha test (Kα) for each reviewer. Interobserver agreements were revealed by using the same method with comparison of three different data

Table 2. Evaluation of lumbar disc pathologies with 2D TSE and 3D TSE

	Reviewer 1				Reviewer 2				Reviewer 3		
	2D TSE		3D TSE		2D TSE		3D TSE		2D TSE		3D TS
Bulging (n)	30		25		28		24		26		26
Protrusion (n)	89		93		91		94		93		92
Extrusion (n)	8		9		8		9		8		9
	N	P	N	P	N	P	N	P	N	P	N
Spinal stenosis (n)	59	68	56	71	61	66	59	68	56	71	61
Foraminal stenosis (n)	55	72	51	76	52	75	55	72	51	76	52

3D TSE = three-dimensional turbo spin-echo, 2D TSE = two-dimensional turbo spin-echo, N = not present, P = pres
n = number of patients. Even a single side with foraminal narrowing in a patient was considered as a "present" result

set from each reviewer for 2D and 3D TSE results. Interobserver and intermethod agreements were calculated using Fleiss' generalized kappa coefficient for each area of disc herniation (zone by zone). For the operated patients, sensitivities of both sequences were calculated by matching the results with surgical outcomes. The level of agreements between 0 and 0.20 accepted as "no agrrement", between 0.21 and 0.39 accepted as "minimal", between 0.40 and 0.54 presented "weak" agreement with regard to kappa values. The kappa values from 0.60 to 0.79 accepted as "moderate", from 0.80 to 0.90 accepted as "strong", and kappa levels > 0.90 indicated "almost perfect" agreement.

RESULTS

Lumbar disc herniation was evaluated by considering disc pathology, herniation area, spinal canal narrowing, and foramina narrowing. There was no disc herniation at levels T12-L1 and L1-2 in the study patients. Table 2 shows the results of interpretations with respect to herniated disc levels. This table also presents the total number of spinal and foraminal stenoses of the disc levels classified as bulging, protrusion, and extrusion.

Considering the disc pathologies, Krippendorff's alpha test (Kα) was used to calculate the interobserver agreements, and the Kα ratios were 0.944 and 0.965 for 2D TSE and 3D TSE, respectively, indicating almost perfect agreement for both MR sequences. The intermethod agreement (agreement of the results between 3D TSE and 2D TSE) was calculated using the same method, and the Kα ratios were 0.888 (strong agreement), 0.868 (strong agreement), and 0.902 (almost perfect agreement) for reviewers 1, 2, and 3, respectively (Table 3).

The same method was used to calculate the results of the disc herniation areas for each reviewer with regard to 2D TSE versus 3D TSE, and the seven zones mentioned in the methods section were assessed. The Kα ratios for interobserver agreements were 0.847 for 2D MRI and 0.894 for 3D TSE, both representing strong agreements. The Kα ratios for intermethod agreements (between 2D and 3D TSE sequences) were 0.722 (moderate agreement), 0.868 (strong agreement), and 0.884 (strong agreement) for

Table 3. Interobserver agreements for 2D TSE, interobserver agreements for 3D TSE, and intermethod agreements between 2D and 3D TSE for each observer in all patients.

	Interobserver agreements for 2D TSE	Interobserver agreements for 3D TSE	Intermethod agreements between 2D and 3D TSE for each observer		
			RW 1	RW 2	RW 3
Disc pathology	0.944	0.965	0.888	0.868	0.902
Areas of disc herniations	0.847	0.894	0.722	0.868	0.884
Spinal canal stenosis	0.970	0.894	0.926	0.868	0.902
Foraminal stenosis	0.924	0.965	0.951	0.884	0.897

3D TSE = three-dimensional turbo spin-echo, 2D TSE = two-dimensional turbo spin-echo. RW 1, RW 2, and RW 3 represent reviewer 1, reviewer 2, and reviewer 3 respectively. The numbers presented above, which were calculated using Krippendorff's alpha test, represent the levels of agreement in Table 2.

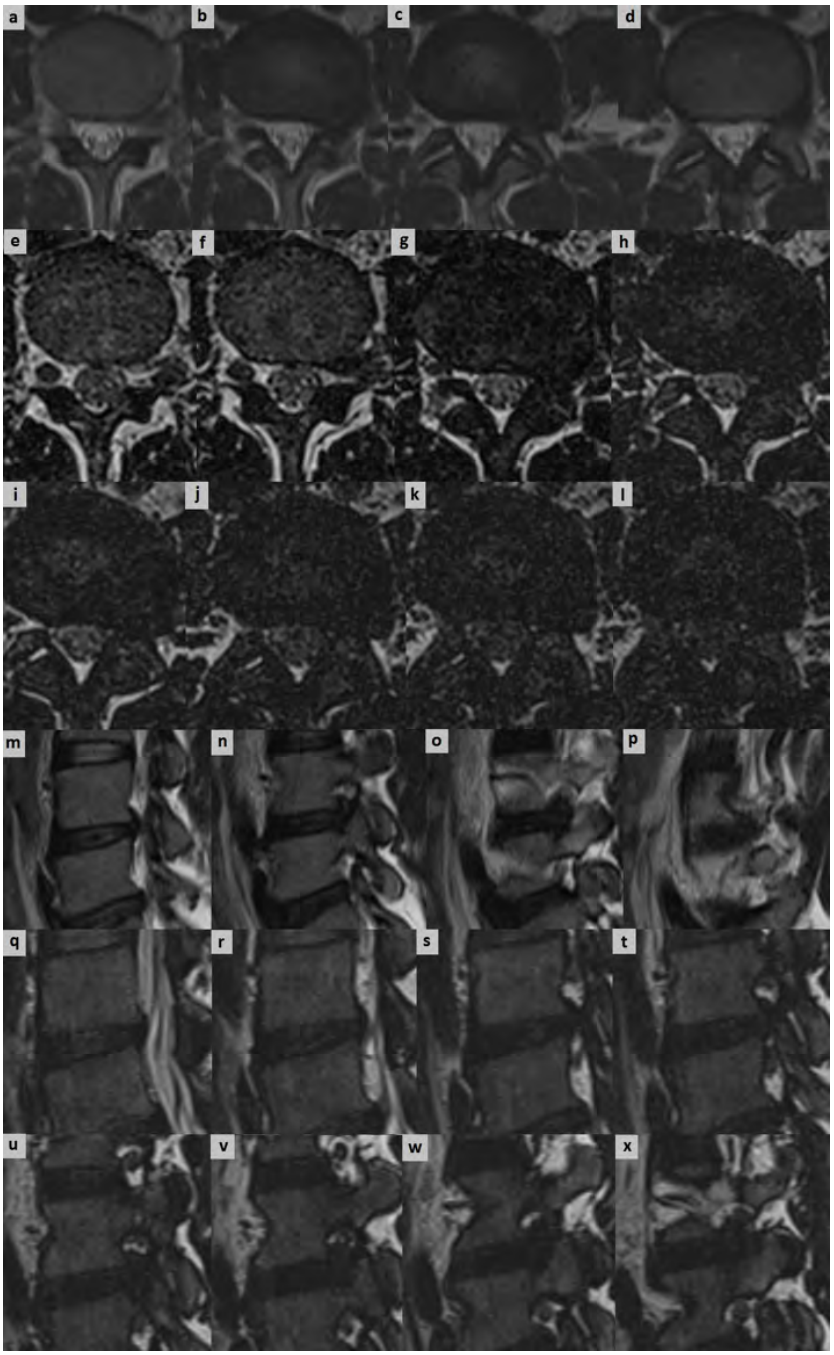


Figure 1. Consecutive images of a 34-year-old woman with L4-5 disc protrusion at the left foraminal and extraforaminal zones. Conventional MRI sequences in (a-d) T2-weighted (T2W) axial images and (m-p) T2W sagittal images. The 3D TSE sequence in (e-l) axial images and (q-x) sagittal images.

reviewers 1, 2, and 3, respectively (Table 3).

When the interobserver agreements of disc herniation areas were calculated separately (zone by zone), the outcomes of the analysis revealed that the left paracentral zone was the best zone and the right extraforaminal zone was the worst zone of agreement for 2D TSE and 3D TSE sequences with regard to Fleiss' generalized kappa coefficient (Table 4).

Spinal stenosis was also assessed with Kα ratios, and the interobserver differences were 0.970 (almost perfect agreement) for 2D TSE and 0.894 (strong agreement) for 3D TSE. Intermethod agreements (using the same analysis) were 0.926 (almost perfect agreement), 0.868 (strong agreement), and 0.902 (almost perfect agreement) for reviewers 1, 2, and 3, respectively (Table 3).

Table 4. Interobserver agreements for each herniation zone for 2D and 3D TSE with respect to Fleiss' generalized kappa coefficient values

Zone	MRI	3D TSE
Central	0.894	0.969
Left paracentral	0.962	1.000
Right paracentral	0.926	0.930
Left foraminal	0.926	0.969
Right foraminal	0.895	0.954
Left extraforaminal	0.747	0.872
Right extraforaminal	0.653	0.798

3D TSE = three-dimensional turbo spin-echo, 2D TSE = two-dimensional turbo spin-echo

With regard to foraminal stenosis, interobserver differences were measured with Kα ratios, and both the 2D and 3D TSE sequences showed almost perfect agreement (0.924 and 0.965, respectively). Intermethod differences were 0.951, 0.884, and 0.897 with regard to foraminal stenosis for reviewers 1, 2, and 3, respectively (Table 3; Figure 1).

Of the 84 patients included in this study, 18 (21 discs) were operated. If we only consider the operated patients, the sensitivities of both 2D and 3D TSE for discal pathologies, herniation zones, spinal stenosis, and foraminal stenosis were 100%, 81%, 100%, and 92.5%, respectively.

DISCUSSION

MRI is a common diagnostic tool for evaluating the pathologies of lumbar intervertebral discs. The results of 3D TSE were promising in this study. We found that 3D TSE was comparable with 2D TSE, and in many aspects, it was better than conventional TSE sequences for evaluating disc pathologies.

Back pain is one of the most common complaints in patients admitted to neurology and neurosurgery departments. Lumbar spinal MRI is one of the most common imaging approaches performed by clinicians and surgeons for the assessment of patients with neurological examination findings consistent with radiculopathy. Conventional T1W and T2W sequences are used to analyze disc herniation, the spinal canal, and the neural foramina in most radiology departments. Radiologists have extensive experience in the interpretation of routine images in daily practice, and MRI has proven to be appropriate for analyzing lumbar disc herniation and other pathologies relevant to herniation, such as neural root or thecal sac indentations and neural root edema, and for determining the exact location of the primary pathology.

On the other hand, MRI has some limitations in the evaluation of disc pathologies. It may be difficult to fully characterize complex anatomy and pathology by using traditional sequences. The borders of lumbar discs may not be visualized clearly, especially in the foraminal regions. Additionally, it can be difficult to determine the relationship between the disc and neural structures that are close to the disc border, such as the thecal sac and nerve roots. In order to overcome these difficulties, new MRI sequences are applied to patients. The TSE T2W 3D sequence, which involves sampling perfection with application-optimized contrast using different flip-angle evolution (SPACE), is an MRI approach that uses variable flip angles for refocusing instead of the conventional 180° refocusing pulse. Tins *et al*. [2] claimed that a 3D SPACE sequence in conjunction with sagittal T1W images was sufficient for routine spinal imaging with increased diagnostic confidence. Aydin *et al*. [12] studied a CISS sequence, which is a gradient-echo technique with steady-state free precession, and quantitative diffusion-weighted imaging for routine lumbar disc imaging, and the authors found that these sequences may be alternative imaging approaches to conventional MRI approaches for assessing lumbar disc hernias [12].

The 3D TSE approach is a relatively new MRI technique, which is available in certain MR machines. This sequence has the potential to supplement (as a problem solver) or replace routine 2D fast spin-echo (FSE) sequences for lumbar imaging [13-15]. Moreover, it has some additional properties, including dynamic modification of the imaging plane using an add-on program to the standard image-viewing software [14, 16]. In the literature, some studies have compared the technical image quality of 3D MRI sequences with that of 2D MRI sequences for the cervical spine [17, 18].

Tins *et al*. [2] tried to use the SPACE sequence in 62 MRI examinations with two examiners in order to determine the suitability of the 3D SPACE sequence for routine imaging of the spine. In their study, with

high interobserver agreement for the SPACE sequence, the depiction of anatomy was very good in 84% of cases. For artifact assessment of SPACE, the kappa value was 0.92 and the confidence interval was between 0.92 and 1.00. They mentioned that the SPACE sequence was superior to routine MRI sequences for the depiction of anatomy and artifact resistance according to their results [2]. Blizzard *et al*. [1] applied the 3D TSE sequence to 80 patients and correlated the results with the 2D FSE sequence. Intermethod reliability was calculated for each interpreter as the point-by-point agreement using 57 criteria, including central canal stenosis and disc herniation. In their study, the intermethod reliability was 85.3% overall and 94.6% according to modified reliability, which excludes disagreements between normal and mild abnormalities. Additionally, intraobserver reliabilities were 82.0% for 2D FSE and 87.2% for 3D TSE, and interobserver reliabilities were 77.4% for 2D FSE and 78.4% for 3D TSE (overall) and 88.3% for 2D FSE and 89.1% for 3D TSE according to calculations for modified reliability [1]. Our interobserver agreements were higher for 3D TSE according to disc pathologies, disc herniation areas, and foraminal stenosis. On the other hand, the 2D TSE sequence showed better agreement with regard to spinal canal stenosis,although the agreement result was classified as strong for 3D TSE.

In 1990, Grenier *et al*. [19] claimed that foraminal and extraforaminal lumbar disk herniations were less frequent than intraspinal herniations and they were more difficult to diagnose. They underlined the difficulty of distinction between disc fragments and enlarged foraminal veins in far lateral zone herniation. They recommended flow sensitive sequences or contrast enhancement, which may aid in the diagnosis and overcome this issue. Within the same year, Epstein *et al*. [20] studied 60 patients with far lateral lumbar disc herniation. Myelo-computed tomography (CT) was found to be more effective and superior to noncontrast CT and MRI in their study. Lejune *et al*. [21] analyzed a series of 83 patients, who were operated specifically for foraminal lumbar disc herniation.They used the same classification for herniation zones as presented in our study. Although they used CT, they mentioned that foraminal herniations might be overlooked because even a moderate bulge of the intervertebral disc could impinge the nerve root in the narrow space of the neural foramen [21]. The limitations of evaluating the foraminal region have long been known. However, because of innovations in MRI technology, magnetic field forces are much stronger and new sequences have been used lately to overcome the limitations and difficulties. Lee *et al*. [22] studied lumbar spinal MRI using a 3.0T MR machine. They compared 2D T2W TSE with 3D T2W SPACE sequences for lumbar neural foraminal stenosis, central spinal stenosis, and nerve compression,with two interpreters. The 3D T2W TSE and 2D T2W SPACE sequences had similar sensitivity ratios for detecting foraminal stenosis at 32 foramen levels (78.9% vs. 78.9%). For spinal stenosis both sequences had 100% sensitivity at 42 spinal levels, and for nerve compression, the sensitivity ratios were 92.9% and 81.8% for 3D T2W TSE and 2D T2W, respectively, at 59 spinal nerves. The kappa values of interobserver agreements (3D T2W TSE vs. 2D T2W TSE) were 0.849 vs. 0.451 for foraminal stenosis, 0.809 vs. 0.503 for spinal stenosis, and 0.681 vs. 0.429 for nerve compression [22]. Our study revealed almost perfect agreements for 2D TSE and 3D TSE. Intermethod agreements were almost perfect for one reviewer and strong for the other two reviewers with regard to foraminal stenosis.

3D TSE provides good visualization for lumbar imaging but is not perfect in all aspects. It is mentioned that wrap around artifacts may occur in reformatted images of a 3D TSE sequence, which does not have an effect on the diagnosis; however, in this research, reformatted images were not used [11]. Reformatted images were not a component of this study due to correlate “the same MRI planes” with conventional sequences in order to reveal and analyze the possibilities and disadvantages of this MRI technique. Although we obtained good results with 3D TSE, most of our patients were not operated after MRI examinations, and this was a limitation of our study. Thus, it was not possible to correlate these two sequences with regard to surgical outcomes in all patients included in this study.

CONCLUSION

In conclusion, the 3D TSE sequence was very useful and the images obtained by this approach were

comparable to images obtained with conventional MRI sequences in the evaluation of lumbar disc herniation. We recommend this sequence for use in radiology departments either alone or combined with routine MRI for lumbar disc hernias.

Author Contributions

Study concept and design: VK, HA; Acquisition of data: VK, SSK, CHY; Analysis and interpretation of data: VK, SSK, HA; Drafting of the manuscript:VK, AKS; Critical revision of the manuscript for important intellectual content: HA, VK, AKS, UM; Statistical analysis: VK, AKS; Administrative, technical, and materialsupport: VK, SSK, CHY; Study supervision: VK; Guarantor of integrity of entire study: VK; Literature research: VK, AKS, UM, CHY

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] Blizzard DJ, Haims AH, Lischuk AW, Arunakul R, Hustedt JW, Grauer JN, et al. 3D-FSE isotropic MRI of the lumber spine novel application of an existing technology. J Spinal Disord Tech 2015;28:152-7.

[2] Tins B, Cassar-Pullicino V, Haddaway M, Nachtrab U. Three-dimensional sampling perfection with application-optimised contrasts using a different flip angleevolutions sequence for routine imaging of the spine: preliminary experience. Br J Radiol 2012;85:e480-9.

[3] Mahmutyazicioglu K, Ozdemir H, Savranlar A, Ozer T, Erdem O, Erdem Z, et al. Comparison of three-dimensional gradient echo, turbo spin echo and steady-state gradient echo sequences in axial MRI examination of the cervical spine. Tani Girisim Radyol 2003;9:432-8.

[4] Baskaran V, Pereles FS, Russell EJ, Georganos SA, Shaibani A, Spero KA, et al. Myelographic MR imaging of the cervical spine with a 3D true fast imaging with steady-state precession technique: initial experience. Radiology 2003;227:585-92.

[5] Meindl T, Wirth S, Weckbach S, Dietrich O, Reiser M, Schoenberg SO. Magnetic resonance imaging of the cervical spine: comparison of 2D T2-weighted turbo spin echo, 2D T2*weighted gradient recalled echo and 3D T2-weighted variable flip-angle turbo spin echo sequences. Eur Radiol 2009;19:713-21.

[6] Held P, Fründ R, Seitz J, Nitz W, Haffke T, Hees H. Comparison of 2-D turbo spin echo and 3-D gradient echo sequences for the detection of the trigeminal nerve and branches anatomy. Eur J Radiol 2001;37:18-25.

[7] Ramlı N, Cooper A, Jaspan T. High resolution CISS imaging of the spine. Br J Radiol 2001;74:862-73.

[8] Murakami N, Matsushima T, Kuba H, Ikezaki K, Morioka T, Mihara F, et al. Combining steady-state constructive interference and diffusion-weighted magnetic resonance imaging in the surgical treatment of epidermoid tumours. Neurosurg Rev 1999;22:159-62.

[9] Yousry I, Camelio S, Schmid UD, Horsfield MA, Wiesmann M, Brückmann H, et al. Visualization of cranial nerves 1-12: Value of 3D CISS and T2W FSE sequences. Eur Radiol 2000;10:1061-7.

[10] Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. N Engl J Med 1994;331:69-73.

[11] Lee S, Lee JW, Yeom JS, Kim KJ, Kim HJ, Chung SK, et al. A practical MRI grading system for lumbar foraminal stenosis. Am J Roentgenol 2010;194:1095-8.

[12] Aydin H, Kızılgöz V, Hekimoğlu B. Compared with the conventional MR imaging, do the constructive interference steady state sequence and diffusion weighted imaging aid in the diagnosis of lumbar disc hernias? Eurasian J Med. 2011;43:152-61.

[13] Kijowski R, Davis KW, Woods MA, Lindstrom MJ, De Smet AA, Gold GE, et al. Knee joint: comprehensiveassessment with 3D isotropic resolution fast spin-echo MR imaging-diagnostic performance compared with that of conventionalMR imaging at 3.0T. Radiology 2009;252:486-95.

[14] Busse RF, Brau AC, Vu A, Michelich CR, Bayram E, Kijowski R, et al. Effects of refocusing flip angle modulation and view ordering in 3D fast spin echo. Magn Reson Med 2008;60:640-9.

[15] Yoon YC, Kim SS, Chung HW, Choe BK, Ahn JH. Diagnostic efficacy in kneeMRI comparing conventional technique and multiplanar reconstructionwith one-millimeter FSE PDW images. Acta Radiol 2007;48:869-74.

[16] Busse RF, Hariharan H, Vu A, Brittain JH. Fast spin echo sequences withvery long echo trains: design of variable refocusing flip angleschedules and generation of clinical T-2 contrast. Magn Reson Med 2006;55:1030-7.

[17] Kwon JW, Yoon YC, Choi SH. Three-dimensional isotropicT2-weighted cervical MRI at 3T: Comparison with two-dimensionalT2-weighted sequences. Clin Radiol 2012;67:106-13.

[18] Meindl T, Wirth S, Weckbach S, Dietrich O, Reiser M, Schoenberg SO. Magnetic resonance imagingof the cervical spine: comparison of 2D T2-weighted turbo spinecho, 2D T2*weighted gradient-recalled echo and 3D T2-weightedvariable flip-angle turbo spin echo sequences. Eur Radiol 2009;19:713-21.

[19] Grenier N, Gréselle JF,Douws C. MR imaging of foraminal and extraforaminal lumbar disk herniations. J Comput Assist Tomogr 1990;14:243-9.

[20] Epstein NC, Epstein JA, Carras R, Hyman RA. Far lateral lumbar disc herniations and associated structural abnormalities: an evaluation in 60 patients of the comparative value of CT, MRI, and myelo-CT in diagnosis and management. Spine 1990;15:534-49.

[21] Lejeune JP, Hladky JP, Cotton A, Vinchon M, Christiaens JL. Foraminal lumbar disc herniation: experience with 83 patients. Spine 1994;10:1905-8.

[22] Lee S, Jee WH, Jung JY, Lee SY, Ryu KS, Ha KY. MRI of the lumbar spine: comparison of 3D isotropic turbo spin-echo SPACE sequence versus conventional 2D sequences at 3.0 T. Acta Radiol 2015;56:174-81.

The European Research Journal 2018;4(4):374-380 ORIGINAL ARTICLE

The impact of cigarette dependence severity on disease outcomes and depression in ankylosing spondylitis

Seyhan Dülger[1], İlknurAykurt Karlıbel[2], Tekin Yıldız[1], Lale Altan[2], Özlem Şengören Dikiş[1], Meliha Kasapoğlu Aksoy[2]

[1]Department of Chest Diseases, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey
[2]Department of Physical Medicine and Rehabilitation, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

DOI: 10.18621/eurj.336935

ABSTRACT

Introduction: Ankylosing spondylitis (AS) is a chronic systemic inflammatory disease. Smoking plays a role in AS pathogenesis and causes difficulties in its treatment. The aim of this study is to investigate the association of disease activity, functional status, spinal mobility, depression, chest expansion, pain, fatigue, quality of life, respiratory function with cigarette dependence severity in patients with AS.

Methods: The study included 71 patients diagnosed as AS. Patients were evaluated on questionnaires and examination scales specific to assessment of AS. The results were compared using the SPSS-23 software.

Results. Out of the total 71 patients, 40 (56.3%) were smokers, 31 (43.7%) were non-smokers. There were no significant differences between the smokers and the non-smokers with respect to the median values in Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Functional Index, Ankylosing Spondylitis Quality of Life questionnaire, Short Form 36 (SF-36), chest expansion, the fingertip-to-floor test and Beck Depression Inventory ($p > 0.05$). However, there were significant differences when comparing the median scores on BASMI ($p = 0.036$), SF-36 physical role strength ($p = 0.004$) and the chest expansion ($p = 0.015$) of the smoker patients placed in the three Fagerström Test for Nicotine Dependence (FTND) subgrouping.

Conclusion: AS patients with smoking have elevated FTND scores and worse values for test of disease activity and quality of life.

Keywords: Smoking, ankylosing spondylitis, life quality

Received: September 6, 2017; Accepted: December 14, 2017; Published Online: February 24, 2018

Ankylosing spondylitis (AS) is a chronic systemic inflammatory disease mainly characterised with symptoms in the sacroiliac and peripheral joints and the spine [1]. Back pain, stiffness, difficulty of spinal movements and fatigue are the main symptoms of the disease [2]. AS prevalence has been reported within the range of 0.1%-1.4% [3]. Total cure of AS with drugs has not yet been achieved therefore, treatment consists of controlling the spinal inflammation and preventing movement limitation and pain [4]. In population based study, incident AS was found associated with current smoking [5]. Smoking has been associated with increased disease activity, functional impairment and low quality of life in AS [6-8]. We have not been able to find out about the relationship between severities of cigarette addiction

Address for correspondence: *Seyhan Dülger, MD., University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Chest Diseases, Emniyet Caddesi No:35, 16115 Yıldırım, Bursa, Turkey*
E-mail: drsdulger@gmail.com, Phone: +90 224 4526648

e-ISSN: 2149-3189

with AS outcomes, despite there were studies what is associated with cumulative smoking history and disease activity.

The aim of this study is to investigate the association of disease activity, functional status, spinal mobility, depression, chest expansion, pain, fatigue, quality of life, respiratory function with cigarette dependence severity in patients with AS

METHODS

AThe study was conducted in accordance with the recommendations of the Helsinki Declaration and was approved by the Bursa Yuksek Ihtisas Training and Research Hospital Ethical Committee (2016/11-04). Written informed consent was obtained from all participants before undertaking any study-related procedures.

The study included 71 individuals diagnosed as AS on the Modified New York criteria and placed under follow up at the Physical Medicine and Rehabilitation Clinic. The exclusion criteria of the study were being outside the age range of 18-65 years, and having chronic systemic diseases such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD) and renal failure.

Evaluation parameters

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI): Patient fatigue, axial pain, peripheral pain, morning imprisonment, disturbance resulting from touching and repression, and general discomfort of the patient are marked on a horizontal visual analogue of 10 cm. The total BASDAI score of the patient varying between 0-10 is calculated [9].

Bath Ankylosing Spondylitis Metrology Index (BASMI): Cervical rotation, tragus-wall distance, lateral flexion, modified Schober and intermalleolar distance are the 5 best clinical measurements that best reflect the axial state. The sum of transformed points of each measurement is calculated. The score is between 5-15, and describes the disease state in AS. The BASMI is rapid (7 min.), reproducible and susceptible to change in the disease spectrum. The lower score shows a better level [10].

Bath Ankylosing Spondylitis Functional Index (BASFI): It is a measure of 10 questions designed to determine the degree of functional restriction in patients with AS. Each question is answered on a 10 cm horizontal visual analogue scale and their average gives the BASFI score (0-10) [11].

Ankylosing Spondylitis Quality of Life questionnaire (ASQol): It is a measure of the quality of life of the patients by questioning each question with a yes or no answer over 18 questions. The sum of the yards gives the score. It is a good, reliable method [12, 13].

Short Form 36 (SF-36): For measure of thirty-six questions that assesses the condition of the illness and loss of power Short Form 36 was done. Eight sub-parameters consisting of physical function (SF-PF), physical role strength (SF-PRS), emotional role strength (SF-ERS), power / live / vitality SF-PLV), emotional health SF-EH), social functioning (SF-SF), pain (SF-P) and general health perception (SF-GHP) are calculated by scoring these questions. High scores show a better level of health [14].

Chest Expansion: The difference is measured by measuring the chest diameter during maximum inspiration and maximum expiration [15].

The Fingertip-to-Floor Test (FTFT): The patient should stand comfortably with his feet pointing forward and be asked to lean forward. He tries to touch his fingertips with his fingers without twisting his knees. The distance between the floor and the fingertips is measured [16].

Beck Depression Inventory (BDI): Multiple choice 21 questions is a tool used to measure the severity of depression. In addition to pessimism, past failures and mistakes, guilt feelings, penalizing feelings, self-esteem, self-criticism, suicidal thoughts and worthless feelings besides sadness, pleasure loss, crying, agitation, indifference, indecision, energy loss, change in sleep patterns, somatic findings such as difficulties in concentration, fatigue, loss of sexual appetite are also examined. Each question is evaluated between 0-3 points [17].

Fagerström Test for Nicotine Dependence (FTND): The cigarette smoking AS patients were further evaluated with the Fagerström Test for Nicotine Dependence (FTND) [18]. FTND is standard tool for assessing Nicotine Dependence. It consists of six questions evaluating smoking. Dependence value is calculated by scoring from 1 to 10 [18]. Patients were mildly between 1-4 points; 5-7 points moderate;

8-10 points were divided into subgroups dependent on severe.

Measurement of Carbon Monoxide in Expiratory Air (Exp. CO): Exp.CO is (PICO Smokerlyzer (PICO SmokerlyzerRBedfont Micro Breath Alyzer, Kent, United Kingdom) device was used. The measurements were evaluated in terms of parts per million (ppm). The cut off level was determined as 6 ppm CO [19]. HLA-B27 was recorded. Flow cytometry method was used for HLA-B27. Nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (Dmard) and tumor necrosis factor alpha inhibitor (TNFα-inh) used by patients were noted.

Statistical Analysis

The data of the cigarette smoker and non-smoker patients accumulated on the questionnaires and measurements were compared using the Statistical Package for Social Sciences (SPSS) (IBM Corp. Released 2015. IBM SPSS Statisticsfor Windows, Version 23.0. Armonk, NY: IBM Corp.). Numerical values were expressed by the mean and the standard deviation; and their distribution was tested with the Kolmogorov-Smirnov test. Categorical values were evaluated with percentages. Comparison of the mean values were carried out using the Student-t Test, the Kruskal-Wallis Test and the Mann-Whitney U Test. Relationships were tested using the Spearman correlation test. The $p < 0.05$ values were accepted to indicate statistical significance.

RESULTS

The cigarette smokers constituted 56.3% (n=40) of the 71 patients included in the study, while 43.7% (n=31) were non-smokers. Demographic findings, education, income, smoking habits, spirometer parameters, HLA-B27, drug use, disease symptoms and diagnostic periods of smokers and non-smokers were given in Table 1. Two (5%) smokers and one (3.2%) non-smoker were not taking any medication. Six (15%) smokers and three (9.7%) non-smokers were using two different medications. Statistically significant differences between the smokers and the non-smokers were not observed with respect to the

Table 1. Patient and disease characteristics in smokers and nonsmokers

		ALL (n = 71)	SMOKER (n = 40)	NON-SMOKER (n = 31)	*p* value
Gender	Male	55 (77.5)	29 (72.5)	26 (83.9)	0.255[a]
	Female	16 (22.5)	11 (27.5)	5 (16.1)	
Age (year)		38 (18-68)	37 (18-57)	38 (22-63)	0.391[b]
BMI		25.08 (19-37)	25.27 (19-37)	24.97 (19-34)	0.963
Education	Primary school	43 (60.6)	21 (52.5)	22 (71)	0.283[a]
	High school	10 (14.1)	7 (17.5)	3 (9.7)	
	University	18 (25.4)	12 (30)	6 (19.4)	
Pay	none	24 (33.8)	14 (35)	10 (32.3)	0.242[a]
	≤ minimum wage	25 (35.2)	11 (27.5)	14 (45.2)	
	> minimum wage	22 (31)	15 (37.5)	7 (22.5)	
NSAID		38 (46.5)	20 (50)	13 (41.9)	0.499[a]
Dmard		33 (46.5)	16 (40)	17 (54.8)	0.214[a]
TNFα-inh		11 (15.5)	8 (20)	3 (9.7)	0.327[a]
Symptom time (years)		10 (1-37)	10 (5-32)	12 (1-37)	0.071[b]
Diagnosis time (years)		4 (1-37)	3 (1-32)	5 (1-37)	0.283[b]
HLA-B27		47 (66.2)	23 (57.5)	24 (77.4)	0.078[a]
FTND	Mild	-	10 (25)	-	-
	Moderate	-	15 (37.5)	-	
	Severe	-	15 (37.5)	-	
Cumulative Smoking (pocket/year)		-	10 (1-49)	-	-
Exp.CO (ppm)		-	6.5 (0-24)	-	-

Data are shown as number (%) or median (minimum-maximum). [a]Pearson Chi-Square test, [b]Mann Whitney-U test. BMI = Body mass index, Dmard = disease-modifying antirheumatic drugs, Exp. CO = Carbon Monoxide in Expiratory Air, FTND = Fagerström Test for Nicotine Dependence, NSAIDs = Nonsteroidal anti-inflammatory drugs, TNFα-inh = tumor necrosis factor alpha inhibitor

mean values of BASDAI, BASFI, BASMI, the SF-36 subsections (SF-PF, SF-PRS, SF-ERS, SF-PLV, SF-EH, SF-SF, SF-P, SF-GHP), ASQol, VAS PAIN (0-100), VAS Fatigue (0-100), the BDI score, chest expansion, FTFT, ESR level, and the CRP level ($p > 0.05$)(Table 2).

Comparison of parameters according to severity of dependence (FTND test) is shown in Table 3. There were significant differences when comparing the median scores on BASMI ($p = 0.036$), SF-36 physical role strength ($p = 0.004$) and the chest expansion ($p = 0.015$) of the smoker patients placed in the three FTND subgrouping. When, however, the mean values of the disease activity and life quality data of the smoking patients with FTND scores of ≤ 4 and FTND > 4 were compared with the corresponding data of the smoking patients, the mean SF-PRS and SF-EH scores of the FTND = 5-10 patients were significantly lower than those of FTND ≤ 4 ($p = 0.029$ and $p = 0.045$, respectively).

There was correlation between Exp. CO and FTFT; Exp. CO and BASFI ($r = 0.280$; $p = 0.022$ and $r = 0.277$; $p = 0.022$, respectively). A correlation was found between SF-PRS and the FTND; Cumulative Smoking (pocket/year) and FTND; Exp. CO And FTND ($r = 0.319$; $p = 0.045$, $r = 0.654$; $p < 0.001$ and $r = 0.344$; $p = 0.03$, respectively). Correlation of BDI with other parameters was shown in Table 4.

DISCUSSION

This The most significant result of our study was the determination of a trend of worsening in the BASMI, SF-PRS and chest expansion data with the severity of nicotine dependence in AS patients. The mean SF-PRS and SF-EH scores of AS patients with mild nicotine dependence were significantly higher as compared to those of the patients with moderate or severe dependence. Also, Exp. CO with BASFI, FTND and FTFT were found to be correlated. There are reports on a worse course of AS in smoking as compared to the non-smoking patients [8, 20-22]. To the best of our knowledge, in our study we

Table 2. Disease activity, quality of life and spinal immobility in smokers and non-smokers

		ALL (n = 71)	SMOKER (n = 40)	NON-SMOKER (n = 31)	*p value*
BASDAI		4.7 (0-10)	4.5 (0-8.4)	4.8 (0-10)	0.289[b]
BASFI		3.8 (0-9.5)	3.7 (0-8)	4.2 (0-9.5)	0.190[b]
BASMI		7 (5-15)	6 (5-15)	7 (5-15)	0.260[b]
CRP (mg/l)		4.12 (0-41.8)	4 (0-39.3)	4.6 (3.1-41.8)	0.429[b]
ESR (mm/h)		13.5 (2-76)	14 (2-76)	13 (2-51)	0.434[b]
ASQol		10 (0-18)	9 (0-17)	11 (0-18)	0.119[b]
Chest Expansion		4 (1-9)	5 (1-9)	4 (1-7)	0.143[b]
FTFT		23.5 (0-65)	20 (0-47)	24 (0-65)	0.253[b]
SF-36	Physical Function	65 (0-100)	67.5 (10-100)	55 (0-95)	0.227[b]
	Physical Role Strength	12.5 (0-75)	37.5 (0-75)	12.5 (0-50)	0.105[b]
	Emotional Role Strength	16.7 (0-100)	16.7 (0-100)	16.7 (0-50)	0.827[b]
	Power/Live/Vitality	40 (0-100)	40 (10-100)	40 (0-90)	0.589[b]
	Emotional Health	56 (4-100)	48 (24-100)	56 (4-84)	0.940[b]
	Social Functioning	62.5 (0-100)	62.5 (0-100)	62.5 (0-100)	0.397[b]
	Pain	45 (0-100)	45 (0-100)	45 (0-100)	0.571[b]
	General Health Perception	30 (0-100)	30 (0-100)	31 (0-85)	0.697[b]
BDI		16 (0-45)	14.5 (0-39)	19 (5-45)	0.304[b]

Data are shown as median (minimum-maximum). [a]Pearson Chi-Square test, [b]Mann Whitney-U test. ASQol = Ank Spondylitis Quality of Life questionnaire, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI Ankylosing Spondylitis Functional Index, BASMI = Bath Ankylosing Spondylitis Metrology Index, BDI = Beck Dep Inventory, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FTFT = the fingertip-to-floor test, S Short Form 36

Table 3. Comparison of parameters according to severity of dependence

		MILD	MODERATE	SEVERE	*p* value*
BASDAI		4.6 (0-8)	5 (1-8.3)	4 (1.1-8.4)	0.659
BASFI		2.6 (0-6.1)	4.9 (0-8)	1.8 (0-7.8)	0.405
BASMI		6 (5-15)	8 (5-14)	6 (5-15)	0.036
CRP (mg/l)		5.5 (0.3-39.3)	3.2 (3.1-29)	5.2 (0-18.7)	0.490
ESR (mm/h)		19.5 (2-76)	13 (6-58)	13.5 (2-36)	0.496
ASQol		8 (0-16)	11 (0-16)	7 (0-17)	0.643
Chest Expansion		5 (2-7)	3.5 (1-7)	6 (2-9)	0.015
FTFT		13.5 (0-34)	25 (5-42)	20 (0-47)	0.382
SF-36	**Physical function**	65 (0-100)	55 (20-100)	75 (10-95)	0.508
	physical role strength	25 (0-50)	12.5 (0-37.5)	37.5 (0-62.5)	0.004
	emotional role strength	25 (0-50)	16.7 (0-50)	16.7 (0-100)	0.714
	power/live/vitality	35 (15-100)	40 (10-85)	50 (10-90)	0.820
	emotional health	62 (40-100)	48 (24-100)	44 (28-96)	0.245
	social functioning	75 (0-100)	50 (12.5-100)	62.5 (25-100)	0.928
	pain	40 (0-90)	45 (0-100)	67.5 (0-90)	0.965
	general health perception	30 (15-100)	25 (0-90)	45 (15-75)	0.248
BDI		14.5 (0-28)	14 (5-39)	19 (0-37)	0.632

Data are shown as median (minimum-maximum). *Kruskal-Wallis test. ASQol = Ankylosing Spondylitis Quality of Life questionnaire, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, BASMI = Bath Ankylosing Spondylitis Metrology Index, BDI = Beck Depression Inventory, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FTFT = the fingertip-to-floor test, SF-36 = Short Form 36

demonstrate the relationship between the disease activity and quality of life, the severity of nicotine dependence and the Exp. CO level in the cigarette smoking AS patients. Zhao *et al*. [8], who studied cumulative smoking and disease activity in AS, found BASFI 2.1 higher in heavy smokers (21-40 pack-years). For cumulative smoking was correlated with FTND and Exp. CO in our study, we indirectly supported Zhao *et al*. [8]. However, although they found that BASDAI was 1.6 higher in heavy smokers, BASDAI among our FTND subgroups was not statistically significant. It's reported that, BASDAI and BASFI were found to be higher in smokers than non-smokers [23-25]. However, Zhao *et al*. [8] did not found difference between smoker and nonsmoker patients' BASDAI and BASFI values like with us.

BASMI, chest expansion and FTFT were tests which shown physical mobility in AS. Chung *et al*. [25] did not find different BASMI between the smokers and nonsmokers patients. These findings were in accordance with our results. On the other hand, Zhang *et al.* [21] reported that smoker patients' BASMI was higher than non-smoker patients. It seems that for the BASMI values of smoking and non-smoking AS patients, there is no consensus among studies. In some studies chest expansion found lower in smokers with AS [26]. However, according to Averns *et al*. [27], chest expansion was not different between AS and non-smoker patients. Zhang *et al*. [21] reported that FTFT was statistically significant differences between smoker and non-smoker patients with AS. In contrast, Chen *et al*. [26], Averns *et al*. [27] and we did not find any significant difference between the smokers and non-smokers.

We used ASQoL and SF-36 tests to assess the quality of life of our patients. ASQoL was not differences between the smoker and non-smoker patients in our study. However, in previous studies, it was observed to be poorer in smokers [7, 23, 28]. SF-36 was associated with smoking by Chung *et al*. [25]. In contrast, Bodur *et al*. [28] found no significant differences in SF-36 among smokers and non-smokers.

In the study of Esen *et al*. [29], it was taken to attention that depression was frequently associated with the disease in chronic pain-related diseases. BDI of AS patients were found to be higher than control group in this study. We also determined the correlation between disease activity, physical mobility and quality of life-related parameters and BDI. There was no

Table 4. Correlation of BDI with other parameters

		p	r
BASDAI		< 0.001	0.553*
BASFI		< 0.001	0.518*
BASMI		0.003	0.342*
ASQoL		< 0.001	0.719*
Chest Expansion		0.029	-0.262*
FTFT		0.001	0.378*
SF-36	Physical function	< 0.001	-0.612*
	physical role strength	0.295	-0.126
	emotional role strength	< 0.001	-0.536*
	power/live/vitality	< 0.001	-0.565*
	emotional health	< 0.001	-0.626*
	social functioning	< 0.001	-0.591*
	pain	< 0.001	-0.563*
	general health perception	< 0.001	-0.552*
Smoking		0.308	-0.123
FTND		0.484	0.114
Exp. CO		0.111	0.195

*Correlation is significant. Correlation coefficient (r), Spearman correlation test was used. ASQol = Ankylosing Spondylitis Quality of Life questionnaire, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, BASMI = Bath Ankylosing Spondylitis Metrology Index, BDI = Beck Depression Inventory, Exp. CO = Carbon Monoxide in Expiratory Air, FTFT = the fingertip-to-floor test, FTND = Fagerström Test for Nicotine Dependence, SF-36 = Short Form 36

significant difference in our study between smokers and non-smokers. However, the median value of non-smoker patients was slightly higher. Perhaps this is why we do not find BASDAI, BASFI, BASMI, ASQoL and SF-36 different in smoker patients with AS. The values that could be expected to be better in non-smokers were covered by depression. In addition, this may have been due to the relatively small numbers of patients included in the study.

HLA-B27 positivity has a role in the pathogenesis of AS. Several studies have also been reported concerning the relationship between HLA-B17 and Interleukin-17 (IL-17) production [30]. There is also a link between IL-17 and cigarettes [6]. All these may suggest that smoking together with HLA-B27 may have an impact on the pathogenesis and activation of AS. HLA-B27 positivity was found as 62.7% of AS patients. It was reported that, in other studies, this rate was given as 48.5% and 85.3%, respectively [5, 31]. Our result is consistent with previous studies.

The Limitations of the Study

The main limitation to our study is the small number of patients investigated. Division of the patient population as the smokers and non-smokers, with further subgrouping of the smoking patients on grounds of the severity of nicotine dependence result in a decrease of the number of patients in each category and this is assumed to affect the statistical evaluations. In addition, our study did not evaluate ex-smoker patients with AS.

Also, it has not been possible to follow-up for an adequate period the response to therapy of the smoking AS patients. The results indicate that after advising a larger population of patients to give up smoking, data on disease activity and quality of life in the smokers and the non-smokers need to be investigated.

CONCLUSION

In this study, significant differences between smoker and non-smoker AS patients on grounds of disease activity and quality of life were not observed. However, that smoker AS patients with elevated FTND scores had worse values for test of disease activity and quality of life. It is believed that, treatment of the cigarette smoking AS patients for the cessation of the smoking habit should be part of the routine therapy.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] Zhang S, Li Y, Deng X, Huang F. Similarities and differences between spondyloarthritis in Asia and other parts of the World. Curr Opin Rheumatol 2011;23:334-8.
[2] O'Dwyer T, Monaghan A, Moran J, O'Shea F, Wilson F. Behaviour change intervention increases physical activity, spinal mobility and quality of life in adults with ankylosing spondylitis: a randomised trial. J Physiother 2017;63:30-9.
[3] Braun J, Sieper J. Ankylosing spondylitis. Lancet 2007;369:1379-90.
[4] Braun J, Brandt J, Listing J, Alten R, Golder W, Gromnica-Ihle E, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 2002;359:1187-93.
[5] Videm V, Cortes A, Thomas R, Brown MA. Current smoking is associated with incident ankylosing spondylitis--the HUNT population-based Norwegian health study. J Rheumatol 2014;41:2041-8.
[6] Wendling D, PratiC. Spondyloarthritis and smoking: towards a new insight into the disease. Expert Rev Clin Immunol 2013;9:511-6.
[7] Mattey DL, Dawson SR, Healey EL, Packham JC. Relationshipbetween smoking and patient-reported measures of disease outcome in ankylosing spondylitis. J Rheumatol 2011;38:2608-15.
[8] Zhao S, Challoner B, Khattak M, Moots RJ, Goodson NJ. Increasing smoking intensity is associated with increased disease activity in axial spondyloarthritis. Rheumatol Int 2017;37:239-44.
[9] Calin A, Nakache JP, Gueguen A, Zeidler H, Mielants H, Dougados M. Defining disease activity in ankylosing spondylitis: is a combination of variables (Bath Ankylosing Spondylitis Disease Activity Index) an appropriate instrument? Rheumatology 1999;38:878-82.
[10] Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol 1994;21:1694-8.
[11] Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281-5.
[12] Nemeth R, Smith F, Elswood J, Calin A. Ankylosing spondylitis - an approach to measurement of severity and outcome: ankylosing spondylitis assessment questionnaire (ASAQ) - a controlled study. Br J Rheumatol 1987;26 (suppl 1):69-70.
[13] Doward LC, Spoorenberg A, Cook SA, Whalley D, Helliwell PS, Kay LJ, et al. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis 2003;62:20-6.
[14] McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247-63.
[15] Moll JM, Wright V. An objective clinical study of chest expansion. Ann Rheum Dis 1972;31:1-8.
[16] Ekedahl H, Jönsson B, Frobell RB. Fingertip-to-floor test and straight leg raising test: validity, responsiveness, and predictive value in patients with acute/subacute low back pain. Arch Phys Med Rehabil 2012;93:2210-5.
[17] Beck AT, Steer RA, Garbin MG. Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. Clinical Psychology Review 1988;8:77-100.
[18] Fagerström KO. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addict Behav 1978;3:235-41.
[19] Moscato U, Poscia A, Gargaruti R, Capelli G, Cavaliere F. Normal values of exhaled carbon monoxide in healthy subjects: comparison between two methods of assessment. BMC Pulm Med 2014;14:204.
[20] Jones GT, Ratz T, Dean LE, Macfarlane GJ, Atzeni F. Disease severity in never smokers, ex-smokers, and current smokers with axial spondyloarthritis: results from the Scotland Registry for Ankylosing Spondylitis. Arthritis Care Res (Hoboken) 2017:69:1407-13.
[21] Zhang S, Li y, Xu X, Feng X, Yang D, Lin G. Effect of cigarette smoking and alcohol consumption on disease activity and physical functioning in ankylosing spondylitis: a cross-sectional study. Int J Clin Exp Med 2015;8:13919-27.
[22] Wang M, Wang S, Zhang X, Xia Q, Cai G, Yang X, et al. Analysis on the situation of subjective well-being and its influencing factors in patients with ankylosing spondylitis. Health Qual Life Outcomes. 2016;14:118.
[23] Kaan U, Ferda O. Evaluation of clinical activity and functional impairment in smokers with ankylosing spondylitis. Rheumatol Int 2005;25:357-60.
[24] Sakellariou GT, Anastasilakis AD, Kenanidis E, Potoupnis M, Tsiridis E, Savvidis M. The effect of smoking on clinical and radiographic variables, and acute phase reactants in patients with ankylosing spondylitis. Rheumatol Int 2015;35:2109-14.
[25] Chung HY, Machado P, van der Heijde D, D'Agostino MA, Dougados M. Smokers in early axial spondyloarthritis have earlier disease onset, more disease activity, inflammation and damage, and poorer function and health-related quality of life: results from the DESIR cohort. Ann Rheum Dis 2012;71:809-16.
[26] Chen CH, Chen HA, Lu CL, Liao HT, Liu CH, Tsai CY et al. Association of cigarette smoking with Chinese ankylosing spondylitis patients in Taiwan: a poor disease outcome in systemic inflammation, functional ability, and physical mobility. Clin Rheumatol 2013;32:659-63.
[27] Averns HL, Oxtoby J, Taylor HG, Jones PW, Dziedzic K, Dawes PT. Smoking and Outcome in Ankylosing Spondylitis. Scand J Rheumatol 1996;25:138-42.
[28] Bodur H1, Ataman S, Rezvani A, Buğdaycı DS, Cevik R, Birtane M et al. Quality of life and related variables in patients with ankylosing spondylitis. Qual Life Res 2011;20:543-9.
[29] Esen SA, Esen İ, Karabulut Y, Atmiş V. Effects of the disease characteristics and the treatment on psychological status in patients with rheumatoid arthritis and ankylosing spondylitis. Curr Rheumatol Rev 2017 Jul 28. doi: 10.2174/1573397113666170728123518.
[30] Park SJ, Kim JH, Pai KS, Shin JI. The link of HLA-B27 with interleukin-23/interleukin-17 axis in coexisting systemic lupus erythematosus and ankylosing spondylitis. Lupus 2011;20:1566.
[31] Jamalyaria F, Ward MM, Assassi S, Learch TJ, Lee M, Gensler LS, et al. Ethnicity and disease severity in ankylosing spondylitis: a cross-sectional analysis of three ethnic groups. Clin Rheumatol 2017;36:2359-64.

The European Research Journal 2018;4(4):381-389 ORIGINAL ARTICLE

An investigation of the prevalence of depression and related factors in pregnant women living in the province of Erzurum

Elif Okşan Çalıkoğlu[1], Banu Bedir[1], Ayşegül Aydın[2], Sinan Yılmaz[1]

[1]Department of Public Health, Atatürk University School of Medicine, Erzurum, Turkey
[2]Department of Public Health, Uludağ University School of Medicine, Bursa, Turkey

DOI: 10.18621/eurj.370640

ABSTRACT

Objectives: Pregnancy is a time of numerous biological and psychosocial changes in women. The purpose of this study was to reveal the risk of depression, an important psychological problem, in pregnant women, and its association with sociodemographic characteristics.

Methods: This descriptive, cross-sectional study was performed between March 1 and May 31, 2015, with pregnant women registered at family health centers in the central districts of Aziziye, Palandöken and Yakutiye in the province of Erzurum. A sociodemographic and obstetric data form and the Beck Depression Inventory (BDI) were used for analysis.

Results: Subjects' mean age was 27.54 ± 6.2 years. Their mean BDI score was 16.09 ± 3.7. The mean BDI score of pregnant women in the first trimester was 16.3 ± 3.7, the mean score of those in the second trimester was 15.8 ± 4.2, and the mean score of those in the third trimester was 16.1 ± 2.5. There was a significant difference between trimesters in terms of risk of depression ($p = 0.006$). Significant associations were determined between the risk of depression and education level, number of pregnancies, and number of living children ($p < 0.05$). The logistic regression analysis results show that a pregnant woman's level of education, length of marriage, number of pregnancies and previous mental state are significant in terms of antenatal depression ($p < 0.05$).

Conclusions: There was a significant risk of depression according to the BDI in women in the first and third trimesters, and this was associated with several sociodemographic variables. This reveals the need for pregnant women to also be evaluated using a holistic approach involving mental state as well as sociodemographic and obstetric characteristics when undergoing medical evaluation.

Keywords: Depression, pregnancy, Beck Depression Inventory

Received: December 25, 2017; Accepted: January 19, 2018; Published Online: February 8, 2018

Depression, a major mental health problem worldwide, lowers quality of life and leads to productivity losses by impacting on functioning, creativity, happiness and satisfaction. Studies have revealed an increased risk of depression with fertility processes in women aged 18-44. Pregnancy is particularly important since this is a time of intense biological and psychosocial changes. While some women are able to adapt easily to changes associated with pregnancy and birth, mild, moderate or severe psychological diseases may occur in others [1, 2]. The prevalence of depressive symptoms in pregnancy has

Address for correspondence: *Banu Bedir, MD., Research Assistant, Atatürk University School of Medicine, Department of Public Health, Erzurum, Turkey*
E-mail: banubedir89@hotmail.com, Phone: +90 442 231 1404

e-ISSN: 2149-3189

been reported to vary depending on trimester, most commonly increasing in the first and third trimesters [3].

Failure to diagnose depression in pregnancy can give rise to very severe obstetric and neonatal outcomes in both mother and fetus as norepinephrine and cortisol elevation associated with changes in the neuroendocrine system during pregnancy reduce blood flow to the uterus [4]. Associated complications such as hypertensive disease such as pre-eclampsia/eclampsia, spontaneous abortion, antenatal bleeding, intensive care requirements, developmental retardation, prematurity, fetal death and low birth weight babies may occur. Antepartum depression is also a risk factor for postpartum depression [5-7]. The American College of Obstetricians and Gynecologists emphasizes the need for women in the perinatal period to be screened for depression at least once [8].

Although there have been several studies of depression in the postpartum period, far fewer have investigated depression during pregnancy. The prevalence of antepartum depression in overseas studies ranges between 17.9% and 30.0% [9-11]. According to studies from Turkey based on various different scales, the prevalence of antepartum depression varies between 14.0% and 36.0% [12-14]. Health workers have important responsibilities in terms of the identification, prevention and treatment of antepartum depression, with its severe consequences. The purpose of our study was therefore to determine the prevalence of depression among pregnant women in the province of Erzurum, the risk factors involved and preventive measures that might be adopted.

METHODS

This descriptive, cross-sectional study was performed with pregnant women registered at family health centers in the Erzurum districts of Aziziye, Palandöken and Yakutiye in March 1-May 31, 2015. According to data from the Provincial Public Health Directorate, the number of pregnant women in the city center when the study began in March 2015 was 3897. Sample calculation was performed using OpenEpi version 8 software. A sample of 569 women was determined at a 99% confidence interval and a 5% margin of error. The research was performed with pregnant women presenting to family health centers during the study period, without high-risk pregnancies and capable of establishing communication. Fifty-seven women refused to take part for various reasons. The final participation rate was 89.0%.

A questionnaire consisting of 55 questions was used as a data collection tool. The first part of the questionnaire contained 34 questions inquiring into sociodemographic and obstetric information. The Beck Depression Inventory (BDI) consisting of 21 questions was used in the second part. Questionnaires were applied by the authors at face-to-face interviews and with verbal consent being obtained from participants. Approval for the research was granted by the Atatürk University Medical Faculty Non-Interventional Research Ethical Committee (No. B.30.2.ATA.0.01.00/53 dated 20.02.2015).

The BDI developed by Beck *et al.* [15] in 1961 is a four-point Likert-type self-report scale consisting of 21 items. The purpose of the inventory is to measure emotional, cognitive and motivational symptoms observed in depression. A depression-related behavioral characteristic is determined in each item. Items are scored from 0 to 3 on a four-point Likert-type scale depending on the severity of depression. Scores of 0-9 indicate no depressive symptom, 10-16 mild, 17-24 moderate and 25 and above severe depressive symptoms. The highest possible score is 63. The aim of the scale is the objective quantification of degree of symptoms, rather than being diagnostic of depression [15]. The inventory was adapted in Turkish in 1989 by Hisli *et al.* [16], and a cut-off point of 19 was determined. Scores of 17 or above indicate depressive symptoms sufficiently severe to require treatment [16].

Statistical Analysis

Data were analyzed on SPSS (Statistical Package for the Social Sciences) 20.0 software. Descriptive statistics were expressed and number and percentage distributions and mean ± standard deviation. Normal distribution of data was assessed using the Kolmogorov-Smirnov test, and data were determined not to comply with normal distribution. Analyses were performed using the chi-square test, the chi-square trend test, the Kruskal-Wallis test, the Mann Whitney U test and logistic regression analysis. Significance

was set at $p < 0.05$. Logistic regression analysis was applied to reveal the effect of independent variables on depressive state. During binominal logistic regression analysis, a dichotomous variable, 'present' or 'absent,' was established on the basis of the depressive state cut-off point. The common features of the variables included in the model are that these are factors affecting or capable of affecting depression according to the previous literature. The Kruskal-Wallis test was used to analyze women's mean depression scores by trimesters, and the Mann-Whitney U test with Bonferroni correction was applied in order to identify the group constituting the source of variation. A p level < 0.016 was regarded as significant.

RESULTS

The mean age of the 512 pregnant women was 27.5 ± 6.2 years. In terms of education, 14.3% of women and 30.5% of spouses were high school or university graduates. Information concerning the sociodemographic characteristics of the pregnant women in the study is shown in Table 1. Housewives constituted 79.7% of the women in this study, and 26.6% of subjects described their monthly income as good while 6.1% described it as poor. Finally, 85.9% of women had social security, and 14.8% lived in families of six members or more.

Of the pregnant women in the study, 31.1% were in the first year of marriage, and 34.2% reported that

Table 1. Risks for depression according to various sociodemographic characteristics of the pregnantwomen in the study

	Depression Status According to the Beck Depression Inventory						
	BDI < 17		**BDI ≥ 17**		**Total**		**x^2, p**
	No.	**%**	**No.**	**%**	**No.**	**%**	
Woman's level of education							
Literate/Primary school	108	29.0	56	40.0	164	32.0	**$x^2 = 9.484$**
Middle/High school	216	58.1	60	42.9	276	53.9	**$p = 0.009$**
College/University	48	12.9	24	17.1	72	14.1	
Spouse's level of education							
Literate/Primary school	52	14.0	40	28.6	92	18.0	**$x^2 = 20.747$**
Middle/High school	212	57.0	52	37.1	264	51.5	**$p < 0.001$**
College/University	108	29.0	48	34.3	156	30.5	
Occupation							
Housewife	292	78.5	116	82.9	408	79.7	$x^2 = 1.362$
White collar worker	44	11.8	12	8.6	56	10.9	$p = 0.506$
Other	36	9.7	12	8.6	48	9.4	
Monthly income							
Good	105	28.2	31	22.1	136	26.6	$x^2=2.628$
Average	243	65.3	102	72.9	345	67.3	$p = 0.269$
Poor	24	6.5	7	5.0	31	6.1	
Social security							
Yes	320	86.0	120	85.7	440	85.9	$x^2 = 0.008$
No	52	14.0	20	14.3	72	14.1	$p = 0.929$
Duration of marriage							
0-1 years	120	32.3	40	28.6	160	31.3	$x^2 = 1.244$
2-5 years	80	21.5	36	25.7	116	22.7	$p = 0.537$
6 or more	172	46.2	64	45.7	236	46.0	
Total	372	72.7	140	27.3	512	100.0	

BDI = Beck Depression Inventory

Table 2. Risk of depression according to various obstetric characteristics

	BDI < 17		BDI ≥ 17		Total		x^2, *p*
	No.	%	No.	%	No.	%	
Number of pregnancies							
1	115	30.9	60	42.9	175	34.2	**x^2=6.759**
2	122	32.8	35	25.0	157	30.6	***p* = 0.034**
3 or more	135	36.3	45	32.1	180	35.2	
Trimester*							
1st trimester	119	32.0	62	44.3	181	35.4	**x^2=10.114**
2nd trimester	163	43.8	43	30.7	206	40.2	***p* = 0.006**
3rd trimester	90	24.2	35	25.0	125	24.4	
Type of delivery in previous pregnancy							
Normal birth	178	69.3	48	60.0	226	67.1	**x^2=6.422**
Cesarean	44	17.1	24	30.0	68	20.2	***p* = 0.040**
Miscarriage /still birth /abortion	35	13.6	8	10.0	43	12.7	
Number of living children							
None	126	33.9	64	45.7	190	37.1	**x^2=7.087**
1	130	34.9	35	25.0	165	32.2	***p* = 0.029**
2 or more	116	31.2	41	29.3	157	30.7	
Was current pregnancy wanted?							
Yes	315	84.7	120	85.7	435	85.0	x^2=0.086
No	57	15.3	20	14.3	77	15.0	*p* = 0.770
Receipt of medical assistance for pregnancy							
None	352	94.6	128	91.4	480	93.8	x^2=5.008
Implantation	16	4.3	12	8.6	28	5.4	*p* = 0.082
IVF	4	1.1	0	0	4	0.8	
Possession of knowledge concerning delivery							
Yes	225	60.5	60	42.9	285	55.7	**x^2 = 12.806**
No	147	39.5	80	57.1	227	44.3	***p* < 0.001**
Total	372	72.7	140	27.3	512	100.0	

*Kruskal-Wallis Test

this was their first marriage. Deliveries among those women with previous histories of pregnancy were by the normal vaginal route in 67.1% and cesarean in 20.2%.

In terms of trimesters, 35.4% of women were in the first trimester, 40.2% in the second and 24.4% in the third. Of the pregnant women in the study, 32.1% already had one child, and 30.7% had two or more. Current pregnancies were wanted in 85.0% of cases. We observed that 6.2% of women had sought medical assistance for their current pregnancies, and that 5.4% had become pregnant via implantation and 0.8% by in vitro fertilization. In addition, 87.5% of pregnant women were under observation by a physician, with 41.3% being monitored by the same physician throughout pregnancy. Finally, 44.3% of women reported possessing no information about types of delivery.

Chronic disease was present in 18.0% of the pregnant women in this study, and 68.0% reported using medications in association with their pregnancies. A further 11.7% reported smoking during pregnancy and 3.1% reported consuming alcohol. Of the women in this study, 76.6% reported being happy with their current pregnancies. In addition, 93.8% reported receiving support from their spouses during pregnancy and 90.6% reported receiving support from first-degree relatives, while 3.7% stated that their current pregnancy had an adverse impact on their marriages. In terms of gender, 21.1% of the women in this study reported that they wished the baby born from their current pregnancies to be a boy, while 23.5% preferred a girl. While 30.9% of the women had experienced anxiety and unease during their current

Table 3. Logistic regression analysıs results of factors affecting risks of depression in pregnant women according to the Beck Depression Inventory

Category	OR	(95% CI)	*p value*
Woman's education level			
Literate/primary school	2.7	1.0-6.8	**0.031**
Middle school/High school	1.2	0.5-2.5	0.615
College/University	1.00 (ref)		
Spouse's education level			
Literate/Primary school	1.5	0.7-3.2	0.276
Middle school/High school	0.4	0.2-0.7	**0.007**
College/University	1.00 (ref)		
Duration of marriage			
0-1 years	1.00 (ref)		
2-5 years	4.0	1.8-8.7	**< 0.001**
6 years or more	2.6	1.2-5.7	**0.011**
Trimester			
1st trimester	1.00 (ref)		
2nd trimester	0.4	0.2-0.6	**0.001**
3rd trimester	0.8	0.5-1.5	0.622
Number of pregnancies			
1	6.7	2.8-15.5	**< 0.001**
2	0.8	0.4-1.6	0.624
3 or more	1.00 (ref)		
Was current pregnancy wanted?			
Yes	1.00 (ref)		
No	1.4	0.7-2.7	0.284
Possession of knowledge concerning delivery			
Yes	1.00 (ref)		
No	1.5	0.9-2.5	0.076
Under monitoring by a physician			
Yes	1.00 (ref)		
No	2.3	1.1-4.9	**0.026**
Mental illness			
Yes	3.8	1.4-10.0	**0.006**
No	1.00 (ref)		

pregnancies, 4.7% reported having a diagnosed psychiatric disease themselves, and 3.9% in their families.

The mean BDI score of the women in the study was 16.0 ± 3.7, with 27.3% of women scoring 17, the cut-off points for the inventory, or higher. The mean age of the women with a BDI score of 17 or above was 26.4 ± 4.8. No significant relation was observed between mean ages and exhibition of depressive symptoms (p = 0.112). Mean BDI scores were 16.3 ± 3.7 among women in the first trimester, 15.8 ± 4.2 among women in the second and 16.1 ± 2.5 among women in the third. Significant variation was observed between trimesters in terms of risk of depression, these differences occurring between the first and second trimesters (p = 0.005) and the second and third trimesters (p = 0.012) (Table 2).

A significant relation was determined in terms of risk of depression in current pregnancies and type of delivery in previous pregnancies. A higher prevalence of depression was determined in women who had previously experienced normal deliveries (p = 0.04) (Table 2). Risk of depression was significantly related to number of pregnancies and number of living children (p = 0.034 and p = 0.029, respectively), deriving from women in their first pregnancies and with no living children (Table 2). A significant difference was observed in terms of risk of depression between women with knowledge of types of delivery and those without. The risk of depression was higher in pregnant women possessing information about the birth process (p < 0.001) (Table 2).

The level of women reporting being monitored by the same physician during their current pregnancies was 51.4%, and there was a significant difference in terms of mean depression scores between women being regularly monitored by the same physician and those not ($p = 0.001$). We also determined a significant association between smoking during pregnancy and the risk of depression ($p < 0.001$). No significant correlation was determined between the risk of depression and support from spouses or relatives among the pregnant women in this study ($p = 0.052$ and $p = 0.081$, respectively).

The logistic regression analysis results are shown in Table 3. The risk of depression according to the BDI was 2.7 times higher in literate/primary school graduate mothers than in high school/university graduates. The risk of depression was 4.0 times higher among women married for 2-5 years compared to those married for 0-1 years, and 2.6 times higher among women married for 6 years or more. The risk of depression was 6.7 times higher in women with no previous pregnancies compared to those with three or more previous pregnancies, and 2.3 times higher in women not being monitored by a physician compared to those receiving monitoring. Finally, the risk of depression was 3.8 times higher among women with no mental illness before pregnancy compared to those with a previous mental illness.

DISCUSSION

The mean age of the 512 pregnant women in this study of the prevalence of depression and related factors among subjects living in the province of Erzurum was 27.5 years. In agreement with our study, the 25-29 age group has the fastest age-specific fertility rate in Turkey [17]. Of the pregnant women in this study, 34.2% had no previous history of pregnancy, while 37.2% of women giving birth in Turkey in 2016 were having their first children. Our study finding is compatible with previous studies [17]. The rate of pregnant women at risk of depression with a BDI score of 17 or more was 27.3%. In other studies from Turkey, Yılmaz *et al.* [18] reported a figure of 25.1%, Yanıkkerem *et al.* [19] a figure of 30.0%, and Erbil *et al.* [20] a figure of 30.9%, all in agreement with our own finding. According to studies from other countries and cultures, prevalences of antepartum depression have been reported of 15.5% in Malta [21], 30.0% in Finland [11], and 19.6% in Brazil [22]. According to a comparative study involving Nicaragua and the Netherlands [23], the prevalence of depression during pregnancy is 54.0% in Nicaragua and 6.0% in the Netherlands. The difference between the two countries may be attributed to levels of development, and may also reflect the importance that they attach to psychosocial services.

In terms of occupation, 79.7% of the expectant mothers in this study were housewives, and no significant variation in risk of depression was determined among the occupational groups. In a study from Manisa in Turkey, Yanıkkerem *et al.* [19] reported significantly higher depression scores among housewives compared to working pregnant women, while in their study from Ankara, Ocaktan *et al.* [24] reported lower mean depression scores among housewives compared to working women. This difference may be attributed to the probability of the study groups having different socioeconomic, sociocultural, educational, spousal and familial characteristics.

Depressive symptoms in our study were higher among pregnant women with no living children, and no significant association was determined with familial support. We observed that 11.7% of women smoked during pregnancy, while Turkish Statistical Institution data for 2016 indicate that 13.3% of women smoked during pregnancy [25]. Risk factors for antepartum depression in other studies include a higher number of living children, lack of familial or social support, smoking, alcohol use, medication use and a history of mental illness [26-28]. The fact that these levels are very close to one another shows that smokers continue to smoke during pregnancy. Smedberg *et al.* [29] reported depression in one in three pregnant women who smoked before pregnancy and who continued to smoke during it.

A history of previous mental illness was reported by 4.7% of all the pregnant women in this study. Depressive symptoms in subjects with mental illness were significantly higher than in those with no such disease, the risk being 3.8-fold greater. In their study from Brazil, Castro e Couto *et al.* [30] identified a history of major depression as the most important risk factor for depression during pregnancy. In our study,

the risk of depression differed significantly among women in the first (44.3%) and third (25.0%) trimesters compared to the second. Erbil *et al.*'s [20] study supports our own findings. The first trimester of pregnancy is a time an intense adaptation process to hormonal changes, and therefore one of great importance.

In terms of type of delivery, 20.2% of the women reported having undergone previous cesarean deliveries in our study. According to data from the 2016 Statistical Yearbook, the incidence of cesarean deliveries in Turkey is 53.1%, considerably higher than that in our study [31]. On the basis of our study findings, greater symptoms of depression were observed among pregnant women with normal deliveries in previous pregnancies. This may be attributed to fear of episiotomy and pain. Concerns over the baby's health during birth may also be a source of stress in expectant mothers. Normal delivery is a process in which expectant mothers play an active role, and uncertainty over when this will take place may also lead to anxiety. The fact that cesarean deliveries are under the control of health personnel may produce a feeling of confidence in the expectant mother. These factors may all explain the high level of cesarean deliveries in Turkey. These points must all be considered in Health Ministry programs intended to encourage natural birth.

According to the Prenatal Care Management Guideline published by the Turkish Ministry of Health, all women must receive at least four sessions of prenatal care from family physicians and family healthy personnel during pregnancy. The guideline states that the first check must take place within the first 14 weeks of pregnancy, the second between weeks 18 and 24, the third between weeks 28 and 32 and the fourth between weeks 36 and 38 [32]. The rate of pregnant women reporting receiving adequate monitoring by a physician was 87.5%. In addition, the risk of depression among women thinking they did not receive sufficient monitoring was twice as high as that in women who thought that they were adequately monitored. Additionally, 51.4% of women reported receiving check-ups from the same physician. Mean BDI scores were significantly lower among women monitored by the same physician than those not seen by the same physician. Being monitored by the same physician can increase communication between the expectant mother and medical staff and can bestow a sense of security on her.

In our study, 44.3% of women reported possessing no knowledge of different types of delivery, the frequency of depression in that group being 57.1%. In agreement with our study, Akbaş *et al.* [33] reported greater symptoms of depression among subjects not receiving information about types of delivery. In support of our findings, Kartal *et al.* [34] reported that possession of information concerning giving birth and the provision of preparatory instruction reduced the risk of depression. The nature of the birth process at the end of pregnancy and potential complications are the principal uncertainties facing expectant mothers. A total of 44.3% of expectant mothers in our study possessed no information about types of delivery. Women frequently only decide in the final weeks of pregnancy on the type of delivery to be performed, and this may not be even be settled until the time of birth. The fact that almost half of expectant mothers possessed no information about types of deliveries is not, therefore, an unexpected finding. The incidence of depression among the group with no information concerning delivery was 57.1%. A higher incidence of depressive symptoms among women in this group was also reported by Akbaş *et al.* [33], in agreement with the present study. In support of our findings, Kartal *et al.* [34] also reported that possession of information concerning delivery and the provision of preparatory training reduce the risk of prenatal depression. The type of delivery and potential complications they may experience represents the principal uncertainty facing pregnant women.

Depressive symptoms were greater among women experiencing their first pregnancy in this study. Logistic regression analysis revealed that the risk of depression was 6.71-fold higher among women in their first pregnancies compared to those with three pregnancies or more. While some previous studies have reported that previous experience of pregnancy represents a risk for depression [33, 35], other have shown a risk in women in their first pregnancies [28, [34]. In the light of these data, it may be concluded that the mental health of women with no previous experience of pregnancy may be adversely affected by physiological and hormonal changes occurring in the body since they are experiencing these for the first time.

The Limitations of the Study

Only the BDI was used to identify depressive states among the expectant mothers in our study, and clinical evaluation diagnostic tools for psychiatric disorders were not employed. This represents the main limitation of our study, but this will be considered in further studies that we plan on this subject.

CONCLUSION

The education levels of the pregnant woman and her spouse, number of pregnancies, week of pregnancy, outcomes of previous pregnancies, number of living children and possession of information about the birth process were identified as factors affecting antenatal depression in this study. As in all periods of people's lives, greater importance must be attached during pregnancy to health, defined as a state of physiological, social and psychological well-being. Early recognition and treatment of depressive disorders, currently standing in eighthplace on the Disability Adjuster Life Year (DALY) in Turkey, are important since these can lead to more serious problems during pregnancy. The requisite importance must therefore be attached to these, starting with studies concerning the preservation of women's health,to psychosocial services during pregnancy monitoring. Early diagnosis and treatment must be provided for gravidas at risk of depression through careful screening of risk factors for mental illness and combining this with education and counseling services.

Conflict of interest

T he authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] Stewart DE, Gagnon A, Saucier J, Wahoush O, Dougherty G. Postpartum depression symptoms in newcomers. Can J Psychiatry 2008;53:121-4.
[2] Cebeci SA, Aydemir Ç, Göka E. [The prevalance of depressive symptom levels in puerperal period: relationship with obstetric risk factors, anxiety levels and social support]. Kriz Dergisi. 2002;10:11-8. [Article in Turkish]
[3] Bunevicius R, Kusminskas L, Bunevicius A, Nadisauskiene RJ, Jureniene K, Pop VJ. Psychosocial risk factors for depression during pregnancy. Acta Obstet Gynecol Scand 2009;88:599-605.
[4] Pearlstein T. Depression during pregnancy. Best Pract Res Clin Obstet Gynaecol 2015;29:754-64.
[5] Muzik M, Marcus SM, Heringhausen JE, Flynn H. When depression complicates childbearing: guidelines for screening and treatment during antenatal and postpartum obstetric care. Obstet Gynecol Clin North Am 2009;36:771-88.
[6] Leung BMY, Kaplan BJ. Perinatal depression: prevalence, risks, and the nutrition link -- a review of the literature. J Am Diet Assoc 2009;109:1566-75.
[7] Szegda K, Markenson G, Bertone-Johnson ER, Chasan-Taber L. Depression during pregnancy: a risk factor for adverse neonatal outcomes? A critical review of the literature. J Matern Fetal Neonatal Med 2014;27:960-7.
[8] Orta OR, Gelaye B, Bain PA, Williams MA. The association between maternal cortisol and depression during pregnancy, a systematic review. Arch Womens Ment Health 2018;21:43-53.
[9] Bödecs T, Horváth B, Kovács L, Diffellné Németh M, Sándor J. [Prevalence of depression and anxiety in early pregnancy on a population based Hungarian sample]. Orv Hetil 2009;150:1888-93. [Article in Hungarian]
[10] Marcus SM, Flynn HA, Blow FC, Barry KL. Depressive symptoms among pregnant women screened in obstetrics settings. J Women's Health (Larchmt) 2003;12:373-80.
[11] Kurki T, Hiilesmaa V, Raitasalo R, Mattila H, Ylikorkala O. Depression and anxiety in early pregnancy and risk for preeclampsia. Obstet Gynecol 2000;95:487-90.
[12] Karaçam Z, Ançel G. Depression, anxiety and influencing factors in pregnancy: a study in a Turkish population. Midwifery 2009;25:344-56.
[13] Eskici L, Demir Akca AS, Atasoy N, Arikan İ, Harma M. [The effects of depression and anxiety disorders in pregnant women on obstetric outcomes and newborn]. Anatolian Journal of Clinical Investigation. 2012;6(1):10-6. [Article inTurkish]
[14] Sevindik F. Elazığ İlinde Gebelikte Depresyon Prevalansı ve Etkileyen Faktörler. Elazığ: Fırat Üniversitesi; 2005.
[15] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arc Gen Psychiatry 1961;4:561-71.
[16] Hisli N. Beck Depresyon Envanterinin üniversite öğrencileri için geçerliği, güvenirliği. Psikoloji Dergisi 1989;7:3-13. [Article in Turkish]
[17] Türkiye İstatistik Kurumu 'Dünya Nüfus Günü' 2017. Available from: http://www.tuik.gov.tr/PreHaberBultenleri.do?id=24639.
[18] Yılmaz Doğru H, Özsoy AZ, Gözdemir E, Gülücü S, Demirtürk F. [Evaluation of depression and anxiety in first trimester]. Med Med J 2015;30:153-8. [Article in Turkish]
[19] Yanıkkerem E, Altan E, Demirtosun P. [Depression of the pregnants who live in the Manisa 1 no village clinic. Kadın Doğum Dergisi 2004;2:301-6. [Article in Turkish]
[20] Erbil N, Oruç H, Karabulut A. [Determination of depression and affecting factors in pregnancy. Turkiye Klinikleri J Gynecol Obstet 2009;19:67-74. [Article in Turkish]
[21] Felice E, Saliba J, Grech V, Cox J. Prevalence rates and psychosocial characteristics associated with depression in pregnancy and postpartum in Maltese women. J Affect Disord 2004;82:297-301.
[22] Faisal-Cury A, Menezes PR. Prevalence of anxiety and depression during pregnancy in a private setting sample. Arch Womens Ment Health 2007;10:25-32.
[23] Verbeek T, Arjadi R, Vendrik JJ, Burger H, Berger MY. Anxiety and depression during pregnancy in Central America: a cross-sectional study

among pregnant women in the developing country Nicaragua. BMC Psychiatry 2015;15:292.
[24] Ocaktan ME, Çalışkan D, Öncü B, Özdemir O, Köse K. Antepartum and postpartum depression in a primary health care center area Birsağlık ocağı bölgesinde doğum öncesi ve doğum sonrası depresyonun değerlendirilmesi. Ankara Üniversitesi Tıp Fakültesi Mecmuası 2006;59:151-7.
[25] Türkiye İstatistik Kurumu, "Türkiye Sağlık Araştırması, 2016 2017. Available from: http://www.tuik.gov.tr/PreHaberBultenleri.do?id=24573.
[26] Vırıt O, Akbaş E, Savaş HA, Sertbaş G, Kandemir H. [Association between the level of depression and anxiety with social support in pregnancy]. Arch Neuropsychiatry 2008;45:9-13. [Article in Turkish]
[27] Akkaş Yılmaz E, Gülümser Ç. The risk factors, consequences, treatment, and importance of gestational depression. Turk J Obstet Gynecol 2015;12:102-13.
[28] de Jesus Silva MM, Peres Rocha Carvalho Leite E, Alves Nogueira D, Clapis MJ. Depression in pregnancy. Prevalence and associated factors. Invest Educ Enferm 2016;34:342-50.
[29] Smedberg J, Lupattelli A, Mårdby A, Øverland S, Nordeng H. The relationship between maternal depression and smoking cessation during pregnancy -- a cross-sectional study of pregnant women from 15 European countries. Arch Womens Ment Health 2015;18:73-84.
[30] Castro e Couto T, Cardoso MN, Brancaglion MY, Faria GC, Garcia FD, Nicolato R, et al. Antenatal depression: prevalence and risk factor patterns across the gestational period. J Affect Disord 2016;192:70-5.
[31] TC Sağlık Bakanlığı, "Sağlık İstatistikleri Yıllığı 2016," 2017. Available from: http://www.metaveri.saglik.gov.tr/book/SIY_2016_Haber_Bulteni.pdf.
[32] Sağlık Bakanlığı 'Doğum Öncesi Bakım Yönetim Rehberi'. Ankara 2014.
[33] Akbaş E, Vırıt O, Savaş AH, Sertbaş G. [Association between sociodemographic variables with the levels of depression and anxiety in pregnancy]. Arc Neuropsychiatry. 2008;45:85-91. [Article in Turkish]
[34] Kartal B, Karataş N, Başer M. The Effect of Education Given to the Primiparous Pregnant Women on Postpartum Depression. Turkiye Klinikleri J Gynecol Obstet 2016;26:197-204.
[35] Ajinkya S, Jadhav PR, Srivastava NN. Depression during pregnancy: Prevalence and obstetric risk factors among pregnant women attending a tertiary care hospital in Navi Mumbai. Ind Psychiatry J 2013;22:37-40.

The European Research Journal 2018;4(4):390-398 ORIGINAL ARTICLE

Nausea and vomiting in pregnant adolescents: impact on health-related quality of life

Elif Yılmaz, Betül Tokgöz, Çağanay Soysal, Seda Şahin Aker, Tuncay Küçüközkan

Department of Obstetrics and Gynecology, Dr. Sami Ulus Maternity and Womens' Health Training and Research Hospital, Ankara, Turkey

DOI: 10.18621/eurj.353985

ABSTRACT

Objectives: To determine the impact of the presence and severity of nause and vomiting in pregnancy (NVP) on health-related quality of life in pregnant adolescents.

Methods: Two hundred and fifty adolescent pregnant women were included in this study. The Rhodes test was performed to determine the severity of nausea and vomiting, and the self-reported 36-Item Short Form Survey (SF-36) Scale was administered. The study was divided into four groups according to nausea severity (no, mild, moderate, severe) groups and SF-36 scores were compared among the groups.

Results: Of the 250 pregnant women included in the study, 74.5% of women reported NVP. Low scores on the SF-36 were found for all items with increasing severity of NVP, with the lowest scores in the severe NVP group and the highest scores in the group with no NVP ($p = 0.001$). Multivariable analyses showed that severity of NVP was the most important factor for both the physical (PCS) and mental component summary (MCS) scales. The number of living children was significantly associated with lower PCS scores and being unable to share problems with spouse/relatives was correlated with lower MCS scores.

Conclusion: The negative impact of nausea and vomiting on health-related quality of life, emphasises the importance of psychological support and optimal management of NVP in pregnant adolescents.

Keywords: Adolescent, pregnancy, nausea, vomiting, health-related quality of life

Received: November 15, 2017; Accepted: January 23, 2018; Published Online: March 24, 2018

The definition of health has changed in recent decades. According to the World Health Organization (WHO), health is a state of complete physical, mental and social well-being [1]. This change in the idea of health has led to an increase in the importance of the quality of life (QoL) concept in recent years. When QoL is considered in the context of health and disease, it is commonly referred to as health-related quality of life (HRQoL). HRQoL is a multi-dimensional concept, that includes physical, emotional and mental perceptions and social functioning. According to the WHO, QoL is the perception of an individual of his/her own position in life in the context of the culture and value systems in which he/she lives and in relation to his/her aims, expectancies, standards and worries [1].

Although pregnancy is accepted as physiological phenomena, both physical and mental aspects of maternal health can be adversely affected during this period. Changes that occur during pregnancy can

Address for correspondence: *Elif Yılmaz, MD., Dr. Sami Ulus Maternity and Womens' Health Training and Research Hospital, Department of Obstetrics and Gynecology, Sihhiye, 06200 Ankara, Turkey*
E-mail: elifakkasyilmaz@gmail.com, Tel: +90 312 3056385

e-ISSN: 2149-3189

reduce a woman's QoL by altering her ability to carry out her usual roles in daily life [2, 3]. As well as a reduction in physical performance, pregnant women have more limitations due to emotional problems and social functioning, which causes a decrease in their perception of level of health and well-being [4, 5]. Another issue to be considered that can lead to a deterioration in HRQoL and that interferes with the physical and psychological condition of pregnant women, is the nausea and vomiting in pregnancy (NVP) experienced by 70-80% of all pregnant women [6-9]. In addition to the deterioration in physical health, the mental and physical stress caused by nausea and vomiting can lead to depressive feelings and promotes a significant negative influence on the family and on the social and occupational functioning of pregnant women who have NVP [8, 10]. An important point to be kept in mind is that the severity of these negative effects seems to be related to the severity of NVP [7, 10, 11]. A more severe form of NVP, hyperemesis gravidarum defined as tenacious vomiting which is associated with metabolic disturbances and more than 5% of pre-pregnancy body weight loss. The prevelance of hyperemesis gravidarum is given as 0.3-2% and defined as the most common reason for hospitalization in first half of pregnancy [12, 13].

Despite the increased importance of health related quality concepts in recent years, only a few studies have focused on the association between NVP and HRQoL in pregnant women. Although a few studies show the impact of the presence or severity of NVP on HRQoL, data on the role of NVP and its severity on HRQoL in pregnant adolescents, which is one of the greatest problems especially in developing countries, are still limited [6-8]. About 16 million adolescent women give birth each year, approximately 11% of all births worldwide, with the number increasing every year, especially in low- and middle-income countries. Thus the aim of this study was to determine the impact of NVP presence and severity on HRQoL during the first 20 weeks of pregnancy in pregnant adolescents.

METHODS

A prospective cross-sectional study was conducted with adolescent pregnant women (≤ 19 years) receiving routine prenatal care at the outpatient obstetric clinics of a major tertiary maternity hospital in Ankara, Turkey, from July-December 2015. The study group consisted of 250 adolescent pregnant women aged between 15-19. The inclusion criteria were having a viable singleton pregnancy ≤ 20 weeks, absence of congenital anomalies, systemic diseases (diabetes, thyroid dysfunction, urinary-hepatobiliary and gastrointestinal disease, hematologic diseases, depressive disorders) and the exclusion criteria were maternal age ≥ 20 years, fetal death and threatened abortion. Hiperemesis gravidarum (defined as severe vomiting resulting in dehydration and weight loss exceeding 5% of prepregnancy body weight) was considered as a different group from severe NVP and used as an exclusion criterium. The study was approved by Ethics Committee. After giving information about the study, and obtaining written informed consent from the patient and from the parents when the participant was younger than 18 years old, instructions were given to the patients on how to fill out the Rhodes and SF-36 Questionnaires. After routine first trimester examinations and determining gestational age by obstetric ultrasonography, sociodemographic questionnaire and the Rhodes test were filled out by face to face interview. The participants were administered the SF-36 with supervision.

NVP was classified according to its severity using the Rhodes Test, as no NVP, mild, moderate and severe NVP. The groups were compared according to SF-36 scores.

Socio-demographic Questionnaire

A questionnaire that included personal and obstetrical information was completed.

Rhodes Test

The Rhodes test, developed by Rhodes *et al* in 1984, is one of the most commonly used scales for evaluating the presence and severity of NVP [14, 15]. The test consists of 8 questions, validated for symptoms that occured in the past 12 hours, which combines physical signs (the number and duration of nausea, vomiting, retching and the volume of vomit at any time) with the feelings of the patient caused by the distress of these symptoms. The total score of the test

ranges from 8-40; a score 8 was considered no NVP, 9-18 mild, 19-32 moderate, and 33-40 severe NVP.

Short Form Health Survey (SF-36)

The Short Form Health Survey(SF-36) is a 36-item, patient-reported survey of patient health. It was developed by the Rand Corporation in 1992 [16]. It is one of the most commonly used scales in evaluating individual patient health status. It is a self-rating scale that can be filled out in a short period of five to ten minutes. One of the most important advantages of the scale is that the positive and negative aspects of health status can be assessed at the same time. It contains 36 questions in eight subscales, which include physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health perceptions. It evaluates the symptoms of the last four weeks [17]. The first four scales are summarized into the physical summary component (PCS) and the last four scales into the mental summary component (MCS). The score for each subscale ranges from 0-100 and is directly proportional to the QoL; the lower the score the more disability, the higher the score the less disability. The reliability and validity study of the scale in Turkish, was established in 1999 [18]. Determination of the population norms for the Turkish version of SF-36 were made by Demiral *et al*. [19] in 2006.

Statistical Analysis

Statistical analyses were performed using SPSS software version 20.0 (SPSS Inc, Chicago, IL). The suitability of the measurements to normal distribution were determined by "Kolmogorov-Smirnov Test" according to sample size (n > 30). Parametric tests were used for normally distributed variables, otherwise analyses were done with non-parametric tests. In the comparison of 3 or more independent groups, "ANOVA" was used as parametric test and "Kruskal-Wallis H" as a non-parametric test. Tukey was used as posthoc test for ANOVA. Categorical variables were analysed with "Chi-Square Test" statistics. "Multivariable linear regression analyses" were used to show independent variables associated with PCS and MCS scores. *P* values < 0.05 were considered to be statistically significant.

RESULTS

Socio-demographic characteristics

The socio-demographic characteristics of the patients are shown in Table 1. According to the Rhodes Test results, 74.8% of the patients had NVP; 36.8% (n = 92) had mild, 28.8% (n = 72) had moderate, and 9.2% (n = 23) had severe symptoms, whereas 25.2% (n = 63) of the patients had no NVP.

Asignificant relationship was found between the severity of NVP and monthly income (p = 0.033). Severe NVP was higher in the high income group whereas no NVP, mild and moderate NVP were higher in the median income level groups. A statistically significant relationship was found between the family structure, number of individuals living in the same home and the severity of NVP. Severe NVP was found to be higher in patients living in an extended family (p = 0.027) and those sharing the same home with a greater number of people (p = 0.008). Willingness of pregnancy was found to be significantly different between the groups (p = 0.033); the severity of NVP was significantly lower in the planned pregnancy group. The severity of NVP was higher in patients who had difficulties in sharing problems with spouse/relatives (p = 0.001) and who had discord/uneasiness within the family (p = 0.001) (see Table 1).

SF-36 Scores

Average SF-36 scores of our whole group in the study were somewhat lower than the general Turkish female population as shown in Table 2. As for SF-36, the PCS median score was 45.20 (min 20.70-max 60.90) and the MCS score was 48.85 (min: 20.30-max: 61.40) in the whole group. The no NVP group was found to have the highest average PCS and MCS scores. The scores of PCS and MCS decreased progressively with increasing severity of NVP and remained below the average of the general population scores in the moderate and severe NVP groups. Statistically significant differences were found both in PCS and MCS scores between the groups, with the highest scores in the group with no NVP (p = 0.001 and p = 0.001, respectively). A significant decrease in scores was observed with increasing severity of NVP (Table 3).

According to the results of the subscores of SF-

Table 1. Distribution of socio-demographic characteristics and family features of the groups

Characteristic	NVP Degree				*p* Value
	None	Mild	Moderate	Severe	
Age (years), median (min-max)	18 (16-19)	19 (15-19)	19 (15-19)	19 (16-19)	0.885
Gestational week, median (min-max)	12 (6-20)	12 (5-20)	11 (6-20)	13 (6-20)	0.653
Number of individuals at home, median (min-max)	2 (2-7)	2 (2-9)	2 (2-9)	3 (2-7)	**0.008**
First antepartum care (week), median (min-max)	7 (5-20)	6 (5-14)	6 (5-20)	7 (5-19)	0.883
Gradiva, median (min-max)	1 (0-3)	1 (0-3)	1 (0-4)	1 (1-3)	0.359
Living children, median (min-max)	0 (0-2)	0 (0-1)	0 (0-2)	0 (0-1)	0.683
Educational level, n (%)					0.415
Elementary school/lower	43 (68.3)	52 (56.5)	48 (66.7)	14 (60.9)	
High school	20 (31.7)	40 (43.5)	24 (33.3)	9 (39.1)	
Employment status, n (%)					0.415
Employed	11 (17.5)	12 (13)	12 (16.7)	0 (0)	
Unemployed	52 (82.5)	80 (87)	60 (83.3)	23 (100)	
Education level of spouse, n (%)					0.553
Elementary school/lower	28 (44.4)	28 (30.4)	25 (34.7)	9 (39.2)	
High school	35 (55.6)	64 (69.6)	47 (65.3)	14 (60.8)	
Emploment status of spouse, n (%)					0.530
Employed	61 (96.8)	86 (93.5)	68 (94.4)	23 (100)	
Unemployed	2 (3.2)	6 (6.5)	4 (5.6)	0 (0.0)	
Health security, n (%)					0.675
Yes	59 (93.7)	84 (91.3)	64 (88.9)	22 (95.7)	
No	4 (6.3)	8 (8.7)	8 (11.1)	1 (4.3)	
Total monthly income, n (%)					**0.033**
≤1300 TL	17 (27)	23 (25)	24 (23.3)	5 (21.7)	
1301-3000 TL	37 (58.7)	44 (47.8)	27 (37.5)	7 (3.5)	
≥3001 TL	9 (14.3)	25 (27.2)	21 (29.2)	11 (47.8)	
Family structure, n (%)					**0.027**
Nuclear	51 (81)	62 (67.4)	50 (69.4)	11 (47.8)	
Extended	12 (19)	30 (32.6)	22 (30.6)	12 (52.2)	
Planned pregnancy, n (%))					**0.033**
Yes	54 (85.7)	76 (82.6)	52 (72.2)	14 (60.9)	
No	9 (14.3)	16 (17.4)	20 (27.8)	9 (39.1)	
Smoking during pregnancy, n (%)					0.590
Yes	12 (19)	18 (19.6)	9 (12.5)	3 (13)	
No	51 (81)	74 (80.4)	63 (87.5)	20 (87)	
Sharing problems with spouse / relatives, n (%)					**0.001**
Yes	62 (88.5)	89 (96.7)	52 (72.2)	13 (56.5)	
No	1 (1.5)	3 (3.3)	20 (27.8)	10 (43.5)	
Discord/uneasiness within the family, n (%)					**0.001**
Yes, always	14 (22.2)	27 (29.3)	37 (51.4)	23 (100)	
No	49 (77.8)	65 (70.7)	35 (48.6)	0 (0)	

NVP = nause and vomiting in pregnancy, TL = Turkish Liras

36, except for Role physical (RP) and Role emotional (RE) subscores, statistically significant differences were found in physical functioning, bodily pain, general health, vitality, social function and mental health subscores between all groups. A significant decrease in the scores was observed with increasing severity of NVP, with the lowest scores in the severe NVP group and the highest scores in the group with no NVP ($p < 0.05$) (Table 3).

RP and RE subscores were similar between the

Table 2. Comparison of SF-36 PCS and MCS scores in our study population with SF-36 scores found general Turkish female population

PCS	Data	MCS	Data
Turkish Female Population	46.6 ±9.9	Turkish Female Population	47.3 ± 9.8
Whole Study Group	44.6 ± 7.8	Whole Study Group	43.9 ± 9.5
No NVP	49.9 ± 5.3	No NVP	50.7 ± 7.3
Mild NVP	48.0 ± 5.7	Mild NVP	46.5 ± 7.5
Moderate NVP	39.2 ± 5.7	Moderate NVP	38.2 ± 6.7
Severe NVP	33.7 ± 5.1	Severe NVP	32.5 ± 9.2

Data are shown as mean ± standard deviation, MCS = Mental summary component, NVP = nause and vomiting in pregnancy, PCS = Physical summary component

groups with no NVP and mild NVP, whereas they were significantly higher inthe moderate and severe NVP groups, with the lowest scores in the severe NVP group.

Multivariable regression analysis that was done to determine the effects of the variables on PCS and MCS scores showed that the severity of NVP and the number of living children were factors significantly associated with PCS scores, whereas sharing problems with spouse/relatives and severity of NVP were found

Table 3. Mean health related quality of life scores for the groups for each of the domains of the Short Form Health Survey (SF36)

Domain	Mean HRQOL scores				*p* Value
	None	Mild NVP	Moderate NVP	Severe NVP	
Physical functioning	85 (50-100)	80 (40-100)	40 (5-100)	45 (0-80)	**0.001** D (1-3,4) (2-3,4)(3-4)
Role physical	75 (0-100)	75 (0-100)	25 (0-100)	0 (0-50)	**0.001** D (1-3,4) (2-3,4)
Bodily pain	84 (32-100)	74 (31-100)	52 (20-100)	41 (0-64)	**0.001** D (1-3,4) (2-3,4)(3-4)
General health	77 (32-97)	62 (32-100)	46 (17-77)	40 (5-65)	**0.001** D (1-2,3,4) (2-3,4)
Vitality	70 (45-100)	60 (30-90)	40 (10-80)	30 (0-75)	**0.001** D (1-2,3,4) (2-3,4)(3-4)
Social function	87.5 (25-100)	75 (25-100)	62.5 (0-100)	50 (0-100)	**0.001** D (1-3,4) (2-3,4)
Role emotional	66.7 (0-100)	66.7 (0-100)	33.30 (0-100)	0 (0-66.7)	**0.001** D (1-3,4) (2-3,4)(3-4)
Mental health	80 (48-100)	72 (36-96)	52 (20-80)	36 (12-92)	**0.001** D (1-2,3,4) (2-3,4)(3-4)
Physical Summary Component	49.85 ± 5.34	47.97 ± 5.66	39.22 ± 5.66	33.70 ± 5.12	**0.001** D (1-3,4) (2-3,4)(3-4)
Mental Summary Component	51.3 (34-61)	47.1 (25-61)	37.7 (26-55)	32.7 (20-56)	**0.001** D (1-2,3,4) (2-3,4)(3-4)

Data are shown as median (minimum-maximum) or mean ± standard deviation. D = Difference , HRQoL = health-related quality of life

Table 4. Multivariable regression analyses showing independent variables associated with PCS score as the dependent variable in studypopulation

Variables	B	Standard Error	β	t	*p*
Constant	58,454	8.547		6.839	**< 0.001**
Age	-0.183	0.422	-0.022	-0.432	0.666
Education	-1.052	0.775	-0.065	-1.357	0.176
Occupation	0.955	1.160	0.043	0.823	0.411
Education of spouse	1.115	0.680	0.089	1.640	0.102
Health security	-1.744	1.413	-0.062	-1.234	0.218
Total income	0.000	0.000	0,020	0.265	0.792
Number of individuals at home	-0.204	1.269	-0.012	-0.161	0.872
Planned pregnancy	-0.449	0.918	-0.024	-0.489	0,625
Number of living children	-1.720	0.789	-0.107	-2.179	**0.030**
Sharing problems with spouse/relatives	-0.342	0.603	-0.032	-0.566	0.572
Uneasiness within the family	0.894	0.677	0.077	1.321	0.188
Severity of NVP	-5.264	0.485	-0.627	-10.843	**< 0.001**

NVP = nause and vomiting in pregnancy, PCS = Physical summary component

Table 5. Multivariable regression analyses showing independent variables associated with MCS score as the dependent variable in study population

Variables	B	Standard Error	β	t	*p*
Constant	59.237	11.001		5.385	**< 0.001**
Age	0.367	0.544	0.036	0.674	0.501
Education	-0.231	0.998	-0.012	-0.232	0.817
Occupation	0.189	1.493	0.007	0.127	0.899
Education of spouse	-0.690	0.875	-0.045	-0.788	0.432
Health security	0.223	1.819	0.007	0.123	0.903
Total income	0.000	0.001	0.006	0.077	0.938
Number of individuals at home	-0.164	1.634	-0.008	-0.101	0.920
Planned pregnancy	-2.241	1.182	-0.097	-1.896	0.059
Number of living children	1.059	1.016	0.054	1.043	0.298
Sharing problems with spouse/relatives	-2.848	0.777	-0.217	-3.667	**< 0.001**
Uneasiness within the family	-0.857	0.871	-0.061	-0.983	0.326
Severity of NVP	-5.474	0.625	-0.536	-8.761	**< 0.001**

MCS = Mental summary component, NVP = nause and vomiting in pregnancy

to be factors that influenced MCS scores with statistical significance. According to the coefficient β, the severity of NVP was found to be the most important predictor of both PCS and MCS scores (Tables 4 and 5).

DISCUSSION

This study demonstrated two important findings. First, both the presence of NVP and its severity had a negative impact on both PCS and MCS, as well as the other subscores of SF-36; with the highest scores in the group with no NVP and a progressive decrease in all scores with increased severity of NVP. Second, based on multivariable regression, the severity of NVP was the most important predictor of HRQoL scores. The number of living children was also found to be associated with poorer PCS scores, and not being able to share problems with spouse/relatives contributed to poorer MCS scores.

NVP is a common medical condition during gestation that can negatively impact the overall well-being of pregnant women. Although it is a very common, age old phenomenon, its outcomes in pregnant adolescents has so far received limited attention in the literature. The overall rate of NVP found in our study was 74.8%, which is similar to

other studies in the literature, with reported rates between 70-80% [9, 11, 20].

The cause of NVP is not well-understood and the etiology of this common condition is still unclear, but it is believed that especially women who have not planned their pregnancy are at higher risk for poor maternal psychosocial adaptation and experience severe NVP, similar to our results [21]. Although there are several studies in the literature reporting increased risk of NVP with younger age, increasing gravidity, and housewife occupational status, we did not find any correlation between NVP and these socio-demographic characteristics [22, 23]. Another factor that is considered to have an adverse effect on NVP is inadequate social support [21, 24]. Similarly, in our study the severity of NVP was higher in patients who had difficulties in sharing problems with spouse/relatives and who had discord/uneasiness within the family. Increased physical and psychological burden on pregnant women living in extended families compared to those living in nuclear families may explain the significant relationship found between the family structure and the increased number of cohabitants living in the same home and the severity of NVP in our study group.

Despite being one of the most enjoyable periods of a woman's life, maternal health can be adversely affected during pregnancy and emotional-physical problems can arise, particulary in adolescents. While much is known about the physiological changes of pregnancy, the affect of these substantial changes on the health status of women during this period has received limited attention [5]. In recent years, studies examining the health status during pregnancy found lower QoL scores in pregnant women, especially in the emotional and physical role subscores [2, 3, 25]. Average SF-36 scores of our whole group in the study were somewhat lower than the general Turkish female population. This result is consistent with the literature and can be explained by the fact that pregnancy alone is a situation that can affect women's HRQoL. In a study done in our country aimed to determine the QoL of pregnant adolescents (< 20 years) and pregnant adults (20-29 years), Taşdemir *et al*. [25] determined lower QoL scores especially in the first trimester of pregnancy. Similarly, Ramirez-Velez [3] reported that limitations in physical function and restrictions in vitality increased over the course of pregnancy and the decline of mental and general health scores in the physical and emotional role subscores was remarkable. In another study aimed to identify normative changes in health status associated with pregnancy, pregnant women had significantly poorer levels of functioning with regard to bodily pain, physical-social functioning and vitality, and also functional limitations than the general population, which also persisted into the puerperal period [4].

Another important aspect related to QoL on which studies have focused in recent years is NVP in pregnancy, which is one of the most common medical conditions characterized by physiological changes, mainly present in the first trimester of pregnancy. In addition to deterioration in physical health, the mental and physical stress caused by nausea and vomiting can lead to depressive feelings and promote a significant negative influence on family, social and occupational functioning of pregnant women [8, 10]. In our study group, the scores of PCS and MCS of mild and moderate NVP groups were similar to or even slightly higher than the general Turkish female population, whereas the scores fell progressively with increasing severity of NVP and remained below the average of the general population in the moderate and severe NVP groups. Similar to our results, in their study Taşdemir *et al*. [25] found that all QoL scores of pregnant adolescents were significantly lower than pregnant adults and attributed these results to the incomplete physical and mental maturation of the adolescent pregnant women due to the early pregnancy. When subgroup scores were examined, pregnant women who had mild and moderate NVP had significantly higher levels of functioning with regard to physical functioning, role physical, bodily pain and general health, which compose the PCS component. A significant decrease in all scores was observed with increasing severity of NVP. It is possible that the physical changes occurring in pregnancy can alter the ability of pregnant women to perform their usual roles. Many studies have shown that physical functioning reduces during pregnancy [4, 26]. In their study, Haas *et al*. [5] found that the physical functioning mean score, which showed the highest decrease, was reduced from 95.2 before pregnancy to 58.1 during pregnancy. Similarly, in the study of Mckee *et al*. [27], results of the SF-36 showed the lowest perceived well-being in physical role

dimensions. In addition to the physical changes occuring during pregnancy, it is possible that the physical load caused by the symptoms of NVP itself also adversely affect life quality scores. In O'Brien and Naber's study [28], in which they aimed to investigate the magnitude of problems that NVP imposes on the lifestyle of pregnant women, all women with NVP reported changes in family, social and occupational functioning. They determined that the lifestyle limitations that NVP causes can have short- and long-term consequences for both the pregnant women and their families [28]. Many pregnant women complain about the difficulty of maintaining their usual life activities and their ability to work as a result of discomfort and weakness caused by NVP. In another study, approximately 50% of working women stated that their work efficiency was reduced because of NVP and as many as 25% required time off from work [29]. In our study, the number of living children was found to be another effective factor in the PCS. This finding also supports the importance of physical burden in the HRQoL of pregnant women.

In addition to its effect on physical QoL, NVP had an impact on mental QoL. A significant decrease in all subscores that compose the MCS (vitality, social function, role emotional, mental health) were observed with increasing severity of NVP. These findings show that the problem goes beyond physical symptoms. Consistent with our findings, an American study found that higher NVP scores contributed to lower QoL in the MCS component [8]. This finding was also replicated in another study done by Attard *et al*. [30], who reported that NVP affected each of the eight health domains and the two summary scales of SF-36. It is possible that the mental stress caused by NVP can lead to depressive feelings and promotes a significant negative influence on the family, social and occupational functioning for pregnant women who have NVP [8, 10]. In addition, adolescents may have fewer life experiences than adult women, making them less able to cope with the life changes they are going through related to pregnancy, which could be a factor enhancing their mental stress.

Another point to remember is that a significant decrease in the scores was observed with increasing severity of NVP, with the lowest scores in the severe NVP group and the highest scores in the group with no NVP in our study. The consensus of most studies in the literature is that more severe NVP is associated with poorer HRQoL and the degree of limitation is associated with the severity of symptoms, consistent with our findings [6-8, 30].

The Limitations of the Study

Our study has some limitations. As the nature of the study was cross-sectional, the observed relationships may not be causal. As we do not know the health status of women prior to pregnancy, it is hard to say that all the low scores of HRQoL were related to NVP. Since the Rhodes test is a self rating scale, judging the severity of NVP physical symptoms does not address well women's own perception of the severity of their condition. In order to assess the severity of NVP in the most accurate way, patients were asked to answer the questions after thorough consideration, with sufficient time allocated for them to do this. In our study median age of patients is 19. Thus our study may not be able to provide complete information for the early adolescence period [10-13]. Despite these limitations, our work broadens the understanding of health quality in adolescent pregnant women who have NVP. To our knowledge, this is the first study carried out with adolescent pregnant women in the literature. Larger prospective studies covering both the pre and ante-partum period are needed to clarify the effect of NVP on HRQoL in adolescent pregnants.

CONCLUSION

We demonstrated that both the presence and severity of NVP have a significant influence on QoL scores in pregnant adolescents. NVP affects both their physical health and psychosocial functioning so as to disrupt their general sense of well-being and day to day life activities. As adolescent pregnant women are already a group at risk, physical care, social and professional support should be provided to increase their QoL levels. Patients with serious NVP should be given psychological support and medical treatment.

Acknowledgements

We are grateful to all mothers for participating the study and sharing their time. We also thank to Melih Uzunoglu who did the statistical analysis of the study

and to P. LeMotte who did the English correction of the study.

Ethical approval

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

Informed consent was obtained from all individual participants included in the study.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] The WHOQOL Group. The World Health Organization Quality of Life Assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med 1995;41:1403-9.
[2] Calou CGP, Pinherio AKB, Castro RCMB, de Oliveira MF, de Souza Aquino P, Antezana F. Health related quality of life of pregnant women and associated factors: an integrative review. Health 2014;6:2375-87.
[3] Ramirez-Velez R. Pregnancy and health-related quality of life: A cross sectional study. Colombia Médica 2011;42:476-81.
[4] Otchet F, Carey MS, Adam L. General health and psychological symptom status in pregnancy and the puerperium: what is normal? Obstet Gynecol 1999;94:935-41.
[5] Haas JS, Jackson RA, Fuentes-Afflick E, Stewart AL, Dean ML, Brawarsky P, et al. Changes in the health status of women during and after pregnancy. J Gen Intern Med 2005;20:45-51.
[6] Smith C, Crowther C, Beilby J, Dandeaus J. The impact of nausea and vomiting on women: a burden of early pregnancy. Aust NZ J Obstet Gynaecol 2000;40:397-401.
[7] Lacasse A, Rey E, Ferreira E, Romero R, Goodwin TM. Nausea and vomiting of pregnancy: what about quality of life? BJOG. 2008;115:1484-93.
[8] Munch S, Korst LM, Hernandez GD, Romero R, Goodwin TM. Health-related quality of life in women with nausea and vomiting of pregnancy: the importance of psychosocial context. J Perinatol 2011;31:10-20.
[9] Verberg MF, Gillott DJ, Al-Fardan N, Grudzinskas JG. Hyperemesis gravidarum, a literature review. Hum Reprod Update 2005;11:527-39.
[10] Yilmaz E, Yilmaz Z, Cakmak B, Karsli MF, Gultekin IB, Guneri Dogan N, et al. Nausea and vomiting in early pregnancy of adolescents: relationship with depressive symptoms. J Pediatr Adolesc Gynecol 2016:29:65-8.
[11] O'Brien B, Naber S. Nausea and vomiting during pregnancy: effects on the quality of women's lives. Birth 1992;19:138-43.
[12] Veenendaal MV, Van Abeelen AF, Painter RC, Van der Post JA, Roseboom TJ. Consequences of hyperemesis gravidarum for offspring: a systematic review and meta-analysis. BJOG 2011;118:1302.
[13] McCarthy FP, Lutomski JE, Greene RA. Hyperemesis gravidarum: current perspectives. Int J Womens Health 2014;6:719-25.
[14] Rhodes V, Watson P, Johnson M. Development of reliable and valid measures of nausea and vomiting. Cancer Nurs 1984;7:33-41.
[15] Koren G, Magee L, Attard C, Kohli M, Atanackovic G, Bishai R, et al. A novel method for the evaluation of the severity of nausea and vomiting of pregnancy. Eur J Obstet Gynecol Reprod Biol 2001;94:31-6.
[16] Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
[17] Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 Healty Survey: Manual and Interpretation Guide. New England Medical Center, Boston: The Health Institute; 1993.
[18] Kocyigit H, Aydemir O, Fisek G. [Reliability and Validity of Turkish Version of Short Form-36]. İlaç ve Tedavi Dergisi 1999;12:102-6. [Article in Turkish]
[19] Demiral Y, Ergor G, Unal B, Semin S, Akvardar Y, Kivircik B, et al. Normative data and discriminative properties of short form 36 (SF-36) in Turkish urban population. BMC Public Health 2006;6:247.
[20] Lee NM, Saha S. Nausea and vomiting of pregnancy. Gastroenterol Clin North Am 2011;40:309-34.
[21] Chou FH, Avant KC, Kuo SH, Fetzer SJ. Relationships between nausea and vomiting, perceived stress, social support, pregnancy planning, and psychosocial adaptation in a sample of mothers: a questionnaire survey. Int J Nurs Stud 2008;45:1185-91.
[22] Louik C, Hernandez-Diaz S, Werler MM, Mitchell AA. Nausea and vomiting in pregnancy: maternal characteristics and risk factors. Paediatr Perinat Epidemiol 2006;20:270-8.
[23] Temming L, Franco A, Istwan N, Rhea D, Desch C, Stanziano G, et al. Adverse pregnancy outcomes in women with nausea and vomiting of pregnancy. J Matern Fetal Neonatal Med 2014;27:84-8.
[24] Kramer J, Bowen A, Stewart N, Muharajine N. Nausea and vomiting of pregnancy: prevalance, severity and relation to psychosocial health. MCN Am J Matern Child Nurs 2013;38:21-7.
[25] Taşdemir S, Balci E, Günay O. Comparison of life quality of pregnant adolescents with that of pregnant adults in Turkey. Ups J Med Sci 2010;15:275-81.
[26] Hueston WJ, Kasik-Miller S. Changes in functional health status during normal pregnancy. J Fam Pract 1998; 47:209-12.
[27] Mckee MD, Cunningnam M, Jankowski KR, Zayas L. Health related functional status in pregnancy: relationship to depression and social support in a multi ethnic population. J Obst Gynecol 2001;97:988-993.
[28] O'Brien B, Naber S. Nausea and vomiting during pregnancy: effects on the quality of women's lives. Birth 1992;19:138-43.
[29] Vellacott D, Cooke EJA, James CE. Nausea and vomiting in early pregnancy. Int J Gyn Obst 1988;27:57-62.
[30] Attard CL, Kohli MA, Coleman S, Bradley C, Hux M, Atanackovic G, et al. The burden of illness of severe nausea and vomiting of pregnancy in the United States. Am J Obstet Gynecol 2002;186(5 Suppl Understanding):S220-7.

The effect of Enterobius vermicularis infection (oxyuriasis) on eosinophil and IgE levels in allergic rhinitis

Fevzi Solmaz[1], Oğuzhan Dikici[1], Davut Akduman[2], Mehmet Haksever[1], İsmail Necati Hakyemez[3], Muhammed Yanılmaz[4]

[1]Department of Otorhinolaryngology, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey
[2]Department of Otorhinolaryngology, Düzce University School of Medicine, Düzce, Turkey
[3]Department of Infection Diseases, Bezmialem University School of Medicine, İstanbul, Turkey
[4]Department of Otorhinolaryngology, Bezmialem University School of Medicine, İstanbul, Turkey

DOI: 10.18621/eurj.344495

ABSTRACT

Objectives: Elevated levels of serum IgE and eosinophilia are the indicators of atopy and intestinal parasitic infections. We evaluated the effect of *Enterobius vermicularis* infection (enterobiasis) on blood eosinophil count and IgE levels in allergic rhinitis.

Methods: A total of 110 patients diagnosed with allergic rhinitis (with symptoms of rhinorrhea, itchy nose and nasal congestion) consisting of 41 (37.27%) males and 69 (62.73%) females were examined. Forty-one (37.27%) patients with enterobiasis were selected as the study group. The remaining 69 (62.73%) patients accepted as the control group.

Results: In the study group the mean serum total IgE level and mean serum eosinophil count were 393.10 ± 159.83 IU/mL and 0.56 ± 0.04 10^3/mL, respectively. In the control group the mean serum total IgE level and mean serum eosinophil count were 236.91 ± 63.55 IU/mL and 0.37 ± 0.12 10^3/mL, respectively. The difference between the two groups was statistically significant for serum total IgE levels ($p < 0.05$) but not for serum eosinophil count ($p > 0.05$). The correlation coefficients between serum total IgE level and eosinophil count were statistically insignificant ($p > 0.05$).

Conclusions: More comprehensive and long-term placebo-controlled studies should be performed in order to find the answer to the question of whether helminth infections play a role in allergic disease.

Keywords: *Enterobius vermicularis* infection, allergic rhinitis, serum IgE level, serum eosinophil count

Received: October 15, 2017; Accepted: December 17, 2017; Published Online: February 27, 2018

Elevated levels of serum IgE and eosinophilia are the indicators of atopy, but intestinal parasitic infections may also play role in alterations of those parameters [1]. In atopic individuals, the secretion of IgE increases depending on type 1 immune response. Human and animal studies have revealed a relationship between allergy and parasitic infections [2]. Elevated serum total IgE levels indicate either chronic parasitic infection or atopy.

Interactions between serum IgE levels, eosinophil count and parasitic infections depend on the duration of infestation and the type of helminth [3]. This is common in the population with endemic helminthic infections [4, 5]. It has been shown that persons with the highest total IgE levels are re-infected after the treatment of helminthic infections in endemic areas.

Address for correspondence: *Fevzi Solmaz, MD., University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Otorhinolaryngology, Emniyet Caddesi No:35, 16115 Yıldırım, Bursa, Turkey*
E-mail: solmazfevzi@hotmail.com, Phone: +90 224 2955000, Fax: +902243660416

e-ISSN: 2149-3189

Such elevated levels of total IgE may be due to environmental factors rather than heredity [6]. On the other hand, experimental and epidemiological studies have provided conflicting results. The phagocytic ability of eosinophils is weaker than that of neutrophils and their major functions are seen after the activation of toxic granule secretion. The main function of eosinophils in the host defense system against parasites is to attach, immobilize and kill parasites. The granular proteins secreted from the activated eosinophils kill parasites but they may cause damage to some mammalian cells. They can then lead to tissue damage and cause asthma or other inflammatory disorders. The most common inflammatory conditions, such as bronchial asthma, allergic eye inflammation, chronic fatigue syndrome, parasitic and bacterial infections, atopic dermatitis, rhinitis, allergic middle ear effusion and autoimmune diseases accompany to the eosinophil activation [7].

IgE is important both for active immunity in type I hypersensitivity reactions (such as asthma, urticaria, and high fever) and against parasites called helminths. A strong correlation is observed between allergy and increased serum IgE levels. The evaluation of serum IgE levels is therefore useful in conditions such as allergic rhinitis, extrinsic asthma, urticaria, atopic eczema, and anaphylaxis.

Eosinophils are leukocytes that eliminate antigen-antibody complexes and are capable of phagocytosis. The number of eosinophils increases in conditions such as allergy and parasitic disease. The granules of these leukocytes contain histamine at a rate of 33% in humans. The amount of IgE in mucosal secretions increases during helminthic infections and allergic diseases [7].

Enterobiasis (pinworm disease or threadworm) is caused by the small nematode *Enterobius vermicularis.* Prevalence rates up to 100% have been recorded in Northwestern Europe and the USA. It is probably the most common helminth to infect humans. *E. vermicularis* eggs have been displayed in a coprolite carbon dated to 7837 BC in western Utah [8].

Routine examination of a fecal sample gives a positive diagnosis in only 5-15% of infected subjects [8]. The best way of diagnosis depends on identification of adult worms or eggs, or both - which can be visualized in perianal region, usually at night [9, 10]. Application of a Sellotape strip to the perianal region is of value; when adherent (sticky side downwards) to a microscope slide, visualization of worms and eggs is straightforward (the debris is cleared with a drop of toluene). Three tests can detect 90% of infections while six consecutive negative results on separate days virtually exclude this diagnosis.

The aim of this study was to determine the effect of *E. vermicularis* infection (enterobiasis) on blood eosinophil count and IgE levels in allergic rhinitis, and to discuss the role of helminths in allergic rhinitis. We compared patients diagnosed with allergic rhinitis who were positive or negative for enterobiasis regarding IgE levels and eosinophil counts.

METHODS

Patients who presented to the Ear, Nose and Throat Clinic and diagnosed with Allergic Rhinitis were evaluated. Informed consent was received from all patients. The Ethical Committee Approval was received from the study center. The diagnosis of allergic rhinitis was established by patient's history, a positive prick test and elevated serum IgE levels (higher than 100 U/mL). Patients diagnosed with both allergic rhinitis and enterobiasis was included in the study group. The diagnosis of enterobiasis was confirmed by 3 consecutive anal cellotape microscopy evaluations while 6 consecutive negative results were required to rule out enterobiasis. Feces microscopy was used to rule out other parasites and patients whose feces were positive for parasite eggs other than *E. vermicularis* were excluded.

After informed consent was received from the patients, a clinical history was taken and a physical examination including nasopharyngeal examination performed. A total of 110 patients diagnosed with allergic rhinitis (with symptoms of rhinorrhea, itchy nose and nasal congestion) consisting of 41 (37.27%) males and 69 (62.73%) females were included in the study. The 41 (37.27%) patients with positive result for *E. vermicularis* eggs were selected as the study group. The remaining 69 (62.73%) patients evaluated as the control group. Factors affecting allergy or atopy were ruled out with questions. We were unable to include a healthy control group and our control group consisted of the subjects with allergic rhinitis in whom

Table 1. The demographic characteristics and laboratory findings of the patients.

	With *E. vermicularis* (n = 41)	Without *E. vermicularis* (n = 69)	*p*
Age (year)	34.25 ± 10.58	34.94 ± 10.84	> 0.05
Gender (M/F)	13/28	28/41	> 0.05
IgE (IU/mL)	393.10 ± 159.83	236.91 ± 63.55	< 0.05
Eosinophil count (10^3/mL)	0.56 ± 0.04	0.37 ± 0.12	> 0.05

Data are shown as mean±standard deviation or number

E. vermicularis eggs were not found on microscopy.

Patients who had used oral antibiotics or corticosteroids and inhaled corticosteroids within the prior 30 days were excluded from the study. A detailed history was taken and an examination was performed and the patients were referred for blood and stool samples.

The samples were evaluated for *E. vermicularis* eggs with a light microscope at a magnification of 10× and 40× by an infectious diseases specialist. Eosinophil levels above 0.5 103/ml in the complete blood count were considered as positive or elevated. The association of total serum IgE levels and eosinophil count with the presence of *E. vermicularis* infections or allergic rhinitis was investigated.

Single-dose mebendazole treatment with a repeated dose a week later used for treatment. The pre-treatment results were also compared with the post-treatment results.

The relationship between total serum IgE and eosinophil count was analyzed using Pearson's Correlation and Spearman's rank tests due to the non-normal distribution of the variables. These analyses can potentially create a basis for treatment. All data were analyzed using the SPSS for Windows v.16.0 software by IBM, USA.

Statistical Analysis

The relationship between total serum IgE and eosinophil count was analyzed using Pearson's Correlation and Spearman's rank tests due to the non-normal distribution of the variables. These analyses can potentially create a basis for treatment. All data were analyzed using the SPSS for Windows v.16.0 software by IBM, USA.

RESULTS

The 110 patients included in the study consisted of 41 (37.27%) males and 69 (62.73%) females. The average age was 32.50 ± 7.42 years. The blood serum IgE levels were 138.00 to 850.00 IU/mL (282.69 ± 129.93 IU/mL). Our patients were selected from subjects with allergic rhinitis and elevated serum IgE levels. Table 1 presents the total IgE level, eosinophil count, and gender and age values of the allergic rhinitis patients. The mean serum total IgE level and mean serum eosinophil count for the 41 patients who were positive for *E. vermicularis* eggs and 69 patients in the control group were also presented in Table 1. The difference between two groups was statistically significant for serum total IgE levels ($p < 0.05$), but not for serum eosinophil count ($p > 0.05$). Table 2 presents the pre- and post-treatment serum eosinophil counts and total serum IgE levels of patients with helminth infections and allergic rhinitis. The difference between the groups was statistically significant for serum total IgE level ($p < 0.05$) but not for serum eosinophil count ($p > 0.05$).

Eggs of *E. vermicularis* were found in 41 (37.27%) patients with the sellotape evaluation repeated 3 times. The correlation coefficients between serum total IgE level and eosinophil count are shown in Tables 3 and 4 and the results were statistically insignificant ($p > 0.05$).

Table 2. Pre- and post-treatment IgE level and eosinophil count.

	Pre-treatment (with *E. vermicularis*)	Post-treatment (with *E. vermicularis*)	*p*
IgE (IU/mL)	393.10 ± 159.83	228.90 ± 84.40	< 0.05
Eosinophil (10^3/mL)	0.56 ± 0.04	0.43 ± 0.07	> 0.05

Data are shown as mean±standard deviation

Table 3. Pearson correlation of IgE level and eosinophil count.

		IgE (n = 41)	Eosinophil (n = 41)
IgE level	Pearson Correlation	1.000	0.162
	Sig. (2-tailed)		0.311
Eosinophil count	Pearson Correlation	0.162	1.000
	Sig. (2-tailed)	0.311	

Table 4. Spearman rank test analysis of IgE level and eosinophil count.

		IgE (n = 41)	Eosinophil (n = 41)
IgE level	Correlation Coefficient	1.000	0.211
	Sig. (2-tailed)		0.186
Eosinophil count	Correlation Coefficient	0.211	1.000
	Sig. (2-tailed)	0.186	

DISCUSSION

Increased serum IgE level and eosinophilia are not specific to the allergic diseases. They are also associated with helminth infections [11, 12]. Nowadays, total serum IgE level is a poor indicator of allergic respiratory diseases. High serum IgE levels resulting from polyclonal activation are caused by chronic infection by geohelmints [13, 14]. Features of helminthic infections are complex in the endemic areas and the immune system response may show individual differences in atopic subjects. Thus, the serum IgE levels may also increase in atopic persons [15].

Geohelmints may also stimulate the release of polyclonal IgE [16]. The helminths, not only increase the production of antiparasite IgE antibody, but also stimulate polyclonal IgE synthesis, resulting in highly elevated levels of total IgE in the blood circulation [17]. Although there is some doubt regarding the relationship between helminthic infections and IgE antibody levels, IgE antibody is an important component of the immune response against parasites [18].

Although helminthic infections are less common in developed countries, atopic diseases are paradoxically more common. Exposure to infections in early childhood decreases the risk of allergy according to the "Hygiene Hypothesis" [19]. Intestinal helminths may decrease polyclonal IgE production in populations with parasitic infection according to this hypothesis [20]. In contrast to the hygiene hypothesis, serum IgE levels of patients with allergic rhinitis only were lower than that of patients with both allergic rhinitis and *E. vermicularis* infection in our study. However, this may be associated with the duration and severity of these disorders in our patients. Some studies have shown no association between helminth infections and allergic diseases [21]. However, it is reported that parasitic helminths can prevent hyperresponsiveness and eosinophilic airway inflammation in experimental animal models [22, 23]. In our study we investigated patients with E. vermicularis only and it may be appropriate to study the effects of other parasitic infections as well.

Eosinophils are located in two different regions: tissue and blood. Although the maturation and life of serum eosinophils depend on interleukin-5 (IL-5), the tissue eosinophils depend on granulocyte and macrophage colony stimulating factor (GM-CSF) [24]. Eosinophil count is therefore normal in the blood, but active eosinophils are filled by eosinophil cationic protein, major basic protein, active granules, and other mediators [24, 25]. The eosinophil levels are normal in some patients since blood eosinophils are down-regulated. The peripheral circulation may not be affected and the inflammatory process may be mild with drug intake and in chronic intestinal parasitic infections [26].

A meta-analysis of the epidemiologic literature by Feary *et al*. [27] has shown that intestinal parasite infections such as geohelminth infections are related to a reduced prevalence of allergic sensitization. The levels of serum total IgE and eosinophils of allergic rhinitis patients with *E. vermicularis* infection were higher than in patients with allergic rhinitis only in our

study, possibly depending on the duration of E. vermicularis infection.

When the intestinal larvae migrate, the eosinophil numbers may decline consequently. Eotaxin is required for chemotaxis [28]. Chronic parasitic infections regulate the immune response and the allergic response is reduced especially in early life. Genetic predisposition to atopy may also provide strong resistance to geohelminth infections. It has been demonstrated that geohelmints may increase the production of specific antibodies [13]. However, the increase in nonspecific polyclonal IgE synthesis and high total IgE levels are directly related to the presence of parasites [14].

The sensitivity of stool examination can be as low as 40% in some cases. When using the stool examination to evaluate parasite infection, one needs to take into account recurrent anti-helminthic treatment and the small amounts of parasite or the larval forms of the parasite [20]. Nyan *et al*. [20] found higher serum total IgE concentration in atopic patients than in non-atopic persons. They suggested that atopic individuals are less infected with helminths than non-atopic persons and that atopy could therefore be a protective factor against helminthic infections. High concentrations of non-specific IgE may prevent the invasion of intestinal parasites. They did not find any relationship between serum IgE concentration and helminth infections.

Since the immune response against parasite infections is variable, mild helminth infections may increase the allergic response in contrast to severe infections [29, 30]. Eosinophilia and elevated serum IgE are often observed in acute illness as a form of immune response [26]. High serum IgE levels may also trigger eosinophilia.

The helminths can induce suppressor T cells and lead to a low response against environmental allergens. Interleukin-10 (IL-10) reduces the number of serum eosinophils and also produces transforming growth factor beta (TGF-B) [26]. Production of polyclonal IgE against helminths is a common characteristic in atopic individuals [30]. The host immune response against intestinal helminths is similar to the allergic response. An IgE response is associated with the helminths in children with an atopic predisposition. Helminths and other infectious agents also increase serum IgE levels by increasing the production of non-specific B cells. Wördemann *et al*. [19] have reported that various relationships are present between helminthic infections and atopic diseases depending on the type of helminth and the allergy.

Lynch *et al*. [5] reported that a history of a strong IgE response in atopic children led to an increased protective response against helminths. The infection intensity was significantly lower compared to non-atopic subjects in that study.

The impact of helminths on allergic reactions is occurred in two ways. Nonspecific IgE synthesis may occur in patients with sporadic helminthic infections as a result of stimulation of the immune system and it may increase the allergic sensitivity in these individuals. Mast cell receptors can also be blocked due to excessive polyclonal IgE development in recurrent infections leading to the inhibition of specific IgE production against allergens [30]. Geller *et al*. [31] found no difference in serum IgE levels between the patient group and control group. Arıdoğan *et al*. [32] detected an elevated total IgE rate of 73.77% in the group infested with helminths and 35.14% in the group without helminths. Herrström *et al*. [33] found *E. vermicularis* in the 23 of 102 nonallergic control subjects and 26 of 70 allergic patients and the difference was statistically significant ($p = 0.037$).

Ganguly *et al*. [34] reported that total and specific IgE levels increased in hookworm-infected patients and then decreased significantly after treatment. In the present study, consistent with the literature, a significant decrease in the serum IgE level after treatment was observed. There was also a decrease in serum eosinophil levels but this was not statistically significant. The results reported in the literature lead to questions about the relationship between parasite infection and allergy. Long-term studies need to be conducted to clearly investigate the causal relationship between helminthic infections and atopic diseases

CONCLUSION

More comprehensive and long-term placebo-controlled studies should be performed in order to find the answer to the question of whether helminth infections play a role in allergic disease.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] Medeiros D, Silva AR, Rizzo JA, Motta ME, Oliveira FH, Sarinho ES. Total IgE level in respiratory allergy: study of patients at high risk for helminthic infection. J Pediatr 2006;82:255-9.
[2] Reddy A, Fried B. Atopic disorders and parasitic infections. Adv Parasitol 2008;66:149-91.
[3] Rîpă C, Bahnea RG, Cojocaru I, Luca MC, Ivan A, Luca M. Atopic diseases and intestinal helminth infections. Rev Med Chir Soc Med Nat Iasi 2010;114:1017-21.
[4] Lynch NR, López R, Istfiriz G, Tenías-Salazar E. Allergic reactivity and helminthic infection in amerindians of the amazon basin. Int Arch Allergy Appl Immunol 1983;72:369-72.
[5] Lynch NR, Medouze L, Di Prisco MC, Verde O, López R, Malavé C. Incidence of atopic disease in a tropical environment: partial independence from intestinal helminthiasis. J Allergy Clin Immunol 1984;73:229-33.
[6] Levin ME, Le Souëf PN, Motala C. Total IgE in urban Black South African teenagers: the influence of atopy and helminth infection. Pediatr Allergy Immunol 2008;19:449-54.
[7] Wardlaw AJ. Eosinophils in 1990s: new perspectives on their role in health and disease. Postgrad Med 1994;70:536-52.
[8] Cook GC. Enterobius vermicularis infection. Gut 1994;35:1159-62.
[9] Hood C. Enterobius vermicularis. Practitioner 1989; 233:503.
[10] Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al; World Health Organization, GA(2)LEN and AllerGen. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 uptade(in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63(suppl 86):8-160.
[11] Arruda LK, Santos AB. Immunologic responses to common antigens in helminthic infections and allergic disease. Curr Opin Allergy Clin Immunol 2005;5:399-402.
[12] Schneider M, Hilgers RH, Sennekamp J. Allergy, total IgE and eosinophils in East and West. Serious effects of different degrees of helminthiasis and smoking. Eur J Med Res 2002;21:63-71.
[13] Cooper PJ, Chico ME, Rodrigues LC, Ordonez M, Strachan D, Griffin GE, et al: Reduced risk of atopy among school-age children infected with geohelminth parasites in a rural area of the tropics. J Allergy Clin Immunol 2003; 111:995-1000.
[14] Sales VS, Rodrigues CE, Cavalcanti GB, Trombone APF, Lima RC, Santos ABR, et al. Infection with Ascaris lumbricoides in preschool children: role in wheezing and IgE responses to inhalant allergens. J Allergy Clin Immunol 2002;109:S27.
[15] Bell RG. IgE, allergies and helminth parasites: a new perspective on an old conundrum. Immunol Cell Biol 1996;74:337-45.
[16] Scrivner S, Yemaneberhan H, Zebenigus M, Tilahun D, Girma S, Ali S, et al. Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case-control study. Lancet 2001;358:1493-9.
[17] Lynch NR, Hagel IA, Palenque ME, Di Prisco MC, Escudero JE, Corao LA, et al. Relationship between helminthic infection and IgE response in atopic and nonatopic children in a tropical environment. J Allergy Clin Immunol 1998;101:217-21.
[18] Allen JE, Maizels RM. Immunology of human helminth infection. Int Arch Allergy Immunol 1996;109:3-10.
[19] Wördemann M, Diaz RJ, Heredia LM, Collado Madurga AM, Ruiz Espinosa A, Prado RC, et al. Association of atopy, asthma, allergic rhinoconjunctivitis, atopic dermatitis and intestinal helminth infections in Cuban children. Trop Med Int Health 2008;13:180-6.
[20] Nyan OA, Walraven GE, Banya WA, Milligan P, Van Der Sande M, Ceesay SM, et al. Atopy, intestinal helminth infection and total serum IgE in rural and urban adult Gambian communities. Clin Exp Allergy 2001;31:1672-8.
[21] Lynch NR, Hagel I, Perez M, Di Prisco MC, Lopez R, Alvarez N. Effect of anthelmintic treatment on the allergic reactivity of children in a tropical slum. J Allergy Clin Immunol 1993;92:404-11.
[22] Smits HH, Hammad H, van NM, Soullie T, Willart MA, Lievers E, et al: Protective effect of Schistosoma mansoni infection on allergic airway inflammation depends on the intensity and chronicity of infection. J Allergy Clin Immunol 2007;120:932-40.
[23] Amu S, Saunders SP, Kronenberg M, Mangan NE, Atzberger A, Fallon PG: Regulatory B cells prevent and reverse allergic airway inflammation via FoxP3-positive T regulatory cells in a murine model. J Allergy Clin Immunol 2010;125:1114-24.
[24] Alan R. Busse WW. The eosinophil, quo vadis? J Allergy Clin Immunol 2004;113:38-42.
[25] Martin LB, Kita H, Eiferman K, Gleich GJ. Eosinophils in allergy: role in disease, degranulation, and cytokines. Int Arch Allergy Immunol 1996;109:207-15.
[26] Klion AD, Nutman TB. The role of eosinophil in host defense against helminth parasites. J Allergy Clin Immunol 2004;113:30-7.
[27] Feary J, Britton J, Leonardi-Bee J. Atopy and current intestinal parasite infection: a systematic review and meta-analysis. Allergy 2011;66:569-78.
[28] Lima C, Perini A, Garcia ML, Martins MA, Teixeira MM, Macedo MS. Eosinophilic inflammation and airway hyper-responsiveness are profoundly inhibited by a helminth (Ascaris suum) extract in a murine model of asthma. Clin Exp Allergy 2002;32:1659-66.
[29] Lynch NR, Hagel I, Vargas V, Pérez M, López RI, Garcia NM, et al. Effect of age and helminthic infection on IgE levels in slum children. J Invest Allergol Clin Immunol 1993;3:96-9.
[30] Hagel I, Lynch N, Pérez M, Di Prisco MC, López R, Rojas E. Modulation of the allergic reactivity of slum children by helminthic infection. Parasite Immunol 1993;15:311-5.
[31] Geller M, Geller M, Flaherty DK, Black P, Madruga M. Serum IgE levels in giardiasis. Clin Allergy 1978;8: 69-71.
[32] Arıdoğan BC, Demirci M. Çocuklarda bağırsak parazitleri ve serum total IgE düzeyleri arasındaki ilişkinin incelenmesi. T Parazitol Derg 2001;25:346-8.
[33] Herrström P, Henricson KA, Råberg A, Karlsson A, Högstedt B. Allergic disease and the infestation of Enterobius vermicularis in Swedish children 4-10 years of age. J Investig Allergol Clin Immunol 2001;11:157-60.
[34] Ganguly NK, Mahajan RC, Sehgal R, Shetty P, Dilawari JB. Role of specific immunglobulin E to excretory-secretory antigen in diagnosis and prognosis of hookworm infection. J Clin Microbiol 1988;26:739-42.

The European Research Journal 2018;4(4):405-410 REVIEW

Hip disorders in cerebral palsy patients: diagnostic and therapeutic approaches

Bülent Karslıoğlu, Ali Çağrı Tekin, Ersin Taşatan, Fatih Mehmet Erkin

Department of Orthopaedics and Traumatology, Okmeydanı Training and Research Hospital, İstanbul, Turkey

DOI: 10.18621/eurj.350577

ABSTRACT

Cerebral palsy (CP) is a neurological disorder of central nervous system that can result with devastating outcomes. Besides all other clinical findings, hip disorders also are common in children with CP. Clinical hip manifestations include wide spectrum from hip subluxation or dislocation to dislocation with painful degeneration. If untreated they may progress to more serious level like painful hip, severe hip contractures or windswept deformity and cause hygiene problems. We aimed to present current and widely accepted information about diagnostic and therapeutic approaches of hip disordes in the patients with CP.

Keywords: Cerebral palsy, hip, disorder, children, surgery

Received: November 10, 2017; Accepted: March 21, 2018; Published Online: March 26, 2018

Cerebral palsy (CP) is a neurological disorder of central nervous system that can result with devastating outcomes. This situation is a static, non-progressive encephalopathy but associated musculoskeletal pathology is usually progressive. Besides all other clinical findings, hip disorders also are common in children with CP. Hip disorders are second most common clinical manifestation after equinus foot deformity [1]. Hip displacement incidence varies from 1% in the patients with spastic hemiplegia to 75% in the patients with spastic quadriplegia [2].

Clinical hip manifestations include wide spectrum from hip subluxation or dislocation to dislocation with painful degeneration [3]. Pathomechanism of spastic hip dysplasia in CP differs from developmental dysplasia of the hip (DDH). Unlike DDH, children with CP have normal hip at birth and up to age of 18 months, hip problems occur due to muscle imbalance and are progressive. If untreated they may progress to more serious level like painful hip, severe hip contractures or windswept deformity and cause hygiene problems.

At this review, we aimed to present current and widely accepted information about diagnostic and therapeutic approaches of hip disordes in the patients with CP.

Epidemiology, Pathophysiology and Natural History

CP is an important cause of childhood physical disability and its prevalence ranges from 1.5 to 2.5 children per 1000 live births in developed countries [4]. Most common deformity seen in children with CP is equinus deformity. Hip disorders are second most seen clinical disorders. Children have significant hip subluxation by the age of 5 years. Disability to rise to standing position by 3 years age correlates with hip subluxation [5]. Progressive hip dislocation or subluxation risk for children with CP is 3-47%.

Address for correspondence: *Bülent Karslıoğlu, MD., Okmeydanı Training and Research Hospital, Department of Orthopaedics and Traumatology, Kaptan Paşa Mahallesi, Darülaceze Cad. No:27, 34384 Okmeydanı-Şişli, İstanbul, Turkey*
E-mail: bukars@gmail.com

e-ISSN: 2149-3189

Subluxation or dislocation occurs often posteriorly. Anterior dislocations are small portions as 1.5% of patients [3].

Classification systems are necessary for the communication between physicians, to assess development or improvement with time or treatment. The Gross Motor Function Classification System (GMFCS) is common classification system used for assessing child's movement ability based on their self-initiated movement with emphasis on sitting, walking, and wheeled mobility. System consists of 5 levels ranging from Level 1, children with minimal or no disability and Level 5, children with totally dependent an external assistance. Within each of the five levels, descriptions of motor function are given for several age bands in the following ranges: before age 2, 2 to 4 years, 4 to 6 years, 6 to 12 years, and 12 to 18 years (12 to 18 years assessments in GMFCS Expanded and Revised) [6].

Painless and stable hip is needed for walking as well as sitting. Severity of hip spasticity determines the prevalence of hip subluxation or dislocation. Spastic quadriplegic children who are unable to walk have highest prevalence of hip dislocation [7]. Spastic hemiplegic children, who are largest proportion of CP patients, usually have few hip problems but more problems at the distal part of lower extremity. Spastic diplegic patients have usually hip problems at later ages . They can walk but gait quality may be affected by hip problems [8].

Primary cause for dislocation or subluxation is spasticity and muscle imbalance. Hip problems occur because of vicious circle. Spasticity causes contractures, contractures cause dislocation or subluxation and this situation aggravates spasticity. At least bony deformities occur and clinical cycle is so completed.

Diagnosis

Physical Examination

Hip is stable at birth but years later dislocation occurs in CP patients. Although hip is unstable at DDH, dislocation occurs at prenatal or perinatal period. Hip joint is normal at birth but spastic muscle imbalance and lack of weight bearing leads hip problems and so CP becomes obvious by the age of 6-9 months. Excessive femoral anteversion, posterolateral acetabular dysplasia, and flexion-adduction contractures are responsible for hip problems [9]. Physician may observe preferential use of limb and asymmetry or gross motor developmental delay [10]. Goals of physical examination in CP patients should be to determine grades of muscle strength, to evaluate muscle tone and determine the clinical type, to evaluate degree of deformity or contracture of each joint and finally to evaluate balance and phase of walking.

Physical examination consists of neurological examination, orthopedic examination and functional examination. Hip examination is an important part of orthopedic examination. Hip abduction, adduction, flexion and extension should be evaluated separately in a detailed way. Adduction contracture is most common hip deformity in CP patients. This hip problem cause hip subluxation, scissoring of the legs and perineal hygiene problems. Second most common hip deformities in CP patients are flexion contractures that bring the body's center of gravity anteriorly and so results with increased lomber lordosis, knee flexion and ankle dorsiflexion [10]. Flexion contractures occur due to increased spasticity in the flexor muscle groups in the early period.

Hip flexion contracture can be determined with Thomas, Ely and Staheli tests. Thomas test is applied by flexing both hips while patient is supine position. One leg stays in flexion and the other leg is brought to extension and adduction. The angle between examination table and extended hip is measured. This angle represents hip flexion contracture.

Ely test is applied at prone position. One hip is stabilized manually and ipsilateral leg moved into flexion position by bending the knee. If the hip elevates from examination table that means quadriceps muscle is spastic or strained.

While applying Staheli test children's body and pelvis stays on the examination table meanwhile legs hang down from the table at prone position. If hips can't be brought to fully extended position one by one, angle between thigh and ground represents amount of flexion contracture.

Leg-length discrepancy (LLD) because of hip disorder is a common problem in CP patients. Coexistence of LLD and impaired motor control cause

gait pattern disturbance. Special hip disorder patterns can cause LLD. Windswept hip is a situation at which one hip at adduction deformity and the other hip at abduction deformity. This special case comes out because of asymmetric activity of the adductors, abductors, internal and external rotator muscle. The child with windswept hip has pseudo-Galeazzi sign because of adduction contracture that causes LLD [11].

Radiologic Evaluation

Early detection of hip displacement is important for early treatment but diagnose with only clinical examination is so difficult. There is a hypotonic phase before pathologic forces begun [3]. Physicians must not miss out this period. For that reason, it is recommended that 6 monthly clinical examinations should be combined with radiological screenings until hip migration is stable between ages 2 and 6 years when hip subluxation typically begins. Faraj *et al*. [12] showed that if hip subluxates, there is a risk of a 10% increase in the migration percentage per year because of increasing adductor muscle contracture. AP Pelvis (serial), false profile view (Faux Profile) and abduction views are sufficient for evaluating hip disorders [13].

Choice of radiological measurement depends on pathology of the disease and age of patient. Migration percentage or migration index, Wibergs's lateral center-edge (LCE) angle and Lequesne's acetabular index are most commonly used measurement parameters in children with CP prior to fusion of the triradiate cartilage.

Migration percentage is the percentage of the femoral head that lies outside of the lateral borders of acetabulum. In 1980 Reimer advocated that this measurement entitled as Reimer's index, is more reliable than the LCE angle to document the extent of lateral hip subluxation [12]. First, Hilgenreiner and Perkins lines are drawn. Femoral head outside the Perkins line called as "a" and total width of femoral head called as "b". A divided by b and multiplied by 100. Migration percentage is commonly used in the management of hip disorders in CP patients. It's also used for monitoring the effect of treatments on the progression of hip subluxation such selective dorsal rhizotomy, hip abduction bracing and soft tissue surgeries. Rate of migration greater than 7% supposed to be a risk factor for progressive hip disorder [14]. Position of child's hip and pelvis especially pelvicrotations may affect the measurement results. Studies on healthy children showed a wide spectrum that can be considered as normal [14]. Upper limit of migration percentage considered as normal is 25% at 4 years age [3]. Also because of wide measurement spectrum between inter and intra measurer with repeated measurements, migration percentage has low reliability and repeatability. Measurement error for migration percentage is ± 10% [12].

Other radiologic measurements for evaluate the lateral coverage of femoral head are Wibergs's LCE and Lequesne's acetabular index in otherwise Tönnis angle. LCE angle is formed by the vertical line through the center of femoral head and the line from center of femoral head to the lateral sourcil. Acetabular index is formed by the line perpendicular to the horizontal axis of pelvis that passing through most medial of the sourcil and the line tangent to sourcil's most lateral tip. High acetabular index is the most powerful predictor for screening hip dislocation [3]. Below 20^0 for LCE and above 12^0 for acetabular index is pathological [15].

There are also lateral center-edge angle (Lequesne's) and acetabular angle. Lateral center-edge angle is used for measuring anterior hip dysplasia and acetabular angle is used for detecting acetabular inclination. They are not commonly used as the measurements mentioned above.

Although at present, X-ray measurements are the most reliable indicator of hip status, there are still some limitations in the usefulness of them because of patient's position depended nature and data we get is two-dimensional information about thethree-dimensional body. Contralateral hip and knee should be maximal flexed to eliminate lomber lordosis to evaluate acetabulum accurately.

Additional imaging studies such as bomputed tomography (CT) and ultrasound may be used to get more information about pathologic hip. Three-dimensional (3D) reconstruction CT gives true information about femoral head deformities and acetabular deficiencies. Hip subluxation or dislocations especially anterior dislocations, may easily be evaluated by the help of CT. Because at

anterior dislocations observer may not detect migration percentage changes since at this cases hips don't dislocate laterally [3].

Treatment

Non-surgical Treatments

Early detection of hip disorders with clinical and radiological screening and set out early conservative treatment to prevent or to slow the progression of dysplasia, to improve walking ability and to provide stable sitting should be main objectives for treatment. Physical therapy is useful for children with CP in the terms of facilitate motor development, enhance their independence in motor skills, self-care, play and leisure activities [16]. Rehabilitation of a child with CP demands a multidisciplinary approach with a team that includes: pediatrician, a pediatric neurologist, an orthopedic surgeon, a physician, an occupational therapist, a pediatric physiotherapist, a child psychologist, and a social worker [17].

Many forms of physical therapy for CP suggested so far such as neurodevelopmental therapy, strength training, conductive education, passive stretching, hydrotherapy, hippotherapy, postural control or orthotic devices [18]. Although there is no evidence showing that physical therapy prevents hip subluxation alone, physical therapy may slow down subluxation. Adductor spasticity is considered as reason for hip subluxation. The purpose of physical therapy must be releasing the adductor spasticity.

Botulinum toxin A (BTX-A) also may be a part of non-surgical treatments. Injections of BTX-A reduce spasticity in the hip adductor muscles for 4 to 6 months and so increase hip range of movements. BTX-A reduces muscular hyperactivity by reversibly blocking acetylcholine release at neuromuscular junction. A study based on changes at dynamic component of muscle tone by using the data's of knee-knee distance and Ashworth scale showed a significant improvement at 4 and 12 weeks after BTX-A injection and so prevented hip migration [19]. Combined usage of BTX-A and abduction brace investigated in a study and results showed that combination reduce surgery requirement at patients with CP. Although rate of displacement was lower in combination group, displacement continued at both groups [20]. Main disadvantage of BTX-A usage is its transient effect so that it can't be permanent treatment.

Surgical Treatments

Surgeries for CP patients are categorized as preventative (adductor release), reconstructive (femoral osteotomies) and salvage surgeries. First steps at treatment should be basic ones as muscle interventions. In young non-ambulatory CP patients with adduction contracture, intramuscular tenotomy of adductor longus and myotomy of gracilis muscle may avoid hip subluxation. This surgical decision is based on the theory of muscle imbalance around the hip joint, with weak abductors and extensors but relatively strong adductors and flexors.

If there is a fixed hip flexion contracture, psoas tenotomy or psoas lengthening must be added to surgical intervention. There is a controversy about the efficiency of complete psoas tenotomy at lesser trochanter level and lengthening in an intramuscular location at pelvic brim but tenotomy at the lesser trochanter level causes more robust improvement at hip extension in ambulatory CP patients according to last studies [21]. Besides if hamstring lengthening is planned for knee flexion contracture, psoas tenotomy also must be done because crouch gait pattern occurs secondary to hip flexion. This mixed surgical intervention skein leads to a new modality: multilevel surgery which means all the contractures of the lower extremity joints must be corrected simultaneously. Nowadays, multilevel orthopedic surgery in the treatment of children with CP has become standard treatment modality at most of institutes [22].

Although preoperative level of migration (< 33% is optimal), GMCSF level and patient's age (before 4 ages) are important factors that influence success rate of soft tissue surgery, radiologic hip subluxation improves in approximately 33% of patient with CP after soft tissue surgeries [23]. For that reason, patients may require bony surgeries such as femoral varus-derotational osteotomy or pelvic osteotomies several years after soft tissue surgery.

Hip reconstruction is indicated for 4 years of age or older CP patients with > 60% migration index but who have not yet started degenerative changes of the femoral head. A study showed that loss of correction of the neck-head angle occurs in 96% of the children operated less than 4-years-old [24]. Also, bony interventions may be suitable for patients younger than

8 years of age with previous failed soft tissue surgery result and older than 8 years of age with an migration index >40% but no signs of degenerative changings at femoral head [3].

Bony procedures usually are used for to correct abnormal femoral anteversion, neck-shaft angle and the acetabular deformity. These procedures include femoral and acetabular osteotomies. Varisation-derotation osteotomy (VDRO) of the femur is used to treat internal rotation gait in CP patients. Soft tissue lengthening is done to achieve at least 450 hip abduction otherwise VDRO surgery results with adduction contracture. Shortening the femur for easy reduction of the femoral head and derotating to gain physiological anteversion is main subject of VDRO surgery. Femoral osteotomy is made for to gain approximately 115-120^0 neck-shaft angle and 15-20^0 anteversion for an anatomically normal gait. Stable fixation of femoral osteotomy is an important factor for immediate mobilization and therapy.

The acetabulum should also be redesigned for an anatomical gait unless triradiate cartilage is closed. Migration percentage is key point for acetabular correction decision. Acetabular osteotomy should be performed when the migration percentage is over 50-70% [25]. Pelvic osteotomies like Degaacetabuloplasty remodel the acetabulum and hip load center. Combined application of femoral osteotomy and acetabular osteotomy as one-stage procedure for hip dislocation-subluxation at cerebral palsy patient is preferable and their results are far better than femoral osteotomy alone [26].

Palliative procedures like resection arthroplasty (Castle procedure), valgus osteotomy of the femur, total hip replacement and hip arthrodesis are used for non-ambulatory patients when other methods are ineffective for decreasing hip pain due to articular cartilage loss, gaining stable sitting comfort and poor perineal hygiene in the presence of there are no other options. There are still controversies about the indications of these procedures. It is a hard and complicated decision because there is no way to get back.

CONCLUSION

It is hard to deal with hip disorders in cerebral palsy patients. The aim is to gain a stable, painless hip that allows perineal hygiene and comfortable sitting. There are lots of choices but the best choice is the choice the fits the best to the patients GMFCS situation.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] Cornell MS. The hip in cerebral palsy. Dev Med Child Neurol 1995;37:3-18.
[2] Dobson F, Boyd RN, Parrott J, Nattrass GR, Graham HK. Hip surveillance in children with cerebral palsy. Impact on the surgical management of spastic hip disease. J Bone Joint Surg Br 2002;84:720-6.
[3] Flynn JM, Miller F. Management of hip disorders in patients with cerebral palsy. J Am Acad Orthop Surg 2002;10:198-209.
[4] Portinaro N, Panou A, Gagliano N, Pelillo F. D.D.S.H.: developmental dysplasia of the spastic hip: strategies of management in cerebral palsy. A new suggestive algorithm. Hip Int 2009;19 Suppl 6:S69-74.
[5] Scrutton D, Baird G. Surveillance measures of the hips of children with bilateral cerebral palsy. Arch Dis Child 1997;76:381-4.
[6] Rosenbaum PL, Walter SD, Hanna SE, Palisano RJ, Russell DJ, Raina P, et al. Prognosis for gross motor function in cerebral palsy: creation of motor development curves. JAMA 2002;288:1357-63.
[7] Howard CB, McKibbin B, Williams LA, Mackie I. Factors affecting the incidence of hip dislocation in cerebral palsy. J Bone Joint Surg Br 1985;67:530-2.
[8] Hoffer MM. Management of the hip in cerebral palsy. J Bone Joint Surg Am 1986;68:629-31.
[9] Heimkes B, Martignoni K, Utzschneider S, Stotz S. Soft tissue release of the spastic hip by psoas-rectus transfer and adductor tenotomy for long-term functional improvement and prevention of hip dislocation. J Pediatr Orthop B 2011;20:212-21.
[10] Agarwal A, Verma I. Cerebral palsy in children: an overview. J Clin Orthop Trauma 2012;3:77-81.
[11] Nwaobi OM, Sussman MD. Electromyographic and force patterns of cerebral palsy patients with windblown hip deformity. J Pediatr Orthop 1990;10:382-8.
[12] Faraj S, Atherton WG, Stott NS. Inter- and intra-measurer error in the measurement of Reimers' hip migration percentage. J Bone Joint Surg Br 2004;86:434-7.
[13] Parrott J, Boyd RN, Dobson F, Lancaster A, Love S, Oates J, et al. Hip displacement in spastic cerebral palsy: Repeatability of radiologic measurement. J Pediatr Orthop 2002;22:660-7.
[14] Pountney T MA. Repeatability and limits of agreement in hip migration percentage in children with bilateral cerebral palsy. Physiotherapy 2003:89;276-81.
[15] Werner C RL. Normal values of Wiberg's lateral center-edge angle

and Lequesne's acetabular index – a coxometric update. Skeletal Radiol 2012;41:1273-8.
[16] Ketelaar M, Vermeer A, Hart H, van Petegem-van Beek E, Helders PJ. Effects of a functional therapy program on motor abilities of children with cerebral palsy. Phys Ther 2001;81:1534-45.
[17] Gunel MK MA, TarsusluT, Livanelioglu A. Relationship among the Manual Ability Classification System (MACS), the Gross Motor Function Classification System (GMFCS), and the functional status (WeeFIM) in children with spastic cerebral palsy. Eur J Pediatr. 2009;168:477-85.
[18] Anttila H, Autti-Ramo I, Suoranta J, Makela M, Malmivaara A. Effectiveness of physical therapy interventions for children with cerebral palsy: a systematic review. BMC Pediatr 2008;8:14.
[19] Mall V, Heinen F, Siebel A, Bertram C, Hafkemeyer U, Wissel J, et al. Treatment of adductor spasticity with BTX-A in children with CP: a randomized, double-blind, placebo-controlled study. Dev Med Child Neurol 2006;48:10-3.
[20] Graham HK BR, Carlin JB, Dobson F, Lowe K, Nattrass G, et al. Does botulinum toxin a combined with hip bracing prevent hip displacement in children with cerebral palsy and 'hips at-risk'? A randomized controlled trial. J Bone Joint Surg Am 2008:90;22-33.
[21] Bialik GM, Pierce R, Dorociak R, Lee TS, Aiona MD, Sussman MD. Iliopsoas tenotomy at the lesser trochanter versus at the pelvic brim in ambulatory children with cerebral palsy. J Pediatr Orthop 2009;29:251-5.
[22] Koca K, Yildiz C, Yurttas Y, Balaban B, Hazneci B, Bilgiç S, et al. [Outcomes of multilevel orthopedic surgery in children with cerebral palsy]. Eklem Hastalik Cerrahisi 2011;22:69-74. [Article in Turkish]
[23] Stott NS, Piedrahita L; AACPDM. Effects of surgical adductor releases for hip subluxation in cerebral palsy: an AACPDM evidence report. Dev Med Child Neurol 2004;46:628-45.
[24] Brunner R, Baumann JU. Long-term effects of intertrochanteric varus-derotation osteotomy on femur and acetabulum in spastic cerebral palsy: an 11- to 18-year follow-up study. J Pediatr Orthop 1997;17:585-91.
[25] Kim HT, Jang JH, Ahn JM, Lee JS, Kang DJ. Early results of one-stage correction for hip instability in cerebral palsy. Clin Orthop Surg 2012;4:139-48.
[26] Al-Ghadir M, Masquijo JJ, Guerra LA, Willis B. Combined femoral and pelvic osteotomies versus femoral osteotomy alone in the treatment of hip dysplasia in children with cerebral palsy. J Pediatr Orthop 2009;29:779-83.

The European Research Journal 2018;4(4):411-415 CASE SERIES

Early detection of brain damage in emergency department and the organ donation process: a case series

İskender Aksoy[1], Mehtap Pehlivanlar Küçük[2], Çağatay Erman Öztürk[2], Ahmet Baydın[1]

[1]Department of Emergency Medicine, Ondokuz Mayıs University School of Medicine, Samsun, Turkey
[2]Department of Anesthesiology and Reanimation, Division of Intensive Care Medicine, Ondokuz Mayıs University School of Medicine, Samsun, Turkey

DOI: 10.18621/eurj.377090

ABSTRACT

Brain death is defined as the irreversible loss of brain function following various pathophysiological changes. In many countries, the brain death diagnosis is carried out in conjunction with organ transplant programs. In Turkey, at third level health institutions in particular, healthcare units established entities that follow similar procedures. The increased number of patients waiting for organs and donor discovery studies have enhanced the public's interest in this topic. Since the emergency department is usually the first line in admitting patients, its staff must have the firsthand knowledge of managing brain death and organ donation process. In this article, we present three clinical cases that we followed and diagnosed with brain death in our emergency department. Due to the lack of studies addressing brain death procedures in the emergency service, we believe that this report will greatly contribute to our awareness and handling of brain death treatment.

Keywords: Brain death, emergency medicine, organ donation

Received: January 10, 2018; Accepted: March 11, 2018; Published Online: April 12, 2018

Brain death is characterized by the irreversible loss of all brain functions, including the brain stem. Diagnosis of brain death is made following clinical determination of deep coma, absence of brainstem reflexes, and apnea test [1]. Emergency rooms (ERs) are the first line of care and where immediate interventions happen. Therefore, it is important to have diagnosing procedures for brain deaths in the ER. In this article, we aimed to draw attention to the procedures for brain death diagnosis in patients with prolonged stay in the ER as a result of limited space in the intensive care unit (ICU). The organ donation process and the process of determining appropriate organ donors will also be discussed.

CASE PRESENTATION

Case 1

A 57-year-old female was admitted to our ER with persistent headache and did not respond to analgesic treatment. The patient's history indicated that she was diagnosed with hydrocephalus with normal pressure and had nausea-vomiting, forgetfulness, and urinary incontinence during the last 3 days. The patient's Glasgow Coma Scale (GCS) was 15 at the time of admission. During the follow-up, the patient developed a respiratory arrest, was intubated, and put on mechanical ventilation support. The routine blood tests did not show any abnormalities except for

Address for correspondence: *İskender Aksoy, MD., Ondokuz Mayıs University School of Medicine, Department of Emergency Medicine, 55100 Samsun, Turkey*
E-mail: driskenderaksoy@hotmail.com, Phone: +90 545 8961555

e-ISSN: 2149-3189

hyponatremia (Na: 126 mEq/L). The brain computed tomography (CT)scan revealed hydrocephalus (Figure 1a). External ventricular drainage was performed by the neurosurgeon. Since there was no room in the ICU, the patient was taken to the ER ICU. The patient's hyponatremia was treated with hypertonic NaCl. On the third day of hospitalization, the patient's sodium levels reached 138 mEq/L. The patient was monitored with the mechanical ventilation without sedation and, at the end of the third day, her GCS was assessed, which was stable at 3. The patients' GCS stayed at 3 and brain death test was initiated. The result of the apnea test was positive. After brain CT angiography and detailed neurological examination, the diagnosis of brain death was finalized. The ER physician informed the family that the patient was brain dead. Afterwards, our hospital's donor organ transplant coordinator informed the family about organ donation. However, the family did not wish to donate the patients' organs. On the 4th day of the hospitalization, the patient died after cardiac arrest.

Case 2

A 64-year-old male patient was referred to our ER following intubation at another healthcare facility. The referring physicians informed us that the patient had a headache and suddenly collapsed after feeling weakness on his left side. His history included hypertension. The physical examination did not reveal light reflex. The patient's blood pressure was 180/100 mmHg at the time of admission, and he was administered intravenous esmolol. Routine blood test revealed hyponatremia (Na 133 mEq/L). The brain CT showed a hematoma at the level of the right basal ganglia (Figure 1b). External ventricular drainage was performed by the neurosurgeon. Since there was no room in ICU, the patient was placed in the ER ICU. The patient's serum creatinine level was 4.97 mg/dl and his blood sodium level was 159 mEq/L. Following a hydration treatment, the patient's serum creatinine level dropped to 1.04 mg/dl, and serum sodium level declined to 143 mEq/dl. The patient's sedation was stopped at an early period and, on the 5th day of hospitalization, his GCS was assessed at three. The neurological and ICU evaluated the patient for brain death. The apnea test result was positive. The neurological examination did not detect any brain stem reflexes. Transcranial Doppler ultrasonography (DUSG) was performed as a confirmatory test, and showed low-speed diastolic negative current in the form of systolic spike in both internal carotid and vertebral arteries. Flow was not detected in intracranial vascular structures, anterior cerebral artery, and/or middle cerebral artery. Clinical examination and supportive imaging scans were used to diagnose brain death. The family was informed about the patient's brain death and the hospital donor organ transplant coordinator informed the family about organ donation. The family declined organ donation. On the 6th day of hospitalization, the patient died due to cardiac arrest.

Case 3

A 59-year-old female was admitted to our ER with a sudden headache and blurring consciousness. At the time of the admission, her GCS was assessed as eight. The patient had no known disease other than hypertension. The brain CT showed hemorrhagic

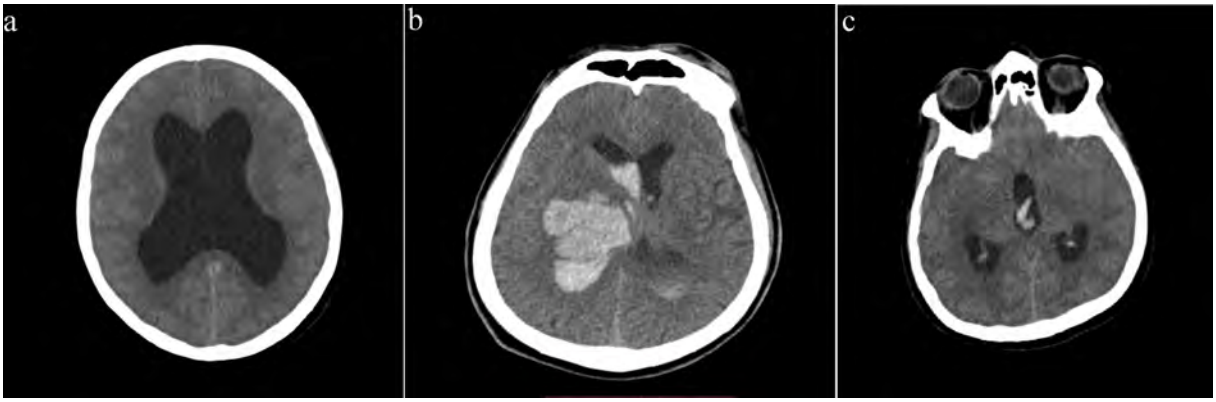


Figure 1. Patients' brain computed tomography images.

densities in peri-mesencephalic cistern, pre-pontinecistern, basal cisterns, and in third and fourth ventricular lumens (Figure 1c). External ventricular drainage was performed by the neurosurgeon and brain edema therapy was initiated. Due to the lack of room in the ICU, the patient was placed in the ER ICU. After approximately 6 hours, the patient developed cardiac arrest. After a 10-minute long successful cardiopulmonary resuscitation, the patient achieved a normal sinus rhythm. A follow-up brain CT scanshowed additional hemorrhages in lateral ventricles. The patient was assessed, and her GCS level was three. The patient did not receive sedation, and 24 hours later was subjected to an apnea test. The apnea test performed in the ER was positive. The transcranial DUSG showed low-rate, high-resistance, and diastolic negative current in both internal carotid arteries. No flow was observed in the intracranial vascular structures. Clinical examination and supportive imaging scans were used to diagnose brain death. The ER doctor informed the family about patient's brain death. Afterwards, our hospital's donor organ transplant coordinator informed the family about the possibility of organ donation. However, the family declined to donate the patient's organs. The patient died after cardiac arrest on the third day of hospitalization.

DISCUSSION

The most common causes of brain death in adults are: traumatic brain injury, intracerebral hemorrhage, subarachnoid hemorrhage, hypoxic brain injury, and ischemic stroke [2]. It is often observed as a result of the increased intracranial pressure following a traumatic intracranial injury.

Brain death is characterized by the irreversible loss of all activities of the brain, brainstem, cerebellum, and the remaining parts of the central nervous system located within the skull. In accordance with the viewpoint of our society, the Turkish Neurological Society considers the concept of brain death as "whole brain death" [1]. In Turkey, the Law on "Regulation of Removing, Storing and Transplant of Organs and Tissues" and "Turkish Ministry of Health's Guidelines on Organ and Tissue Transplantation Appendix 1explain the legal aspects of brain death [3, 4]. These guidelines state that brain death can only be confirmed based on medical evidence and by an unanimous decision made by a group of doctors comprised of neurologist/neurosurgeon, and an anesthesiologist/ICU specialist.

ERs have a fast turnover rate whereby early interventions and treatments are performed. Brain death is more common in patients admitted to ER and the central nervous system pathologies progressively worsened after intervention. Often, however, these patients are often lost before any diagnosis is made from them or they are taken into surgery and placed in the corresponding ICU following surgery. For these reasons, it is very difficult to track brain death and organ donation stages in accidents and emergency services. It is therefore not possible to make a sound and informed follow-ups especially for end-of-life care and towards the stages of organ donations.

Different rules apply to the evaluation of prognosis of the patients with brain damage. However, there is no established guideline with regard to how and when to apply those rules to day-to-day clinical practices. In 2015, Neurocritical Care Society has

Table 1. The patients' apnea test results

		Case 1		Case 2		Case 3	
Age (year)/Gender		57/Female		64/Male		59/Female	
GCS at admittance		15		3		8	
		Before	After	Before	After	Before	After
Results of the apnea test	pH	7.35	7.11	7.45	7.25	7.35	7.16
	pCO_2	36	63	36	57	35	70
	pO_2	482	434	209	282	241	110
	HCO_3	22.1	16.1	23.2	21.9	20	19.9
	SO_2	99	99	97	99	99	99

GCS = Glasgow coma scale

suggested to postpone any decisions regarding end-of-life care for brain damaged patients within the first 72 hours in order not to miss any chance of positive outcomes regardless of how big they might be [5]. The mentioned time corresponds the time when the patients are first seen in emergency services, and therefore it is vital to increase awareness on organ donation in ERs.

The end result of our hospital's organ transplant coordination team was to work to increase awareness and sensitivity regarding organ transplantation. In the past 2 years, 65 cases of brain death were diagnosed and organ donation resulted in 23 (35%) cases. In the entire country, there were 3,847 cases of brain deaths and 1,074 (28%) organ donations in the last two years [6]. The average organ donation numbers of our hospital were above Turkey's average. As a part of the organ transplant coordination team, our ER carefully assesses patients with high probability of mortality and patients with severe head trauma in terms of brain death and possible organ donation after the first intervention. Moreover, immediate communication with the ICU was established.

As observed in the above presented three cases, unresponsive patients cannot be transferred to the ICU and must stay at the ER. Similarly, a new study reports that initiation of end-of-life care in acute settings and lack of knowledge and experience in organ donation practices outside ICUs results in under of patients who could potentially donate [7].

The physician in charge of the ER should suspect brain death and should initiate appropriate diagnostic procedures. The patient should meet certain conditions before the diagnosis of brain death is made. First of all, the diagnosis of the cause that may have led to brain death must be confirmed. The presence of irreversible severe structural brain injury must be demonstrated by an imaging method (brain CT or magnetic resonance imaging). There should bean unresponsiveness to all treatment interventions, systolic blood pressure should be ≥ 100 mmHg (this condition can also be achieved with vasopressor support), central body temperature should be ≥ 36°C, and there should be an electrolyte imbalance and/or metabolic disturbance that would prevent brain stem reflexes. In addition, the patient should not be under the influence of any drugs that may affect the level of consciousness. After these conditions are met, brain death must be confirmed with clinical cardinal findings. These findings include deep coma with complete absence of response (GCS: 3), loss of brain stem reflexes (light reflex, corneal reflex, oculo-cephalic reflex, vestibulo-ocular reflex, and retching and cough reflex), no spontaneous respiratory movements, and verified positive apnea test. If there are any findings that suggest brain death after the first neurological examination, a second examination should be performed after a certain time tosee if there areany changes in those findings. This waiting period is 48 hours in infants younger than two months, 24 hours in children between 2 months and 1 year, 12 hours in children over 1 yearto adults, and 24 hours in patients that have undergone CPR. In cases where cardinal findings of brain death are shown in the first examination, there is no need to complete the waiting period if supportive evidence and cerebral circulatory arrest are indicated (1). In our study, the aforementioned preconditions were met in all three patients, the apnea test was positive (Table 1), and following the results of supportive testing (brain CT angiography in one patient, transcranial DUSG in the other two patients) the diagnosis of brain death was confirmed. Subsequently, with the cooperation of the organ transplant coordinator, neurology, and the ICU, the relatives of the patient were informed about brain death and the option of organ donation was discussed. However, the families of all three of our patients did not accept organ donation. Due to the rapid patient flow in the ER and limited communication time with patient relatives, it is very difficult to manage the organ donation process. In cases where brain death and subsequent organ donation is a possibility, it is very important to develop a relationship with the relatives of the patient in order to establish trust between the physician and the family.

Increase in organ transplantations depends on increases in number of donations. Research show that certain factors have impact on organ donations and these factors are influenced by psychological, sociological, demographic, cultural and religions thoughts. It was also found related to thoughts about organ donations, and knowledge on how the system works and media's impact. In the sense, it is important to understand that the terms of organ donation and organ transplant are multi-discipliner concepts. Therefore it is important to recognise the concepts like

brain death, organ donation and organ transplant, and its social aspects in the process of making a decision on becoming a donor [8, 9]. Previous studies have shown that organ donors in the United States and other European countries are missed in the emergency department [10, 11]. We believe that, as ER physicians become more experienced in this area, the success rate of donation acceptance will increase in patients that are suitable for organ donation.

CONCLUSION

The patient in the course of brain death should be monitored very closely regardless of the possibility of organ donation. The detection and close monitoring of these patients should be initiated in the ER. After the possible candidates are identified in ER, the intensive care and organ transplant coordination team should be informed and their experience in this process management should be utilized. Although proper initial treatment, effective resuscitation, and close follow-up cannot always save the life of a patient, they can direct the process in terms of preserving the organs for the donation process. For this reason, although every emergency physician's goal is to save lives, they also should keep in mind the possibility of brain death and organ donation in patients with poor prognosis. This is especially true for those with isolated central nervous system damage.

Informed consent

Written informed consent was obtained from the patients for the publication of this case series

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgements

We would like to acknowledge the www.makaletercume.com and Dr. Merih Fidan Bektaş or their outstanding scientific proofreading and editing services that was provided for this manuscript.

REFERENCES

[1] Arsava EM, Demirkaya Ş, Dora B, Giray S, Gökçe M, Güler A, et al. [Turkish Neurological Society - Diagnostic guidelines for brain death]. Turk J Neurol 2014;20:101-4. [Article in Turkish]
[2] Nathan S, Greer DM. Brain death. Semin Anesth Perioper Med Pain 2006;25:225-31.
[3] Organ ve Doku Alınması, Saklanması, Aşılanması ve Nakli Hakkında Kanun, Pub. L. No. 2238 Stat. 16655 (29/5/1979).
[4] Organ ve Doku Nakli Hizmetleri Yönetmeliği Stat. 28191 (01/02/2012).
[5] Souter MJ, Blissitt PA, Blosser S, Bonomo J, Greer D, Jichici D, et al. Recommendations for the critical care management of devastating brain injury: prognostication, psychosocial, and ethical management: A Position Statement for Healthcare Professionals from the Neurocritical Care Society. Neurocrit Care 2015;23:4-13.
[6] Organ, Doku Nakli ve Diyaliz Hizmetleri Daire Başkanlığı Resmi Sayfası [cited 2017 01/12/2017]. Available from: https://organkds.saglik.gov.tr/KamuyaAcikRapor.aspx?q=YOBIS.
[7] Witjes M, Kotsopoulos A, Herold IHF, Otterspoor L, Simons KS, van Vliet J, et al. The influence of end-of-life care on organ donor potential. Am J Transplant 2017;17:1922-7.
[8] Sever M. [Problems and solution suggestions in renal transplantation in Turkey]. Türk Nefroloji Diyaliz ve Transplantasyon Dergisi 2008;17(Suppl 1):3-8. [Article in Turkish]
[9] Kahveci E, Topçuoğlu BCV. Beyin ölümünden organ nakline - temel ilkeler ve pratik uygulamalar. Özyurt Matbaacılık: Ankara., 2015.
[10] Le Conte P, Riochet D, Labastire L, Auneau JC, Legeard E, Van Tricht M, et al. Identification of potential organ donors of advanced age in EDs. Am Emerg Med 2012;30:170-3.
[11] Riker RR, White BW. Organ and tissue donation from the emergency department. J Emerg Med 1991;9:405-10.

The European Research Journal 2018;4(4):416-420 CASE REPORT

A challenging palliation via novel therapeutic approach for unusual presenting with gingival metastasis from renal cell carcinoma relapsed eight years after nephrectomy

Asım Armağan Aydın[1], Ahmet Şükrü Alparslan[2], Hülya Ayık[3], Erkan Kayıkçıoğlu[1], Banu Öztürk[1]

[1]*Department of Medical Oncology, Antalya Training and Research Hospital, Antalya, Turkey*
[2]*Department of Interventional Radiology, Antalya Training and Research Hospital, Antalya, Turkey*
[3]*Department of Gynaecologic Oncology, Akdeniz University School of Medicine, Antalya, Turkey*

DOI: 10.18621/eurj.348318

ABSTRACT

Renal cell carcinoma (RCC) is the third most frequently seen primary source of metastatic lesions of the oral cavity. Still oral cavity metastasis is a rarely seen clinical manifestation during the course of RCC. In a patient with a known history of RCC, in the presence of newly emerged oral and maxillofacial lesion(s), possibility of metastasis should be always thought of and pathological investigation should be performed as soon as possible. In RCC, metastatic involvement of oral cavity is generally accompanied by involvement of other organs with resultant lower chance of cure and poor prognosis. Especially in conditions which adversely affect functions of chewing and swallowing consequently nutrition and quality of life, surgery is contraindicated and local interventional methods transarterial chemoembolization, microwave ablation and radiofrequency ablation can be good palliative treatment alternatives. In advanced stages of the diseases with systemic involvement application of local interventional methods either solely or in combination with radiotherapy and surgery increases compliance to the systemic treatment and can contribute markedly to the prolongation of survival. Herein we aimed to present a case with unusual histopathological characteristics and presentation in whom we achieved a longer period of disease-free survival using a different local treatment method.

Keywords: Renal cell carcinoma; gingiva, metastasis; transarterial chemoembolization, microwave ablation

Received: November 1, 2017; Accepted: March 31, 2017; Published Online: April 1, 2018

Malignant tumors rarely metastasize to soft tissue of oral cavity and constitute only 1% of all malignancies of the oral region [1]. More than 80% of metastatic tumors arise from jaw bone and especially from its premolar and molar regions. However predominantly, soft tissue of gingiva (54%) and tongue (33%) are involved [1-4]. In most of the patients, previous diagnosis of primary tumor is already known, however oral cavity metastasis can encounter us as the first sign in 22-25% of the patients [1]. Based retrospective data, as a primary source of oral cavity metastases, RCC ranks third after lung and breast cancers [1]. In 15% of the cases with disseminated renal cell carcinoma (RCC), oral cavity metastases can be seen and in most of the patients' synchronous involvement of other body regions can be observed. Clinical manifestations resemble to those detected in frequently seen inflammatory reactive and non-malignant systemic diseases of the oral cavity [4]. In differential diagnosis, in addition to

Address for correspondence: *Asım Armağan Aydın, MD., Antalya Training and Research Hospital, Department of Medical Oncology, Meltem Boulevard, Muratpaşa, Antalya, Turkey*
E-mail: armaganaydin1981@hotmail.com

e-ISSN: 2149-3189

histopathological examination, immunohistochemical staining is a very useful guiding tool in the characterization of primary tumor. Herein, we presented a patient who had undergone curative treatment with initial diagnosis of a local disease and applied to our clinic with symptoms of gingival involvement and concomitant systemic metastatic disease long after the establishment of the diagnosis. In this case we encountered difficulties in the differential diagnosis and especially treatment and thanks to alternative interventional methods of palliation his systemic treatment could be maintained, his quality of life, vital functions and survival could be improved. Under currently updated data, because of histopathological characteristics of the tumor (papillary type), its being an atypical metastasis of RCC and difference in the treatment applied, this is the first shared case in the literature. We aimed to present a unique case of RCC presented with a gingival metastasis treated with a novel local treatment.

CASE PRESENTATION

A 72-year-old male patient had undergone left radical nephrectomy 8 years ago with the diagnosis of papillary type RCC. His medical history revealed presence of hypertension and smoking. Because of early stage disease (T2N0M0) his clinical follow-ups were performed initially at 6 month, then yearly intervals with recommendations of NCCN. The patient presented to a private dental clinic with a broken tooth and subsequent edema and started to receive IV antibiotherapy with the diagnosis of periodontal infection. Partial treatment response was achieved and the patient applied to our oncology clinic with complaints of a mass on the right side of the mandibular, which gradually increased in size and caused severe pain, bleeding and swelling within the last one month. On his physical examination a hemorrhagic, erythematous and edematous mass lesion on the right mandibular region which restricted mandibular movements and measuring nearly 3-4 cm was detected (Figure 1A). Facial magnetic resonance imaging (MRI) revealed a destructive lesion on the right half of the mandibula. For staging purposes, 18-F FDG PET/CT was performed which detected a hypermetabolic soft tissue lesion which caused destruction of the right lateral side of the mandibula (Suv max 17.8) and lesions consistent with metastatic involvement of mediastinum, right adrenal gland and L1, L2 and right iliac bone (Figures 1B and 1C).

Biopsy material obtained from the right mandibular gingiva revealed findings consistent with RCC. In immunohistochemical examination also vimentin, EMA and CD-10 positivity and S-100 and CEA negativity were observed. In addition to RCC, initial diagnosis of odontogenic carcinoma and clear cell tumor of salivary gland was considered. Pathology preparations of the specimens obtained during the surgery performed 8 years ago were comparatively reevaluated and diagnosis of metastasis of papillary type RCC was confirmed (Figures 2A, 2B and 2C). The patient did not accept surgical treatment so palliative radiotherapy was initiated for the treatment of pain and chewing functions of the patient. However, on the 7th day of the treatment, no response to the

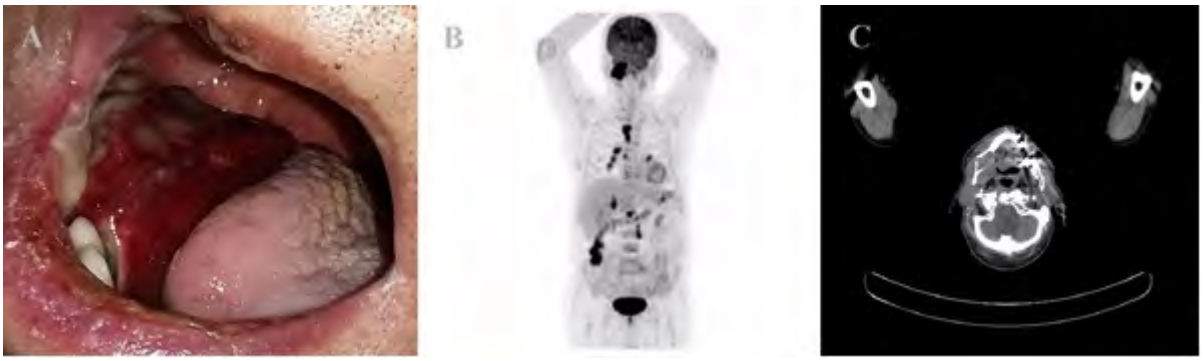


Figure 1. (A) A lesion on the right mandibular region nearly 4 cm in size surrounded by edematous and hemorrhagic tissue, (B and C) hypermetabolic soft tissue lesion which caused destruction of the bone tissue on 18-F FDG PET-CT.

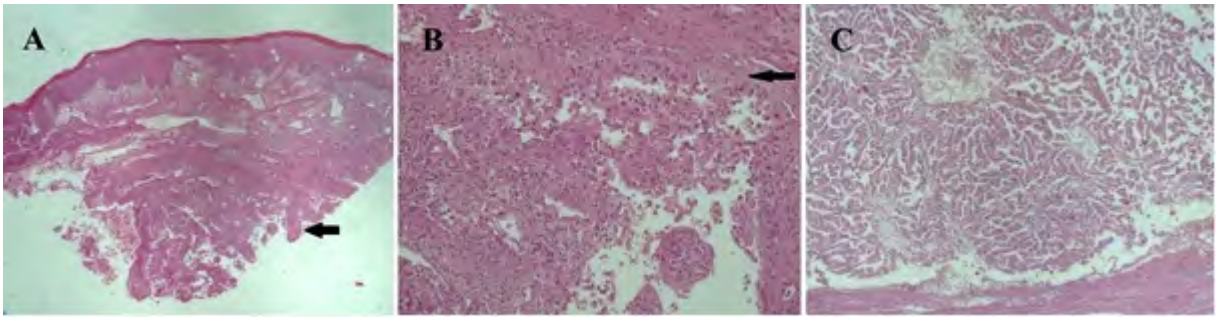


Figure 2. (A) Submucosal metastasis of malignant epithelial tumor (H&E×20), (B) Malignant papillary cells with eosinophilic cytoplasm examined under high magnification (H&E×100), (C) Renal cell carcinoma of papillary type (H&E×40).

therapy was taken, cause of increase in the size of the mass and intractable bleeding necessitated termination of radiotherapy. Interventional radiologist performed transarterial chemo-embolization (TACE) and microwave ablation (MA) for the mass perfused via temporal superficial artery. A catheter was inserted through femoral artery into the right external carotid artery to perform selective angiography. On angiograms two arteries supplying the right buccal mass (mandibular and angular arteries) were detected. Both of these arteries were embolized with Glue delivered via transarterial route. Since lesion on the right buccal region was a bilobar mass, one entry site was used for MA and 60 watt was delivered to both of these sites for 2 and 3 minutes (Figures 3A, 3B and 3C). Marked tumoral shrinkage was observed after early post-TACE and post-MA period in the patient whose bleeding problem ceased and chewing function improved. Palliative treatment was restarted and completed. At the same time administration of thyrosine kinase inhibitor (sunitinib maleate) was initiated for the treatment of systemic disease. At present, at the first year of the treatment, the patient's condition is stable ,and he is leading a healthy life.

DISCUSSION

RCC constitutes 2% of all malignancies in the whole world and every year. RCC has been associated with 300,000 new cases and 100,000 cases of death [5]. The most important risk factors associated with RCC are smoking, obesity and hypertension. Major histological variants include in order of decreasing incidence rates are clear cell (75-80%), papillary (10-15 %), chromophobe (5%), sarcomatoid tumors (5%) and tumors of the collecting tubuli (1%). In patients who are initially diagnosed as local disease, rates of local recurrence and distant metastases are 2-5% and 20-35%, respectively. In patients who have synchronous distant metastases at the time of diagnosis, survival rates are lower than those

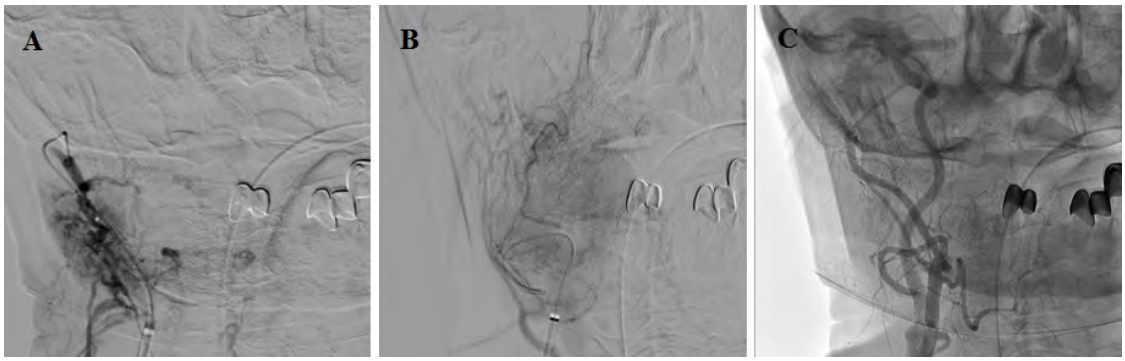


Figure 3. Selective angiographic images (A and B), Image of the lesion following microwave ablation procedure (C).

developed metastases after nephrectomy. In our case, following curative treatment of local disease, systemic relapse emerged 8 years later and especially presentation of the first symptom concurrently with gingival involvement was a surprising and unexpected condition. In most of the patients, distant metastases are seen on multiple regions without any chance of curative intervention [4, 6]. Still survival rates and quality of life of the patients who can undergo cytoreductive surgery and metastasectomy are more favorable. The most frequently seen regions of distant metastases are lungs, bone, liver, renal fossa and brain, however metastatic lesions can be seen in any organ. RCC very rarely metastasize into head and neck region and generally scarce number of case reports have been cited in the literature [7-13]. In local disease risk of metastasis into head and neck region is only 1%, while in disseminated disease it rises up to 15%. Tumor metastases into head and neck region are explained by retrograde flow through venous channels by way of prevertebral and vertebral venous plexuses because of increase in intraabdominal and intrathoracic pressures. Through this pathway RCC can metastasize through hematogenous route into head and neck region by bypassing pulmonary capillary circulation [14]. An unexpected clinical manifestation emerging on an atypical region during the course of RCC in a patient whose diagnosis is known, should always suggest the possibility of metastasis. Gingival inflammation may also facilitate settlement of the metastatic cells on gingiva. Therefore, oral hygiene is important.

Metastasis of solid tumors is a very rarely seen condition and constitute 1% of all oral cavity tumors. Still even though tumors metastasizing into jaw cannot be detected radiologically, especially in autopsy studies its incidence may be conceivably higher (16%) than expected. In men most frequently seen primary sources are lungs, kidney, liver and prostate gland, while in women primary sources are mostly breast, genital organs, kidney, and colorectal region [15]. However, metastatic tumors of the oral cavity are more frequently seen at a somewhat earlier age in women, when compared with men (women; 5. decade, and men, 7. decade). Though jaw and especially mandibula are most frequently affected regions, gingiva leads the way in soft tissue involvement.

Clinical presentations in metastatic tumors of oral cavity can be observed in a wide spectrum including jaw pain, ulcerated exophytic lesion, lassitude, impaired chewing and swallowing functions and tooth loss. Similar symptoms can be seen in odontogenic infections, pyogenic granulomas, trauma, benign odontogenic tumors or they can manifest as symptoms of neurologic involvement as amyloidosis, sarcoidosis, multiple sclerosis or a non-metastatic disease. Because of extreme rarity of metastatic tumors of oral cavity and patients' presentation with subtle dental symptoms, especially clinicians should be very attentive in making differential diagnosis [15, 16]. As is the case with our case, findings as faster growth and bone tissue destruction are strong indicators of metastatic disease. In a patient with a known history of RCC, newly emerging oral and maxillo-facial lesion should always suggest the presence of metastases and especially in patients with a known history of primary tumor, histopathological examination should be performed as soon as possible.

Although a routine algorithm concerning imaging techniques has not been formulated, in this case in the evaluation of local involvement and systemic disease, MRI and 18-F FDG PET-CT were used successively. Although histopathological examination is the gold standard in the differential diagnosis of primary tumor in suspect cases, immunohistochemical examination plays a guiding role in difficult cases similar to ours. Pax-8, CD-10 and vimentin positivity reinforces diagnosis of RCC. In our case, surgical material of the previously performed nephrectomy was compared histopathologically with gingival biopsy material and vimentin, EMA and CD-10 positivity was very helpful for definitive confirmation of the diagnosis.

Metastatic involvement of oral cavity is generally an indicator of end-stage disease. Most frequently, metastatic lesions in many other regions are present. Prognosis is unfavorable and treatment does not go beyond palliation in the majority of patients. In the literature mean survival time after oral cavity metastases has been reported as less than 1 year (range, 3.7-8.25 months) [1, 6]. In this case the reasons of survival times longer than anticipated include correction of vital functions as chewing and swallowing using local vascular interventional methods, completion of radiotherapy, improvement of quality of life, performance and nutritional status of the patient together with effective application of

systemic treatment. In the light of current information, surgery is the standard treatment of isolated gingival metastasis of RCC. Limited number of literature data concerning use of local non-surgical methods in cases with metastatic lesions of head and neck region are available. However as is seen in this case, in patients whose clinical status is not amenable to surgery, those with systemic organ involvement or in patients who reject surgical treatment, in specialized centers radiotherapy as monotherapy or in combination with local interventional methods can be safely and reliably used so as to achieve improved palpation and quality of life and also increase patient compliance with resultant favorable contribution to his/her survival.

CONCLUSION

The right mandibular gingival lesion biopsy revealed findings consistent with RCC. Local interventional methods, transarterial chemoembolization, microwave ablation were done. At the first year of the treatment, the patient's condition is stable, and he is leading a healthy life. This approach may aid in the improvement of complications and vital functions and also it may exert favorable effects facilitating administration of palliative treatment modalities as radiotherapy. We think that by this means, compliance to systemic treatment may contribute substantially to the prolongation of survival.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] Hirshberg A, Shnaiderman-Shapiro A, Kaplan I, Berger R. Metastatic tumours to the oral cavity pathogenesis and analysis of 673 cases. Oral Oncol 2008;44:743-52.
[2] Servato JP, de Paulo LF, de Faria PR, Cardoso SV, Loyola AM. Metastatic tumours to the head and neck: retrospective analysis from a Brazilian tertiary referral centre. Int J Oral Maxillofac Surg 2013;42:1391-6.
[3] McClure SA, Movahed R, Salama A, Ord RA. Maxillofacial metastases: a retrospective review of one institution's 15-year experience. J Oral Maxillofac Surg 2013;71:178-88.
[4] Owosho AA, Xu B, Kadempour A, Yom SK, Randazzo J, Ghossein RA, et al. Metastatic solid tumors to the jaw and oral soft tissue: A retrospective clinical analysis of 44 patients from a single institution. J Craniomaxillofac Surg 2016;44:1047-53.
[5] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-917.
[6] Van der Waal RI, Buter J, van der Waal I. Oral metastases: report of 24 cases. Br J Oral Maxillofac Surg 2003;41:3-6.
[7] Jatti D, Puri G, Aravinda K, Dheer DS. An atypical metastasis of renal clear cell carcinoma to the upper lip: a case report. J Oral Maxillofac Surg 2015; 3:371.e1-6.
[8] Narea-Matamala G, Fernandez-Toro Mde L, Villalabeitia-Ugarte E, Landaeta-Mendoza M, Rojas-Alcayaga G. Oral metastasis of renal cell carcinoma, presentation of a case. Med Oral Patol Oral Cir Bucal 2008;13:E742-4.
[9] Abbaszadeh-Bidokhty H, Motallebnejad M, Rajabi-Moghaddam M. Metastatic renal cell carcinoma presenting as a clear-cell tumor in tongue: a case report. Iran J Otorhinolaryngol 2014;26:185-90.
[10] Yoshitomi I, Kawasaki G, Mizuno A. Nishikido M, Hayashi T, Fujita S, et al. Lingual metastasis as an initial presentation of renal cell carcinoma. Med Oncol 2011;28:1389-94.
[11] Ahmadnia H, Amirmajdi NM, Mansourian E. Renal cell carcinoma presenting as mandibular metastasis. Saudi J Kidney Dis Transpl 2013;24:789-92.
[12] Ray A, Bhattacharya J, Ganguly S. Renal cell carcinoma presenting with oral tongue metastasis: a rare case presentation. J Cancer Res Ther 2013;9:117-8.
[13] Selvi F, Faquin WC, Michaelson MD, August M. Three synchronous atypical metastases of clear cell renal carcinoma to the maxillary gingiva, scalp and the distal phalanx of the fifth digit: a case report. J Oral Maxillofac Surg 2016;74:1286-e1-9.
[14] Bianchi M, Sun M, Jeldres C, Shariat SF, Trinh QD, Briganti A, et al. Distribution of metastatic sites in renal cell carcinoma: a population-based analysis. Ann Oncol 2012;23:973-80.
[15] Hirshberg A, Berger R, Allon I, Kaplan I. Metastatic tumors to the jaws and mouth. Head Neck Pathol 2014;8:463-74.
[16] D'Silva NJ, Summerlin DJ, Cordell KG, Abdelsayed RA, Tomich CE, Hanks CT, et al. Metastatic tumors in the jaws: a retrospective study of 114 cases. J Am Dent Assoc 2006;137:1667-72.

The European Research Journal 2018;4(4):421-424 CASE REPORT

Treating daytime blindness with eye movement desensitization and reprocessing: a case report

Fatma Dilara Altunbaş

Department of Psychology, Üsküdar University, Institute of Social Sciences, İstanbul, Turkey

DOI: 10.18621/eurj.372040

ABSTRACT

Medically unexplained physical symptoms (MUPS) are physical complaints which are difficult to diagnose by the medical analysis. According to studies, traumatic life events, and adverse childhood experiences underlie the occurrence of MUPS. Eye movement desensitization and reprocessing (EMDR) is a therapy that is applied to treat post-traumatic stress disorder (PTSD), and recently it is known that EMDR can be used in the treatment protocol of other mental health problems. This case report demonstrates efficaciousness of EMDR therapy on PTSD-related daytime blindness (hemeralopia).

Keywords: Daytime blindness, eye movement desensitization and reprocessing, hemeralopia, medically unexplained physical symptoms, psychological trauma

Received: December 27, 2017; Accepted: April 5, 2018; Published Online: April 14, 2018

Medically unexplained physical symptoms (MUPS) or medically unexplained symptoms (MUS) are defined as physical complaints which are not explained by a consistent or clear organic pathology [1]. MUPS, chronic functional syndromes (CFS) or bodily distress syndrome (BDS) have been experienced by 25% to 33% of outpatients who apply to primary care services [2, 3]. According to studies, it has been difficult to diagnose MUPS by the clinicians for many years [4], and the annual cost of it is $256 billion dollar for the United States alone [5]. The somatic problems (such pain, ache, etc.) might affect almost all the body system.

It is known that post-traumatic stress disorder (PTSD) is associated with "ill-defined" or "medically unexplained" somatic syndromes such unexplained dizziness, tinnitus and cloudy vision, therefore syndromes that can be categorized as somatoform disorders (DSM-IV-TR); moreover a series of physical conditions, with a preponderance of cardiovascular, respiratory, musculoskeletal, neurological, and gastrointestinal disorders, chronic pain, sleep disorders and other immune-mediated disorders in lots of studies [6]. It is crucial to notice the "trauma-related MUPS" on patients who are diagnosed with PTSD. Afari *et al*'s [7] meta-analysis displayed that people, who were exposed to a traumatic event, have 2.7 times higher risk of developing functional somatic symptoms than people who are without traumatic experiences.

Pathogenesis of trauma-related MUPS is explained with neuroscience, psychology, biology, and social processes [8]. Especially adverse childhood experiences (ACE), and lifetime traumatic events are some of the well known risk factors that lead to poor mental health outcomes [9]. According to van Rood and de Roos [10], unprocessed traumatic experiences might remain somatic complaints, triggers of the negative event, emotions and physical sensations.

Address for correspondence: *Fatma Dilara Altunbaş , MA., Üsküdar University, Institute of Social Sciences, Department of Psychology, Altunizade Mh. Haluk Türksoy Sk. No:14, Üsküdar, 34662 İstanbul, Turkey*
E-mail: dilarausta@gmail.com

e-ISSN: 2149-3189

Cognitive behavioral therapy (CBT), graded exposure therapy, combined therapy, and EMDR are some of the implemented treatment ways for trauma-related MUPS [11]. However, some other studies report that healing effect of CBT lasts in 1 year to 5 years [12], also, most of the patients, who are diagnosed with MUPS, revert to their baseline state as a result of the discontinuation of special caring [13].

For the other therapy techniques,which are used to treat PTSD-related MUPS, it is essential to continuethe special care for a while [14]. However, the opportunity of receiving psychotherapy on a regular basis might not be provided for every patient. Also, getting successful clinical outcomes from these therapy disciplines might take a long time [15].

Use of EMDR in the Treatment of Trauma-Related MUPS

It is known that EMDR is a useful therapy technique for revealing PTSD symptoms, including trauma-related MUPS or somatoform disorders. According to van Rood and de Roos [10], unprocessed traumatic experiences might lead to unexplained physical symptoms in two ways; the first one is the complaint/pain can be experienced during the traumatic event, and this traumatic experience has not been processed properly. The second one is the stimulators in the environment might trigger the traumatic memory including the physical sensations, which were experienced during the traumatic event [10]. Symptoms of our case fit into the first definition, indeed, van der Kolk, and Fisler defined this experience as physical re-experience [16].

Some MUPS that are associated with trauma (e.g., hypochondriasis and irritable bowel syndrome) have not yet been described in case studies [10]. In this case report, a case with trauma-related MUPS and her treatment with EMDR will be presented.

CASE PRESENTATION

A 35-year-old female was kindergarten teacher and Caucasian. She applied to psychiatry clinic with complaints of a poor vision in good illumination but a better vision in poor light. She reported that she had undergone medical examinations for separate medical departments such neurology, ophthalmology, and internal diseases; according to the results, there is not found any pathology related to the problem. After the assessment session, she reported that she experienced a rape attempt from one of her family friend, who has been known by the patient for almost 5 years. According to her report, her family friend was at her family house as a guest towards evening, and she was about to leave the house to go somewhere. Later on, her family friend asked to give her a lift, and she saw no harm in accepting his request. Her family friend was driving the car and she was sitting in the front passenger seat. While the vehicle was moving, her family friend changed the direction immediately to the forest. The patient reported that the forest was extremely dark and it was almost impossible to see anything. Her family friend attempted to rape on her and she begins to grapple with him. After she put up a fight with her family friend, she could run for her life. After this event, her complaints rise to the surface and she had to resign from her kindergarten job. She could not keep children under her control in sunlight because of her limited vision.

Diagnosis of PTSD was confirmed via the Structured Clinical Interview for DSM-IV (SCID). PTSD symptom severity was assessed using the Clinician-Administered PTSD Scale (CAPS) [17, 18], whereas depression symptom severity was measured with the Beck Depression Inventory (BDI), and severity of anxiety symptoms was measured with Beck Anxiety Inventory (BAI). Measuring the effect of routine life stress, everyday traumas and acute stress were made with Impact of Events Scale-Revised (IES-R).

Following our initial assessment session and application of psychiatric scales, we tried to find a "safe place" for the patient in the second therapy session. "Safe place" is an imaginary or an existed place that must be peaceful, relax, safe, and calm for the client, moreover, a keyword is found with the client for the purpose of remembering the place. We also tested which method of Bilateral Stimulation (BLS) would work best with the patient, eye movements, and then tactile sensors were tried.

We defined a traumatic index incident with the patient, and she identified the worst picture from the traumatic memory. She identified the moment of rape attempt and grappling with her family friend as the worst picture with the associated negative belief of "I

am insufficient", feelings of frustration, and dread, furthermore Subjective Unit of Disturbance (SUD) as 10 out of 10, which she felt tension on her muscles. After a number of sets BLS application, she declared she had felt less distressed by the worst image but she began to feel guilty about why she entered her family friend's car. We told about her family friend was her relative and she just did what anybody would do. Then BLS was repeated for a few times, and she noticed her mind has changed and her mood became more positive. She reported that SUD as 7 out of 10, and less tension on her muscles.

At the next session, and for the most of the sessions following this, we focused the memory of how her blindness has emerged. We discussed the memory of when she first noticed her day-time blindness (on returning to her kindergarten job after a while) and after effects of her traumatic life event. Negative cognitions mostly focused on not being in control and believing she was insufficient. Whereupon the level of severity of the distress had stabilized at 2 out of 10, the positive cognition of "I did my best" was installed, that recruited for strengthening the belief of her family friend in her capability to control her distress.

At our last session, Session 9, the patient expressed that she was no longer bothered by her day-time blindness complaints. She reported that she felt less depressed and her eye vision clarity became much better than pre-treatment times. She identified the level of SUD as 0 out of 10, also she said that she believes she did her best to get rid of her family friend's rape attempt.

Table 1. Comparison of pre- and post-treatment test results

	Pre-treatment	Post-treatment	Follow-up (3 months)
CAPS	75	10	7
BDI	23	6	4
BAI	14	3	3
IES-R	22	12	11

BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, CAPS = Clinician-Administered Post-traumatic stress disorder Scale, IES-R = Impact of Events Scale-Revised

At the end of the last session, pre-treatment psychiatric and cognitive scales were applied to the patient again to compare before and after treatment scores. CAPS, BDI, BAI, and IES-R were applied during pre- and post-treatment to Miss G. Table 1 shows the before and after treatment test results.

Full written consent was obtained from the client prior to writing this article.

DISCUSSION

In our study, we found EMDR therapy is helpful to relieve symptoms of trauma-related daytime blindness and helps to eliminate the symptoms of PTSD, depression, and anxiety. In the current case report, the patient was suffering from trauma-related daytime blindness symptoms which are the poor vision in illuminated places and under sunlight, being obligated to wear sunglasses in bright field, and being incapable of doing her job as a kindergarten teacher. The outcomes of the EMDR therapy were considerable for the patient; her vision began to become much clearer under sunlight and bright field, she began to feel better about her past experiences and she has come to believe the rape attempt wasn't her fault. She became more self-confident and her depressive symptoms have been relieved.

As this case report displayed, it is clear that EMDR had a beneficial effect on the patient. In the present study, the daytime blindness (hemeralopia) was considered as trauma-related MUPS and treated with EMDR; the study is different from other MUPS and EMDR studies [15, 19, 20] with not treating only physical pain or ache. Moreover, EMDR was not only helped to reduce the PTSD-related daytime blindness, also the treatment was beneficial to decrease anxiety and depression severity of our case.

CONCLUSION

Being exposed to traumatic life events is a risk factor to develop some medical disorders such as fibromyalgia, somatoform disorders, dissociation, anxiety disorders, and gastrointestinal problems [17]. For treatments of PTSD-related MUPS and other somatoform disorders, EMDR can be used as an

alternative treatment option. Variety of studies applied EMDR therapy to treat medically non-diagnostic physical aches, pain or muscle tensions. The present case report is beneficial to demonstrate how adverse life events can affect human physical health beside mental health. EMDR therapy helped to prevent the continuation of harmful effects of PTSD-related hemeralopia and gaining self-confidence back.

This case report may contribute to fill the gap in the literature regarding to treat PTSD-related somatoform disorders with EMDR. More research is necessary to analyze if the method is effective with other trauma-related MUPS cases.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] Kirmayer L, Groleau D, Looper K, Dao M. Explaining medically unexplained symptoms. Can J Psychiatry 2004;49;663-72.
[2] Kroenke K. Patients presenting with somatic complaints: epidemiology, psychiatric comorbidity and management. Int J Methods Psychiatr Res 2003;12;34-43.
[3] Landa A, Peterson BS, Fallon BA. Somatoform pain: a developmental theory and translational research review. Psychosom Med 2012;74;717-27.
[4] Aronowitz RA. When do symptoms become a disease? Ann Intern Med 2001;134, 803-8.
[5] Barsky AJ, Orav EJ, Bates DW. Somatization increases medical utilization and costs independent of psychiatric and medical comorbidity. Arch Gen Psychiatry 2005;62,903-10.
[6] Gupta, M. Review of somatic symptoms in post-traumatic stress disorder. Int Rev Psychiatry 2013;25;86-99.
[7] Afari N, Ahumada SM, Wright LJ, Mostoufi S, Golnari G, Reis V, et al. Psychological trauma and functional somatic syndromes: a systematic review and meta-analysis. Psychosom Med 2014;76:2-11.
[8] Morton L, Elliott A, Cleland J, Deary V, Burton C. A taxonomy of explanations in a general practitioner clinic for patients with persistent "medically unexplained" physical symptoms. Patient Educ Couns 2017;100;224-30.
[9] Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. The relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 1998;14;245-58.
[10] van Rood YR, de Roos C. EMDR in the treatment of medically unexplained symptoms: a systematic review. J EMDR Pract Res 2009;3;248-63.
[11] Donta ST, Clauw DJ, Engel CC, Guarino P, Peduzzi P, Williams DA, et al. Cognitive behavioral therapy and aerobic exercise for Gulf War veterans' illnesses: a randomized controlled trial. JAMA 2003;289;1396-404.
[12] Deale, A, Husain, K, Chalder, T, Wessely, S. Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. Am J Psychiatry 2001;158;2038-42.
[13] Whiting P, Bagnall A, Sowden AJ, Cornell JE, Mulrow CD, Ramírez G. Interventions for the treatment and management of chronic fatigue syndrome. JAMA 2001;286;1360.
[14] Smith R, Lein C, Collins C, Lyles J, Given B, Dwamena F. et al. Treating patients with medically unexplained symptoms in primary care. J Gen Intern Med 2003;18;478-89.
[15] Russell MC. War-related medically unexplained symptoms, prevalence, and treatment: utilizing EMDR within the armed services. J EMDR Pract Res 2008;2;212-25.
[16] Van der Kolk BA, Fisler R. Dissociation and the fragmentary nature of traumatic memories: Overview and exploratory study. J Trauma Stress 1995;8;505-25.
[17] Aker AT, Özeren M, Başoğlu M, Kaptanoğlu C, Erol A, Buran B. [Clinician-Administered Post-Traumatic Stress Disorder Scale (CAPS): A validity and reliability study]. Türk Psikiyatri Dergisi 1999;10:286-93. [Article in Turkish]
[18] Blake D, Weathers F, Nagy L, Kaloupek D, Gusman F, Charney D, et al. The development of a clinician-administered PTSD scale. J Trauma Stress 1995;8;75-90.
[19] Proudlock S. EMDR and the treatment of medically unexplained symptoms. SAGE Open 2015;5:1-5.
[20] Taycan O, Sar V, Celik C, Erdogan-Taycan S. Trauma-related psychiatric comorbidity of somatization disorder among women in eastern Turkey. Compr Psychiatry 2014;55;1837-46.

Acute myocardial infarction associated with the induction of general anesthesia

Murathan Küçük[1], Necmettin Korucuk[2], Veysel Tosun[3], Fatma Ertuğrul[4], Aytül Belgi Yıldırım[1]

[1]*Department of Cardiology, Akdeniz University School of Medicine, Antalya, Turkey*
[2]*Department of Cardiology, Erciş State Hospital, Van, Turkey*
[3]*Department of Cardiology, Şanlıurfa Training and Research Hospital, Şanlıurfa, Turkey*
[4]*Department of Anesthesia and Reanimation, Akdeniz University School of Medicine, Antalya, Turkey*

DOI: 10.18621/eurj.349353

ABSTRACT

Perioperative acute myocardial infarction (AMI) is the most common cause of postoperative morbidity and mortality. It is a rare but important and fatal complication. Recognizing this situation may be difficult due to the influence of general anesthesia. Early diagnosis and treatment can decrease the morbidity and mortality of this fatal complication. In this case we present a 56-year-old female planned nephrectomy. After induction of general anesthesia acute inferoposterior myocardial infarction occurred and coronary angiograhy showed the proximal portion of the circumflex coronary artery (Cx) was occluded by thrombus, the left anterior descending coronary artery and the right coronary artery were plaque. Percutaneous transluminal coronary angioplasty and the stenting resulted in successful dilatation of the Cx and she was discharged at the fifth day of intervention without any complication.

Keywords: Myocardial infarction, general anesthesia, perioperative care

Received: November 5, 2017; Accepted: December 21, 2017; Published Online: March 12, 2018

Perioperative acute myocardial infarction (AMI) is the most common cause of postoperative morbidity and mortality [1, 2]. It is a rare but can be a fatal complication [3, 4]. It was reported that the mortality of perioperative myocardial infarction was %30-50 [3]. Although there are many risk factors for development of perioperative AMI such as surgical and anesthetic risk factors according to patient situation, it may occur without any conventional risk factors. Especially two distinct mechanisms can cause perioperative AMI; the first, atherosclerotic plaque rupture and the second, supply-demand imbalance in myocardial oxygen [1]. Several factors can contribute to atherosclerotic plaque rupture in perioprerative period. Physiological and emotional stresses are known to be predisposing factors for AMI. The high levels of the catecholamines and the cortisol after hemodynamic changes, pain, surgical intervention, anemia and hypothermia result in increased heart rate, blood pressure and vascular shear stress. All these situations can lead to plaque instability [5-8]. Also it is known that some anesthetic agents sensitizes the myocardium to the catecholamines [9, 10]. Early diagnosis and treatment of this situation can decrease the morbidity and mortality despite recognizing may be difficult due to the influence of general anesthesia.

Address for correspondence: *Necmettin Korucuk, MD., Erciş State Hospital, Department of Cardiology, Van, Turkey.*
E-mail: mdnecmettin@gmail.com

e-ISSN: 2149-3189

CASE PRESENTATION

A 56-year-old female admitted to urology department of our hospital and was diagnosed the right nonfunctioning kidney with the repetitive urinary tract infection. For this reasons the nephrectomy operation was planned. The patient has not been using any drugs regularly and had no cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, smoking, family history. She had a suspected transient ischemic attack 2 years ago but not documented. Preoperative electrocardiograpy (ECG) showed the sinus rhythm with right bundle branch block (Figure 1a). The functional capacity of the patient was NYHA class I and her hemodynamics values were normal (110/70 mmHg, 72/beats). The preoperative cardiology consultation was not requested so no treatment was given perioperatively. In the operating room she was premedicated with midazolam (0.01-0.1mg/kg), induction of anesthesia was done with thiopental sodium (5-6 mg/kg), fentanyl (0.2 µg/kg), rocuronium (0.6 mg/kg) and it continued with desflurane as a volatile inhalation and remifentanil infusion. After intubation, the patient has bradycardia (40 beats/min) and hypotension (70-75 mmHg systolic) with ST segment elevation in DII lead. Immediately resuscitated with norepinephrine and saline infusions to normalized the blood pressure. The 12-lead ECG showed ST segment elevation in inferior leads and depression in V1-3 (Figure 1b).

The echocardiographic examination revealed that left ventricular dysfunction with ejection fraction of 40-45%, hypokinetic inferior and posterior wall without any pericardial effusion. Acute inferoposterior myocardial infarction was diagnosed and the patient was immediately transported to the catheterization laboratory in about ten minutes. The angiography showed that the proximal portion of the circumflex coronary artery (Cx) was occluded by thrombus, the left anterior descending coronary artery (LAD) and the right coronary artery (RCA) were plaque. Percutaneous transluminal coronary angioplasty (PTCA) and the bare metal stent implantation resulted in successful dilatation of the Cx and the ST changes improved instantly (Figure 2).

The patient was taken to the coronary intensive care unit and extubated after three hours after the intervention. On third day, the echocardiographic examination repeated and left ventricular ejection fraction was %55, other findings were similar with

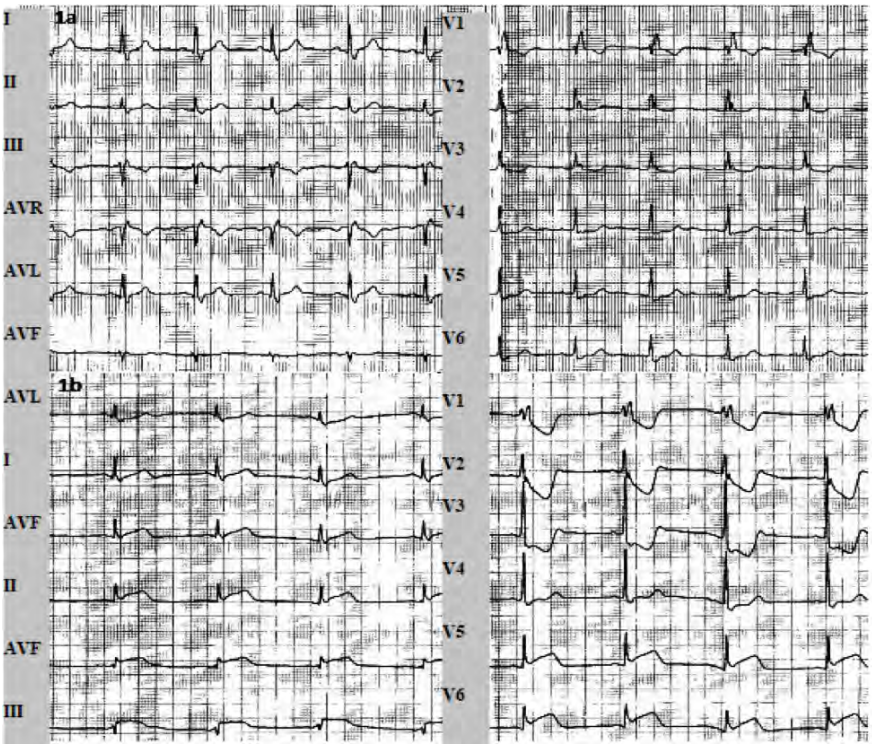


Figure 1. Sinus rhythm with right bundle branch block (a). ST segment elevation in inferior leads and depression in V1-3 (b).

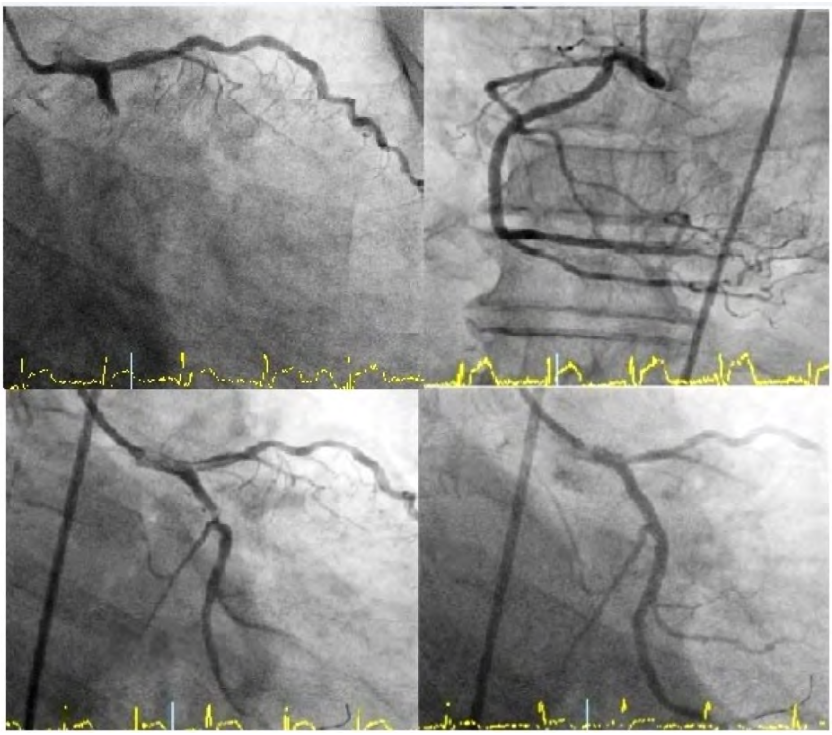


Figure-2. Proximal portion of the Cx was occluded, LAD and RCA were plaque. PTCA and the stenting resulted in successful dilatation of the Cx.

better wall movements. Her nephrectomy operation postponed 6 months later because of this acute coronary syndrome. She was discharged at the fifth day of admission without any complication.

DISCUSSION

Perioperative AMI, is a rare but can be a fatal complication [3, 4]. Several factors can cause the myocardial ischemia in perioperative period. Martinez *et al*. [11] reported that the optimization of supply-demand balance in myocardial oxygen decreased the mortality rate in sixth months. The patients with abnormal preoperative ECG findings such as in our case, have more cardiovascular risk than those with normal ECG findings [12]. Hence, it is important to evaluate the preoperative ECG as a marker of cardiac diseases before operation. In our case, no cardiology recommendations were taken. It is known that some agents (beta blockers, statins etc.) used in perioperative period can decrease such complications. Also monitorization of ST segment is effective in detecting ischemia and prevent infarct in perioperative period [13]. As in our case, the close monitoring of ST segment and the hemodynamic values are very important to recognize AMI during the operation despite to the influence of general anesthesia. Because of increasing levels of the catecholamines and the cortisol after hemodynamic changes or as a result from pain, surgical trauma, anemia and hypothermia, heart rate, blood pressure and vascular shear stress can increase and these conditions can lead to plaque instability [5-8]. Also it is well known that some anesthetic agents such as halothane sensitizes the myocardium to the catecholamines [9, 10]. It was reported that the adrenaline and the noradrenaline stimulate platelet aggregation such as thromboxane A_2, ADP and collagen. For these reason, it can be said that high levels of perioperative adrenaline and noradrenaline might cause to cardiac complications. Thereby ventricular arrhytmias and other adverse events such as perioperative AMI, can be seen during the surgical stress period.

CONCLUSION

Such as in our case, it can be said that preoperative cardiac evaluation and recommendations must be

taken in suspicious patients also close monitoring of the hemodynamic parameters and the ST segment during surgical procedures is very important for recognizing perioperative cardiac complications which is the most common cause of postoperative morbidity and mortality. Early diagnosis and treatment of these complications can decrease the morbidity and mortality.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS. Perioperative myocardial infarction. Circulation 2009;119:2936-44.
[2] Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major non-cardiac surgery. Circulation 1999;100:1043-9.
[3] Haagensen R, Steen PA. Perioperative myocardial infarction. Br J Anaesth 1988;61:24-37.
[4] Mangano DT. Perioperative cardiac morbidity. Anesthesiology 1990;72:153-84.
[5] Breslow MJ, Parker SD, Frank SM, Norris EJ, Yates H, Raff H, et al. Determinants of catecholamine and cortisol responses to lower extremity revascularization. PIRAT Study Group. Anesthesiology 1993;79:1202-9.
[6] Chernow B, Alexander HR, Smallridge RC, Thompson WR, Cook D, Beardsley D, et al. Hormonal responses to graded surgical stress. Arch Intern Med 1987;147:1273-8.
[7] Frank SM, Higgins MS, Breslow MJ, Fleisher LA, Gorman RB, Sitzmann JV, et al. The catecholamine, cortisol, and hemodynamic responses to mild perioperative hypothermia: a randomized clinical trial. Anesthesiology 1995;82:83-93.
[8] Fukumoto Y, Hiro T, Fujii T, Hashimoto G, Fujimura T, Yamada J, et al. Localized elevation of shear stress is related to coronary plaque rupture. J Am Coll Cardiol 2008;51:645-50.
[9] Katz RL, Bigger JT. Cardiac arrhythmias during anesthesia and operation. Anesthesiology 1970;33:193-213.
[10] Rodrigo MRC, Moles TM, Lee PK. Comparison of the incidence and nature of cardiac arrhythmias occurring during isoflurane or halothane anesthesia. Studies during dental surgery. Br J Anaesth 1986;58:394-400.
[11] Martinez E, Kim L, Rosenfeld B, Faraday N, Bass E, Perler B, et al. Early detection and real-time intervention of postoperative myocardial ischemia: the STOPMI (Study for the Treatment of Perioperative Myocardial Ischemia) Study. Abstract presented at Association of University Anesthesiologists; May 16-18, 2008; Durham, NC.
[12] Noordzij PG, Boersma E, Bax JJ, Feringa HH, Schreiner F, Schouten O, et al. Prognostic value of routine preoperative electrocardiography in patients undergoing noncardiac surgery. Am J Cardiol 2006;97:1103-6.
[13] Fleisher LA, Nelson AH, Rosenbaum SH. Postoperative myocardial ischemia: etiology of cardiac morbidity or manifestation of underlying disease? J Clin Anesth 1995;7:97-102.
[14] Kimura Y, Okuda H. Effects of alpha- and beta-adrenergic antagonists on epinephrine- induced aggregation and intracellular free calcium concentration in human platelets. Biochem Biophys Res Commun 1994;202:1069-75.
[15] Wu KK. Platelet activation mechanism and markers in arterial thrombosis. J Int Med 1996;239:17-34.
[16] Baldassare D, Mores N, Colli S, Pazzucconi F, Sitori CR, Tremoli E. Platelet alpha2-adrenergic receptors in hypercholesterolemia: relationship between binding studies and epinephrine-induced platelet aggregation. Clin Pharmacol Ther 1997;61:684-91.
[17] Alanko J, Riutta A, Mucha I, Kerttula T, Kaukinen S, Vapaatalo H, et al. Adrenaline stimulates thromboxane and inhibits leukotriene synthesis in man. Eicosanoids 1992;5:169-75.

The European Research Journal 2018;4(4):429-431 CASE REPORT

Complicated acute appendicitis presenting as a necrotizing fasciitis of the abdominal wall: a case report

Betül Tiryaki Baştuğ[1], Berkay Subaşı[1], Emre Emekli[1], Kübra Parpucu[2], Mahmut Kebapçı[1]

[1]*Department of Radiology, Eskişehir Osmangazi University School of Medicine, Eskişehir, Turkey*
[2]*Department of Emergency Medicine, Eskişehir Osmangazi University School of Medicine, Eskişehir, Turkey*

DOI: 10.18621/eurj.346464

ABSTRACT

Acute appendicitis is one of the most common surgical diseases, but necrotizing fasciitis of the abdominal wall because of perforation is extremely rare. A 50-year-old male presented to the emergency department with severe right-sided abdominal pain for a week. He was hypothermic, hypotensive, and tachycardic. His abdomen was distended, with a large, tender, erythematous region over the right abdominal wall. Laboratory evaluation revealed leukocytosis, acute kidney injury. Computed tomography revealed large collections of fluid and gas in the right abdominal wall as well as inflammation surrounding the right colon. The patient was resuscitated with intra-venous fluid, started on broad-spectrum antibiotics, and emergently brought to the operating room. The patient underwent an exploratory laparotomy, and was found to have appendicitis, which perforated into his abdominal wall resulting in a necrotizing soft tissue infection. It is important to recognize this complication early and proceed immediately to the operating room.

Keywords: Perforated appendicitis, abdominal wall abscess, necrotizing fasciitis

Received: October 25, 2017; Accepted: December 11, 2017; Published Online: February 27, 2018

Acute appendicitis is one of the most common surgical diseases, but necrotizing fasciitis of the abdominal wall because of perforation is extremely rare. The diagnosis of perforated appendicitis resulting in necrotizing fasciitis is often delayed due to the unusual presentation of this common disease. Necrotizing fasciitis is associated with significant mortality and requires immediate intervention.

We present a case with complicated acute appendicitis, which perforated into abdominal wall resulting in a necrotizing soft tissue infection.

CASE PRESENTATION

A 50-year-old man presented to our emergency department with abdominal pain for a week. Over the preceding 3 days, the patient's condition had declined rapidly with general weakness and severe escalating but rather superficial abdominal pain. He denied additional symptoms, including nausea, emesis, constipation and diarrhea. He had no history of similar episodes in the past.

On admission, the patient complained of abdominal pain. His temperature was 35.1°C, blood pressure was 80/50 mmHg, and heart rate was 90 beats/minute. His physical examination revealed an irregular patch of erythema and tenderness in the right lower quadrant, and crepitation on palpation. The skin in the area of the erythema was hypoesthesic.

Initial laboratory test results showed a C-reactive protein of 330 mg/L and revealed leukocytosis (white

Address for correspondence: *Betül Tiryaki Baştuğ, MD., Assistant Professor, Eskişehir Osmangazi University School of Medicine, Department of Radiology, Eskişehir, Turkey.*
E-mail: ,betultryak@yahoo.com

e-ISSN: 2149-3189

blood cell count of 14.4) with 81% neutrophils. His serum creatinine was 0.54 mg/dL, sodium was 132 mmol/L, potassium was 5.47 mmol/L and glukoz was 330 mg/dL. Hemoglobin level was 9.6 gr/dL. An immediate abdominal computed tomography (CT) was performed. CT scan revealed collections of fluid and gas in the right inferoposterior abdominal wall as well as inflammation surrounding the right colon (Figure 1). The patient was resuscitated with intravenous fluid, started on broad-spectrum antibiotics, and emergently brought to the operating room. There was no intraabdominal free fluid. However subcutaneous collection was noted.

The patient underwent an exploratory laparotomy, and was found to have appendicitis, which perforated into his abdominal wall resulting in a necrotizing soft tissue infection. He underwent a washout, and abdominal wall debridement. Cultures grew *Enterococcus faecium, Escherichia coli* and *Enterobacter aerogenes.* Pathology of the skin and subcutaneous tissue was consistent with acute inflammation and necrosis.

DISCUSSION

Necrotizing fasciitis is a rare soft tissue infection. Disease can involve the superficial fascia, subcutaneous fat, and deep fascia. Giuliano *et al*. [1] divided necrotizing fasciitis into two groups, based on the analysis of bacteriologic culture results: Type 1, which is polymicrobial and involves non-group A streptococci plus anaerobes and/or facultative anaerobes and also often involves enterobacteriaceae; Type 2, also known as hemolytic streptococcal gangrene, in which the pathogen population is composed of group A β-hemolytic streptococci alone or in combination with a *Staphylococcus* bacterium. Necrotizing fasciitis can occur in any region of the body, but is found most commonly in the abdominal wall, extremities, and perineum [2].

A diagnosis of necrotizing fasciitis is primarily based on the clinical and physical examinations. Patients complain of severe pain. The examination features are edema, tenderness, cutaneous erythema, crepitus, and skin vesicles. CT examination is very useful for confirming the diagnosis of necrotizing fasciitis.

Perforated appendicitis resulting in necrotizing fasciitis of the abdominal wall is rare. This occurs when the appendix perforates into abdominal wall tissues and causes a rapidly progressive bacterial infection of the fascia. The diagnosis is often delayed due to the unusual presentation. Necrotizing fasciitis is a life-threatening event, which requires urgent debridement and broad-spectrum antibiotic treatment, as delay in debridement is associated with significant mortality [3].

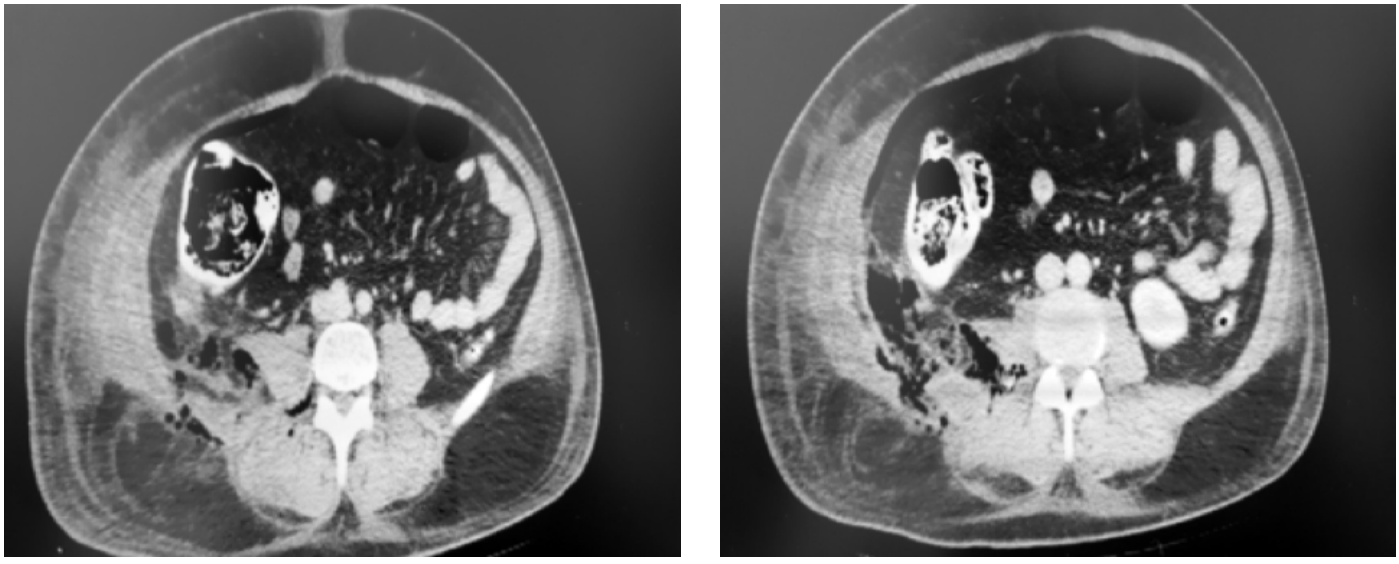


Figure 1. Axial images from a computed tomography scan of the abdomen revealing collections of fluid and gas in the right inferoposterior abdominal wall as well as inflammatory change adjacent to the right colon

Necrotizing fasciitis due to a perforated appendix is nearly always associated with perforation of a retrocecal appendix due to delayed diagnosis and treatment. There are two orifices that have been described: the inferior and superior lumbar triangles (known as Petit and Grynfeltt-Lesshaft triangles). As these two triangles void of muscular layers are areas of relative weakness in the abdominal wall [4]. Retroperitoneal inflammation resulting from perforated acute appendicitis can pass through these two triangles to the flank and the lumbar area, and can lead to necrotizing fasciitis [5].

Selected axial views of CT from our case showing retroperitoneal inflammation and abscesses resulting from perforated acute appendicitis that passes through these two triangles to the flank and the lumbar area, leading to the occurrence of necrotizing fasciitis.
Necrotizing soft tissue infections may spread rapidly and develop along fascial planes, skin and underlying muscle [6]. These patients experience pain, fever, rapid deterioration, gas or crepitus, and a systemic inflammatory response syndrome with elevated inflammatory markers [7].

Our patient showed rapidly progressing erythema with severe pain, hemodynamic instability, oliguria, crepitation, and septic shock syndrome, which were highly doubtful for necrotizing fasciitis. A Risk Indicator for Necrotizing Fasciitis (LRINEC) score developed to distinguish between soft tissue infection and necrotizing fasciitis was 8 points, representing a risk of over 90% for necrotizing fasciitis. This score includes routine laboratory values, such as C-reactive protein, white blood cell count, sodium, creatinine, glucose, and hemoglobin levels [8].

The use of CT is helpful to affirm the diagnosis of a soft tissue infection and it can supply information about involvement of intraabdominal organs. Magnetic resonance imaging (MRI) has been shown to be the most definitive imaging method to differentiate between a simple subcutaneous infection and necrotizing fasciitis [9]. However, MRI examination is time-consuming and not always available. Confirmation or exclusion of the diagnosis of necrotizing fasciitis can be reached only during surgical exploration with histological and microbiological workup.

CONCLUSION

In Intraabdominal causes (e.g., appendicitis) should be considered when faced with a patient with abdominal wall cellulitis, and cross-sectional abdominal imaging should be performed prior to surgical debridement.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] Giuliano A, Lewis F Jr, Hadley K, Blaisdell FW. Bacteriology of necrotizing fasciitis. Am J Surg 1977;134:52-7.
[2] Elliott DC, Kufera JA, Myers RA. Necrotizing soft tissue infections. Risk factors for mortality and strategies for management. Ann Surg 1996;224:672-83.
[3] Chen CW, Hsiao CW, Wu CC, Jao SW, Lee TY, Kang JC. Necrotizing fasciitis due to acute perforated appendicitis: case report. J Emerg Med 2010;39:178-80.
[4] Ishigami K, Khanna G, Samuel I, Dahmoush L, Sato Y. Gas-forming abdominal wall abscess: unusual manifestation of perforated retroperitoneal appendicitis extending through the superior lumbar triangle. Emerg Radiol 2004;10:207-9.
[5] Hua J, Yao L, He Z-G, Xu B, Song Z-S. Necrotizing fasciitis caused by perforated appendicitis: a case report. Int J Clin Exp Pathol 2015;8:3334-8.
[6] Gujral S, Hughes JM, Wiberg A. Necrotizing fasciitis. Eplasty 2014;14:ic15.
[7] McHenry CR, Piotrowski JJ, Petrinic D, Malangoni MA. Determinants of mortality for necrotizing soft-tissue infections. Ann Surg 1995;221:558-65.
[8] Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med 2004;32:1535-41.
[9] Schmid MR, Kossmann T, Duewell S. Differentiation of necrotizing fasciitis and cellulitis using MR imaging. AJR Am J Roentgenol 1998;170:615-20.

An unusual intraosseous calcaneal lipoma: case report

Ender Alkan[1], Hasan Erdoğan[2], Turgay Kara[2]

[1]*Department of Radiology, Aksaray University School of Medicine, Aksaray, Turkey*
[2]*Department of Radiology, Konya Training and Research Hospital, Konya, Turkey*

DOI: 10.18621/eurj.360318

ABSTRACT

Intraosseous lipoma, a rare primary benign tumor of the skeleton, is most commonly found in the calcaneus. It may contain homogenous fat, but it may also contain necrosis, calcification, or ossification. It usually does not show contrast enhancement, but there is an interface enhancement between the outer fat plan and the inner fluid part. Herein, we present an unusual 22-year-old male case of calcaneal intraosseous lipoma with contrast enhancement in the fatty component. The lesion was totally curetted and replaced with bone graft. The pathological diagnosis was reported as an intraosseous lipoma. The correct diagnosis of an atypical calcaneal intraosseous lipoma is very important to prevent an unnecessary biopsy and treatment.

Keywords: Intraosseous lipoma, calcaneus, magnetic resonance imaging

Received: December 2, 2017; Accepted: March 8, 2018; Published Online: April 3, 2018

Lipoma of bone is a benign neoplasm of adipocytes that typically arises within the medullary cavity of bone. Although there is a large amount of fatty tissue in bone marrow, intraosseous lipoma occurs very rarely, with a 0.1-2.1% prevalence [1-3]. However, this probably is not the actual incidence number because the lesions are frequently asymptomatic. Calcaneus bone is reported to be the most frequent site of intraosseous lipoma [4]. Herein, we present an unusual case of calcaneal intraosseous lipoma with contrast enhancement in the fatty component.

CASE PRESENTATION

A 22-year-old male patient presented with pain on his right heel and no abnormality in his laboratory results. Direct X-ray revealed a lytic lesion surrounded by sclerosis in the medullary of the right calcaneus bone (Figure 1). A contrasted magnetic resonance image (MRI) of the right heel and ankle was performed for initial diagnosis, which was a simple bone cyst and intraosseous lipoma. A 33×28×24 mm mass, which had a hypo intense lobulated sclerotic rim on the T1 and T2 weighted sequences was discovered via MRI. There was a peripherally fatty component, which was hyper intense on T1 and T2 sequences and suppressed on fatty suppressed sequences and there was cystic-degenerated areas centrally. After the injection of contrast medium, contrast uptake in the peripheral fatty component was detected (Figure 2). Overall, the lesion was diagnosed as an intraosseous lipoma with these MRI findings. According to Milgram's classification, the lesion was graded as a stage 3 calcaneal lipoma because of necrosis, centrally cystic transformed areas and sclerosis in the wall. The patient underwent operation, and the lesion was totally curetted away and replaced with bone graft. The pathological diagnosis was reported as an intraosseous lipoma (Figure 3).

Address for correspondence: *Ender Alkan, MD., Assistant Professor, Aksaray University School of Medicine, Department of Radiology, Nevsehir Cad. Zafer Sk. No: 125, Aksaray, Turkey*
E-mail: drealkan@gmail.com, Phone: +90 0382 288 29 00

e-ISSN: 2149-3189

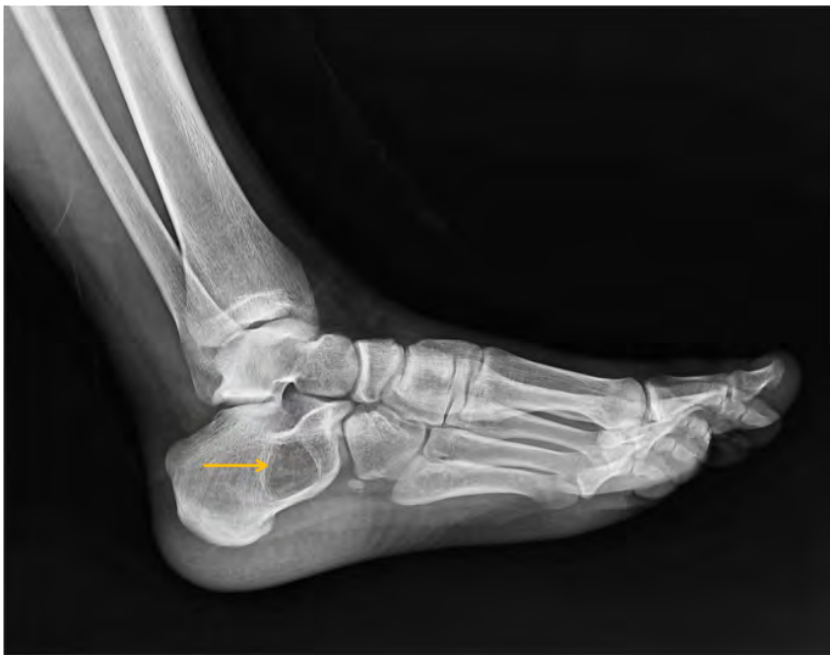


Figure 1. Right foot x-ray showing a centrally lytic, peripherally sclerotic lesion in the medulla of the calcaneus.

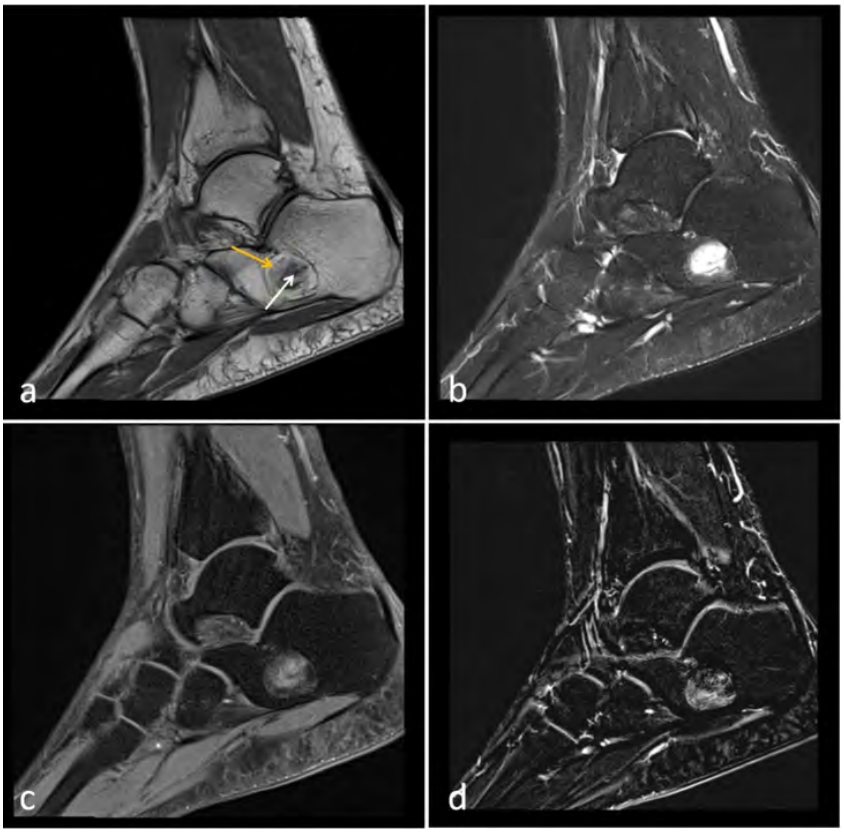


Figure 2. MRI study of the right ankle; there is hypo intense rim around the lesion in T1-weighted (a) and fat-suppressed T2 (b) weighted images consistent with sclerosis. Hyper intense fatty tissue is observed in the periphery of the lesion (yellow arrow) which is suppressed at fat-suppressed sequences (b, c). Also there is a cystic component in the central of the lesion which is hypo intense in T1-weighted image (a) and hyper intense in T2-weighted image (b). In subtraction images (d), contrast enhancement is seen in the fat components after contrast medium injection.

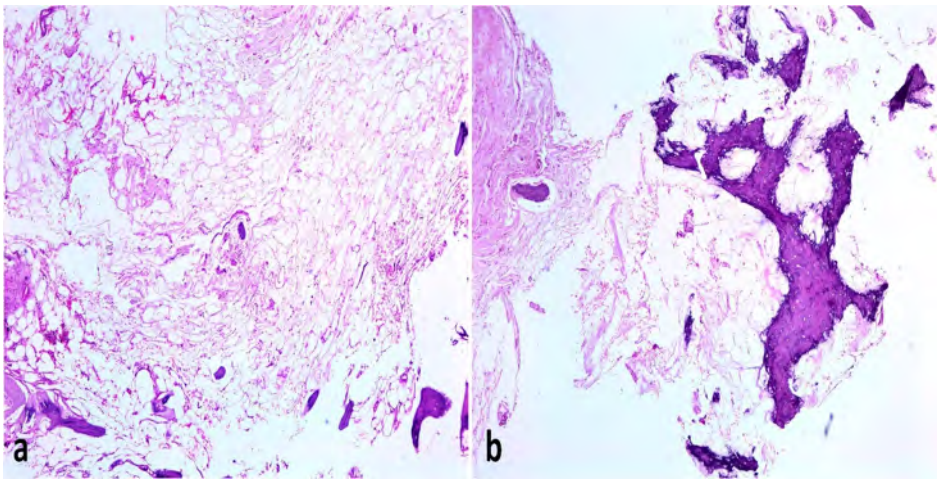


Figure 3. Intraosseous lipomas, microscopic image; (a) thin bone trabeculae are observed in the lower part. At the upper part, fat texture without cellular elements compatible with lipoma is observed. Hematoxylin and eosin (H&E) stain, ×40 magnification. (b) Dystrophic calcifications are seen on the intraosseous lipoma. H&E stain, ×40 magnification.

DISCUSSION

Intraosseous lipomas, which occur in both males and females, are generally present in the fourth and fifth decades of life, with a prevalence of 0.1-2.1%. However, the real prevalence is thought to be higher than this estimate because most cases are asymptomatic [2, 3]. Therefore, most cases have been detected incidentally. Pain is the major complication in symptomatic patients, and they present with pathological fractures.

Although intraosseous lipoma can occur anywhere in the skeletal system, 71% of these lipomas are located in the lower extremities, and usually appears in the calcaneus (32%), in which the most frequently found tumor is also the intraosseous lipoma. The upper extremities, skull, mandible, spine, and costs are involved with decreasing frequencies. Intraosseous lipomas located in long bones usually affect the metaphysis [5-8]. Basically, simple bone cysts called intraosseous ganglia are present in intraosseous lipomas. On X-rays, intraosseous lipomas appear as benign, osteolytic lesions with well-defined limits, and it is difficult to identify them only based on X-ray findings. Computerized tomography (CT), especially MRI, is useful in differential diagnosis. Radiographic diagnosis of a lipoma may not be straightforward and so there may be differential diagnosis that may include simple bone cyst, no ossifying fibroma, aneurysmal bone cyst, fibrous dysplasia, bone infarct, giant cell tumor, chondroid tumor or fungal infections. The appearance of these lesions on radiographs, CT scans and MRIs can vary as result of their degree of involution and necrosis. It is important to make a correct diagnosis on the basis of multi-method imaging studies, especially MRI.

In the classifications performed by Milgram et al. [4], intraosseous lipomas are divided into three stages based on fat necrosis: Stage 1A - sharply limited lesion with homogenous fat content; Stage 2 - Dominantly fatty lesions with central necrosis, calcification, or ossification, and Stage 3 - A heterogeneous, fat-containing lesion involving multiple necrotic areas, cystic transformations, sclerosis, or ossification in the wall. Our case was staged as 3 according to this classification.

In intraosseous lipomas, there is usually no enhancement of contrast, and occasionally there is an interfacial enhancement between the external fat plan and the internal fluid. Contrast enhancement has not been reported in the inner and extra-lesional part of bones. Our case is important in that it demonstrates contrast enhancement in the inner part of the lesion, which has not been reported until now. Because calcaneal lipomas do not affect bone stability, conservative treatment can be applied. The fracture can be treated with curettage and bone graft in cases of doubt. There is usually no recurrence after surgery [5].

CONCLUSION

As a result, intraosseous lipomas can be diagnosed easily with their fatty component, especially via MRI. It is generally accepted that intraosseous lipomas are not contrasting, or that there is contrast enhancement only at the fat-liquid interface. However, as we have shown in our case, contrast enhancement can also be seen in the inner part of the lesion. The correct diagnosis of an atypical calcaneal intraosseous lipoma is very important to prevent an unnecessary biopsy and treatment.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] Campanacci M, Enneking WF. Bone and soft tissue tumors: clinical features, imaging, pathology and treatment. 2nd ed. Berlin: Springer, 1999, pp. 683-9.
[2] Myhre-Jensen OA. Consecutive 7-year series of 1331 benign soft tissue tumors. Clinicopathologic data. Comparison with sarcomas. Acta Orthop Scand 1981;52:287-93.
[3] Unni KK, Inwards CY. Dahlin's bone tumors: general aspect and data on 10165 cases. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2006, pp. 298-300.
[4] Milgram JW. Intraosseous lipomas. Clin Orthop Relat Res 1988;231:277-302.
[5] Campbell RS, Grainger AJ, Mangham DC, Beggs I, Teh J, Davies AM. Intraosseous lipoma: report of 35 new cases and a review of the literature. Skeletal Radiol 2003;32:209-22.
[6] Blacksin MF, Ende N, Benvenia J. Magnetic resonance imaging of intraoeeous lipomas: a radiologic-pathologic correlation. Skletel Radiol. 1995; 24:37-41.
[7] Bagatur AE, Yalcinkaya M, Dogan A, Gur S, Mumcuoglu E, Albayrak M. Surgery is not always necessary in intraosseous lipoma. Orthopedics 2010;33:306.
[8] Hassani M, Gharehdaghi M, Khooei AR, Ghodsi E, Nazarzadeh H. Bilateral intraosseous tumor of the calcaneus with imaging-pathologic discordance: a case report and literatures review. Arch Bone Jt Surg 2014;2:238-42

The European Research Journal 2018;4(4):436-438 CASE REPORT

Intrathoracic extramedullary hematopoiesis as a posterior mediastinal tumor: a case report

Elçin Ersöz Köse[1], Gökay Reyhan[1], Serda Kanbur Metin[2], Serdar Evman[2], Çağatay Tezel[2], İrfan Yalçınkaya[2]

[1]Department of Thoracic Surgery, University of Health Sciences, Sultan Abdülhamid Han Training and Research Hospital, İstanbul, Turkey
[2]Department of Thoracic Surgery, University of Health Sciences, Süreyyapaşa Chest Disease and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey

DOI: 10.18621/eurj.345666

ABSTRACT

Extramedullary hematopoiesis (EMH) is a rare disorder, defined as the appearance of hematopoietic elements outside the bone marrow or peripheral blood. Usually it is diagnosed incidentally and very rarely it presents as a posterior mediastinal mass clinically mimicking with many other benign or malignant mediastinal tumors. Intrathoracic EMH is a rare condition and only very few case reports have been described in patients with chronic myeloproliferative disorders specially myelofibrosis with myeloid metaplasia and spherocytic anemias. The paravertebral area is an uncommon site for EMH, with the possible exception of sporadically reported intrathoracic manifestations. In this study, a 38-year-old male patient was followed for myeloproliferative disease. Tumor-like lesions at the bilateral posterior mediastinum were detected in the patient who applied to our clinic due to fall. Excision was planned with video- assisted thoracoscopic surgery to differentiate from mediastinal tumors, but the mass unblock was removed with posterolateral thoracotomy because of the appearance of the lesion and large size. Histopathologic diagnosis was reported as extramedullary hematopoiesis. Patient was presented because of its rare location.

Keywords: Extramedullary hematopoiesis, posterior mediastinum, myeloproliferative disease

Received: October 22, 2017; Accepted: March 20, 2017; Published Online: March 23, 2018

Extramedullary hematopoiesis (EMH) is production of blood cells, other than bone marrow, and is a compensatory mechanism of various hematological diseases such as thalassemia, sickle cell anemia, myelofibrosis, hereditary sferositozis. Thorax is a rare area where extramedullary hematopoiesis is seen. EMH focuses are usually microscopic and in some cases they are in the form of mass-like lesions and often seen in liver, spleen, lymph nodes, but have been reported in almost all organs. Intrathoracic EMH is usually asymptomatic and rarely requires treatment. Treatment is recommended in case of massive pleural effusion and haemothorax presence and when dyspnea develops in pulmonary parenchymal involvement. As a treatment, these patients can be given low-dose radiation therapy. Surgical excision is required in complications including bleeding in the mass, spinal cord compression or spinal canal invasion. In this article, a rare intrathoracic extramedullary hematopoiesis is presented.

Address for correspondence: *Elçin Ersöz Köse, MD., University of Health Sciences, Sultan Abdülhamid Han Training and Research Hospital, Department of Thoracic Surgery, İstanbul, Turkey*
E-mail: elcinersoz@hotmail.com

e-ISSN: 2149-3189

CASE PRESENTATION

A 38-year old male patient with no complaints has been followed due to myeloproliferative disorder and chronic hemolytic anemia and he has a history of frequent blood transfusion. The patient was examined upon detection of lesions in bilateral mediastinal areas, distinctly in the left side, on the chest X-ray performed 1 month ago after fall history. In the family history of the patient, who had a history of smoking 20 packs/year, existed splenectomy in his sister due to myeloproliferative disease and lung cancer in his father. There were no abnormalities in his physical examination apart from hepatosplenomegaly and icterus in the scleras. FEV1 values were determined as 3.66-89% in pulmonary function test. In thorax computed tomography (CT) of the patient, distinct nodular homogeneous soft tissue density areas in the left side of bilateral paravertebral region in the mediastinum were observed. In position emission tomography (PET)/CT, mediastinal masses showing involvement with a size of 36×49×70 mm in the left lower lobe posteromediobasal segment neighborhood on T8-T10 vertebra (SUV max: 3), and with a size of 11×23 mm in the right lower lobe mediobasal segment neighborhood on T8 vertebra (SUV max: 2.7) were detected (Figure 1). Initially, low grade lymphoma was considered, operation planned for the biopsy. The patient, for whom preoperative hematology consultation was required, was recommended 20mg/kg TDP. At first, we planned the posterior mediastinal mass biopsy with video-assisted thoracoscopy (VATS) (Figure 2). The macroscopic image of the lesion removed us from the lymphoma, and the mass had a size of 7×5 cm, so we decided to remove all of the mass with thoracotomy incision. The left posterolateral incision was inserted into the thorax from the fifth intercostal space. The mass adhered to posterior wall of the chest, and the advanced adhesions were separated with the dissection. All of the lesion was removed unblock. Postoperative hemogram values were within normal limits. His drain was terminated in the post-operative third day and he was discharged in the postoperative fourth day. The pathology report was initially reported as Hodgkin lymphoma but the final report was finalized as extramedullary hematopoiesis. As hemogram fell to 5g/dl in the postoperative first month follow-up, it was applied to hematology and splenectomy was performed on the outer center. The patient showed no recurrence during the follow-ups

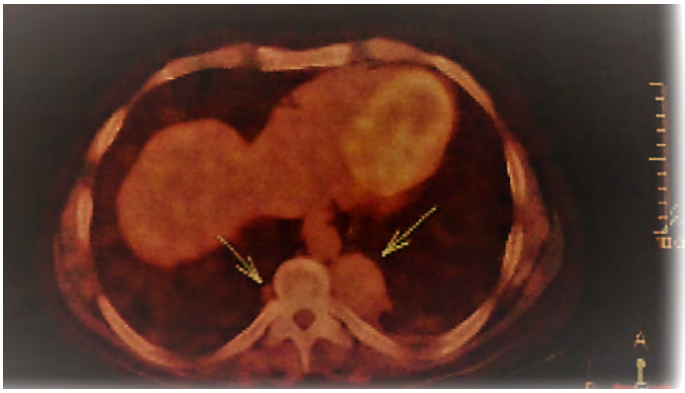


Figure 1. Bilateral posterior mediastinal masses in PET-CT scans

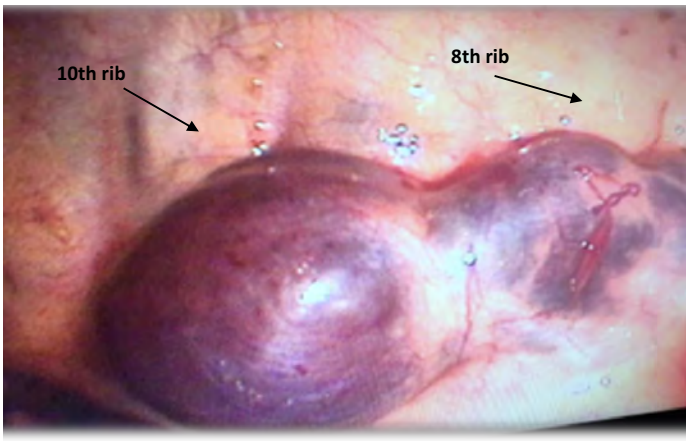


Figure 2. Peroperative appearance of the posterior mediastinal mass at the VATS.

DISCUSSION

Extramedullary hematopoiesis (EMH) is blood production in various parts of the body as a compensatory mechanism in the course of various blood diseases. EMH usually occurs as a response to bone marrow erythropoiesis fault and it can be seen in myeloproliferative disorders, hemoglobinopathies or bone marrow infiltration [1]. In most cases, it is situated in the posteroinferior mediastinum, and usually accompanied by chronic hemolytic anemia presenting in a male adult predominantly. These intrathoracic neoplasms could be solitary or multiple masses, even unilaterally or bilaterally [2]. Similar to the literature in our case, adult male patient has been

followed due to myeloproliferative disorder and chronic hemolytic anemia and he has a history of frequent blood transfusion.

Mimicking tumor in the intrathoracic cavity, presence of EMH, especially as posterior mediastinal mass, is very rare. EMH is usually characterized by development of soft tissue masses in the paravertebral area in the thorax. These masses very rarely cause distinct symptoms but may lead to hemothorax and pleural effusion [3]. In our case, the case was asymptomatic and EMH was detected incidentally.
Magnetic resonance imaging (MRI) and thorax computed tomography (CT) scans are the most commonly used diagnostic method for EMH. They appear as lobular masses in the paravertebral region [4]. In diagnosis, PET/CT scan may be useful. So far, only a few cases have been reported with an EMH diagnosis, using PET/CT scan [5] and it can be considered as a benign mass with low SUV max values and normal appearance in the tissue. Concomitant presence of underlying hematopoietic disorder suggests EMH diagnosis. In our case, we determined masses in the bilateral paravertebral region at the thorax CT incidentally. The patient underwent PET/CT to differentiate between benign and malignant lesion. PET/CT scan showed that the lesion had low SUV max values.

Although fine-needle aspiration biopsies or surgical biopsies support the diagnosis, they are not recommended for those with underlying hematologic diseases due to bleeding risk. In the presence of anemia, preoperative EMH diagnosis can be considered, however EMH was not considered as a potential diagnosis initially in our case because hemogram values were normal in preoperative examinations.

Hematopoietic tissue is particularly radiosensitive and it undergoes shrinkage with radiotherapy; excellent results have been obtained with radiotherapy alone in EMH patients. In EMH patients, surgical excision is required in complications including bleeding in the mass, spinal cord compression or spinal canal invasion [6]. Such an excision not only allows controlling bleeding and/or decompression, but also provides histological diagnosis. In EMH, postoperative radiotherapy may prevent reoccurrence or facilitate complete remission [6]. We planned incisional biopsy because we thought the lymphoma before surgery, but the macroscopic view of the lesion removed us from the lymphoma. At first if we thought EMH, we could plan radiotherapy instead of surgery.

CONCLUSION

If symmetric posterior mediastinal masses are detected in the patients with hematologic diseases, extramedullary hematopoiesis should be considered in the differential diagnosis. Surgical resection and radiotherapy should be considered as treatment options for EMH.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] An J, Weng Y, He J, Li Y, Huang S, Cai S, et al. Intrathoracic extramedullary hematopoiesis presenting as tumor-simulating lesions of the mediastinum in α-thalassemia: a case report. Oncol Lett 2015;10:1993-6.
[2] Ng CS, Wan S, Lee TW, Sihoe AD, Wan IY, Arifi AA, et al. Video-assisted thoracic surgery for mediastinal extramedullary hematopoiesis. Ann R Coll Surg Engl 2002;84:161-3.
[3] Özdemir L, Özdemir B, Durkaya S, Topal C, Çalışkan SN, Ersoy A, et al. [A rare cause of posterior mediastinal masses: extramedullary hematopoiesis (two cases)]. Respir Case Rep 2014;3:156-8. [Article in Turkish]
[4] Paydaş S, Sargın Ö, Gönlüşen G. PET CT imaging in extramedullary hematopoiesis and lung cancer surprise in a case with thalassemia intermedia. Turk J Haematol 2011;28:60-2.
[5] Zade A, Purandare N, Rangarajan V, Shah S, Agrawal A, Ashish J, et al. Noninvasive approaches to diagnose intrathoracic extramedullary hematopoiesis: 18F-FLT PET/CT and 99mTc-SC SPECT/CT scintigraphy. Clin Nucl Med 2012;37:788-9.
[6] Yeom SY, Lim JH, Han KN, Kang CH, Park IK, Kim YT. Extramedullary hematopoiesis at the posterior mediastinum in patient with hereditary spherocytosis: A case report. Korean J Thorac Cardiovasc Surg 2013;46:156-8.

The European Research Journal 2018;4(4):439-443 CASE REPORT

Idiopathic ileoileal intussusception without lead point in a 4-year-old child

Ayşe Selcan Koç[1], Zerrin Özçelik[2], Feride Fatma Görgülü[1]

[1]*Department of Radiology, University of Health Sciences, Adana City Hospital, Adana, Turkey*
[2]*Department of Pediatric Surgery, University of Health Sciences, Adana City Hospital, Adana, Turkey*

DOI: 10.18621/eurj.375051

ABSTRACT

Intussusception is common abdominal emergency in early childhood. Idiopathic ileoileal intussusceptions are rare in children without an apparent predisposing cause. Patients present with vomiting and colicky abdominal pain, which can mimic many conditions. We report a case with primary ileoileal intussusception, which was successfully reduced manually during exploratory laparotomy. There was no evidence enlarged mesenteric lymph nodes.

Keywords: Intussusception, childhood; ileoileal, idiopathics, lead point, laparoscopic surgery

Received: January 4, 2018; Accepted: February 27, 2018; Published Online: April 4, 2018

Intussusception is the second most common cause of acute abdomen in early children, following appendicitis and it is located in the ileocolic, ileocecal, or ileoileocolic part of the bowel [1, 2]. Isolated ileoileal intussusception is rare and it is frequently associated with pathological lead points while its occurrence at young children [3-5]. Presentation of small bowel intussusception is typically subacute and therefore difficult to diagnose preoperatively [5].

In this paper we present acase of a 4-year-old boy with surgically proven ileoileal intussusception without lead point.

CASE PRESENTATION

A previously healthy 4-year-old boy presented with a 2-day history of right upper-middle quadrant abdominal pain and low-grade fever. He had no nausea, vomiting or chills. According to his mother last normal bowel movement of the child was 6 hours ago, and his mother reported no urinary complaints, a history of taking any medications in the past.

On examination his abdomen was non-distended, tender to palpation and rebound on right upper-middle quadrant. He had normal active bowel sounds. There was no palpable mass and costo-vertebral angle tenderness. Rectal examination was normal with hemoccult negative brown stool. The genitourinary examination was also unremarkable.

His white blood cell (WBC) count was 3.8×10^3/L, C-reactive protein of 0.34 g/L, erythrocyte sedimentation rate (ESR) was 8 mm/h, uric acid was 2.32 mg/dL, alanine aminotransferase (ALT) was 123.3 U/L and other serum electrolytes were within normal limits. The results of other blood tests and urine analysis were within normal ranges.

Plain abdominal radiography was performed and did not show signs of obstruction or perforation (Figure 1). The abdominal axial and longitudinal

Address for correspondence: *Ayşe Selcan Koç, MD., Assistant Professor, University of Health Sciences, Adana City Hospital, Department of Radiology, Adana, Turkey*
E-mail: drayseselcankoc@gmail.com, Tel: +90 506 2425989

e-ISSN: 2149-3189

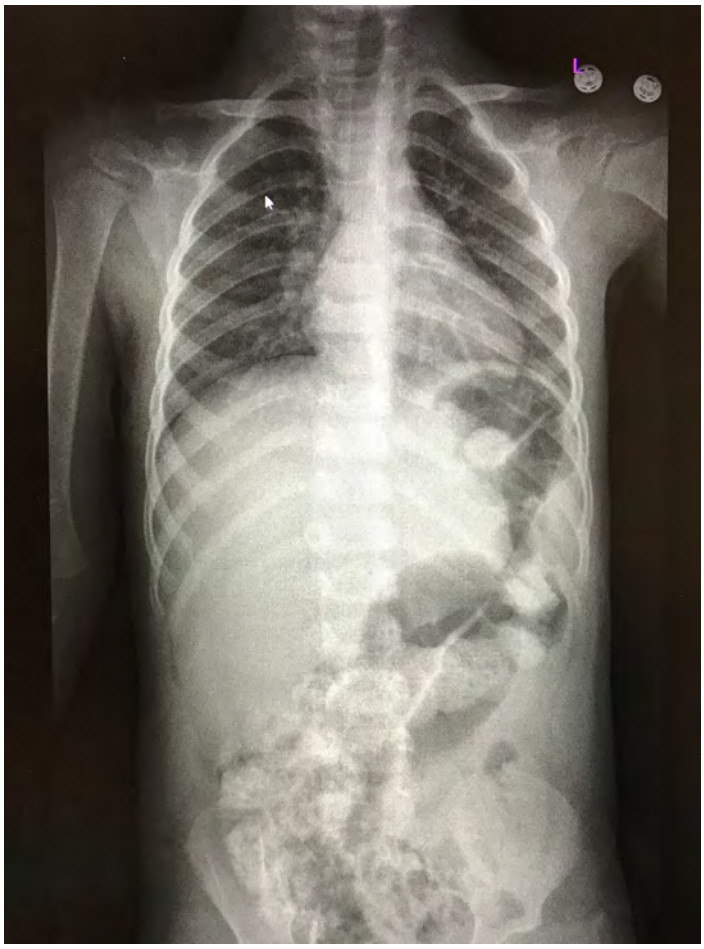


Figure 1. There are no signs of obstruction or perforation on plain abdominal radiography.

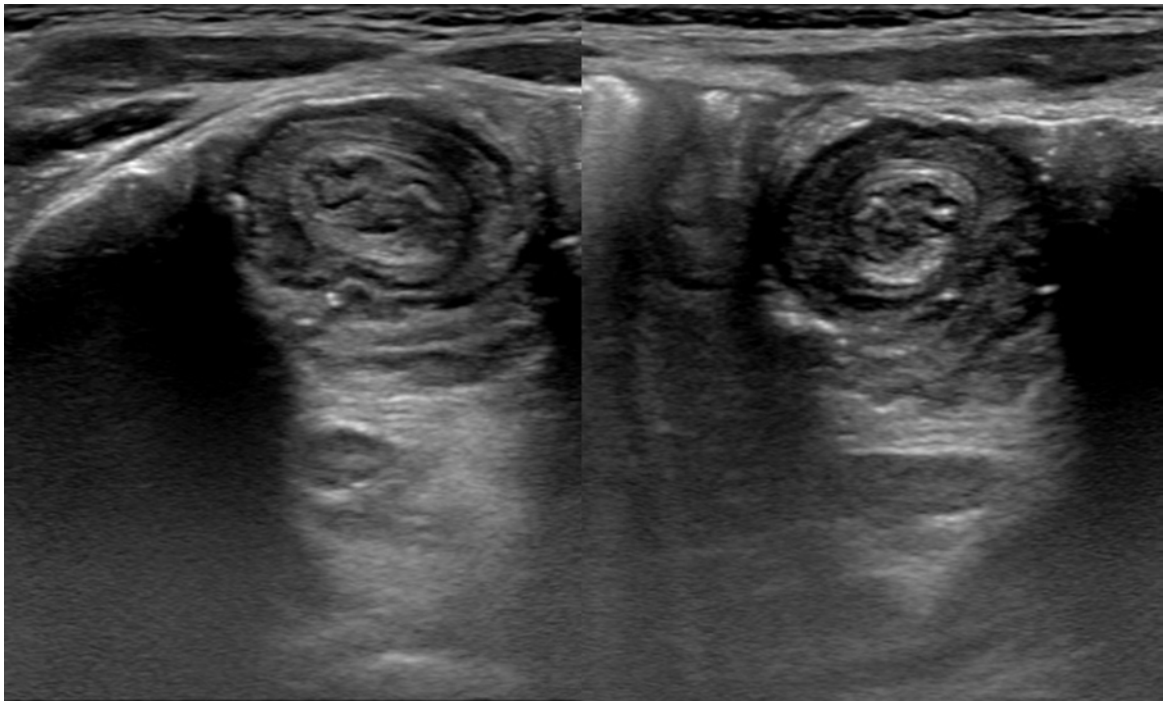


Figure 2. Abdominal ultrasonographic axial images show an increase of intestinal wall thickness like doughnut sign.

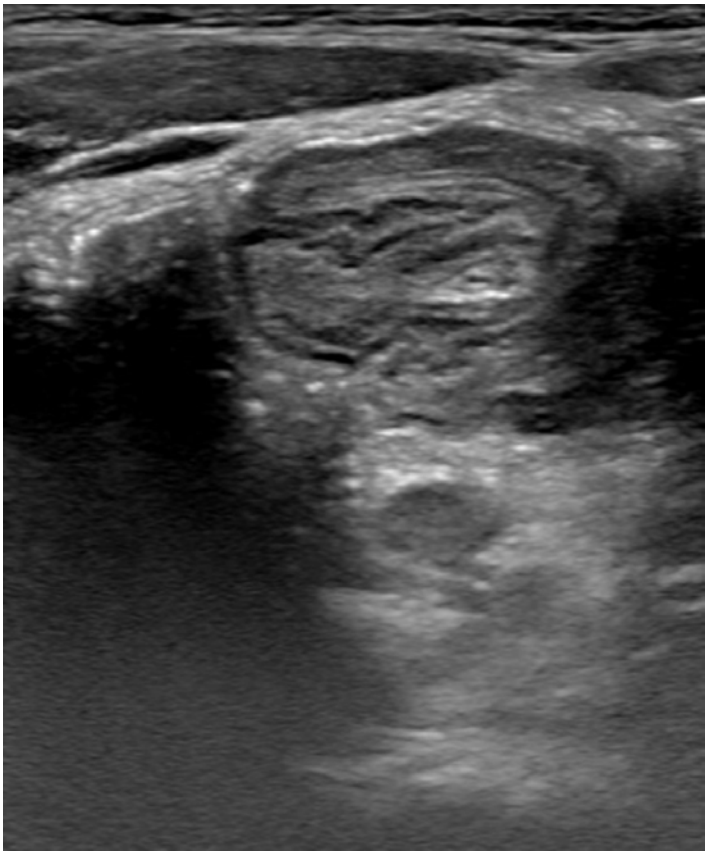


Figure 3. Abdominal ultrasound longitudinal image shows an increase of intestinal wall thickness.

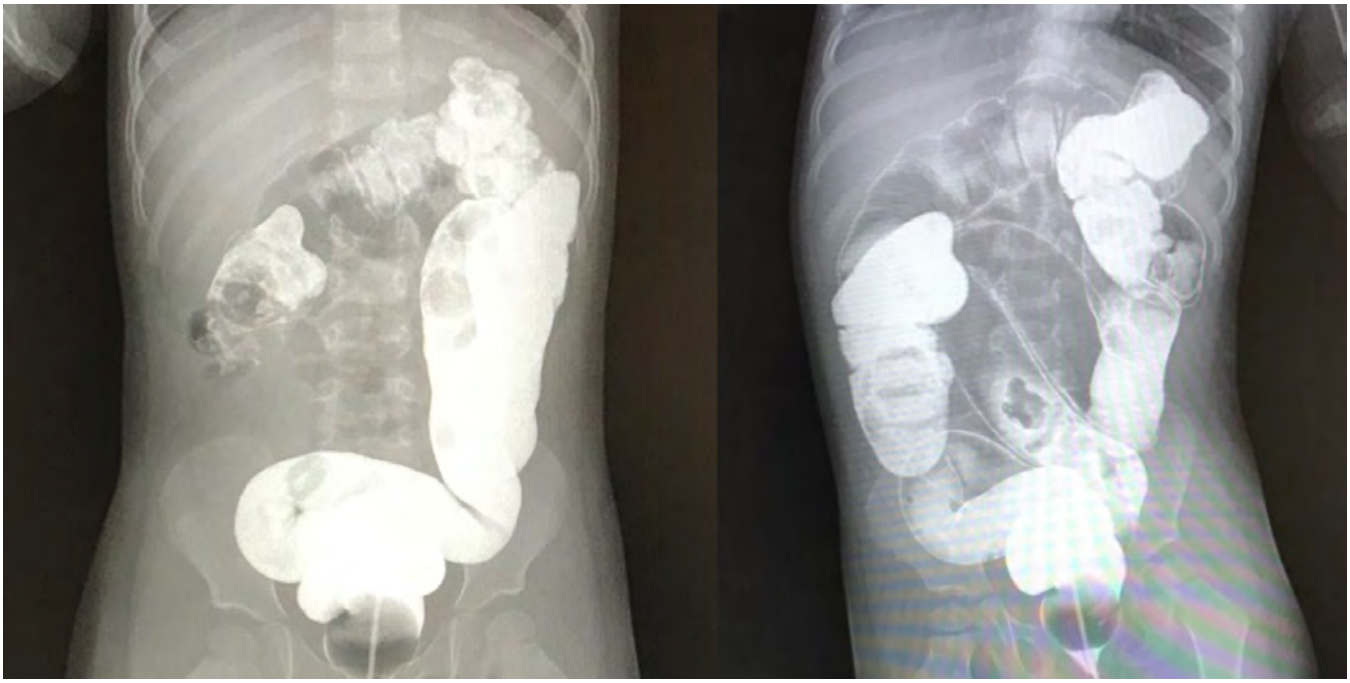


Figure 4. Hydrostatic reduction with barium enema under fluoroscopy.

abdominal ultrasonographic images showed an increase of intestinal wall thickness like doughnut sign and the intestinal wall was measured as 2.7 cm at the widest point in the right upper-middle quadrant (Figures 2 and 3). Color Doppler ultrasound demonstrated no significant loss of intestinal perfusion. Hydrostatic reduction with barium enema under fluoroscopy was performed but reduction did not successfully (Figure 4).

He underwent exploratory laparotomy and primary ileoileal intussusception was found and manual reduction was successful. There was no evidence enlarged mesenteric lymph nodes. The postoperative recovery was uneventful.

DISCUSSION

Intussusception is the second most common cause of acute abdomen in early children, following appendicitis [1]. It occurs when a segment of intestine invaginates into the near intestinal lumen. Frequently, the terminal ileum telescopes into the colon but colo-colic and ileo-ileal variants can also occur. Seventy percent of cases occur in the first year of life, with its incidence declining rapidly thereafter to < 2% in 10-15 years of age. Intussusception confined to small bowel, however, is unusual. It accounts for 1-10% of all cases of childhood intussusception, but up to 50% of cases in older children [1]. Ileoileal intussusception is more common in neonates and older children (> 5 years old) [2]. The age and presentation of the patient plays an important role in differentiating type and pathology of the intussusception [8, 9].

Classic presentation of intussusceptions involves colicky abdominal pain, vomiting, palpable mass, and blood per rectum or currant jelly stools (occurring in 20% of patients) [3]. The classic clinical features of palpable abdominal mass and bloody stools are rare in small bowel intussusceptions [3, 4]. Small bowel intussusceptions usually present with vomiting and colicky abdominal pain, which can mimic many conditions [5]. Moreover, presentation of small bowel intussusception is typically subacute and therefore difficult to diagnose preoperatively. Telescoping of a segment of the intestine into the adjacent bowel loop can cause mechanical obstruction and ischemia. Early diagnosis and prompt treatment are of most importance in childhood intussusception in order to lessen discomfort and to avoid bowel ischemia or gangrene. A diagnostic ultrasound should be conducted in all school-age children presenting with acute abdominal pain [5, 6]. Ultrasound is highly accurate for the diagnosis of ileo-colic intussusception with a reported sensitivity of 98% to 100%; however, the diagnosis of small bowel intussusception is more difficult with an ultrasound detection rate approaching only as high as 84% [7]. Ultrasound may illustrate small bowel intussusception as a crescent- in-doughnut or multilayered ‘onion skin’ round mass on a transverse scan and as the short segment sandwich sign on longitudinal scan.

If treatment is delayed, cascade beginning with vascular congestion and edema of intussuscepted intestinal wall may demonstrate a highly morbid, even fatal course, with tissue ischemia, necrosis, and intestinal perforation.

In the pediatric population, treatment depends on the type of intussusception. Ileocolic intussusception, the most common type in children, requires reduction by ultrasound-guided or fluoroscopic pneumatic or hydrostatic enema, and is successful in 85 to 90% of cases [8, 9]. Small bowel intussusception can usually be safely monitored and will reduce spontaneously without surgery [8]. Persistent small bowel intussusception, however, has been associated with a lead point or bowel necrosis, and would likely require surgical intervention [8]. Regardless of intussusception type, surgery (operative, manual reduction and/or resection or enterostomy intervention as needed) is indicated when enema reduction or close observation is unsuccessful.

Intussusception is affiliated with submucosal haemorrahage at Henoch-Schonlein purpura, cystic fibrosis, hematologic dyscrasias, postoperative changes, or lead points [10]. Other possible causes are viral inducers including rotavirus, rotavirus vaccine, and common upper respiratory illnesses. Lead points are found in 2% to 12% of children, as age increases, so does the occurrence of a lead point, and the chance of a non-surgical reduction becomes less common [10]. Unlike ileocolic intussusceptions, small bowel intussusception is frequently associated with pathological lead points (in > 29% of patients) or occurs postoperatively [7-11]. Furthermore, after 2 years of age, pathological lead points are found in one

third of patients whereas toddler and younger children are more likely to have idiopathic intussusception [5]. In previous studies, two patients older than 2 years old with confirmed ileoileal intussusceptions had no identifiable pathologic lead point [10, 11]. The only other case report of idiopathic intussusceptions in a teenage boy was that of a caecocolic intussusception [11]. These, together with the present case, highlight that small bowel intussusception is an important cause of abdominal pain and should be ruled out using appropriate investigations. Speculated factors predisposing to idiopathic small bowel intussusception are: swelling of small bowel wall, abnormal gastrointestinal motility, and scars or adhesions of the bowel from previous insult e.g. prior surgery [11, 12]. The common association of ileocolic intussusceptions and lymphoid hyperplasia may lend support to the above speculation [13].

The diagnosis of intussusception in children is challenging because of a varied clinical presentation and a wide differential diagnosis. Thus it is very important to always diagnosis of intussusception and presence of any associated diseases. In our case, we used radiology and laboratory testing for diagnosis according to the general protocol. We had diagnosed intussusception without lead point through ultrasound, performed air reduction, exploratory laparotomy.

CONCLUSION

Intussusception is a relatively common and presentation of small bowel intussusception is typically sub-acute and therefore difficult to diagnose preoperatively and is easily overlooked clinically. Small bowel intussusception is frequently associated with pathological lead points. Plain X-ray and ultrasonography are important to identify cases of intussusception in children presenting with acute abdominal pain prior to surgery.

Informed consent

Written informed consent was obtained from the patient's family for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgements

We wish to thank the staff of the University of Health Sciences - Adana Health Practices and Research Center for their assistance in the management of the patient.

REFERENCES

[1] Waseem M, Rosenberg HK. Intussusception. Pediatr Emerg Care 2008;24:793-800.
[2] Ikeda T, KoshinagaT, Inoue M, Goto H, Sugitou K, Hagiwara N. Intussusception in children of school age. Pediatr Int 2007;49:58-63.
[3] Al-Salem AH. Ileoileal intussusceptions: a report of four cases. Ann Saudi Med 2000;20:310-2.
[4] Kaiser AD, Applegate KE, Ladd AP. Current success in the treatment of intussusceptions in children. Surgery 2007;142:469-75.
[5] Stringer MD, Pablot SM, Brereton RJ. Paediatric intussusceptions. Br J Surg 1992;79:867-76.
[6] Smyth R, McCallion WA, Patterson WA. Total jejunoileal intussusceptions: a case report and literature review. Ulster Med J 2009;78:10-2.
[7] Applegate KE. Intussusception in children: evidence-based diagnosis and treatment. Pediatr Radiol 2009;39 (Suppl 2):S140-3.
[8] Marsicovetere P, Ivatury SJ, White B, Holubar SD. Intestinal intussusception: etiology, diagnosis, and treatment. Clin Colon Rectal Surg 2017;30:30-9.
[9] Bergman K, Mones R, Matuozzi W. Idiopathic cecolic intussusceptions in a 16-year old boy. Pediatr Surg Int 2009;25:819-21.
[10] Doi O, Aoyama K, Hutson JM. Twenty-one cases of small bowel intussusceptions: the pathophysiology of idiopathic intussusceptions and the concept of benign small bowel intussusceptions. Pediatr Surg Int 2004;20:140-3.
[11] Ko SF, Lee TY, Ng SH, Wan YL, Chen MC, Tiao MM, et al. Small bowel intussusception in symptomatic pediatric patients: experiences with 19 surgically proven cases. World J Surg 2002;26:438-43.
[12] Moore SW, Kirsten M, Muller EW, Numanoglu A, Chitnis M, Le Grange E, et al. Retrospective surveillance of intussusception in South Africa, 1998-2003. J Infect Dis 2010;202 Suppl:S156-161.
[13] Yoon CS, Hur J, Kim MJ. Transient small-bowel intussusception: is it related with viral infection in young children? Biomed Imaging Interv J 2007;3: e12-e240.

The European Research Journal 2018;4(4):444-447 CASE REPORT

Metastatic gastric adenocarcinoma in a pregnant woman

Raikan Büyükavcı, Hakan Apaydın, Semra Aktürk

Department of Physical Medicine and Rehabilitation, İnönü University School of Medicine, Malatya, Turkey

DOI: 10.18621/eurj.368205

ABSTRACT

Gastric cancers occur in only 0.025% to 0.1% of all pregnancies. We present a pregnant woman with gastric adenocarcinoma associated with bone metastasis. She is 36-year-old (gravida:4, para:0) 16-week pregnancy, complaining of nausea, vomiting, weight loss (~15 kg) and low back pain. Although the patient considered the condition to be related with pregnancy and underestimated its importance. She had high erythrocyte sedimentation rate (107 mm/h) and anemia (hemoglobin = 9.4 gr/dl). Lumbar magnetic resonance imaging showed L4 vertebrae malign compression fracture and diffuse bone metastasis. Because of the patient's melena, esophagogastroduodenoscopy was performed and biopsy result was reported as stomach adenocarcinoma. It is important to evaluate the symptoms of low back pain and pregnancy related symptoms carefully and do not cause delays in diagnosis due to overlapping symptoms.

Keywords: pregnancy, lower back pain, stomach neoplasms

Received: December 18, 2017; Accepted: January 19, 2018; Published Online: April 17, 2018

Low back pain during pregnancy is a common symptom. About half of pregnancies may have complain of low back pain. There are many reasons for the etiology, such as postural changes caused by fetal growth, hormonal factors, nucleus pulpous, tumors and infections [1]. The most important cause of low back pain in pregnancy is considered to be postural changes. With the progress of pregnancy, the center of gravity slides forward and the load on the spine tends to increase [2]. The second important cause is laxity in the joints due to increased levels of the hormone relaxing during pregnancy [3, 4]. Rarely, low back pain due to primary or secondary tumors can be seen in pregnancies. Gastric cancer is occurring in only 0.025% to 0.1% of all pregnancies. Diagnosis is often difficult due to symptoms such as sickness, vomiting, or abdominal disturbance that often disappears during pregnancy [5]. In this case report, we present a case of gastric adenocarcinoma diagnosed in a pregnant patient with low back pain secondary to lumbar bone metastasis.

CASE PRESENTATION

A 36-year-old (gravida:4, para:0) 16-week pregnant woman applied to our clinic for low back pain and pain in both legs. She stated that low back pain started from the time of detection of her pregnancy, gradually increased and spreading to her right leg. She stated that her pain was increasing with the movement and sitting for a long time. Right leg pain was also accompanied by numbness and tingling. At the same time, there were some complaints such as nausea, vomiting, loss of appetite and weight loss of about 15 kg from the beginning of her pregnancy.

Address for correspondence: *Raikan Büyükavcı, MD., Assistant Professor, İnönü University School of Medicine, Department of Physical Medicine and Rehabilitation, Malatya, Turkey*
E-mail: rsoydemir@yahoo.com, Tel: +90 422 3410660, Fax: +90 422 3412708

e-ISSN: 2149-3189

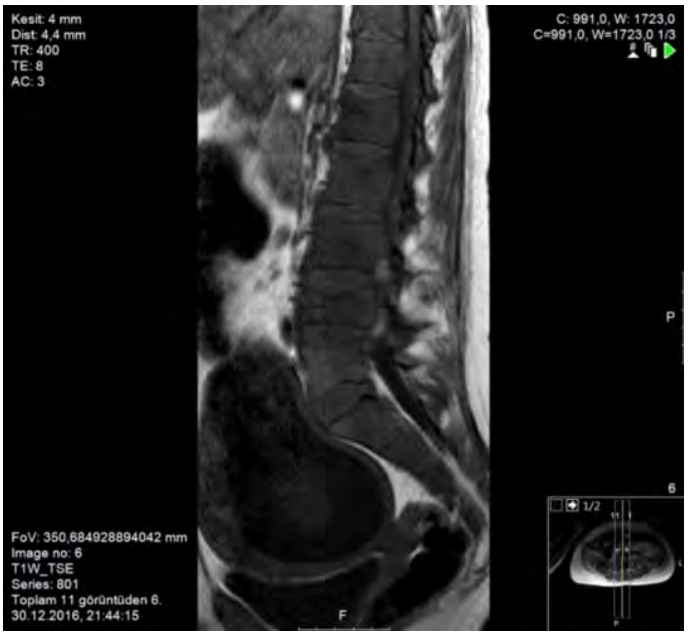


Figure 1. Lumbar MRI on T1-weighted image: L4 vertebra compression.

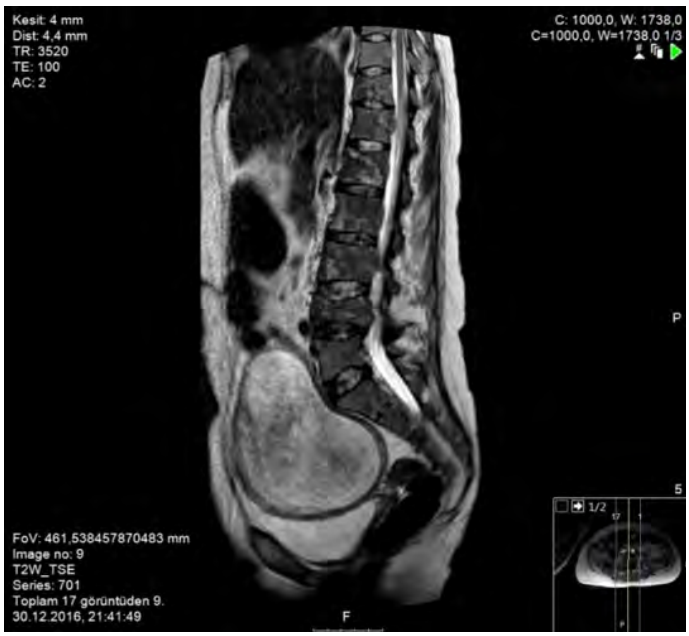


Figure 2. Lumbar MRI on T2-weighted images: L4 vertebra malignant compression fracture and diffuse bone metastasis.

There was no fever or no night sweats. Her past medical and family histories were unremarkable. She went to different doctors (a neurosurgeon, a physiatrist and orthopedist) before applying to our clinic and she had no blood result with her. On physical examination, she looked pale on inspection; palpation to lumbar spinous processes and paravertebral muscles was sensitive. Lumbar region joint movements were painful and limited, especially in flexion. Lasegue test, to detect whether the low back pain has an underlying herniated disk was bilateral negative. There was a short-distance antalgic gait supported by two people. The lumbar pain level measured by visual analog scale (VAS): 10. In laboratory investigation, erythrocyte sedimentation rate was 107 mm/h, C-reactive protein was 10.6 mg/dl, procalcitonin was 0.101 ng/ml, white blood cell account was 10.000/mm3, hemoglobin was 9.4 gr/dl and Brucella agglutination tests were negative. Lumbar magnetic resonance imaging (MRI) findings showed signal loss due to degeneration in L4-5 disc, marked heterogeneous bone marrow signal pattern in vertebral discs, marked heterogeneity in discs. The L4 vertebrae showed a height loss of less than 50%, a compression fracture on T1-weighted image (Figure 1).

Because of the patient's melena, esophagogastroduodenoscopy was performed in the gastroenterology clinic. Biopsy result was reported as stomach adenocarcinoma. In view of further examination and treatment, a lumbosacral MRI with contrast agent was obtained with the opinion of an obstetric specialist. The MRI result was evaluated as L4 vertebrae malignant compression fracture and diffuse bone metastasis on T2-weighted image (Figure 2).

Therapeutic abortus was performed with the approval of the patient and relatives. Chemotherapy and radiotherapy treatments were initiated by the oncology clinic. About one month later, the patient died due to sudden cardiac arrest.

DISCUSSION

It is known that 20-90% of pregnancies experience low back, back and hip pain, because of the laxity of ligaments and postural changes. The biomechanical load is often the cause of such pains. However, these findings are mostly confronted during the second trimester of pregnancy. Also, gestational age is found to be a risk factor for low back pain [6]. The present case was a middle-aged pregnant who applied during the 2nd trimester with low back pain, and was not different from the other cases reported. However,

accompanying weight loss required further investigation with pathological evaluation and laboratory tests.

The incidence of cancer during pregnancy is approximately 0.1% [7], and of that gastric cancer is lower at 0.026 to 0.1% of all pregnancies [8]. In the literature, malignancies with vertebral metastases during pregnancy are mostly detected as gestational choriocarcinoma. These cases are mostly diagnosed with vertebral metastasis, after detection of a primary lesion during or after pregnancy [9, 10].

Pacheco *et al*. [5] reported 3 cases of gastrointestinal malignancy detected during pregnancy. All patients presented with epigastric pain and weight loss. A biopsy was performed by gastro-endoscopy, and the cases were diagnosed as gastric cancer. The authors emphasized that gastric carcinomas are rarely seen in pregnancy, that pregnancy masks the findings of this disease, but early diagnosis improves treatment and survival, which is why it is very important to identify the disease.

Chen *et al*. [11] reported a case of gastric adenocarcinoma that metastasized to the placenta. In the patient who received emergency cesarean section due to 34-week preeclampsia, chylous acid was detected during surgery and it was reported as primer gastric adenocarcinoma metastasis to the intervillous space and placenta. The patient was in the 2nd trimester of pregnancy and had complaints of constant vomiting and epigastric pain. The authors noted that early gastric cancer diagnosis is delayed due to pregnancy-induced gastrointestinal problems.

Gastric cancer in pregnancy has poor prognosis [12]. Therefore, pregnancy-associated gastric cancer is extremely rare, and in many cases, it is diagnosed at an advanced stage because the symptoms during pregnancy are generally overlooked [5]. Additionally, the diagnosis of gastric cancer is often delayed in pregnant women because it is difficult to distinguish between symptoms of gastric cancer and common pregnancy-induced symptoms, such as the hyperemesis and pressure resulting from the enlargement of the uterus. Furthermore, the physician and patient are often hesitant to conduct diagnostic examinations during pregnancy [13, 14]. One- and 2-year survival rates are 18.0 % and 15.1%, respectively. When gastric cancer is diagnosed prior to 22 weeks of gestation, the patient should be treated after termination of the pregnancy by abortion [8].

CONCLUSION

In conclusion, our case is a rare case in the literature of gastric adenocarcinoma presenting with bone metastasis detected in the second trimester of pregnancy. Pregnancy-associated gastric cancers are extremely rare, especially with bone metastasis. It is important to carefully evaluate the symptoms of low back pain and pregnancy-related nausea, vomiting, loss of appetite and weight loss symptoms that are common in pregnancy. The accurate diagnosis due to these overlapping symptoms should not be delayed.

Author Contributions

RB: corresponding author, writing manuscript, HA: collect patient's data, and SA: edit manuscript

Informed Consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of Interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] Franklin ME, Conner-Kerr T. An analysis of posture and back pain in the first and third trimesters of pregnancy. J Orthop Sports Phys Ther 1998;28:133-8.
[2] Ritchie JR. Orthopedic considerations during pregnancy. Clin Obstet Gynecol 2003;46:456-66.
[3] Kristiansson P, Svardsudd K, Von Schoultz B. Serum relaxin, symphyseal pain, and back pain during pregnancy. Am J Obstet Gynecol 1996;175:1342-7.
[4] Chan YL, Lam WW, Lau TK. Back pain in pregnancy: magnetic resonance imaging correlation. Clin Radiol 2002;57:1109-12.
[5] Pacheco S, Norero E, Canales C, Martínez JM, Herrera ME, Muñoz C, et al. The rare and challenging presentation of gastric cancer during pregnancy: a report of three cases. J Gastric Cancer 2016;16:271-6.
[6] Carvalho MECC, Lima LC, de Lira Terceiro CA, Pinto DRL, Silva MN, Cozer GA, et al. Low back pain during pregnancy. Rev Bras Anestesiol 2017;67:266-70.
[7] Cardonick E, Lacobucci A. Use of chemotherapy during human pregnancy. Lancet Oncol 2004;5:283-91.
[8] Nishie H, Mizushima T, Suzuki Y, Fukusada S, Inoue T, Kachi K, et

al. Chemotherapy treatment of a pregnant woman with progressive gastric cancer. Intern Med. 2015;54:1207-12.
[9] Ishiguro T, Serikawa T, Yahata T, Enomoto T. Gestational choriocarcinoma: rare spinal metastasis during a viable pregnancy. J Obstet Gynaecol Res 2017;43:421-24.
[10] Naito Y, Akeda K, Kasai Y, Matsumine A, Tabata T, Nagao K, et al. Lumbar metastasis of choriocarcinoma. Spine (Phila Pa 1976) 2009;34:538-43.
[11] Chen Y, Li Y, Wang H, Lu J, Jin M, Zhang Z. Maternal gastric carcinoma with metastasis to the placenta: a case report. Oncol Lett 2014;8:2509-10.
[12] Cift T, Aydogan B, Akbaş M, Aydın B, Demirkiran F, Bakkaloglu DV, et al. Case report: gastric carcinoma diagnosed at the second trimester of pregnancy. Case Rep Obstet Gynecol 2011;2011:532854.
[13] Fujino T, Nakamura M, Sato T. [Pregnancy and gastric cancer]. Shusanki Igaku (Perinatal Medicine) 2002;32:1049-55. [Article in Japanese]
[14] Jaspers VK, Gillessen A, Quakernack K. Gastric cancer in pregnancy: do pregnancy, age or female sex alter the prognosis? Case report and review. Eur J Obstet Gynecol Reprod Biol 1999;87:13-22.

The European Research Journal 2018;4(4):448-451 CSASE REPORT

Fatty necrosis of falciform ligament due to torsion mimics falciform ligament cyst on MRI

İlknur Özdeniz[1], Ali Önder Devay[2], Ediz Tevfik Özgan[2]

[1]*Department of Radiology, Bursa State Hospital, Bursa, Turkey*
[2]*Department of General Surgery, Bursa State Hospital, Bursa, Turkey*

DOI: 10.18621/eurj.347535

ABSTRACT

The falciform ligament which is a broad and thin peritoneal ligament, divides the left and right subphrenic compartments. Some pathologies of this ligament can be a rare cause of acute abdomen. Mostly its pathologies present a challenge for diagnose. In a case who was admitted with acute abdomen, we determined a fatty necrosis of the falciform ligament during surgery. This rare primary pathology of the falciform ligament mimics falciform ligament cyst on MRI, which is another rare pathology.

Keywords: Falciform ligament, fatty necrosis, cyst, MRI

Received: October 28, 2017; Accepted: December 26, 2017; Published Online: March 17, 2018

The falciform ligament is a double layer of peritoneum that goes from the upper and anterior surfaces of the liver to the lower surface of the diaphragm and the back of the linea alba. Its line of attachment divides the liver into left and right lobes [1]. It attaches the liver to the remnants of the umbilical veins. It contains the ligamentum teres, obliterated umbilical vein and paraumbilical veins. The falciform ligament artery mostly arises from middle or left hepatic artery [2]. Furthermore, falciform ligament-related conditions are very rare.

In this paper, we present a case with falciform ligament necrosis undergoing surgery, that it was clinically thought as acute cholecystitis. It was diagnosed by surgery and histologic findings. This pathology confirmed with unusual MRI feature mimics falciform ligament cyst and disappeared after 1-month on MRI.

CASE PRESENTATION

A 46-year-old female patient was admitted with the complaints of pain in the right upper quadrant. The patient's history revealed an abdominal pain for 6 hours with an increasing severity, as well as nausea and vomiting. Physical examination suggested acute cholecystitis with a systolic blood pressure 160/85 mmHg, pulse rate of 97 bpm, and body temperature of 37.4°C. Laboratory test results showed a leukocyte count of 15.000/mm3 (normal range: 4.000-10.000/mm3). Serum chemistry tests and electrolyte measurements did not indicate any pathology related to acute abdomen (ALT 8 U/L, AST 10 U/L, amylase 52 U/L, total bilirubin 1,1 mg/dL).

Abdominal ultrasonography was requested because of suspected acute cholecystitis and demonstrated gallbladder with bile stone. However its

Address for correspondence: *İlknur Özdeniz, MD., Bursa State Hospital, Department of Radiology, Hastayurdu Caddesi, Tophane, Bursa, Turkey.*
E-mail: ilknurozdeniz@gmail.com

e-ISSN: 2149-3189

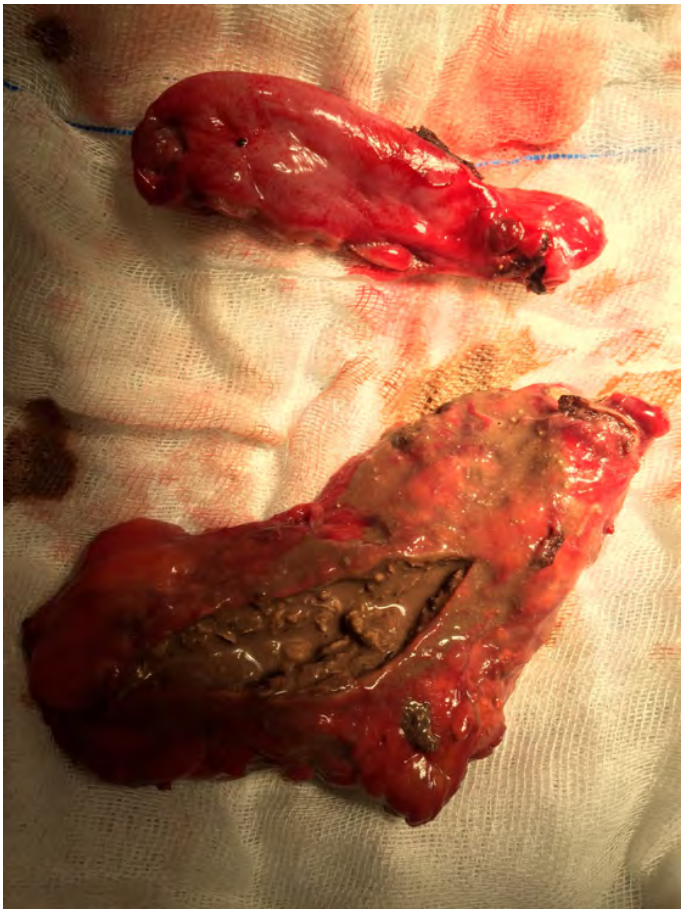


Figure 1. Macroscopic view of excised cystic structure and gallbladder

wall thickness was normal without edema. There was no heterogeneity localized in the falciform ligament. It's not completely suitable for the diagnosis of acute cholecystitis. Because the clinical condition of the patient supports this pathology, the patient accepted as acute cholecystitis and she underwent the surgery. In the operation, the gallbladder was resected but on the falciform ligament location there was a cystic-liquefied structure without any normal falciform ligament portions (Figure 1). No pathology responsible for falciform ligament necrosis was observed. This cystic-necrotic structure could not completely resected. Since cystic necrotic structure was seen on falciform ligament location, it's taught that this structure can be evaluated better on MRI. So MRI was performed on the 4th day of the operation. Also due to the emergency conditions of patient before the operation, CT/MRI could not be done.

Postoperative 4th day, on MRI there was a cystic remnant on the falciform ligament location (Figures 2, 3, 4 and 5). The histopathological examination of

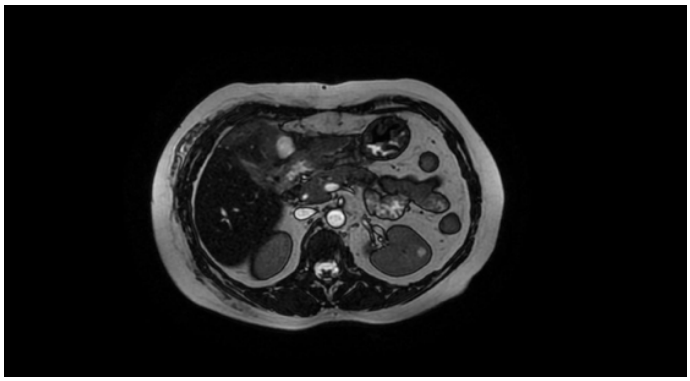


Figure 2. Postoperative 4th day, axial FIESTA MRI scan shows the remnant of cystic structure (This can also be post-surgical fluid collection, but in this case the most important cause that lead us to think as falciform ligament necrosis is the correlation with surgical findings. We knew that some part of the necrosed falciform ligament is resected by surgery).

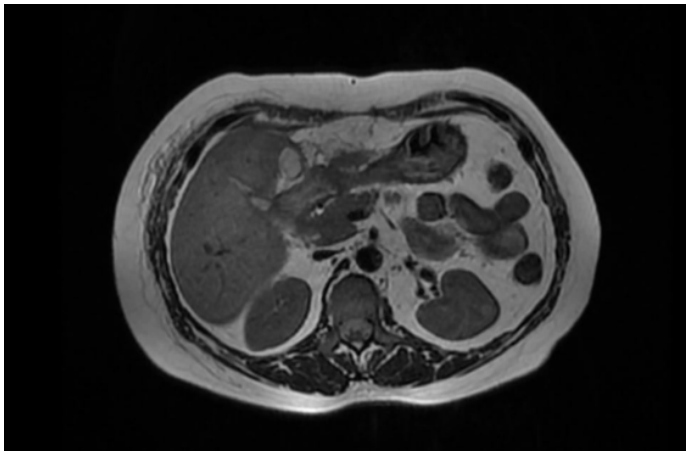


Figure 3. The same structure is hyperintense on axial T2 weighted image.

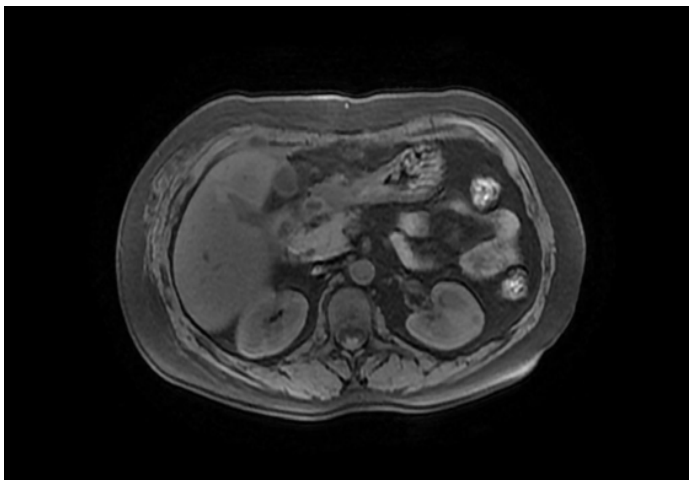


Figure 4. It is hypointense on axial T1 FSPGR fat saturated image.

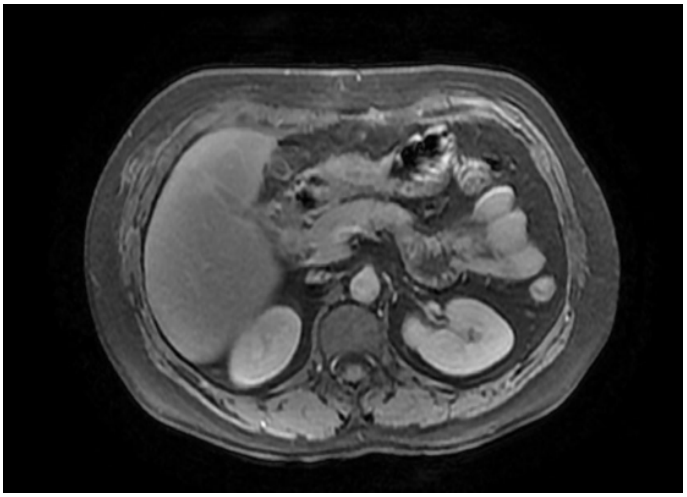


Figure 5. It is not enhanced on post-gadolinium axial T1 FSPGR fat saturated image.

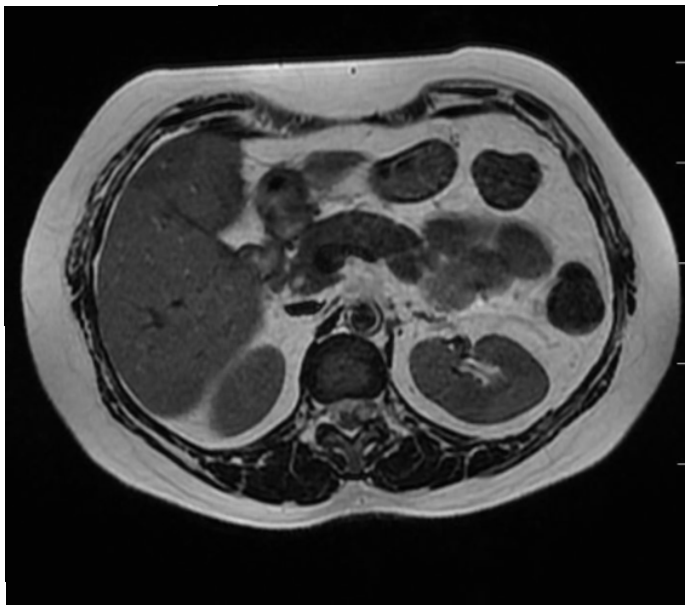


Figure 6. Postoperative 1st month the structure disappeared on axial T2 image.

surgical specimen revealed a falciform ligament fatty necrosis with liquefaction. One month after surgery, cyst on the falciform ligament location was disappeared (Figures 6 and 7).

DISCUSSION

Although the anatomical structure and variations of the falsiform ligament are well known, the associated pathologies are still unclear. The congenital

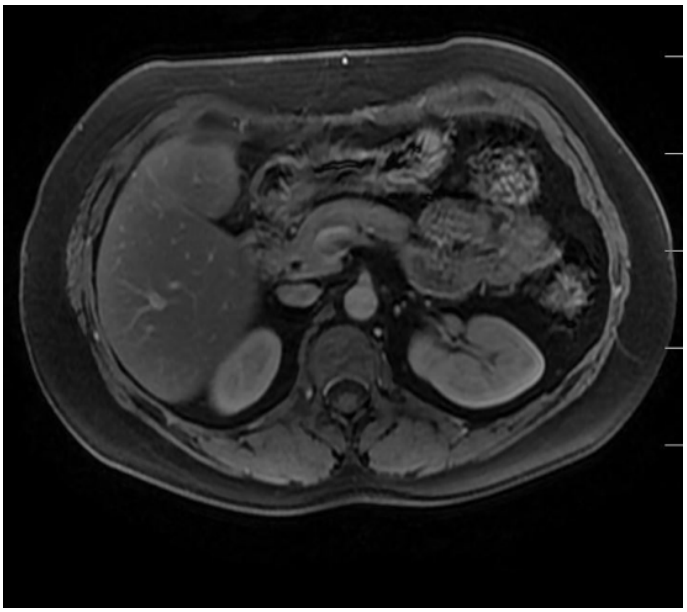


Figure 7. Postoperative 1st month post-gadolinium axial T1 FSPGR fat saturated image (this image is changed due to reviews).

pathologies including derivation and partial ligament defects are the best known anomalies of the falsiform ligament. The most common pathologies of this ligament are abnormal vascularity due to portal hypertension, tumors and ligament cysts [3]. There are still difficulties in diagnose of falciform ligament necrosis came with right upper quadrant pain as in our case.

The falciform ligament artery which arises from the left or middle hepatic artery, runs down the anterior surface of the liver, and reaches the umbilical region. Venous drainage flows directly into the paraumbilical vein and portal vein, while lymphatic drainage flows directly into the retroperitoneum [2]. Falciform ligament necrosis may likely develop, if the embolization of such a narrow artery or collateral venous flow fails due to vein thrombosis. Necrosis due to an occlusion of arterial supply is a rare primary falciform ligament disease [3].

The clinical picture and laboratory values are often nonspecific and may point wrongly towards diagnosis of biliary colic or cholecystitis as in our patient. Although very rare, radiologists should know this fatty necrosis of the falciform ligament, in order to avoid diagnostic error and optimize patient management.
It was reported that the contrast-enhanced abdominal computed tomography is the gold standard for

diagnosis of intraperitoneal fat necrosis as well as the follow-up of the disease [4]. However, there are few recent data on MRI in the literature about falciform ligament pathologies. The liquefaction of the falciform ligament due to fatty necrosis can mimics falciform ligament cysts on MRI as in our case.

Although there have been defined falciform ligament cysts in literature, most recently published in 2009 [5]. Primary cysts include congenital developmental defects of mesenteric origin; secondary cysts include infectious origins (echinococcal cyst and abscess), traumatic causes (liquefaction of a hematoma and bile extravasation), and neoplasms with cystic degeneration [5]. Radiologic features should be evaluated with clinical and histologic findings to distinguish ligament cysts from necrosis.

CONCLUSION

In conclusion, falciform ligament necrosis which is an extremely rare cause of acute abdomen can have different imaging features. It can mimic other pathologies of falciform ligament especially on imaging modalities and also during surgery. It is important to consider clinical, histologic and radiologic findings all together.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] Maccallum C, Eaton S, Chubb D, Franzi S. Torsion of fatty appendage of falciform ligament: acute abdomen in a child. Case Rep Radiol 2015;2015:293491.
[2] Ibukuro K, Fukuda H, Tobe K, Akita K, Takeguchi T. The vascular anatomy of the ligaments of the liver: gross anatomy, imaging and clinical applications. Br J Radiol 2016;89:20150925.
[3] Ozkececı ZT, Ozsoy M, Celep B, Bal A, Polat C. A rare cause of acute abdomen: an isolated falciform ligament necrosis. Case Rep Emerg Med 2014;2014:570751.
[4] Coulier B. Contribution of US and CT for diagnosis of intraperitoneal focal fat infarction (IFFI): a pictorial review. JBR-BTR 2010;93:171-85.
[5] Patel A, Lefemine V, Ramanand BS. A rare case of a peritoneal cyst arising from the falciform ligament. Cases J 2009;2:134.

Bilateral obstetric brachial plexus paralysis: a case report

Canan Çelik[1], Fazıl Kulaklı[1], Asiye Mukaddes Erol[2], Şeniz Akçay Yalbuzdağ[3], Kadir Hacıoğlu[4]

[1]Department of Physical Medicine and Rehabilitation, Giresun University School of Medicine, Giresun, Turkey
[2]Department of Physical Medicine and Rehabilitation, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey
[3]Department of Physical Medicine and Rehabilitation, Bozyaka Training and Research Hospital, İzmir, Turkey
[4]Department of Physical Medicine and Rehabilitation, Sultan 1. Murat State Hospital, Edirne, Turkey

DOI: 10.18621/eurj.376344

ABSTRACT

We aim to report a case with bilateral obstetric brachial plexus paralysis rarely seen after cesarean section. A 28-month-old girl was admitted to our outpatient clinic with weakness in both upper extremities. Shoulders were adducted and internally rotated, elbows were extended with flexion fingers. The 37-year-old mother, fetal breech presentation, premature birth and probably traction forces applied at birth were considered among the risk factors. With this case, it is emphasized that obstetric brachial plexus paralysis occurs rarely bilateral and after cesarean section.

Keywords: Bilateral brachial plexus palsy, infant, cesarean, obstetrics

Received: January 8, 2018; Accepted: February 2, 2018; Published Online: February 13, 2018

Obstetrical brachial plexus injury is defined as a flaccid paresis of an upper extremity due to brachial plexus injury at birth [1]. The incidence varies between 1 and 1.5 per 1000 live births [2]. Hardy [3] reported that five percent of obstetric brachial plexus palsies are bilateral. We aim to report a case with bilateral obstetric brachial plexus paralysis rarely seen after cesarean section.

CASE PRESENTATION

A 28-month-old girl, was admitted to our outpatient clinic with weakness in both upper extremities. Her mother was 37 years old when had given birth. She had received 15 kg during pregnancy and she was 75 kg at birth. There was no uterine anomaly. At 36th weeks with breech presentation, she had given birth by cesarean section under general anesthesia. The infant weighed 2.5 kg and heightened 47 cm at birth. According to Gilbert Shoulder Scale right upper extremity was 1 and left was 0, and according to Mallet's Scale right extremity was 2 and left was 1 [4]. Her proximal muscles of upper extremities were atrophic. Shoulders were adducted and internally rotated, elbows were extended with flexion fingers ("waiter's tip" [1]) (Figure 1).

Cranial, cervical magnetic resonance imaging, and electroencephalography were normal. Evaluated bilateral upper extremity nerve conduction studies and electromyography examination were consistent with moderate neuropathy characterized by axonal degeneration in the bilateral upper-middle-lower trunk.

The rehabilitation program consists of the gently passive range of motion exercises, supporting of joints

Address for correspondence: *Fazıl Kulaklı, MD., Assistant Professor, Giresun University School of Medicine, Department of Physical Medicine and Rehabilitation, Giresun, Turkey.*
E-mail: drfzl46@gmail.com

e-ISSN: 2149-3189

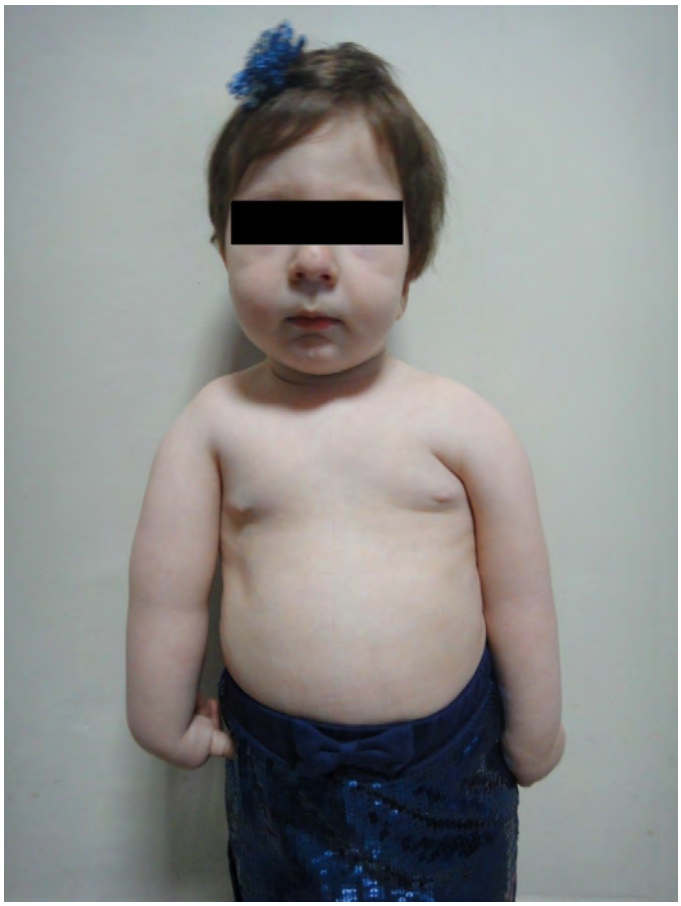


Figure 1. Bilateral adducted shoulders and extended elbows and atrophic proximal muscles were seen ("waiter's tip").

and proper positioning, active assistive exercises and stretching muscle groups to prevent contractures have performed.

An informed consent form was signed by the parents of the patient to approve the use of patient information or material for scientific purposes.

DISCUSSION

Obstetric brachial plexus palsy is a serious problem in infancy that can be prevented. Although 70-92% of patients can able to return to normal function, some patients result in prolonged and persistent disability [1]. Hardy [3] and Dragu *et al.* [5] indicated that bilateral cases represent a more severe condition than unilateral cases.

Neonatal brachial plexus may be damaged by being stretched, compressed, infiltrated, or deprived of oxygen. Stretch is the most common responsible mechanism. Predisposing factors include maternal causes (of greater than 35 maternal age, diabetes mellitus, excessive weight gain during pregnancy, obesity, primiparity), factors associated with labor (shoulder dystocia, breech presentation, instrumented delivery, epidural anesthesia, shortness of second stage of labor) and fetal factors (macrosomia > 4 kg, decreased fetal arm movements, the presence of a first cervical rib and clavicle fracture) [1, 2, 5, 6]. Brachial injury occurs more frequently with breech deliveries, which are usually combined with low birth weight [1]. Maternal older age (37 years old), fetal breech presentation, and premature birth can be considered as the risk factors in our case.

The risk of an obstetrical brachial plexus palsy is lower with cesarean section than with vaginal delivery [1, 6]. The actual incidence of birth palsy in newborns delivered by cesarean section is unknown [7]. Al-Quattan *et al.* [7] demonstrated that only 1% of 1561 newborns with obstetrical brachial plexus injury were delivered by cesarean section.

It has been reported that the cases of obstetric brachial palsy in cesarean sections occur as a result of forceful traction and manipulation by the obstetrician [1]. Besides the importance of traction, the interaction of the physical strength to oppose the forces (brachial plexus nerve bundle, shoulder muscles, bone structure) also plays a significant role. Spontaneous or induced uterine contractions as a driving force can contribute to the traction forces. Some researchers believe that intrauterine maladaptation is responsible for the brachial plexus palsy when considering there are not significant traction forces during the implementation of the suspect or a proven cause at the birth [2, 5]. We think the existence of a possible traction and manipulation forces during the cesarean section in our case.

Bilateral lesions are often associated with breech presentations and are reported in 0-23% of all cases [1]. Dragu *et al.* [5] reported a case with bilateral obstetric brachial plexus lesions and low birth weight (800 g), indicated that this case is very rare. Baliarsing *et al.* [8] reported that a case with bilateral obstetric brachial plexus injury affected C5 and C6 nerve roots. This patient had been born at full term by vertex

presentation. Unlike the cases reported, there was a breech presentation in our case, and birth was carried out by cesarean section, not vaginal. We did not find bilateral obstetric brachial plexus palsy after cesarean section in the literature similar to our case.

CONCLUSION

Bilateral obstetric brachial plexus paralysis is very rare incidence in infants. We consider that maternal older age, fetal breech presentation, premature birth and probably traction and manipulation forces applied at cesarean section are among the risk factors. As a result of the case, it is emphasized that obstetric brachial plexus paralysis occurs rarely bilateral and after cesarean section.

Informed consent

Written informed consent was obtained from the patient's parents for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] Zafeiriou DI, Psychogiou K. Obstetrical brachial plexus palsy. Pediatr Neurol 2008;38:235-42.
[2] Alfonso DT. Causes of neonatal brachial plexus palsy. Bull NYU Hosp Jt Dis 2011;69:11-6.
[3] Hardy AE. Birth injuries of the brachial plexus: incidence and prognosis. J Bone Joint Surg Br 1981;63:98-101.
[4] Vergara-Amador E. Latissimus dorsi transposition for sequelae of obstetric palsy. Colomb Med 2010;41:248-55.
[5] Dragu A, Horch RE, Wirth S, Ingianni G. Bilateral obstetric brachial plexus paralysis: a case report. Klin Padiatr 2009;221:57-9.
[6] Ouzounian JG. Risk factors for neonatal brachial plexus palsy. Semin Perinatol 2014;38:219-21.
[7] al-Qattan MM, el-Sayed AA, al-Kharfy TM, al-Jurayyan NA. Obstetrical brachial plexus injury in newborn babies delivered by caesarean section. J Hand Surg Br 1996;21:263-5.
[8] Baliarsing AS, Doi K, Hattori Y. Bilateral elbow flexion reconstruction with functioning free muscle transfer for obstetric brachial plexus palsy. J Hand Surg Br 2002;27:484-6.

The European Research Journal 2018;4(4):455-459 CASE REPORT

The appearance of pulmonary alveolar microlithiasis on dual-energy X-ray absorptiometry

Ahmed Fathala, Alaa Alduraibi

Department of Radiology, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

DOI: 10.18621/eurj.376484

ABSTRACT

Dual-energy X-ray absorptiometry (DEXA) scan has been widely used as standard method of assessing bone density. Artefacts and incidental findings are frequently encountered on the DEXA scan images, some of which may affect bone mineral density values and the others are only of incidental findings. In this case report, we present a 44-year-old male diagnosed with pulmonary microlithiasis that was confirmed on a transbronchial biopsy. To our knowledge, we report the first case in the literature, describing the appearance of pulmonary alveolar microlithiasis on DEXA scan with brief review of literature on both pulmonary alveolar microlithiasis and artifacts and incidental findings encountered on DEXA scan.

Keywords: Dual-energy X-ray absorptiometry, artefacts, incidental findings, pulmonary alveolar microlithiasis

Received: January 9, 2018; Accepted: February 26, 2018; Published Online: March 30, 2018

Incidental findings can be defined as findings that are unrelated to the clinical indications for the imaging examination. The frequency of the incidental findings depends on the imaging modalities, body regions, and age of the patients. The majority of the incidental findings in the published studies focused on computed tomography (CT) and magnetic resonance imaging (MRI). There are very few studies that reported the prevalence, clinical significance of incidental findings on dual-energy X-ray absorptiometry (DEXA). DEXA belongs to same family of imaging techniques, based as it is a conventional X-ray source of energy with similar physical and technological principles. Pulmonary alveolar microlithiasis (PAM) is a rare disease characterized by accumulation of intra-alveolar minute calculi called microliths [1]. PAM is frequently described incidentally in subjects undergoing chest radiography for other reasons. We report, a case of PAM that was seen on DEXA scan, with brief literature review of both PAM and incidental findings of DEXA scan.

CASE PRESENTATION

A 44-year-old male diagnosed with pulmonary microlithiasis that was confirmed on a transbronchial biopsy. He was referred to our hospital for lung transplant workup. His main complaint was exertional dyspnea and breathless on walking long distance and climbing stairs. Routine work up for lung transplant included chest X-ray, chest CT, pulmonary function test, perfusion lung scan, and DEXA scan. Chest X-ray revealed diffuses bilateral micronodular opacities and apical pleural calcifications consistent with pulmonary microlithiasis (Figure 1). Chest CT showed bilateral alveolar calcification in keeping with the

Address for correspondence: *Ahmed Fathala, MD., King Faisal Specialist Hospital and Research Center, Medical Imaging Service/Department of Radiology, MBC#28, 3354 Riyadh, Saudi Arabia*
E-mail: ahm35799@hotmail.com, Tel: +966552532402 Fax: +966144224841

e-ISSN: 2149-3189

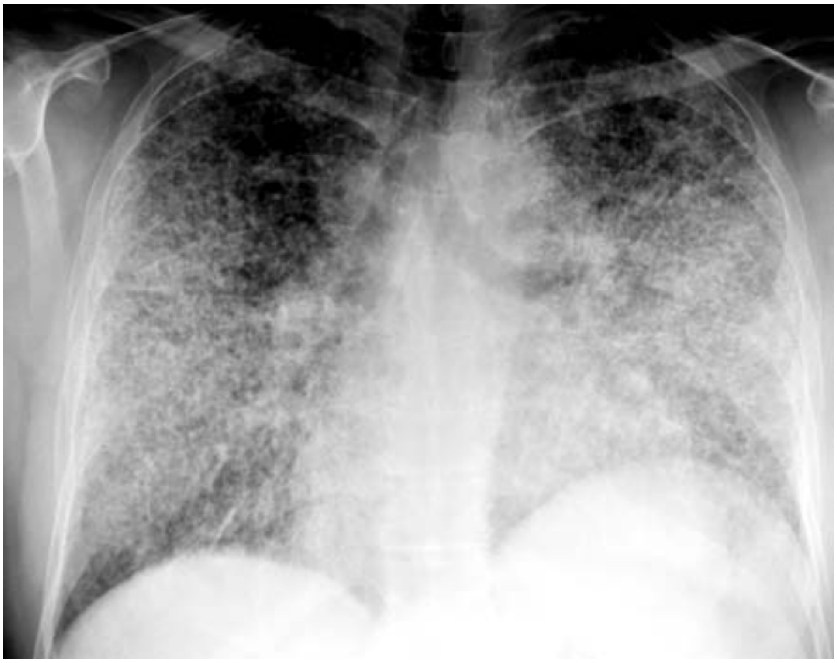


Figure 1. Posterior anterior chest X-ray of the patient showing bilateral symmetrical micronodular alveolar opacities.

diagnosis of pulmonary microlithiasis (Figure 2). Bone densitometry showed normal Z and T scores with extensive dense miliary shadow involving both lungs (Figure 3). His perfusion lungs scan showed heterogeneous lung perfusion bilaterally without evidence of pulmonary embolism (images not shown), His pulmonary function tests were consistent with restrictive lung disease.

DISCUSSION

PAM is a rare autosomal recessive that is characterized by wide spread intra-alveolar accumulation of innumerable minute calculi called microliths [1]. The disease affects both sexes, with a slight predominance among male worldwide. Although cases of PAM described at all ages, the

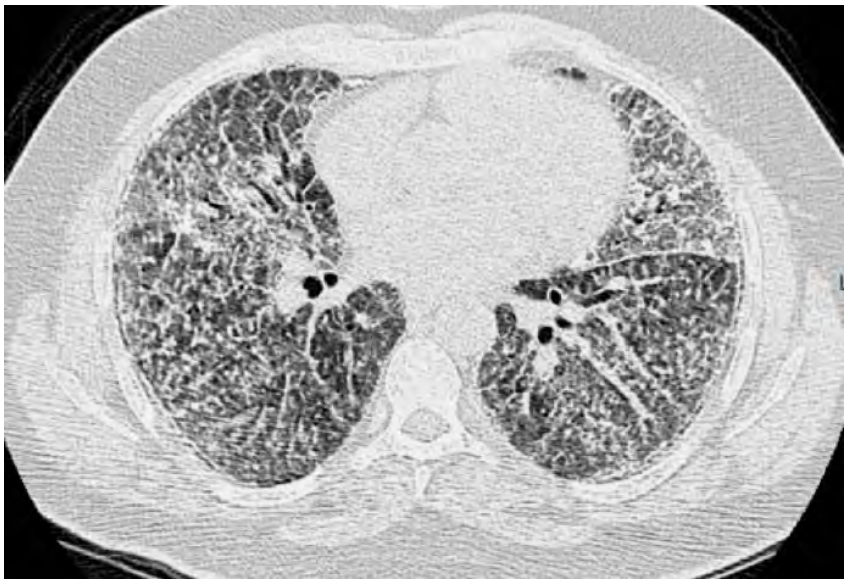


Figure 2. Lung window of the chest CT of the patient demonstrating bilateral parenchymal micronodular opacities and ground glass appearance.

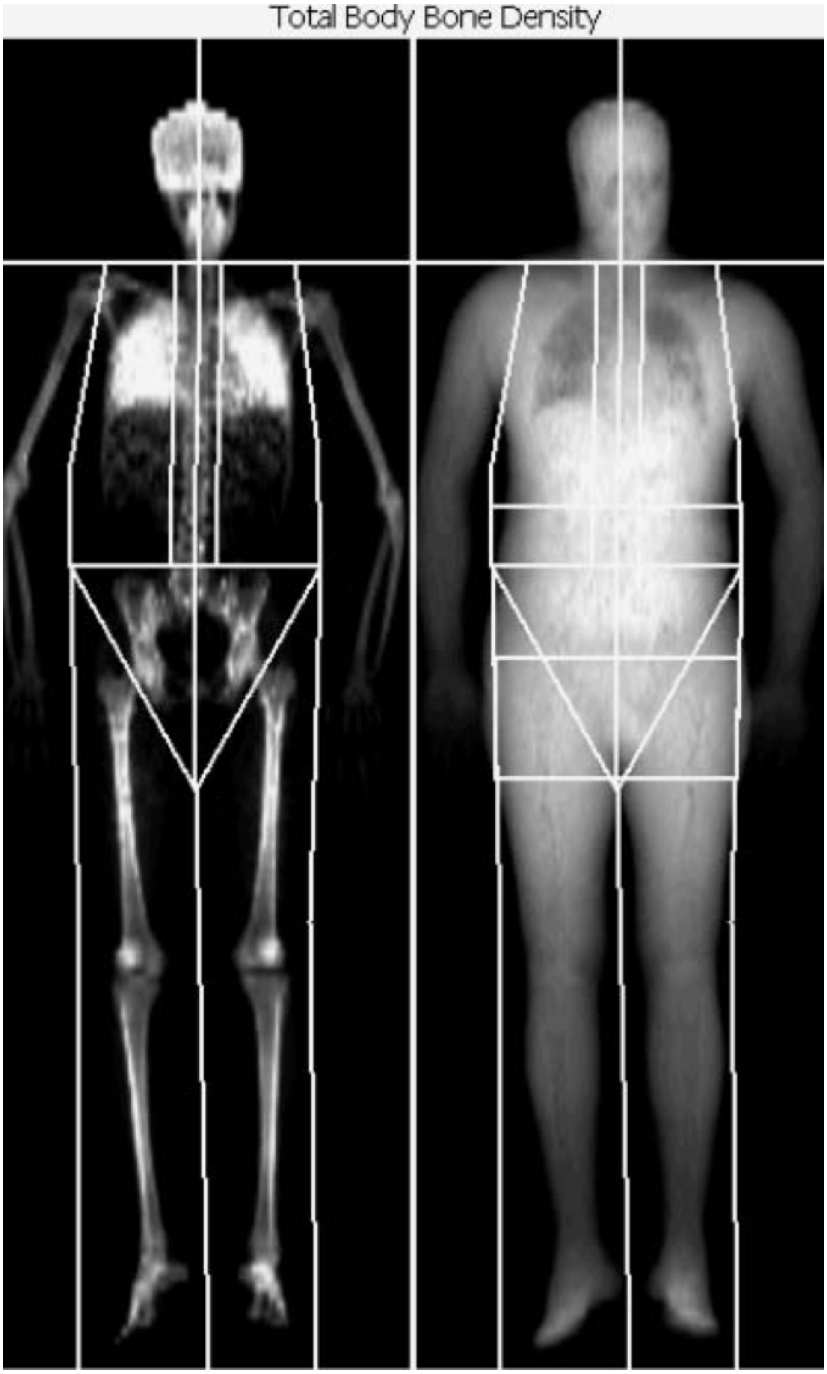


Figure 3. Whole body DEXA scan demonstrates bilateral lung parenchymal opacification consistent with known pulmonary alveolar microlithiasis.

second and third decade were found to be more frequently involved and very few cases in the elderly. Several report have a familial occurrence, with a frequency ranging between 32% to 61% [2]. The clinical presentations are very heterogeneously, ranging from totally asymptomatic to progressive respiratory failure [3]. The clinical course of the disease varies from being stationary in term of both symptoms and of the radiological and functional findings to cor pulmonale and respiratory failure. Diagnosis of PAM may be established by both radiological tests and pathological samples, such as bronchoalveloar lavage, transbronchial biopsy, and open lung biopsy.

Radiological diagnosis is usually made as an incidental finding in chest X-ray performed for

unrelated reasons. Chest X-ray typically shows sand-like calcification distributed through the lungs, bilateral distribution with middle to lower zone predilection, and black pleural lines (Figure 1) [4]. High-resolution CT shows numerous sand-like calcification through the lungs with pleural and peribronchial distribution (typically 1 mm), other additional high-resolution CT features include: crazy paving pattern, calcific interlobular septae, small subpleural cysts, black pleural signs, and ground glass opacities that tend to be more common in children (Figure 2) [5]. The bone scintigraphy scanning agents, such as technetium (Tc)-99m methylene diphosphonate shows diffuse bilateral uptake of radiotracer throughout the lung parenchyma especially in early phases of the disease when not typical chest X-ray findings are detected [6]. PAM may be seen on DEXA scan as diffuse bilateral pulmonary calcification (Figure 3). On MRI the calcific lesions usually show hypointensity or signal void on T1- and T2-weighted images. Interstitial fibrosis and thickened alveolar walls are often seen in advanced stages of PAM, but these changes show higher signal intensity on T2- than T1-weighted images [7]. Low ^{18}F-flurodeoxyglucose (FDG) uptake on positron emission computed tomography (PET) is noted in calcification of PAM and lower FDG accumulation in the lung parenchyma without micronodular opacities. It has been postulated that higher FDG uptake may be a poor prognosis predictor for PAM [8].

In the literature studies dealing with incidental findings on DEXA mainly case reports and few single center retrospective studies. Bazzochi *et al.* [9], retrospectively and randomly reviewed 739 DEXA examinations. The population included 208 male and 531 female. Incidental findings were detected in 117 (15.8%) of 739 examinations. In all cases the key markers used to detect new information from DEXA examination we represented by change in density or shape of tissue. In 76 (65%) of all detected findings, calcifications were the primary sign of physiological or pathological process, in 41 (35%) anatomical features and morphology guided identification. However, only 50 among all incidental findings could be visualized by other imaging modalities [9]. There are several non-osseous causes of elevated bone mineral density measurements. For example, the effects of aortic calcifications on lumbar spine bone mineral density is much discussed the literature, though not universal, most studies reported that vascular calcification have no significant effects on bone mineral density [10]. Cholelithiasis, nephrolithiasis, and calcific leiomyofibroma are frequently seen on DEXA such as porcelain gall bladder, mesenteric calcifications, phleboliths, and calcinosis cutis [11]. Heterotopic calcification of the hip has been described as causes of apparent increase in bone mineral density [12]. These extra-skeletal calcifications represent a common manifestation of several pathological processes.

CONCLUSION

In summary, PAM is a rare genetic disease characterized by numerous intra-alveolar accumulations of microliths. Diagnosis of PAM can be made on the basis of the typical chest X-ray and chest CT. However, it may be seen as incidental finding in many other imaging modalities such as bone scan and DEXA scan.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] Barbolini G, Rossi G, Bisetti A. Pulmonary alveolar microlithiasis. N Eng J Med 2002;347:69-70.
[2] Sosman MC, Dodd GD, Jones WD, Pillmore GU. The familial occurrence of pulmonary alveolar microlithiasis. Am J Roentgenol Radium Ther Nucl Med 1957;77:947-1012.
[3] Mariotta S, Ricci A, Papale M, De Clementi F, Sposato B, Guidi L, et al. Pulmonary alveolar microlithiasis: report on 576 cases published in the literature. Sarcoidosis Vasc Diffuse Lung Dis 2004;21:173-81.
[4] Helbich TH, Wojnarovsky C, Wunderbaldinger P, Heinz-Peer G, Eichler I, Herold CJ. Pulmonary alveolar microlithiasis in children: radiographic and high-resolution CT findings. AJR Am J Roentgenol 1997;168:63-5.
[5] Gasparetto EL, Tazoniero P, Escuissato DL, Marchiori E, Frare E Silva RL, Sakamoto D. Pulmonary alveolar microlithiasis presenting with crazy-paving pattern on high resolution CT. Br J Radiol

2004;77:974-6.
[6] Fallahi B, Ghafary B, Fard-Esfahani A, Eftekhari M. Diffuse pulmonary uptake of bone-seeking radiotracer in bone scintigraphy of a rare case of pulmonary alveolar microlithiasis. Indian J Nucl Med 2015;30:277-9.
[7] Hoshino H, Koba H, Inomata S, Kurokawa K, Morita Y, Yoshida K, et al. Pulmonary alveolar microlithiasis: high-resolution CT and MR findings. J Comput Assist Tomogr 1998;22:245-8.
[8] Ito K, Kubota K, Yukihiro M, Izumi S, Miyano S, Kudo K, et al. FDG-PET/CT finding of high uptake in pulmonary alveolar microlithiasis. Ann Nucl Med 2007;21:415-8.
[9] Bazzocchi A, Ferrari F, Diano D, Albisinni U, Battista G, Rossi C, et al. Incidental findings with dual-energy X-ray absorptiometry: spectrum of possible diagnoses. Calcif Tissue Int 2012;91:149-56.
[10] Frye MA, Melton LJ 3rd, Bryant SC, Fitzpatrick LA, Wahner HW, Schwartz RS, et al. Osteoporosis and calcification of the aorta. Bone Miner 1992;19:185-94.
[11] Martineau P, Bazarjani S, Zuckier LS. Artifacts and incidental findings encountered on dual-energy X-ray absorptiometry: atlas and analysis. Semin Nucl Med 2015;45:458-69.
[12] Stewart CA, Hung GL, Garland DE, Rosen CD, Adkins R. Heterotopic ossification. Effect on dual-photon absorptiometry of the hip. Clin Nucl Med 1990;15:697-700.

THE ASSOCIATION OF HEALTH
RESEARCH AND STRATEGY