e-ISSN:2602-2079

Volume 3
Issue 3
2019

JOURNAL of Surgery and Medicine

International Medical Journal

Volume: 3 - Issue: 3

1.858 | 2.120

Contents

Importance of autophagy in colorectal cancer: A cross-sectional study (http://dergipark.gov.tr/josam/issue/38949/536733) / Pages: 246-249 PDF (/download/article-file/668383)
Hilmi Erdem Sümbül, Hikmet Akkız

Investigation of concordance between referral diagnosis and electroneuromyographic diagnosis (http://dergipark.gov.tr/josam/issue/38949/519328) / Pages: 250-253 PDF (/download/article-file/669360)
Ali Rıza Sonkaya, Mustafa Karaoğlan

Variations of tuberculin skin test in patients with rheumatologic disorders and under anti-TNF treatment (http://dergipark.gov.tr/josam/issue/38949/537201) / Pages: 254-257 PDF (/download/article-file/669365)
Tayfun Özdemir, Serpil Tuna, Özlem Karataş, Mehmet İhsan Arman

A modified method for punctoplasty: “Excisional punctoplasty with the guidance of a 27 G Rycroft cannula” (http://dergipark.gov.tr/josam/issue/38949/537361) / Pages: 258-261 PDF (/download/article-file/671906)
Onur Temizsoylu, Gözde Şahin, Alev Koçkar, Alper Şengül, Erdal Yüzbaşıoğlu

Case report

Computed tomography findings of mesenteric ischemia related to acute superior mesenteric vein thrombosis: A case report (http://dergipark.gov.tr/josam/issue/38949/470446) / Pages: 262-264 PDF (/download/article-file/671994)
Emrah Doğan, Marwa Mouline Doğan, Süha Gül, Bünyamin Güney

A case of parathyroid carcinoma mimicking parathyroid adenoma (http://dergipark.gov.tr/josam/issue/38949/473603) / Pages: 265-267 PDF (/download/article-file/671995)
Semra Demirli Atıcı, Değercan Yeşilyurt, Dudu Solakoğlu Kahraman, Emre Dikmeer, Hakan Öğücü, Halit Batuhan Demir, Gökhan Akbulut

Liver alveolar hydatid cyst diagnosed patient with right intrahepatic biliary tract obstruction: A case report with special emphasis on radiological features (http://dergipark.gov.tr/josam/issue/38949/478202) / Pages: 268-270
Fatih Ateş, Turgay Kara, Halil İbrahim Şara, Muhammed Sami Çoban, Mehmet Sedat Durmaz, Funda Gökgöz Durmaz PDF (/download/article-file/671997)

Case of incomplete fibular hemimelia with tarsal coalition, pes planus, ball and socket ankle (http://dergipark.gov.tr/josam/issue/38949/470613) / Pages: 271-273 PDF (/download/article-file/631481)
Emrah Doğan, Süha Gül, Neşat Çullu, Marwa Mouline Doğan

A rare and incidental finding during colonoscopy: solitary polypoid ganglioneuroma: A case report (http://dergipark.gov.tr/josam/issue/38949/502639) / Pages: 274-275 PDF (/download/article-file/656383)
Elif Usturalı Keskin, Tufan Yılmaz, Gürol Şen

Thymolipoma with massive pleural effusion: A case report (http://dergipark.gov.tr/josam/issue/38949/507306) / Pages: 276-277 PDF (/download/article-file/664829)
Zeynep Bayramoğlu, Ethem Ömeroğlu, Yaşar Ünlü

Pseudo-septic arthritis developed after hyaluronic acid injection: A case report (http://dergipark.gov.tr/josam/issue/38949/538939) / Pages: 278-279 PDF (/download/article-file/671638)
Özlem Karataş, Tiraje Tuncer

Issue Full File (/download/issue-full-file/38949)

ULAKBİM Dergi Sistemleri v 19.02.2 (//dergipark.gov.tr/)

J Surg Med. 2019;3(3):202-205.
DOI: 10.28982/josam.457554

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

When to apply propess to provide the best activity: In the morning or evening?

En iyi propess aktivitesi için ideal uygulama zamanı nedir: Sabah mı, akşam mı?

Gül Nihal Büyük [1], Seval Sarıaslan [1], Hatice Kansu Çelik [1], Özlem Uzunlar [2]

[1] Ankara Dr. Zekai Tahir Burak Women's Health Application and Research Center, University of Healty Sciences, Department of Obstetrics and Gynecology, Ankara, Turkey
[2] Ankara Dr. Zekai Tahir Burak Women's Health Application and Research Center, University of Healty Sciences, Department of Reproductive Endocrinology, Ankara, Turkey

ORCID ID of the author(s)

GNB: 0000-0003-4405-2876
SS: 0000-0003-4368-0766
HKÇ: 0000-0002-8443-7239
ÖU: 0000-0003-3453-3852

Corresponding author / Sorumlu yazar:
Gül Nihal Büyük
Address / Adres: Zekai Tahir Burak Kadın Sağlığı Uygulama ve Araştırma Merkezi Hacettepe Mahallesi, Talatpaşa Bulvarı, 06230 Samanpazarı, Altındağ, Ankara, Türkiye
E-mail: gnu@windowslive.com

Ethics Committee Approval: Ethical approval has been obtained from the ethical committee of Zekai Tahir Burak hospital.
Etik Kurul Onayı: Bu çalışma için Zekai Tahir Burak hastanesinin etik kurulundan etik onay alındı.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 05.09.2018
Accepted / Kabul Tarihi: 08.11.2018
Published / Yayın Tarihi: 24.11.2018

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Abstract

Aim: Propess is a drug of choice in our daily practice for induction of labor. The dosing plan of the drugs can be idealized by arranging them according to the chronobiological model. The aim of this study is to investigate the "time of administration" suggestions on chronotherapy for propess.

Methods: Our study was conducted retrospectively by examining the records of pregnant women who were given propess at Zekai Tahir Burak Women's Health Training and Research Hospital between 2008 and 2018. A total of 2694 patients were included in the study. Two groups were allocated according to the time of drug administration. The time from application to birth was calculated.

Results: Logistic regression analysis was performed for risk factors and we found that the time of drug administration was effective on duration to labor. The time from drug administration to labor was 18.0±4.0 hours in the morning group and 19.1±3.9 hours in the evening group ($p<0.001$)

Conclusion: It appears; drugs used for labor induction in the morning may increase drug efficacy and bioavailability. At this point birth becomes compatible with body biorhythm and the time to labor can be shortened.

Keywords: Chronotherapy, Labor induction, Dinoprostone

Öz

Amaç: Propess, doğum indüksiyonu için günlük pratiğimizde sık tercih edilen bir ilaçtır. İlaçların etkinliği, uygulama zamanları kronobiyolojik modele göre düzenlenerek idealize edilebilir. Bu çalışmanın amacı, propess uygulama zamanının ilaç etkinliğine olan etkisini araştırmaktır.

Yöntemler: Çalışmamız 2008-2018 yılları arasında Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesinde doğum indüksiyonu amacıyla propess uygulanmış gebe kadınların kayıtları inceleyerek retrospektif olarak yapıldı. Çalışmaya toplam 2694 hasta dahil edildi. İlaç uygulaması zamanına göre, hastalar sabah uygulananlar ve akşam uygulananlar olarak iki gruba ayrıldı. Uygulamadan doğuma kadar geçen süre saat olarak hesaplandı.

Bulgular: Risk faktörleri için lojistik regresyon analizi yapıldı ve ilaç uygulama zamanının doğum eylemi süresi üzerinde etkili olduğu bulundu. İlaç uygulamasından doğuma kadar geçen süre sabah grubunda 18,0±4,0 saat, akşam grubunda ise 19,1±3,9 saat olarak bulundu ($p<0,001$).

Sonuç: Görünüşe göre; Sabah doğum indüksiyonu için kullanılan ilaçlar, ilaç etkinliğini ve biyoyararlanımını arttırabilir. Bu noktada doğum vücut bioritmi ile uyumlu hale gelir ve doğum zamanı kısaltılabilir.

Anahtar kelimeler: Kronoterapi, Doğum indüksiyonu, Dinoproston

How to cite / Atıf için: Büyük GN, Sarıaslan S, Çelik HK, Uzunlar Ö. When to apply propess to provide the best activity: In the morning or evening? J Surg Med. 2019;3(3):202-205.

Introduction

Induction of labor; refers to the stimulation of uterine contractions by any mechanical process or pharmacological drug in the presence of ruptured or non-ruptured membranes before spontaneous birth [1].

In obstetric practice, birth induction is becoming an increasingly common medical procedure in proportion to the increased knowledge and experience in the perinatal field. Oxytocin is a safe and effective initiator of uterine contractions in labor induction but depends on the condition of the cervix. In cases where the cervix is not suitable, the start of labor is usually difficult and long, cesarean rate increases. This can lead to poor obstetric outcomes for both mother and baby [2]. By adjusting the cervix, the time from the beginning of induction to the time of birth is shortened and the need for caesarean section is reduced [3]. Various mechanical and medical methods are used to mature the cervix in term pregnancies. Medical methods; prostaglandins and relaxation, mechanical methods include finger enlargement, removal of fetal membranes and balloon catheterization [4]. Prostaglandin preparations are generally accepted for the preparation of a cervix not suitable for induction. There are different prostaglandin preparations used for this purpose. A locally administered dinoprostone formulation, PROPESS vaginal insert; cervical ripening was approved in 1995 for use. It is used to initiate cervical ripening in patients with a Bishop score of 6 or less in the absence of fetal and maternal contraindications, in the presence of a singleton cephalic condition [5].

Cervical ripening is a gradual process. Dinoprostone requires several hours of exposure. Prolonged cervical ripening times for pregnant women who require labor induction in the hospital may be a psychological distress [6]. Patients should be monitored for fetal wellbeing and uterine contractions until cervical ripening is achieved and the patient enters the travail. For this reason, it often takes more than 12 hours for hospitalized patients. Long hospitalization is not desirable as far as patients are concerned in terms of health personnel and health care institutions [7].

Propess is a drug of choice in our daily practice due to its consistently low doses of dinoprostone, controlled release, withdrawal system, which allows the end of the 12-hour dosing period or the termination of prostaglandin release during active labor [7]. Although it is a frequently used drug, studies have not yet been found in the literature on the most appropriate timing of propess administration. Chronotherapy involves the administration of medication in coordination with the body's circadian rhythms to maximize therapeutic effectiveness [8]. The dosing plan of the drugs can be idealized by arranging them according to the chronobiological model. The safety and efficacy of the drug can be brought to the peak by coordinating with the circadian rhythm [9].

The first use of chronotherapy in practice was introduced in the 1960s when morning ingestion of corticosteroid medication was adopted to reduce its adverse effects [10]. For this purpose they made a rapid release tablet formulation accompanying the cortisol release from the circulation by the adrenal cortex [11].

The aim of this study is to investigate the "time of administration" suggestions on chronotherapy for propess.

Materials and methods

Our study was conducted retrospectively by examining the records of pregnant women who were given propess at Zekai Tahir Burak Women's Health Training and Research Hospital between 2008 and 2018. Ethical committee approval was obtained in our work. A total of 3987 patient files were scanned. A total of 2694 patients were included in the study. Demographic information and antenatal information of the patients were obtained from the patient files. All patients were singleton pregnancies with occipital presentation, no vaginal delivery contraindication. Patients were between 37 and 42 weeks of gestation. All patients had a Bishop score below 5. The Bishop Score (also known as Pelvic Score) is the most commonly used method to rate the readiness of the cervix for induction of labor. The Bishop Score gives points to 5 measurements of the pelvic examination dilation, effacement of the cervix, station of the fetus, consistency of the cervix, and position of the cervix. If the Bishop score is 6 or less the chances of having a vaginal delivery are low and the cervix is said to be unfavorable or "unripe" for induction. Preterm cases, patients with additional disease (as; diabetes, thyroid disease, systemic infection) and patients with missing data were not included. Patients who underwent epidural anesthesia were also excluded. Time of drug administration and birth times of patients were recorded. The time from application to birth was calculated. Two groups were allocated according to the time of drug administration. First group; in the morning, the second group consisted of evening drug applications. Patients with caesarean section were not included in the calculation. Primer outcome measures were the time from drug administration to labor and vaginal birth rate; seconder outcomes were cesarean section birth rate, cesarean section indications, need for oxytocin, neonatal intensive care need and low APGAR score.

Statistical analysis

All data were analyzed by statistics software SPSS 19.0. Results were given as mean ± SD or percentage, time intervals were analyzed with ANOVA test, other data were analyzed with Chi-square test for qualitative and U Mann-Whitney test for quantitative variables. Logistic regression analysis was performed for risk factors effective on delivery time. All tests were two-sided, $p<0.05$ was considered statistically significant.

Results

Between 2008 and 2018, 134644 patients were delivered in our hospital. 3987 of these patients were administered propess for induction of labor. Of these patients, 287 were due to preterm, 177 due to additional disease, 246 due to epidural anesthesia and 583 were not included in the study because their records were not fully accessible. A total of 2694 patients who were able to access the data were included (Figure 1). Patients were divided into two groups according to daytime application time. First group; in the morning: 1548 (57.5%), the second group consisted of evening: 1146 (42.5%) drug applications.

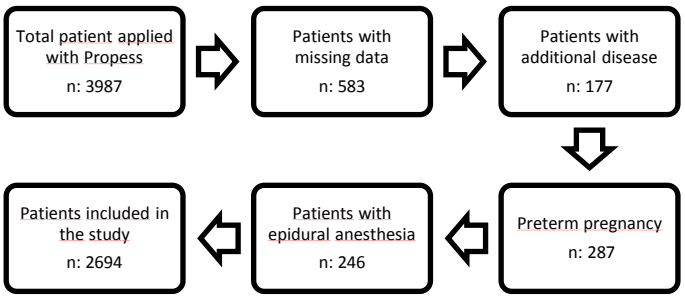

Figure 1: Patient selection flow chart

Of the patients participating in the study, 510 (18.9%) were multigravid and 2184 (81.1%) were primigravid. The ages of the patients ranged from 18 to 42 years. Pregnancy weeks were between 37 and 42 weeks. The BMI of the patients ranged from 22.6 to 34.2. The time from drug administration to labor ranged from 8 to 42 hours. The birth weight of the babies was between 2500 and 4450. Age, BMI, parity, gestational week were statistically similar in both groups. Oxytocin requirement was lower in the first group than in the second group (22.2% versus 30.6%). There was no difference between the two groups in terms of neonatal intensive care need and low Apgar score (Table 1).

A total of 262 patients were caesarean sections. Indications were as follows; 114 (43.5%) cefalopelvic disproportion, 98 (37.4%) fetal distress, 38 (14.5%) non progressive action, 7 (2.7%) placenta ablation, and 5 (1.9%) was caesarean section due to uterine rupture. There was no difference between groups in terms of cesarean rates and indications (Table 2).

Logistic regression analysis were performed for risk factors and we found that the time of drug administration was effective on duration to labor. The time from drug administration to labor was18.0±4.0 hours in the morning group and 19.1±3.9 hours in the evening group (p<0.001) (Table 3).

Table 1: Demographic and clinical characteristics of the subjects

Variables	Morning (n:1548)	Evening (n:1176)	p value
Age(yrs)	27.0±6.1	26.9±6.2	0.387*
BMI (kg/m2)	27.5±3.0	27.7±3.4	0.311
Primipar	1245(80.4%)	939(81.9%)	0.322¶
Birthweight(gr)	3293±319	3273±344	0.163*
Gestationalage (wks)	39.8±1.3	39.9±1.2	0.084*
Delivery route			0.075¶
Vaginal	1411(91.1%)	1021(89.1%)	
C-section	137(8.9%)	125(10.9%)	
Delivery time (hrs)	18.0±4.0	19.1±3.9	<0.001*
Oxytocin	344 (22.2%)	351(30.6%)	<0.001¶
Nicuadmission	57(3.7%)	44(3.8%)	0.832¶
5th minuteApgar<7	62(4.0%)	57(5.0%)	0.226¶

Mean ± standard deviation and number (percentage).*Mann Whitney-U test, ¶ Chisquare test. A p value<0.05 is considered statistically significant

Table 2: Comparison of the group saccording to the delivery route

Variables	C-section (n:262)	Vaginal birth (n:2434)	p value
Age(yrs)	33.2±7.0	26.3±5.6	<0.001*
Primipar	211(80.5%)	1973(81.1%)	0.816¶
Birthweight(gr)	3363±416	3276±318	<0.001*
Gestationalage (wks)	39.8±1.3	39.9±1.3	0.506*
Day time			0.075
Morning	137(52.3%)	1411(58%)	
Evening	125(47.7%)	1021(42%)	
Delivery time (hrs)	19.3±4.0	18.4±4.0	0.001*
Oxytocin	61(23.3%)	634 (26.1%)	0.327¶
Nicuadmission	21(8.1)	80(3.3%)	<0.001¶
5th minuteApgar<7	29(11.1%)	90(3.7%)	<0.001¶

Mean ± standard deviation and number (percentage).*Mann Whitney-U test, ¶ Chisquare test. A p value<0.05 is considered statistically significant.

Table 3: Multivariate logistic regression analysis of risk factors effective on delivery time

Variable	Wald	p value	Odds ratio	95% CI
Daytime	-0.124	<0.001	-1.004	-1.299-0.710
Parity	-0.266	<0.001	-2.709	-3.154-2.265
Oxytocin	-0.017	0.370	-0.153	-0.486-0.181
Gestationalweek	-0.004	0.828	-0.013	-0.126-0.101
Birthweight	-0.018	0.341	0.000	-0.001-0.000
Age	0.036	0.098	0.023	-0.004-0.051
BMI	-0.011	0.629	-0.013	-0.068-0.041

BMI: body mass index, CI: confidence interval. A p value<0.05 is considered as statistically significant

Discussion

The main objective of obstetrics is to provide a healthy fetal birth with minimal trauma to the mother. Sometimes it may be necessary to terminate the pregnancy because of maternal or fetal reasons [12]. Although induction of labor is necessary for a variety of obstetric and medical reasons, inability to cervical ripeness is often a negative factor affecting the success of labor induction [13]. Many agents are used to prepare the cervix for breeding and for inducing uterine changes that can respond to induction with oxytocin. Among these agents, prostaglandin analogs have an important place [14].

The use of prostaglandin E2 (dinoprostone) increases the likelihood of successful induction, reduces the incidence of prolonged labor and reduces maximum oxytocin doses. Propess; is the drug of choice in our daily practice due to its ability to provide continuous low dose dinoprostone, controlled release, withdrawal system that allows it to stop prostaglandin release at the end of the 12-hour dosing period or during active labor [15].

Various investigations have been made to keep the drug activity and bioavailability at the optimum level. As a result of the chronotherapy, the safety and efficacy of the drug can be brought to the peak by coordinating with the circadian rhythm. The first use of chronotherapy in practice was introduced in the 1960s when morning ingestion of corticosteroid medication was adopted to reduce its adverse effects. For this purpose they made a rapid release tablet formulation accompanying the cortisol release from the circulation by the adrenal cortex [10].

At the beginning of a normal term birth, the function of the hormones is great. This process provides the fetus fundamentally through the placenta, fetal membranes and the endocrine system of the mother. In the case of chronic stress, the hypothalamic axle is stimulated and pathological corticotropin releasing hormone (CRH) begins to be released. Pathological CRH stimulates uterine contractions and causes birth to start [16]. CRH plays the most basic role in determining the duration of pregnancy or the time of birth in term or preterm labor. The increase in levels of cortisol released from the adrenal glands causes an increase in placental oxytocin, Prostaglandin E2, Prostaglandin F2 and placental CRH. Following these changes, contraction of the uterus and maturation of the cervix are ensured. As a result of all this, labor starts [17].

In this study we found that the time from drug administration to labor were 18.0±4.0 hours in the morning group and 19.1±3.9 hours in the evening group. This situation looks like the time of drug administration was effective on duration to labor. A few hours' difference in time of delivery due to high cortisol levels in the morning. Starting induction of labor while high cortisol levels may be causing the shortening of the labor until birth.

Conclusion

Drugs used for labor induction in the morning may increase drug efficacy and bioavailability. At this point birth becomes compatible with body biorhythm and the time to labor can be shortened.

References

1. ACOG Committee on Practice Bulletins—obstetrics. ACOG practice bulletin no. 107. Induction of labor. Obstet Gynecol. 2009;114(3):86–97.
2. Alfirevic Z, Keeney E, Dowswell T, Welton NJ, Dias S, Jones LV, Navaratnam K, Caldwell DM. Labor induction with prostaglandins: a systematic review and network meta-analysis. BMJ. 2015;5(350):h217.
3. Coonrod DV, Bay RC, Kishi GY. The epidemiology of labor induction: Arizona, Am J Obstet Gynecol. 2000;18:1355-62.
4. Rodney KE, Douglas SR. Preinduction Cervical Assesment. Clinical Obstetrics and Gynecology. 2000;43:3440-6.
5. Aghideh FK, Mullin PM, Ingles S, Ouzounian JG, Opper N, Wilson ML, Miller DA, Lee RH. A comparison of obstetrical outcomes with labor induction agents used at term. J Matern Fetal Neonatal Med. 2014;27(6):592–6.
6. Geeta K, Swamy MD. Current methods of labor induction. Semin Perinatol. 2012;36(5):348–52.
7. Riboni F, Garofalo G, Pascoli I, et al. Labour induction at term: clinical, biophysical and molecular predictive factors. Arch Gynecol Obstet. 2012;286:1123-9.
8. Lemmer B. Chronopharmacology and controlled drug release. Expert Opin. Drug Deliv. 2005;2:667–81. doi: 10.1517/17425247.2.4.667.
9. Lemmer B. The clinical relevance of chronopharmacology in therapeutics. Pharmacol Res. 1996;33:107–15. doi: 10.1006/phrs.1996.0016.
10. Smolensky MH, Peppas NA. Chronobiology, drug delivery, and chronotherapeutics. Adv Drug Deliv Rev. 2007;59:828–51. doi: 10.1016/j.addr.2007.07.001.
11. Nainwal N. Chronotherapeutics A chronopharmaceutical approach to drug delivery in the treatment of asthma. J Control Release. 2012;163:353–60. doi: 10.1016/j.jconrel.2012.09.012.
12. Boulvain M, Kelly AJ, Irion O. Intracervical prostaglandins for induction of labour. Cochrane Database of Systematic Reviews, 2008, Issue 1. Art. No.: CD006971. DOI: 10.1002/14651858.CD006971.
13. Kelly AJ, Malik S, Smith L, et al. Vaginal prostaglandin (PGE2 and PGF2α) for induction of labour at term. Cochrane Database of Systematic Reviews, 2012;5.
14. Caughey AB, Sundaram V, Kaimal AJ, et al. Systematic Review: Elective Induction of Labor Versus Expectant Management of Pregnancy. Ann Intern Med. 2009;151:252-63.
15. Cunningham FG, MacDonald PC, Gant NF, et al., eds. Williams Obstetrics. 2001,21th ed. Stamford, Conn.: Appleton & Lange.
16. Latendresse G. The interaction between chronic stress and pregnancy: preterm birth from a biobehavioral perspective. J Midwifery Womens Health. 2009;54(1):8–17.
17. Laursen, M. Hedegaard, M., Johansen, C. Fear of childbirth: predictors and temporal changec among nulliparous women in the Danish National Birth Cohort. BJOG An International Journal of Obstetrics and Gynaecology. 2008;115:354-60.

J Surg Med. 2019;3(3):206-209.
DOI: 10.28982/josam.465499

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Association between nephropathy and QT dispersion in type 2 diabetic patients

Tip 2 diabetes hastalarında proteinüri ve QT dispersiyonu arasındaki ilişki

Beyza Oluk [1]

[1] **Arnavutköy State Hospital, Internal Medicine Clinic, Istanbul, Turkey**

ORCID ID of the author(s)
BO: 0000-0002-7515-5571

Corresponding author / Sorumlu yazar:
Beyza Oluk
Address / Adres: Eski Edirne Asfaltı, Arnavutköy Devlet Hastanesi, 4.kat Dahiliye Kliniği, Arnavutköy, İstanbul, Türkiye
E-mail: drbeyzasen@gmail.com

Ethics Committee Approval: Ethics committee approval was not received because the study design was retrospective.
Etik Kurul Onayı: Çalışma retrospektif olması nedeniyle etik kurul onayı alınmamıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 28.09.2018
Accepted / Kabul Tarihi: 24.11.2018
Published / Yayın Tarihi: 26.11.2018

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Abstract

Aim: Due to increased diabetes and diabetes-related mortality all over the world, the importance of appropriate and readily available screening tests for diabetic patients is increasing. In this study, we investigated the relationship between urine protein/creatinine ratio and QT dispersion. We aimed to determine the association between nephropathy and autonomic neuropathy, the two significant complications of diabetes, through simple and achievable tests.

Methods: We retrospectively evaluated the medical records of 45 male and 50 female patients, who were attended at diabetes outpatient clinic with a diagnosis of type 2 diabetes in one month period. A 12-lead electrocardiogram (ECG), HbA1 and glucose levels were evaluated. Urinary protein/creatinine ratios (P/K) were measured at spot intervals. ECGs were transferred to the computer environment, and QT intervals were calculated and corrected for the patient's heart rate using Bazett's formula. QT-max (longest QT interval), QT-min (shortest QT interval) and QT-dispersion analyzes were performed in two groups, in all patients by excluding those with ischemic heart disease. The threshold value for proteinuria detection was 91 mg/g. Spot urine protein/creatinine ratio of less than 91mg/g was accepted as normal, and those with over 91mg/g were classified as proteinuric.

Results: The mean QT-min (388.50 ± 27.28 ms), QT-max (441.25 ± 29.76 ms) and QT dispersion (52,74 ± 16,80 ms) were significantly higher than the reference values in both groups-in all patients by excluding those with ischemic heart disease. When all cases and those with ischemic heart disease were excluded, QT dispersion value was higher in patients with proteinuria (those with urine P/K levels 91 mg/g and above). This difference was not statistically significant. (p> 0.05) In this study, we found that QT durations were long independent of cardiovascular disease in diabetic patients, but not associated with protein/creatinine ratio

Conclusion: As a result, in this study, we examined the relationship between spot urine protein/creatinine ratio and QT intervals in diabetic patients, and we did not find a significant association between the two parameters. Although there have been studies in the literature showing that there is a relationship between albumin/creatinine ratio and QT intervals, we could not find an association with P/K ratio.

Keywords: Proteinuria, QT dispersion, Urine protein creatinine ratio

Öz

Amaç: Tüm dünyada artan diyabet ve diyabete bağlı mortalite nedeniyle diyabet hastalarında uygun ve kolay ulaşılabilir tarama testlerinin önemi artmaktadır. Idrar protein/kreatinin oranı ve QT dispersiyonu arasındaki ilişkiyi araştırdığımız bu çalışmada amacımız diyabetin iki önemli komplikasyonundan nefropati ve otonom nöropati arasındaki ilişkiyi basit ve ulaşılabilir testler ile saptayabilmekti.

Yöntemler: Bir aylık süre içinde, tip 2 diyabet tanısı ile diyabet polikliniğine başvuran, 45 erkek, 50 kadın hastanın tıbbi kayıtları retrospektif olarak tarandı. Hastalara 12 derivasyonlu elektrokardiyogram (EKG), HbA1c, glukoz değerleri bakıldı. İdrar protein kreatinin oranı(P/K), spot idrar örneklerinden ölçüldü. EKG'ler bilgisayar ortamına aktarılarak QT süreleri hesaplandı ve kalp hızına göre Bazett formülü ile düzeltildi. QT-max (en uzun QT süresi), QT-min (en kısa QT süresi) ve QT-dispersiyonu analizleri tüm hastalar ve iskemik kalp hastalığı olanlar hariç tutularak iki grup olarak çalışıldı. Proteinüri için eşik değer 91mg/g olarak lındı. 91mg/g ve üzeri proteinüri , 91mg/g altında olanlar normal olarak gruplandırıldı.

Bulgular: Hastaların QT-min (388,50±27,28 msn), QT-max (441,25±29,76 msn) ve QT-dispersiyonu (52,74±16,80 msn) değerleri ortalaması iskemik kalp hastalığı olanlar çıkarılsa da referans değerlerden uzun bulundu. Hem tüm olgularda, hem de iskemik kalp hastalığı olan olgular hariç tutulduğunda idrar protein/kreatinin oranına göre, proteinürisi olanlarda (idrar P/K 91mg/g ve üzerinde olanlar), QT dispersiyon değerleri normal olanlara göre (idrar P/K 91 mg/g'dan az olanlar) daha yüksek bulundu. Bu fark istatistiksel olarak anlamlı saptanmamıştır (p>0,05). Çalışmamızda, QT sürelerinin diyabet hastalarında kardiyovasküler hastalıklardan bağımsız olarak uzun olduğunu ancak protein/kreatinin oranı ile anlamlı ilişkisi olmadığını tespit ettik.

Sonuç: Sonuç olarak, diyabetik hastalarda spot idrar protein/kreatinin oranı ile QT intervalleri arasındaki ilişkiyi incelediğimiz bu çalışmada iki parametre arasında anlamlı ilişki saptanamamıştır. Literatürde A/K oranı ile QT intervalleri arasında ilişki olduğunu gösteren çalışmalar bulunsa da P/K oranı ile ilişki saptayamadık.

Anahtar kelimeler: Proteinüri, QT dispersiyonu, İdrar protein kreatinin oranı

Introduction

Diabetes Mellitus (DM) is the fastest growing mortality and morbidity cause throughout the world over the last 20 years. Especially in developed and developing countries, the prevalence is increasing due to changing eating habits, industrialization, and a sedentary lifestyle. Diabetes is known to cause many serious complications such as coronary heart disease, chronic renal failure, and retinopathy. A multinational study by the World Health Organization (WHO) has shown that coronary heart disease, in patients with type 2 diabetes, was the most important cause of death [1]. The cause of 34% of deaths resulting from DM worldwide is coronary artery disease.

Cardiac autonomic neuropathy is a common complication, associated with increased mortality of diabetes. Increased cardiovascular death and neuropathy are associated with many systemic symptoms and functional decline [2,3]. Assessment of QT interval is an inexpensive method of determining the risk of high cardiovascular complications and sudden death. The prolonged QT and QT dispersion in the general population reflect the abnormality of ventricular myocardial repolarization. Diabetes itself a well-known cardiovascular risk factor continues to threat health even after normalization with other classical risk factors such as hypertension, dyslipidemia, smoking, homocysteinemia and lack of exercise. The QT interval adjusted for heart rate was reported to be significantly and independently associated with the presence and severity of cardiac autonomic neuropathy in diabetic patients [4]. QT interval and QT dispersion may be found to be prolonged in both hypoglycemia and hyperglycemia [5,6].

Proteinuria is considered both to be an independent risk factor for cardiovascular and renal diseases and to demonstrate the target organ damage [7]. In particular, the detection of elevated protein excretion in the urine is known to have diagnostic value in the detection of the onset of renal diseases, and the amount of protein elicited is used to assess the disease process and the efficacy of the treatment [8,9]. The National Kidney Foundation recommends regular screening of protein excretion in urine in patients at risk of developing the renal disease [10]. In practice, as a screening test, detection of proteinuria in strips is often used in spot urine, and protein determination in 24-hour urine samples is used as the gold standard for quantitative evaluation because of changes in urinary protein excretion during the day [11]. It was reported that there was a strong correlation between spot urine protein/creatinine ratio (P/K) and proteinuria at 24 h in the studies performed, and protein ablation could be used as a reliable indicator [11-14].

The aim of this study was to investigate the relationship between proteinuria and QT dispersion, indicated with nephropathy and autonomic neuropathy in diabetic patients, through achievable tests.

Materials and methods

The study was conducted between November and December 2013, in the Haseki Education Research Hospital Diabetes outpatient clinic. Among 200 patients followed up with a diagnosis of type 2 diabetes, those who were receiving medications that affect QT duration, with complete bundle branch block, atrial fibrillation and second or third-degree atrioventricular block were excluded. 50 females (52.6%) and 45 males (47.4%) eligible for the study protocol were included. The 12-lead ECG and biochemical examination including fasting blood glucose, HbA1c, creatinine, LDL, triglyceride, and spot urine protein/creatinine ratio were performed. The hospital records were reviewed for the presence of neuropathy, and retinopathy, and for the medications. The ECGs were scanned at high resolution and transferred to the computer as a jpeg file. Using the Adobe Photoshop CC (Adobe Inc., USA) program measurements were performed. From the beginning of the Q wave to the end of the T wave range was measured as QT interval. QT intervals corrected with Bazzet formula for heart rate. ($Qtc = QT / \sqrt{RR}$) Measured at least three QT intervals from each successive corridor. The difference between the longest QT (QTmax) and the shortest QT (QT min) was calculated as QT dispersion (Qtd). The measurements were checked by two different investigators. P/K were measured at spot intervals. The threshold value for proteinuria detection was 91 mg/g [15]. Spot urine protein/creatinine ratio of less than 91mg/g was accepted as normal, and those with over 91mg/g were classified as proteinuric.

Statistical analysis

The IBM SPSS Statistics 23 (IBM Ltd, USA) program was used for descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Ratio, Minimum, Maximum). Student's t-test was used for two group comparisons of the parameters that showed a normal distribution. Mann Whitney U test was used for two group comparisons of the parameters that showed abnormal distribution. Pearson correlation analysis and Spearman correlation analysis were used to evaluate the inter-parameter relationships. The significance level was set at $p < 0.01$ and $p < 0.05$.

Results

Of the 95 patients included in the study, 52.6% (n = 50) were female, 47.4% (n = 45) were male. The ages of the patients ranged from 33 to 81 years with an average of 57.52 ± 10.47 years. Patients' diabetes duration ranged from 1 to 35 years with an average of 12.34 ± 7.11 years. Ischemic heart disease (coronary artery bypass grafts, coronary stent tissue) was present in 23.1% (n = 22) of all patients. QT-max, QT-min and QT-dispersion analyzes were performed in two groups, in all patients by excluding those with ischemic heart disease. Demographic characteristics are summarized in Table 1.

The mean QT-min (mean 388.50 ± 27.28 ms), QT-max (mean 441.25 ± 29.76 ms) and QT dispersion (mean 52.74 ± 16.80 ms) were significantly higher than the reference values in both groups. Corrected QT (QTc) was above 440 milliseconds (ms) in the majority of patients with untreated, genetically determined hereditary long QT syndrome. QTc in healthy controls was at 440-465 ms. These values were taken as the basic levels, and QTc values below 420 ms were strictly normal, values between 420-440 ms were at the limit, and QTc values above 440 ms were considered high [16,17].

Table 1: Demographic characteristics of patients

		All patients (n=95)		Excluding those with ischemic heart disease (n=73)	
		n	%	n	%
Gender	Female	50	52.6	42	57.5
	Male	45	47.4	31	42.5
Hypertension		58	61.1	36	49.3
Retinopathy		36	37.9	25	34.2
Neuropathy		49	51.6	33	45.2
		Min-Max	Mean±SD	Min-Max	Mean±SD
Age		33-81	57.52±10.47	33-80	56.04±10.73
DM duration		1-35	12.34±7.11	1-35	11.66±6.98
Plasma glucose		90-368	177.09±69.77	94-368	183.01±73.12
HbA1c		5.9-14.0	8.05±1.53	5.9-14.0	8.17±1.63
Urine P/K		0.0-2.5	0.32±0.47	0.0-2.5	0.35±0.53
LDL		35-225	114.56±36.93	35-225	114.29±35.38
Total cholesterol		91-309	189.84±43.48	91-309	189.90±43.38
Triglycerides		51-752	151.65±92.36	51-752	157.30±99.40
QT-max		391-533	441.25±29.76	391-529	440.57±29.99
QT-min		341-463	388.50±27.28	341-463	390.29±26.88
QT-dispersion		18-95	52.74±16.80	18-95	50.08±16.60

DM= Diabetes Mellitus,P/K= Urine protein/creatinine ratio, QT-max= longest QT, QT-min= shortest QT

There was no statistically significant correlation between QT dispersion value and DM duration, Hb1Ac, BUN, triglyceride and P /K ratio (p> 0.05 for all). A statistically significant negative correlation was found between QT dispersion value and LDL level at the level of 21.0% (R: - 0,215, p: 0,037, p <0.05).

In gender comparison, QT-max (447.36±33.98 msn in females, 434.47±23.28 msn in males) and QT-min (397.04±26.92 msn in females, 379.02±20.91 msn in males) values in women were significantly longer than those in men. QT dispersion was found to be longer in males than in females (50.33 ± 17.19 ms in females, 55.44 ± 16.22 ms in males), but this difference was not statistically significant. (P> 0.05)

When all cases and those with ischemic heart disease were excluded, QT dispersion value was higher in patients with proteinuria (those with urine P/K levels 91 mg/g and above). This difference was not statistically significant. (P> 0.05) (Table 2, 3). There was no significant relationship between QT values and neuropathy and retinopathy.

Table 2: QT-max, QT-min and QT-dispersion analyzes in all patients

(n=95)	Urine P/K		p
	Normal (n=25)	Proteinuric (n=70)	
QT-max	432.08±22.28	444.53±31.76	0.074
QT-min	382.48±20.07	390.66±27.33	0.175
QT dispersion	49.60±13.77	53.87±17.77	0.279

Student's t test

Table 3: QT-max, QT-min and QT-dispersion analyzes in those with ischemic heart disease were excluded

(n=73)	Urine P/K		p
	Normal (n=18)	Proteinuric (n=55)	
QT-max	434.00±20.16	442.35±31.79	0.312
QT-min	385.59±17.27	391.75±27.06	0.381
QT dispersion	48.41±11.28	50.60±17.58	0.631

Student's t test

Discussion

QT dispersion has been used frequently in recent years as a noninvasive and inexpensive method that reflects the repolarization heterogeneity of ventricular myocardium. The repolarization of the ventricles occurs in integrity. However, under normal conditions, repolarization does not start at the same moment throughout the entire ventricle and not at the same time. This is named as repolarization dispersion. In pathological conditions, homogeneity in repolarization deteriorates further and is detected as prolonged QT dispersion. QT interval abnormalities were associated with coronary artery disease, left ventricular hypertrophy, blood pressure, autonomic dysfunction and metabolic syndrome. There are also studies showing the relationship between microalbuminuria and QT interventions in patients with type 1 and type 2 diabetes [14,18]. In a study comparing healthy individuals with impaired fasting glucose, no difference was found in QT dispersion, but QT changes between heart rates were found to be higher in the group with impaired glucose tolerance [19].

In this study, all patients were selected from diabetic individuals and the mean QT values of the patients were found to be longer than the reference interval. However, due to the absence of a control group, the contribution of other parameters is not known. Twenty-two (23.1%) of our patients had ischemic heart disease (coronary artery bypass graft or coronary angiography stenosis and stent). Since it is known that ischemic heart diseases affect QT intervals, statistical analyzes were performed for both all patients and excluding those with ischemic heart disease. QT periods were also found to be longer when patients with ischemic heart disease were excluded. This is consistent with the literature that diabetes affects the QT interval independently of cardiovascular complications [20,21].

In our study, we aimed to investigate the relationship between QT intervals and urinary protein creatinine ratio in type 2 diabetic patients. Despite studies done with the ratio of albumin/creatinine in the literature, there is no study with more commonly used protein/creatinine ratio. In recent years, the use of spot urine P/K ratio has become widespread as it is more advantageous than the measurement of albumin/creatinine ratio due to cost and availability. Some researchers have found that there is a strong correlation between spot urine P/K ratio and 24-hour urinary protein levels, but these two tests cannot be used interchangeably [22]. However, in many studies, different threshold values of P/K ratio have been determined. This is why researchers should try to set different thresholds for different clinical situations. In a study conducted by Yamamoto et al., The P/K ratio and the albumin/creatinine ratio were compared to find that the 91 mg/g threshold value for the total P/K ratio measured in the spotting of microalbuminuria in diabetic patients was 90.8% sensitive and 91.9% specific [15]. In this study, 91 mg/mg value was accepted as the threshold value for microalbuminuria. There was no statistically significant difference in the proteinuria between the normal (n = 25) and proteinuric (n = 70) groups while QT intervals were longer in the proteinuria group. Previous studies suggest a relationship between microalbuminuria and QT dispersion in studies using albumin/creatinine ratio. Psallas et al., in their research of QT dispersion and microalbuminuria in patients with type 1 and type 2 diabetes, found that patients with type 2 diabetes had significantly higher QT dispersion of microalbuminuria as an independent indicator. In a study comparing 63 type 1 diabetes, 121 type 2 diabetes and healthy control groups, QT dispersion was found to be significantly longer in those with microalbuminuria in the type 2 diabetes group. It is argued that microalbuminuria is the most reliable predictor of QT dispersion in patients with type 2 diabetes [18]. Rutter et al. [23] compared microalbuminuric and normoalbuminuric groups regarding QT dispersion, and QTmax

was found to be longer in the microalbuminuric group and QT dispersion was found to be similar. As a result of this study, it was commented that the QT intervals were changed by microalbuminuria-related blood pressure and Factor XIIa rather than albumin excretion. In these two studies, Albumin/creatinine ratio was used as the microalbuminuria test.

In our study, significant differences were found between QT intervals between male and female groups. QTmin and QTmax values were found to be longer in female patients than in males. QT dispersion was longer in men, but the difference was not statistically significant. In all studies on gender, it was shown that QT interval is longer in females. In women, accordingly, long QT syndrome and associated clinical situations such as QT prolongation induced by drug have been found to be higher risk than men [24,25].

In our study, patients' QT-max and QT-min values were positively correlated with HbA1c, a statistically significant relationship was determined. In a study conducted on 27 healthy volunteers and examining the effect of acute hyperglycemia on the QT interval, acute hyperglycemia was found to increase both QT max duration and QT dispersion [6]. The authors suggested that in addition to the mechanisms that cause QT interval prolongation in diabetic patients, hyperglycemia may also be a contributing mechanism. In another study, QT distances were measured in patients admitted to the hospital with the new diagnosis of diabetes and hyperglycemia, pre-treatment and after normoglycemia with insulin treatment. The QTmax and QTdispersion distances before treatment were significantly high. There was no significant change in QTmax and QTdispersion durations after treatment, but QTdispersion durations after treatment were significantly longer compared to the healthy control group [26]. In a study from Turkey to investigate the relationship between QT and blood glucose changes, hypoglycemia and hyperglycemia were associated with prolonged QT and QT dispersion [27]. These results demonstrate the importance of optimal glycemic control regarding cardiovascular mortality.

The limitation of this study is that, the study was conducted retrospectively and we did not have a control group. Due to the absence of a control group, the contribution of parameters that could affect QT duration is not known.

As a result, in this study, we examined the relationship between spot urine protein/creatinine ratio and QT intervals in diabetic patients, and we did not find a significant association between the two parameters. Although there have been studies in the literature showing that there is a relationship between albumin/creatinine ratio and QT intervals, we could not find an association with P/K ratio. Because the P/K ratio is inexpensive, readily applicable and achievable test for determining microalbuminuria, we believe that comprehensive studies can be performed.

References

1. Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. JAMA. 1999;281:1291-7.
2. Vinik AI, Erbas T. Recognizing and treating diabetic autonomic neuropathy. Cleve Clin J Med. 2001;68:928–44.
3. Freeman R. The peripheral nervous system and diabetes. In: Weir G, Kahn R, King GL, editors. Joslin's Diabetes Mellitus. Philadelphia: Lippincott; 2002.
4. Tentolourıs N, Katsilambros N, Papazachos G et al. Corrected QT interval in relation to severity of diyabetic autonomic neuropathy. Eur J Clin Invest. 1997;27:1049-54.
5. Robinson RT, Harris ND, Ireland RH, Macdonal IA, Heller SR. Changes in cardiac repolarization during clinical episodes of nocturnal hypoglycaemia in adults with type 1 diabetes. Diabetologia. 2004;7:312-5.
6. Marfella R, Nappo F, De Angelis L, Siniscalhi M, Rossi F, Giugliano D. The effect acute hyperglycemia on Qtc duration in healthy man. Diabetologia. 2000;43:571-5.
7. Barnas U, Schmidt A, Haas M, Kaider A, Tillawi S, Wamser P, et al. Parameters associated with chronic renal transplant failure. Nephrol Dial Transplant. 1997;12:82-5.
8. Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G. Urinary protein excretion rate is the best independent predictor of ESRF in nondiabetic proteinuric chronic nephropathies. Kidney Int. 1998;53:1209-16.
9. Redon J. Renal protection by antihypertensive drugs: insights form microalbuminuria studies. J Hypertens. 1998;16:2091.
10. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis. 2002;39(1):1-266.
11. Koopman MG, Krediet RT, Koomen GCM, Strackee J, Arisz L. Circadian rythm of proteinuria: consequences of the use of protein: creatinine ratios. Nephrol Dial Transplant. 1989;4:9-14.
12. Xin G, Wang M, Jiao LL, Xu GB, Wang HY. Protein to- creatinine ratio in spot urine samples as a predictor of quantitation of proteinuria. Clin Chim Acta. 2004;350:35-9.
13. Gai M, Motta D, Giunti S, Masini S, Mezza E, Segoloni GP, Lanfranco G. Comparison between 24-h proteinuria, urinary protein/creatinine ratio and dipstick test in patients with nephropathy: patterns of proteinuria in dipstick-negative patients. Scan J Clin Lab Invest. 2006;66:299-308.
14. Lane C, Brown M, Dunsmuir W, Kelly J, Mangos G. Can spot urine protein/creatinine ratio replace 24 h urine protein in usual clinical nephrology? Nephrology (Charlton). 2006;11:245-9.
15. Yamamoto K, Komatsu Y, Yamamoto H, Izumo H, Sanoyama K, et al. Establishment of a method to detect microalbuminuria by measuring the total urinary protein-to-creatinine ratio in diabetic patients. Tohoku J exp med. 2011;225:195-202.
16. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome. An update. Circulation. 1993;88:782-4.
17. Vincent GM, Timothy KW, Leppert M, et al. The spectrum of symptoms and QT intervals in carriers of the gene for the long QT syndrome. N Engl J Med. 1992;327:846-52.
18. Psallas M, Tentolouris N, Papadogiannid D, Doulgerakis D, Kokkinos A, Cokkinos VD, et al. QT dispersion comparison between participants with type 1 and 2 diabetes and association with microalbuminuria: J Diabetes Complications. 2006;20:88-97.
19. Orosz A, Baczko I, Nyiraty S, Körei AE, Putz Z, Takacs R, et al. Increased short-term beat-to-beat QT ınterval variability in patients with ımpaired glucose tolerance. Frontiers in Endocrinology. 2017;6(8):129.
20. Cardoso C, Salles G, Bloch K, Deccache W, Siqeira-Filho AG. Clinical determinants of increased QT dispersion in patients with diabetes mellitus. Int J Cardiol. 2001;79(2-3):253-62.
21. Veglio M, Giunti S, Stevens LK, Fuller JH, Perin PC. Prevalence of QT interval dispersion in type 1 diabetes and its relation with cardiac ischemia: the EURODIAB IDDM complications study group. Diabetes Care. 2002;25(4):702-7.
22. Chitalia VC, Kothari J, Wells EJ, Livesey JH, Robson RA, Searle M, et al. Cost benefit analysis and prediction of 24-hour proteinuria from the spot urine protein-creatinine ratio. Clin Nephrol. 2001;55:436-47.
23. Rutter M, Viswanath S, McComb J M, Kesteven P, MarshallS M. QT prolongation in patients with type 2 diabetes and microalbuminuria. Clin Auton Res. 2002;12:366-72.
24. Chapman N, Mayet J, Ozkor M, Foale R, Thom S, Poulter N. Ethnic and gender differences in electrocardiographic QT length and QT dispersion in hypertensive subjects. J Hum Hypertens. 2000;14:403-5.
25. Wolbrette D, Naccarelli G, Curtis A, Lehmann M, Kadish A. Gender differences in arthythmias. Clin Cardiol. 2002;25:49-56.
26. Ersoy U. Tip 2 diyabetli hastalarda kan şekeri düzeyi ile QT parametreleri arasındaki ilişkinin değerlendirilmesi [dissertation]. Haydarpaşa numune eğitim araştırma hastanesi; İstanbul 2008.
27. Sertbas Y, Ozdemir A, Sertbas M, Dayan A, Sancak S, Uyan C. The effect of glucose variability on Qtc duration and dispersion in patients with type 2 diabetes mellitus. Pak J Med Sci. 2017;33(1):22-6.

J Surg Med. 2019;3(3):210-213.
DOI: 10.28982/josam.474012

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Postoperative radiotherapy in the treatment of endometrial cancer: Review of 158 patients

Endometrial kanserin tedavisinde postoperatif radyoterapi: 158 hastanın gözden geçirilmesi

Fadwa Allouche [1], Fatima Zahra Terrab [1], Ghammad Sanae [1], Rajae Ennouichi [1], Zineb Alami [1], Touria Bouhafa [1], Khalid Hassouni [1]

[1] **Radiotherapy Department at University Hospital Center of Fez, Morocco**

ORCID ID of the author(s)
FA: 0000-0002-6793-4911
FTZ: 0000-0001-6508-5066
GS: 0000-0002-7940-8396
RE: 0000-0002-1518-1989
ZA: 0000-0003-3349-1793
TB: 0000-0002-9857-1594
KH: 0000-0002-1442-255X

Abstract

Aim: Endometrial cancer is the most common gynecological cancer in the West. It is the third cancer of women after that of the breast and intestine. It mainly concerns menopausal women. Our aim is to highlight, through a retrospective study and in light of literature data, the role of radiotherapy in the management of this cancer.

Methods: This is a retrospective cohort study concerning patients' records for endometrial in the radiotherapy department at university hospital center of FEZ for a period of 5 years from January 2012 to December 2016.

Results: We collected 158 patients of mean age 64 years (36 to 92 years), all patients had a total hysterectomy with (76% of cases) or without (24% of cases) ganglion dissection. Type 1 was the most common histological type (96% of cases). The myometrial invasion was greater than 50% in 51% of cases, histological grade III in 36% of cases, and cervical invasion was observed in 16% of cases. Therapeutically, 18% of patients received exclusive external radiotherapy at a dose of 50 Gy in conventional fractionation and spreading, a TEN at a dose of 46 Gy followed by a brachytherapy dam in 58% of cases, and 24% of patients received brachytherapy alone. After an average follow-up of 25 months, 91% of the patients are in good locoregional control, 9% of the patients had distant metastases.

Conclusion: Radiotherapy retains an important place in the therapeutic strategy of high endometrial cancers, or with unfavorable histological characters, and thus allows the reduction of locoregional recurrence rates.

Keywords: Endometrium, Cancer, Surgery, Radiotherapy

Öz

Amaç: Endometrial kanser, Batı'da en sık görülen jinekolojik kanserdir. Göğüs ve bağırsaktan sonraki üçüncü kadın kanseridir. Esas olarak menopozdaki kadınlarla ilgilidir. Amacımız, retrospektif bir çalışma ve literatür verileri ışığında, bu kanserin yönetiminde radyoterapinin rolünü vurgulamaktır.

Yöntemler: Ocak 2012 ile Aralık 2016 arasında 5 yıllık bir süre için FEZ'nin üniversite hastanesinde radyoterapi bölümünde hastaların endometriyal kayıtları ile ilgili retrospektif bir kohort çalışmasıdır.

Bulgular: Yaş ortalaması 64 olan (36-92 yaş arası) 158 hasta topladık, tüm hastaların histerektomi (olguların %76'sı) veya (olguların %24'ü) ganglion diseksiyonu yoktu. Tip 1 en sık görülen histolojik tipti (olguların %96'sı). Olguların %51'inde miyometriyal invazyon %50'den, vakaların %36'sında histolojik derece III ve %16'sında servikal invazyon görülmüştür. Terapötik olarak, hastaların %18'i konvansiyonel fraksiyonasyon ve yaymada 50 Gy'lik bir dozda özel eksternal radyoterapi aldı, 46 Gy dozunda bir TEN, %58'inde brakiterapi barajı ve hastaların sadece %24'ü brakiterapi aldı.

Ortalama 25 aylık takipten sonra hastaların %91'i iyi lokal kontrolde, %9'unda uzak metastaz vardı.

Sonuç: Radyoterapi, yüksek endometriyal kanserlerin terapötik stratejisinde veya istenmeyen histolojik karakterlerde önemli bir yer tutmaktadır ve bu nedenle lokal nüks oranlarının azaltılmasına izin vermektedir.

Anahtar kelimeler: Endometrium, Kanser, Cerrahi, Radyoterapi

Corresponding author / Sorumlu yazar:
Fadwa Allouche
Address / Adres: Radiotherapy Department at University Hospital Center of Fez, Morocco
E-mail: dr.allouch.fadwa@gmail.com

Ethics Committee Approval: Ethics committee approval was not received because the study design was retrospective.
Etik Kurul Onayı: Çalışma retrospektif olması nedeniyle etik kurul onayı alınmamıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 23.10.2018
Accepted / Kabul Tarihi: 28.11.2018
Published / Yayın Tarihi: 20.12.2018

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite / Atıf için: Allouche F, Terrab FZ, Sanae G, Ennouichi R, Alami Z, Bouhafa T, Hassouni K. Postoperative radiotherapy in the treatment of endometrial cancer: Review of 158 patients. J Surg Med. 2019;3(3):210-213.

Introduction

Endometrial cancer is the most common gynecological cancer in the West [1]. It mainly concerns menopausal women [1]. The majority of endometrial cancers are diagnosed at early stages. Two histological types of endometrial cancer are described: type I and II, with histological, epidemiological and molecular specificities [2]. Surgery is the treatment of reference. It makes it possible to specify the stage according to the classification of the FIGO and thus to guide the indications of the adjuvant treatment [3-5]. Its prognosis remains relatively favorable with a cancer mortality rate that remains the lowest in comparison with other female cancers. The purpose of our work is to report the experience of the radiotherapy department to the National Institute of Oncology in the management of endometrial cancer.

Materials and methods

We conducted a retrospective cohort study through a series of 158 cases followed for endometrial cancer in the radiotherapy department at university hospital center of FEZ during a period of 5 years from January 2012 to December 2016. The data collected from the medical records of our patients, based on a record of exploitation, concerned the epidemiological, clinical, therapeutic and evolutionary aspects of this cancer. The diagnosis was clinical and histological. The tumors were classified according to the FIGO classification; the radiological assessment of the locoregional extension was an abdominopelvic computed tomography (CT); the distance extension assessment was based on the signs of call. The treatment was mainly based on surgery, which allows staging of the tumor and then indicates adjuvant treatment: external radiotherapy and / or brachytherapy of the vaginal fundus. The surgery consisted of a total hysterectomy or even a total colo-hysterectomy with or without an adnexectomy, with or without lymphadenectomy. External radiotherapy was delivered by four beams of high energy X photons (18 to 25 MV). The total dose delivered to the isocenter was 46 Gy in 23 fractions, two Gy per fraction. Brachytherapy was high dose rate (HDR), the total dose delivered varied according to whether it is brachytherapy exclusive or associated with external beam radiotherapy. It was 14 Gy in two weekly fractions, 7 Gy per fraction or 24 Gy in four weekly fractions, 6Gy per fraction.

Results

We collected 158 patients of average age 64 years (36 to 92 years), 87% were menopausal. The average consultation time was 6 months (2-36 months). At the first consultation, 157 of the patients complained of metrorrhagia, a single incidental finding, all patients had a total hysterectomy with (76% of cases) or without (24% of cases) ganglion dissection. Type 1 was the most common histological type (96% of cases). The myometrial invasion was greater than 50% in 51% of cases, histological grade III in 36% of cases, and cervical invasion was observed in 16% of cases. 58% of our patients were classified in the high-risk group, and 42% of the cases in the intermediate risk group. Therapeutically, 18% of patients received exclusive external radiotherapy at a dose of 50 Gy in conventional fractionation and spreading, a TEN at a dose of 46 Gy followed by a brachytherapy dam in 58% of cases, and 24% of patients received brachytherapy alone. After an average follow-up of 25 months, 91% of the patients are in good locoregional control, 9% of the patients had distant metastases.

Discussion

Endometrial cancers are the most common gynecological cancers in the West. More than 75% of patients are postmenopausal at the time of diagnosis and only 3% are under 40 years of age [1], in our series 87% of our patients were menopausal. Among the risk factors for this cancer, treatment with tamoxifen is mainly distinguished between obesity, diabetes and hypertension [1,2]. Hereditary forms represent 2 to 5% of endometrial cancers; they are mainly found in Lynch syndrome (hereditary non-polyposis colorectal cancer, endometrial, stomach, small bowel, pancreatic, ovarian, hepatobiliary cancer) [3], in our series no case of form hereditary has not been reported. Two clinical and prognostic forms are currently described. Endometrioid carcinoma type 1 is slow-moving and has a favorable prognosis. The context is that of a state of hyperestrogenism and overweight. It is most often adenocarcinoma well to moderately differentiated. This form of endometrial cancer is often associated with genetic mutations (K-ras genes, RER genes) [2]. Type 2 carcinoma develops faster than usual risk factors (obesity, diabetes, hyperestrogenism). Histologically, these are low-differentiated serous or clear-cell types. This second form of endometrial cancer is thought to be associated with p53 and/or HER2 gene mutations [2].

The tumor grade represents the degree of differentiation and has a significant influence on the prognosis. It is most often an endometrioid adenocarcinoma. Other histological forms are mucinous carcinoma, clear cell carcinoma, serous papillary carcinoma, sarcoma and carcinosarcoma; in our series Type 1 was the most common histological type (96% of cases). Clear cell carcinoma and serous papillary carcinoma are considered Grade 3 and is aggressive forms. Sarcomas account for about 5% of malignant tumors of the uterus and include mixed mesoderm tumors, leiomyosarcomas and endometrial sarcomas (stroma). Sarcomas are more aggressive, more frequently causing distant metastases [3]. For the circumstances of discovery, it is essentially post-menopausal or peri-menopausal metrorrhagia, usually spontaneous, painless and scanty. Other clinical signs are rare, they can be leucorrhea, heaviness or pelvic pain, urinary disorders. In our series 98% of our patients, the clinical sign of discovery was metrorrhagia. The clinical examination is generally uninformative. Indeed, cervical examination is usually normal except for stages II with cervical extension. The exploration of ganglionic areas, the palpation of the liver, the search for ascites, and the examination is always indicated [2].

The pre-therapeutic extension assessment includes hysteroscopy, abdominopelvic magnetic resonance imaging (MRI), which has now become the best examination for the evaluation of myometrial penetration, and cervical invasion, or failing in pelvic abdomen scan [4]. In our series our patients received a pelvic abdomen scan.

Surgery is the gold standard treatment for endometrial cancer. It consists of a total hysterectomy with bilateral salpingo-

oophorectomy. Additional procedures are lymphadenectomy, omentectomy for clinical stage, histological type and histological grade [5]. Surgery can be used to specify the stage and establish the prognostic factors [3-5].

External radiotherapy is performed according to the conformational modalities and according to the recommendations of the Radiation Therapy oncology group (RTOG), with photons of very high energy (at least equal to 10 MV). The volume of irradiation depends on the tumor extension. It is limited to the pelvis, in the absence of common iliac lymph node involvement or lomboaortic. In the case of lumba-like lymph node involvement, the irradiation volume includes the lumba region. The total dose is 45 to 50 Gy, with 5 weekly fractions of 1.8 to 2 Gy. In case of exclusive irradiation, not preceded by surgery, an overprint of lymph nodes suspected of invasion by imaging can be proposed until 'at a total dose of at least 60 Gy [6,7]. Vaginal brachytherapy is no longer useful at all stages of the disease.

Postoperative vaginal brachytherapy is performed preferentially at high dose rates, avoiding hospitalization and decubitus complications. A dose of 21 to 24 Gy is delivered in 3 sessions of 7 Gy or in 4 sessions of 5 to 6 Gy, calculated at 5 mm of thickness. In case of pulsed brachytherapy or low dose rate, a dose of 50 Gy is delivered, calculated at 5 mm thick. When HDR brachytherapy is performed in addition to external radiotherapy, a dose of 10 Gy is delivered in 2 sessions of 5 Gy, calculated at 5 mm thick. In the case of pulsed or low dose rate brachytherapy, a dose of 15 Gy is delivered, calculated at 5 mm thickness [8,9].

Pelvic radiotherapy improves the rate of local pelvic control of the disease in poorly prognostic forms (stage II, grade 3, myometrial infiltration greater than 50%). It has no impact on metastatic evolution or survival [7].

Management of patients with endometrial cancer is based on surgery, which establishes the stage of the disease according to the FIGO classification and identifies the factors of poor prognosis on which the decision of a treatment the most recognized adjuvant is: stage, histological grade, degree of myometrial infiltration, histological type, age, endocervical infiltration and the presence of intravascular tumor emboli [7]. Thus, for stage I, there are three prognostic groups [10].

The low-risk group includes endometrioid adenocarcinoma without myometrial invasion or with an invasion limited to less than 50% of the grade 1 or 2 myometrium. Retrospective studies and a randomized Swedish trial published in 2009 all confirmed that, although brachytherapy vaginal vault is a well-tolerated therapy, it has no significant impact on local control. No adjuvant treatment can therefore be justified for these patients who have a risk of vaginal recurrence low, estimated at less than 3%, especially since these recurrences are accessible to radiation treatment [10], so for stage IA and grade 1 or 2 cancers, no further treatment is therefore recommended.

The intermediate risk group consists of type I carcinomas without myometrial invasion or with invasion limited to less than 50% of grade 3 myometrial (IA), and carcinomas invading more than 50% of the thickness of the myometrium (IB) of grades 1 and 2. Vaginal brachytherapy is standard adjuvant therapy [10]. Four therapeutic trials demonstrated that in other patients in the group, pelvic radiotherapy improved the rate of local pelvic control of the disease but had no impact on metastatic evolution or survival. This made discuss the interest of this irradiation vis-a-vis brachytherapy only potentially as effective and less toxic. This question was posed by the PORTEC 2 trial (Post-Operative Radiation Therapy in Endometrial Carcinoma) 2. The presentation of the preliminary results at three years suggested that the two therapeutic modalities had similar efficacy in terms of recurrence-free survival and overall survival. [11]. The group at high risk of recurrence includes type I carcinomas with more than 50% invasion of grade 3 myometrial (IB) thickness and type II carcinomas (IA and IB). For these patients, it is recommended to do external pelvic radiotherapy and brachytherapy of the vaginal vault, which does not, however, reduce the risk of recurrence to less than 10%. In these patients, the rate of metastatic progression is also high, which makes discussing concomitant chemoradiotherapy followed by adjuvant chemotherapy [12].

In the case of stage II tumors: the recommended therapeutic course of action is surgery followed by radiotherapy with or without brachytherapy. In the advanced stages (III and IV): the therapies must be more aggressive. Surgery is proposed where possible because, combined with radiotherapy; it provides better results than exclusive irradiation. In advanced forms or at high risk of recurrence, trials including chemotherapy, exclusive or concomitant to irradiation, have been conducted in recent years. The results of these trials have shown the potential value of chemotherapy to decrease [13].

Conclusion

Endometrial cancer is usually of good prognosis whose treatment is based on surgery. Radiotherapy retains an important place in the adjuvant therapeutic strategy in the high-risk group, or with unfavorable histological characters. It thus allows the reduction of locoregional metastases and thus improves the prognosis.

References

1. Haie-Medera C, Paumiera A, Lessarda N, et al. Traitements adjuvants et rôle de la radiothérapie dans les formes évoluées de cancer de l'endomètre. Cancer Radiother. 2008;12(67):630–2.
2. Collinet P, Poncelet E, Vinatiera D. Cancer de l'endomètre. J Gynecol Obstet Biol Reprod. 2008;37(2): F5763.
3. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet. 2005; 366 (9484):491–505.
4. Narducci F, Lambaudie E, Sonoda Y, et al. Endometrial cancer: what's new? Gynecol Obstet Fertil. 2003;31(7-8):581–96.
5. Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer: a Gynecological Oncology Group Study. Cancer. 1987 Oct 15;60(8 Suppl):203541.
6. Kong A, Powell M, Blake P. The Role of Postoperative Radiotherapy in Carcinoma of the Endometrium. Clin Oncol (R Coll Radiol). 2008;20(6):457–62.
7. Greven K, Winter K, Underhill K, et al. Final analysis of RTOG 9708: adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer. Gynecol Oncol. 2006;103(1):155-9.
8. Anderson JM, Stea B, Hallum AV. High dose rate postoperative vaginal cuff irradiation alone for stage IB and IC endometrial cancer. Int J Radiat Oncol Biol Phys. 2000;46(2):41725.
9. Moreau-Claeys MV, Brunaud C, Hoffstetter S, et al. High dose rate vaginal brachytherapy in endometrial cancer after surgery. Cancer Radiother. 2011;15(3):169-75.
10. Mazeron R, Monniera L, Belaida A, et al. Adjuvant radiotherapy in patients with endometrial cancers. Cancer Radiother. 2011;15(4):323-9.
11. Peignaux K, Truc G, Blanchard N, et al. Cancer de l'endomètre de stade I. Cancer Radiother. 2008;12(6-7):625–9.
12. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial

adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004;92(3):744–51.

13. Alvarez Secord A, Havrilesky LJ, Bae-Jump V, et al. The role of multimodality adjuvant chemotherapy and radiation in women with advanced stage endometrial cancer. Gynecol Oncol. 2007;107(2):285–91.

J Surg Med. 2019;3(3):214-217.
DOI: 10.28982/josam.473045

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Evaluation of self-care agency of patients with diabetic foot infection: A cross-sectional descriptive study

Diyabetik ayak enfeksiyonlu hastaların öz bakım gücünün değerlendirilmesi: Kesitsel tanımlayıcı bir çalışma

Selçuk Nazik [1], Hülya Nazik [2], Ahmet Rıza Şahin [1], Selma Ateş [1]

[1] Department of Infectious Disease and Clinical Microbiology, Kahramanmaraş Sütçü İmam University, Kahramanmaraş, Turkey
[2] Department of Dermatology, Kahramanmaraş Sütçü İmam University, Kahramanmaraş, Turkey

ORCID ID of the author(s)
SN: 0000-0003-0587-0104
HN: 0000-0003-4004-3964
ARŞ: 0000-0002-4415-076X
SA: 0000-0002-2515-8578

Corresponding author / Sorumlu yazar:
Selçuk Nazik
Address / Adres: Kahramanmaraş Sütçü İmam Üniversitesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Kahramanmaraş, Türkiye
E-mail: dr.selcuknazik@hotmail.com

Ethics Committee Approval: Ethical committee of Kahramanmaraş Sütçü İmam University; Date: 14.02.2018, Session: 2018/04, no:06.
Etik Kurul Onayı: Kahramanmaraş Sütçü İmam University Etik Komitesi; Tarih: 14.02.2018, Toplantı: 2018/04, Sayı:06.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 22.10.2018
Accepted / Kabul Tarihi: 25.12.2018
Published / Yayın Tarihi: 08.01.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Abstract

Aim: Diabetes mellitus is a chronic disease and causes a major complication such as diabetic foot infection. Accordingly, we think that the mobilization of patients will decrease and self-care will decrease. The aim of this study was to evaluate the self-care agency of patients with diabetic foot infection.

Methods: This is a questionnaire-based cross-sectional study to identify the self-care agency of 97 patients with diabetic foot infection. Data were collected by face to face interview technique, using a questionnaire the Self-care Agency Scale which is consists of a total of 35 questions.

Results: When the self-care agency of the participants was evaluated, it was observed that 30.9% (n = 30) of the cases were low, 58.8% (n = 57) were moderate, and 10.3% (n = 10) were high. There was a statistically significant positive correlation between amputation time and self-care agency total score (r = 0.514, p = 0.002).

Conclusion: As a result, diabetes and its complications are an important group of diseases that we frequently encounter. We think that self-care will be better with education to be given to patients and their relatives.

Keywords: Diabetes, Diabetic foot infection, Self-care agency

Öz

Amaç: Diabetes mellitus kronik bir hastalıktır ve diyabetik ayak enfeksiyonu gibi önemli bir komplikasyona neden olur. Buna bağlı olarak hastaların mobilizasyonu azalacak ve öz bakımının düşeceğini düşünmekteyiz. Bu çalışmanın amacı diyabetik ayak enfeksiyonu olan hastaların öz bakım gücünün değerlendirmektir.

Yöntemler: Bu çalışma diyabetik ayak enfeksiyonu olan 97 hastanın öz bakım gücünü tanımlamak için yapılan anket temelli kesitsel tanımlayıcı bir araştırmadır. Veriler 35 sorudan oluşan öz bakım gücü ölçeği kullanılarak yüz yüze görüşme yöntemi ile toplanmıştır.

Bulgular: Katılımcıların öz bakım gücü değerlendirildiğinde olguların %30.9'u (n=30) düşük seviyede, %58.8'inin (n=57) orta seviyede, %10.3'ünün (n=10) ise yüksek seviyede olduğu gözlendi. Amputasyon süresi ile öz bakım gücü toplam skoru arasında pozitif yönde istatistiksel olarak anlamlı ilişki olduğu saptanmıştır (r=0.514, p=0.002).

Sonuç: Sonuç olarak diyabet ve diyabete bağlı komplikasyonlar sıkça karşılaştığımız önemli bir hastalık grubudur. Hastalara ve hasta yakınlarına verilecek eğitim ile öz bakımın daha iyi olacağı düşüncesindeyiz.

Anahtar kelimeler: Diyabet, Diyabetik ayak enfeksiyonu, Öz bakım gücü

How to cite / Atıf için: Nazik S, Nazik H, Şahin AR, Ateş S. Evaluation of self-care agency of patients with diabetic foot infection: A cross-sectional descriptive study. J Surg Med. 2019;3(3):214-217.

Introduction

Diabetes mellitus is a chronic disease caused by the hereditary and / or acquired deficiency in the production of insulin by the pancreas or by the ineffectiveness of the produced insulin. This causes a high level of glucose in the blood. As a result, different complications occur. These include diabetic retinopathy, diabetic nephropathy, cardiovascular disease, diabetic neuropathy, and diabetic foot infections [1,2].

Diabetic foot disease often leads to ulcers and limb amputation due to changes in blood vessels and nerves. It is one of the most costly complications of diabetes especially in societies with insufficient footwear. Diabetic foot infections are caused by both vascular and neurological disease processes. Diabetes is the most common cause of non-traumatic amputation of the lower extremity. To prevent this, foot examination of diabetic patients should also be performed [1].

It is estimated that approximately 150 million people worldwide have diabetes and this number can be doubled by 2025. The majority of this increase will occur in developing countries and will be due to population growth, ageing, unhealthy diets, obesity and sedentary lifestyles [1,2,5].

Diabetes; it is a chronic disease that is lifelong, directly related to individuals and their relatives of all ages, has a high economic burden due to irreversible and chronic damage, affects self-care activities and shortens the life span [2-5].

Self-care is that individuals do their part to protect their lives, health and well-being individually. The goal in self-care is to ensure that the individual has all responsibilities related to his / her health [6]. It is important to meet self-care needs in patients with chronic diseases such as diabetes. Most individuals who are diagnosed with diabetes have to monitor and implement self-care regulations at some stages of their lives [7,8]. 98% of diabetes care is self-care. In order to control the diseases of diabetes patients; adopt self-care activities such as appropriate diet, regular exercise, control of blood glucose, appropriate use of oral antidiabetics, recognition of the effects and side effects of insulin therapy, not to be used smoking and alcohol, prevention of complications of diabetes, adaptation to lifelong drug treatment [9-11].

The aim of this study was to evaluate the self-care agency scores of patients with diabetic foot infection.

Materials and methods

This is a questionnaire-based cross-sectional study to identify the self-care agency of patients with diabetic foot infection. Ethics committee approval was obtained for the study (14.02.2018; session 2018/04; decision no. 06). Informed consent was filled in the patients included in the study. A total of 97 patients with diabetic foot infection were included in the study.

Age, gender, educational status of the cases (not literate, primary school, secondary school and high school, university), marital status (married, single, widowed, divorced), income status (low, medium, high divided into three groups), working status (working, not working), number of individuals in the family, status and duration of amputation (No, <1, 1-6, 6-12, <12 months), mobilization status (Alone, device-supported, person- supported), additional disease status was recorded.

The data related to self-care agency scale were obtained by mutual interview method. The scale of self-care agency created by Kearney and Fleischer is a scale that aims to determine the self-care and strength of people. Scale validity and reliability study in healthy subjects in Turkey in 2004 by Nahcivan, in chronic diseases was made by Pınar 1995. Self-care agency scale can be found in appendix 1 as English and appendix 2 as Turkish [12-14].

In this scale, which consists of thirty-five items, the person prefers the expression of being engaged in the situation of self-care. The scale is a Likert type that measures attitudes and behaviors by using the changing response options. Each question of the scale is scored from zero to four points (does not define me at all = 0 points, does not define me very much = 1 point, I have no idea = 2 points, defines me a little = 3 points, defines me exactly = 4 points). The scale consists of a total of 35 statements and questions of 3, 6, 9, 13, 19, 22, 25, 26 and 31 are read in reverse and evaluated as negative. If the scale score is less than 82, it is low, 82-120 means moderate self, and higher than 120, which means high self-care power [15].

Statistical analysis

The data obtained from the study were statistically analyzed with SPSS v.17.0 package program (SPSS Inc., Chicago, Illinois, USA). Continuous data as mean, standard deviation; categorical data were expressed as number and percentage. For comparisons between groups; Chi-square (X^2) test was used for the evaluation of two independent groups, Student-t test was used for the evaluation of two non-categorical independent groups and Pearson correlation analysis was used for the evaluation of the correlation between the groups. Statistical significance was taken as $p < 0.05$.

Results

Ninety-seven patients were included in the study. 70.1% (n = 68) of the cases were male and 29.9% (n = 29) were female. The mean age of the patients was 57.3 ± 12.8 years (minimum-maximum: 26-84 years).

The self-care agency total score was 92.02 ± 22.5 (minimum-maximum: 37-130). When the self-care agency of the participants was evaluated, it was observed that 30.9% (n = 30) of the cases were low, 58.8% (n = 57) were moderate, and 10.3% (n = 10) were high. The relationship between the data of the participants and the self-care agency is presented in Table 1.

When the relationship between gender and self-care agency was evaluated, it was observed that 26.5% of the male patients were at low level, 61.8% at mid-level and 11.8% at high level. 41.4% of the female patients were at low level, 51.7% at middle level and 6.9% at high level. There was no statistically significant difference in male and female patients compared to males (p = 0.149).

When the education levels of the patients were evaluated, 13.4% (n = 13) were not literate, 56.7% (n = 55) were primary school, 18.6% (n = 18) were secondary school, 10.3% (n = 10) high school and 1% (n = 1) university. While 17.5% (n = 17) of the cases were able to work, 82.5% (n = 80) could not work. When the number of individuals in the family was

examined, all patients had at least one person. The number of individuals in the family was found to be 58.8% in 2-4, 37.1% in 5-7, and 4.1% in 8-10.

In 44% (n = 33) of the cases with diabetic foot infection, amputation occurred. 24.2% (n = 8) <1 month, 24.2% (n = 8) 1-6 months, 6.1% (n = 2) 6-12 months after amputation 45.5% was> 12 months.

The correlation between the data of the participants and the self-care agency score is presented in Table 2.

Table 1: The relationship between the data of the participants and the self-care agency

Features of the cases (n=97)	Self Care Agency Score n(%) Low 30 (30.9)	Moderate 57 (58.8)	High 10 (10.3)	p
Gender				
Male	18 (26.5)	42 (61.8)	8 (11.8)	0.149
Female	12 (41.4)	15 (51.7)	2 (6.9)	
Education Status				
Not literate	4 (30.8)	9 (69.2)	0 (0)	
Primary school	16 (29.1)	33 (60.0)	6 (10.9)	
Secondary school	6 (33.3)	8 (44.5)	4 (22.2)	0.556
High school	4 (40.0)	6 (60.0)	0 (0)	
University	0 (0)	1 (100)	0 (0)	
Income status				
Low	10 (34.5)	19 (65.5)	0 (0)	
Moderate	20 (32.3)	32 (51.6)	10 (16.1)	0.038
High	0 (0)	6 (100)	0 (0)	
Marital status				
Single	0 (0)	2 (100)	0 (0)	
Maried	26 (32.1)	45 (55.6)	10 (12.3)	
Widowed	2 (33.3)	4 (66.7)	0 (0)	0.694
Divorced	2 (25.0)	6 (75.0)	0 (0)	
Mobilization Status				
Alone	16 (28.1)	31 (54.4)	10 (17.5)	
Device supported	4 (50.0)	4 (50.0)	0 (0)	0.063
Person supported	10 (31.3)	22 (68.8)	0 (0)	
Number of individuals in the family				
2-4	18 (31.6)	33 (57.9)	6 (10.5)	
5-7	8 (22.2)	24 (66.7)	4 (11.1)	0.022
8-10	4 (100)	0 (0)	0 (0)	

Table 2: The correlation between the data of the participants and the self-care agency score.

	p*	r
Age	0.487	- 0.071
Education level	0.753	0.032
The number of individuals in the family	0.108	- 0.046
Amputation time	0.002	0.514

* Pearson correlation test was used. Statistical significance level was accepted as p <0.05.

Discussion

Diabetic foot infections are an important problem that is common and involves many departments at the same time. This disease leads to complicated skin soft tissue infection and osteomyelitis, leading to limb amputation [16]. This situation affects the lives of people in the long term and a decrease in self-care agency is observed.

The high self-care agency refers to the self-sufficiency of individuals to meet their needs without being dependent on anyone [17]. Only 10.3% of the cases in our study had high self-care agency.

When the studies performed due to diabetic foot infection, it was observed that there were similar data about the average age. The mean age of the study was 58.1 ± 12 years [18]. In another study, the average age of women was 62.3 years, the mean age of men was 56.4 years, and the average age of all patients was 59 years [19]. The age distribution in our study was consistent with the literature.

In the literature, there are different results in the studies evaluating the relationship between self-care agency and gender. In a study conducted by nursing homes by Altay and Avcı [20], it was determined that the self-care agency of men is higher than women (p = 0.246). In a study by Nazik et al. [21], it was evaluated the relationship between sex and self-care agency scores in a study of patients with Leprosy. The mean score was 83.5 ± 14.0 in males and 76.4 ± 17.7 in females. There was no statistically significant difference between self-care agency total score and gender (p = 0.278). In another study by Karakurt et al. [22], in patients with diabetes, self-care agency scores were higher in women (83.8 ± 21) than men (81.6 ± 18.3) (p = 0.589). In our study, although self-care agency score was higher in males, there was no statistically significant difference.

When the educational status and self-care agency scores were evaluated together, it was found that self-care agency score increased when the education level increased. In a study by Altay et al., there was a positive correlation between education level and self-care agency scores (p = 0.022) [20]. In the study by Karakurt et al. [22], it was observed that as the level of education increased, self-care agency scores increased but there was no significant difference between the groups (p = 0.552). However, In another study on diabetic patients conducted by Özçakar et al. [23], there was no significant relationship between education level and self-care agency scores (p = 0.865). In our study, no significant relationship was found between the educational level and the self-care agency score.

In the study by Muz and Eğlence [24], it was performed by patients with hemodialysis, it was found that the self-care agency score decreased as the duration of HD increased and it was statistically significant (p = 0.023). In another study conducted with type 1 diabetes mellitus patients, it was found that self-care agency decreased as the disease duration increased [22]. In contrast to the literature in our study, it was observed that the self-care agency score increased as the amputation duration increased. This condition was thought to be related to the acceptance of the disease.

Family support is an important factor in improving self-care. It is known that the number of individuals in the family also affects this situation. In a study, it was found that there was a positive relationship between the number of individuals in the family and the self-care agency scores (r = 0.302, p = 0.134) [21]. In our study, a negative correlation was found.

In a study evaluating the self-care agency score and economic status in diabetic patients, it was found that the economic status was not related to self-care agency score (p = 0.993) [23]. In another study, self-care agency score was found to be the highest in economic income in moderate (p <0.001) [22]. In another study conducted in patients with leprosy, there was no correlation between economic status and self-care agency scores (p = 0.340) [21]. Data obtained in our study were reported by Karakurt et al. [22] similar results were obtained.

Low number of samples of our study and the use of revised self-care agency scale were the limitations of our study.

In conclusion, diabetes and its complications are an important group of diseases that we frequently encounter. The self-care of the patients is reduced because of the mobilization of these patients, especially with the loss of limbs and with device support and / or person support. We think that self-care will be better with education to be given to patients and their relatives.

References

1. http://www.who.int/mediacentre/factsheets/fs138/en/ Last access date 21.10.2018.
2. Yılmaz C. Giriş. Yılmaz C, editor. Diyabet Hemşiresi El Kitabı. İzmir: Asya Tıp Yayıncılık; 2002. 1-12.
3. Elkin M. Laboratory Tests. In Elkin ME, Perry AG, Potter PA, editors. Nursing Interventions & Clinical Skills. 3th Edition. United States of America: Mosby, An Affiliate of Elsevier Science; 2004. p. 360-5.
4. Smeltzer SC, Bare B. Brunner & Suddarth's Textbook of Medical Surgical Nursing. 10th Edition, Philadelphia: Lippincott Williams &Wilkins A Wolters Kluwer Company; 2004. p.1149-203.
5. Masharani U, Karam JH. Diabetes Mellitus & Hypoglycemia. In Tierney LM, McPhee SJ, Papadakis MA, editors. Current Medical Diagnosis & Treatment. Adult Ambulatory & Inpatient Management. Fort-First Edition, NewYork: McGrow Hill Companies; 2002. p. 1203-38.
6. Fadıloğlu Ç. Diyabetin yönetimi ve hemşirelik. İçinde Yılmaz C, editor. Diyabet Hemşiresi El Kitabı. İzmir: Asya Tıp Yayıncılık; 2002. p. 74-120.
7. Balcı G. Özbakım gücü ve yaşam kalitesinin etkilendiği bazı durumlar ve hemşirenin rolü. Hacettepe Üniversitesi Hemşirelik Yüksekokulu Dergisi. 2003;10(2):69-76.
8. Catharine H, Johnston B, Lewis MA, Garg S. Self Efficacy impacts self-care and HbA1c in young adults with type 1 diabetes. Psychosomatic Medicine. 2002;64:43-51.
9. Toljama M, Hentinen M. Adherence to self-care and glycaemic control among people with insülin-dependent diabetes mellitus. Journal of Advanced Nursing. 2001;34(6):780-6.
10. Van den Arend IJM, Stolk RP, Ruttent GEHM, Schrijvers GJP. Education integrated into structured general practice care for type 2 diabetic patients results in sustained improvement of disease knowledge and self –care. British Diabetic Association. Diabetic Medicine. 2000;17:190-7.
11. Hosley JB, Molle-Mathews EA. Lippincott's Textbook for Clinical Medical Assisting. Philadelphia: Wolter Kluwer Company; 1999. p. 320-34.
12. Kearney BY, Fleischer BJ. Development of an instrument to measure exercise of self-care agency. Res Nurs Health. 1979;2:25-34.
13. Nahçivan NÖ. Turkish Language Equivalence of the Exercise of Self-Care Agency Scale. Western Journal of Nursing Research. 2004;26(7):813-24.
14. Pınar R. A new aspect of health-related research: quality of life, evaluation of reliability and validity of a quality of life survey in patients with chronic diseases. Hemşirelik Bülteni. 1995;9:85–95.
15. Yılmaz SD, Beji NK. Gebelikte öz bakım gücünün değerlendirilmesi. Genel Tıp Derg. 2010;20(4):137-42.
16. Kanatlı U. Diyabetik ayak enfeksiyonları. TOTBİD Dergisi. 2011;10(4):296-305.
17. Mohammadpour A, RahmatiSharghi N, Khosravan S, Alami A, Akhond M. The effect of a supportive educational intervention developed based on the Orem's self-care theory on the self-care ability of patients with myocardial infarction: a randomised controlled trial. J Clin Nurs. 2015;24(11-12):1686-92.
18. Bozkurt F, Tekin R, Çelen MK, Ayaz C. Diyabetik Ayak İnfeksiyonlarında Tedavi Yaklaşımı. Konuralp Tıp Dergisi. 2012;4(2):15-9.
19. Şenoğlu S, Karabela ŞN, Yaşar KK, Durdu B, Gedik H, Ersöz B, et al. Diyabetik Ayak Enfeksiyonlu Yirmi Yedi Olgunun Retrospektif Olarak Değerlendirilmesi. Med Bull Haseki. 2017;55:56-60.
20. Altay B, Avcı İA. Huzurevinde yaşayan yaşlılarda özbakım gücü ve yaşam doyumu arasındaki ilişki. Dicle Med J. 2009;36(4):275-82.
21. Nazik H, Gül FÇ, Gül FC, Nazik S, Okay RA, Mülayim MK, et al. Evaluation Of Self-Care Power In Leprosy Patients. Kocaeli Med J. 2018;7(1):77-82.
22. Karakurt P, Aşılar RH, Yıldırım A. Diyabetli hastaların öz bakım gücü ve algıladıkları sosyal desteğin değerlendirilmesi. ADÜ Tıp Fakültesi Dergisi. 2013;14(1):1–9.
23. Özçakar N, Mehtap KM, Kuruoğlu E. Diyabet hastalarının özbakım bilinci. Türk Aile Hek Derg. 2009;13(1):17-22.
24. Muz G, Eğlence R. Hemodiyaliz Uygulanan Hastalarda Öz Bakım Gücü ve Öz Yeterliliğin Değerlendirilmesi. Balikesir Saglik Bil Derg. 2013;2 (1):15-21.

Appendix 1: Self-Care Agency Scale

	1	2	3	4	5
1. If my health is concerned I can leave some of my habits					
2. I like myself					
3. I usually do not have enough energy to meet my needs for health.					
4. When I feel my health is getting worse, I know what to do.					
5. I'm proud to do what I need to stay healthy.					
6. I tend to neglect my personal needs.					
7. When I can't look at myself, I call for help.					
8. I like to start new projects.					
9. I mostly postpone doing things that I know will be useful to me.					
10. I take some precautions not to be ill.					
11. I try to make my health better.					
12. I feed balanced.					
13. I constantly complain about issues that bothers me and I do nothing more.					
14. I look for better protection methods to pay attention to health.					
15. I believe that my health will reach a very good level.					
16. I believe that I deserve all the efforts to preserve my health.					
17. I apply my decisions until the end.					
18. I understand how my body works.					
19. I rarely apply my personal decisions about my health.					
20. Mate with myself.					
21. I take care of myself.					
22. It is a coincidence that my health is better.					
23. I regularly rest and do body movements.					
24. I would like to know how various diseases occur and what kind of effects they have.					
25. Life is a pleasure.					
26. I cannot fulfill my duties within the family.					
27. I take responsibility for my own actions.					
28. As the years went by, I realized what was needed to be healthier.					
29. I know what kind of food I have to eat to stay healthy.					
30. I am interested in learning everything about my body's work.					
31. Sometimes, when I get sick, I don't care about my illnesses, and I expect it to pass.					
32. To look at myself, I try to get information.					
33. I feel that I am a valued member of my family.					
34. As I remember the history of my health check, I also know the history of my future health check.					
35. I understand myself and my needs quite well.					

1: It doesn't describe me at all, 2: It doesn't describe me much, 3: I have no idea, 4: It defines me a bit, 5: It defines me a lot

Appendix 2: Öz Bakım Gücü Ölçeği

	1	2	3	4	5
1.Eğer sağlığım söz konusu ise bazı alışkanlıklarımı memnuniyetle bırakabilirim					
2.Kendimi beğeniyorum					
3.Sağlığımla ilgili ihtiyaçlarımı istediğim gibi karşılamak için yeterli enerjiye genellikle sahip değilim.					
4.Sağlığımın kötüye gittiğini hissettiğim zaman, ne yapmam gerektiğini biliyorum.					
5.Sağlıklı kalmak için ihtiyacım olan şeyleri yapmaktan gurur duyarım.					
6.Kişisel ihtiyaçlarımı ihmal etmeye meyilliyim.					
7.Kendime bakamadığım zaman, yardım ararım.					
8.Yeni projelere başlamaktan hoşlanırım.					
9.Benim için yararlı olacağını bildiğim şeyleri yapmayı çoğunlukla ertelerim.					
10.Hasta olmamak için bazı önlemler alırım.					
11.Sağlığımın daha iyi olmasına çaba gösteririm.					
12.Dengeli beslenirim.					
13.Beni rahatsız eden konularda fazla bir şey yapmadan sürekli yakınırım.					
14.Sağlığıma dikkat etmek için daha iyi korunma yolları araştırırım.					
15.Sağlığımın çok iyi bir düzeye ulaşacağına inanıyorum.					
16.Sağlığımı korumak için yapılan çabaların tümünü hak ettiğime inanıyorum.					
17.Kararlarımı sonuna kadar uygularım.					
18.Vücudumun nasıl çalıştığını anlıyorum.					
19.Sağlığımla ilgili kişisel kararlarımı nadiren uygularım.					
20.Kendimle dostum.					
21.Kendime iyi bakarım.					
22.Sağlığımın daha iyi olması benim için tesadüfi bir durumdur.					
23.Düzenli olarak istirahat ederim ve beden hareketleri yaparım.					
24.Çeşitli hastalıkların nasıl meydana geldiğini ve ne çeşit etkileri olduğunu öğrenmek isterim.					
25.Yaşam bir zevktir.					
26.Aile içindeki görevlerimi yeterince yerine getiremiyorum.					
27.Kendi davranışlarımın sorumluluğunu üstlenirim.					
28.Yıllar geçtikçe, daha sağlıklı olmak için gereken şeylerin farkına vardım.					
29.Sağlıklı kalmak için ne çeşit yiyecekler yemem gerektiğini biliyorum.					
30.Vücudumun çalışması ile ilgili her şeyi öğrenmeye ilgi duyuyorum.					
31.Bazen hastalandığımda, rahatsızlıklarımı önemsemez ve geçmesini beklerim.					
32.Kendime bakmak için bilgilenmeye çalışırım.					
33.Ailemin değerli bir üyesi olduğumu hissediyorum.					
34.Son sağlık kontrolümün tarihini hatırladığım gibi, gelecek sağlık kontrolümün tarihini de biliyorum.					
35.Kendimi ve ihtiyaçlarımı oldukça iyi anlarım.					

1:Beni hiç tanımlamıyor, 2:Beni pek tanımlamıyor, 3:Fikrim yok, 4: Beni biraz tanımlıyor, 5:Beni çok tanımlıyor

J Surg Med. 2019;3(3):218-222.
DOI: 10.28982/josam.465600

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Long-term outcomes of pure olive oil to prevent postoperative peritoneal adhesions in rats

Ratlarda postoperatif peritoneal adezyonların önlenmesinde saf zeytinyağının uzun dönem etkinliği

Dilan Altıntaş Ural [1], Haluk Sarıhan [2], İsmail Saygın [3], Duygun Altıntaş Aykan [4], Alper Ural [5], Mustafa İmamoglu [2]

[1] Kahramanmaras Necip Fazıl City Hospital, Depatment of Pediatric Surgery, Kahramanmaras, Turkey
[2] Karadeniz Technical University Faculty of Medicine, Department of Pediatric Surgery, Trabzon, Turkey
[3] Karadeniz Teknik University, Faculty of Medicine Department of Pathology, Trabzon, Turkey
[4] Kahramanmaras Sutcu Imam University, Department of Pharmacology, Kahramanmaras, Turkey
[5] Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Plastic and Reconstructive Surgery, Kahramanmaras, Turkey

ORCID ID of the author(s)
DAU: 0000-0002-1976-9122
HS: 0000-0002-0991-8235
İS: 0000-0002-6013-6378
DAA: 0000-0001-8224-4006
AU: 0000-0001-8135-6444
Mİ: 0000-0001-8267-9755

Corresponding author / Sorumlu yazar:
Dilan Altıntaş Ural
Address / Adres: Karadeniz Teknik Üniversitesi Tıp Fakültesi, Çocuk Cerrahisi Anabilim Dalı, Trabzon, Türkiye
E-mail: dilanaltintas@yahoo.com

Ethics Committee Approval: Animal trials were initiated after approval from the local ethics committee of Karadeniz Teknik University, Faculty of Medicine (Approval date: 15.04.2015, approval no: 2).
Etik Kurul Onayı: Karadeniz Teknik Üniversitesi Tıp Fakültesi yerel etik kurulundan onay alındıktan sonra çalışma başlatıldı (Onay tarihi: 15.04.2015, onay no: 2).

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 15.11.2018
Accepted / Kabul Tarihi: 14.01.2019
Published / Yayın Tarihi: 18.01.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Abstract

Aim: Postoperative peritoneal adhesion (PPA) that occur after abdominopelvic surgery are the current problems of surgeons. The aim of this study was to investigate the effect of pure olive oil in preventing PPA.

Methods: Thirty-two rats were randomly divided into four groups: (1) Sham group: 5 ml pure olive oil was injected percutaneously into the peritoneal cavity without laparotomy, (2) Adhesion group: A standard adhesion model was formed on jejunum, ileum and caecum. (3) Adhesion + olive oil: A standard adhesion model was formed on jejunum, ileum and caecum. Subsequently the area on jejunum, ileum and caecum was covered with 5 ml of pure olive oil. (4) Olive oil + adhesion: The area on jejunum, ileum and caecum was covered with 5 ml of pure olive oil. Subsequently the standard adhesion model was formed on this area. Four weeks later, abdominal cavities of rats were examined for PPA, using Evan's adhesion classification and Zühlke's histopathological grade scales.

Results: PPA was not found in Group 1 in which olive oil was injected intraperitoneally. PPA was present in all rats in Group 2. Microscopic adhesion scores in Group 3 and 4 were significantly lower than Group 2. The collagen fiber fractions were significantly lower and there was a significant decrease in fibrosis. There was no statistically significant difference in microscopic adhesion scores in Group 3 compared to Group 4.

Conclusion: We found that antiinflammation, tissue regeneration and hydroflotation effect of pure olive oil decreased PPA formation in rats by maintaining a long lasting effect on the wounded peritoneal surface. Thus olive oil, a cheap and easy to obtain product, can be used in cases of PPA in surgery clinics.

Keywords: Postoperative peritoneal adhesions, Olive oil, Surgery

Öz

Amaç: Abdominopelvik cerrahi sonrası ortaya çıkan postoperatif peritoneal adezyonlar (PPA) cerrahların güncel sorunlarındandır. Bu çalışmanın amacı, saf zeytinyağının PPA önlenmesindeki etkisini araştırmaktır.

Yöntemler: 32 rat randomize dört gruba ayrıldı: (1) Sham grubu: Laparotomisiz peritoneal kaviteye perkütan olarak 5 ml saf zeytinyağı enjekte edildi, (2) Adezyon grubu: Jejunum, ileum ve çekum üzerine standart bir adezyon modeli oluşturuldu. (3) Adezyon + zeytinyağı: Jejunum, ileum ve çekumda standart bir adezyon modeli oluşturuldu. Daha sonra jejunum, ileum ve çekum üzerindeki alan 5 ml saf zeytinyağı ile kaplandı. (4) Zeytinyağı + adezyon: Jejunum, ileum ve çekum üzerindeki alan 5 ml saf zeytinyağı ile kaplandı. Daha sonra bu alanda standart adezyon modeli oluşturuldu. Dört hafta sonra, sıçanların karın boşlukları, PPA için Evans'ın adezyon sınıflandırması ve Zühlke'nin histopatolojik derecelenme ölçekleri kullanılarak incelendi.

Bulgular: Zeytinyağının intraperitoneal olarak enjekte edildiği Grup 1'de herhangi bir adezyon bulunmadı. Grup 2'deki tüm ratlarda PPA mevcuttu. Grup 3 ve 4'ün mikroskopik adezyon skorları Grup 2'den istatistiksel olarak anlamlı düzeyde daha azdı. Kollajen lif fraksiyonları belirgin şekilde daha düşüktü ve fibrozisde belirgin bir azalma gözlendi. Grup 3, Grup 4 ile karşılaştırıldığında ise, mikroskopik adezyon skoru açısından istatistiksel olarak anlamlı fark yoktu.

Sonuç: Saf zeytinyağının antiinflamasyon, doku rejenerasyonu ve hidroflotasyon etkisinin, yaralanmış peritoneal yüzey üzerinde uzun süreli etki sağlayarak ratlarda PPA oluşumunu azalttığını bulduk. Bu nedenle, ucuz ve satın alınması kolay bir ürün olan zeytinyağı, cerrahi kliniklerinde PPA vakalarında kullanılabilir.

Anahtar kelimeler: Postoperatif peritoneal adezyon, Zeytinyağı, Cerrahi

How to cite / Atıf için: Ural DA, Sarıhan H, Saygın İ, Aykan DA, Ural A, İmamoglu M. Long-term outcomes of pure olive oil to prevent postoperative peritoneal adhesions in rats. J Surg Med. 2019;3(3):218-222.

Introduction

Postoperative peritoneal adhesion (PPA) that occur after abdominopelvic surgery are the current problems of surgeons as they can lead to complications such as intestinal obstruction, infertility, pelvic pain and difficulties during re-operations. The best surgical techniques alone are insufficient to prevent PPA [1]. Approximately 90% of patients undergoing intraabdominal surgery develop PPA, and approximately 3% develop intestinal obstruction. PPA causes infertility approximately in 15-20% of women [2]. Intestinal obstruction is associated with PPA with a ratio of 75%, and this association might be higher up to 93% after multiple operations [3].

Damages to peritoneal and serosal surfaces, due to the chemical, thermal, foreign body reactions, infections or traumatic factors initiate the events resulting in adhesion formation [4]. Peritoneal or serosal injury results in release of histamine and vasoactive kinins from mast cells, leading to an increase in capillary permeability and accumulation of serous liquid [5]. The damage of mesothelial surface causes the contact of connective tissue with peritoneal fluid. This results in increased levels of leukotriene B4 (LTB4) and prostaglandin E2 (PGE2) in peritoneal fluid and inhibition of tissue plasminogen activator activity (tPAA). Increase in LTB4 and PGE2 stimulates the adhesion formation, whereas inhibition of tPAA reduces fibrin degradation; ultimately the balance changes further in adhesion formation. Peritoneal injury activates coagulation cascade, and a release in thromboplastin level and the fibrin formation occurs. If fibrin degradation is not enough, fibrin provides matrix for adhesion formation [6,7].

Olive oil has taken a focus of attention due to various effects of its phenolic components. Biological properties of olive oil have been evaluated extensively in vitro and in vivo animal models and human studies. Currently, anti-inflammatory, antioxidant, antineoplastic and antimicrobial effects of phenolic components have been documented in large number of studies [8-10]. There is also lubricant and mechanical barrier action of olive oil. Since pure olive oil is a highly viscous fluid, it is important that lubrication effect of olive oil on serosal and peritoneal surfaces may be used to minimize abrasion during surgical operations. Hence, olive oil may prevent abdominal adhesions due to mechanical separation (hydroflotation) effects between the traumatized surfaces.

In this study, we aimed to investigate the effect of pure olive oil in the prevention of PPA after long-term follow-up in rats undergoing an adhesion model.

Materials and methods

This study was carried out at pediatric surgery department. Animal trials were initiated after approval from the local ethics committee. A total number of thirty-two female Wistar-Albino rats (bodyweight 250-300 g) in eight groups were randomly selected in the study. Animals were kept at an ambient temperature of 22°C and 60±5% humidity with a 12-hr light/dark cycle and access to food and water ad libitum.

Pure olive oil preparation

Pure olive oil was produced in agricultural engineering with cold presecting method. Olive oil was sterilized by filtration through 0.45 nm porosity to sterile centrifuge tube. The pH value of olive oil was the same as that of peritoneal dialysis liquid (pH 6.8).

Experimental design and peritoneal adhesion model

Rats were given two weeks to acclimatize to the surroundings and handling prior to the experiments. Rats were starved for 12 hours prior to surgery, and experiment was started after appropriate anesthesia with ketamine 75 mg/kg (Ketalar, Pfizer, Istanbul, Turkey) and xylazine 10 mg/kg (Rompun, Bayer). All surgical procedures were performed under sterile conditions.

Experimental adhesion model was provided with a special designed device, with a movable arm for its floating action. We used a weight of 0.5 kg, an area of 2x2 cm², and applied the floating action ten times to the intestinal surface for standard adhesion model. Thus, a standardized peritoneal trauma was created on a selected intestinal surface with respect to weight, area and number.

Rats were divided randomly into four groups, each containing eight rats: Group 1 (sham group): 5 ml pure olive oil was injected percutaneously into the peritoneal cavity without laparotomy; Group 2 (adhesion group): Vertical midline incision of 3 cm was inserted, and a standard adhesion model was created with adhesion apparatus on jejunum, ileum and caecum; Group 3 (adhesion + olive oil): Vertical midline incision of 3 cm was inserted, and a standard adhesion model was created with adhesion apparatus on jejunum, ileum and caecum. Subsequently, the area on jejunum, ileum and caecum was covered with 5 ml of pure olive oil; Group 4 (olive oil + adhesion): Vertical midline incision of 3 cm was inserted, and the area on jejunum, ileum and caecum was covered with 5 ml of pure olive oil. Then the standard adhesion model was created with adhesion apparatus on this area.

Incisions were closed by continuous technique with 3/0 propylene suture. On the 30th postoperative day, the rats were sacrificed by cervical dislocation. Through the initial laparotomy scar, abdomen was re-opened using a midline incision from cranial to caudal to view the extent of intraabdominal adhesion formation. The adhesions were macroscopically graded according to Evans' adhesion classifications (Table 1), and microscopically graded according to Zühlke's histopathological classifications (Table 2) by an experienced pathologist who was blinded to the different treatment groups.

Macroscopic assessment of PPA

Macroscopic assessment of PPA was performed according to the method described by Evans [11]. A pathologist, who was uninformed about the groups, examined the intraabdominal adhesions of each rat. Through this examination, the interactions of the olive oil with the peritoneum and its efficacy in preventing adhesions were evaluated. PPA was classified according to the strength and area of adhesions (Table 1).

Histopathological assessment of PPA

The area of 2x2 cm2 on jejunum, ileum, anterior caecum from all rats, and adhesions on this surface were excised. The tissues were fixed in a 10% buffered formaldehyde solution and embedded in paraffin following dehydration. Tissue sections of 5 µm thickness were obtained and stained with hematoxylin

and eosin. These sections were evaluated using light microscopy at a magnification of 100x. The histopathological grade was evaluated according to histopathological grading of Zühlke's classification [12] (Table 2).

Table 1: Evans's scoring system

Adhesion area score (Grade)	Adhesion strength score (Grade)
0: no adhesion	0: no adhesion
1: 25% of the area has adhesion	1: spontaneously separating adhesions
2: 50% of the area has adhesion	2: adhesions separating by traction
3: complete area has adhesion	3: adhesion separated by dissection

Table 2: Zühlke's histopathological classification

Grade 1	Loose connective tissue, cell-rich, old and new fibrin, fine reticulin fibrils
Grade 2	Connective tissue with cells and capillaries, few collagen fibers
Grade 3	Connective tissue more firm, fewer cells, more vessels, few elastic and smooth muscle fibers
Grade 4	Old firm granulation tissue, cell-poor, serosal layers hardly distinguishable

Statistical analysis

SPSS 13.01 was used for statistical analysis. Kruskal Wallis test was used to evaluate the distribution of data. Categorical variables were expressed as n(%), continious date were as mean±standard deviation or median (interquartile range). Chi square test was for the analysis of categorical variables. Kruskal Wallis test was used for multiple group analysis and Bonferroni corrected Mann Whitney U test in posthoc subgroup comparisons. The results were evaluated at 95% confidence interval and at $p<0.05$ level.

Results

We did not find any peritoneal reaction, toxic effect or adhesion in group 1, in which olive oil was injected intraperitoneally without laparotomy. When group 3 and group 4 were separately compared to group 2, we found that the adhesion strength scores of group 3 and group 4 were statistically lower than group 2 ($p<0.001$). There was no statistically significant difference in the adhesion strength when compared group 3 to group 4 (Table 3). When group 3 and group 4 were separately compared to group 2, scores of adhesion areas in group 3 and group 4 were significantly lower than group 2 ($p <0.001$). When we compared group 3 to group 4, there was no significant difference in the score of adhesion area (Table 3).

The microscopic adhesion score evaluations of jejunum, ileum and caecum's were shown in Table 4. The microscopic adhesion scores of groups 3 and 4 were statistically lower than group 2 ($p <0.001$). There was no significant difference in microscopic adhesion score when compared group 3 to group 4.

Table 3: The macroscopic adhesion score in jejunum, ileum and caecum of the groups according to Evans's scoring system

Adhesion Strength Assessment, n (%)					
Group no	Score 0	Score 1	Score 2	Score 3	Total
2	0 (0%)	0 (0%)	1(12.5%)	7 (87.5%)	8 (100%)
3	5 (62.5%)	3 (37.5%)	0 (0%)	0 (0%)*	8 (100%)
4	7 (87.5%)*	1 (12.5%)	0 (0%)	0 (0%)*	8 (100%)
Adhesion Area Assessment, n (%)					
Group no	Score 0	Score 1	Score 2	Score 3	Total
2	0 (0%)	0 (0%)	6 (75.0%)	2 (25.0%)	8 (100%)
3	5 (62.5%)	3 (37.5%)	0 (0%)**	0 (0%)	8 (100%)
4	6 (87.5%)**	2 (12.5%)	0 (0%)**	0 (0%)	8 (100%)

* refers to the significant difference between group 3-4 and group 2 in adhesion strength scores ($p <0.001$)
** refers to the significant difference between group 3-4 and group 2 in scores of adhesion areas ($p <0.001$)

Table 4: The microscopic adhesion score in jejunum, ileum and caecum of the groups according to Zühlke's histopathologic classification

Group no	Score 0	Score 1	Score 2	Score 3
	Jejenum, n (%)			
2	0 (0%)	3 (37.5%)	1 (12.5%)	4 (50%)
3	6 (75%)*	2 (25%)	0 (0%)	0 (0%)
4	7 (87.5%)*	1 (12.5%)	0 (0%)	0 (0%)
	Ileum, n (%)			
2	0 (0%)	5 (62.5%)	2 (25%)	1 (12.5%)
3	7 (87.5%)**	1(12.5%)	0 (0%)	0 (0%)
4	8 (100%)**	0 (0%)	0 (0%)	0 (0%)
	Caecum, n (%)			
2	0 (0%)	1 (12.5%)	4 (50%)	3 (37.5%)
3	7 (87.5%)***	1 (12.5%)	0 (0%)	0 (0%)
4	7 (87.5%)***	1 (12.5%)	0 (0%)	0 (0%)

* refers to the significant difference between group 3-4 and group 2 in histopathologic adhesion in jejenum ($p <0.001$)
** refers to the significant difference between group 3-4 and group 2 in histopathologic adhesion in ileum ($p <0.001$)
*** refers to the significant difference between group 3-4 and group 2 in histopathologic adhesion in caecum ($p <0.001$)

Discussion

Adhesion is known as a type of physiologic peritoneal healing process. However, there are two main processes that can prevent the formation of PPA: decreasing the frequency of number of the peritoneal trauma, and performing less traumatic surgical techniques. It is much simpler and more effective to apply the first option. It's simple, because all should be done is to build a barrier that will prevent the formation of trauma. It's effective, since the process of wound healing after trauma is quite complicated. These options would have a low chance of success unless clarifying the underlying physiopathology. Despite the increasing number of laparoscopic surgeries over the years, an expected reduction in the percentage of adhesions has not been obtained. Clinical trials have shown that laparoscopic procedures reduce the area of adhesions but do not reduce the incidence of PPA [13].

Various experimental models such as abrasion, local peritoneal excision, ischemic damage, emplacement of foreign bodies into the peritoneal cavity, thermal damage and bacterial contamination have been developed to generate PPA [14,15]. Any manipulations performed by hand or surgical instruments during laparotomies are known as mechanical trauma and they are the most common cause of PPA [16,17]. We used abrasion model in this study because it simulated the mechanical trauma.

Fibrin is known to provide the matrix for adhesion formation [6,7]. The number of clinical and experimental studies demonstrating anti-adhesive and anti-phlogistic effects of materials that inhibit fibrin accumulation is not large. In an experimental study, no significant difference was found between aprotinin, dextran or lipid emulsion compared to the control group in preventing the frequency of PPA [18]. Isotonic NaCl and hypertonic dextrose solutions were used to remove fibrin, but their effects were limited because of their rapid absorbtion from peritoneum. In previous studies, pepsin, trypsin and papain, which remove fibrin by mechanical or enzymatic processes, have been recommended. However, subsequent studies have shown that these enzymes were rapidly neutralized by the peritoneum, and that there was no effect in preventing adhesions [19]. Sodium citrate, heparin, dicumarol, meclofenamate, tolmetin, ibuprofen, nimesulide, oxyphenbutazone, corticosteroid, aspirin, disodium cromoglycate, methylene blue, Mn-desferoxamine, allopurinol, mannitol, pentoxifylline, catalase and vitamin E were dosens of chemicals that had been used to prevent the

inflammatory response and prevent fibrinous exudate. Due to their barrier-forming properties which reduce fibroblastic activity and provide lubrication, soybean oil, aloe vera gel, honey, canola oil have been tried but not enough therapeutic results have been obtained [20,21].

Another method that was used to prevent PPA is the plication method in place of intestinal transmesenteric sutures. However, it presented operative difficulties and complications such as fistulas, prolonged postoperative ileus and abdominal pain. The simplest technique to decrease the frequency of contact between serosal surfaces was replacement of the omentum between intestines and abdominal wall. However, inability of omentum to prevent adhesions that may be occured between intestines has left this method inadequate [22,23]. In previous studies, oxygen, 32% dextran, 5% polyethylene glycol, paraffin, amniotic fluid, lanolin, dextrose solutions, silver foil, silk and silicone have been used as barriers to enhance the intraperitoneal fluid by increasing oncotic pressure and to reduce the frequency of contact between tissues [24].

In our study, we used olive oil because it is a low-cost product that can be easily obtained and used without too much processing. Previous studies regarding PPA prevention had focused on short-term treatment. Our study is the first survey that surveyed pure olive oil prevented PPA in the long term follow-up on jejenum, ileum and caecum in rats. We administered pure olive oil before or after forming an adhesion model and found that PPA was significantly reduced. This effect may depend on olive oil's anti-inflammatory, tissue regenerative and hydroflotting actions. We think that olive oil has long-term effect as a result of late absorption. We had two reasons for choosing pure olive oil to prevent PPA: the first fact was, phenolic components of pure olive oil had positive effects on wound healing due to its well-known anti-atherogenic, antioxidant, antineoplastic and anti-inflammatory effects. The second fact was because it is a liquid with high viscosity, so it can prevent PPA by the effect of hydroflotation. Anti-inflammatory effect is due to its major components including erythrodiol, beta sitosterol, squalene; and minor components including oleuropein, tyrosol, hydroxytyrosole and caffeic acid [9]. Cicerale et al have shown that the phenolic components exhibit antiinflammatory effects by reducing the release of thromboxane B2, LTB4, arachidonic acid, and inhibiting cyclooxygenase-1 and 2 [25]. Pure olive oil inhibited the stress ulcer formation by reducing tangential and shear forces, and prevented the wound dehiscence in immobilized patients [26].

In our study, we administered 5 ml of pure olive oil into the peritoneal cavity of rats in group-1 without laparotomy. Our aim was to explore the potential toxic effects of pure olive oil in the intact peritoneal cavity. However, we did not find any macroscopic or histopathological adhesions or any toxic reactions in the peritoneal cavity in this group. This result suggests that olive oil does not cause any inflammation in the peritoneal cavity in the long term.

The reason of thirty days-follow up is that there is a steady increase in collagen production till the 21st postoperative day. This is defined as maturation phase, known as the longest phase in wound healing. It indicates that chronic process begins with granulation tissue, re-epithelization and keratinocyte migration. After 21st day, a reduction in collagen synthesis and rearrangement of collagen is observed [27]. Hence we waited for the maturity phase to be completed before starting our assessments.

In our previous study of traumatic adhesion model in rats, we have found that 1 ml pure olive oil administered on a single adhesion area on caecum prevented PPA after a 10-days-follow up (a short-term study). Current study is a long-term study lasting up to four weeks. We found that olive oil is effective after four weeks indicating that it remains in the peritoneum without absorption and extends its hydroflotting action. In our long-term study, we showed that when abrasion was done before or after applying the olive oil, PPA was prevented in both.

On the other hand, the insignificant postoperative adhesions seen in groups 3 and 4 are due to the differences in individual fibronolithic processes. There is the possibility that individual genetic differences in fibrinolysis may result in PPA despite all the efforts to prevent their formation. These adhesions were grade 1 and simple adhesions that did not cause any intestinal obstructions.

Our study has some limitations. We did not evaluate the anti-inflammatory properties of olive oil on proinflammatory markers. In addition, we did not compare the positive effects of olive oil on adhesion-induced inflammation with a positive control group such as locally administrated non-steroidal antiinflammatory agents. However, according to the data in this experimental study, we conclude that administration of pure olive oil, an effective and readily available agent, prevented PPA.

It is necessary to evaluate the clinical usefulness of olive oil in surgery patients. As to light on the future studies, components of olive oil can be purified and individual effects may be investigated.

References

1. Liakakos T, Thomakos N, Fine PM, Dervenis C, Young RL. Peritoneal adhesions: etiology, pathophysiology, and clinical significance. Recent advances in prevention and management. Dig Surg. 2001;18(4):260-73.
2. Menzies D. Postoperative adhesions: their treatment and relevance in clinical practice. Ann R Coll Surg Engl. 1993;75(3):147-53.
3. Tolu A, Gökçe Ö. Adezyonların Sebepleri ve Önlenmesi. T Klin Tıp Bilimleri. 1992;12(3):244-9.
4. Arnold PB, Green CW, Foresman PA, Rodeheaver GT. Evaluation of resorbable barriers for preventing surgical adhesions. Fertil Steril. 2000;73(1):157-61.
5. Kırdak T, Uysal E, Korun N. Karın içi yapışıklıkların önlenmesinde metilprednizolonun farklı dozlarının etkinliğinin incelenmesi. Ulus Travma Acil Cerrahi Derg. 2008;14(3):188-91.
6. Ryan GB, Grobety J, Majno G. Postoperative peritoneal adhesions. A study of the mechanisms. Am J Pathol. 1971;65(1):117-48.
7. Gomel V, Urman B, Gurgan T. Pathophysiology of adhesion formation and strategies for prevention. J Reprod Med. 1996;41(1):35-41.
8. Speroni E, Guerra MC, Minghetti A, Crespi-Perellino N, Pasini P, Piazza F, et.al. Oleuropein evaluated in vitro and in vivo as an antioxidant. Phytother. Res., 1998;12:98-100.
9. De la Puerta R, Martinez Dominguez E, Ruiz-Gutierrez V. Effect of minor components of virgin olive oil on topical antiinflammatory assays. Z Naturforsch. 2000;55:814-9.
10. Tranter HS, Tassou SC, Nychas GJ. The effect of the olive phenolic compound, oleuropein, on growth and enterotoxin B production by Staphylococcus aureus. J. Appl.Bacteriol. 1993;74:253-9.
11. Evans DM, McAree K, Guyton DP. Dose dependency and wound healing aspects of the use of tissue plasminogen activator in the prevention of intra-abdominal adhesions. Am J Surg. 1993;165(6):229-32.
12. Zühlke HV, Lorenz EM, Straub EM, Savvas V. Pathophysiology and classification of adhesions. Langenbecks Arch Chir Suppl II Verh Dtsch Ges Chir 1990:1009-16.

13. Audebert AJ, Gomel V. Role of microlaparoscopy in the diagnosis of peritoneal and visceral adhesions and in the prevention of bowel injury associated with blind trocar insertion. Fertil Steril. 2000;73(3):631-5.
14. Millamiemi H, Frolander M. The effect of glove powders and their constituents on adhesions and granuloma formation in the abdominal cavity of the rabbit. ACTA Chir Scand. 1966;131:312-8.
15. Blauer KL, Collins RL. The effect of intraperitoneal progesterone on postoperative adhesion formation in rabbit. Fertil Steril. 1988;49:144-9.
16. Drollette CM, Badawy SZA. Pathophysiology of pelvic adhesions: modern trends in preventing infertility. J Reprod Med. 1992;37:107-21.
17. Ryan G, Grobety J, Majino G. Postoperative peritoneal adhesions: a study of mechanism. Am J Pathol. 1971;65:117-48.
18. Demirel H, Altay K, Sultanoğlu E, Dolgun A, Odabaş Ö. Postoperatif İntraperitoneal Adezyonların Proflaksisinde Aprotinin, Dextran 7 Ve %1'luk Yağ Emülsiyonu ile Karşılaştırmalı Bir Çalışma. Türkiye Klinikleri Tıp Bilimleri Araştırma Degisi. 1990;8(6):524-8.
19. Tolu A, Gökçe Ö. Adezyonların Sebepleri ve Önlenmesi. T Klin Tıp Bilimleri. 1992;12(3):244-9.
20. Galili Y, Ben-Abraham R, Rabau M, Klausner J, Kluger Y. Reduction of surgery-induced peritoneal adhesions by methylene blue. Am J Surg. 1998;175(1):30-2.
21. De la Portilla F, Ynfante I, Bejarano D, Conde J, Fernandez A, Ortega JM, et al. Prevention of peritoneal adhesions by intraperitoneal administration of vitamin E: an experimental study in rats. Dis Colon Rectum. 2004;47(12):2157-61.
22. Dargenio R, Cimino C, Ragusa G, Garcea N, Stella C. Pharmacological prevention of postoperative adhesions experimentally induced in the rat. Acta Eur Fertil. 1986 Jul-Aug;17(4):267-72.
23. Özçelik A, Yurdakul İ. İntraabdominal Adezyonlar ve Önlenmesi. Veteriner Cerrahi Dergisi. 2006;12(1-4):62-7.
24. Holmdahl L, Eriksson E, Eriksson BI, Risberg B. Depression of peritoneal fibrinolysis during operation is a local response to trauma. Surgery. 1998;123(5):539-44.
25. Cicerale S, Lucas L, Keast R. Biological activities of phenolic compounds present in virgin olive oil. Int J Mol Sci. 2010 Feb 2;11(2):458-79.
26. Ellis H. The magnitude of adhesion-related problems. In: M.D. GSd, eds. Peritoneal Surgery. New York: Springer; 2000. pp. 297-306.
27. Baum C, Arpey C. Normal cutaneous wound healing: Clinical correlation with cellular and molecular events. Dermatol Surg. 2005;31(6):674-8661.

J Surg Med. 2019;3(3):223-226.
DOI: 10.28982/josam.485247

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Evaluation of index of cardio-electrophysiological balance and Tp-e/QT ratio in patients with coronary artery ectasia

Koroner arter ektazisi olan hastalarda kardiyo-elektrofizyolojik denge indeksi ve Tp-e/QT oranının değerlendirilmesi

Yakup Alsancak [1], Ahmet Seyfeddin Gürbüz [1], Beyza Saklı [2], Abdullah İçli [1]

[1] Department of Cardiology, Necmettin Erbakan University, Faculty of Medicine, Meram, Konya, Turkey
[2] Department of Cardiology, Devrek State Hospital, Zonguldak, Turkey

ORCID ID of the author(s)
YA: 0000-0001-5230-2180
ASG: 0000-0002-9225-925X
BS: 0000-0002-8255-0983
Aİ: 0000-0002-7047-811X

Corresponding author / Sorumlu yazar:
Yakup Alsancak
Address / Adres: Necmettin Erbakan Üniversitesi, Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Meram, Konya, Türkiye
E-mail: dryakupalsancak@gmail.com

Ethics Committee Approval: Local Ethical committee of Necmettin Erbakan University, Meram Faculty of Medicine, 2018/1935.
Etik Kurul Onayı: Necmettin Erbakan Üniversitesi, Meram Tıp Fakültesi Etik Kurul, 2018/1935.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 19.01.2019
Accepted / Kabul Tarihi: 04.02.2019
Published / Yayın Tarihi: 14.02.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Abstract

Aim: Index of cardiac electrophysiological balance (iCEB), calculated as QT interval divided by QRS duration, has been described as a novel risk marker for predicting malignant ventricular arrhythmia. Increased levels of iCEB predict to torsades de pointes (TdP) and decreased levels of iCEB predict to non-torsades de pointes mediated ventricular tachycardia or ventricular fibrillation. The aim of this study is to evaluate arrhythmogenic risk by using iCEB in patients with coronary ectasia (CAE).

Methods: Our study, designed as case-control, included 130 patients who were admitted to our outpatient clinic. 75 patients with isolated CAE (study group) and 55 healthy subjects (control group) were included in the study. Both groups underwent a standard 12-lead surface electrocardiogram and Tp-Te interval, QT interval, QRS interval, Tp-Te/QT ratio and QT/QRS ratio (iCEB) of patients were recorded and compared between groups.

Results: Tp-e intervals and Tp-e/QT ratio is significantly higher in study group (p=0.001). And, iCEB was found as tend to be numerically higher in study group, but we could not match a statistically difference between groups (p=0.118). Tp-e and Tpe/QT ratio were higher in patients with two or three vessels CAE than one vessel (p value; for Tp-e p=0.024 and Tpe/QT ratio p=0.028). Although iCEB was found as higher with affected number of coronary artery, there was no statistically difference between groups.

Conclusion: Our results demonstrate that CAE patients have significantly higher values of Tp-Te and Tp-Te/QT than controls. We need further studies to show increased arrhythmogenesis risk using iCEB for individuals with CAE.

Keywords: Arrhythmia, Coronary artery ectasia, iCEB, QT/QRS ratio

Öz

Amaç: QRS süresine bölünmüş QT intervali olarak hesaplanan, kardiyak elektrofizyolojik denge indeksi (iCEB), malign ventriküler aritmileri öngörmek için yeni bir risk belirleyicisi olarak tanımlanmıştır. iCEB'nin artmış seviyeleri torsades de pointes (TdP) ve azalan iCEB düzeylerinin ise torsades de pointes olmayan ventriküler taşikardi veya ventriküler fibrilasyona neden olduğunu öngörmektedir. Bu çalışmanın amacı koroner ektazisi (KAE) olan hastalarda iCEB kullanılarak, bu hastalardaki aritmojenik riski değerlendirmektir.

Yöntemler: Vaka kontrolü olarak tasarlanan çalışmamıza polikliniğimize başvuran 130 hasta dahil edildi. İzole KAE'si olan 75 hasta (çalışma grubu) ve 55 sağlıklı birey (kontrol grubu) çalışmaya dahil edildi. Her iki gruba da 12 adet standart elektrokardiyografi çekildi. Tp-Te intervali, QT intervali, QRS intervali, Tp-Te / QT oranı ve QT / QRS oranları (iCEB) kaydedilerek gruplar arasında karşılaştırma yapıldı.

Bulgular: Tp-e intervalleri ve Tp-e / QT oranı çalışma grubunda anlamlı olarak daha yüksek saptandı (p=0,001). Ayrıca iCEB'in, çalışma grubunda sayısal olarak daha yüksek olma eğilimi olduğu bulunmuştur, ancak gruplar arasında istatistiksel olarak anlamlı bir fark bulunamamıştır (p=0,118). Tp-e ve Tpe / QT oranı, iki veya üç damar KAE'si olan hastalarda, tek damar ektazisi olanlardan daha yüksekti (Tp-e için p≤0,024 ve Tpe/QT oranı için p=0,028). iCEB, etkilenen koroner arter sayısı ile daha yüksek bulunmasına rağmen, gruplar arasında istatistiksel olarak fark saptanmadı.

Sonuç: Bulgularımız, KAE hastalarının sağlıklı kontrollere göre daha yüksek Tp-Te ve Tp-Te / QT değerlerine sahip olduğunu göstermektedir. KAE'li bireyler için iCEB kullanılarak artmış aritmojenik riski göstermek için daha fazla çalışmaya ihtiyacımız vardır.

Anahtar kelimeler: Aritmi, Koroner arter ektazisi, iCEB, QT/QRS oranı

How to cite / Atıf için: Alsancak Y, Gürbüz AS, Saklı B, İçli A. Evaluation of index of cardio-electrophysiological balance and Tp-e/QT ratio in patients with coronary artery ectasia. J Surg Med. 2019;3(3):223-226.

Introduction

Coronary artery ectasia (CAE) is considered as an atypical form of coronary atherosclerosis which characterized by impairment of the internal and external elastic lamina and also thought to be a rare congenital or acquired coronary anomaly [1,2]. The clinical and prognostic significance of CAE is not clearly understood. CAE may be a cause of coronary rupture, spasm, dissection, thrombosis, myocardial ischemia and even sudden cardiac death eventually [3,4]. As a result this condition may not be accepted completely benign as it is associated with adverse coronary events [5].

In addition, it has been demonstrated that diffuse coronary ectasia without any obstructive lesion may trigger myocardial ischemia due to increased lactate levels in the coronary sinus with incremental atrial pacing [6]. Besides it is well known that myocardial ischemia is thought to be the important cause of sudden cardiac death in most cases due to malignant arrhythmias [7]. Previously published studies showed that Tp-Te and Tp-Te/QT ratio, which are accepted as marker of increased ventricular repolarization and dispersion, are significantly higher in patients with coronary ectasia than control group [8]. Moreover, prolonged QT interval and increased QT dispersion was also detected in patients with coronary artery ectasia [3]. It has been suggested that these findings may indicate increased arrhythmogenic risk in individuals with coronary artery ectasia.

Index of cardiac electrophysiological balance (iCEB), calculated as QT interval divided by QRS duration, has been described as a novel risk marker for predicting malignant ventricular arrhythmias [9]. It was shown that increased iCEB level is a predictor of torsades de pointes (TdP) whereas decreased iCEB level is associated with non-torsades de pointes ventricular tachycardia or ventricular fibrillation [10].

In this study, we aimed to investigate the iCEB and its association between Tp-Te and Tp-Te/QT ratio in patients with CAE, to evaluate pro-arrhythmogenic effect of this benign disease.

Materials and methods

Study population

Our study, designed as case-control, included 130 patients who were admitted to our outpatient clinic of the Necmettin Erbakan University, Meram Faculty of Medicine, Department of Cardiology, Konya, Turkey. The patients who underwent elective coronary angiography (positive cardiac stress test, ischemia in myocardial perfusion scintigraphy, patients with recently detected left ventricular wall motion abnormalities or patients with stable angina pectoris) between February 2017 and May 2018 were prospectively included in this study. Participants were divided into two groups as study group (patients with CAE) (n = 75) and control group that age/sex-matched individuals with a normal coronary angiogram (n = 55). Exclusion criteria were determined as elevated serum creatinine levels, any kind of bundle branch blocks, previously documented atrial fibrillation, atrial, ventricular or atrioventricular pre-excitations, acute or chronic inflammatory disease, electrolyte abnormalities or a known receiving any drugs that may have an effect on the cardiac conduction (antiarrhythmic drugs, digitalis, β-blocker, or calcium-channel blocker medication). Demographic characteristics, cardiovascular risk factors (diabetes mellitus, smoking, hypertension, family history of coronary artery disease, hyperlipidemia) and routine blood tests results were recorded.

A power analysis for sample size was performed with an online calculator (https://clincalc.com/stats/samplesize.aspx) by a professional statistician. According to analyses, assuming a power of 90 % and $\alpha = 0.05$, a study population including at least 52 individuals were needed. Ethics committee approval was received for this study from the local ethics committee.

Coronary angiography

6F sheath was inserted to femoral artery with Seldinger method and coronary angiography was performed with Judkins method, 20% of angiogram was performed via the radial access. Angiography results were evaluated by at least two cardiologists blinded to the patients. Isolated CAE was defined as an enlargement of coronary vessel's segment 1.5 times or higher that of an adjacent normal parts of the same vessel without any stenotic lesion [11]. Coronary artery ectasia without coronary artery stenosis was accepted as isolated CAE and Markis classification system was used to define the severity of isolated coronary artery ectasia [12]. According to this system; diffuse ectasia of two or three vessels was classified as Type 1, diffuse disease in one vessel and localized disease in another vessel as Type 2, diffuse ectasia of only one vessel as Type 3, and localized segmental ectasia as Type 4.

Electrocardiographic parameters

The standard 12-lead surface ECGs of study population were recorded after a 30-min resting period in the supine position (filter range; 10 mV/mm and a paper speed of 25 mm/s and machine of Marquette Case, Hellige Medical System, Cardiosmart Hellige Instrument Company, Freiburg, Germany). Heart rate, QT interval, QRS interval, T wave, Tpeak-Tend interval were recorded from their electrocardiograms. All ECGs were scanned and transferred to a digital platform to decrease margin of error during measurement and then a software (Adobe Photoshop) was used for x300% magnification.

The Tp-Te interval was calculated from the peak of the T wave to the end of the T wave. Measurements of the Tp–e interval were performed from precordial leads [13,14]. QT interval was calculated from the beginning of the QRS complex to the end of the T-wave that defined as the return to the T–P is electric line and corrected for heart rate using the Bazett formula: $cQT = QT\sqrt{(R–R\ interval)}$. The measurements were executed on lead II and lead V5 and then the longest QT interval was used for analysis (14). The Tp-Te/QT ratio was defined as Tp-Te in lead V5 divided by QT interval in the same lead. Patients with U waves on their ECGs were excluded from the study. iCEB was calculated as QT interval divided by QRS interval in the same leads.

Statistically analysis

We used SSPS version 16.0 (SPSS, Inc., Chicago, IL, USA) for statistical analyses. Quantitative variables with a normal distribution were specified as the mean ± standard deviation, and those with non-normal distribution were specified with median (Interquartile range (IQR) 25-75); categorical variables were specified with number and percentage values.

Kolmogorov Smirnov test was used to test normality of distribution. Mean values of continuous variables were compared between groups using the t-test, one way ANOVA test, or Kruskal-Wallis test where appropriate. The chi-square test was performed to compare the differences between categorical variables. The Spearman rank correlation was used to assess the correlation between iCEB levels and Tp-Te/QT ratio. P values below 0.05 were considered statistically significant in our study.

Results

The demographic features, laboratory parameters and electrocardiographic characteristics of the study population are summarized in Table 1. A total of 130 patients were aged 57.7±11.3 years and 60 (46.2%) were women in study population. There was no statistically significant difference between study group and the control group in terms of, age, sex, body mass index and lipid profile, percent of smokers, current of diabetes mellitus or hypertension. Heart rate, QT and QTc values were similar between groups. Although QRS interval was shorter in study group than control group, without statistical difference (p=0.452). Tp-e intervals and Tp-e/QT ratio is significantly higher in study group (p=0.001). And, iCEB or iCEBc values were tend to be numerically higher in study group, but there was no statistical difference between groups (p values 0.118 and 0.105, respectively).

In subgroup analysis, we did not find any relationship between CAE localization (left anterior descending, circumflex or right coronary artery) or ECG parameters like Tp-Te/QT ratio, Tp-Te and iCEB. Moreover, Tp-e and Tpe/QT ratio were higher in patients with two or three vessels CAE (type 1) than one vessel (p value; for Tp-e p=0.024 and Tpe/QT ratio p=0.028). But the same parameters did not differ between two and three vessels CAE (p=0.289). In addition, there was higher iCEB level as affected number of coronary artery increase, but there was no statistically difference between groups (p=0.811) (Figure 1).

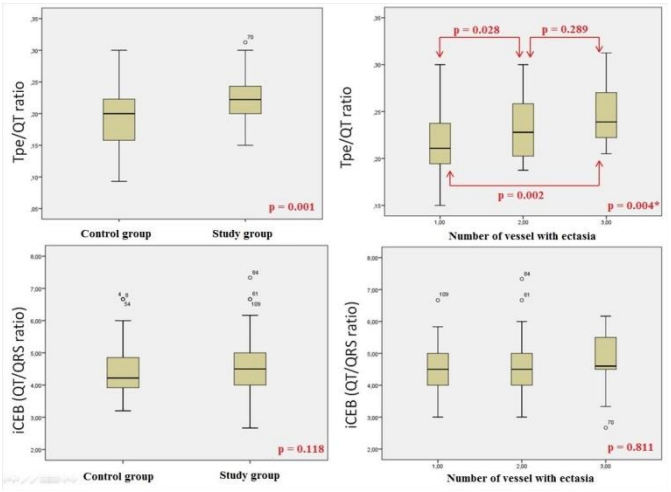

Figure 1: Comparing of Tpe interval, Tpe/QT ratio and index of cardio-electrophysiological balance (iCEB) between groups

In Markis classification, Tp-Te/QT ratio was significantly higher in Type IV compare to other types, but it did not showed statistically significant difference due to limited number of patients with Type IV. And iCEB and iCEBc levels were not different in groups according to Markis classification. Electrocardiographic characteristics of the ectasia and subgroups are summarized in Table 2.

Table 1: Demographic, clinical and laboratory characteristics of study population

	Control group (n: 55)	Study group (n: 75)	p
Age (years)	56.5±11.4	58.6±11.4	0.316
BMI (kg/m^2)	26.7±4.5	27.0±3.7	0.661
Sex (female), n (%)	26 (47.3)	34 (45.3)	0.822
DM, n (%)	16 (29.1)	20 (26.7)	0.763
Hypertension, n (%)	28 (50.9)	38 (50.7)	0.971
Smoking, n (%)	18 (32.7)	29 (38.7)	0.482
LVEF (%)	56.6±6.2	54.6±8.6	0.209
Creatinine (mg/dl)	0.77±0.12	0.78±0.12	0.630
Hb (g/dl)	13.8±1.6	13.9±1.7	0.765
Platelet (10^3/mm3)	266.4±79.1	245.3±75.1	0.139
Leukocyte (10^3/mm3)	6.76 (5.57-8.08)	7.85 (6.36-9.30)	0.006
FBG (mg/dl)	97 (87-121)	102 (90-113)	0.534
Total cholesterol (mg/dl)	201.8±43.8	192.4±46.3	0.256
LDL-C (mg/dl)	123.9±36.9	117.9±38.5	0.388
HDL-C (mg/dl)	47.9±12.9	43.9±10.5	0.067
Triglyceride (mg/dl)	155.0±97.6	160.7±91.6	0.732
Electrocardiographically findings			
Heart rate (bpm)	74.7±11.1	74.6±15.5	0.989
QT interval (ms)	379.9±34.3	384.2±42.3	0.541
QTc interval (ms)	421.3±34.6	423.1±38.1	0.784
QRS interval (ms)	87.2±12.6	84.9±20.3	0.452
Tp-e interval (ms)	73.5±17.7	85.9±14.6	0.001
Tp-e/QT ratio	0.20±0.05	0.23±0.03	0.001
iCEB (QT/QRS)	4.45±0.78	4.72±1.1	0.118
iCEBc (QTcB/QRS)	4.92±0.73	5.21±1.2	0.105

* BMI; Body Mass Index, DM; diabetes mellitus, FBG; fasting plasma glucose, Hb; hemoglobin, HDL-C; high-density lipoprotein cholesterol; iCEB; index of cardio-electrophysiological balance, iCEBc; corrected index of cardio-electrophysiological balance, LVEF; left ventricular ejection fraction, LDL-C; low-density lipoprotein cholesterol.

Table 2: Tpe interval, Tpe/QT ratio and iCEB according to characteristics of coronary ectasia

Ectasia Location	n (%)	Tp-e	Tp-e/QT	iCEB (QT/QRS)
LAD	44 (58.6)	88.5±15.4	0.23±0.03	4.70±1.15
RCA	49 (65.3)	86.6±15.6	0.23±0.04	4.81±1.07
LCx	28 (37.3)	91.5±13.1	0.24±0.03	4.62±0.98
Number of Vessel	n (%)			
One-vessel	38 (50.6)	80.7±12.7	0.21±0.03	4.65±1.01
Two-vessel	24 (32)	88.9±14.7*	0.23±0.03*	4.77±1.02
Three-vessel	13 (17.3)	95.7±14.2*	0.25±0.03*	4.82±1.19
Markis classification	n (%)			
Type I	2 (2.6)	85.0±7.07	0.24±0.05	4.44±0.62
Type II	16 (21.3)	86.9±15.7	0.23±0.04	4.85±1.40
Type III	13(17.3)	80.6±14.6	0.23±0.03	4.53±0.79
Type IV	44 (58.6)	87.2±14.6	0.20±0.04	4.75±1.03

+CAE; coronary artery ectasia, iCEB; index of cardio-electrophysiological balance, LAD; left anterior descending artery, LCX, left circumflex artery, RCA; right coronary artery, * a significant difference for Tp-e; p = 0.024 between one and two vessel ectasia, p = 0.001 between one and three vessel ectasia, * a significant difference for Tp-e/QT; p = 0.028 between one and two vessel ectasia, p = 0.002 between one and three vessel ectasia

Discussion

In the current study, we failed to demonstrate a positive or negative association between CAE and iCEB (QT/QRS)/iCEBc (QTc/QRS). We also found a higher Tp-e interval and Tp-e/QT ratio that known as a predictor for malignant ventricular arrhythmias in patients with CAE and we showed that these values tend to elevate as the number of affected coronary artery by ectasia increases.

Recently, a novel non-invasive marker named as iCEB, calculated as QT interval divided by QRS duration, has been defined as a potential risk marker for drug-induced ventricular arrhythmias in an animal study model [9]. And it has been demonstrated that iCEB is equal to the cardiac wavelength λ (λ = effective refractory period (ERP) x conduction velocity) and that an increased or decreased ratio of iCEB might potentially predict TdP or non-TdP mediated VT/VF, respectively [9,10]. Previously, the association between malignant ventricular arrhythmias and cardiac wavelength λ was well described [15]. Therefore, Robyns T and colleges, as a result of their human study, speculated that iCEB may be a noninvasive and easy to measureable marker of increased arrhythmogenesis considering that the iCEB is equivalent of cardiac wave length [10].

Based on these findings, Yumurtacı O et al. [16] found that iCEB and heart rate-corrected QT(QTc)/QRS ratio was higher in patients with acute myocarditis who had ventricular

arrhythmic episodes compare to uneventful control group. Recently, Ucar FM et al. [17] have investigated the balance of ventricular depolarization and repolarization in patients with rheumatoid arthritis by using iCEB. And they found that iCEB (QT/QRS) is higher in patients with rheumatoid arthritis than in healthy subjects. Moreover, they have found a positive correlation between iCEB and hsCRP levels. Finally, they speculated that the increased frequency of sudden cardiac death due to ventricular arrhythmias in patients with rheumatoid arthritis may be TdP-related and can be clarified by the new index of balance between depolarization and repolarization [17]. Another study demonstrated that higher iCEB is associated with higher pericardial fat volume which is related with subclinical atherosclerosis and increased inflammatory response and atrial fibrillation or other cardiac conduction problems [18,19]. But interestingly, Nafakhi H et al. [18] have not found a statistically significant relationship between iCEB and coronary artery calcification values. Another remarkable feature of these studies are that Tp-e/QT ratio was compatible with iCEB where higher values are useful in predicting ventricular arrhytmias in patients with myocarditis, rheumatoid arthritis and thicker pericardial fat.

Tp-Te interval is considered as an index of transmural dispersion of left ventricular repolarization and Tp-Te/QT ratio is also used as a novel electrocardiographic index of ventricular arrhythmogenesis. Previously published studies demonstrated that a prolonged Tp-Te interval and higher Tp-Te/QT ratio has been associated with an increased risk of ventricular arrhythmias [20,21]. Karaagac and collegues [8] found a significantly higher value of Tp-Te and Tp-Te/QT ratio in patients with CAE than healtly individuals and they suggested that these parameters may predict an increased risk of arrhythmogenesis in patients with CAE. Our findings were not different from this study and we also did not find a correlation between iCEB and Tp-Te/QT ratio. One of the most remarkable results of our study is that increased number of ecstatic coronary arteries is associated with higher Tp-e and Tp-Te/QT ratio.

The frequency of CAE may increase with routine use of conventional coronary angiography or other imaging methods. Angina pectoris is a frequent complaint of patients with isolated CAE and several mechanism have been proposed to explain of myocardial ischemia due to CAE such as microvascular dysfunction, impaired coronary flow reserve, delayed coronary blood flow [22], increased coronary spasm phenomenon [23], micro thrombi and coronary dissections [24], epicardial and microvascular perfusion failure [25]. Moreover, interestingly isolated coronary ectasia may cause ischemia even without significant coronary stenosis [6]. Ischemia is a well-known risk factor for malignant arrhythmias and it is reasonable to think that the risk of arrhythmia is attributable to above mentioned mechanisms in patients with coronary artery ectasia. Therefore, sudden cardiac death may occur in these patients.

This study has some limitations like a relatively small-sized prospective study conducted in a single center without follow up period. Diagnostic electrophysiological studies were not performed each of patients. And another major limitation of our study is the lack of comparison in patients with CAE with and without a history of malignant arrhythmia.

Conclusion

In the present study, our findings indicate that QT/QRS (iCEB) measurement, which is easily-obtainable from surface ECG, is tend to be higher in patients who have CAE than healthy controls. Higher iCEB is associated with TdP ventricular tachycardia and CAE may be associated with sudden cardiac death as a result of TdP. A prospective long term follow-up study with the same population may give us more information about the role of iCEB to predict ventricular arrhythmias and/or sudden death. Further prospective studies are needed to conceive exact role of iCEB in identifying high risk patients with coronary ectasia.

References

1. Sultana R, Sultana N, Ishaq M, Samad A. The prevalence and clinical profile of angiographic coronary ectasia. J Pak Med Assoc. 2011;61:372-5.
2. Demopoulos VP, Olympios CD, Fakiolas CN, Pissimissis EG, Economides NM, Adamopoulou E, et al. The natural history of aneurysmal coronary artery disease. Heart. 1997;78(2):136-41.
3. Karakaya O, Saglam M, Barutcu I, Esen AM, Turkmen M, Kargin R, et al. Effects of isolated coronary artery ectasia on electrocardiographic parameters reflecting ventricular heterogeneity. J Electrocardiol. 2007;40(2):203-6.
4. Doi T, Kataoka Y, Noguchi T, Shibata T, Nakashima T, Kawakami S, et al. Coronary Artery Ectasia Predicts Future Cardiac Events in Patients With Acute Myocardial Infarction. Arterioscler Thromb Vasc Biol. 2017;37(12):2350-5.
5. Amit Malviya, Pravin K.Jha, Animesh Mishra. Isolated coronary artery ectasia: Clinical, angiographic, and follow up characteristics. Indian Heart Journal. 2017;69:619–23.
6. Kruger D, Ulrich S, Herrmann G, Simon R, Sheikhzadeh A. Exercise-induced myocardial ischemia in isolated coronary artery ectasia and aneurysms (dilated coronopathy). J Am Coll Cardiol. 1999;34:1461-70.
7. Davies MJ. Pathological view of sudden cardiac death. Br Heart J. 1981;45:88-97.
8. Karaagac K, Yontar OC, Tenekecioglu E, Vatansever F, Ozluk OA, Tutuncu A, et al. Evaluation of Tp-Te interval and Tp-Te/QTc ratio in patients with coronary artery ectasia. Int J Clin Exp Med. 2014;15;7(9): 2865-70.
9. Lu HR, Yan GX, Gallacher DJ. A new biomarker–index of cardiac electrophysiological balance (iCEB)–plays an important role in drug-induced cardiac arrhythmias: Beyond QT-prolongation and torsades de pointes (TdPs). J Pharmacol Toxicol Methods. 2013;68:250–9.
10. Robyns T, Lu HR, Gallacher DJ, Garweg C, Ector J, Willems R, et al. Evaluation of Index of Cardio-Electrophysiological Balance (iCEB) as a New Biomarker for the Identification of Patients at Increased Arrhythmic Risk. Ann Noninvasive Electrocardiol. 2016;21(3):294-304.
11. Hartnell GG, Parnell BM, Pridie RB. Coronary artery ectasia, its prevalence and clinical significance in 4993 patients. Br Heart J. 1985;54:392-5.
12. Markis JE, Joffe CD, Cohn PF, Feen DJ, Herman MV, Gorlin R. Clinical significance of coronary arterial ectasia. Am J Cardiol. 1976;37:217-22.
13. Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, Dorantes Sánchez M, Dorticós Balea F, Zayas Molina R, et al. Tpeak-Tend and Tpeak-Tend dis¬persion as risk factors for ventricular tachycar¬dia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol. 2006;47:1828-34.
14. Shimizu M, Ino H, Okeie K, Yamaguchi M, Nagata M, Hayashi K, et al. T-peak to T-end interval may be a better predictor of high-risk patients with hypertrophic cardiomyopathy associated with a cardiac troponin I mutation than QT dispersion. Clin Cardiol. 2002;25(7):335-9.
15. Girouard SD, Rosenbaum DS. Role of wavelength adaptation in the initiation, maintenance, and pharmacologic suppression of reentry. J Cardiovasc Electrophysiol. 2001;12(6):697-607.
16. Yumurtacı O, Kurt C, Ucar MF, O Cihan. Usefulness Of Electrocardiographic Markers To Predict Ventricular Arrhythmias In Acute Myocarditis Patients. Turkish Med. Stud. J. 2017;4:6-10.
17. Ucar FM, Yılmaztepe MA, Taylan G. Evaluation of Index of Cardioelectrophysiological Balance (iCEB) in Patients with Rheumatoid Arthritis. Erciyes Med J. 2018;40(1):8-12.
18. Nafakhi H, Al-Mosawi AA, Alareedh M, Al-Nafakh HA. Index of cardiac electrophysiological balance and transmural dispersion of the repolarization index relationships with pericardial fat volume and coronary calcification. Biomark Med. 2018;12(4):321-8.
19. Sengul C, Özveren O. Epicardial adipose tissue: a review of physiology, pathophysiology, and clinical applications. Anadolu Kardiyol Derg. 2013;13(3):261-5.
20. Hetland M, Haugaa KH, Sarvari SI, Eriksen G, Kongsgaard E, Edvardsen T. A novel ECG-index for prediction of ventricular arrhythmias in patients after myocardial infarction. Ann. Noninvasive Electrocardiol. 2014;19;330–7.
21. Gupta P, Patel C, Patel H, Narayanaswamy S, Malhotra B, Green JT, et al. T(p-e)/QT ratio as an index of arrhythmogenesis. J. Electrocardiol. 2008;41:567–74.
22. Akyurek O, Berkalp B, Sayin T, Kumbasar D, Kervancioğlu C, Oral D. Altered coronary flow properties in diffuse coronary artery ectasia. Am Heart J. 2003;145:66-72.
23. Suzuki H, Takeyama Y, Hamazaki Y, Namiki A, Koba S, Matsubara H, et al. Coronary spasm in patients with coronary ectasia. Cathet Cardiovasc Diagn. 1994;32:1-7.
24. Perlman PE, Ridgeway NA. Thrombus and anticoagulation therapy in coronary ectasia. Clin Cardiol. 1989;12:541-2.
25. Güleç S, Atmaca Y, Kılıçkap M, Akyürek O, Aras O, Oral D. Angiographic assessment of myocardial perfusion in patients with isolated coronary artery ectasia. Am J Cardiol. 2003;91:996-9.

J Surg Med. 2019;3(3):227-230.
DOI: 10.28982/josam.503850

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Evaluation of clinical and laboratory findings of 147 patients with systemic lupus erythematosus: The relationship between anti-CCP and arthritis

Sistemik lupus eritematozuslu 147 hastanın klinik ve laboratuvar bulgularının değerlendirilmesi: Anti CCP ile artrit arasındaki ilişkinin incelenmesi

Ali Ekin [1], Ayşe Ergüney Çefle [2]

[1] Department of Internal Medicine, Bingol State Hospital, Bingol, Turkey
[2] Department of Internal Medicine, Division of Rheumatology, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey

ORCID ID of the author(s)
AE: 0000-0003-3692-1293
AEÇ: 0000-0002-3273-7969

Corresponding author / Sorumlu yazar:
Ali Ekin
Address / Adres: Bingöl Devlet Hastanesi, İç Hastalıkları Kliniği, Bingöl, Türkiye
e-Mail: aliekin49@hotmail.com

Ethics Committee Approval: Kocaeli University, Clinical Research Ethics Committee, Project code no: 2015/184 Decision No: 1/11.
Etik Kurul Onayı: Kocaeli Üniversitesi, Klinik Araştırmalar Etik Kurulu, Proje kod no: 2015/184 Karar No:1/11.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 27.12.2018
Accepted / Kabul Tarihi: 19.02.2019
Published / Yayın Tarihi: 25.02.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Abstract

Aim: Anti-cyclic citrullinated peptide antibodies (Anti-CCP) is considered as a novel marker in the assessment of rheumatoid disorders. Some studies have emphasized the importance of anti-CCP in indicating erosive arthropathy in Systemic Lupus Erythematosus (SLE), like Rheumatoid Arthritis (RA). These studies have reported that the chance of erosive arthritis development is significantly increased in anti-CCP-positive patients. This study aimed to investigate the relationship between anti-CCP and arthritis along with other clinical and laboratory parameters in patients with SLE.

Methods: A total of 147 SLE patients who had been admitted to Kocaeli University Medical Faculty, Department of Internal Medicine, Division of Rheumatology between January 2001 and October 2015 were included in this retrospective study. SLE diagnosis was verified according to American College of Rheumatology (ACR) and/or The Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) criteria. Patients whose diagnosis was not definite and not having anti-CCP were excluded.

Results: Female/male ratio was found as 5.6, and the mean age was calculated as 43.9±11.85 years. The mean follow-up period was 73.3±44.97 months. Anti-CCP was found to be positive in ten patients whereas arthritis was found to be present in 100 patients. Anti-CCP was positive in seven patients with arthritis. RF (Rheumatoid Factor) was found as positive in 50 patients of whom 40 had arthritis. A relationship was found between Anti-CCP and RF. There was no relationship between anti-CCP and arthritis.

Conclusions: Anti-CCP has been reported to be significantly related to arthritis and other characteristics of rheumatoid disorders, particularly RA in several studies. There are conflicting results about the relationship between anti-CCP and arthritis in patients with SLE. These conflicting results may be derived from different subtypes of anti-CCP (citrulline-dependent), different cut-off values, and characteristics of the patient population. We did not observe any relationship between the Anti-CCP and arthritis.

Keywords: Systemic lupus erythematosus, Anti-cyclic citrullinated peptide antibodies, Arthritis

Öz

Giriş: Anti-siklik sitrülline peptid antikorları (Anti-CCP), romatoid hastalıkların değerlendirilmesinde yeni bir belirteç olarak kabul edilir. Bazı çalışmalar Romatoid Artrit (RA) gibi sistemik lupus eritematozus'da (SLE) eroziv artropatinin gösterilmesinde Anti-CCP'nin önemini vurgulamıştır. Bu çalışmalar, Anti-CCP pozitif hastalarda eroziv artrit gelişme ihtimalinin anlamlı şekilde arttığını bildirmiştir. Bu çalışmanın amacı, SLE'li hastalarda Anti-CCP ve artrit ile diğer klinik ve laboratuvar parametreleri arasındaki ilişkiyi araştırmaktır.

Yöntemler: Ocak 2001 - Ekim 2015 tarihleri arasında Kocaeli Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı'na başvuran SLE'li toplam 147 hasta çalışmaya dahil edildi. SLE tanısı Amerikan Romatoloji Birliği (ACR) ve / veya Sistemik Lupus Eritematozus Uluslararası İşbirliği Klinikleri (SLICC) kriterleri ile doğrulandı. Kesin olmayan ve Anti-CCP si olmayan hastalar çalışma dışı bırakıldı.

Bulgular: Kadın / erkek oranı 5,6, yaş ortalaması 43,9±11,85 idi. Ortalama takip süresi 73,3±44,97 aydı. 10 hastada anti-CCP pozitifti, 100 hastada ise artrit vardı. Artritli hastaların yedisinde Anti-CCP pozitifti. RF (Romatoid Faktör), 40'ı artritli olan 50 hastada pozitif bulundu. Anti-CCP ile RF arasında bir ilişki olduğu tespit edildi. Anti-CCP ile artrit arasında ise ilişki yoktu.

Sonuçlar: Bazı çalışmalarda, özellikle RA gibi romatolojik hastalıkların artrit ve diğer özelliklerinin Anti-CCP ile bağlantısı olduğu rapor edilmiştir. SLE'li hastalarda anti-CCP ile artrit arasındaki ilişkiyle ilgili çelişkili sonuçlar vardır. Bu çelişkili sonuçlar farklı Anti-CCP alt tiplerden (sitrülin bağımlı), farklı cut-off değerlerinden ve hasta popülasyonunun özelliklerinden kaynaklanabilir. Anti-CCP ile artrit arasında herhangi bir ilişki gözlemlemedik.

Anahtar kelimeler: Sistemik lupus eritematozus, Anti-siklik sitrülline peptid antikorları, Artrit

How to cite / Atıf için: Ekin A, Çefle AE. Evaluation of clinical and laboratory findings of 147 patients with systemic lupus erythematosus: The relationship between anti-CCP and arthritis. J Surg Med. 2019;3(3):227-230.

Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, inflammatory disorder with an unknown etiology, which can lead to involvements of various tissues and organs. Autoantibodies and immune complexes play a role in the pathophysiology of SLE[1,2].The female/male ratio is 9/1 in general population, and it is most commonly seen in the 3rd and 4th decades[3].

Immune complexes and autoantibodies, which have developed against components of the nucleus, are responsible for tissue damage, causing various symptoms. Genetic factors, immune response disorders, defective immunological regulation, apoptosis, cytokine pathway disorders and hormonal and environmental factors play important roles in the etiology and pathophysiology of the disease. The primary pathological findings can be listed as inflammation, vasculitis, immune complex deposition, and vasculopathy [4].

Citrulline is an amino acid which is formed by the post-translational enzymatic alterations of arginine residues. It is located in filaggrin molecule. Citrulline autoantibodies are very specific to rheumatoid arthritis (RA), and they can be used in the differentiation of RA from other rheumatoid disorders [5]. Cyclic citrullinated peptide (CCP) antibodies have great importance in the early diagnosis of RA, with serum levels found to be increased in 79% of RA patients during the early stages of the disease. They can be found as positive in 40% of rheumatoid factor(RF)-negative patients[6]. Several studies have reported that the development of radiologically positive arthritis is more common in anti-CCP-positive patients when compared to the negative ones [5, 7]. Although there is a correlation between RF and anti-CCP in RA patients and it has been used mostly in the diagnosis of RA, anti-CCP can be helpful in the diagnosis of other rheumatological disorders such as SLE [8]. It was reported that anti-CCP test might result in positive up to 8% in Behcet's disease, fibromyalgia, gout, juvenile rheumatoid arthritis, reactive arthritis, and SLE [9,10].

RF is found as positive in 20-60% of SLE patients which makes it difficult to use RF in discriminating the RA and SLE patients, whereas anti-CCP is found less frequent in SLE compared to RF [11]. However, the rate of anti-CCP in SLE patients has been reported to be between 10-15% in some studies [12-15].

Anti-CCP was found to be higher in RA patients with erosive arthropathy. Some studies have emphasized the importance of anti-CCP in indicating erosive arthropathy in SLE like RA. These studies have reported that the chance of erosive arthritis development is significantly increased in anti-CCP-positive patients [16-23]. This study aimed to investigate the relationship between anti-CCP and arthritis, as well as other clinical manifestations and laboratory parameters in patients with SLE.

Materials and methods

AA total of 147 SLE patients who had been admitted to Kocaeli University Medical Faculty, Department of Internal Medicine, Division of Rheumatology between January 2001 and October 2015 were included in this retrospective study. The diagnosis was confirmed according to the diagnostic criteria of American College of Rheumatology (ACR) (1997 revised criteria) and/or 2012 SLICC criteria. Patients with indefinite diagnosis and those without anti-CCP result were excluded from the study.

Age, anti-CCP, the dates of disease onset, diagnosis, and hospital admission, the duration between the onset of symptoms and the diagnosis, total period of the disease, duration of the follow-up, presence of malar rash, discoid rash, photosensitivity, oral ulcer, presence and type of arthritis(mono, oligo, polyarthritis), proteinuria (>500 mg/day), renal, pulmonary, cardiac, neurological, and hematological involvements, the C3 (Complement 3) and C4 (Complement 4) levels, the cardiolipin antibody result, the lupus anticoagulant and/or Venereal Disease Research Laboratory (VDRL) result, direct coombs test result, RF result, and Extractable Nuclear Antigen (ENA) profile were recorded.

Statistical analysis

IBM SPSS 20.0 0 (SPSS Inc. Chicago, IL, USA) was used for the statistical analysis. Normal distribution was evaluated by Kolmogorov-Smirnov test. Numerical variables with normal distribution were given as mean ± standard deviation (minimum-maximum value, median) and numerical variables which did not show normal distribution were given as median (25th percentile - 75th percentile). Categorical variables were expressed as frequencies (percentages). The differences between the groups were analyzed by Mann-Whitney U test. The correlation between categorical variables was evaluated by Chi-square analysis. $p<0.05$ was considered as statistically significant.

Results

The mean age was calculated as 43.9±11.85 (min-max: 19-74, median: 42) years. 22 out of 147 patients were male, whereas remaining 125 patients were female. F/M (Female/Male) ratio was found as 5.6. Presence of malar rash, discoid rash, photosensitivity, oral ulcer, alopecia, arthritis, kidney involvement, serositis, neurological involvement, hematological involvement, and Raynaud's phenomenon were observed in 72 (49%), 23 (15.6%), 86 (58.5%), 43 (29%), 17 (11.5%), 100 (68%), 73 (49.6%), 43 (29%) 14 (9.5%), 131 (89.1%) and 14 (9.5%) patients, respectively (Table 1).

A total of 100 patients were found to have arthritis with none of them being erosive arthritis. Anti-CCP was found as positive in 10 (6.8%) patients, whereas the remaining 137 patients resulted as negative. The mean of anti-CCP measurement was found as 77.56±74.62 (min-max: 5-200, median: 74.18). RF was found as positive in 50 (34%) patients, with 40 of these patients having arthritis. The mean RF measurement was found as 86.12±93.35 IU/ml. There was no relationship between anti-CCP and arthritis (p=1.000).

All clinical and laboratory parameters were included in the analysis. The p values of the tests were summarized in Table 2. Anti-CCP was found to be significantly correlated with RF only (p=0.032). No other significant result was determined. Out of ten anti-CCP positive patients, seven had arthritis with all involvements having the polyarthritis form. RF was found to be

positive in five of seven anti-CCP-positive patients with arthritis. Both RF and anti-CCP were found to be positive in five patients.

Table 1: Clinical findings of the SLE patients

Clinical Findings	n	%
Malar rash	72	49.0
Discoid rash	23	15.6
Photosensitivity	86	58.5
Oral ulcer	43	29.0
Alopecia	17b	11.5
Arthritis	100	68.0
Kidney involvement	73	49.6
Serositis	43	29.0
Neurological involvement	14	9.5
Hematological involvement	131	89.1
Raynaud Phenomenon	14	9.5

Table 2: The relationship between the anti-CCP result, laboratory results, and clinical findings

	Anti-CCP (+) n:10	Anti-CCP (-) n:137	p
Gender (Female)	7	118	0.173
Malar rash (+)	4	68	0.746
Discoid rash (+)	2	21	0.656
Photosensitivity (+)	6	80	1.000
Oral ulcers (+)	2	41	0.724
Alopecia (+)	0	17	0.606
Arthritis (+)	7	93	1.000
Renal involvement (+)	5	68	1.000
Serositis(+)	5	38	0.157
Pleural involvement (+)	3	26	0.414
Pericardial involvement (+)	3	27	0.427
Neurological involvement (+)	0	14	0.599
Hematological involvement (+)	8	123	0.298
Hemolytic anemia (+)	0	14	0.599
Lymphopenia <1500/mL) (+)	8	122	0.325
Leucopenia (<4000/ mL) (+)	2	61	0.189
Thrombocytopenia(<100.000/mL) (+)	2	24	0.691
Anti-dsDNA (+)	6	85	1.000
Anti-Sm(Smith) (+)	2	15	0.325
C3 (low)	6	80	1.000
C3 (normal)	4	56	
C4 (low)	6	65	0.561
C4 (normal)	4	71	
ACA (Anticardiolipin Antibodies) (+)	0	25	0.228
ACA (Anticardiolipin Antibodies) (-)	9	87	
LAK (Lupus Anticoagulant) (+)	2	23	0.832
LAK (Lupus Anticoagulant) (-)	5	58	
Direct Coombs (+)	2	39	0.768
Direct Coombs (-)	2	32	
ENA profile (+)	6	101	0.461
Ro-52 (+)	0	39	0.063
Ss-A(+)	0	41	0.062
Ss-B (+)	0	19	0.361
Nucleosomes (+)	3	51	0.746
dsDNA (+)	4	40	0.487
Sm-RNP (+)	2	28	1.000
Sm (+)	2	12	0.243
Histones (+)	4	32	0.260
Ribosomal Protein (+)	0	10	1.000
Rheumatoid Factor (RF) (+)	7	43	0.032*
Age of Diagnosis (y)	47.5 (30.50-59.25)	42.00 (34.00-52.00)	0.672
Time between symptoms and diagnosis(m)	7.00 (0.75-47.25)	5.00 (1.00-24.00)	0.856
Follow-up period (m)	54.00 (12.75-121.50)	73.72 (37.00-0.00)	0.595
Duration of the disease (m)	79.00 (13.50-121.75)	86.00 (48.00-145.00)	0.250

Ss-A: Sjögren's Syndrome related antigen A, Ss-B: Sjögren's Syndrome related antigen B, m: month, y: years

Discussion

SLE is an inflammatory rheumatic disorder, characterized by autoantibody and immune complex production, heterogeneous clinical and laboratory findings as well as the involvements of the skin, serous membranes, joints, and the kidney [1, 2]. The prevalence of arthritis in SLE was reported to be 48-90%, and it is one of the most common symptoms of SLE [23-26].

Several studies have been recently conducted for investigation of the roles of various novel autoantibodies in SLE, including anti-CCP. Arthritis has non-erosive and non-deforming characteristics in most cases, not leading to direct irreversible function loss. In our study, all arthritis cases had non-erosive and non-deforming characteristics.

It has been indicated that the risk of erosive arthritis development is increased in anti-CCP-positive patients [16-23].However, there are also other studies indicating that there is no significant relationship between anti-CCP and arthritis [23,27]. None of the patients included in this study had erosive arthritis, and seven out of 10 anti-CCP-positive patients had arthritis in the type of polyarthritis. In another study, anti-CCP was found as positive in only one patient out of eight SLE patients with erosive arthropathy [23].

Citrulline-dependent anti-CCP reacts with citrullinated peptide, whereas it does not react with unmodified arginine-containing peptide. In most of the studies investigating the relationship between anti-CCP and SLE, commercial anti-CCP ELISA kit was used, and it was not investigated whether it was citrulline-dependent or not. In the study of Kakamanu et al. [17], including 329 SLE patients, and which indicated a relationship between citrulline-dependent anti-CCP and arthritis, anti-CCP was found as positive in 56(17%) patients. In the same study, citrulline-dependent anti-CCP was found as positive in 26 patients. Since most of the studies indicating the relationship between SLE and anti-CCP did not mention whether it was citrulline-dependent or not, it is likely that the relationship between anti-CCP and SLE might be associated with the citrulline-dependent portion of anti-CCP. This difference may be the reason of difference amongst studies conducted on this topic. It was also indicated that arthritis seen in SLE might also be related with citrulline-dependent anti-CCP, like RA [14,17-19,21-23].

A recent study has reported that the majority of anti-CCP-positive cases were citrulline-dependent in non-RA rheumatological disorders including six of nine SLE patients [28]. There are conflicting results about the relationship between anti-CCP and erosive arthritis. The rate of erosive or deforming arthritis with positive anti-CCP was reported to be 13% and 7% in studies of Mediwake et al. and Damian et al., whereas it was reported to be 80% and 50% in the studies of Martinez et al. and Chan et al. [18,21-23]. Furthermore, it was reported that the level of anti-CCP had not significantly increased in SLE patients, even with erosive arthropathy. It was asserted that anti-CCP could be used in the differential diagnosis of RA and SLE [18,23]. Although anti-CCP is not a definitive tool for distinguishing RA and SLE patients with erosive arthropathy, it can be used as a supportive parameter. It was asserted that conflicting results might be derived from different cut-off values, which leads to the miscalculation of positive and negative anti-CCP results [28]. There is another type of arthritis called Jaccoud's arthritis, which is a non-erosive type of deforming arthritis, developing in 4-13% of SLE patients [24,29-31]. The characteristic deformity in Jaccoud's arthritis is the reversible ulnar deviation in most cases, and the severity of lesions is much less when compared to the severity of the deformity. It was indicated that anti-CCP level was not significantly increased in SLE patients with erosive arthropathy, and the patients with significantly increased anti-CCP levels had Jaccoud's arthropathy which likely has different pathogenesis [17]. Although it is known that the deformity in Jaccoud's type arthropathy in SLE patients is different from the

deformity in RA, it may be possible that these two deformities can be somehow related with each other since the citrulline-dependent anti-CCP levels are significantly increased in these patients.

In a recent study of Ball et al., it has been reported that MRI was highly sensitive in identifying synovitis, bone edema, and erosive deformities, independent from anti-CCP and RF in SLE patients [32].This finding indicates that arthritis can be present even when anti-CCP and RF levels are not elevated. This finding supports the studies that were unable to show the relationship between anti-CCP and arthritis in patients with SLE. It was also reported that several factors such as smoking could affect the result of the anti-CCP test. We did not record the smoking status; therefore, we cannot make any assumption about smoking. However, the different demographic and clinical features of the patients might have been associated with the conflicting results.

Limitations

Our study was conducted in a single hospital, and the design of the study was retrospective. Citrulline dependency of the anti-CCP test also was not evaluated, which could have provided a valuable data for the analysis. These factors can be listed as the limitations of the study.

Conclusion

This study aimed to investigate the relationship between anti-CCP and arthritis along with all other clinical and laboratory parameters in SLE patients. It is the study that includes all clinical and laboratory parameters in a large patient population in Turkey. Since the characteristics of SLE vary in different regions, we can assert that this study provides an important source of information about the diagnostic value of anti-CCP in SLE patients.

References

1. Liu Z, Davidson A. Taming lupus-a new understanding of pathogenesis is leading to clinical advances. Nat Med. 2012;18(6): 871-82.
2. Dema B, Charles N. Advances in mechanisms of systemic lupus erythematosus. Discov Med. 2014;17(95):247-55.
3. Osio-Salido E, Manapat-Reyes H. Epidemiology of systemic lupus erythematosus in Asia. Lupus. 2010;19(12):1365-73.
4. Clark MR, Liu L, Clarkson SB, Ory PA, Goldstein IM. An abnormality of the gene that encodes neutrophil Fc receptor III in a patient with systemic lupus erythematosus. J Clin Invest. 1990;86(1):341-6.
5. Bizzaro N, Mazzanti G, Tonutti E, Villalta D, Tozzoli R. Diagnostic accuracy of the anti-citrulline antibody assay for rheumatoid arthritis. ClinChem. 2001;47(6):1089-93.
6. Kastbom A, Strandberg G, Lindroos A, Skog T. Anti-CCP antibody test predicts the disease course during 3 years in early rheumatoid arthritis (the Swedish TIRA project). Ann Rheum Dis. 2004;63(9):1085-9.
7. van Boekel MA, Vossenaar ER, van den Hoogen FH, van VenrooijWJ. Autoantibody systems in rheumatoid arthritis: specificity, sensitivity and diagnostic value. Arthritis Res. 2002;4(2):87-93.
8. Kasper D, Fauci A, Hauser S, Longo D. Jameson JL, Loscalzo J. Harrison's principles of internal medicine. 19th edition.ed. 2 volumes. 2015; xxxviii, pp. 2770 I-200.
9. Choi SW, Lim MK, Shin DH, Park JJ, Shim SC. Diagnostic Performances of Anti-Cyclic Citrullinated Peptides Antibody and Antifilaggrin Antibody in Korean Patients with Rheumatoid Arthritis. J Korean Med Sci. 2005;20(3):473-8.
10. Schellekens GA, de Jong BA, van den Hoogen FH, van de Putte LB, van Venrooij WJ. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. J Clin Invest. 1998;101(1):273-81.
11. Avouac J, Gossec L, Dougados M. Diagnostic and predictive value of anti-cyclic citrullinated protein antibodies in rheumatoid arthritis: a systematic literature review. Ann Rheum Dis. 2006;65(7):845-51.
12. Matsui T, Shimada K, Ozawa N, Hayakawa H, Hagiwara F, Nakayama H, et al. Diagnostic utility of anti-cyclic citrullinated peptide antibodies for very early rheumatoid arthritis. J Rheumatol. 2006;33(12):2390-7.
13. Sauerland U, Becker H, Seidel M, Schotte H, Willeke P, Schorat A, et al. Clinical utility of the anti-CCP assay: experiences with 700 patients. Ann N Y Acad Sci. 2005;1050:314-8.
14. Takasaki Y, Yamanaka K, Takasaki C, Matsushita M, Yamada H, Nawata M, et al., Anticycliccitrullinated peptide antibodies in patients with mixed connective tissue disease. Mod Rheumatol. 2004;14(5):367-75.
15. Vasishta A. Diagnosing early-onset rheumatoid arthritis: the role of anti-CCP antibodies. Am Clin Lab. 2002;21(7):34-6.
16. Qing YF, Zhang QB, Zhou JG, Yuan GH, Wei J, Xing Y, et al. The detecting and clinical value of anti-cyclic citrullinated peptide antibodies in patients with systemic lupus erythematosus. Lupus. 2009;18(8):713-7.
17. Kakumanu P, Sobel ES, Narain S, Li Y, Akaogi J, Yamasaki Y, et al. Citrulline dependence of anti-cyclic citrullinated peptide antibodies in systemic lupus erythematosus as a marker of deforming/erosive arthritis. J Rheumatol. 2009;36(12):2682-90.
18. Damian-Abrego GN, Cabiedes J, Cabral AR. Anti-citrullinated peptide antibodies in lupus patients with or without deforming arthropathy. Lupus. 2008;17(4):300-4.
19. Amezcua-Guerra LM, Springall R, Marquez-Velasco R, Gómez-García L, Vargas A, Bojalil R, et al. Presence of antibodies against cyclic citrullinated peptides in patients with 'rhupus': a cross-sectional study. Arthritis Res Ther. 2006;8(5):R144.
20. Amezcua-Guerra LM, Marquez-Velasco R, Bojalil R. Erosive arthritis in systemic lupus erythematosus is associated with high serum C-reactive protein and anti-cyclic citrullinated peptide antibodies. Inflamm Res. 2008;57(12):555-7.
21. Chan MT, Owen P, Dunphy J, Cox B, Carmichael C, Korendowych E, et al. Associations of erosive arthritis with anti-cyclic citrullinated peptide antibodies and MHC Class II alleles in systemic lupus erythematosus. J Rheumatol. 2008; 35(1):77-83.
22. Martinez JB, Valero JS, Bautista AJ, Restrepo JF, Matteson EL, Rondon F, et al. Erosive arthropathy: clinical variance in lupus erythematosus and association with anti-CCP case series and review of the literature. Clin Exp Rheumatol. 2007;25(1):47-53.
23. Mediwake R, Isenberg DA, Schellekens GA, van Venrooij WJ, et al. Use of anti-citrullinated peptide and anti-RA33 antibodies in distinguishing erosive arthritis in patients with systemic lupus erythematosus and rheumatoid arthritis. Ann Rheum Dis. 2001;60(1):67-8.
24. van Vugt RM, Derksen RH, Kater L, Bijlsma JW, et al. Deforming arthropathy or lupus and rhupus hands in systemic lupus erythematosus. Ann Rheum Dis. 1998;57(9):540-4.
25. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore). 2003;82(5):299-308.
26. Cronin ME. Musculoskeletal manifestations of systemic lupus erythematosus. Rheum Dis Clin North Am. 1988;14(1):99-116.
27. Tani C, D'Aniello D, DelleSedie A, Carli L, Cagnoni M, Possemato N, et al. Rhupus syndrome: assessment of its prevalence and its clinical and instrumental characteristics in a prospective cohort of 103 SLE patients. Autoimmun Rev. 2013;12(4):537-41.
28. Vannini A, Cheung K, Fusconi M, Stammen-Vogelzangs J, Drenth JP, Dall'Aglio AC, et al. Anti-cyclic citrullinated peptide positivity in non-rheumatoid arthritis disease samples: citrulline-dependent or not? Ann Rheum Dis. 2007;66(4):511-6.
29. Spronk PE, ter Borg EJ, Kallenberg CG. Patients with systemic lupus erythematosus and Jaccoud's arthropathy: a clinical subset with an increased C reactive protein response? Ann Rheum Dis. 1992;51(3):358-61.
30. Alarcón-Segovia D, Abud-Mendoza C, Diaz-Jouanen E, Iglesias A, De los Reyes V, Hernández-Ortiz J, et al. Deforming arthropathy of the hands in systemic lupus erythematosus. J Rheumatol. 1988;15(1): 65-9.
31. Esdaile JM, Danoff D, Rosenthall L, Gutkowski A. Deforming arthritis in systemic lupus erythematosus. Ann Rheum Dis. 1981;40(2):124-6.
32. Ball EM, Tan AL, Fukuba E, McGonagle D, Grey A, Steiner G, et al. A study of erosive phenotypes in lupus arthritis using magnetic resonance imaging and anti-citrullinated protein antibody, anti-RA33 and RF autoantibody status. Rheumatology (Oxford). 2014;53(10):1835-43.

J Surg Med. 2019;3(3):231-234.
DOI: 10.28982/josam.534758

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Evaluation of stroke mortality and related risk factors: A single-center cohort study from Gaziantep, Turkey

İnmede mortalite ve ilişkili risk faktörleri: Türkiye, Gaziantep'ten tek merkezli kohort çalışma

Betül Kocamer Şimşek [1], Gökhan Özer [2]

[1] Sanko University, Medicine Faculty, Department of Anesthesiology and Reanimation, Gaziantep, Turkey
[2] Sanko University, Medicine Faculty, Department of Neurology, Gaziantep, Turkey

ORCID ID of the author(s)
BKŞ: 0000-0001-8220-9542
GÖ: 0000-0003-0039-2350

Abstract

Aim: In most cases diabetes worsens the outcome of acute stroke. Acute hyperglycemia, higher C-reactive protein (CRP) and fibrinogen levels predict increased risk of in-hospital mortality. However, pneumonia is found to be major causes of death after stroke. In this study we aimed to define the risk factors of mortality of ischemic stroke.

Methods: This study was an analysis of retrospectively collected data of patients treated in intensive care unit (ICU) due to ischemic stroke.

Results: One hundred twenty-eight patients' files were evaluated. Mortality rate was 30.4% (n=39). The risk of stroke death was higher in presence of adverse events in ICU, presence of pneumonia findings, trans-tracheal intubation, long ICU stay, higher heart beats, lower SPO2 and pH levels, higher blood glucose and fibrinogen levels, higher CRP levels and the variation of CRP, higher APACHI-II, A^2DS^2 (risk of stroke) scores and lower GCS scores. Pneumonia was the most adverse event in ICU and the second most reason of the death.

Conclusions: APACHI-II, A^2DS^2 scores and GCS scores can predict the stroke death, and preventing the pneumonia may decrease acute mortality rate of ischemic stroke. CRP together with fibrinogen levels can be used as a prognostic factor in ischemic stroke.

Keywords: Stroke, Mortality, C-reactive protein, Fibrinogen

Öz

Amaç: Çoğu durumda diyabet akut inme sonucunu kötüleştirir. Akut hiperglisemi, yüksek CRP ve fibrinojen seviyeleri hastane içi mortalite riskinde artışın bir prediktörüdür. Ancak, pnömoni inme hastalarının en sık ölüm nedeni olarak görülmektedir. Bu çalışmada iskemik inmede mortalite için risk faktörlerini tanımlamayı amaçladık.

Yöntemler: Bu çalışma yoğun bakım ünitesinde (YBÜ) tedavi görmüş inme hastalarının retrospektif olarak toplanan verilerinin bir analizidir.

Bulgular: Yüz yirmi sekiz hastanın dosyası değerlendirildi. Mortalite oranı % 30,4 idi (n = 39). YBÜ'deki yan etkiler, pnömoni bulgularının varlığı, trans-trakeal entübasyon, uzun YBÜ'de kalma süresi mortalite ile ilişkiliydi. Yüksek nabız, düşük SPO2 ve pH seviyeleri de mortalite ile ilişkiliydi. Yüksek kan şekeri ve fibrinojen seviyeleri, yüksek CRP seviyeleri ve CRP varyasyonu mortalite ile ilişkili bulundu. Yüksek APACHI-II, A^2DS^2 skorları ve düşük GKS skorları mortalite ile ilişkili bulundu. Pnömoni YBÜ'deki en sık görülen advers olaydı ve ikinci en fazla ölüm nedeni oldu.

Sonuç: APACHI-II, A^2DS^2 skorları ve düşük GKS skorları mortaliteyi öngörebilir, pnömoniyi önlemek iskemik inmenin akut mortalite oranını azaltabilir. CRP, iskemik inme hastalarında fibrinojen düzeyleri ile birlikte prognostik faktörler içinde yer alması gerektiğini düşünmekteyiz.

Anahtar kelimeler: İnme, Mortalite, C-reaktif protein, Fibrinojen

Corresponding author / Sorumlu yazar:
Betül Kocamer Şimşek
Address / Adres: İncilipınar mahallesi, Ali fuat cebesoy bulvarı, No: 45, Şehitkamil, Gaziantep, Türkiye
e-Mail: btlkcmr@yahoo.com

Ethics Committee Approval: The approval for the study is obtained from the local Institutional Ethics Committee.
Etik Kurul Onayı: Çalışmanın onayı yerel Kurumsal Etik Komitesi'nden alınmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 02.03.2019
Accepted / Kabul Tarihi: 06.03.2019
Published / Yayın Tarihi: 06.03.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite / Atıf için: Şimşek BK, Özer G. Evaluation of stroke mortality and related risk factors: A single-center cohort study from Gaziantep, Turkey. J Surg Med. 2019;3(3):231-234.

Introduction

Acute occlusion of an intracranial vessel causes reduction in blood flow. If this reduction lasts longer than several seconds cerebral ischemia occurs. Sudden death is very rarely because of cerebral infarction. Case fatality rate is about 20% at 1 month for stroke in general [1]. For all that, stroke remains the major cause of severe disability over the last two decades [2]. The most important factors that were found to affect the prognosis of a patient include severity of stroke, commonly measured by National Institute of Health Science scale (NIHSS), modified Rankin score (mRS), and Glasgow Coma Scale (GCS) scores [2,3].

Majority of acute stroke patients have disorders of glucose metabolism, and in most cases diabetes worsens the outcome of acute stroke. Acute hyperglycemia predicts increased risk of in-hospital mortality after ischemic stroke [4]. However, pneumonia is found to be major causes of death after stroke [5].

Several large prospective studies identified high fibrinogen plasma levels as an independent predictor of ischemic stroke and higher fibrinogen levels and CRP elevation increases risk of all-cause mortality in patients with acute ischemic stroke [6-9].

In this study, we aimed to define the risk factors of mortality of acute ischemic stroke.

Materials and methods

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

This study was an analysis of retrospectively collected data of ischemic stroke patients treated in intensive care unit (ICU) in one hospital from January 2016 to June 2018. All patients' data were retrospectively recorded from hospitals' archives.

Age, gender, smoking history, anticoagulant drug history, former stroke history, immobilization, presence of pneumonia findings on the chest X-ray at the first day, intubation during the whole days in ICU, adverse events (pneumonia, hyperglycemia, acute renal failure etc.) in ICU, first day laboratory findings as glucose, potassium (K) sodium (Na), fibrinogen, troponin, creatine kinase (CK), Activated Partial Thromboplastin Clotting Time (APTT), international normalized ratio (INR), C-reactive protein (CRP), creatinine, arterial blood gas values as pH, PO_2, PCO_2, vital signs as pulse, systolic blood pressure, SPO_2, Glasgow Coma Scale (GCS) score, APACHI-II score and A^2DS^2(risk of stroke) (table 1) scores were recorded. If these items were not found in the hospital records, cases were excluded the study.

Statistical analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) and PAST 3 (Hammer, Ø., Harper, D.A.T., Ryan, P.D. 2001. Paleontological statistics) were used to analyze the variables. The conformity of the data to a normal distribution was assessed by the Shapiro-Wilk test and the variance homogeneity by the Levene test. For multivariate normal distribution Mardia (Dornik and Hansen omnibus) test and variance homogeneity were evaluated by Box omm test. Independent-Samples T test was used with Bootstrap results to compare normal distribution variables and Mann-Whitney U test was used with Monte Carlo results in comparison of variables that did not show normal distribution. The Wilcoxon Signed Ranks Test was used in conjunction with the Monte Carlo results in comparing two repetitive measurements of the CRP variable which did not show normal distribution. Pearson Chi-Square and Fisher Exact results were used to compare mortality with categorical variables, and odds ratio was calculated with 95% confidence intervals for meaningful results. Multiple Logistic regression test was used with the Backward (Wald) method in order to determine the cause - effect relationship with significant variables in univariate analyzes with mortality. The quantitative variables were shown as mean ± SD (Standard Deviation) and median (Maximum/Minimum), while the categorical variables were shown as n (%) in the tables. The variables were analyzed at 95% confidence level and the p-value was accepted as significant when it was lower than 0.05.

Table 1: Basic prognostic score (A^2DS^2 Score) (0-10 points)

Clinical Variables on Admission	Assigned Points
Age 75+	1
Atrial fibrillation	1
Dysphagia	2
Sex (male)	1
Stroke severity (NIHSS)*	
0-4	0
5-15	3
16+	5

*NIHSS: National Institute of Health Science scale

Results

Total 128 patients' files were evaluated in the study. Median age was 70 years (33-95) and female/male proportion was 62/66. All patients were charged to the ICU because of acute ischemic stroke. Mortality rate was determined as 30.4% (n=39).

In table 2 patient characteristics were evaluated. Age, gender, history of smoking, former stroke history, and taking any anticoagulant or anti-platelet drugs were not related to the risk of stroke. However the risk of stroke death was higher in presence of adverse events in ICU charge like pneumonia, hyperglycemia, hypertension etc., presence of pneumonia findings on chest X-ray at first day, trans-tracheal intubation in any day in ICU, long ICU stay duration. Also vital signs and arterial blood gas values of first day in ICU were evaluated (table 3). Higher heart beats, lower SPO_2 and pH levels were related to higher risk of stroke. On the other hand PO_2 and PCO_2 levels were not related to the risk of stroke.

Table 3 shows the laboratory findings. Higher blood glucose levels, higher fibrinogen and troponin levels, higher CK, creatinine values were related to the mortality. Higher CRP levels of the first day and the last day were related to the risk of stroke. In addition, the variation of CRP in days was related to the mortality. Na, K, APTT and INR levels were not related to the risk of stroke. APACHI-II, A^2DS^2 and GCS scores of first day are shown in table 3 too, and higher APACHI-II, A^2DS^2 scores and lower GCS scores were related to the mortality.

Infarct areas determined with the radiographic examination were evaluated, 43 of were left hemisphere, 42 right hemisphere and 39 of were pons.

Adverse events are shown in table 4 and pneumonia was the most adverse event noticed in ICU. The most common reason

of the stroke death was the severity of stroke, and pneumonia was the second common reason (table 5).

Table 2: Patient characteristics

	Total (n=128) Median (Min/Max)	Alive (n=89) Median (Min/Max)	Dead (n=39) Median (Min/Max)	p
Age	70 (33 / 95)	70 (33 / 90)	73 (40 / 95)	0.060 [1]
	n (%)	n (%)	n (%)	
Gender				
Female	62 (48.4)	43 (48.3)	19 (48.7)	0.999 [2]
Male	66 (51.6)	46 (51.7)	20 (51.3)	
Anticoagulants or antiplatelet medication history				
No	40 (31.3)	27 (30.3)	13 (33.3)	0.445 [2]
Yes	88 (68.8)	62 (69.7)	26 (66.7)	
Adverse events in ICU				
No	73 (57.0)	58 (65.2)	15 (38.5)	0.007 [2]
Yes	55 (43.0)	31 (34.8)	24 (61.5)	
Smoking				
No	97 (75.8)	67 (75.3)	30 (76.9)	0.999 [2]
Yes	31 (24.2)	22 (24.7)	9 (23.1)	
Former Stroke history				
No	97 (75.8)	63 (70.8)	34 (87.2)	0.071 [2]
Yes	31 (24.2)	26 (29.2)	5 (12.8)	
Pneumonia findings on admission at chest X-ray				
No	68 (53.1)	58 (65.2)	10 (25.6)	<0.001 [2]
Yes	60 (46.9)	31 (34.8)	29 (74.4)	
Days of under intubation	7 (1 / 120)	3 (2 / 95)	7 (1 / 120)	0.445 [2]
Days of staying in ICU	8 (1 / 120)	7 (2 / 95)	12 (1 / 120)	0.006 [2]
Intubation				
No	83 (64.8)	82 (92.1)	1 (2.6)	<0.001 [2]
Yes	45 (35.2)	7 (7.9)	38 (97.4)	

[1] Mann Whitney U Test (Monte Carlo), [2] Independent samples t-Test (Bootstrap)

Table 3: Laboratory findings, clinical scores and other clinical descriptive values

	Total (n=128) Mean±SD	Alive (n=89) Mean±SD	Dead (n=39) Mean±SD	p
Systolic blood pressure (mmHg)	137.66±33.12	138.81±28.58	135.05±42.01	0.625 [1]
	Median (Min/Max)	Median (Min/Max)	Median (Min/Max)	
Pulse/min	88.5 (52 / 125)	88 (52 / 122)	101 (60 / 125)	0.028 [2]
SPO_2 %	94 (50 / 100)	94 (85 / 100)	93 (50 / 100)	0.045 [2]
PO_2 (mmHg)	80 (16 / 364)	83 (29 / 257)	74 (16 / 364)	0.404 [2]
PCO_2 (mmHg)	39 (18 / 80)	39 (24 / 48)	39 (18 / 80)	0.122 [2]
pH	7.4 (7.16 / 7.52)	7.41 (7.19 / 7.52)	7.37 (7.16 / 7.52)	0.008 [2]
Glucose level (mg/dl)	153.5 (51 / 490)	136 (71 / 440)	226 (51 / 490)	0.001 [2]
Potassium (mmol/L	4.2 (2.9 / 6.6)	4.2 (2.9 / 6.1)	4.2 (3.2 / 6.6)	0.874 [2]
Sodium (mmol/L)	140 (124 / 159)	140 (129 / 159)	140 (124 / 155)	0.454 [2]
APACHI-II score	16 (8 / 36)	14 (8 / 32)	19 (8 / 36)	<0.001 [2]
A^2DS^2 score	6 (0 / 10)	5 (0 / 9)	8 (4 / 10)	<0.001 [2]
Fibrinogen (µmol/L)	407 (190 / 964)	396 (190 / 754)	428 (229 / 964)	0.020 [2]
Troponin (mg/dl)	0.02 (0 / 23.3)	0.018 (0 / 16.3)	0.05 (0 / 23.3)	<0.001 [2]
Creatine Kinase (mmol/L)	86 (8 / 34295)	76 (8 / 1713)	119 (22 / 34295)	0.003 [2]
Creatinine (mg/dl)	0.97 (0.01 / 9.9)	0.9 (0.01 / 5.17)	1.2 (0.61 / 9.9)	0.002 [2]
APTT (sec)	33.45 (20.7 / 226.6)	33.5 (20.7 / 226.6)	33.4 (20.8 / 72.1)	0.403 [2]
INR	1.19 (0.94 / 4.59)	1.16 (0.94 / 4.59)	1.25 (1.02 / 4.36)	0.055 [2]
Days of under intubation	7 (1 / 120)	3 (2 / 95)	7 (1 / 120)	0.445 [2]
Days of staying in ICU	8 (1 / 120)	7 (2 / 95)	12 (1 / 120)	0.006 [2]
GCS	10 (3 / 15)	11 (3 / 15)	5 (3 / 12)	<0.001 [2]
CRP on admission (mg/L)	20 (3 / 285)	16.7 (3 / 269)	44.2 (3 / 285)	0.021 [2]
CRP on the last day (mg/L)	49.7 (3 / 325)	26 (3 / 271)	154 (21 / 325)	<0.001 [2]
Variation of CRP (first day-last day)	9.45 (-235.4 / 312.6)	5 (-235.4 / 254.3)	73.4 (-113.6 / 312.6)	<0.001 [2]

APTT: Activated Partial Thromboplastin Clotting Time, INR: International normalized ratio, CRP: C-reactive protein, GCS: Glasgow Coma Scale, [1] Mann Whitney U Test (Monte Carlo), [2] Independent samples t-Test (Bootstrap), [3] Wilcoxon sing ranks Test (Monte Carlo), Min: Minimum, Max: Maximum, SD: Standard deviation

Table 4: Number of adverse events in ICU

Adverse events	n (%)
Pneumonia	22 (17.18)
Pneumonia + renal problems	6 (4.6)
Pneumonia + seizure	3 (2.3)
High blood pressure	8 (6.25)
Hyperglycemia	3 (2.34)
Seizure	3 (2.34)
High blood pressure + Hyperglycemia	1 (0.78)
Acute renal failure	2 (1.56)
Myocardial infarction	2 (1.56)
Lung edema due to congestive heart failure	1 (0.78)
Gastrointestinal system hemorrhage	1 (0.78)
None	76 (59.3)

Table 5: The causes of death

Causes	n (%)
Severity of stroke	26 (66.6)
Pneumonia	8 (20.5)
Cardiac problems	3 (7.6)
Gastrointestinal system hemorrhage	1 (2.5)
Acute renal failure	1 (2.5)

Discussion

We determined that mortality of ischemic stroke rate was high in this study. Thirty-nine of these patients died. Fatality rate of 30.4% which is quite high but slightly lower than previous studies [10,11]. We should underline that 13 (33.3%) patients died within the first week. The first two weeks after the stroke enclose the acute phase. That's why the acute period is the critical period for patients with stroke. Treatments at the acute phase to decrease mortality would be best targeted. Morbidity and mortality after stroke usually ascend from complications. These include both medical and neurological complications. The neurological complications include brain edema, hemorrhagic transformation, seizures, delirium and recurrent stroke. Medical complications are said to be less frequent than the medical complication [12]. Pneumonia is the most seen complication after stroke. The incidence of pneumonia among the majority of neurology ICU (NICU) studies ranged between 9.5 and 56.6% [13-18]. Among mixt type ICU studies, this incidence has ranged between 17 and 50% [19-22] and appeared to be similar to NICU studies. Similar to these studies pneumonia rate in our study was 24%. Also presence of pneumonia findings at chest X-ray on admission was related to mortality.

In-hospital mortality is related to stroke severity and related complications [12,23]. NIHSS, mRS, and GCS are directly related to early mortality in ischemic stroke. NIHSS more than 15, mRS more than 3, A^2DS^2 score between 5 and 10 and GCS <8 were significantly associated with high mortality similar to previous studies [24,25].

Atrial fibrillation, ischemic heart disease, and diabetes, history of stroke, ex-smoker status, older age, and more severe stroke are accepted as predictive factors of mortality in most of the previous studies. More than half of acute mortality was scribed to the secondary complications, especially pneumonia [25,26]. However in our study, smoke status and taking anticoagulants or antiplatelet medications due to cardiac problems were not related to mortality.

Higher blood glucose level at the time of admission was related to high mortality. It is known that hyperglycemia increases growth of the infarct core in patients with surrounding hypoperfusion, suggesting that hyperglycemic blood is toxic to ischemic brain [27].

Several large prospective studied identified high fibrinogen plasma levels as an independent predictor of myocardial infarction and ischemic stroke [6-8]. Similarly to these studies fibrinogen levels were higher in ischemic stroke patients in our study (407µmol/L), also higher fibrinogen levels were related to mortality (396/428 µmol/L).

This study also demonstrated that CRP elevation was associated with an increased risk of all-cause mortality in patients with acute ischemic stroke [9]. In our study median CRP levels of death patients were more than 2 folds of survived patients. Furthermore, differently from other studies we found that CRP levels on admission, on the last day and the variation of CRP were all related to the mortality rate.

Conclusion

APACHI-II, A^2DS^2 score and GCS score can predict the mortality, pneumonia was the most adverse event noticed in

ICU, and pneumonia was the second most common cause of the mortality after severity of stroke. Therefore preventing the pneumonia may decrease the acute mortality rate of ischemic stroke. CRP together with fibrinogen levels should be used as prognostic factor for severity in ischemic stroke patients.

References

1. Mittal SH, Goel D. Mortality in ischemic stroke score: A predictive score of mortality for acute ischemic stroke. Brain Circ. 2017 Jan-Mar;3(1):29-34.
2. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. Lancet. 2008;371:1612–23.
3. Langhorne P, Dey P, Woodman M, Kalra L, Wood-Dauphinee S, Patel N, et al. Is stroke unit care portable? A systematic review of the clinical trials. Age Ageing. 2005;34:324–30.
4. Ekeh B, Ogunniyi A, Isamade E, Ekrikpo U. Stroke mortality and its predictors in a Nigerian teaching hospital. Afr Health Sci. 2015 Mar;15(1):74–81.
5. Alonso A, Ebert AD, Kern R, Rapp S, et al. Outcome Predictors of Acute Stroke Patients in Need of Intensive Care Treatment. Cerebrovasc Dis. 2015;40:10–7.
6. Eidelman RS, Hennekens CH. Fibrinogen: a predictor of stroke and marker of atherosclerosis. Eur Heart J. 2003;24:499–500.
7. Siegerink B, Rosendaal FR, Algra A. Genetic variation in fibrinogen; its relationship to fibrinogen levels and the risk of myocardial infarction and ischemic stroke. J Thromb Haemost. 2009;7:385–90.
8. Chuang SY, Bai CH, Chen WH, Lien LM, Pan WH. Fibrinogen independently predicts the development of ischemic stroke in a Taiwanese population: CVDFACTS study. Stroke. 2009;40:1578–84.
9. Wong AA, Read SJ. Early changes in physiological variables after stroke. Ann Indian Acad Neurol. 2008;11:207-20.
10. Yu B, Yang P, Xu X, Shao L. C-reactive protein for predicting all-cause mortality in patients with acute ischemic stroke: a meta-analysis. Bioscience Reports. 2019 Feb 19;39(2):BSR20181135.
11. Balami J S, Chen R, Grunwald IQ, Buchan AN. Neurological complications of acute ischaemic stroke. Lancet Neuro. 2011;10:357-71.
12. Hilker R, Poetter C, Findeisen N, et al. Nosocomial pneumonia after acute stroke: implications for neurological intensive care medicine. Stroke. 2003;34:975–81.
13. Walter U, Knoblich R, Steinhagen V, Donat M, Benecke R, Kloth A. Predictors of pneumonia in acute stroke patients admitted to a neurological intensive care unit. J Neurol. 2007;254:1323–9.
14. Yilmaz GR, Cevik MA, Erdinc FS, Ucler S, Tulek N: The risk factors for infections acquired by cerebral hemorrhage and cerebral infarct patients in a neurology intensive care unit in Turkey. Jpn J Infect Dis. 2007;60:87–91.
15. Dettenkofer M, Ebner W, Els T, et al: Surveillance of nosocomial infections in a neurology intensive care unit. J Neurol. 2001;248:959–64.
16. Sui R, Zhang L: Risk factors of stroke-associated pneumonia in Chinese patients. Neurol Res. 2011;33:508–13.
17. Yeh SJ, Huang KY, Wang TG, et al: Dysphagia screening decreases pneumonia in acute stroke patients admitted to the stroke intensive care unit. J Neurol Sci. 2011;306:38–41.
18. Kasuya Y, Hargett JL, Lenhardt R, et al. Ventilator-associated pneumonia in critically ill stroke patients: frequency, risk factors, and outcomes. J Crit Care. 2011;26:273–9.
19. Upadya A, Thorevska N, Sena KN, Manthous C, Amoateng-Adjepong Y. Predictors and consequences of pneumonia in critically ill patients with stroke. J Crit Care. 2004;19:16–22.
20. Kostadima E, Kaditis AG, Alexopoulos EI, Zakynthinos E, Sfyras D. Early gastrostomy reduces the rate of ventilator-associated pneumonia in stroke or head injury patients. Eur Respir J. 2005;26:106–11.
21. Hassan AE, Chaudhry SA, Zacharatos H, et al. Increased rate of aspiration pneumonia and poor discharge outcome among acute ischemic stroke patients following intubation for endovascular treatment. Neurocrit Care. 2012;16:246–50.
22. Yang CC, Shih NC, Chang WC, Huang SK, Chien CW. Long-term medical utilization following ventilator-associated pneumonia in acute stroke and traumatic brain injury patients: a case-control study. BMC Health Serv Res. 2011;11:289.
23. Hannawi Y, Hannawi B, Rao CP, Suarez JI, Bershad EM. Stroke-associated pneumonia: major advances and obstacles. Cerebrovasc Dis. 2013;35(5):430-43.
24. Towfighi A, Saver JL. Stroke declines from third to fourth leading cause of death in the United States: Historical perspective and challenges ahead. Stroke. 2011;42:2351-5.
25. Bhatia RS, Garg RK, Gaur SP, Kar AM, Shukla R, Agarwal A, et al. Predictive value of routine hematological and biochemical parameters on 30‑day fatality in acute stroke. Neurol India. 2004;52:220-3.
26. Zhang X, Yu S, Wei L, Ye R, Lin M, et al. The A2DS2 Score as a Predictor of Pneumonia and In-Hospital Death after Acute Ischemic Stroke in Chinese Populations. PLoS One. 2016 Mar 7;11(3):e0150298.
27. Hartmann A, Rundek T, Mast H, Paik MC, Boden-Albala B, et al. Mortality and causes of death after first ischemic stroke: The Northern Manhattan stroke study. Neurology. 2001;57:2000-5.

J Surg Med. 2019;3(3):235-238.
DOI: 10.28982/josam.536365

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Publication of physiology theses in scientific journals: Analysis of the status from Turkey

Fizyoloji tezlerinin bilimsel dergilerde yayınlanması: Türkiye'den durum analizi

Nurten Seringeç Akkeçeci [1]

[1] **Department of Physiology, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey**

ORCID ID of the author(s)
NSA: 0000-0003-1915-2330

Abstract

Aim: Theses, one of the main sources of scientific articles, are the main indicators of scientific productivity of the country. To the best our knowledge, the publication status of physiology specialty thesis have not been reported before. This study was planned in order to evaluate the publication status in scientific journals of specialty theses by physiology departments in our country.

Methods: An observational study is planned. Eighty-two physiology specialty theses available in the Council of Higher Education National Thesis Center web database (https://tez.yok.gov.tr/UlusalTezMerkezi/) on February 2019, which were entered in the system via the departmental physiology units of all medical faculties in our country and published between 2004 and 2014, were included in this study. These theses were examined regarding the year they were conducted, whether the thesis is clinical or animal study, the gender of the author, the academic title of the thesis advisor, the publication status and the other characteristics of the thesis authors.

Results: Forty-seven (57.3%) out of 82 physiology specialty theses that are included in our study were published in the scientific journals. Fifteen (18.3%) of these were published in a journal with Science Citation Index (SCI), 17 (20.7%) in Science Citation Index-Expanded (SCI-E), 9 (11.0%) in the other international indexes, 5 (6.1%) in Ulakbim TR index, 1 (1.2%) was published in the national peer-reviewed journals.

Conclusion: It is asserted that the publication rate of the theses as articles that were written at the end of the physiology specialization training is quite high.

Keywords: Physiology, Thesis, Publication

Öz

Amaç: Bilimsel makalelerin ana kaynaklarından biri olan tez çalışmaları, ülkenin bilimsel verimliliğinin temel göstergeleridir. Bildiğimiz kadarıyla, fizyoloji uzmanlık tezlerinin yayınlanma durumu daha önce bildirilmemiştir. Bu çalışma ülkemizdeki fizyoloji anabilim dalları tarafından yayınlanan fizyoloji tıpta uzmanlık tezlerinin bilimsel dergilerde yayınlanma durumunun değerlendirilmesi amacıyla planlanmıştır.

Yöntemler: Gözlemsel olan bu çalışmaya Şubat 2019 tarihinde Yüksek Öğretim Kurulu Başkanlığı Ulusal Tez Merkezi internet veri tabanında (https://tez.yok.gov.tr/UlusalTezMerkezi/) yer alan, ülkemizdeki tüm tıp fakültelerinin fizyoloji anabilim dalı birimlerinden sisteme girilmiş 2004- 2014 yılları arasında yayınlanmış 82 adet fizyoloji uzmanlık tezi dahil edildi. Bu tezler yapıldıkları yıl, yapıldıkları kurum, tezin klinik ya da hayvan deneyi olma durumu, yazar cinsiyeti, tez danışmanın akademik ünvanı, yayınlanma durumu, yayına ait özellikler ve tez yazarlarına ait diğer özellikler açısından incelendi.

Bulgular: Çalışmamıza dahil edilen 82 adet fizyoloji uzmanlık tezinin 47'si (%57.3) bilimsel dergilerde yayınlanmıştı. Bu yayınların 15'i (18.3%) Science Citation Index (SCI), 17'si (20.7%) Science Citation Index-Expanded (SCI-E), 9'u (11.0%) uluslararası diğer indekslerde, 5'i (6.1%) Ulakbim TR dizin, 1'i (1.2%) ulusal hakemli dergilerde yayınlanmıştı.

Sonuç: Çalışmamızda fizyoloji uzmanlık eğitimi sonunda yazılan uzmanlık tezlerinin makale olarak yayınlanma oranının oldukça yüksek olduğu ortaya konulmuştur.

Anahtar kelimeler: Fizyoloji, Tez, Yayın

Corresponding author / Sorumlu yazar:
Nurten Seringeç Akkeçeci
Address / Adres: Kahramanmaraş Sütçü İmam Üniversitesi Tıp Fakültesi, Fizyoloji Anabilim Dalı, Bahçelievler Kampüsü, 46100, Kahramanmaraş, Türkiye
e-Mail: seringec@hotmail.com

Ethics Committee Approval: The approval for the study is obtained from the local Institutional Ethics Committee.
Etik Kurul Onayı: Çalışmanın onayı yerel Kurumsal Etik Komitesi'nden alınmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 06.03.2019
Accepted / Kabul Tarihi: 08.03.2019
Published / Yayın Tarihi: 09.03.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite / Atıf için: Akkeçeci NS. Publication of physiology theses in scientific journals: Analysis of status from Turkey. J Surg Med. 2019;3(3):235-238.

Introduction

Physiology is the discipline that tries to explain the normal operation of the human body, the functions of the organs and tissues, the relationship between these functions and the mechanisms of these functions. Physiology specialization student participates in the educational activities that are predetermined by the department. This training aims to enable the student to learn the basic subjects of physiology, to acquire the basic knowledge and skills necessary for conducting experimental research and carrying out and evaluate the practical student applications.

It is mandatory to conduct a thesis study in the physiology specialization of the medical faculties in our country. Thesis preparation provides the students in medicine the skill of generating a hypothesis, designing a study to prove the hypothesis, data collection, data analysis, interpretation of the results and writing it as a scientific text. The publication of the thesis provides significant contributions to personal, academic progress and science. Publication of the theses is a very challenging process, and according to the studies, it is seen that the rates of the specialty theses in medicine turning into publications are quite low [1-4]. No studies evaluating the publication status of the physiology specialty theses published in our country on the scientific journals were found in the literature.

This study was planned in order to evaluate the publication status in the scientific journals of the physiology specialty theses by the physiology departments of the medical faculties in Turkey.

Materials and methods

In this study, which is descriptive research, the scanning model was used. All steps of the study were carried out according to the basic principles of Helsinki declaration. The study was approved by Local Ethics Committee.

All of the physiology specialty theses available in the Council of Higher Education National Thesis Center internet database (https://tez.yok.gov.tr/UlusalTezMerkezi/) on February 2019, which were entered in the system via the departmental physiology units of all medical faculties in our country and published between 2004 and 2014, are included in this study. Considering that the period of the thesis turning into publication might be prolonged, the specialty theses published between 2015 and 2019 were not included in the study. Additionally, theses with multiple entries (e.g., Subject: Physiology and ophthalmology, Subject: physiology and emergency medicine, etc.) were examined one by one, and the theses which did not belong to physiology department were excluded from the study.

Whether or not the thesis turned into publication was determined by comparing the title and abstract of the article with the title, subject and abstract of the thesis through using the names and surnames of the thesis author and advisor and the Turkish and English title of the thesis via Google scholar (https://scholar.google.com.tr/) and PubMED Central (PMC) (https://www.ncbi.nlm.nih.gov/pubmed). The publications with full text, abstract or author names and the articles that have titles specifying being derived from thesis were evaluated. Which database among Science Citation Index (SCI), Science Citation Index-Expanded (SCI-E), the other international platforms (PubMED, Medline, Scopus, Index Copernicus, etc..), Ulakbim TR index, national peer-reviewed journals, the journals that the theses were published on were included in was asserted through the examination of the websites of these databases and journals? Whether the physicians who wrote the theses are working as physicians or in another field and the institutions that they are currently working were determined through web scanning. The gender of the thesis author, the faculty of medicine in which the thesis is conducted, the institution that the author is currently employed, continuation to career in the field of physiology, the order of the thesis author's name in the publication, the academic title of the thesis advisor, the case whether the thesis is clinical or animal study, the national or international index in which the article was published in and the time is taken for the publication of the thesis were evaluated.

Statistical analysis

The data were analyzed by using the SPSS 15.0 package program. The numerical data were indicated as mean ± standard deviation and the categorical variables as number and percentage. Chi-square test was used to analyze the categorical data. The test results were considered statistically significant if $p < 0.05$.

Results

A total of 122 physiology specialty theses which were published between 2004 and 2018 in the National Thesis Center internet database were reached. No thesis that was entered in the system via a departmental physiology unit of any medical faculty was found in 2019. A total of 14 theses were excluded from the study since they were published between 2015 and 2018. 29 out of the remaining 108 theses were determined to have multiple entries in the subject section, and 9 of them were physiology specialty theses whereas the remaining 20 belonged to other fields. In addition, 1 thesis which was entered to the system as a specialty thesis in 2009 was determined to be a master's thesis indeed, similarly, 4 theses which were entered to the system as specialty theses in 2004 were determined to be master's theses indeed and these 5 master's theses were excluded from the study.

Additionally, 1 specialty thesis that was entered to the system in 2009 was determined to be dated 2001 and was excluded from the study. A total of 82 physiology specialty theses published were included in the study after evaluation of eligibility.

Thirty-six of the thesis owners were male (43.90%), and 46 were female (56.10%). 55 (64.7%) of the thesis advisors were professors, 21 (24.7%) associate professors, 8 (9.4) doctor faculty members, 1 was the thesis owner himself (1.2%).

It was determined that 47 (57.3%) of the specialty theses conducted in the field of physiology between 2004 and 2014 were published in a scientific journal and 35 (42.7%) were not published. 15 (18.3%) of the publications were published in SCI, 17 (20.7%) were published in SCI-E, 9 (11.0%) were published in the other international indexes, 5 (6.1%) of them were published in Ulakbim TR index, 1 (1.2%) was published in national peer-reviewed journals. The publication status of the theses is provided in Table 1.

Table 1: Publication pattern of physiology specialty thesis

Publication	n	%
SCI	15	18.3
SCI-E	17	20.7
Other international indexes	9	11.0
Ulakbim TR	5	6.1
National peer-reviewed journal	1	1.2
Total published	47	57.3
Total unpublished	35	42.7

In 2 (2.4%) of the theses cell culture study was performed, in 20 (24.4%) theses clinical study was performed and in 60 (73.2%) theses animal study was performed. 38 (63.3%) of the animal studies and 9 (45.0%) of the clinical studies were published. The cell culture studies were not published. Among the 47 theses published, 38 (80.9%) were animal studies, and 9 (19.1%) were clinical studies. The publication rate of the animal studies was found higher than the others (p=0.037).

The mean number of people in the publications was 5.23±2.07 (2-11). Thesis owners were the first name in 40 of the publications (85.1%), the second name in 6 (12.8%) of the publications and the third name in 1 (2.1%) of the publications.

When the distribution of the theses according to the universities that they were conducted in was evaluated, in the first 5 ranks there were Hacettepe University (HU) (8 theses, 9.8%), Ondokuz Mayıs University (OMU) (7 theses, 8.5%), Istanbul University (IU) (6 theses, 7.3%), Ankara University (AU) (6 theses, 7.3%) and Fırat University (FU) (5 theses, 6.1%). When the publication status of the theses according to the universities were evaluated, HU had the first rank with 5 publications (10.6%), IU and OMU had the second rank with 4 publications (8.5%), AU, FU and Marmara University (MU) had the third rank with 3 publications (6.4%). There was no statistically significant difference in terms of the publication status of the theses according to the universities and the journals in which they were published according to the universities (p=0.480, p=0.155, respectively).

When the institutions that the thesis owners currently working are examined, 38 (46.3%) of them were working as faculty members in the physiology departments of the medical faculties of various universities, 36 (43.9%) of them were working as specialist doctors in various hospitals, 7 (8.5%) of them were working as specialist doctors in clinical branches and 1of them (1.2%) was working as a physiology teacher at TUS private teaching institution. Among the 38 people who worked as physicians in the physiology departments of various medical faculties, 17 (44.7%) were male, and 21 (55.3%) were female. Among the 38 physiology specialists, 14 (36.8%) were employed as faculty members at the university where they received their specialization training, and 24 (63.2%) were working as faculty members in the physiology department in the faculty of medicine of a different university. Among the 38 people working in the physiology departments in the medical faculties of various universities, the theses of 28 of them (73.7%) were published in a scientific journal (9 in SCI, 12 in SCI-E, 4 in the other international indexes, 3 in Ulakbim TR index), the theses of 10 (26.3%) of them were not published. Among the 36 people working as specialist doctors in various hospitals, the theses of 15 of them were published in a scientific journal (6 in SCI, 3 in SCI-E, 3 in the other international indexes, 2 in Ulakbim TR index, 1 in the national peer-reviewed journal, the theses of 21 (58.3%) of them were not published.

Discussion

This is the first study evaluating the status of publication in the scientific journals of the physiology specialty theses published in our country. In our study, the publication rate of the physiology specialty theses between 2004 and 2014 was found to be 57.3%.

Our primary aim was to demonstrate the current results. Similar to the other studies in the literature, we also evaluated an 11-year process in our study [2,3]. Scherer et al. [5] reported that 5 years are necessary for a study to turn into a publication. Therefore, we did not include the data after 2014 in our study. In some SCI journals, the period between sending of the publication and publishing is 3.5 years [6]. Çetin et al. [7] found that the mean period for otorhinolaryngology specialization theses to be published was 3.15 years in the study that they conducted in 2017, in which they evaluated the publication rate of the otorhinolaryngology specialization theses on the scientific journals in the years between 2007-2012. In our study, the mean period to be published was 3.02±1.95 (0-8) years.

In our study, the publication rate of the physiology specialty theses between 2004 and 2014 was found to be 57.3%. It was seen that 15 of these publications were published in SCI (18.3%), 17 (20.7%) were published in SCI-E, 9 (11.0%) were published in the other international indexes, 5 (6.1%) were published in Ulakbim TR index, 1 (1.2%) was published in the national peer-reviewed journals. It is remarkable and pleasing that the rates determined in our study are quite high compared to the rates reported from different branches in our country. In Turkey, there are many studies examining the rates of the theses conducted in various specialization fields turning into publications [1-4, 7-10]. In these studies, the rate of the thesis turning into publications vary between 6.5% and 49.7% [1-4, 7-10]. Özgen et al. [1] reported that the rate of 22,625 medical theses conducted between 1980-2005 turning into publications in the journals within the scope of SCI-E was 6.2%. Yüksel et al. [8] reported that the publication rate of urology specialization theses was 49.7% and 32.7% of these publications were published in SCI-E, 10.4% in international journals, 6.5% in the other international journals and 6.5% in the national indexed journals in the study that they conducted in 2017, in which they evaluated the publication rate of the urology specialization theses written between 2008-2011 in the scientific journals. Çetin et al. [7] reported that the publication rate of otorhinolaryngology specialization theses was 35.6%, the publication rate in the national journals was 14.1%, and the publication rate in the international journals was 21.4%. Cevik et al. [9] reported that the publication rate of the theses conducted in the field of Emergency Medicine between 1998 and 2013 was 27.1% and Öğrenci et al. [2] reported that the publication rate of the theses conducted in the field of neurosurgery between 2004-2013 on the indexed journal was 18.0%. Sipahi et al. [3] reported that the rate of turning into publication for the doctorate theses was 13.7%, for the Microbiology and Clinical Microbiology specialization theses was 10.7%, for the Infectious Diseases and Clinical Microbiology specialization theses was 10.2%, in the study they

conducted in 2014, in which they evaluated the publication rates in the international journals of the specialization in medicine theses and doctorate theses conducted in the fields of Medical Microbiology, Clinical Microbiology and Infectious Diseases and written between 1997-2007. In a study examining the total of 538 theses -243 doctorate theses and 295 specialization theses- conducted in the field of public health between 1978 and 2010, the publishing rate in the international journals was reported to be 11.9%, 9.9% of the doctorate theses and the 13.6% of the specialization theses were published in the international journals [10]. It was reported that the publication rate in the scientific journals of the thesis at the end of the family medicine specialization training was 11.5%, 0.8% of them were published in SCI journals, 3.1% in SCI-E journals and 7.6% in national journals [4].

Among the 82 theses included in our study, in 2 (2.4%) of the theses cell culture studies was performed, in 20 (24.4%) theses clinical studies was performed and in 60 (73.2%) theses animal studies was performed. 38 (63.3%) of the animal studies and 9 (45.0%) of the clinical studies were published. The cell culture studies were not published. Among the 47 theses published, 38 (80.9%) were animal studies, and 9 (19.1%) were clinical studies. In our study, the publication rate of the animal studies was found higher than the others.

When the institutions that the thesis owners currently working are examined, 38 (46.3%) of them were working as faculty members in the physiology departments of the medical faculties of various universities, 36 (43.9%) of them were working as specialist doctors in various hospitals, 7 (8.5%) of them were working as specialist doctors in clinical branches and 1of them (1.2%) was working as a physiology teacher at TUS private teaching institution. The publication rate of those who were working as faculty members in the physiology departments of the medical faculties of various universities was 73.7%, whereas the publication rate of those who were working as specialist doctors in various hospitals was 41.7%.

However, this study has some limitations. Firstly, the change of the title of the thesis during the conversion to the article may have caused the missing evaluation. Secondly, the change of the female authors' surname may have caused the missing evaluation.

In conclusion, it is asserted that the publication rate of the theses as articles that were written at the end of the physiology specialization training is quite high.

References

1. Özgen Ü, Eğri M, Aktaş M, Sandıkkaya A, Öztürk ÖF, Can S, etal. Publication Pattern of Turkish Medical Theses: Analysis of 22.625 Medical Theses Completed in Years 1980-2005. Turkiye Klinikleri J Med Sci. 2011;31(5):1122-31.
2. Öğrenci A, Eksi MS, Ozcan-Eksi EE, Koban O. From idea to publication: Publication rates of theses in neurosurgery from Turkey. Neurol Neurochir Pol. 2016;50:45-7.
3. Sipahi OR, Serin DC, Pullukcu H, Tasbakan M, Ulu DK, Yamazhan T, etal. Publication rates of Turkish medical specialty and doctorate theses on Medical Microbiology, Clinical Microbiology and Infectious Diseases disciplines in international journals. [Article in Turkish] Mikrobiyol Bul. 2014;48(2):341-5.
4. Üçer H, Keten HS. Have dissertations made in the field of Family Medicine published as a scientific article? [Article in Turkish] KSU Tıp Fak Der. 2016;11(1):22-5.
5. Scherer RW, Dickersin K, Langenberg P. Full publication of results initially presented in abstracts. A meta-analysis. JAMA. 1994;272:158-62.
6. Kalcioglu MT, Ileri Y, Karaca S, Egilmez OK, Kokten N. Research on the Submission, Acceptance and Publication Times of Articles Submitted to International Otorhinolaryngology Journals. Acta Inform Med. 2015;23:379-84.
7. Çetin A, Boran C, Erdağ TK. Do the otorhinolaryngology specialization thesis turn into publications? [Article in Turkish] Kulak Burun Bogaz İhtis Derg. 2017;27(4):185-93.
8. Yüksel M, İpekçi T, Tunçkıran A. Publication rates of dissertations written in medical faculties of Turkey in the field of urology between the years 2008, and 2011, and citation analysis: A cross-sectional study. Turk J Urol. 2018;44(4):341-5.
9. Cevik E, Karakus Yılmaz B, Acar YA, Dokur M. Systematic analysis of thesis in the field of emergency medicine in Turkey. Turk J Emerg Med. 2015;15(1):28-32.
10. Sipahi H, Durusoy R, Ergin I, Hassoy H, Davas A, Karababa AO. Publication rates of public health theses in international and national peer-review journals in Turkey. Iran J Public Health. 2012;41(9):31-5.

J Surg Med. 2019;3(3):239-241.
DOI: 10.28982/josam.523350

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Toxoplasma gondii seroprevalence in rheumatoid arthritis patients treated with biological agents

Biyolojik ajanlarla tedavi edilen romatoid artritli hastalarda Toxoplasma gondii seroprevalansı

Ali İnal [1], Dilaver Taş [2]

[1] Başkent University, Istanbul Education and Research Hospital, Department of Allergy and Immunology, Istanbul, Turkey
[2] Başkent University, Istanbul Education and Research Hospital, Department of Pulmonology, Istanbul, Turkey

ORCID ID of the author(s)
Aİ: 0000-0002-0690-2529
DT: 0000-0003-2785-2492

Corresponding author / Sorumlu yazar:
Dilaver Taş
Address / Adres: Başkent Üniversitesi, İstanbul Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Anabilim Dalı, Altunizade, Üsküdar, İstanbul, Türkiye
e-Mail: dilavertas@gmail.com

Ethics Committee Approval: The approval for the study is obtained from the local Institutional Ethics Committee.
Etik Kurul Onayı: Çalışmanın onayı yerel Kurumsal Etik Komitesi'nden alınmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 06.02.2019
Accepted / Kabul Tarihi: 10.03.2019
Published / Yayın Tarihi: 11.03.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Abstract

Aim: Toxoplasma gondii infection appears to be asymptomatic in most of the patients but its mortality rate is high in immunocompromised patients and in those taking immunosuppressive drugs, when reactivated and untreated. Severe infections are well-known to occur in rheumatoid arthritis (RA) patients treated with immunosuppressive drugs such as tumor necrosis factor alpha antagonist. TNF-alpha is essential for granuloma formations, which are important for the defense against intracellular pathogens and the process. It seems it is inevitable that anti-TNF agents being used in RA disease treatment are going to create an incline towards all kind of infections, especially tuberculosis and other granulomatous infections (toxoplasmosis, histoplasmosis, etc.). We investigated the T. gondii seroprevalence in RA patients treated with biologic agents and disease modifying anti-rheumatic drugs, systemic lupus erythematosus patients treated with immunosuppressive drug combinations and compared them with healthy controls.

Methods: In this study we investigated the T. gondii seroprevalence in 33 rheumatoid arthritis (RA) patients treated with biologic agents, 26 RA patients treated with disease modifying anti-rheumatic drugs (DMARD), 15 Systemic lupus erythematosus (SLE) patients treated with immunosuppressive drug combinations and in 19 healthy controls.

Results: Toxoplasma IgM enzyme linked immunosorbent (ELISA) assay was negative for all groups. Whereas 29 (87.9%) of rheumatoid arthritis patients treated by the biologic agents, 21(80.8%) of rheumatoid arthritis patients treated by disease modifying antirheumatic drugs, 15 (100%) of Systemic lupus erythematosus patients and 4 (21.1%) of the controls were seropositive for Toxoplasma Ig G.

Conclusion: During the immunosuppressive treatment the risk of toxoplasma infection should be taken into consideration.

Keywords: Toxoplasma gondii, Rheumatoid arthritis, Biological agents

Öz

Amaç: Toxoplasma gondii enfeksiyonu çoğu hastada asemptomatik seyreder; ancak immun yetmezliği olan ve immunsupresif ilaç alan hastalarda nüks durumunda veya tedavi edilmediğinde mortalite oranı yüksektir. Romatoid artritli (RA) hastaların tümor nekrozis faktör alfa (TNF-alfa) antagonisti gibi immunsupresif ilaçlarla tedavi edildiğinde ciddi enfeksiyonlar gelişebileceği bilinmektedir. TNF-alfa romatoid artrit patogenezindeki önemi ile birlikte diğer inflamatuvar cevaplar ve immün sistemin enfeksiyonlarla mücadelesinde etkin rol oynayan önemli bir sitokindir.TNF alfa özellikle hücre içi patojenlere karşı savunmada önemli olan granülamatöz oluşumlar ve idame sürecinde çok önemlidir.Bu nedenle RA tedavisinde yaygın olarak kullanılan anti-TNF ajanların başta tüberküloz ve benzeri (toksoplazmozis,histoplazmozis vb.) granülomatöz enfeksiyonlar olmak üzere her türlü enfeksiyona karşı yatkınlık oluşturması kaçınılmaz görünmektedir.

Yöntemler: Bu çalışmada biyolojik ajanla tedavi edilen 33 romatoid artritli (RA), hastalığı modifiye edici ajanla tedavi edilen 26 RA'li, immunsupresif ilaç kombinasyonları ile tedavi edilen 15 sistemik lupus eritematozuslu (SLE) hasta ve 19 sağlıklı kontrolde enzim linked immunosorbent assay yöntemi ile Toxoplasma gondii seroprevelansı incelenmiştir.

Bulgular: Toxoplasma IgM düzeyleri ELISA yöntemi ile tüm gruplarda negatifti. Ancak biyolojik ajanla tedavi edilen 29 (%87.9) RA'li, hastalığı modifiye edici ajanla tedavi edilen 21(%80.8) RA'li ve 15 (%100) SLE'li hastada ve kontrol grubunda 4 (%21.1) kişide Toxoplasma Ig G seropozitifti.

Sonuç: Immun supresif tedavi sırasında hastalarda toxoplasma enfeksiyonu riski göz önünde bulundurulmalıdır.

Anahtar kelimeler: Toxoplasma gondii, Romatoid artrit, Biyolojik ajanlar

How to cite / Atıf için: İnal A, Taş D. Toxoplasma gondii seroprevalence in rheumatoid arthritis patients treated with biological agents. J Surg Med. 2019;3(3):239-241.

Introduction

Toxoplasma gondii is a widespread zoonotic protozoon of birds and mammals [1]. Researches show that about 30-40% of people can be infected with the protozoon during their lives. This infection appears asymptomatic in most of the people but in immunocompromised patients, including those with organ transplants, AIDS, cancer and in those taking immunosuppressive drugs, reactivated and untreated toxoplasmosis has a high mortality rate. Toxoplasmosis can cause severe neurologic or ocular disease in the fetus and adults [2]. Rheumatoid arthritis (RA) is a common crippling disease characterized by destructive joint inflammation and the production of rheumatoid factor (RF) auto-antibodies. RF producing B cells can be activated by the mitogenic effects of infectious agents (bacterial lipopolysaccharides, EBV, etc.). Stimulation of normal human B cells by EBV in vitro releases low affinity IgM RFs from B-1 (CD5+) cells. Antibodies stimulated in this way are usually polyreactive with restricted V-gene usage, little somatic mutation and idiotypical crossreactive. This could be the result of classical cross reactivity between microbial epitopes and IgG Fc. An-other possibility is that RFs are cross reactive with other autoantigens, and some RFs react with nuclear antigens [3].

The treatment of Rheumatoid arthritis (RA) has changed dramatically in recent years following the introduction of biologic agent therapies. Interleukin-1 (IL-1) and Tumor necrosis factor alpha (TNF-α) orchestrate many of the pathophysiological abnormalities including the local and systemic effects of inflammation and the development of joint damage. Clinical trials have shown the efficiency of cytokine inhibitors in reducing inflammatory activity as well as inhibiting joint destruction in patients with active RA [4].

Although biologic inhibitors have been shown to be effective in the treatment of patients with RA, in the long –term surveillance of the patients treated with TNF-α inhibitors, serious adverse events, particularly intracellular microorganism infections such as Tuberculosis, and other granulomatous infections (histoplasmosis, toxoplasmosis, listeriosis etc.) were observed. In the recent years several RA cases have been published who developed toxoplasmic chorioretinitis and cerebral toxoplasmosis during the treatment with anti-TNF-alpha agents [5,6].

In this study we investigated the T. gondii seroprevalence in RA patients treated with biologic agents and, disease modifying anti-rheumatic drugs, Systemic Lupus Erythematosus (SLE) patients treated with immunosuppressive drug combinations and compared them with healthy controls.

Materials and methods

We designed a cross sectional study with control group. Local Ethical Committee approval was obtained. In our study, we planned four groups; Group 1: RA patients treated with biologic agents, Group 2: RA patients treated with disease modifying antirheumatic drugs (DMARDs), Group 3: SLE patients treated with immunosuppressive drug combinations (cyclophosphamide + corticosteroids + chloroquine) and Group 4 (control group): healthy controls.

Inclusion criteria for the cases were as follows: a) Having one of the diagnoses of RA, SLE and healthy person b) patients suffering from RA and SLE attending in the Rheumatology at least for a year. c) 18 years and older c) any gender d) who voluntarily participate in the study.

We used the enzyme linked immunosorbent assay (ELISA) sandwich technique (Virion-Serion Sandwich ELISA T. gondii IgM and IgG kits) for the detection of anti-T.gondii IgG and IgM anti-Bodies (lot number: Anti-T.gondii IgG; SHX.CB/08.09, Anti-T.gondii IgM; SFX.AQ/08.11).

Statistical analysis

The statistical analysis was performed by NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA). One-way analysis of variance was used in the comparison of descriptive statistical methods (mean, standard deviation) as well as normal distribution variables, while Tukey multiple comparison test was used for subgroup comparisons and chi-square test was used for comparison of qualitative data. The difference in groups and controls were analyzed using Mann-Whitney U Test. A p value less than 0.05 was considered as statistically significant.

Results

Of Group 1, 23 were female and 10 were male. Their mean age was 38.9±9 years and the average disease duration was 7.9±3.1 years. Of Group 2, 20 of them were female and 6 were male. Their mean age was 33±5.4 years and the average of disease duration was 7.6±2.1 years Of Group 3, 10 of them were female and 5 were male with a mean age of 39±6.9 years and the average disease duration was 8.4±2.8 years. 14 of Group 4 were female and 5 of them were male with a mean age of 39.1±6.2 years. No statistically significant difference was observed between the gender distributions of group1, Group 2, Group3 and Group 4 (p=0.887). A statistically significant difference was observed between the mean age of group1, Group 2, Group3 and Group 4 (p=0.007). The mean age of Group 2 was significantly lower than the men age of Group 1, Group 3 and Group 4 (p=0.024, p=0.017 and p=0.011, respectively), but no statistically significant difference was found between the mean age of the other groups (p>0.05). Demographic differences can be seen in Table 1.

Sixteen of Group 1 were on infliximab therapy with the mean duration of 21.3±2.8 months, 8 of them were on etanercept therapy with a mean duration of 19.4±4.1 months and 9 of them were on adalimumab with a mean duration of 24.8±3.1 months. Treatment period and drugs can be seen in Table 2.

Table 1: Demographic differences

Patient groups	Male	Female	p	Mean age±SD	p	Treatments	Disease period (years)
Group 1	10	23		38.9±9		Biologic agents	7.9±3.1
Group 2	6	20		33±5.,4		DMARDs	7.6±2.1
Group 3	5	10	0.887	39±6.9	0.007	Immunosuppressive drug combination	8.4±2.8
Group 4	5	14		39.1±6.2		-	-

Table 2: Treatment period and drugs

Groups	Number	Drugs	Period
Group 1	16	Infliximab	21.3±2.8 months
Group 1	8	Etanercept	19.4 ±4.1 months
Group 1	9	Adalimumab	24.8±3.1 months
Group 2	26	DMARDs	7.6±2.1 years
Group 3	15	(Immunosuppressive drug combination: cyclophosphomide + corticosteroids + chloroquine)	8.4±2.8 years

Toxoplasma Ig M ELISA was negative for all groups. Whereas 29 (87.9%) of RA patients treated by the biologic agents, 21 (80.8%) of RA patients treated by DMARDs, 15 (100%) of SLE patients and 4 (21.1%) of the controls were seropositive for Toxoplasma Ig G. The seropositivity ratio was statistically significant and higher ($p<0.001$) in all patient groups regardless of the treatment type according to control group, although there were no statistically significant difference in seropositivity ratio between the patient groups ($p=0.08$).

Discussion

Toxoplasmosis is one of the most important zoonotic diseases worldwide and is caused by the protozoan T. gondii. Members of innate immunity; T cells, NK cells and cytokines are the main response cells for T.gondii. İnterferon gamma (IFN-gamma), TNF-α, IL-2, IL-6, IL-10, IL-12 and IL-15 are the most important cytokines in response to the infection [7].

In our country many researchers have been made about toxoplasmosis. In these studies the prevalence of toxoplasmosis was found about 12-60 % [7]. Hazardous infections are well-known to occur in RA patients treated with TNF-α antagonists [8]. At the Arthritis Advisory Committee Meeting that was held in March 2003, 2782 cases of opportunistic infections during the treatment with etanercept and 1100 cases of opportunistic infections during the treatment with infliximab were reported through August 2000 [8]. The most common organism was Mycobacterium tuberculosis. Other organisms that cause opportunistic infections include fungi such as Histoplasma capsulatum and Coccidioides immitis, Pneumocystis jirovecii, yeasts such as Cryptococcus neoformans and candida species, molds such as Aspergillus, bacteria such as Listeria monocytogenes and Nocardia, the protozoan Toxoplasma, and the Cytomegalovirus [9,10].

Immunosuppressive treatment for SLE and anti-TNF-α treatment for RA, affects the patient's quality of life [11]. Although the most clinical expressions of acquired toxoplasmosis cases are asymptomatic, 10 % of the infections may cause serious morbidity and mortality in immunocompromised patients and congenitally infected infants [12]. Toxoplasmosis persists as a latent infection for the lifetime of the host. Toxoplasmosis can reactivate when the host becomes immunocompromised. Recently a few infections like cerebral toxoplasmosis and toxoplasmic chorioretinitis were reported due to these treatments [5,6].

T. gondii can infect and replicate in all nucleated cells. Different studies have showed that some proteins of T.gondii antigen can induce T cell proliferation and cytokine production. The production of IFN-gamma has been particularly shown in Toxoplasmosis, but there are limited data about IL-5 in clinical studies. These studies showed that the changes in IFN-gamma and IL-5 production are related to antibody responses in patients with different stages of toxoplasmosis [12]. On the other hands, it shouldn't be forgotten that polyclonal activation in RA can show cross-reactivity against specific antibodies in toxoplasmosis. This reactivation, which to be developed against RF, can affect the clinical process of RA patients.

There are a number of methods for the diagnosis of toxoplasmosis; however, serologic tests are the usual means of establishing the diagnosis. ELISA is used commonly due to its overall performance and cost. There is no single serologic test that can be used to support the diagnosis of acute or chronic infection [13].

In acute infection, IgM antibodies appear within the first week of infection, which expresses the acute phase of the infection. In the next phase, T.gondii IgM antibody titers decrease and IgG type antibody titer increase in serum within the two weeks of primary infection. These IgG type antibodies remain in serum lifelong at certain levels. IgM antibody disappears but the decline rate is variable from individual to individual, it takes months, sometimes years. For the understanding of approximate contagion date of toxoplasma infections 'IgG' avidity ELISA tests are being used. IgG antibodies appearing early in toxoplasma infection bind to antigen less avidly than antibodies appearing later, which bind with high avidity. Although the change of avidity from low to high varies from individual to individual, the presence of high avidity indicates that the infection occurred at least 3 to 5 months earlier [14]. In this study, patient and controls were evaluated by non-avidity ELISA tests. In our cases, there were no IgM type antibodies that express the acute toxoplasmosis infection. When the IgG antibody positivity frequency was obtained, no significant differences were found between controls and patients.

A limitation of the present study was a small sample size of patients suffering from RA and SLE. Further studies should have a larger sample size of patients.

In conclusion, during the immunosuppressive treatment the risk of toxoplasma infection should be considered as a result of increased seropositivity ratio. Awareness of the associated adverse events is necessary when using biological therapies in the treatment of RA. Patients should be advised for the risk of infections and must be closely monitored for early signs of infection. When opportunistic infections occur, withdrawal of biological therapies may be considered earlier until the infection has been identified and controlled.

References

1. Elmore SA, Jones JL, Conrad PA, Patton S, Lindsay DS, Dubey JP. Toxoplasma gondii: epidemiology, feline clinical aspects, and prevention. Trends Parasitol. 2010;26:190-6.
2. Yazar S, Demirtaş F, Yalcın S, Yaman O, Tokgöz B, Utaş C. Anti-Toxoplasma gondii antibodies in haemodialysis patients with chronic renal failure. Yonsei Med J. 2003;44:288-92.
3. Casali P, Notkins A. CD5+ B lymphocytes, polyreactive antibodies and the human B- cell repertoire. Immunol Today. 1989;10:364-8.
4. Listing, J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum. 2005;52:3403-12.
5. Lassoued S., Lassoued S, Zabraniecki L, Billey T. Toxoplasmic chorioretinitis and antitumor necrosis factor treatment in rheumatoid arthritis. Semin Arthritis Rheum. 2007;36:262-3.
6. Young JD, Mc Gwire BS. Infliximab and reactivation of cerebral toxoplasmosis. N Engl J Med. 2005;353:1530-1.
7. Korkmaz İ, Oğuztürk H, Beydilli İ. The prevalence of Toxoplasma gondii antibodies in diabetic patients. Cumhuriyet Üniversitesi Tıp Fakültesi Dergisi. 2006;1:7-10.
8. Imperato AK, Smiles S, Abramson SB. Long-term risks associated with biologic response modifiers used in rheumatic diseases. Curr Opin Rheumatol. 2004;16:199-205.
9. Ellerin T, Rubin RH, Weinblatt ME. Infections and anti-tumor necrosis factor alpha therapy. Arthritis Rheum. 2003;48:3013-22.
10. Lee JH, Slifman NR, Gershon SK, Edwards ET, Schwieterman WD, Siegel JN, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. Arthritis Rheum. 2002;46:2565-70.
11. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001;345:1098-04.
12. Delibaş SB, Tutgay N, Gürüz YA. The role of cytokines in the immunopathogenesis of toxoplasmosis. Türkiye Klinikleri J.Med Sci. 2009;29:1217-21.
13. Liesenfeld O, Press C, Flanders R, Ramirez R, Remington JS. Study of Abbott Toxo IMx system for detection of immunoglobulin G and immunoglobulin M toxoplasma antibodies: value of confirmatory testing for diagnosis of acut toxoplasmosis. J Clin Microbiol. 1996;34(10):2526-30.
14. Liesenfeld O, Montaya JG, Kinney S, Press C, Remington JS. Effect of testing for IgG avidity in the diagnosis of Toxoplasma gondii infection in pregnant women: experience in a US reference laboratory. J Infect Dis. 2001;183(8):1248-53.

J Surg Med. 2019;3(3):242-245.
DOI: 10.28982/josam.536426

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Evaluation of serum irisin levels in patients with endometrial hyperplasia: A controlled cross-sectional study

Endometrial hiperplazili hastalarda serum irisin düzeylerinin değerlendirilmesi: Kontrollü kesitsel çalışma

Erdem Şahin [1], Mefküre Eraslan Şahin [2], Yusuf Madendağ [1], İlknur Çöl Madendağ [3], Ahter Tanay Tayyar [4], Murat Gözüküçük [5], Çiğdem Karakükçü [6], Gökhan Açmaz [1]

[1] Department of Obstetrics and Gynecology, Erciyes University Medicine Faculty, Kayseri, Turkey
[2] Department of Obstetrics and Gynecology, Kayseri Pinarbasi Government Hospital, Kayseri, Turkey
[3] Department of Obstetrics and Gynecology, Kayseri City Hospital, Kayseri, Turkey
[4] Department of Obstetrics and Gynecology, Maslak Acıbadem Hospital, Istanbul, Turkey
[5] Department of Obstetrics and Gynecology, Ankara Education and Research Hospital, Ankara, Turkey
[6] Department of Biochemistry Clinic, Kayseri City Hospital, Kayseri, Turkey

ORCID ID of the author(s)
EŞ: 0000-0001-9492-6223
MEŞ: 0000-0001-6484-9132
YM: 0000-0002-7622-2991
İÇM: 0000-0001-6700-2236
ATT: 0000-0001-9491-9998
MG: 0000-0001-9858-3272
ÇK: 0000-0002-4418-7570
GA: 0000-0002-4215-3676

Corresponding author / Sorumlu yazar:
Mefkure Eraslan Sahin
Address / Adres: Pınarbaşı Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, Kayseri, Türkiye
e-Mail: mefkureee@hotmail.com

Ethics Committee Approval: The study was approved by the Ethics Committee of Erciyes University (Decision number: 2016/466).
Etik Kurul Onayı: Çalışma Erciyes Üniversitesi Etik Kurulu tarafından onaylandı (Karar numarası: 2016/466).

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 06.03.2019
Accepted / Kabul Tarihi: 10.03.2019
Published / Yayın Tarihi: 11.03.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Abstract

Aim: Irisin, which is proteolytically splited form of fibronectin type III domain containing 5 (FNDC5), is a protein with 112 amino acid. Irisin is an exercise-induced hormone excreted primarily by cardiac muscle and skeletal cells which can be described as an exercise hormone and a new potential target for the treatment of metabolic diseases and obesity. Our goal was to evaluate the serum irisin levels in patients with endometrial hyperplasia (EH).

Methods: An observational study is planned. The study population consisted of two groups: 1) the EH group (study group), consisting of participants who had been histopathologically diagnosed with simple EH without atypia and 2) the control group, consisting of healthy participants admitted to the clinic for an annual examination without any complaints or symptoms. Primary outcome of the study was evaluation irisin status. Serum irisin levels were determined by an enzyme-linked immunosorbent assay (ELISA) method.

Results: After sample size analysis, 52 participants enrolled into the study as study group (EH group) (n=26) and control group (n=26). The mean age was 39.5±3.8 years in the EH group and 40.7±2.4 years in the control group (p=0.258). Mean BMI was 28.8±2.1 kg/m^2 in the EH group and 28.5±1.2 kg/m^2 in the control group (p=0.666). Gravidity, parity, systolic blood pleasure, diastolic blood pleasure, fasting glucose levels, smoking status, alcohol use were similar for both groups (p=0.499, p=0.278, p=0.248, p=0.424, p=0.646, p=0.486 and p=0.153, respectively). In control group regular exercise rates was significantly higher than EH group (26.9%, 3.84%, respectively p<0.001). The mean serum irisin level was 1.9±0.7 µg/ml in the EH group and 3.5±2.0 µg/ml in the control group. Serum irisin levels were found to be significantly lower in the EH group compared to the control group (p<0.001).

Conclusion: The data from the current study indicate that serum irisin levels were significantly decreased in patients with endometrial hyperplasia. Serum irisin levels may open up new horizons for therapeutic targets for the treatment of patients with EH.

Keywords: Endometrial hyperplasia, Obesity, Sedentary life, Physical activity, Irisin

Öz

Amaç: Proteolitik olarak bölünmüş 5 (FNDC5) içeren fibronektin tip III alan formunda olan irisin, 112 amino asitli bir proteindir. İrisin, temel olarak kalp kası ve iskelet hücreleri tarafından salgılanan, egzersiz hormonu ve metabolik hastalıkların ve obezitenin tedavisi için yeni bir potansiyel hedef olarak tanımlanabilen, egzersiz kaynaklı bir hormondur. Amacımız endometrial hiperplazi (EH) hastalarında serum irisin düzeylerini değerlendirmektir.

Yöntemler: Çalışma popülasyonu iki gruptan oluşmaktadır: 1) histopatolojik olarak atipisiz basit EH tanısı almış EH grubu ve 2) kliniğe herhangi bir yakınması ve şikayeti olmadan yıllık muayene için başvuran kontrol grubu. Çalışmanın primer sonucu serum irisin seviyelerinin araştırılmasıdır. Serum irisin düzeyleri, enzyme-linked immunosorbent assay (ELISA) yöntemiyle belirlendi.

Bulgular. Örneklem büyüklüğü analizi sonrası toplam 52 katılımcı çalışmaya dahil edildi (EH grubu (n=26) ve kontrol grubu (n=26)). Ortalama yaş EH grubunda 39,5±3,8, kontrol grubunda 40,7±2,4 idi (p=0,262). EH grubunda ortalama VKI 28,8±2,1 kg/m2, kontrol grubunda 28,5±1,2 kg/m2 idi (p=0,666). Gravidite, parite, sistolik kan basıncı, diyastolik kan basıncı, açlık glikoz seviyeleri, sigara içme durumu, alkol kullanımı her iki grup için benzerdi (sırasıyla p=0,499, p=0,278, p=0,248, p=0,424, p=0,646, p=0,486 ve p=0,153). Kontrol grubunda düzenli egzersiz oranları EH grubundan anlamlı olarak yüksekti (sırasıyla %26,9, %3,84, p<0,001). Ortalama serum irisin düzeyi EH grubunda 1,9±0,7 µg/ml ve kontrol grubunda 3,5±2,0 µg/ml idi. Serum irisin düzeyleri EH grubunda kontrol grubuna gore anlamlı olarak düşük bulundu (p<0,001).

Sonuç. Mevcut çalışmadan elde edilen veriler, endometrial hiperplazili hastalarda serum irisin düzeylerinin anlamlı derecede azaldığını göstermektedir. Serum irisin düzeyleri, EH'li hastaların tedavisinde terapötik hedefler için yeni ufuklar açabilir.

Anahtar kelimeler: Endometrial hiperplazi, Obesite, Sedanter yaşam, Fiziksel aktivite, İrisin

Introduction

Endometrial cancer (EC) is the most common gynecological malignancies worldwide, with approximately 50,000 new cases annually identified in the United States [1]. Estrogen-dependent EC (type 1 EC) accounts for approximately 80% of cases. Endometrial hyperplasia (EH), which is a pre-cancerous lesion, occurs via abnormal proliferation of the uterine endometrial layers, characterized by an increased endometrial gland-to-stroma ratio with changing of shape and size [2]. EH and EC have similar risk factors, and the most notable factors are unopposed estrogen, obesity, inadequate physical activity and sedentary behavior [3].

Irisin, which is proteolytically splited form of fibronectin type III domain containing 5 (FNDC5), is a protein with 112 amino acid. Irisin is an exercise-induced hormone excreted primarily by cardiac muscle and skeletal cells. Small amounts of this myokine have been identified in, subcutaneous glands, adipose tissue, spleen, stomach, testis brain, and liver [4]. Irisin release increases during exercise. Irisin synthesis rises owing to the activation of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α) in muscle cells. The primarily effects of brown fat tissue are provided by the activation of high volumes of uncoupling protein 1 (UCP1) in their mitochondria; in other words, the feature of brown fat tissue is the over-expression of PGC1α and UCP1. Because of the irisin effect, PGC1α and UCP1 levels, which are lowly expressed in white fat tissue, are stimulated, and their expression is increased. Therefore, white fat tissues phenotypically become brown fat tissues [4].

There are few studies in literature to evaluate irisin levels and irisin effect in cell proliferation and tumor progression, but results were different and irisin effect on cell proliferation is not fully illuminated today [5-7].Therefore in the present study we aimed to evaluate relationship between serum irisin levels and endometrial hyperplasia.

Materials and methods

This cross-sectional study was conducted at the Kayseri Education and Research Hospital, Kayseri, Turkey. The study was approved by the Ethics Committee of Erciyes University (Decision number: 2016/466) and was carried out in compliance with the Declaration of Helsinki. All participants gave informed consent before the study.

The study population consisted of two groups: 1) the EH group, consisting of participants who had been histopathologically diagnosed with simple EH without atypia who were from 35 to 50years of age, and 2) the control group, consisting of healthy participants admitted to the clinic for an annual examination without any complaints or symptoms. Patients were excluded from the study in the presence of malignancy or pregnancy and also liver, cardiovascular, metabolic or kidney disease, type 1 or 2 diabetes mellitus, hypertension, immune suppressive drug usage or extreme exercise in previous months. Demographic parameters, including age, gravidity, parity, ethnicity, body mass index (BMI), smoking status, alcohol use, regular exercise and systolic and diastolic blood pressure were recorded.

Three 3 cc peripheral venous blood samples were drawn from each participant into serum separating tubes for the measurement of serum irisin levels. Blood samples were collected from the participants with EH during a control visit after endometrial sampling and from the control group during regular clinic visits in a follicular menstrual phase. Until analysis, blood samples were stored at –80oC in a freezer after which they were centrifuged at 4,000 rpm for 10 min. All blood samples were analyzed on the same day at the Kayseri Education and Research Hospital of Medicine Biochemical clinics after four months of storage from the time of the first blood sample. Serum irisin levels were determined by an enzyme-linked immunosorbent assay method (ELISA) (Biovision K4761-100).

Statistical analysis

The Shapiro-Wilk test was used to test the normality assumption of the data. Levene's test was used to test the variance homogeneity assumption. Values are expressed as mean ± standard deviation, median (25th–75th percentile), or n (%). Parametric comparisons were made using a t-test or a z-test, and nonparametric comparisons were made using the Mann-Whitney U test. All comparisons were made with the PASW Statistics 18 program and a p-value of <0.05 was considered statistically significant.

Results

Overall, 52 participants enrolled in the study: 26 were in the EH group, and 26 were in the healthy control group. The mean age was 39.5±3.8 years in the EH group and 40.7±2.4 years in the control group (p=0.258). Mean BMI was 28.8±2.1 kg/m2 in the EH group and 28.5±1.2 kg/m2 in the control group (p=0.666). Gravidity, parity, systolic blood pleasure, diastolic blood pleasure, fasting glucose levels, smoking status, alcohol use were similar for both groups (p=0.499, p=0.278, p=0.248, p=0.424, p=0.646, p=0.486 and p=0.153, respectively). In control group regular exercise rates was significantly higher than EH group (26.9%, 3.84%, respectively, p<0.001). A comparison of the patients' characteristics is shown in Table 1.

Table 1: Comparison of patients' characteristics between groups

Characteristic	Study group n=26	Control group n=26	p
Age (year)	39.5±3.8	40.7±2.4	0.258
Gravity (min-max)	(1-5)	(1-5)	0.499
Parity (min-max)	(1-4)	(1-4)	0.278
BMI (kg/m^2)	28.8±2.1	28,5±1,2	0.666
SBP (mmHg)	120.7±10.5	118,4±7,8	0.248
DBP (mmHg)	79.2±8.1	77,6±8,9	0.424
Fasting blood glucose (mg/mL)	82.0±5.6	82,6±3,6	0.646
Smoking status (n%)	4 (15.3%)	6 (23.0%)	0.486
Alcohol use (n%)	2 (7.6%)	0 (0%)	0.153
Exercise regularly (n%)	1 (3.84%)	7 (26,9%)	<0.001
Serum irisin (µg/mL)	1.9±0.7	3.5±2.0	<0.001

BMI: Body mass index, SBP: Systolic blood pleasure, DBP: Diastolic blood pleasure

A comparison of the serum irisin levels is shown in Figure 1. The mean serum irisin level was 1,9±0,7µg/ml in the EH group and 3.5±2.0 µg/ml in the control group. Serum irisin levels were found to be significantly lower in the EH group compared to the control group (p<0.001).

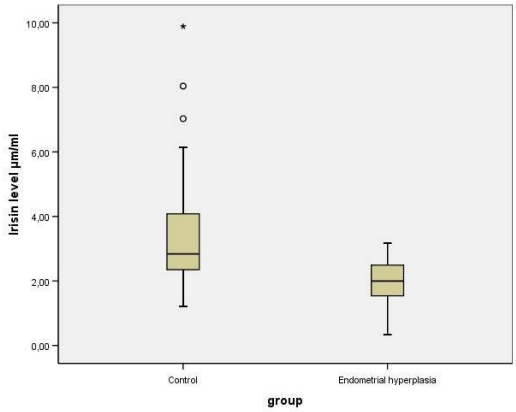

Figure 1: Comparison of serum irisin levels between groups.

Scatter dot plots of serum irisin levels in patients with cases of endometrial hyperplasia and controls. Mean values ± standard deviation are also denoted. Serum irisin levels were significantly lower in the endometrial hyperplasia patients compared to controls (1.9±0.7 vs. 3.5±2.0 µg/ml, p<0.001)

Discussion

Obesity and lifestyle factors are increasingly being studied for their associations with cancer. Sedentary behavior and inadequate physical activity are related with an increased risk of various cancers especially endometrial cancer. The goal of present study was to examine serum irisin levels that can be described as an exercise hormone in patients with EH. Our results indicated that serum irisin levels were significantly decreased in patients with EH.

In the present study we found that serum irisin levels were significantly decreased in patients with EH. In the literature, there are a few studies which evaluated the role of irisin in regulating cell proliferation and malign potential of mouse and human cancer cell lines. Gannon et al. suggested that irisin was a potential therapeutic agent for cancer and had a suppressive effect on the cell number and migratory characteristics in malignant breast cancer cells and induced apoptotic cell death in malignant breast cells [5]. In another study, Provatopoulou et al. [6] reported that irisin could be potentially used as an adipokine and a new diagnostic indicator of breast cancer. Irisin is crucial in early detection of breast cancer because it can efficiently differentiate between diseased and healthy individuals with 62.7% sensitivity and 91.1% specificity with a cut-off value of 3.21 µg/mL [6]. In contrast, Moon and Mantzoros declared irisin did not affect the malign potential of obesity-associated cancer cell lines in vitro at physiological and high physiological and/or high pharmacological concentrations [7].

In the current study we found that BMI was similar between groups and regularly exercise rates was significantly higher in control group. Considering that BMI is equal in both groups, it is possible to explain this difference in serum irisin levels with regular exercise rates. It is declared that exercise increases circulating irisin levels [8-10]. We may be able to explain our results with physical activity and changes in circulating concentrations of insulin, insulin-related pathways, and inflammation [11]. It is well documented that exercise has beneficial changes in circulating concentrations of insulin, insulin-related pathways, and inflammation [12]. The effects of sedentary behavior and physical activity on the immune system that related to cancer development are well documented [13,14].Additionally, it is showed that time spent sitting was associated with an increased risk of metabolic syndrome, increased insulin resistance, and higher levels of C-reactive protein [15,16].

Various risk factors that are associated with EH and EC are addressed. In a study of Beavis et al. [3] it is reported that physical activity was inversely associated with EC. In another cohort study Borch KB et al. [17] declared that 21.9% of endometrial cancers could be avoided if women with low levels of physical activity increased their physical activity level. In addition it is reported that higher levels of sedentary behavior were associated with increased risk of EC incidence [18-20]. Therefore, managing obesity is warranted in these patients. Diet, exercise, and weight loss are the preventive measures recommended for obese women diagnosed with EH [21]. Similar lifestyle modifications can help to treat diabetes or metabolic syndrome, but effective management requires pharmacologic interventions. It is clear that irisin levels can be a therapeutic target for obesity, diabetes, insulin resistance and metabolism regulation [22-27]. No studies have quantified the magnitude of therapeutic benefit. However, morbidity and mortality are significantly alleviated through lifestyle modifications than using temporary pharmacologic therapies. Thus, lifestyle modifications have a pivotal role in a comprehensive management plan. Of course, prospective studies with a greater number of patients are required in this area. There are several limitations of study. Small sample size and cross sectional design are major limitations. Additionally new further prospective studies that included patients with atypical EH and EC can be explain mechanisms more clearly.

Conclusion

The data from the current study indicate that serum irisin levels were significantly decreased in patients with endometrial hyperplasia. Serum irisin levels may open up new horizons for therapeutic targets for the treatment of patients with EH.

References

1. Sahin E, Eraslan Sahin M, Dolanbay M, et al. Induction of apoptosis by metformin and progesterone in estrogen-induced endometrial hyperplasia in rats: involvement of the bcl-2 family proteins. Gynecol Endocrinol. 2018 May;34(5):433-6.
2. Daud S, Jalil SS, Griffin M, et al. Endometrial hyperplasia - the dilemma of management remains: a retrospective observational study of 280 women. Eur J Obstet Gynecol Reprod Biol. 2011 Nov;159(1):172-5. doi: 10.1016/j.ejogrb.2011.06.023. PubMed PMID: 21764501.
3. Beavis AL, Smith AJ, Fader AN. Lifestyle changes and the risk of developing endometrial and ovarian cancers: opportunities for prevention and management. Int J Womens Health. 2016;8:151-67. doi: 10.2147/IJWH.S88367. PubMed PMID: 27284267; PubMed Central PMCID: PMCPMC4883806.
4. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev. 2004 Jan;84(1):277-359. doi: 10.1152/physrev.00015.2003. PubMed PMID: 14715917.
5. Gannon NP, Vaughan RA, Garcia-Smith R, et al. Effects of the exercise-inducible myokine irisin on malignant and non-malignant breast epithelial cell behavior in vitro. Int J Cancer. 2015 Feb 15;136(4):E197-202. doi: 10.1002/ijc.29142. PubMed PMID: 25124080.
6. Provatopoulou X, Georgiou GP, Kalogera E, et al. Serum irisin levels are lower in patients with breast cancer: association with disease diagnosis and tumor characteristics. BMC Cancer. 2015 Nov 11;15:898. doi: 10.1186/s12885-015-1898-1. PubMed PMID: 26560078; PubMed Central PMCID: PMCPMC4642638.
7. Moon HS, Mantzoros CS. Regulation of cell proliferation and malignant potential by irisin in endometrial, colon, thyroid and esophageal cancer cell lines. Metabolism. 2014 Feb;63(2):188-93. doi: 10.1016/j.metabol.2013.10.005. PubMed PMID: 24268368.
8. Blizzard LeBlanc DR, Rioux BV, Pelech C, et al. Exercise-induced irisin release as a determinant of the metabolic response to exercise training in obese youth: the EXIT trial. Physiological reports. 2017;5(23).
9. Aydin S, Aydin S, Kuloglu T, et al. Alterations of irisin concentrations in saliva and serum of obese and normal-weight subjects, before and after 45 min of a Turkish bath or running. Peptides. 2013 Dec;50:13-8. doi: 10.1016/j.peptides.2013.09.011. PubMed PMID: 24096106.
10. Winn NC, Grunewald ZI, Liu Y, et al. Plasma Irisin Modestly Increases during Moderate and High-Intensity Afternoon Exercise in Obese Females. PLoS One. 2017;12(1):e0170690. doi: 10.1371/journal.pone.0170690. PubMed PMID: 28125733; PubMed Central PMCID: PMCPMC5268488.
11. Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence. Lancet Oncol. 2017 Aug;18(8):e457-e471. doi: 10.1016/S1470-2045(17)30411-4. PubMed PMID: 28759385.

12. Ballard-Barbash R, Friedenreich CM, Courneya KS, et al. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. J Natl Cancer Inst. 2012 Jun 6;104(11):815-40. doi: 10.1093/jnci/djs207. PubMed PMID: 22570317; PubMed Central PMCID: PMCPMC3465697.
13. Hibler E. Epigenetics and Colorectal Neoplasia: the Evidence for Physical Activity and Sedentary Behavior. Curr Colorectal Cancer Rep. 2015 Dec;11(6):388-396. doi: 10.1007/s11888-015-0296-z. PubMed PMID: 27212896; PubMed Central PMCID: PMCPMC4869522.
14. Robinson MM, Dasari S, Konopka AR, et al. Enhanced Protein Translation Underlies Improved Metabolic and Physical Adaptations to Different Exercise Training Modes in Young and Old Humans. Cell Metab. 2017 Mar 7;25(3):581-592. doi: 10.1016/j.cmet.2017.02.009. PubMed PMID: 28273480; PubMed Central PMCID: PMCPMC5423095.
15. Wiseman AJ, Lynch BM, Cameron AJ, et al. Associations of change in television viewing time with biomarkers of postmenopausal breast cancer risk: the Australian Diabetes, Obesity and Lifestyle Study. Cancer Causes Control. 2014 Oct;25(10):1309-19. doi: 10.1007/s10552-014-0433-z. PubMed PMID: 25053405.
16. Lynch BM, Dunstan DW, Healy GN, et al. Objectively measured physical activity and sedentary time of breast cancer survivors, and associations with adiposity: findings from NHANES (2003-2006). Cancer Causes Control. 2010 Feb;21(2):283-8. doi: 10.1007/s10552-009-9460-6. PubMed PMID: 19882359.
17. Borch KB, Weiderpass E, Braaten T, et al. Physical activity and risk of endometrial cancer in the Norwegian Women and Cancer (NOWAC) study. Int J Cancer. 2017 Apr 15;140(8):1809-1818. doi: 10.1002/ijc.30610. PubMed PMID: 28108996.
18. Schmid D, Leitzmann MF. Television viewing and time spent sedentary in relation to cancer risk: a meta-analysis. J Natl Cancer Inst. 2014 Jul;106(7). doi: 10.1093/jnci/dju098. PubMed PMID: 24935969.
19. Biswas A, Oh PI, Faulkner GE, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Ann Intern Med. 2015 Jan 20;162(2):123-32. doi: 10.7326/M14-1651. PubMed PMID: 25599350.
20. Shen D, Mao W, Liu T, et al. Sedentary behavior and incident cancer: a meta-analysis of prospective studies. PLoS One. 2014;9(8):e105709. doi: 10.1371/journal.pone.0105709. PubMed PMID: 25153314; PubMed Central PMCID: PMCPMC4143275.
21. Linkov F, Edwards R, Balk J, et al. Endometrial hyperplasia, endometrial cancer and prevention: gaps in existing research of modifiable risk factors. Eur J Cancer. 2008 Aug;44(12):1632-44. doi: 10.1016/j.ejca.2008.05.001. PubMed PMID: 18514507.
22. Polyzos SA, Anastasilakis AD, Efstathiadou ZA, et al. Irisin in metabolic diseases. Endocrine. 2018;59(2):260-74.
23. Jang HB, Kim HJ, Kang JH, et al. Association of circulating irisin levels with metabolic and metabolite profiles of Korean adolescents. Metabolism. 2017 Aug;73:100-108. doi: 10.1016/j.metabol.2017.05.007. PubMed PMID: 28732566.
24. Bastu E, Zeybek U, Gurel Gurevin E, et al. Effects of Irisin and Exercise on Metabolic Parameters and Reproductive Hormone Levels in High-Fat Diet-Induced Obese Female Mice. Reprod Sci. 2018 Feb;25(2):281-91. doi: 10.1177/1933719117711264. PubMed PMID: 28594316.
25. Ural UM, Sahin SB, Tekin YB, et al. Alteration of maternal serum irisin levels in gestational diabetes mellitus. Ginekol Pol. 2016;87(5):395-8. doi: 10.5603/GP.2016.0013. PubMed PMID: 27304658.
26. Huh JY. The role of exercise-induced myokines in regulating metabolism. Arch Pharm Res. 2018 Jan;41(1):14-29. doi: 10.1007/s12272-017-0994-y. PubMed PMID: 29177585.
27. Shoukry A, Shalaby SM, El-Arabi Bdeer S, et al. Circulating serum irisin levels in obesity and type 2 diabetes mellitus. IUBMB Life. 2016 Jul;68(7):544-56. doi: 10.1002/iub.1511. PubMed PMID: 27220658.

J Surg Med. 2019;3(3):246-249.
DOI: 10.28982/josam.536733

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Importance of autophagy in colorectal cancer: A cross-sectional study

Otofajinin kolorektal kanserde önemi: Kesitsel bir çalışma

Hilmi Erdem Sümbül [1], Hikmet Akkız [2]

[1] Department of Internal Medicine, University of Health Sciences, Adana Health Practice and Research Center, Adana, Turkey
[2] Department of Internal Medicine, Cukurova University, Balcalı Health Practice and Research Center, Adana, Turkey

ORCID ID of the author(s)
HES: 0000-0002-7192-0280
HA: 0000-0001-9745-8875

Corresponding author / Sorumlu yazar:
Hilmi Erdem Sümbül
Address / Adres: Adana Sağlık Uygulama ve Araştırma Merkezi, Sağlık Bilimleri Üniversitesi, İç Hastalıkları Anabilim Dalı, Adana, Türkiye
e-Mail: erdemsumbul@gmail.com

Ethics Committee Approval: The approval was obtained from the ethics committee of Çukurova University Faculty of Medicine.
Etik Kurul Onayı: Onay Çukurova Üniversitesi Tıp Fakültesi Etik Kurulundan alınmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 07.03.2019
Accepted / Kabul Tarihi: 10.03.2019
Published / Yayın Tarihi: 11.03.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Abstract

Aim: Colon cancer is the third most common cancer in women and men all over the world. Colorectal cancer (CRC) is diagnosed in over 1.2 million people globally each year. The disease is responsible for approximately 609,000 deaths a year (10% of all cancer cases in women and men). Autophagy is the basic catabolic mechanism that involves cell degradation of unnecessary or dysfunctional cellular components through the actions of lysosomes. The development of autophagy plays a great role in the pathogenesis of many diseases. It was found that autophagy could influence on tumor progression and stimulation. The purpose of this study is to determine the relationship between autophagy and autophagy related ATG5, ATG12, Beclin-1 gene and protein expressions and clinicopathological features of colorectal cancer.

Methods: An observational study is planned. After approval of the ethical committee, the patients (n=45) operated for colorectal cancer was included to the study. There were totally 90 tissue samples taken and banked in liquid nitrogen: 1 tissue sample from tumor and 1 from normal from each patient. ATG5, ATG12, Beclin-1 gene expression levels in all samples were examined using SYBR- Green qPCR method, and, ATG5, Beclin-1, LC3 protein levels were analyzed using Western blotting technique. Expression levels were compared to clinicopathologic characteristics.

Results: Gene and protein expression in both tumor and normal tissue equivalents were studied in most of the examples. There was no significant correlation between gene expression levels and demographic or clinicopathological features. The TNM stage of cases significantly correlated with perineural invasion and lymphovascular invasion.

Conclusion: The results of this study suggest that autophagy may play a role in carcinogenesis of colorectal cancers. The further studies are required to determine the relationship between autophagy and clinicopathologic features associated with colorectal cancers.

Keywords: ATG, Autophagy, Colorectal cancer

Öz

Amaç: Kolon kanseri tüm dünyada kadınlar ve erkeklerde üçüncü en sık gözlenen kanserdir. Yılda yaklaşık 1.200.000 yeni vaka ve yaklaşık 609.000 ölüm tahmin edilmektedir. Erkek ve kadınlardaki kanserlerin yaklaşık %10'unu oluşturmaktadır. Otofaji, hücresel proteinlerin otofajik vakuoller aracılığı ile lizozomal degredasyonudur. Otofaji gelişimde, uzun yaşamda ve kanser gibi pek çok hastalığın patogenezinde büyük rol oynamaktadır. Tümör gelişimi ve uyarılması üzerine bazı etkiler gösterdiği saptanmıştır. Bu çalışmanın amacı, otofajinin, otofaji ilişkili ATG5, ATG12 ve Beclin-1genlerinin ve proteinlerinin ekspresyonu ve kolorektal kanserin klinikopatolojik özellikleri ile ilişkisinin belirlenmesidir.

Yöntemler: Çukurova Üniversitesi Tıp Fakültesi Hastanesi Genel Cerrahi Anabilim Dalında kolorektal kanser nedeniyle opere edilen 45 hasta dahil edildi. Hastaların hem tümör hem de eşlenik normal kolon dokularından alınan örnekler ameliyathaneden itibaren sıvı azotta bankalandı. Daha sonra SYBR Green qPCR yötemiyle ATG5, ATG12, Beclin-1 gen ekspresyonlarına ve Western Blot yöntemiyle ATG5, Beclin-1, LC3 protein ekspresyonlarına bakıldı. Ekspresyon düzeyleri ile klinikopatolojik özellikler karşılaştırıldı.

Bulgular: Gen ve protein ekspresyonları hem tümör hem de eşlenik normal doku örneklerinin çoğunda saptandı. Gen ekspresyon düzeyleriyle klinikopatolojik ve demografik veriler arasında anlamlı ilişki saptanamadı. Örneklerin TNM evreleriyle perinöral invazyon ve lenfovasküler invazyon arasında anlamlı ilişki saptandı.

Sonuç: Bu çalışmanın sonuçları otofajinin kolorektal karsinogenezisde işe karıştığını önermektedir. Genişletilmiş çalışmaların yapılması otofaji ve kolorektal kanser ile ilişkili klinikopatolojik özellikleri belirlemede faydalı olabilecektir.

Anahtar kelimeler: ATG, Otofaji, Kolorektal kanser

How to cite / Atıf için: Sümbül HE, Akkız H. Importance of autophagy in colorectal cancer: A cross-sectional study. J Surg Med. 2019;3(3):246-249.

Introduction

Colon cancer is the third most common cancer among men and women worldwide. Approximately 1,200,000 new cases and 609,000 deaths per year are observed. It accounts for about 10% of all cancers in men and women. In the United States, CRC is responsible for 10% of new cancer cases and 9% of cancer-related deaths, according to 2009 data. Despite the current treatment regimens, 5-year survival expectancy does not exceed 30-40% [1].

The incidence of colon cancer has decreased in western countries as a result of effective care and lifestyle changes. The interaction of genetic and environmental factors has an important role in colorectal carcinogenesis. Although the molecular mechanism behind colorectal cancer (CRC) is better understood in the last two decades compared to other solid tumors, especially in advanced stages, its prognosis was not significantly improved. According to the Survey Epidemiology and Results (SEER) program database analysis, 5-year survival rates increased from 56.5% for patients diagnosed in the early 1980s to 63.2% for patients diagnosed in the early 1990s and to 64.9% with early diagnosis and treatment lately [2]. The incidence of colon cancer has decreased in the last 30 years and mortality has decreased by 35% between 1990 and 2007. Possible reasons for this are the improvements about early diagnosis and treatment [3].

Primary treatment of early-stage CRC is surgery and cure can be achieved with high possibility. However, the prognosis of recurrence and metastatic patients is poor and the median survival time is 24 months for these patients [4]. Approximately half of the patients develop metastasis. The main treatment option in these patients is chemotherapy. Response rates and life expectancy are increased with targeted therapy agents and new chemotherapy agents [5].

Median survival of patients with metastatic CRC (mCRC) does not exceed 24 months despite these new agents. This may be due to the lack of enough biomarkers to select patients who will benefit from these agents [6].

Disorders of cell death signaling are one of the most important obstacles to the curative treatment of cancer [7]. Autophagy was first identified in yeasts in the 1970s, and then observed as an evolutionary conserved programmatic cell death mechanism in mammals. Several studies have been conducted in recent years on the role of autophagy in carcinogenesis. In these studies, there is evidence that autophagy can serve as a mechanism for both the survival of cancer cells, the initiation of carcinogenesis and, in contrast, the elimination of cancer cells escaping apoptosis. Thus, it has been suggested that treatment can be accomplished by the manipulation of autophagy (inhibition or activation). However, the available data are still insufficient to clarify these questions. Many studies focus on this subject lately.

Autophagy means literally self-eating. Autophagy is known as the process of disintegrating long-lasting proteins, damaged organelles, microorganisms and viruses in the cell by transporting them to the lysosome [8,9]. Autophagy genes (ATG); play a role in the regulation of autophagy [10]. Autophagy is defined by the presence of double-membrane vesicles in the cytoplasm called autophagosomes. Recent studies have shown that autophagy plays a role in metabolism, cancer, neurodegenerative diseases, infections, morphogenesis, aging, cell death and immune system [11].

Autophagy has two opposite roles; both cell survival and cell death [12]. Autophagy is called "programmed cell death II" because it causes cell death [13]. As a result of studies that demonstrate the relationship between autophagy and cancer, drugs are being developed to target autophagy-signaling pathways as new treatment strategies in cancer. For example, mTOR inhibitors that mediate the autophagy pathway are clinically used to treat renal carcinoma [15].

The mutation of UVRAG gene is defined in colorectal and gastric cancers [15]. It has been suggested that UVRAG, Bif1 genes can suppress tumorogenesis and these two genes may be tumor suppressor genes [15,16]. Somatic mutations have been described in the Atg5 gene in hepatocellular and gastric cancer and in Atg2B, Atg5, Atg9B genes in colorectal and gastric cancers [9,17]. As a result of these studies, it has been argued that the expression of autophagic genes decreases in cancer cells and autophagy plays an important role in carcinogenesis as a tumor suppressing mechanism [18]. It is a hypothesis that the role of autophagy in cancer can be regulated by tumor suppressors and oncogenes and autophagy genes may be tumor suppressors at the molecular level [19,20].

Disorders in apoptotic mechanisms cause both abnormal proliferation and resistance to cytotoxic therapy. Therefore, in the last decade studies on new agents that induce apoptosis have intensified [21]. Although autophagic response to starvation in cancer cells is less prominent, it appears as an important survival mechanism in many tumor types [22]. It is thought that suppression of carcinogenesis can also be achieved with autophagy. Another mechanism for the destruction of cancer cells, which evade apoptosis, may be autophagy [23]. In this study, the relationship between the clinical and pathological features of colorectal cancer and autophagy were investigated.

Materials and methods

Collection of samples

Between January 2015 and March 2015, 45 patients who underwent surgery for CRC were included in this study. Thirty of the patients were male and 15 were female. Before the study, the approval was obtained from the ethics committee of Çukurova University Faculty of Medicine. Written informed consent was obtained from all participants. Demographic (age, gender), pathological features (tumor localization, histological type, differentiation, vascular and perineural invasion, lymph node involvement), clinical stage and laboratory results of the patients included in the study were recorded.

Gene expression

We use chemicals such as TRIZOL (Guanidinium thiocyanate-phenol chloroform), Chloroform, %75 ethanol, İzopropanol and DEPC-water. For cDNA Synthesis we use PCR. Before starting the cDNA analysis, the total amount of RNA in each sample was determined using Nano drop to ensure the equalize reaction conditions of the samples. Accordingly, cDNA analysis is started by taking the determined volumes from the

tubes. The total amount of RNA from each tube should be 1000 ng/ul.

Protein Isolation

RIPA solution is placed according to the amounts in the tube and crushed on ice with homogenization bars. After dissolving well, it is centrifuged at maximum speed (14000 rpm) for 15 minutes. The supernatant between the top layer of fat and the bottom pellet is obtained. Proteins are in this supernatant. 1 ml of this supernatant and 29 ml of distilled water are added into the new tube to determine the total amount of protein in the spectrometer. 10 ml of this new heterogeneous mixture is taken and after adding 190 ml Bradfort solution the specimen is measured on the 595 nm wavelength spectrometer.

Statistical Analysis

In the statistical analysis of the data, SPSS package program was used. Descriptive statistics were expressed as number and percentage (%) for categorical measurements, mean and standard deviation for continuous measurements (median and minimum-maximum where necessary). In the comparison of continuous measurements between groups, distributions were checked and one-way Anova test was used for the parameters that are normally distributed according to the variables. Chi-square test statistics was used to compare categorical variables.

Results

In this study, 45 patients were included. Demographic and clinical data's of the study were given in Table 1. Thirty patients were male and fifteen were female. Before starting the study, approval was obtained from the ethics committee of Çukurova University Faculty of Medicine. Written informed consent was obtained from all patients.

Table 1: Demographic, clinical and pathological data

	n	%
Gender		
Female	15	33.33
Male	30	66.66
Localization		
Rectum	18	40.0
Cecum	5	11.1
Ascending colon	9	20.0
Sigmoid	10	22.2
Descending	1	2.2
Transvers	2	4.4
Histology		
Adenocarcinoma	41	91.1
Mucinous adenocarcinoma	1	2.2
Lymphovascular invasion		
Positive	37	82.2
Negative	5	11.1
Perineural invasion		
Positive	20	44.4
Negative	22	48.8
Histological Grade		
High	5	11.1
Low	36	80

RNA and protein expression were evaluated in twenty patients included in the study. Fifteen patients (75%) had low histologic grade and five patients (25%) had a higher histologic grade. The expression of ATG5, ATG12 and Becklin-1 was analyzed by SYBR Green qPCR in both tumor tissues and intact tissues of these patients. The quantification of the reference and target genes by using the cycle threshold (Ct) values obtained from the device was calculated and quantified. We referenced the GAPDH gene and the results were normalized to the intact tissue of patient number fifteen. Two patients were excluded on the basis of the inadequate RNA content of 1 (5%) low histological grade and 1 (5%) high histological grade of the gene expression before the cDNA synthesis phase.

There was no significant correlation between lymphovascular and perineural invasion and histological grade (p=0.104 and p=0.666, respectively). The relationship between TNM stages and perineural invasion and lymphovascular invasion was statistically significant (p=0.014). Becklin-1 gene expression with SYBR Green qPCR method in tumor tissue and intact tissue showed no significant correlation between TNM levels (p=0.093). Becklin-1 gene expression with SYBR Green qPCR method in tumor tissue and intact tissue showed no significant correlation with lymphovascular invasion (p=0.756). There was no significant relationship between ATG5 gene expression and TNM levels in tumor tissue and intact tissue by the SYBR Green qPCR method (p=0.055). There was no significant relationship between ATG12 gene expression in tumor tissue and intact tissue with TNPR Green qPCR method (p=0.292).

Discussion

CRC occurs as a result of the transformation of normal colon mucosa into invasive cancer with the accumulation of step by step genetic and epigenetic changes. Most of the CRC develops from adenomas that already exist and include the genetic characteristics of malignancy [24].

Autophagy has two opposite roles in cell death and life. Debates about the role of autophagy in cancer continue. Autophagy development suppresses the tumorigenic activity of cancer cells and inactivation of autophagy increases the tumor development as in the case of Beclin1 and UVRAG. However, blockade of autophagy makes resistant cells sensitive to radiotherapy [15].

Furthermore, the expression of Beclin1 and LC3 protein, which are autophagy-related proteins, up regulated in colon and gastric cancers indicates compensatory overexpression due to ATG mutations. These data indicate that autophagy genes have different roles in cell death and life depending on the content of the cell. In addition, autophagy is likely to have different roles in the progression of cancer and the treatment of cancer. Further functional studies are needed to investigate the contribution of mutations in ATG genes to the development, progress and treatment of cancer [22].

Especially in patients receiving metastatic CRC treatment, 5-year survival rates and treatment responses cannot exceed a certain percentage. The etiology, mechanisms of action and the role of autophagy in the progression of CRC are therefore important [5,6]. In this study, we tried to determine the role of autophagy in tumor samples of patients with CRC. The presence of autophagy in both normal and cancerous tissue may be due to changes in colorectal carcinogenesis in both tissues.

Limitation

The results we found in our study should be confirmed with larger patient series. However, the relationship between autophagy and CRC clinical characteristics can be better elucidated by planning the studies to eliminate the evaluation errors caused by the number of samples resulting from sub-groups by increasing the number of samples.

Conclusion

In addition to contributing to both tumor development and progression, autophagy has a negative effect on tumor development. In our study, ATG5, ATG12 and LC3 protein expression levels and ATG5, ATG12 and Beclin-1 RNA expression levels related to autophagy pathway, which is thought to have an important role in the early stages of cancer formation and in the progression of advanced cancers both in tumor tissue and conjugated normal colon.

RNA and protein expressions were detected in both tumor tissue and normal tissue. These results were compared with the demographic and histopathological features of the patients and there was no significant relationship between them.

As in all cancers, CRC requires more specific and less toxic treatment options. By identifying the characteristics of CRC and autophagy, it will be possible to reveal new markers and treatment options that include especially tumor development, prognosis, metastasis and treatment. In our study, optimal conditions were obtained in terms of study techniques and tissues were stored peroperatively and stored in liquid nitrogen until protein and RNA expression analyzes were performed. The tissues taken in the operating room were transferred to liquid nitrogen tanks where they were placed in Cryo tubes without being wasted at any time.

Acknowledgments

We would like to thank the participants in the study, our colleagues, Devrim Gözüaçık and his laboratory team from Sabancı University for their cooperation.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60(5):277-300.
2. Miller BA, Chu KC, Hankey BF, Ries LA. Cancer incidence and mortality patterns among specific Asian and Pacific Islander populations in the U.S. Cancer Causes Control. 2008;19(3):227-56.
3. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin. 2011;61(4):212-36.
4. Poston GJ, Figueras J, Giuliante F, Nuzzo G, Sobrero AF, Gigot JF, et al. Urgent need for a new staging system in advanced colorectal cancer. J Clin Oncol. 2008;26(29):4828-33.
5. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004;22(2):229-37.
6. Prenen H, Vecchione L, Van Cutsem E. Role of targeted agents in metastatic colorectal cancer. Target Oncol. 2013;8(2):83-96.
7. Melet A, Song K, Bucur O, Jagani Z, Grassian AR, Khosravi-Far R. Apoptotic pathways in tumor progression and therapy. Adv Exp Med Biol. 2008;615:47-79.
8. Eisenberg-Lerner A, Kimchi A. The paradox of autophagy and its implication in cancer etiology and therapy. Apoptosis. 2009;14(4):376-91.
9. Kang MR, Kim MS, Oh JE, Kim YR, Song SY, Kim SS, et al. Frameshift mutations of autophagy-related genes ATG2B, ATG5, ATG9B and ATG12 in gastric and colorectal cancers with microsatellite instability. J Pathol. 2009;217(5):702-6.
10. Kim MS, Song SY, Lee JY, Yoo NJ, Lee SH. Expressional and mutational analyses of ATG5 gene in prostate cancers. APMIS. 2011;119(11):802-7.
11. Cao Y, Klionsky DJ. Physiological functions of Atg6/Beclin 1: a unique autophagy-related protein. Cell Res. 2007;17(10):839-49.
12. Baehrecke EH. Autophagy: dual roles in life and death? Nat Rev Mol Cell Biol. 2005;6(6):505-10.
13. Hannigan AM, Gorski SM. Macroautophagy: the key ingredient to a healthy diet? Autophagy. 2009;5(2):140-51.
14. LoRusso PM. Mammalian target of rapamycin as a rational therapeutic target for breast cancer treatment. Oncology. 2013;84(1):43-56.
15. Knaevelsrud H, Ahlquist T, Merok MA, Nesbakken A, Stenmark H, Lothe RA, et al. UVRAG mutations associated with microsatellite unstable colon cancer do not affect autophagy. Autophagy. 2010;6(7):863-70.
16. Furuya N, Yu J, Byfield M, Pattingre S, Levine B. The evolutionarily conserved domain of Beclin 1 is required for Vps34 binding, autophagy and tumor suppressor function. Autophagy. 2005;1(1):46-52.
17. Akar U, Chaves-Reyez A, Barria M, Tari A, Sanguino A, Kondo Y, et al. Silencing of Bcl-2 expression by small interfering RNA induces autophagic cell death in MCF-7 breast cancer cells. Autophagy. 2008;4(5):669-79.
18. Hippert MM, O'Toole PS, Thorburn A. Autophagy in cancer: good, bad, or both? Cancer Res. 2006;66(19):9349-51.
19. Wei H, Guan JL. Pro-tumorigenic function of autophagy in mammary oncogenesis. Autophagy. 2012;8(1):129-31.
20. Gong C, Bauvy C, Tonelli G, Yue W, Delomenie C, Nicolas V, et al. Beclin 1 and autophagy are required for the tumorigenicity of breast cancer stem-like/progenitor cells. Oncogene. 2013;32(18):2261-72,72e 1-11.
21. Fesik SW. Promoting apoptosis as a strategy for cancer drug discovery. Nat Rev Cancer. 2005;5(11):876-85.
22. Gozuacik D, Kimchi A. Autophagy as a cell death and tumor suppressor mechanism. Oncogene. 2004;23(16):2891-906.
23. Paglin S, Hollister T, Delohery T, Hackett N, McMahill M, Sphicas E, et al. A novel response of cancer cells to radiation involves autophagy and formation of acidic vesicles. Cancer Res. 2001;61(2):439-44.
24. Al-Sohaily S, Biankin A, Leong R, Kohonen-Corish M, Warusavitarne J. Molecular pathways in colorectal cancer. J Gastroenterol Hepatol. 2012;27(9):1423-31.

J Surg Med. 2019;3(3):250-253.
DOI: 10.28982/josam.519328

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Investigation of concordance between referral diagnosis and electroneuromyographic diagnosis

Klinik ön tanı ile elektronöromiyografik tanı uyumunun araştırılması

Ali Rıza Sonkaya [1], Mustafa Karaoğlan [2]

[1] Okmeydani Training and Research Hospital, Department of Neurology, Istanbul, Turkey
[2] Ankara Training and Research Hospital, Department of Neurology, Ankara, Turkey

ORCID ID of the author(s)
ARS: 0000-0001-9218-4502
MK: 0000-0001-9420-2663

Corresponding author / Sorumlu yazar:
Ali Rıza Sonkaya
Address / Adres: Okmeydani Eğitim ve Araştırma Hastanesi, Nöroloji Anabilim Dalı, İstanbul, Türkiye
e-Mail: drsonkay@gmail.com

Ethics Committee Approval: The study was approved by local ethics committee (Protocol no: 48670771-514.10).
Etik Kurul Onayı: Çalışma yerel etik kurul tarafından onaylandı (Protokol no: 48670771-514.10).

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 29.01.2019
Accepted / Kabul Tarihi: 12.03.2019
Published / Yayın Tarihi: 13.03.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Abstract

Aim: Electroneuromyography (ENMG) is an electrophysiological method of examination for neurophysiological state of motor neuron, peripheral nerve and muscle functions. This study was aimed to investigate the concordance of between referral diagnosis and ENMG diagnosis in patients referred to the electrophysiology laboratory.

Methods: A retrospective cohort study is planned. Patients, whose evaluations of ENMG were requested by the orthopedic, neurology and physical therapy and rehabilitation physicians between June 2015 and December 2018, were included in this study. Descriptive statistics and Cohen's Kappa Test were run for data set analysis.

Results: A total of 486 patients are included in the study. Of the 486 patients undergoing ENMG examination, 362 were female (74.5%) and 124 were male (25.5%). The mean age was 46.71±12.41. 35.2% (n=171) of the referral diagnoses were requested by orthopedics, 32.7% (n=159) by physical therapy and rehabilitation and 32.1% (n=156) by neurology clinics. When the consistency between the preliminary diagnosis and post-ENMG diagnosis was examined; 65.4% of the results were found to be compatible. According to the clinics; 76.3% of the requests referred by the neurology clinic and 64.8% of the requests referred by the physical therapy and rehabilitation clinic, 56.1% of the requests referred by the orthopedic clinic were confirmed by ENMG. As a result of the Cohen's Kappa test, the total (κ) correlation between clinical preliminary diagnosis and ENMG diagnosis was found to be 0.574 ($p<0.001$). These findings demonstrated a moderate (0.41-0.60) concordance. When examined according to the clinics, compliance values; for the orthopedic clinic were 0.484 ($p<0.001$), 0.571 for the physical therapy and rehabilitation clinic ($p<0.001$) and 0.685 for the neurology clinic ($p<0.001$).

Conclusion: This study confirmed that ENMG should be considered as an extension of neurological examination.

Keywords: Electroneuromyography, Clinical preliminary diagnosis

Öz

Amaç: Elektronöromiyografi (ENMG) motor nöron, perifer sinir ve kas fonksiyonlarının nörofizyolojik olarak değerlendirilmesinde kullanılan yöntemdir. Bu retrospektif çalışmada Nörofizyoloji laboratuvarında değerlendirilmiş olan hastaların klinik ön tanıları ile ENMG tanıları arasındaki uyumun araştırılması amaçlanmıştır.

Yöntemler: Çalışmada, Haziran 2015- Aralık 2018 yılları arasında Ortopedi, Nöroloji ve Fizik Tedavi ve Rehabilitasyon (FTR) uzmanları tarafından ENMG istemleri yapılmış olan 486 hastanın sonuçları, ön tanı ile elektrodiagnostik uyumluluğu açısından retrospektif olarak incelendi. Verilerin analizinde betimsel istatistik ve Cohen's Kappa Testi kullanıldı. ENMG incelemesi yapılan toplam 486 hastanın 362'si kadın (%74,5), 124'ü erkekti (%25,5) ve hastaların yaş ortalaması 46.71±12.41 idi.

Bulgular: Hastaların %35,2'sinin (n=171) istemi Ortopedi, %32,7'sinin (n=159) istemi FTR, %32,1'inin (n=156) istemi Nöroloji kliniklerinden yapılmıştı. En çok ön tanı Karpal Tünel Sendromu (%44,4) idi. Ön tanılar ile ENMG sonrasında raporlanan tanılar arasındaki tutarlılık incelendiğinde; sonuçların %65,4 oranında uyumlu olduğu görüldü. Kliniklere göre değerlendirme yapıldığında ise Nöroloji kliniğince yapılan isteklerin %76,3'ü, FTR kliniğince yapılan isteklerin %64,8'i ve Ortopedi kliniğince yapılan isteklerin %56,1'i ENMG ile doğrulanmıştı. Ön tanıların ENMG ile desteklenme oranları incelendiğinde; peroneal nöropati (%78,8) en yüksek orana sahipti. Chen's Kappa testi sonucunda toplamda klinik ön tanılar ile ENMG tanıları arasındaki uyum (κ) değeri 0,574 olarak bulundu ($p<0,001$). Bu, orta düzeyde (0,41-0,60) bir uyumu gösteriyordu. Kliniklere göre incelendiğinde ise uyum değerleri; Ortopedi kliniği için 0,484 ($p<0,001$), FTR kliniği için 0,571 ($p<0,001$) ve Nöroloji kliniği için 0,685 ($p<0,001$) idi.

Sonuç: Bu çalışma ENMG'nin nörolojik muayenenin bir uzantısı olarak görülmesi gerektiğini doğruladı.

Anahtar kelimeler: Elektronöromiyografi, Klinik ön tanı

How to cite / Atıf için: Sonkaya AR, Karaoğlan M. Investigation of concordance between referral diagnosis and electroneuromyographic diagnosis. J Surg Med. 2019;3(3):250-253.

Introduction

Electroneuromyography (ENMG) is an electrophysiological method of examination for neurophysiological state of motor neuron, peripheral nerve and muscle functions. Although an important diagnostic tool such as genetic examination and fast-growing imaging techniques nowadays, ENMG has frequently been used examination and treatment response of entrapment neuropathies, anterior horn motor neuron disease, neuropathy, polyneuropathy, radiculopathy, nerve muscle junction disease and muscle diseases since the year 1940 [1,2]. ENMG still maintains its importance despite advanced diagnostic tools also it is considered as the gold-standard tool to evaluate the nerve function [3,4]. Main parameters of the electrophysiological studies are latency, amplitude and conduction velocity. Furthermore, ENMG can identify subclinical changes in nerve functions at up to 12 weeks before becoming clinically detectable [5].

ENMG provides significant information about the diagnosis and differentiation of peripheral nerve diseases, muscle diseases, radiculopathy, motor neuron diseases and motor endplate diseases, determination of their severity and prevalence, localization of the lesion and prediction of prognosis [6,7]. In addition, ENMG contributes the proper and effective use of other laboratory tests, guides the selection and planning of medical or surgical treatments and has an important role in the follow-up of the response to treatment [4,8]. Therefore, ENMG is accepted as a continuation of the neurological examination of the clinicians. In addition to directing the clinician to a correct diagnosis, the patient also provides the opportunity for better clinical improvement [1,9].

In addition to neurologists, ENMG is a valid technique in the diagnosis of many diseases which affects peripheral nervous system either alone or by ancillary methods for many clinicians in different areas such as neurosurgery, physical therapy and rehabilitation and orthopedics [10].

ENMG is an experience that can be uncomfortable for the patient due to its electrical stimulation and needle inspection requirement [11]. In addition, the clinical findings of the patient before the ENMG and the preliminary diagnosis of the referring physician should be taken into consideration [12]. For this reason, it is very important to be known the clinical findings and referral diagnosis [13]. Referring the patient without preliminary diagnosis to ENMG examination, it can be resulted in unnecessary prolongation of the procedure and unnecessary procedures for the patient [14]. These procedures can be reduced the value of electro-diagnostic test and results in elongation of waiting time, unnecessary patient intensity, lots of time and sources [7].

Concordance between preliminary diagnosis and post-ENMG diagnosis of patients has been discussed in many studies. Different consistency rates were determined in these studies [3,9]. It is thought that the present study will contribute to the existing literature. Therefore, this retrospective study was aimed to investigate the concordance of the referral diagnosis and post-ENMG diagnosis of patients referred to the electrophysiology laboratory.

Materials and methods

This study was conducted at Health Science University Okmeydani Training and Research Hospital. The patients, aged between 18 and 85 years, whose ENMG evaluations were requested by the orthopedic, neurology and physical therapy and rehabilitation physicians between June 2015 and December 2018 were included in the study.

All laboratory procedures had been carried out using the MEDELEC Synergy ENMG instrument. All ENMG recordings were performed by the same experienced researcher and if it was a needle ENMG, it was performed with a concentric needle electrode. It was followed to be the guidelines recommended on the basis of clinical findings and preliminary diagnosis for selection of nerve conduction studies [2]. The study was approved by local ethics committee (Protocol no: 48670771-514.10).

Demographic data, techniques used during ENMG, referral diagnoses and post-ENMG diagnoses were all recorded for each patient. The referral diagnoses and post-ENMG diagnoses were classified into groups. The consistency between referring diagnosis and post-ENMG diagnosis was compared. For the purpose of comparison, 'consistency' was described as a similarity between the referral diagnosis and the post-ENMG diagnosis. 'Inconsistency' was described as the difference between the referral diagnosis and the post-ENMG diagnosis or a normal ENMG result.

Statistical analysis

SPSS 25.0 for Windows (Statistical Package for Social Sciences Inc. Chicago, IL, USA) is used for analysis. Statistical analysis of the data was performed using descriptive statics and Cohen's Kappa Test. Cohen's Kappa Test is a statistical measure created by Jacob Cohen in 1960 to be a more accurate measure of reliability between two raters making decisions about how a particular unit of analysis should be categorized [15]. Kappa measures not only the percentage of agreement between two raters; it also calculates the degree to which agreement can be attributed to chance [16].

Results

A total of 486 patients undergoing ENMG examination included in the study, 362 were female (74.5%) and 124 were male (25.5%). The mean age was 46.71±12.41 (range 18-84). 35.2% (n=171) of the referral diagnoses were requested by orthopedics, 32.7% (n=159) by physical therapy and rehabilitation and 32.1% (n=156) by neurology clinics.

According to frequency sequence, the preliminary diagnoses of the ENMG request was followed as Carpal tunnel syndrome (CTS) in 216 (44.4%), ulnar entrapment neuropathy in 78 (16.0%), polyneuropathy in 75 (15.4%), peroneal neuropathy in 66 (13.6%) and brachial plexopathy in 51 (10.5%).

Post-ENMG diagnosis were found to be 147 (30.2%) for carpal tunnel syndrome, 138 (28.4%) for normal, 54 (11.1%) for polyneuropathy, 52 (10.7%) for peroneal neuropathy, 40 (8.2%) for brachial plexopathy, 39 (8.0%) for ulnar entrapment neuropathy and 16 (3.3%) for others.

When the consistency between the referral diagnoses and post-ENMG diagnoses ratio were examined; the

concordance ratio was found to be 78.8% (n=52) for peroneal neuropathy, 70.6% (n = 36) for brachial plexopathy, 68.1% (n=147) for carpal tunnel syndrome, 58.7% (n=44) for polyneuropathy and 50% (n=39) for ulnar entrapment neuropathy. The compliance rate was 65.4% (n=318) in all patients (Table 1).

Table 1: Concordance of clinical preliminary diagnosis and ENMG diagnosis

Clinic	Diagnosis	Number of requests (n=486)		Confirmed with ENMG (n=318)		Unconfirmed with ENMG (n=168)	
		n	%	N	%	n	%
Orthopedy	Ulnar entrapment neuropathy	33	19.3	12	36.4	21	63.6
	Carpal tunnel syndrome	66	38.6	42	63.6	24	36.4
	Brachial plexopathy	24	14.0	15	62.5	9	37.5
	Polyneuropathy	27	15.8	9	33.3	18	66.7
	Peroneal neuropathy	21	12.3	18	85.7	3	14.3
	Total of Clinic	171	100.0	96	56.1	75	43.9
Neurology	Ulnar entrapment neuropathy	18	11.5	15	83.3	3	16.7
	Carpal tunnel syndrome	81	51.9	60	74.1	21	25.9
	Brachial plexopathy	12	7.7	12	100.0	0	0.0
	Polyneuropathy	21	13.5	14	66.7	7	33.3
	Peroneal neuropathy	24	15.4	18	75.0	6	25.0
	Total of Clinic	156	100.0	119	76.3	37	23.7
Physical Medicine and Rehabilitation	Ulnar entrapment neuropathy	27	17.0	12	44.4	15	55.6
	Carpal tunnel syndrome	69	43.4	45	65.2	24	34.8
	Brachial plexopathy	15	9.4	9	60.0	6	40.0
	Polyneuropathy	27	17.0	21	77.8	6	22.2
	Peroneal neuropathy	21	13.2	16	76.2	5	23.8
	Total of Clinic	159	100.0	103	64.8	56	35.2
Total	Peroneal neuropathy	66	13.6	52	78.8	14	21.2
	Brachial plexopathy	51	10.5	36	70.6	15	29.4
	Carpal tunnel syndrome	216	44.4	147	68.1	69	31.9
	Polyneuropathy	75	15.4	44	58.7	31	41.3
	Ulnar entrapment neuropathy	78	16.0	39	50.0	39	50.0
	Total	486	100.0	318	65.4	168	34.6

As a result of the Cohen's Kappa test, the total (κ) correlation between clinical preliminary diagnoses and post-ENMG diagnoses were found to be 0.574 (p<0.001). These findings demonstrated a moderate (0.41-0.60) concordance.

When examined according to the clinics, compliance value (κ) was found to be 0.484 (p<0.001) for the orthopedic clinic (n=171) and 0.571 (p<0.001) for the physical therapy and rehabilitation clinic (n=159). It was observed a moderate concordance between referral diagnosis and post-ENMG diagnosis in these two clinics. As for ENMG requests of patients in the neurology clinic (n=156), compliance value (κ) was found to be 0.685 (p<0.001) between referral diagnosis and ENMG diagnosis. According to these findings, it was observed a concordance (0.41-0.60) at good level (Table 2).

Table 2: Concordance of referral diagnosis and post-ENMG diagnosis according to Cohen's Kappa Test

Clinic	Diagnosis	ENMG Diagnosis (1)	(2)	(3)	(4)	(5)	Other	Normal	Total	Cohen's Kappa Test	p
Orthopedic	Ulnar entrapment neuropathy (1)	12	0	4	0	0	5	12	33	0.484	<0.001
	Carpal tunnel syndrome (2)	0	42	0	3	0	0	21	66		
	Brachial plexopathy (3)	0	0	15	0	0	3	6	24		
	Polyneuropathy(4)	0	0	0	9	0	0	18	27		
	Peroneal neuropathy (5)	0	0	0	3	18	0	0	21		
	Total of Clinic	12	42	19	15	18	8	57	171		
Neurology	Ulnar entrapment neuropathy (1)	15	0	0	0	0	0	3	18	0.685	<0.001
	Carpal tunnel syndrome (2)	0	60	0	1	0	2	18	81		
	Brachial plexopathy (3)	0	0	12	0	0	0	0	12		
	Polyneuropathy(4)	0	0	0	14	0	0	7	21		
	Peroneal neuropathy (5)	0	0	0	0	18	3	3	24		
	Total of Clinic	15	60	12	15	18	5	31	156		
Physical Medicine and Rehabilitation	Ulnar entrapment neuropathy (1)	12	0	0	0	0	1	14	27	0.571	<0.001
	Carpal tunnel syndrome (2)	0	45	0	3	0	0	21	69		
	Brachial plexopathy (3)	0	0	9	0	0	0	6	15		
	Polyneuropathy(4)	0	0	0	21	0	0	6	27		
	Peroneal neuropathy (5)	0	0	0	0	16	2	3	21		
	Total of Clinic	12	45	9	24	16	3	50	159		
Total	Ulnar entrapment neuropathy (1)	39	0	4	0	0	6	29	78	0.574	<0.001
	Carpal tunnel syndrome (2)	0	147	0	7	0	2	60	216		
	Brachial plexopathy (3)	0	0	36	0	0	3	12	51		
	Polyneuropathy(4)	0	0	0	44	0	0	31	75		
	Peroneal neuropathy (5)	0	0	0	3	52	5	6	66		
	Total of Clinic	39	147	40	54	52	16	138	486		

Discussion

According to our results, 35.2% (n=171) of the referral diagnosis were requested by orthopedics, 32.7% (n=159) by physical therapy and rehabilitation and 32.1% (n=156) by neurology clinics. The referral diagnosis of the ENMG request was existed; carpal tunnel syndrome in 216 (44.4%), ulnar entrapment neuropathy in 78 (16.0%), polyneuropathy in 75 (15.4%), peroneal neuropathy in 66 (13.6%) and brachial plexopathy in 51 (10.5%). The highest ratio of carpal tunnel syndrome was found to be compatible and 44.4% ratio was similar with the literature. Otherwise, post-ENMG diagnosis were found to be 30.2% for carpal tunnel syndrome, 11.1% for polyneuropathy, 10.7% for peroneal neuropathy, 8.2% for brachial plexopathy, 8.0% for ulnar entrapment neuropathy and 3.3% for others. According to these findings the highest ratio was found to be in carpal tunnel syndrome, and it was in a line with the literature. Even so, this ratio was lower than the previous studies [1,4,8].

Frequency sequence of other referral diagnosis was found to be generally different from the literature. For example, ulnar entrapment neuropathy was found to be second and polyneuropathy was found to be third common in our study while polyneuropathy was found to be second and ulnar entrapment neuropathy was found to be fourth common in study which was carried out by Okuyucu et al [1] and Türkel et al [4]. In addition, in our study the ratio of polyneuropathy was found to be 15.4% in referral diagnosis which was higher than the ratios of Atalay et al [8] (8.3%) and Ustaömer et al [7] (14%). Also, in this study the ratio of polyneuropathy was found to be lower when compared to the ratios of Okuyucu et al [1] and Türkel et al [4], which were reported 17.1% and 27.7% in these studies, respectively.

The ratio of ulnar entrapment neuropathy was 16% within referral diagnosis in this study. This ratio was higher when compared to previous studies carried out by Okuyucu et al [1], Türkel et al [4] and Atalay et al [8]. The ratios were reported 7.3%, 6.6% and 9.5% in these studies, respectively.

When the consistency between the preliminary diagnosis and post-ENMG diagnosis was examined; 65.4% of the results were found to be compatible. Although, this ratio was found to be in a parallel way with the literature, it was also higher than the results of previous studies [1,4,7,8].

When the consistency between the referral diagnoses and the reported diagnoses post- ENMG ratio was examined; the concordance ratio was found to be 78.8% for peroneal neuropathy, 70.6% for brachial plexopathy, 68,1% for carpal tunnel syndrome, 58,7% for polyneuropathy and 50% for ulnar entrapment neuropathy. According to the clinics; 76.3% of the requests sent by the neurology clinic and 64.8% of the requests sent by the physical therapy and rehabilitation clinic, 56.1% of the requests sent by the orthopedics clinic were confirmed by ENMG.

As a result of the Cohen's Kappa test, which excludes the chance factor, the total (κ) correlation between clinical preliminary diagnoses and ENMG diagnoses was found to be 0.574 (p<0.001). This demonstrated a moderate (0.41-0.60) concordance. When examined according to the clinics,

compliance values were found to be 0.484 ($p<0.001$) for the orthopedic clinic, 0.571 for the physical therapy and rehabilitation clinic ($p<0.001$) and 0.685 ($p<0.001$) for the neurology clinic. These findings demonstrated a good level concordance between referral diagnosis and ENMG in neurology clinic, and also showed moderate levels in other clinics.

In conclusion, our results confirmed that ENMG is an extension of neurological examination. Especially, the ratio as a 76.3% and Kappa value as a 0.65 was found in this study and these findings supported a good level concordance between referral diagnosis and ENMG in neurology clinic. However, in this study it was also found to be 23.7% for inconsistency Kappa value. This relatively low Kappa value demonstrated the inconsistency which is not underestimate and necessity of its shortened. We believe that it can be increased by taking precautions such as taking the detailed medical history and physical examination of the patients.

References

1. Okuyucu EE, Turhanoğlu AD, Duman T, Savaş N, Mengüllüoğlu N, Melek İM. Klinik ve elektrofizyolojik tanılar arasındaki tutarlılık. J Türk Nöroloji Dergisi. 2009;15(3):129-33.
2. Shapiro B, Katirji B, Preston D. Clinical electromyography. J Neuromuscular disorders in clinical practice. 2002:80-140.
3. Porto FHDG, Porto GCLM, Brotto MWL. Additional tests to investigate neuropathic pain. The value of electroneuromyography for neuropathic pain. J Revista Dor. 2016;17:23-6.
4. Türkel Y, Sandıkçı U, Er D, Yazıcı T, Bayrak AO, Türker HY. Elektronöromiyografik İnceleme Ne Kadar Uyumlu? J Clin Anal Med. 2014;5(5):366-8.
5. Lima PODP, Cunha FMB, Goncalves HDS, Aires MAP, De Almeida RLF, Kerr LRFS. Correlation between clinical tests and electroneuromyography for the diagnosis of leprosy neuropathy. J Leprosy review. 2016;87(1):60-71.
6. On AY. Bel ve boyun ağrılarında elektronöromiyografi. TOTBID Dergisi. 2017;16:97-102.
7. Ustaömer K, Sarıfakıoğlu AB. Ön Tanı-Elektrodiyagnostik Tanı; Ne Kadar Uyumlu? Namık Kemal Tıp Dergisi. 2018;6(1):1-8.
8. Atalay NŞ, Akkaya N, Şahin F. Klinik ön tanı ile elektronöromiyografik tanı uyumunun araştırılması. J AJCI. 2012;6(2):113-6.
9. Azabou E, Fischer C, Guerit JM, Annane D, Mauguiere F, Lofaso F, et al. Neurophysiological assessment of brain dysfunction in critically ill patients: an update. J Neurological Sciences. 2017;38(5):715-26.
10. Robinson LR. Role of neurophysiologic evaluation in diagnosis. J JAAOS-Journal of the American Academy of Orthopaedic Surgeons. 2000;8(3):190-9.
11. Preston DC, Shapiro BE. Electromyography and Neuromuscular Disorders E-Book: Clinical-Electrophysiologic Correlations (Expert Consult-Online): Elsevier Health Sciences; 2012.
12. Adam M, Leblebıcı B, Bağş S, Akman MN. Elektronöromiyografik İnceleme İsteminin Uygunluğu. J Turkish Journal of Physical Medicine Rehabilitation /Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi. 2007;53(4).
13. Medicine AAOE, Nerve. Guidelines in electrodiagnostic medicine. J Muscle. 1992;15(2):229-53.
14. Yağci İ, Ofluoğlu D, Gündüz H, Güven Z, Berker N, Akyüz G. Pediatrik Olgularda Klinik Ön Tanı ve Elektrofizyolojik Tanıların Uyumu. J Turkish Journal of Physical Medicine Rehabilitation. 2008;54(3).
15. Bayazıt ZZ. The Use of Functional Near Infrared Spectroscopy Technique in the Field of Neurolinguistics. Edt. Murat Cem Demir. Gece Publication, Ankara, Turkey, 2018.
16. Kılıç S. Kappa Testi. Journal of Mood Disorders. 2015;5(3):142-4.

J Surg Med. 2019;3(3):254-257.
DOI: 10.28982/josam.537201

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Variations of tuberculin skin test in patients with rheumatologic disorders and under anti-TNF treatment

Anti-TNF tedavisi uygulanan romatoloji hastalarında Tüberkülin deri testi seviyelerinin değişimi

Tayfun Özdemir [1], Serpil Tuna [1], Özlem Karataş [2], Mehmet İhsan Arman [1]

[1] Akdeniz University, Medical School, Department of Physical Medicine and Rehabilitation Antalya, Turkey
[2] University of Health Sciences, Antalya Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Antalya, Turkey

ORCID ID of the author(s)
TÖ: 0000-0002-1999-7002
ST: 0000-0001-8717-1141
ÖK: 0000-0003-3053-9333
MİA: 0000-0002-3433-8101

Abstract

Aim: Nowadays PPD is the most inexpensive and easy to apply modality of test in identification of latent tuberculosis infection. Isoniazid (INH) prophylaxis must be given before usage of anti-TNF-α agents for patients. We aimed to investigate the change in Tuberculin skin test (TST) levels and Isoniazid (INH) prophylaxis rates in patients with inflammatory rheumatic diseases treated with anti-tumor necrosis factor alpha (TNF-α) agents.

Methods: A cross-sectional study was planned. Patients with inflammatory rheumatic diseases treated with anti-TNF agents were included in the study. Demographic data, initial TST level and INH prophylaxis had obtained from patient's files. Control TST tests had done at tuberculosis dispensaries in different time periods such as 1-2 / 2-3 / 3-4 / ≥4 years of anti TNF treatment. INH prophylaxis rates according to initial and control TST tests were compared. The relationship between INH prophylaxis and duration of anti-TNF therapy were examined.

Results: A total of 117 patients were included in the study. The mean age of the patients (81 male, 36 female) was 40.4±12.90. The control TST levels was significantly higher than initial TST (p=0.001). INH prophylaxis was given to total 99 (84.6%) of 117 patients (to 63 (53.8%) according to initial and to 36 (30.8%) according to control TST tests). There was no relationship between duration of anti TNF therapy and INH prophylaxis initiation (p=0.180).

Conclusion: Anti-TNF treatments may reduce the rates of false-negative TST in patients with rheumatic diseases and latent tuberculosis (LTBI) at any stage of the treatment. Therefore, LTBI, which is not determined with initial TST tests, may be determined with TST test applied in the later stages of anti-TNF treatment, and the risk of active tuberculosis can be reduced by INH prophylaxis in this patients.

Keywords: Tumor necrosis factor inhibitors, Rheumatic diseases, Tuberculin skin test, Tuberculosis, Minor side effect

Öz

Giriş: Günümüzde Latent tüberküloz tanısında kullanılan en ucuz ve kolay uygulanan test PPD'dir. Öneriler doğrultusunda anti TNF ajanlarla tedavi öncesi izoniazid (İNH) profilaksisi verilmektedir.

Amaç: Çalışmamızda anti TNF-α tedavisi alan enflamatuvar romatizmal hastalığı olan hastalarda tedavi öncesi tüberkülin deri testi (PPD) düzeyleri ve anti TNF-α tedavisi sırasındaki kontrollerde tekrarlanan PPD düzeyindeki değişimleri değerlendirilmesi amaçladık.

Yöntemler: Çalışamaya anti-TNF tedavisi alan enflamutuvar romatizmal hastalığı olan toplam 117 hasta dahil edilmiştir. Anti TNF ilaç kullanan hastaların tedavi öncesi rutin olarak bakılan PPD düzeyleri, kontrollerde tekrarlanan PPD değişimleri, başlangıç ve kontrol PPD sonuçlarına göre İNH profilaksisi başlanma oranları değerlendirildi.

Bulgular: Çalışmamızda anti TNF ilaç kullanan 117 hastanın yaş ortalaması (81 erkek, 36 kadın) 40.4±12.90. Anti TNF ilaç kullanımı sonrası kontrol PPD ortalamasında başlangıç PPD seviyeleri ortalamasına göre istatistiksel olarak anlamlı bir artış saptandı. (p=0,001) Çalışmamıza alınan 117 hastanın 99'una (%84,6) İNH profilaksisi verilmiş, İNH profilaksisi verilen 99 hastanın 63'üne (%53) başlangıç PPD sonucuna göre, kalan 54 hastanın ise 36'sına (%30) daha kontrol PPD sonucuna göre İNH profilaksisi verildiği görüldü. Kontrol PPD sonucuna göre İNH profilaksisi başlanması ile hastalık tanısı ve kullanılan anti TNF ilaç çeşidi arasında anlamlı bir ilişki saptanmadı. (p=0,18)

Sonuç: Anti-TNF ilaç tedavisi alan romatizmal hastalarda, tedavi sürecinde immun cevabın düzenlenmesi ile PPD düzeyini değiştirip yalancı negatiflik oranını azaltabilir. Bu yüzden proflaksi alması gereken hastaları belirlemek için tedavinin ileri dönemlerinde de belli aralıklarla PPD testi tekrarlanması ve hastaların profilaksi açısından tekrar değerlendirilmesi önerilebilir.

Anahtar kelimeler: Tumor nekroz faktör inhibitörü, Romatolojik hastalık, Tüberkülin deri testi, tüberküloz, Yan etki

Corresponding author / Sorumlu yazar:
Özlem Karataş
Address / Adres: Antalya Eğitim ve Araştırma Hastanesi, Sağlık Bilimleri Üniversitesi, Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, Antalya, Türkiye
e-Mail: ozlemkaratas@outlook.com

Ethics Committee Approval: Local ethics committee approved the study protocol.
Etik Kurul Onayı: Yerel etik kurul çalışma protokolünü onayladı.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 08.03.2019
Accepted / Kabul Tarihi: 12.03.2019
Published / Yayın Tarihi: 13.03.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite / Atıf için: Özdemir T, Tuna S, Karataş Ö, Arman Mİ. Variations of tuberculin skin test in patients with rheumatologic disorders and under anti-TNF treatment. J Surg Med. 2019;3(3):254-257.

Introduction

Tumor necrosis factor alpha (TNF-α) is a cytokine that holds important place in the pathogenesis of inflammatory rheumatic diseases [1,2]. In recent years, biological agents acting by blocking the effect of TNF-α had been used with success in the treatment of rheumatic diseases.

Following the widespread use of anti TNF therapy, the high incidence of active tuberculosis (TB) was reported in patients treated with anti TNF, which is usually associated with the reactivation of latent tuberculosis infection (LTBI) [3,4]. Afterwards, the screening of LTBI began to be performed before initiation of anti-TNF treatment [5]. Tuberculin skin test (TST) is the most widely used test for identification of LTBI, but TST is affected by immunosuppressive therapy and inflammatory disorders [4,6-8]. Therefore, TST values in patients with inflammatory rheumatic diseases may change during the anti-TNF treatment process [9,10]. In literature, there are few studies that evaluate the TST response in the patients receiving short-term anti TNF treatment. Herewith, to the best knowledge of the authors, a study investigating changes in TST levels in the later years of anti TNF treatment is not available in the literature.

We aimed to investigate the changes of the TST levels and prophylaxis initiation rates into the later years of anti TNF treatment in patients taking anti TNF therapy for inflammatory rheumatic diseases more than a year.

Materials and methods

In this study, patients who were followed between 2005 and 2013 at rheumatology clinic and diagnosed as rheumatologic disorders were included. Patients who had malignancies, solid tumors and active infection were excluded. Patients were informed about the study procedure and they consented to participate. Local ethics committee approved the study protocol.

Demographic data, diagnoses, diagnosis time, anti TNF drug duration, initial TST level, control TST level, control TST time and INH prophylaxis had obtained retrospectively from patient files. TST tests had done at tuberculosis dispensaries. Measured TST results were divided into two groups: TST negative (0 to 4 mm), and TST positive (≥ 5 mm). INH prophylaxis were started to the patients with TST≥5mm or TST=0 in 2 repeats. INH prophylaxis as started by the initial and control TST level were recorded. Also, control TST times were assessed into 4 groups as 1-2 / 2-3 / 3-4 / ≥4 years of anti TNF treatment (Figure 1).

Statistical analysis

All statistical data was analyzed using the program PASW 18 (SPSS / IBM, Chicago, IL, USA). To define the sample, descriptive statistics like frequency distribution, mean, standard deviation were used. In cases where the assumptions of parametric tests provided, the average difference of two independent groups was determined via "Student t test", difference between more than two groups was determined via "variance analysis". In cases where the assumptions of parametric tests not provided, nonparametric alternatives; "Mann-Whitney" and "Kruskal-Wallis" tests were used. Categorical data was examined via "chi-square test" or "Fisher's Exact test". To identify differences in analysis, 5% significance level (or margin of error α =0.05) was used.

Results

One-hundred-seventeen patients were included in the study. These were 27 rheumatoid arthritis (RA), 77 ankylosing spondylitis (AS), 6 psoriatic arthritis (PsA), 7 juvenile chronic arthritis (JKA) patients receiving anti TNF treatment for longer than a year, a total of 117 patients were included. Eighty-one (69.2%) of the patients were male, 36 (30.8%) were female. The mean age of the patients was 40.4±12.90 (16-68). Diagnosis and demographic characteristics of patients are summarized in Table 1.

The majority of RA patients were female (16, 59.3%), whereas the majority of AS patients was male (61, 79.2%). While ETA was more in RA patients (40, 52.0%), İNF was more in AS patients (18, 66.7%).

The mean control TST levels were 8.29 ± 6.40 while the mean initial TST levels were 5.87±5.45. The mean of control TST levels was significantly higher than initial (p=0.001) (Table 2).

Table 1: Diagnosis and demographic characteristics of patients

		Mean±SD (Min-Max)
Age (year)		40.4±12.90 (16-68)
How many years patient had the disease?		14.29±6.88 (2-16)
Anti TNF treatment times (years)		4.60±2.02 (1-11)
		n (%)
Female		36 (30.8)
Male		81 (69.2)
Diseases	RA	27 (23.1)
	AS	77 (65.8)
	PsA	6 (5.1)
	JKA	7 (6.0)
Anti TNF drug	IFN	45 (38.4)
	ETA	47 (40.2)
	ADA	25 (21.4)
Anti TNF treatment times	1-2 years	20 (17.1)
	2-3 years	16 (13.7)
	3-4 years	26 (22.2)
	≥4 years	55 (47.0)

SD: Standard deviation

Table 2: The initial and control TST levels and INH prophylaxis rates

	Initial TST (n= 117)	Control TST (n=54)	p	Total INH prophylaxis
TST levels (Mean ± Std)	5.87±5.45	8.29±6.40	0.001*	
0 mm	8 (6.8%)	5 (9.3%)		13
1-4mm	54 (46.2%)	18 (33.3%)		0
≥ 5 mm	55 (47.0%)	31 (57.4%)		86
Total INH prophylaxis	63 (53.8%)	36 (66.7%)		99 (84.6%)

*: p < 0.05

INH prophylaxis was given before starting anti TNF treatment to 63 (53.8%) patients according to initial (TST ≥ 5mm or 2 repeats TST=0). The control TST were converted from negative to positive in 31 (57.4%) and anergy developed in 5 (9.3%) patients of 54 patients not given INH prophylaxis at initial. INH prophylaxis was started in 36 (30.8%) of total 117 patients according to control TST. To total 99 (84.6%) of 117 patients, INH prophylaxis was given (Table 2).

There was no relationship between duration of anti TNF therapy and INH prophylaxis initiation according to control TST levels (p=0.180) (Table 3).

When compared to INH prophylaxis rates according to diagnosis of disease and the anti-TNF drugs, there was no relation between diagnosis of disease and the anti TNF drugs

used with INH prophylaxis initiation (p=0.990, p=0.349) (Table 4).

Table 3: INH prophylaxis initiation according to duration of anti-TNF therapy

Control TST (n=54)	Anti TNF treatment times 1-2 years	2-3 years	3-4 years	≥4 years	p
INH prophylaxis (+) (n=36)	7 (87.5%)	3 (60.0%)	12 (75.0%)	14 (56.0%)	0.18
INH prophylaxis (-) (n=18)	1 (12.5%)	2 (40.0%)	4 (25.0%)	11 (44.0%)	
Total (n=54)	8 (100%)	5 (100%)	16 (100%)	25 (100%)	

Table 4: INH prophylaxis according to diagnosis of disease and the anti-TNF drugs

INH prophylaxis Rates	Diseases						Anti TNF			
	n (%)	RA	AS	PsA	JKA	p	INF	ETA	ADA	p
İnitiation	63 (53.8%)	12	43	4	4	-	26	19	18	-
Control	36 (30.8%)	9	23	2	2	0.98	14	18	4	0.15
Total	99 (84.4%)	21	66	6	6	0.99	40	37	22	0.35

Discussion

In this study where we aimed to evaluate the changes in TST levels during anti TNF treatment in patients with inflammatory rheumatic diseases, we found that the mean of control TST levels were significantly increased compared to initiation TST levels and INH prophylaxis to one of three patients was started according to their control TST results. But, there was no relationship between INH prophylaxis and duration of anti-TNF therapy.

After anti TNF agents came into use, TB cases started to be reported among the patients who were under anti TNF treatment and studies showed that TB ratio in these patients were more than control groups [10-13]. In 2001, among 147.000 patients treated with Infliximab, 70 TB cases were reported. 2 months later this number had risen to 117. Thus, it has been accepted that these agents increases the risk of developing TB, especially in those who have LTBI [14,15]. The increased TB risk in this patients may be due to blocking TNF-α because it is an effective mediator in the regulation of cellular immune responses [9,16]. It has also been reported that active TB cases can be reduced by 50-90% with the diagnosis and treatment of LTBI [17-19]. Therefore, before anti TNF treatment, all patients are evaluated with TST for LTBI and the patients who develop endurance 5mm or 0mm are given TB prophylaxis. In our study, TST was applied to all of our patients and prophylaxis was initiated in 63 of them.

The TST test is an important technique for predicting active disease in patients with LTBI. However accuracy and reliability of TST is affected by immune suppressive therapy and the activity of underlying inflammatory diseases [20]. İn countries where TB is epidemic, the decreased responses to TST were found in patients diagnosed with RA compared to control groups [21,22]. Sezer et al. [23] have detected that TST levels were higher in healthy controls than in patients with AS and RA. Therefore, among the patients with inflammatory rheumatic diseases, false negative TST results can be said to be higher than the normal population. But, TST levels are expected to increase during treatment in patients taking anti-TNF when the immune system re-regulation and disease remission achieved. Indeed, Çağatay et al. [9] have reported that mean TST levels after 1 year were significantly higher than levels at initiation, and the negative initial TST were converted to positive at 1-year repeat in 26 (30%) patients. Joven at al. [22] have been reported that TST response increased in patients using anti-TNF agent. In a study by Bonfiglioli at al. [24], they reported that the negative initial TST were converted to positive at 5 of 51 patients who had negative TST in 36 months of anti-TNF treatment.

In our study, the mean of control TST levels was significantly higher than initial and INH prophylaxis was started in 36 (30.8%) of total 117 patients according to control TST. The reason for this higher rate from the literature in our study may be that TST was also repeated even in patients in the later stages of treatment and TB prevalence varies among societies. This condition suggests that TST can be transformed into positive at different times in different patients. In our study, all patients could not be evaluated with TST in each year of the treatment process due to retrospective nature of the study. This issue is a major limitation of our study. We think that these results need to be supported with prospective follow-up studies.

Conclusion

Our results support that the immune system re-regulation and disease remission may occur at any stage of the treatment process and may reduce the rates of false-negative TST in patients treated with anti-TNF. Thereby, TST sensitivity rises in patients with LTBI. Consequently, the patients with LTBI not determined with initial TST may be determined with TST test repeated applied in the later stages of anti-TNF treatment and INH prophylaxis reduce the risk of active TB in this patients.

References

1. Keystone EC, Ware CF. Tumor necrosis factor and anti-tumor necrosis factor therapies. J Rheumatol Suppl. 2010;85:27-39.
2. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacol Ther. 2008;117(2):244-79.
3. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001;345(15):1098-104.
4. Shim TS. Diagnosis and Treatment of Latent Tuberculosis Infection in Patients with Inflammatory Bowel Diseases due to Initiation of Anti-Tumor Necrosis Factor Therapy. Intest Res. 2014;12(1):12-9.
5. Hazlewood GS, Naimark D, Gardam M, Bykerk V, Bombardier C. Prophylaxis for latent tuberculosis infection prior to anti-tumor necrosis factor therapy in low-risk elderly patients with rheumatoid arthritis: a decision analysis. Arthritis Care Res (Hoboken). 2013;65(11):1722-31.
6. Yun JW, Lim SY, Suh GY, Chung MP, Kim H, Kwon OJ, et al. Diagnosis and treatment of latent tuberculosis infection in arthritis patients treated with tumor necrosis factor antagonists in Korea. Journal of Korean Medical Science. 2007;22(5):779-83.
7. Campbell JR, Krot J, Elwood K, Cook V, Marra F. A Systematic Review on TST and IGRA Tests Used for Diagnosis of LTBI in Immigrants. Mol Diagn Ther. 2015;19(1):9-24.
8. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Ann Intern Med. 2007;146(5):340-54.
9. Cagatay T, Kilicaslan Z, Cagatay P, Mertsoylu M, Gulbaran Z, Yildiz R, et al. TNF-alpha antagonist therapy modify the tuberculin skin test response. Rheumatol Int. 2011;31(9):1147-51.
10. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum. 2003;48(8):2122-7.
11. Mohan AK, Cote TR, Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis. 2004;39(3):295-9.
12. Yamada T, Nakajima A, Inoue E, Tanaka E, Hara M, Tomatsu T, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis in Japan. Ann Rheum Dis. 2006;65(12):1661-3.
13. Carmona L, Hernandez-Garcia C, Vadillo C, Pato E, Balsa A, Gonzalez-Alvaro I, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol. 2003;30(7):1436-9.
14. Hochberg MC, Lebwohl MG, Plevy SE, Hobbs KF, Yocum DE. The benefit/risk profile of TNF-blocking agents: findings of a consensus panel. Semin Arthritis Rheum. 2005;34(6):819-36..
15. Mutlu GM, Mutlu EA, Bellmeyer A, Rubinstein I. Pulmonary adverse events of anti-tumor necrosis factor-alpha antibody therapy. Am J Med. 2006;119(8):639-46
16. Hamdi H, Mariette X, Godot V, Weldingh K, Hamid AM, Prejean MV, et al. Inhibition of anti-tuberculosis T-lymphocyte function with tumour necrosis factor antagonists. Arthritis Res Ther. 2006;8(4):R114.
17. Society AT, Control CfD, Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med. 2000;161:S221-S47.
18. Smith BM, Menzies D. Treatment of latent TB: first do no harm. Expert Review of Anti-Infective Therapy. 2011;9(5):491-3.
19. Chee CB, KhinMar KW, Gan SH, Barkham TM, Pushparani M, Wang YT. Latent tuberculosis infection treatment and T-cell responses to Mycobacterium tuberculosis-specific antigens. Am J Respir Crit Care Med. 2007;175(3):282-7.
20. Vukmanovic-Stejic M, Reed JR, Lacy KE, Rustin MH, Akbar AN. Mantoux Test as a model for a secondary immune response in humans. Immunol Lett. 2006;107(2):93-101.

21. Ponce de Leon D, Acevedo-Vasquez E, Sanchez-Torres A, Cucho M, Alfaro J, Perich R, et al. Attenuated response to purified protein derivative in patients with rheumatoid arthritis: study in a population with a high prevalence of tuberculosis. Ann Rheum Dis. 2005;64(9):1360-1.
22. Joven BE, Almodovar R, Galindo M, Mateo I, Pablos JL. Does anti-tumour necrosis factor alpha treatment modify the tuberculin PPD response? Ann Rheum Dis. 2006;65(5):699.
23. Sezer I, Kocabas H, Melikoglu MA, Arman M. Positiveness of purified protein derivatives in rheumatoid arthritis patients who are not receiving immunosuppressive therapy. Clin Rheumatol. 2009;28(1):53-7.
24. Bonfiglioli K, Ribeiro A, Moraes J, Saad C, Souza F, Calich A, et al. LTBI screening in rheumatoid arthritis patients prior to anti-TNF treatment in an endemic area. The International Journal of Tuberculosis and Lung Disease. 2014;18(8):905-11.

J Surg Med. 2019;3(3):258-261.
DOI: 10.28982/josam.537361

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

A modified method for punctoplasty: "Excisional punctoplasty with the guidance of a 27 G Rycroft cannula"

Punktoplasti operasyonunun bir modifikasyonu: "27G Rycroft kanül kullanarak yapılan eksizyonel punktoplasti"

Onur Temizsoylu [1], Gözde Şahin [1], Alev Koçkar [2], Alper Şengül [2], Erdal Yüzbaşıoğlu [2]

[1] Erzurum Regional Training and Research Hospital, Ophthalmology Department, Erzurum, Turkey
[2] Bilim University, Ophthalmology Department, Istanbul, Turkey

ORCID ID of the author(s)
OT: 0000-0001-5950-9790
GŞ: 0000-0001-9954-1525
AK: 0000-0002-1457-8511
AŞ: 0000-0003-1313-6970
EY: 0000-0003-3421-4523

Corresponding author / Sorumlu yazar:
Onur Temizsoylu
Address / Adres: Erzurum Bölge Eğitim ve Araştırma Hastanesi, Oftalmoloji Bölümü, Erzurum, Türkiye
e-Mail: onurtemizsoylu@hotmail.com

Ethics Committee Approval: Local ethics committee approved the study protocol.
Etik Kurul Onayı: Yerel etik kurul çalışma protokolünü onayladı.

Informed Consent: The authors stated that the written consent was obtained from the patients presented with images in the study.
Hasta Onamı: Yazar çalışmada görüntüleri sunulan hastalardan yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 08.03.2019
Accepted / Kabul Tarihi: 14.03.2019
Published / Yayın Tarihi: 14.03.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Abstract

Aim: We modified conventional 2-snip punctoplasty to ease procedure and to perform with simple equipment which is widely accessible in the operation rooms.

Methods: This new procedure has been performed to 10 eyes of 6 patients. After the appropriate width has been provided, a 27G anterior chamber cannula which is actually manufactured for cataract surgery was inserted to punctum and pushed forward 2 mm vertically and 1 mm horizontally. After that, the surgeon exposed the tip of cannulas by opening conjunctiva with conjunctival scissors (Westcott Conjunctival Scissors) from the projection site of the tip of the cannula. The Rycroft cannula is used for better guidance for canaliculus anatomy instead of lacrimal cannulas. After canaliculus was hanged with the cannula, a conjunctival incision was made from the entrance of cannula to the punctum towards the point where the cannula exposed from conjunctiva via Westcott scissors. In the next step, two sides of the formed flap were held with toothed forceps orderly and were removed by cutting with conjunctival scissors.

Results: After 6 month follow-up, none of the patients complained with epiphora and satisfied with the surgery. All participants have been defined with the presence of Grade 3-5 punctal aperture with the references of Punctum Size Grading by Slit-Lamp Examination.

Conclusion: In this article, we could apply this method to a very limited number of patients and our follow-up (6 months) is relatively short to claim the re-stenosis ratio but in the immediate postoperative period, we didn't encounter any re-stenosis.

Keywords: Punctal stenosis, Punctoplasty, Surgical technique, Surgical revision, Epiphora

Öz

Amaç: Bu çalışmada, yaygın olarak bulunan ameliyat aletleri ile yapılabilmesi ve daha kolay uygulanabilmesi amacıyla, geleneksel 2-kesili punktoplasti ameliyatının bir modifikasyonunu tanımladık.

Yöntemler: Bu yeni operasyon tekniği 6 hastanın 10 gözüne uygulandı. Punktumda yeterli genişlik oluşturulduktan sonra, katarakt operasyonu için üretilmiş olan 27G ön kamara kanülü punktuma yerleştirildi, 2 mm dikey ve 1 mm yatay düzlemde ilerletildi. Daha sonra, kanülün konjonktivaya izdüşümünden Westcott konjonktiva makasıyla kesi yapılarak kanül ucu dışarı çıkarıldı. Kanalikül Rycroft kanülü ile asıldıktan sonra punktum ile konjonktivadan çıkan kanül arasına kesi yapıldı. Daha sonra, oluşturulan flep dişli penset ile tutulup konjonktiva makasıyla kesilerek operasyona son verildi.

Bulgular: 6 aylık takip sonrasında hiçbir hastada epifora şikayetine rastlanmadı. Tüm hastalarda punktum büyüklüğü evreleme sistemine göre evre 3 ile 5 arasında açıklık bulunduğu görüldü.

Sonuç: Bu makalede tanımladığımız operasyon oldukça sınırlı sayıda hastaya yapılmıştır. Ayrıca kontrol süremiz (6ay) tekrar tıkanma oranını belirlemekte kısa sayılabilecek bir süredir. Ancak bu sürede hiçbir hastada yeniden tıkanma olmaması umut vadedicidir.

Anahtar kelimeler: Punktum tıkanıklığı, Punktoplasti, Cerrrahi teknik, Cerrahi revizyon, Epifora

How to cite / Atıf için: Temizsoylu O, Şahin G, Koçkar A, Şengül A, Yüzbaşıoğlu E. A modified method for punctoplasty: "Excisional punctoplasty with the guidance of a 27 G Rycroft cannula". J Surg Med. 2019;3(3):258-261.

Introduction

Epiphora is one of the most mentioned symptoms by patients that apply to the ophthalmology departments with a wide range of differential diagnosis. External lacrimal punctal stenosis is one of the causes of epiphora [1]. Anatomically, acquired punctal stenosis is a condition in which the external opening of the lacrimal canaliculus, located in the nasal part of the palpebral margin, is narrowed or occluded [2]. In literature, many factors have been reported in the pathogenesis of acquired external punctal stenosis [3]. The supposed pathogenesis is involutional changes involving the external lacrimal punctum leading to its narrowing or occlusion. Aging has been identified in several studies as a cause of punctal stenosis. Chronic lid inflammation, especially chronic blepharitis, remains a widely identified cause of acquired punctal stenosis. The pathogenesis asserted is chronic inflammation of the external punctum leading to gradual fibrotic changes in the ostium, followed by progressive occlusion of the duct. Infections involving the eyelid, such as trachoma and herpes simplex, may also result in stenosis [4,5]. Other factors associated with punctal stenosis have been shown in Table 1.

Table 1: Etiology of acquired punctal stenosis

Etiology	
Involutional	Tobramycin
Aging	Indomethacin
Inflammatory	Dexamethasone
Chronic blepharitis	Tropicamide
Ocular cicatricial pemphigoid	Naphazoline
Graft-versus-host disease	Artificial tears
Dry eye syndrome	Mitomycin-C
Eyelid malposition	Systemic medications
Infectious	5-Fluorouracil
Chlamydia trachomatis	Docetaxel
Actinomyces	Paclitaxel
Herpes virus	Idoxuridine
Human papilloma virus	Neoplastic (rare)
Topical medications	Peripunctal tumors
Timolol	Systemic diseases
Latanoprost	Acrodermatitis enteropathica
Betaxolol	Porphyria cutanea tarda
Dipivefrine hydrochloride	Other
Echothiophate iodide	Local irradiation
Pilocarpine	Photodynamic therapy for macular disease
Prednisolone acetate-phenylephrine hydrochloride	Trauma
Adrenaline	Idiopathic
Chloramphenicol	

In 1853, Bowman et al. [6] presented a 1-snip procedure, supported in 1873 by Arlit [7]. The procedure involved an incision of the entire length of the canaliculus with a canaliculus knife. This had the significant disadvantage of destroying the capillary action of the canaliculus. In 1926, Graves described his posterior ampullectomy, refined into the modern 3-snip by Thomas [8] in 1951 and Viers [9] in 1955. In 1962, Jones [10] re-popularized the 1-snip with a single vertical snip down the ampulla.

Basic surgical techniques for punctal stenosis involve 1, 2, or 3-snip punctoplasty. The difference between procedures is the number of cuts or the direction of the snip(s) that is best to prevent recurrence of epiphora and achieve anatomic and functional success. The 1-snip procedure refers to a single vertical snip down to the ampulla, which produces a high rate of failure attributable to the fusion of cut edges [11].

Jones et al [10] suggested a 2-snip variation of the surgery that consists of removing a V-shaped wedge from the vertical portion of the canaliculus on the conjunctival surface. Recently, the 3-snip procedure has become more applicable 1 or 2 snip procedure. The traditional 3-snip, specifically the triangular 3-snip procedure, is a posterior ampullectomy, which removes the triangular-shaped ampulla by a first cut at the vertical canaliculus, followed by a second cut along the horizontal canaliculus and a final snip at the base. A rectangular 3-snip punctoplasty, which involves 2 vertical snips at either side of the ampulla and a cut at the base, was recently reported to have high functional and anatomic success rates. The higher success rates are thought to be attributable to the preservation of physiology, as only the vertical portion of posterior ampulla is excised, and the anatomy and physiological functions of the lacrimal system are preserved [12].

Therefore, we tried to introduce a new revised method with the usage of cannula guidance for punctoplasty. The advantages of this method have been reported as the requirement of less surgical instrument, high rates of success, less recurrence of re-stenosis, easier way to perform, safer because of anatomical protection, application in less time and easy to apply in office conditions.

Materials and methods

This paper is related with the description of a revision in previous punctoplasty procedures. This study adhered to the tenets set forth in the Declaration of Helsinki, and the approval of local ethics committee was also obtained.

This new procedure has been performed to 10 eyes of 6 patients that applied to Istanbul Bilim University Ophthalmology Department with presenting epiphora. After detailed ophthalmologic examination including best-corrected visual acuity (BCVA), intraocular pressure measurement, slitlamp biomicroscopy, and dilated fundus examination; patients who had epiphora and severe stenosis of the lower eyelid puncta and/or the upper lid puncta included in this study. The punctal dilation was performed with a punctal dilatator but was not sufficient to allow the 2 vertical cuts to the ampulla. The patency of the canaliculi and nasolacrimal duct was confirmed by probing and irrigation. Patients with other causes of epiphora, such as canalicular stenosis, nasolacrimal duct obstruction, punctal malposition, lid laxity, entropion, and ectropion, were excluded. After punctal stenosis is defined, all participants were evaluated according to the severity of punctum size by slit-lamp examination with the references of Punctum Size Grading by Slit-Lamp Examination (Table 2). All participants have defined with the presence of Grade 0-1 punctal stenosis.

All patients had undergone the standardized surgical procedure by the same surgeon (O.T). The surgical procedure started with the local injection of 0.3 cc of 2% lidocaine with 1:100.000 epinephrine that administered transconjunctivally, 2 mm below the punctum and later punctal dilatation was performed with punctum dilatator. After the appropriate width has been provided, a 27G anterior chamber cannula, 40 x 22.0mm (27 G x 7/8 in), Anterior Chamber Cannula [Rycroft], angled 45 degrees, 6 mm from end, (BD Visitec™ from Beaver-Visitec International, South San Francisco, USA) which is actually manufactured for cataract surgery was inserted to punctum and pushed forward 2 mm vertically and 1 mm horizontally. After that the surgeon exposed the tip of cannulas by opening conjunctiva with conjunctival scissors (Westcott

Conjunctival Scissors with Lightly curved 16mm blades, blunt tips) from projection site of the tip of the cannula. The Rycroft cannula is used for better guidance for canaliculus anatomy instead of lacrimal cannulas. After canaliculus was hanged with cannula, a conjunctival incision was made from the entrance of cannula to the punctum towards the point where the cannula exposed from conjunctiva via Westcott scissors. In the next step, two sides of the formed flap were held with toothed forceps orderly and was removed by cutting with conjunctival scissors (Figure 1).This method is the first procedure described with cannula guidance for excisional punctoplasty. Topical antibiotics (Moxifloxacin hydrochloride 0.5% Vigamox, Alcon Canada Inc.; 4 times per day) and steroids (Loteprednol etabonate ophthalmic solution 0.5%, Lotemax, Bausch & Lomb Incorporated Tampa, Florida, USA; 4 times per day) were given for 1 week postoperatively, an approximate follow-up visit was 6 months.

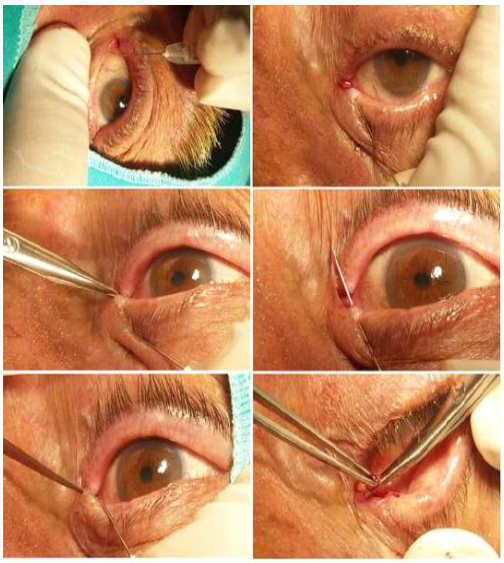

Figure 1: Surgery Technique

Results

After 6 month follow-up, none of the patients complained of epiphora and satisfied with the surgery. In 3-month and 6-month follow-up; the patency of the canaliculi and the nasolacrimal duct was confirmed by probing and irrigation. All participants have been defined with the presence of Grade 3-5 punctal aperture with the references of Punctum Size Grading by Slit-Lamp Examination (Table 2). This grading scale is appropriate for anatomical surgical success evaluation but the functional surgical assessment is necessary for detection of the level of quality of life. The subjective epiphora score (Munk score, Table 3) is utilizable for functional success ratio [13].

Table 2: Punctum Size Grading by Slit-Lamp Examination

Grade	Clinical finding
0	No papilla and punctum (punctal atresia)
1	Papilla is covered by a membrane or fibrosis and difficult to recognize
2	Less than normal size but recognizable
3	Normal
4	Small slit (<2 mm)
5	Large slit (>2 mm)

Table 3: Subjective Evaluation of Tearing by Munk Score

Grade	Clinical finding
0	No epiphora
1	Occasional epiphora requiring wiping with a tissue less than twice a day
2	Epiphora requiring 2 to 4 wipings per day
3	Epiphora requiring 5 to 10 wipings per day
4	Epiphora requiring >10 wipings per day or continuous tearing

Discussion

Ordinarily, a few methods are currently used in the management of punctal stenosis. The simplest method involves the use of perforated punctal plugs, which is a reversible procedure. Minor surgical techniques require an incision of the puncta. In the 1, 2 or 3 snip punctoplasty, the main issue was the re-stenosis of punctum.

Different surgical procedures have haven described to reduce further the risk of reapproximation. Placing the lid under tension with a 4-0 suture and anchoring the tarsus to a sterile button was contemplated by Dolin and Hecth in 1986 [14]. In 1993, Lam and Tessler [15] suggested topical instillation of mitomycin C as an adjunctive treatment. After that, Offutt and Cowen proposed a new approach in which the punctum was removed and the vertical canaliculus was externalized [16].

Success rates as high as 90% with the three-snip procedure were reported by Caesar and McNabb, but these results may not reflect sustained long-term success, because the duration of follow-up was not reported [11].

In a large retrospective study of 169 patients with appropriate preoperative evaluation, two-snip punctoplasty was compared with three-snip punctoplasty [17]. A two-snip procedure entails a vertical cut to the medial and lateral wall of the punctum, followed by removal of the tissue left between the incisions. This last step is accomplished by performing a third cut at the base of the tissue bridging the cuts). The three-snip punctoplasty involves a vertical cut down the ampulla, followed by a horizontal cut along the roof of the canaliculus, thus forming a free flap connected to the floor of the canaliculus-ampulla complex. Subsequently, the base of the flap is incised, leaving a broadened canalicular ostium. In this study, 91% of patients achieved anatomical success, while 64% achieved functional success. Partial functional success was evident in 14%. Seventy-one percent of the patients were satisfied with the results. The data suggest that both two-snip and three-snip punctoplasty were satisfactory in yielding anatomical success, with 91.1% for the two-snip procedure and 94.1% for the three-snip procedure (P = 0.7). The mean follow-up duration in this study was 23 (range 1–208) weeks, and so, once again, it is unclear whether the snip procedures provide long-term relief of epiphora.

Another retrospective study of 75 patients with a mean follow-up of 0.68 years suggested that rectangular punctoplasty (two vertical incisions at either side of the vertical canaliculus and one cut at the base) may be more effective than the common triangular three-snip procedure [12].

Even with the presence of different surgical approach, there is no gold standard surgical procedure. Most of these surgical methods require a blinded attempt to canaliculi to uncover the incision. In our revised surgical method, the application of 27 G anterior chamber cannula guidance provides a similar anatomical aperture in canaliculus and this technique distorts lacrimal drainage physiology lesser than conventional procedures. Because of the lack of removal of ampulla's posterior wall totally in other procedures, we performed adjustment of both up and down walls of ampulla properly via cannula guidance. so that we predict that the wound healing will

not cause re-stenosis. Also having a simple anterior chamber cannula can provide a safer method for punctoplasty with similar anatomical structure with proximal lacrimal duct system. The guidance of anterior chamber cannula maintains less hemorrhage because of the protection of the capillary system unlike other methods so that it can be applicable in office conditions.

In this article, we could apply this method to a very limited number of patients and our follow-up (6 months) is relatively short to claim the re-stenosis ratio but in the immediate postoperative period, we haven't encountered any re-stenosis. Also, we did not evaluate Munk score and this is one of the most important shortcomings of this study. Further prospective, randomized, and large-scale studies are needed to evaluate the results about re-stenosis and anatomical or functional success ratios in this excisional punctoplasty with a 27 G Rycroft cannula assistance method.

In conclusion, our modification can be implemented in surgeries which are performed in the shortage of equipment. Furthermore, the patency of punctoplasty is ensured due to the features of our technique. These properties make our technique unique, whereas, it should be confirmed by further researches.

References

1. Ulusoy MO, Atakan M, Kıvanç SA. Prevalence and associated factors of external punctal stenosis among elderly patients in Turkey. Arq Bras Oftalmol. 2017 Sep-Oct;80(5):296-99. doi: 10.5935/0004-2749.20170072.
2. Soiberman U, Kakizaki H, Selva D, Leibovitch I. Punctal stenosis: definition, diagnosis, and treatment. Clin Ophthalmol. 2012;6:1011. doi: 10.2147/opth.S31904.
3. Kashkouli MB, Beigi B, Murthy R, Astbury N. Acquired external punctal stenosis: etiology and associated findings. Am J Ophthalmol. 2003;136.6:1079-84. doi: 10.1016/S0002-9394(03)00664-0
4. Tabbara KF, Bobb AA. Lacrimal system complications in trachoma. Ophthalmology. 1980;198787(4); 298-301.
5. Jager GV, Bijsterveld OPV. Canalicular stenosis in the course of primary herpes simplex infection. Br J Ophthalmol. 1997;81(4):332.
6. Bowman W. Methode de traitement applicable a l'epiphora dependent du renversement en dehors ou de l'obliteration des points lacrymaux. Ann Oculist. 1853;29:52–5.
7. Graves B. Making a new lacrimal punctum. Am J Ophthalmol. 1926;9:675–7.
8. Thomas JBT. A modification of Graves' operation for epiphora due to stenosis of the lacrimal punctum. Br J Ophthalmol. 1951;35:306.
9. Viers ER. Disorders of the canaliculus in the lacrimal system, New York: Grune and Stratton.1955);46-7.
10. Jones LT. The cure of epiphora due to canalicular disorders, trauma and surgical failures on the lacrimal passages. Trans Am Acad Ophthalmol Otolaryngol. 1962;66:506–24.
11. Caesar R, McNab A. A brief history of punctoplasty: the 3-snip revisited. Eye (Lond). 2005;19(1):16. doi:10.1038/sj.eye.6701415
12. Chak M, Irvine F. Rectangular 3-snip punctoplasty outcomes: preservation of the lacrimal pump in punctoplasty surgery. Ophthalmic Plast Reconstr Surg. 2009;25(2):134-5. doi: 10.1097/IOP.0b013e3181994062.
13. Munk PL, Lin DT, Morris DC. Epiphora: treatment by means of dacryocystoplasty with balloon dilation of the nasolacrimal drainage apparatus. Radiology. 1990;177(3):687–90.
14. Dolin SL, Hecht SD. The punctum pucker procedure for stenosis of the lacrimal punctum. Arch Ophthalmol. 1986;104(7):1086-7.
15. Lam S, Tessler H. Mitomycin as adjunct therapy in correcting iatrogenic punctal stenosis. Ophthalmic Surg. 1993;24(2):123-4.
16. Cowen D. Stenotic puncta: microsurgical punctoplasty. Ophthalmic Plast Reconstr Surg. 1993;9(3):201-5.
17. Shahid H, Sandhu A, Keenan T, Pearson A. Factors affecting outcome of punctoplasty surgery: a review of 205 cases. Br J Ophthalmol. 2008;92(12):1689-92. doi: 10.1136/bjo.2008.140681.

J Surg Med. 2019;3(3):262-264.
DOI: 10.28982/josam.470446

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Computed tomography findings of mesenteric ischemia related to acute superior mesenteric vein thrombosis: A case report

Akut superior mezenterik ven trombozuna bağlı mezenterik iskeminin bilgisayarlı tomografi bulguları: Olgu sunumu

Emrah Doğan [1], Marwa Mouline Doğan [2], Süha Gül [1], Bünyamin Güney [3]

[1] Muğla Sıtkı Koçman University Education and Research Hospital, Department of Radiology, Mugla, Turkey
[2] Université de Mohammed V, Département de Cardiologie, Rabat, Morocco
[3] Muğla Sıtkı Koçman University Education and Research Hospital, Faculty of Medicine, Mugla, Turkey

ORCID ID of the author(s)
ED: 0000-0002-9446-2294
MMD: 0000-0002-3401-895X
SG: 0000-0001-5625-5385
BG: 0000-0002-0853-4184

Corresponding author / Sorumlu yazar:
Emrah Doğan
Address / Adres: Muğla Sıtkı Koçman Üniversitesi Eğitim ve Araştırma Hastanesi, Radyoloji Anabilim Dalı, Muğla, Türkiye
e-Mail: dr_e_dogan@hotmail.com

Informed Consent: The author stated that the written consent was obtained from the patient presented in the study.
Hasta Onamı: Yazar çalışmada sunulan hastadan yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş tarihi: 15.10.2018
Accepted / Kabul tarihi: 22.11.2018
Published / Yayın tarihi: 08.01.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Abstract

Acute mesenteric ischemia (AMI) is a condition caused by a decrease in blood flow due to occlusion of the mesenteric vessels, vasospasm or hypoperfusion. Approximately 5-15% of all AMI are related to mesenteric venous thrombosis (MVT). MVT has high mortality rate despite of advanced medical technologies. Thus, early diagnosis is crucial in the prognosis of the disease. Contrast-enhanced computed tomography (CT) and CT angiography are the most helpful radiological examinations for early diagnosis. We present the case of 55 years old patient with AMI accompanied by radiological images. Our patient was admitted to hospital with severe abdominal pain persistent since a week. The patient had upper gastro-intestinal system (GIS) bleeding history due to peptic ulcer a month ago. In the CT imaging, we found thrombosis along superior mesenteric vein up to distal portal junction. There was pneumatosis intestinalis as a consequence of necrosis, ileal walls were concentric, thick and hypodense because of edema. Total intestinal segments were dilated with air-fluid levels. Ileus was present without obstruction. The findings support the diagnosis of AMI due to MVT.

Keywords: Mesenteric ischemia, Venous infarct, Mesenteric venous thrombosis

Öz

Akut mezenterik iskemi (AMI), mezenterik damarların tıkanması, vazospazm veya hipoperfüzyonun kan akışında azalmaya neden olduğu bir durumdur. Tüm AMI'nin yaklaşık% 5-15'i mezenterik venöz tromboz (MVT) ile ilgilidir. MVT, ileri medikal teknolojilere rağmen yüksek ölüm oranına sahiptir. Bu nedenle, hastalığın prognozunda erken tanı önemlidir. Kontrastlı bilgisayarlı tomografi (BT) ve BT anjiyografi erken tanı için en yararlı radyolojik incelemelerdir. Radyolojik görüntüleri olan 55 yaşındaki hastayı sunduk. Hastamız bir hafta boyunca mevcut olan şiddetli karın ağrısı ile hastaneye başvurdu. MVT'yi distal portal kavşağına kadar superior mezenterik ven boyunca izledik. Hasta bir ay önce başka bir hastanede peptik ülsere bağlı olarak üst gastrointestinal sistem kanama öyküsüne sahipti. Nekroz nedeniyle pnömatozis intestinalis vardı, ileal duvarlar konsantrik kalın ve ödem nedeniyle düşüktü. Segmental ileus bu olaya engel olmaksızın eşlik ediyordu. Radyolojik olarak, MVT'nin neden olduğu AMI olarak değerlendirdik.

Anahtar kelimeler: Mezenterik iskemi, Venöz infarkt, Mezenterik venöz tromboz

Introduction

Acute mesenteric ischemia (AMI) is a condition caused by a decrease in blood flow due to occlusion of the mesenteric vessels, vasospasm or hypoperfusion [1]. Most common reasons are arterial. However, AMI can be rarely related to venous problems [2]. Its mortality rate is less than of arterial ischemia but it is remarkable. Delayed diagnosis is very common in mesenteric venous thrombosis. The reason of this is the absence of specific abdominal signs and symptoms. Thus, early diagnosis is crucial in the prognosis of the disease [3]. Advances in radiology have increased rate of early recognition of the disease [4,5]. Consensus has not been yet formed but offers possibilities in non-surgical treatment methods such as anticoagulant treatment [3]. Contrast-enhanced computed tomography (CT) and CT angiography are the most helpful radiological examinations for early diagnosis. The accurate and effective interpretation of these tests led to a significant decrease in mortality and morbidity rates [5]. We present the case of 55 years old female patient with AMI related to venous thrombosis.

How to cite / Atıf için: Doğan E, Doğan MM, Gül S, Güney B. Computed tomography findings of mesenteric ischemia related to acute superior mesenteric vein thrombosis: A case report. J Surg Med. 2019;3(3):262-264.

Case presentation

The patient was admitted to hospital with complaint of abdominal pain. In the patient's story, there were peptic ulcer and upper gastro-intestinal system (GIS) bleeding a month ago. No significate signs were found in ultrasound. Only common gas artefacts were present; thus, CT examination was requested. Contrast-enhanced CT revealed thickening up to 1.5 cm in ileal segments and air in the mucosa related to necrosis (pneumatosis intestinalis). In the jejunal segments, air-liquid levels were present because of ileus (Figure 1). Minimal free fluid was monitored in the lower quadrant of the abdomen. Intestinal attenuations were hypodense due to edema. Contrast enhancement was not observed in distended necrotic intestinal segments. CT angiography revealed a filling defect extending to the splenic vein and portal vein junction throughout the superior mesenteric venous pathway. The 3D reconstruction images supported the findings in the conventional CT (Figure 2). The written consent was obtained from the patient presented in the study.

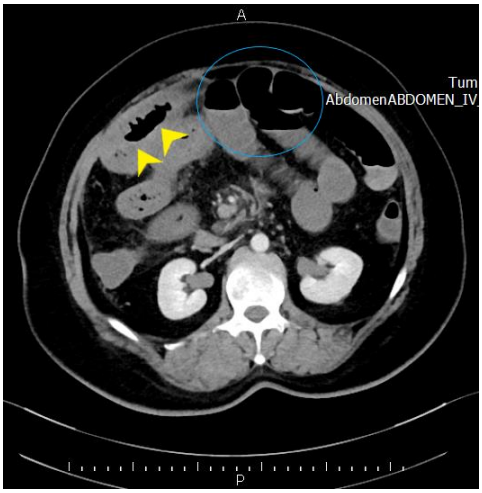

Figure 1: Yellow arrows: concentric thick air inside the necrotic ileal segments, Blue circle: ileus air liquid levels

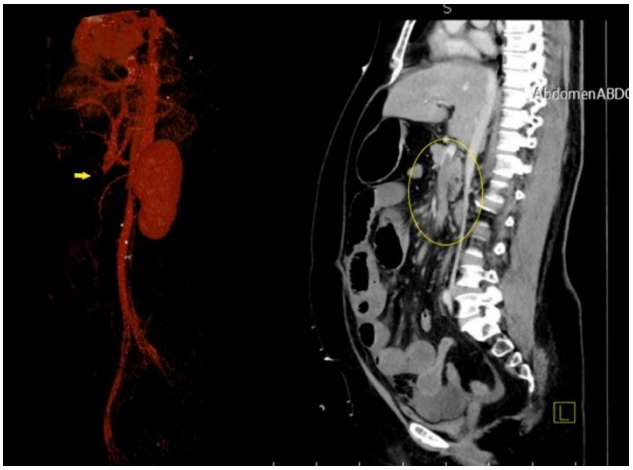

Figure 2: Yellow arrow: defect of superior mesenteric vein yellow ring: thrombosed superior mesenteric vein

Discussion

Mesenteric venous thrombosis (MVT) is the third reason of mesentery ischemia after mesenteric arterial embolism (50%) and mesenteric arterial thrombosis (15–25%) [6]. About 5 to 15% of all intestinal infarctions is related to MVT [2]. Delayed diagnosis in MVT can lead to destructive outcomes. Although the disease has not been known since 1895, Elliot first time described intestinal gangrene due to mesenteric venous occlusion, but in 1935, MVT was accepted like a clinical entity in the detailed publication of Warren and Eberhardt [3].

Delayed diagnosis is very common in MVT. In arterial occlusion, abdominal pain has acute onset and is actually unchanged but in MVT there is no specific clinical finding [7], it may be more insidious at the beginning in venous occlusion or low flow situations. Vomiting is common, sometimes a bloody diarrhea can occur but the classical triad of mesenteric ischemia (abdominal pain, fever, bloody stool) usually cannot be seen in examination. Abdominal pain is not proportional to physical findings. Early diagnosis is largely dependent on clinical awareness and suspicion [3].

Arterial occlusions are associated with cardiac arrhythmia, valve disease, previous embolism, myocardial infarction, congestive heart failure and hypotension [8]. Venous occlusions are related to primary or secondary portal hypertension, hypercoagulation and intra-abdominal malignancy [9,10].

Doppler ultrasound sometimes can show thrombus in the vessel but it is operative dependent and is not as sensitive as a CT or Magnetic resonance imaging (MRI). Contrast-enhanced CT scanning is the main diagnostic modality. Increased use of CT scanning for abdominal pain in the emergency department led to decrease of diagnosis time from 1 week to 1 day [11]. Filling defect in mesenteric vein is the most common radiological finding. Thickening and enlargement of the intestinal wall, pneumatosis intestinalis are findings linked with intestinal ischemia [11]. In CT examination, normal intestinal wall ranges from 3 to 5 mm thick depending on the degree of intestinal distention [10]. On contrast-enhanced CT, thrombus in the mesenteric and portal veins is usually visible. Mesenteric venous obstruction is confirmed by CT in more than 90% of cases [10].

The mortality rate is still not acceptable despite all of the advances in diagnostic tools, treatment modalities and intensive care facilities. Venous Mesenteric Infarct (30-49%), albeit low compared with arterial ischemia and thrombosis (60-90%) [5]. Our case is a good sample for MVT with blurred clinic, slow onset and remarkable radiological features: it attributed necrosis to the delayed diagnosis. There was no hypercoagulability problem which is known as a predisposing factor.

MVT is a rare entity with a high mortality rate. Although advanced investigation methods significantly reduced the delayed diagnosis, the mortality rates are still not reasonable. CT and CT angiography are the main radiological evaluation methods. For proper diagnosis, the vascular structures should be examined in detail and the structure of the identified thrombus should be indicated in the report.

References

1. Herbert GS, Steele SR. Acute and chronic mesenteric ischemia. Surg Clin North Am. 2007;87:1115-34.
2. Brunaud L, Antunes L, Adler SC, Marchal F, Ayav A, Bresler L, et al. Acute mesenteric venous thrombosis: Case for nonoperative management. J Vas Surg. 2001;34:673-9.

3. Al Salamah S, Mirza SM. Acute Mesenteric Venous Thrombosis: Management Controversies. 2004;11:242-7.
4. Rhee RY, Gloviczki P. Mesenteric venous thrombosis. Surg Clin North Am. 1997;77:327-39.
5. Adaba F, Askari A, Dastur J, et al. Mortality after acute primary mesenteric infarction: a systematic review and meta-analysis of observational studies. Colorectal Dis. 2015;17(7):566-77.
6. Bala M, Kashuk J, Moore EE, Kluger Y, Biffl W, Gomes CA, et al. Acute mesenteric ischemia: guidelines of the World Society of Emergency Surgery. World J Emerg Surg. 2017 Aug 7;12:38.
7. Chang RW, Chang JB, Longo WE. Update in management of mesenteric ischemia. World J Gastroenterol. 2006;12:3243-7.
8. Williams LF. Mesenteric ischemia. Surg Clin North Am. 1988;68:331-53.
9. Witte CL, Brewer ML, Witte MH, Pond GB. Protean manifestations of Pyelothrombosis. Ann Surg. 1985;202:191-202.
10. Furukawa A, Kanasaki S, Kono N, Wakamiya M, Tanaka T, Takahashi M, Murata K. CT diagnosis of acute mesenteric ischemia from various causes. AJR Am J Roentgenol. 2009 Feb;192(2):408-16.
11. Hmoud B, Ashwani K, Kamathz PS. Mesenteric Venous Thrombosis. Journal of Clinical and Experimental Hepatology. 2014;4(3):257–63.

J Surg Med. 2019;3(3):265-267.
DOI: 10.28982/josam.473603

Journal of Surgery and Medicine
e-ISSN: 2602-2079

A case of parathyroid carcinoma mimicking parathyroid adenoma

Paratiroid adenomunu taklit eden paratiroid karsinomu olgusu

Semra Demirli Atıcı [1], Değercan Yeşilyurt [1], Dudu Solakoğlu Kahraman [2], Hakan Öğücü [1], Emre Dikmeer [1], Halit Batuhan Demir [1], Gökhan Akbulut [1]

[1] Department of General Surgery, University of Health Sciences, Tepecik Training and Research Hospital, Turkey
[2] Department of Pathology, University of Health Sciences, Tepecik Training and Research Hospital, Turkey

ORCID ID of the authors
SDA: 0000-0002-8287-067X
DY: 0000-0001-6938-2076
DSK: 0000-0002-4126-5326
HÖ: 0000-0003-4089-1162
ED: 0000-0001-9442-0273
HBD: 0000-0002-2746-7941
GA: 0000-0002-9054-1446

Corresponding author / Sorumlu yazar:
Semra Demirli Atıcı
Address / Adres: S.B.Ü. Tepecik Eğitim ve Araştırma Hastanesi Güney Mahallesi, 1140/1. Sk. No:1, 35180 Yenişehir, Konak, İzmir, Türkiye
e-Mail: smrdemirli@hotmail.com

Informed Consent: The author stated that the written consent was obtained from the patient presented in the study.
Hasta Onamı: Yazar çalışmada sunulan hastadan yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Previous presentation: This case report has been presented as a poster presentation in National Surgical Congress, in 2018, Antalya, Turkey
Önceki sunum: Bu olgu sunumu 2018, Antalya, Türkiye, Ulusal Cerrahi Kongresi'nde poster sunumu olarak sunulmuştur.

Received / Geliş tarihi: 22.10.2018
Accepted / Kabul tarihi: 17.12.2018
Published / Yayın tarihi: 29.12.2018

Copyright © 2018 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Abstract
Parathyroid carcinoma is one of the rare endocrine tumors and constitutes 1% of the cases with primary hyperparathyroidism. Because of similar imaging modalities and similar clinical findings, it is difficult to distinguish between preoperative parathyroid adenomas and parathyroid carcinoma. A 70-year-old female patient presented with fatigue and generalized bone pain. Her laboratory tests, neck and parathyroid scintigraphy were compatible with primary hyperparathyroidism with a significantly elevated level of parathormone. With the imaging methods which supported parathyroid adenoma, the patient was operated with a presumptive diagnosis of primary hyperparathyroidism due to parathyroid adenoma. The postoperative course was unremarkable and she was discharged on the postoperative fifth day. Postoperative pathology was reported as parathyroid carcinoma developed in a parathyroid adenoma. Parathyroid carcinoma and parathyroid adenoma have similar clinically and imaging methods, it is difficult to diagnose preoperatively.
Keywords: Hypercalcemia, Primary hyperparathyroidism, Parathyroid adenoma, Parathyroid carcinoma

Öz
Paratiroid karsinomu nadir görülen endokrin tümörlerden biri olup primer hiperparatiroidizmli olgularının %1'ini oluşturmaktadır. Benzer görüntüleme yöntemleri ve benzer klinik bulgular nedeniyle preoperatif paratiroid adenomları ve paratiroid karsinomu ayırt etmek zordur. 70 yaşında kadın hasta, yorgunluk ve yaygın kemik ağrısı şikayeti ile başvurdu. Laboratuvar testleri, artmış parathormon düzeyi, boyun ultrasonografisi ve paratiroid sintigrafisi, primer hiperparatiroidizm ile uyumluydu. Paratiroid adenomunu destekleyen görüntüleme yöntemleri ile hasta paratiroid adenomuna bağlı primer hiperparatiroidi ön tanısı ile opere edildi. Ameliyat sonrası problem saptanmayan hasta, postoperatif beşinci günde sorunsuz bir şekilde taburcu edildi. Postoperatif patoloji paratiroid adenomunda gelişen paratiroid karsinomu olarak rapor edildi. Paratiroid karsinomu ve paratiroid adenomu benzer klinik ve görüntüleme yöntemlerine sahiptir, preoperatif tanı koymak zordur.
Anahtar kelimeler: Hiperkalsemi, Primer hiperparatiroidizm, Paratiroid adenomu, Paratiroid karsinomu

Introduction

Approximately 1% of the cases of primer hyperparathyroidism constitute parathyroid carcinoma, which was a rare type of endocrine tumor [1]. Patients usually have symptoms of hyperparathyroidism, except that clinically parathyroid carcinoma has no significant findings. The mainly diagnosis of the disease is made with histopathological evaluation. The precise etiology of parathyroid carcinoma is unknown; radiotherapy history in neck region, some sporadic and familial tumors such as hereditary hyperparathyroidism jaw tumor (HPT-JT) and multiple neuroendocrine neoplasia type 1 (MEN1) mutations being accused in the etiology [2].

How to cite / Atıf için: Atıcı SD, Yeşilyurt D, Kahraman DS, Öğücü H, Dikmeer E, Demir HB, Akbulut G. A case of parathyroid carcinoma mimicking parathyroid adenoma. J Surg Med. 2019;3(3):265-267.

Case presentation

A 70-year-old female presented with weakness, fatigue, and generalized bone pain. She had a history of hemigastrectomy due to peptic ulcer, cholecystectomy, and deep vein thrombosis. Her laboratory tests were reported Calcium: 11.8 mg/dL (normal range 8.8-10.6 mg/dL) Phosphor: 3.2 mg/dL (normal range 2.5-4.5 mg/dl), 25 Hydroxy Vitamin D: 15.47 ng/dL and significantly elevated Parathormone (PTH): 1459 pg/mL (normal range 18.5-88.0 pg/mL). Thyroid ultrasonography showed a 2.5x3 cm sized semisolid lesion at the posterior right thyroid lobe which was extending into the retrosternal area. A 99m Sestamibi computerized tomography (CT) scan confirmed increased uptake in the topography of the right lobe inferior, which was first evaluated in favor of parathyroid adenoma. The presumptive diagnosis of primary hyperparathyroidism due to parathyroid adenoma surgery was performed. Written informed consent which was necessary was obtained from the patient for treatment, surgery, and publication. During surgery, palpable, fixed lymph node which was enlarged was send frozen. The enlarged lymph node was reported as reactive and right parathyroidectomy was performed. On gross pathology revealed a cystic nodule which was measured as 35x28x27 mm (Figure 1). Histopathological examination showed features compatible with parathyroid carcinoma which has revealed capsular and vascular invasion (Figure 2, 3). Surgical margins of the specimen were free for tumor. Eleven lymph nodes were reactive. Postoperative first day PTH and patient's serum calcium level performed. PTH levels decreased 15.6 pg/mL and calcium levels declined to 8.4 mg/dL. The patient postoperative course was unremarkable and she was discharged on the postoperative 5th day. She was directed to the oncology department for follow-up and treatment. The patient was in follow-up at postoperative nearly one year with no local recurrence or distant metastasis.

Figure 1: Gross pathology: parathyroid carcinoma, cystic nodule (35x28x27 mm)

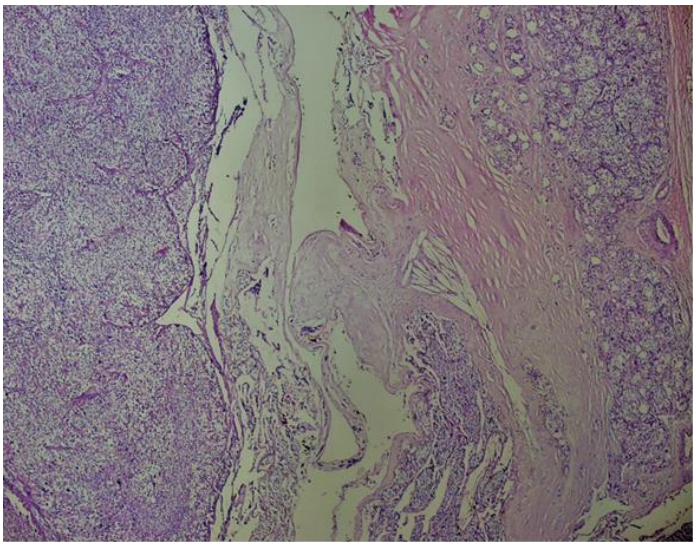

Figure 2: Right side of the figure: ordinary parathyroid tissue, Left side: encapsulated tumor. Tumor invasion into capsule and vascular space; Hematoxylin and Eosin ×40

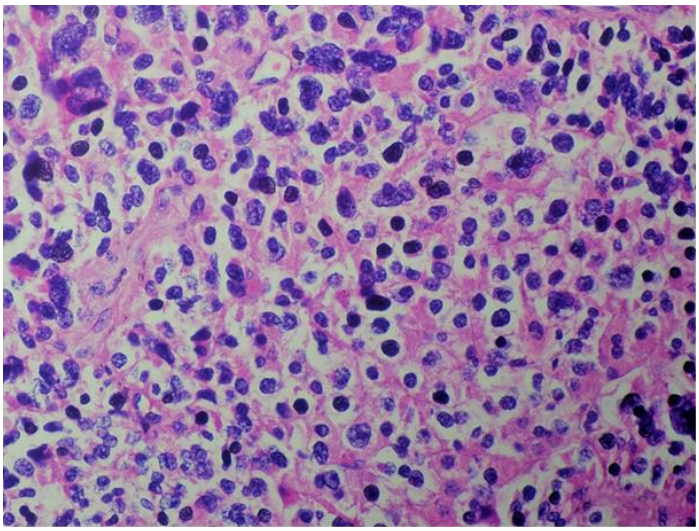

Figure 3: Tumor cells containing pleomorphic nuclei with macronucleoli. Hematoxylin and Eosin ×400

Discussion

Parathyroid carcinoma is a rare endocrine tumor with an incidence of 0.0002% [1]. The incidence of parathyroid carcinoma is equal in both men and women and especially seen fifth decade of life [2]. Parathyroid carcinoma constitutes 1% of the cases with primary hyperparathyroidism [1]. Patients usually present with complaints of weakness, fatigue, nausea, vomiting, anorexia, constipation, and common bone pain [1]. Etiopathogenesis of parathyroid carcinoma is mainly unclear. Parathyroid carcinoma incidence is increasing with the patient who has radiotherapy history in the neck region, secondary hyperparathyroidism due to renal insufficiency and some sporadic and familial tumors such as HPT-JT and MEN type 1 [2,3].

Imaging methods like ultrasound, CT, magnetic resonance imaging (MRI) is helpful in determining tumor localization but cannot help to differentiate if it is benign/malign [4]. But, MRI with gadolinium can give us detailed information, about supplement the assessment because of showing best detail on soft tissues of the neck [5].

Typically, high blood calcium levels which were >14mg/dl and high parathormone >5 times the upper limit, which were >300 pg/dl, levels should be clinically suspicious in

preoperative laboratory tests. Although a definitive diagnosis is usually made with postoperative pathology specimen reports [6]. Preoperatively with high suspicious parathyroid carcinoma diagnostic fine needle aspiration biopsy is deprecated because of the risk of seeding the tumor and also the high possibility of false negatives [7].

If we suspected about parathyroid carcinoma per-operatively frozen can be studied. However, since some pathologic features may be observed with parathyroid carcinoma in some benign adenomas, the frozen study is generally not reliable [8]. However, studies show that the best opportunity of surgical treatment for parathyroid carcinomas is en-bloc resection of the tumor with the ipsilateral thyroid lobe which provides better local disease control and improves long term-survival significantly [9]. In our case, we performed only parathyroidectomy and near one year follow up the patient has no local recurrence or distant metastasis. As our case during surgery enlarged, suspicious enlarged lymph nodes can be resected but studies shows that unnecessary prophylactic radical neck dissection can increase the risk of surgical complications [10].

For treatment of parathyroid carcinoma, except some case reports and small studies, adjuvant chemotherapy and radiotherapy didn't found effective [11]. Postoperative adjuvant radiation therapy might be useful in the treatment of patients with lymph node metastases and histologically tumor -positive surgical margin [12]. Local recurrence is very commonly seen. Most patients present with symptoms of increasing serum calcium levels and laboratory tests show accompanying high levels of PTH. Also distant metastases to bone, lung, and liver can be seen in parathyroid carcinoma. For local or distant metastasis diseases the goal of treatment is controlling hypercalcemia and symptoms of hypercalcemia. Localized diseases which were resectable, surgical resection can be performed [5,9].

In conclusion, although it is possible to obtain information about preoperative mass localization with similar clinical findings and imaging methods, it is difficult to distinguish between parathyroid adenomas and carcinomas. High parathormone levels should cause clinical suspicious in us about parathyroid carcinoma.

References

1. Shane E. Clinical review 122: Parathyroid carcinoma. J Clin Endocrinol Metab. 2001 Feb;86(2),:485-93.
2. Haven CJ, van Puijenbroek M, Tan MH, Teh BT, Fleuren GJ, van Wezel T, et al. Identification of MEN1 and HRPT2 somatic mutations in paraffin-embedded (sporadic) parathyroid carcinomas. Clin Endocrinol. 2007;67:370-6.
3. Wassif WS, Moniz CF, Friedman E, Wong S, Weber G, Nordenskjöld M, Peters TJ, Larsson C. Familial isolated hyperparathyroidism: a distinct genetic entity with an increased risk of parathyroid cancer. J Clin Endocrinol Metab. 1993 Dec;77(6):1485-9.
4. Tamler R, Lewis MS, LiVolsi VA, Genden EM. Parathyroid carcinoma: ultrasonographic and histologic features. Thyroid. 2005 Jul;15(7):744-5.
5. Fernandes JMP, Paiva C, Correia R, Polónia J, Moreira da Costa A. Parathyroid carcinoma: From a case report to a review of the literature. Int J Surg Case Rep. 2018;42:214-217. doi: 10.1016/j.ijscr.2017.11.030.
6. Marcocci C, Cetani F, Rubin MR, Silverberg SJ, Pinchera A, Bilezikian JP. Parathyroidcarcinoma. J Bone MinerRes. 2008;23:1869-80.
7. Spinelli C, Bonadio AG, Berti P, Materazzi G, Miccoli P. Cutaneous spreading of parathyroid carcinoma after fine needle aspiration cytology. J Endocrinol Invest. 2000 Apr;23(4):255-7.
8. Chiofalo MG, Scognamiglio F, Losito S, Lastoria S, Marone U, Pezzullo L. Huge parathyroid carcinoma: clinical considerations and literature review. World J Surg Oncol. 2005 Jun 23;3:39.
9. Koea JB, Shaw JH. Parathyroid cancer: biology and management. Surg Oncol. 1999 Nov;8(3):155-65.
10. Sandelin K, Auer G, Bondeson L, Grimelius L, Farnebo LO. Prognostic factors in parathyroid cancer: a review of 95 cases. World J Surg. 1992 Jul-Aug;16(4):724-31.
11. Givi B, Shah JP. Parathyroid carcinoma. Clin Oncol (R Coll Radiol). 2010 Aug;22(6):498-507.
12. Munson ND, Foote RL, Northcutt RC, Tiegs RD, Fitzpatrick LA, Grant CS, et al. Parathyroid carcinoma: is there a role for adjuvant radiation therapy? Cancer. 2003;98(11):2378–84.

J Surg Med. 2019;3(3):268-270.
DOI: 10.28982/josam.478202

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Liver alveolar hydatid cyst diagnosed patient with right intrahepatic biliary tract obstruction: A case report with special emphasis on radiological features

Alveolar kist hidatik tanılı hastada gelişen sağ intrahepatik safra yollarında obstrüksiyon: Radyolojik özelliklerinin vurgulandığı olgu sunumu

Fatih Ateş [1], Turgay Kara [1], Halil İbrahim Şara [1], Muhammed Sami Çoban [1], Mehmet Sedat Durmaz [2], Funda Gökgöz Durmaz [3]

[1] Department of Radiology, Education and Research Hospital, Health Sciences University, Konya, Turkey
[2] Department of Radiology, Selcuk University Medical Faculty, Konya, Turkey
[3] Karatay Community Health Center Department of Family Medicine, Konya, Turkey

ORCID ID of the authors
FA: 0000-0002-2693-4616
TK: 0000-0001-8448-9066
HİŞ: 0000-0001-9075-9237
MSÇ: 0000-0003-3078-0231
MSD: 0000-0002-1340-2477
FGD: 0000-0003-3043-5809

Corresponding author / Sorumlu yazar:
Fatih Ateş
Address / Adres: Sağlık Bilimleri Üniversitesi, Radyoloji, Eğitim ve Araştırma Hastanesi, Bölümler, Konya, Türkiye
e-Mail: fatih_ates81@hotmail.com

Informed Consent: The author stated that the written consent was obtained from the patient presented in the study.
Hasta Onamı: Yazar çalışmada sunulan hastadan yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş tarihi: 03.11.2018
Accepted / Kabul tarihi: 08.01.2019
Published / Yayın tarihi: 09.01.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Abstract

Hepatic alveolar echinococcosis is a rare parasitic disease caused by Echinococcosis multilocularis. The disease is diagnosed by a combination of serological tests, radiological modalities and histology of needle biopsy specimens. In this case, we present magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) findings in a patient with right intrahepatic biliary tract obstruction due hepatic alveolar echinococcosis. A 66-year-old female patient who was diagnosed as liver alveolar hydatid cyst at the external university hospital in her anamnesis presented for evaluation of right upper-quadrant abdominal pain. MRI and MRCP were taken to patient. Lesion with hyper-intense and iso-intense components were observed in T2A images with a diameter of approximately 70x65 mm, length of 76 mm, heterogeneous intensities, no definite boundaries in liver segment 6-7 on MRI and MRCP. Continuation of right intrahepatic bile ducts was not observed due secondary to pressure of lesion. The lumen was slightly prominent in the traceable segment of approximately 7 mm. In lesion's peripheral segments, intrahepatic bile ducts were dilated in segment 6-7 due secondary pressure of lesion. The intrahepatic main bile ducts were normally wide on the left. The diameter of the choledochus was measured approximately 9 mm at its most prominent location and is normally expanded. The gallbladder was hydropic and had a transverse diameter of approximately 48 mm. There was no calculi or matter occupying the lumen. Alveolar echinococcosis lesions mimic slow-growing tumors of the liver parenchyma that tend to infiltrate adjacent structures, especially the portal hilum, hepatic veins, inferior vena cava, and biliary system, and spread to other organs by means of hematogenous dissemination. These lesions may be misdiagnosed as malignant neoplasms if the diagnosis is based on clinical features and imaging findings of local invasion and regional or distant metastases, without serologic testing. If left untreated, alveolar echinococcosis is eventually fatal. Effective treatment options include benzimidazole therapy and surgical resection or liver transplantation.

Keywords: Echinococcosis, Magnetic Resonance cholangiopancreatography, Liver, Biliary tract obstruction

Öz

Hepatik elveolar ekinokokkozis Echinococcus multilocularis'e bağlı gelişen nadir bir parazitik hastalık olup tanı serolojik, radyolojik ve histopatolojik değerlendirme ile konur. Bu vakada alveolar ekinokokkozis tanılı hastada gelişen sağ intrehepatik safra yollarında obstrüksiyonun manyetik rezonans görüntüleme (MRG) ve manyetik rezonans kolanjiopankreotografi (MRKP) bulgularını sunduk. Hikayesinde üniversite hastanesinde karaciğer alveolar hidatik kist tanısı olduğunu öğrendiğimiz 66 yaşında kadın hasta sağ üst kadran ağrısı ile kliniğe başvurdu. Hastaya MRG ve MRKP tetkikleri çekildi. Karaciğer segment 6-7 de yaklaşık 70x65 mm çaplarında, 76 mm uzunluğunda, heterojen intensitede, sınırları net seçilemeyen, T2A görüntülerde hiperintens ve izointens komponentleri bulunan alan izlendi. Sağda intrahepatik safra yolları devamlılığı lezyon basısına sekonder izlenmedi. İzlenebilen distal yaklaşık 7 mm'lik segmentte lümeni hafif belirgindi. Lezyon periferik kesimlerinde segment 6-7'de intrahepatik safra yolları dilate görünümde olup intrahepatik ana safra kanalları solda normal genişlikte saptandı. Koledok çapı en belirgin yerinde yaklaşık 9 mm ölçülmüş olup normalden genişti. Safra kesesi hidropik görünümde olup transvers çapı yaklaşık 48 mm ölçülmüştür, lümeninde yer kaplayan lezyon yoktu. Alveoler ekinokokkoz lezyonları, komşu yapılara, özellikle portal hiluma, hepatik venlere, inferior vena kava ve safra sistemine infiltre olan ve hematojen yayılım yoluyla diğer organlara yayılan, karaciğer parankiminin yavaş büyüyen tümörlerini taklit eder. Bu lezyonlar, serolojik testler olmaksızın, lokal invazyon ve bölgesel veya uzak metastazların klinik özelliklerine ve görüntüleme bulgularına dayanarak, malign neoplazmalar olarak yanlış teşhis edilebilir. Tedavi edilmezse, alveoler ekinokokkozun sonunda ölümcül olur. Etkin tedavi seçenekleri arasında benzimidazol tedavisi ve cerrahi rezeksiyon veya karaciğer transplantasyonu yer alır.

Anahtar kelimeler: Kistik ekinokokkozis, Manyetik rezonans kolanjiopankreotografi, Karaciğer, Safra yolu obstrüksiyonu

How to cite / Atıf için: Ateş F, Kara T, Şara Hİ, Çoban MS, Durmaz MS, Durmaz FG. Liver alveolar hydatid cyst diagnosed patient with right intrahepatic biliary tract obstruction: A case report with special emphasis on radiological features. J Surg Med. 2019;3(3):268-270.

Introduction

The liver with portal system and hepatic arterial blood flow is one of the solid organs in which hematogenous pathologies are the most common. Parasitic liver cysts occur due to Echinococcus granulosus and Echinococcus alveolaris. Alveolar echinococcosis is a parasitic cyst form with as malignant and local invasion and distant organ metastases. Lesions cause destructive and infiltrative effects on the liver with biliary tracts or vascular invasions, causing liver dysfunction, biliary obstruction or abscess formation. These patients require mass resection or liver transplantation [1].

In practice, ultrasonography (US) is the most commonly used method in the evaluation and typing of liver hydatid cysts. Although computed tomography (CT) is more effective in demonstrating other organ cysts such as peritoneum and lung with cyst calcification and infection, CT can be inadequate in showing and typing the cyst content. Cyst content can be better shown by magnetic resonance imaging (MRI) in compatible patients and it is more suitable for follow-up after percutaneous treatment especially because it does not contain radiation. In addition, cystobiliary fistulas in special shots with magnetic resonance cholangiopancreatography (MRCP) or liver specific agents can be evaluated non-invasively [2].

In this case, we present MRI and MRCP findings in a patient with right intrahepatic biliary tract obstruction due hepatic alveolar echinococcosis.

Case presentation

A 66 year old female patient with diagnosed liver alveolar hydatid cyst in external university hospital in her anamnesis presented for evaluation of right upper-quadrant abdominal pain.

Lesion with a diameter of approximately 70x65x76 mm, with hyper-intense and isointense components, no definite boundaries were observed in T2A weighted images, in liver segment 6-7 on MRI and MRCP (Figure 1). Continuation of right intrahepatic bile ducts was not observed due to the pressure of lesion. The lumen was slightly prominent in the traceable segment of approximately 7 mm. Intrahepatic bile ducts were dilated in segment 6-7 due secondary pressure of lesion. The intrahepatic main bile ducts were normally wide on the left. The diameter of the choledochus was measured approximately 9 mm at its most prominent location and was dilatated. The gallbladder was hydropic in appearance and had a transverse diameter of approximately 48 mm, with no mass occupying the lumen. The pancreatic duct was normally wide (Figure 2). In laboratory, total bilirubin was 0.7 mg/dL and alkaline phosphatase was 113 IU/L. Gamma glutamyl transferase was 41.9. There was no abnormality in the hemogram examination. The case that we presented continued the follow-up and treatment in the university hospital. While preparing the case report, we informed the patient and obtained the consent.

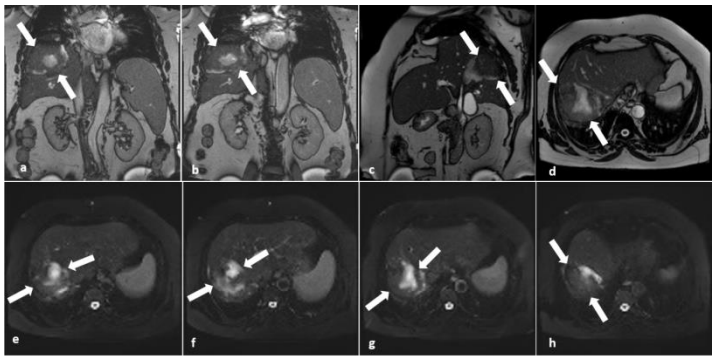

Figure 1: In the magnetic resonance cholangiopancreatography images; the coronal T2 (a, b), sagittal T2 (c), axial T2 (d) and fat-suppressed axial T2 (e-h) sections for liver; in the right lobe posterior superior segment; a mass lesion with solid components (arrow) of 76x70x65 mm diameter, heterogeneous intensity, with no borderline clearance, hyper-intense cystic T2A images, isointense with liver parenchyma was observed.

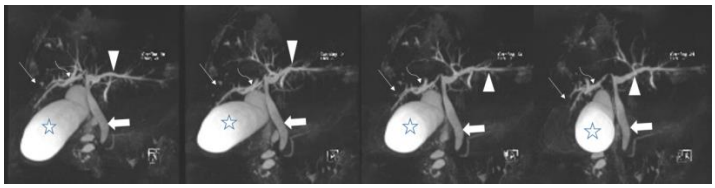

Figure 2: In the magnetic resonance cholangiopancreatography images obtained using the T2-weighted sequence; the gallbladder was observed in hydropic appearance (star). The choledochus was dilated and the blunt end was distal (arrow). Distal segment of right intrahepatic biliary tract was seemed occlusal due to mass compression (thin arrow) and was dilated in the proximal part (curved arrow).

Discussion

Hydatid cyst disease is a widespread human infection caused by the larval stage of the tapeworms of Echinococcus [3,4]. The clinical presentation of the disease varies with regard to the involvement of the held organ, the size of the cyst, the enlarged cyst and the adjacent organs. Liver hydatid cysts may cause a feeling of fullness in the abdomen, abdominal pain, vomiting and jaundice [5,6]. USG measurements have shown that cysts can grow 1-50 mm per year or remain unchanged for many years. They can also spontaneously rupture, collapse or disappear. They usually have no symptoms until they reach a diameter of 5 cm. Liver hydatid cysts show slower growth than in lungs [7]. As the size grows, it shows clinical signs due to pressure and occlusive effects.

The diagnosis of hydatid cyst is made by demonstration of cysts by various imaging methods. The diagnosis can be confirmed by serological tests [8]. Hydatid cysts can present with various clinical manifestations due to both the ability to perform various organ involvement and complications.

The liver is the most frequently affected organ, with a rate of 60-75%. Especially the right hepatic lobe is affected by the left lobe with a rate of 80%. Less common sites are the lungs, spleen, peritoneum, kidneys, brain, etc. [9]. Hydatid cysts are mostly asymptomatic and many hydatid cysts represent incidental clinical or radiological findings. Most symptomatic cysts are either complicated by rupture or secondary bacterial infection, or have symptoms of large size causes such as upper abdominal pain, swelling and discomfort [10]. Untreated Echinococcal cysts expose mass effect on the surrounding liver tissue. If not intervened, cystic pressure can exceed the pressure in the bile ducts by 5-30% of patients, resulting in cysts ruptured or fistulized into the bile ducts, spontaneous decompression of the cyst and cholangitis [11]. Imaging findings in biliary echinococcosis can be seen as filling defects due to biliary duct

dilatation which may extend to the peripheral channels, cystobiliary fistulas and biliary cysts or leaf-like membranes in the bile duct. In addition, irregularity / absence of the cyst wall, direct contact with the biliary tract, fluid-liquid levels in the cyst, or cystobiliary fistulae of fat particles should be considered [11,12].

In Echinococcus multilocularis infection, multiloculated alveolar cysts are observed and unlike E. granulosus, pericyst does not occur in the host and invasion to the surrounding tissue. The inflammatory process directly affects the biliary tract and portal vein branches, causing dilatation of the channels and parenchymal atrophy. In the imaging, E. multilocularis is an unclear infiltration that does not show contrast enhancement and contains solid and cystic areas. Biliary dilatation or direct parasitic biliary invasion due to hilar infiltration can be detected on MRI [11,12].

Visualization of biliary tracts often requires various imaging methods and is accepted as a US starting method. While the use of MRCP is increasing, ERCP is preferred for treatment purposes. It is clear that imaging methods have different contributions to each other, their weaknesses, and hence, to diagnosis. In order to avoid unnecessary examinations, the most appropriate methods should be determined and radiological findings should be evaluated as a whole. Interpretation of imaging findings together with clinical and laboratory findings is also very important for accurate diagnosis.

Alveolar echinococcosis mimics malignancy, also is frequently confused with other malignant liver lesions and has an infiltrative pattern [13]. Early diagnosis of the disease is very important in terms of treatment. Radiological findings have an important role and contribution in the diagnosis of the disease.

References

1. Haider HH, Nishida S, Selvaggi G, Levi D, Tekin A, Moon JI, Tzakis AG. Alveolar Echinococcosis induced liver failure: salvage by liver transplantation in an otherwise uniformly fatal disease. Clin Transplant. 2008;22:664-7.
2. Koc M. The investigation of clinical and radiological findings of hepatic alveolar cyst hydatid disease. Annals of Medical Research. 2018;25(4)768-71.
3. Biava FM, Dao A, Fortier B. Laboratory diagnosis of cystic hydatic disease. World J Surg. 2001;25:10-14.
4. Chautems R, Bubler L, Gold B, Chilcott M, Morel P, Mentba G. Long term results after complete or incomplete surgical resection of liver hydatid disease. Swiss Med Wkly. 2003;133:258-62.
5. Turkyilmaz Z, Sonmez K, Karabulut R, Demirogullari B, Gol H, Basaklar AC, et al. Conservative surgery for treatment of hydatidcysts in children. World J Surg. 2004;28:597-601.
6. Kurul IC, Topcu S, Altinok T, Yazici U, Tastepe I, Kaya S, et al. Onestage operation for hydatid disease of lung and liver: principles oftreatment. J Thorac Cardiovasc Surg. 2002;124:1212-5.
7. Altintaş N. Past to present: echinococcosis in Turkey. Acta Tropica. 2003;85:105-12.
8. Ciftci N, Ates F, Turkdagi H, Findik D. Evaluation of seropositivity of patients with cystic echinococcosis. Genel Tıp Derg. 2017;27(3):91-4.
9. Beggs I. The radiology of hydatid disease. AJR Am J Roentgenol. 1985;145(3):639-48.
10. Radford AJ. Hydatid Disease. In: Weatherall DJ, Ledingham JGG, Warell DA, eds.Oxford textbook of medicine. Oxford: Oxford University Press. 1982:5.442-4.
11. Catalano OA, Sahani DV, Forcione DG, et al. Biliary Infections: Spectrum of Imaging Findings and Management. Radiographics. 2009;29:2059-80.
12. Czermak BV, Akhan O, Hiemetzberger R, et al. Echinococcosis of the liver. Abdom Imaging. 2008;33:133-43.
13. Yanık F, Karamustafaoğlu YK, Yoruk Y. Dıagnostıc dılemma in discrimination between hydatıd cyst and Tumor, for two cases. Namık Kemal Medical Journal. 2017;5(1):44-9.

J Surg Med. 2019;3(3):271-273.
DOI: 10.28982/josam.470613

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Case of incomplete fibular hemimelia with tarsal coalition, pes planus, ball and socket ankle

Inkomplet fibular hemimelia'ya eşlik eden tarsal koalisyon, pes planus, ball-socket ayak bileği deformitesi olgusu

Emrah Doğan [1], Süha Gül [1], Neşat Çullu [2], Marwa Mouline Doğan [3]

[1] Mugla Sıtkı Koçman University EARH, Radiology, Turkey
[2] Mugla Sıtkı Koçman University, Faculty of Medicine, Radiology, Turkey
[3] Universite Mohammed VI, Department de Cardiologie, Morocco

ORCID ID of the author(s)
ED: 0000-0002-9446-2294
SG: 0000-0001-5625-5385
NÇ: 0000-0002-5045-3919
MMD: 0000-0002-3401-895X

Abstract

Fibular hemimelia (FH) is a congenital disease with a clinical spectrum ranging from mild fibular hypoplasia to fibular aplasia. There is no proven genetic factor. Some anomalies can accompany FH such as tarsal coalition, ulnar hemimelia, amelia, syndactyly, several extremity anomalies, renal anomalies and cardiac anomalies. Our case is about unilateral and incomplete type of right-side FH in a 14 years old female patient. Tibia was curved (bowing) and short. Disparity of measure with left lower extremity was monitored. Tarsal coalition in osseous form, tibial curve anomaly and small bone part placed in fibula distal region compatible with FH, were visualized. There was curved joint form in the same ankle with hemimelia compatible with ball and socket ankle deformity. Calcaneal inclination angle was 120°. The findings were compatible with pes planus.

Keywords: Fibular hemimelia, Tarsal coalition, Fibular hypoplasia

Öz

Fibular hemimelia (FH), hafif fibular hipoplazi'den fibular aplaziye kadar uzanan klinik spektrumu olan bir konjenital hastalıktır. Kanıtlanmış bir genetik faktör yoktur. Tarsal koalisyon, ulnar hemimelia, amelia, sindaktili, kardiyak anomaliler, renal anomaliler ve çeşitli ekstremite anomalileri anomaliye eşlik edebilir. On dört yaşında kız olguda sağda tek taraflı ve parsiyel tipte FH mevcuttu. Tibia kavisli (eğimli), kısa ve ekstemiteler arasında uzunluk bakımından uyumsuzluk mevcuttu. Osseöz formda tarsal koalisyon deformiteye eşlik etmekteydi. Fibula distal parçası mevcuttu. Aynı taraf ayak bileğinde ball-socket deformitesi saptandı. Kalkaneal eğim açısı 120° idi. Bulgular pes planus ile uyumluydu.

Anahtar kelimeler: Fibular hemimelia, Tarsal koalisyon, Fibular hipoplazi

Introduction

Fibular hemimelia (FH) is a congenital disease characterized by the absence of a partial or complete part of the fibula. It occurs between 7/1000000 and 10/1000000 live births [1]. The word "Hemimelia" originates from the Greek word "Hemi and melos" meaning half limb because of shortening extremity [2]. This anomaly was defined by Gollier in 1698 for the first time. Stevens PM and Arms D [3] stated that this pathology is not only fibular deficiency but also accompanied by many deformities. Therefore, he emphasized that the terms FH or fibular aplasia, hypoplasia was insufficient to define this pathology and he defined this disease as postaxial hypoplasia of the lower extremity. This paper reports, with clinical and radiological findings, the case of a patient incomplete fibular hemimelia with tarsal coalition, pes planus, ball and socket ankle.

Corresponding author / Sorumlu yazar:
Emrah Doğan
Address / Adres: Muğla Sıtkı Koçman Üniversitesi Eğitim ve Araştırma Hastanesi, Radyoloji Anabilim Dalı, Muğla, Türkiye
e-Mail: dr_e_dogan@hotmail.com

Informed Consent: The author stated that the written consent was obtained from the parents of the patient presented in the study.
Hasta Onamı: Yazar çalışmada sunulan hastanın ebeveyinlerinden yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş tarihi: 15.10.2018
Accepted / Kabul tarihi: 29.11.2018
Published / Yayın tarihi: 15.01.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite / Atıf için: Doğan E, Gül S, Çullu N, Doğan MM. Case of incomplete fibular hemimelia with tarsal coalition, pes planus, ball and socket ankle. J Surg Med. 2019;3(3):271-273.

Case presentation

Our patient is a 14 years old female who was followed for FH since childhood ages. The patient could walk but there was postural discrepancy and pain. Pain was mild range therefore no analgesic treatment was necessary. Abdominal ultrasound and cardiac evaluation were performed. Neither congenital anomaly nor variation was monitored. Upper extremities were normal. Disparity of extremities length was caused by curvature of the tibia (Figure 1). There was tarsal coalition in osseous form (Figure 2) and small part bone was visualized in the fibula distal region. There was no connection between tibia and hemimelic fibula part (Figure 3). In addition, calcaneal inclination angle was 120° which is compatible with pes planus. Furthermore, there was curved junction between tibia and talar bone corresponding to ball and socket ankle. The consent form was taken from the parents of the patient presented in this study.

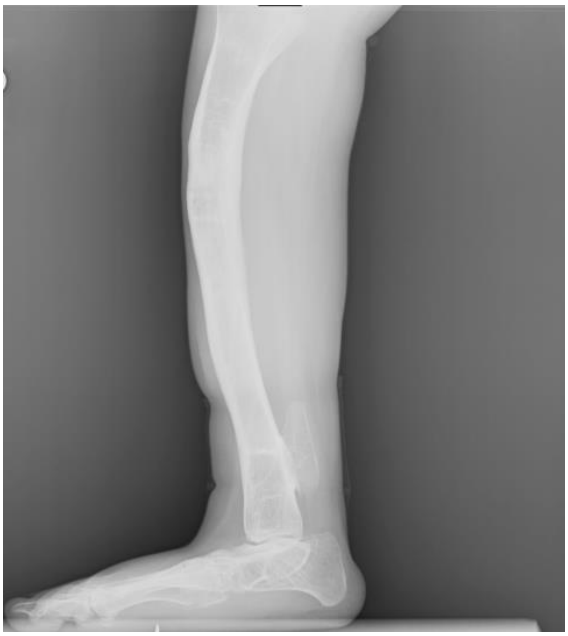

Figure 1: Curved tibia and tibial range was short

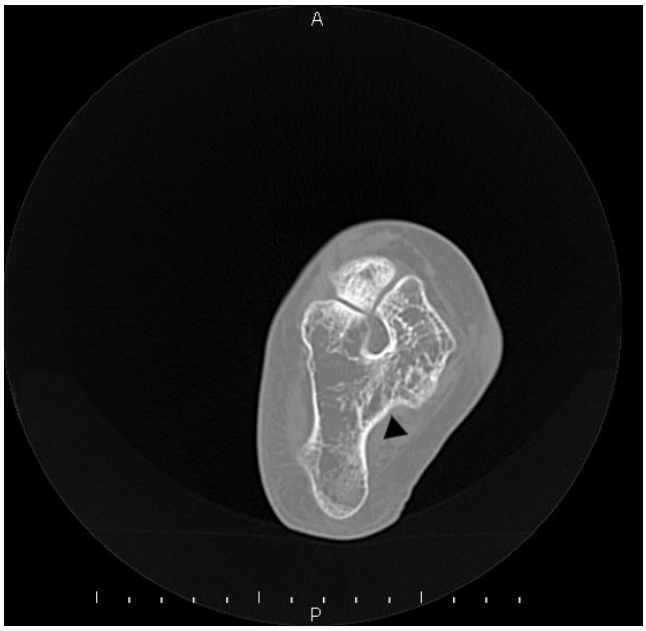

Figure 2: Arrow head: tarsal osseous coalition

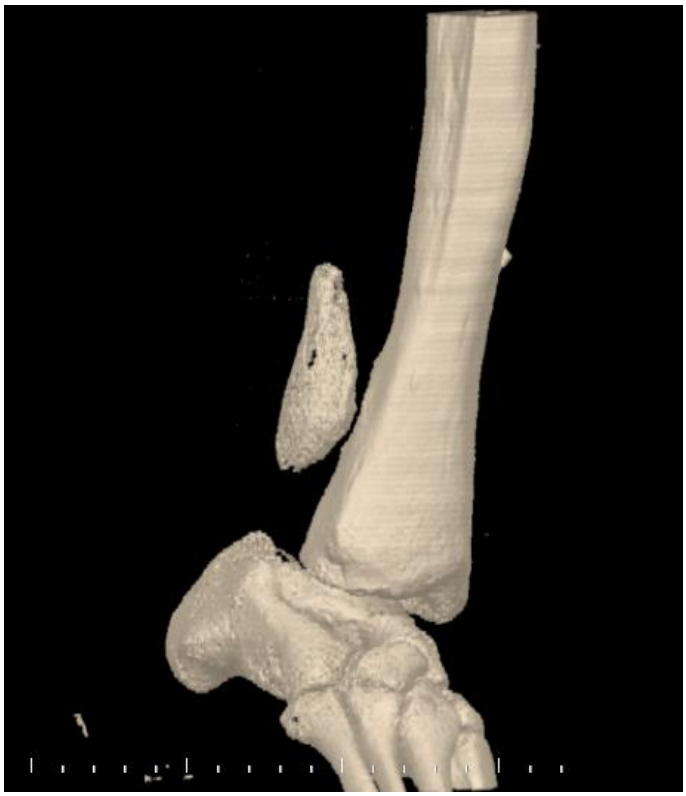

Figure 3: In 3D images hemimelic fibula and no connection with tibia

Discussion

FH has a clinical spectrum ranging from mild fibular hypoplasia to fibular aplasia. The complete form is more common than the incomplete form; unilateral involvement is more common than bilateral and the right side is more commonly affected than the left [4]. The etiology of this anomaly, which is generally seen as unilateral, is not known exactly. No genetic predisposition was detected and most cases occurred sporadically [5]. It is seen twice more in boys than in girls [1].

There are various classification methods in literature. Most common used ones belong to Stanitski and Achterman-Kalamchy [1,2].

Three types of fibular hemimelia are described according to Stanitski [6]:

- Type I: It is mild type of FH. There is partial absence of fibula and tibial curving, without foot defect. Functional impairment is limited and bone defect is visible only on radiological examination.
- Type II: It is moderate type of FH. There is a complete or almost complete absence of the fibula. Lesion may be unilateral or sometimes bilateral. This type is linked with equinovalgus deformity of the foot and anteromedial bowing of the tibia. Bones of the foot may be hypoplastic or absent. There may be also tarsal coalition with development of a ball-and-socket ankle. There is moderate to marked limb shortening.
- Type III: It is severe type of FH. There is bilateral absence of the fibula. It may be associated with proximal femoral deficiency, deformities of the upper extremities or hemivertebra

Another classification according to Achterman and Kalamchi [7]:

- Type IA: Fibula is present. Epiphyses are small and mildest tibial growth defects are present
- Type IB: Partial absence of the fibula. Proximally 30% to 50% the fibula's length is absent. Distally, the fibula is present but does not support the ankle.
- Type II: Complete absence of the fibula

Our case can be classified as type II according to Stansky and between type IB and II according to Ackerman.

FH is a complex entity which has several anomalies including different organ and systems. The first visible sign of FH is the inequality in leg length. This may be due not only to the tibial shortness, but also to the proximal absence of the femur. The second important finding is bowing of the tibia in the anteromedial medial axis. This deformity in the sagittal and coronal plane may be accompanied by rotation. Most common anomaly associated to FH is tarsal coalition [1,8]. There was tibial bowing, leg length shortening and tarsal coalition with FH in our patient. Femur was normal.

Tarsal coalition is the fusion between the talus and calcaneus. The plain radiography is the most common diagnostic modality to visualize a tarsal coalition. However, tarsal coalitions can be completely cartilaginous. The radiographic diagnosis becomes more difficult. Computed tomography provides superior imaging capabilities, but it is not used routinely. A talocalcaneal coalition represents the failure of the embryonic precursors of the talus and the calcaneus to segment completely from one another. These coalitions are most often cartilaginous in young children. It can be visible only after progressive ossification [9].

The reported prevalence of tarsal coalition is ranging from 1% to 2%, however a recent cadaveric study demonstrated a prevalence of 13%. Middle facet talocalcaneal coalitions are noticed in 45% of all tarsal coalitions. Between the ages of eight and sixteen years, tarsal coalitions cause gradual flattening of the longitudinal arch and stiffness of the subtalar joint. Pain, which is present in about 25% of feet with a tarsal coalition, is the consensual indication for treatment [10]. Our patient presented a middle joint osseous type calcaneo-naviculer coalition. There was only mild degree of pain. No detected stiffness in subtalar joint but flattened longitudinal arc was present.

FH can accompany ulnar hemimelia, amelia, syndactyly, acetabular dysplasia, external rotational deformity, shortening varus/valgus femoral neck, hypoplastic lateral condyle, genu valgum, anterior cruciate ligament deficiency, posterior cruciate ligament deficiency, ball and socket deformity, valgus deformity, instability, dislocation, equinovalgus, tarsal coalition, absent rays, equinovarus, renal anomalies and cardiac anomalies [8]

Another important anomaly which was present in our patient is pes planus. It results from loss of the medial longitudinal arch and can be either rigid or flexible. Radiography is the main method for the evaluation. The longitudinal arch of the foot must be assessed on a weight bearing lateral foot radiography [11,12]. Inclination angle is low in pes planus (<20°) [13]. It is linked to ball-and-socket ankle deformity [14].

The ball-and-socket ankle joint is a malformation of the ankle in which the articular surface of the talus is hemispherical in both the anteroposterior and lateral projections. Congenital type of ball-and-socket ankle joint can be associate with tarsal coalition, short limb, ray fusion and deletion anomalies with or without FM [14].

FH is part of a multisystemic entity which also referred to postaxial hypoplasia. There are no proven genetic predisposing factors about this entity. There are sporadic cases with a few anomalies added to FH. That's why some aspect of FH is blurred. Our patient was admitted to hospital with mild symptoms and presented small part of the listed anomalies. Nevertheless, type of FH was not mild according to classification 'type IB'. In addition to discordance between clinical and radiological findings, our patient with FH presented not only a tarsal coalition which is a common anomaly but also rare deformities like pes planus and ball and socket ankle.

References

1. Yıldız C, Koca K, Cakmak G, Basbozkurt M. Fibular hemimelia. Türk Ortopedi ve Travmatoloji Birliği Derneği Dergisi. 2009;8:48-57.
2. Barawi AR, Amen ZJ. Management of fibular hemimelia (Congenital absence of fibula) using ilizarov method in sulaimani. European Scientific Journal. 2015;11:304-16.
3. Stevens PM, Arms D. Postaxial hypoplasia of the lower extremity. J Pediatr Orthop. 2000 Mar-Apr;20(2):166-72.
4. Sidhu AS, Mann HS, Tanwar YS, Kumar A, Gursukhman DS. Fibular hemimelia - a case report. Pb Journal of Orthopaedics. 2010;12:40-3.
5. Cheng JC, Cheung KW, Ng BK. Severe progressive deformities after limb lengthening in type-II fibular hemimelia. Journal of Bone & Joint Surgery - British. 1998;80(5):772-6.
6. Stanitski DF, Stanitski CL. Fibular hemimelia: a new classification system. J Pediatr Orthop. 2003;23(1):30-4.
7. Achterman C, Kalamchi A. Congenital deficiency of the fibula. J Bone Joint Surg Br. 1979;61(2):133-7.
8. Hamdy R, Makhdom AM, Saran N, Birch J. Congenital fibular deficiency review article. American Academy of Orthopaedic Surgeons. 2014;22(4):246-54.
9. Dennis Y, Grogan P, Holt GR, Ogden JA. Talocalcaneal coalition in patients who have fibular hemimelia or proximal femoral focal deficiency. The Journal of Bone and Joint Surgery. 1994;76(9):1363-70.
10. Mosca VS, Bevan WP. Talocalcaneal tarsal coalitions and the calcaneal lengthening osteotomy: The role of deformity correction. J Bone Joint Surg Am. 2012;94:1584-94.
11. Dimmick S, Chhabra A, Grujic L, Linklater JM. Acquired flat foot deformity: postoperative imaging. Semin Musculoskelet Radiol. 2012;16(3):217-32.
12. Staheli LT, Chew DE, Corbett M. The longitudinal arch. A survey of eight hundred and eighty-two feet in normal children and adults. J Bone Joint Surg Am. 1987;69(3):426-8.
13. Gentili A, Masih S, Yao L, Seeger LL. Foot axes and angles. The British Journal of Radiology. 1996;69(826):968–74.
14. Pistoia F, Ozonoff MB, Wintz P. Ball-and-socket ankle joint. Skeletal Radiol. 1987;16(6):447-51.

J Surg Med. 2019;3(3):274-275.
DOI: 10.28982/josam.502639

Journal of Surgery and Medicine
e-ISSN: 2602-2079

A rare and incidental finding during colonoscopy: solitary polypoid ganglioneuroma: A case report

Kolonoskopide nadir ve insidental bulgu: soliter polipoid ganglionörom: Olgu sunumu

Elif Usturalı Keskin [1], Tufan Yılmaz [1], Gürol Şen [2]

[1] Mustafakemalpaşa State Hospital, Department of Pathology, Bursa, Turkey
[2] Mustafakemalpaşa State Hospital, Department of General Surgery, Bursa, Turkey

ORCID ID of the author(s)
EUK: 0000-0003-0656-2576
TY: 0000-0001-9834-583X
GŞ: 0000-0002-8897-5616

Abstract
Ganglioneuromas (GNs) are benign, slow growing and well differentiated neuroectodermal neoplasias. They are derived from developing neuronal cells of the sympathetic nervous system. They occur mostly in children and are located in the posterior mediastinum, retroperitoneum. We present a case of incidental solitary polypoid ganglioneuroma of the colon. A 70 year old woman underwent colonoscopy for colon cancer screening. She has no abdominal or intestinal symptoms. In hepatic flexure of the colon a spherical polypoid lesion that was 1.4 cm in diameter was detected endoscopically. Biopsy was taken from the polyp. The histopathology revealed a biphasic polypoid tumor with ganglion cells and schwannian stroma on hematoxylin and eosin stain. Final histopathological diagnosis was polypoid ganglioneuroma of the colon. Ganglioneuromatous polyposis and diffuse ganglioneuromatosis are associated with several systemic syndromes. Solitary GNs are generally asymptomatic. Treatment of GNs depends on their size, location, and clinical findings such as bleeding or obstruction. Prognosis is usually excellent. Polypectomy is curative for polypoid GN. However the patients with ganglioneuromatous polyposis and diffuse form may need colectomy.
Keywords: Endoscopy, Ganglioneuroma, Colon polyp, Polypoid ganglioneuroma

Öz
Ganglionöromlar (GNs) benign, yavaş büyüyen ve iyi diferansiye nöroektodermal neoplazilerdir. Sempatik sinir sisteminde gelişen nöronal hücrelerden köken alırlar. Çoğunlukla çocuklarda ve posterior mediasten, retroperiton yerleşimlidir. Kolonun insidental soliter polipoid ganglionöromu olgusunu sunduk. 70 yaşında kadın hastaya kanser taraması için kolonoskopi uygulandı. Abdominal ya da intestinal semptomu yoktu. Kolonoskopide kolon hepatik fleksurada 1.4 cm çaplı yuvarlak polipoid lezyon saptandı. Polipten biyopsi alındı. Hematoksilen eozin boyalı histopatolojik kesitlerde ganglion hücreleri ve schwanian stromadan oluşan bifazik polipoid tümör izlendi. Ganglionöromatoz polipozis ve diffüz ganglionöromatozis çeşitli sistemik sendromlarla ilişkilidir. Soliter ganglionöromlar genellikle asemptomatiktir. Ganglionöromlarda tedavi boyut, lokalizasyon, kanama ve obstruksiyon gibi klinik bulgulara bağlıdır. Prognoz genellikle mükemmeldir. Polipoid GN da tedavi polipektomidir. Ganglionöromatoz polipozis ve diffüz formlardaki hastalara kolektomi gerekebilir.
Anahtar kelimeler: Endoskopi, Ganglionörom, Kolon polip, Polipoid ganglionörom

Corresponding author / Sorumlu yazar:
Elif Usturalı Keskin
Address / Adres: Mustafakemalpaşa Devlet Hastanesi, Patoloji Anabilim Dalı, Bursa, Türkiye
e-Mail: drelifkeskin@gmail.com

Informed Consent: The author stated that the written consent was obtained from the patient presented in the study.
Hasta Onamı: Yazar çalışmada sunulan hastadan yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş tarihi: 25.12.2018
Accepted / Kabul tarihi: 21.02.2019
Published / Yayın tarihi: 22.02.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Introduction

Ganglioneuromas (GNs) are benign, slow growing and well differentiated neuroectodermal neoplasia that does not contain immature elements. They are derived from developing neuronal cells of the sympathetic nervous system [1].

GNs are rarely found gastrointestinal tract and uncommon in the colon. They occur mostly in children and are located in the posterior mediastinum, retroperitoneum [2]. A review of published cases revealed that GNs have a predilection for the head, neck and or adrenal glands [3].

In this study we present a case of incidental solitary polypoid ganglioneuroma of the colon.

Case presentation

A 70 year old woman underwent colonoscopy for colon cancer screening. She has no abdominal or intestinal symptoms and family history. On laboratory test hemoglobin was 10.2 g/dL, hematocrit was 33.3%. In hepatic flexure of the colon a spherical polypoid lesion that was 1.4 cm in diameter was detected endoscopically (Figure 1). Biopsy was taken from the polyp. Multiple diverticula were also found in different segments of the colon. The histopathology revealed a biphasic polypoid tumor with ganglion cells and schwannian stroma on hematoxylin and eosin stain (Figure 2). The ganglion cells were mature with prominent nucleoli. Final histopathological diagnosis was polypoid ganglioneuroma of the colon. Polypectomy of the lesion was planned and the patient was referred to another center for polypectomy. Informed consent was obtained from the patient due to this case report.

How to cite / Atıf için: Keskin EU, Yılmaz T, Şen G. A rare and incidental finding during colonoscopy: solitary polypoid ganglioneuroma: A case report. J Surg Med. 2019;3(3):274-275.

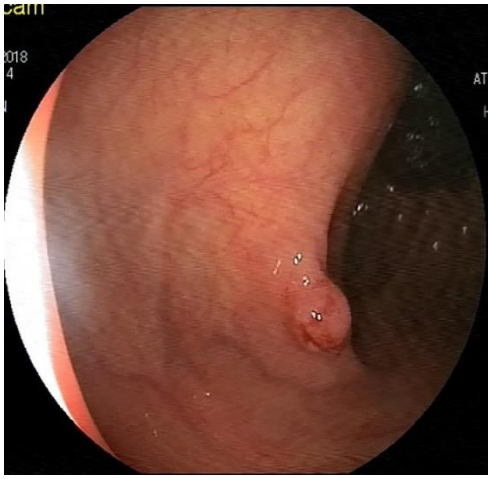

Figure 1: Endoscopic image of a sessile polyp with a diameter 1.4cm is observed in the colon

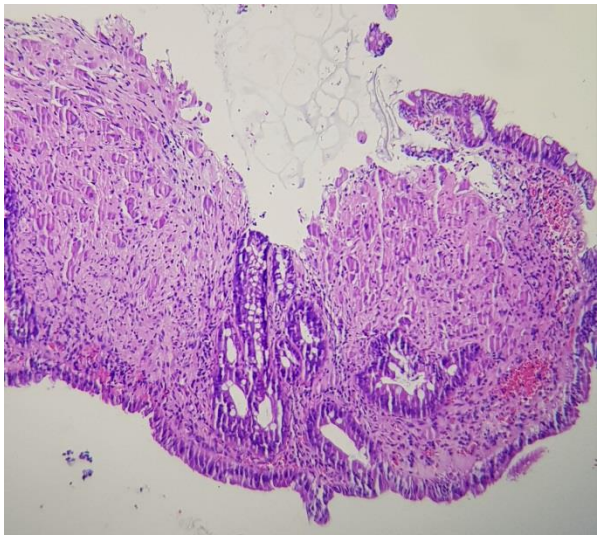

Figure 2: Hematoxylin and eosin stain of the ganglioneuroma. Ganglion cells and stromal cells are present in the lamina propria (magnification 4x)

Discussion

GNs may arise anywhere along paravertebral sympathetic plexus. Common sites of origin are retroperitoneal, mediastinal, or cervical region [4]. GNs of the gastrointestinal tract are extremely rare [2]. They may confine to the mucosa and produce polypoid lesions [2].

Gastrointestinal GNs consist of 3 subgroups: 1) solitary polypoid GN, 2) ganglioneuromatous polyposis, 3) diffuse ganglioneuromatosis [5]. Polipoid GNs are often small and may be sessile or pedunculated [1]. Ganglioneuromatous polyposis usually has many polyps, often 20 or more [6]. Diffuse ganglioneuromatosis is nodular and diffuse tissue that is transmural or mucosal. These lesions cover the myenteric plexus and can be ranging up to 17cm [6]. Ganglioneuromatous polyposis and diffuse ganglioneuromatosis are associated with several systemic syndromes such as multiple endocrine neoplasia type IIB, neurofibromatosis type I, juvenile polyposis, tuberous sclerosis, and Cowden's syndrome [1,3]. Solitary GNs are generally asymptomatic [3]. The patients with ganglioneuromatous polyposis may have a family history of multiple intestinal polyps, adrenal myolipomas, and nodular goiter [2]. Our patient has no family or medical history.

Clinical presentation of GN is mostly asymptomatic [3]. They often lead to thickening of the bowel wall, submucosal nodularities and strictures. Patients can present with constipation, obstruction, abdominal pain, weight loss, and bleeding [6]. Fifteen intestinal GNs cases were reported and only 4 cases presented with bleeding [6]. The patient in present case was asymptomatic but on laboratory tests blood counting was associated anemia. She was probably bleeding.

Although GNs usually develop in children they are often detected in adults because of slow growing [4]. They rarely observed over the age of 60 years [4]. Although mature GNs are generally hormonally inactive, they rarely produce catecholamine. The patients with hormone producing tumor may present with hypertension, diarrhea and flushing [4].

GNs are hamartomatous tumors derived from the autonomic nervous system. GNs are not differentiated from hyperplastic or adenomatous polyps endoscopically [1]. In these report a solitary polypoid GN was incidentally find out during endoscopy. Intestinal ganglioneuroma is always a microscopic diagnosis. The diagnosis can be made on routine hematoxylin and eosin stains. GNs are characterized by hyperplasia of ganglion cells, nerve fibers, and supporting cells of the enteric nervous system.

There is no specific treatment for GNs. It depends on their size, location, and clinical findings such as bleeding or obstruction [1]. Prognosis is usually excellent. Morbidity rate is very low in the mucosal variant [2]. A study of 28 patients with solitary GNs found that after 8 years follow up, none of the patients evolved complications [7]. Polypectomy is curative for polypoid GN. However the patients with ganglioneuromatous polyposis and diffuse form may need colectomy [1]. In our case polypectomy was planned.

Although there is no data on the association of polypoid GN and colon cancer, patients should be screened for associated genetic syndromes and for tumors in thyroid, colon, breast and uterus [6]. However some authors claim that it is unnecessary because of benign nature of polypoid GN [1].

Conclusion

Solitary polypoid ganglioneuroma may lead to weight loss and bleeding, may be associated with systemic syndromes in multiple cases and should be kept in mind in the differential diagnosis of colon polyps.

References

1. Fiori E, Pozzessere C, Lamazza A, Leone G, Borrini F, Schillaci A, Mingazzini P. Endoscopic treatment of ganglioneuroma of the colon associated with a lipoma: a case report. J Med Case Rep. 2012 Sep 14;6:304. doi: 10.1186/1752-1947-6-304.
2. Sayki Arslan M, Ekiz F, Yilmaz G, Coban S, Savas B, Ensari A, Ormeci N. Ganglioneuromatous polyposis of the colon in a patient with multiple adenomatous polyps. Turk J Gastroenterol. 2012;23(6):780-3.
3. Ofori E, Ona M, Ramai D, Huang T, Xiao P, Reddy M. Colonic Ganglioneuroma: A Rare Finding during Colorectal Cancer Screening. Case Rep Gastroenterol. 2017 Aug 8;11(2):434-439. doi: 10.1159/000477716. eCollection 2017 May-Aug.
4. Kumar S, Singh S, Chandna A. Organ Preservation in a Case of Retroperitoneal Ganglioneuroma: A Case Report and Review of Literature. Case Rep Surg. 2016;2016:6597374. doi: 10.1155/2016/6597374. Epub 2016 Sep 7.
5. Matthews MA, Adler BH, Arnold MA, Kumar S, Carvalho R, Besner GE. Diffuse intestinal ganglioneuromatosis in a child. J Pediatr Surg. 2013 May;48(5):1129-33. doi: 10.1016/j.jpedsurg.2013.03.066.
6. Abraham G, Prakash SR. Solitary Colonic Ganglioneuroma: A Rare Incidental Finding of Hematochezia. Case Rep Gastrointest Med. 2015;2015:794985. doi: 10.1155/2015/794985. Epub 2015 May 14.
7. Shekitka KM, Sobin LH. Ganglioneuromas of the gastrointestinal tract. Relation to Von Recklinghausen disease and other multiple tumor syndromes. Am J Surg Pathol. 1994 Mar;18(3):250-7.

J Surg Med. 2019;3(3):276-277.
DOI: 10.28982/josam.507306

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Thymolipoma with massive pleural effusion: A case report

Masif plevral efüzyon ile seyreden timolipom: Olgu sunumu

Zeynep Bayramoğlu [1], Ethem Ömeroğlu [1], Yaşar Ünlü [1]

[1] Konya Training and Research Hospital, Department of Pathology, Konya, Turkey

ORCID ID of the author(s)
ZB: 0000-0001-7075-8819
EÖ: 0000-0002-4943-6871
YÜ: 0000-0002-3951-8881

Abstract
Thymolipoma is a rare and benign lesion originating from the anterior mediastinum. Thymolipoma is mostly diagnosed incidentally. However, cough, dyspnea and chest pain can be seen. A 35-year-old male patient presented to our hospital with the complaint of shortness of breath lasting for one month. The physical examination revealed a massive pleural effusion on the right. In computed tomography (CT) imaging of the thorax, a soft tissue density of 7.5x5x5 cm in size, containing calcifications were observed in the anterior mediastinum. A right thoracotomy was performed for the treatment and to make a definite diagnosis. The histopathological examination resulted in the diagnosis of a thymolipoma. We presented our case with its differential diagnosis because of its rarity.
Keywords: Thymus, Thymolipoma, Mediastinum

Öz
Timolipomlar nadir görülen, ön mediastenden köken alan benign tümörlerdir. Genellikle insidental olarak bulunmakla birlikte öksürük, dispne ve göğüs ağrısı görülebilir. 35 yaşında erkek hastamız, bir aydır devam eden nefes darlığı şikayeti ile hastanemize başvurmuştur. Hastamızda sağ masif plevral effüzyon saptandı. Bilgisayarlı toraks tomografisinde (BT) anterior mediastende kalsifikasyonlar içeren 7,5x5x5 cm boyutlarında yumuşak doku dansitesi izlenmiştir. Tedavi ve kesin tanı için hastaya sağ torakotomi yapılmıştır. Histopatolojik inceleme, timolipom tanısını konuldu. Olgumuzu nadir olması nedeniyle ayırıcı tanıları ile birlikte sunduk.
Anahtar kelimeler: Timus, Timolipom, Mediasten

Introduction

Thymolipoma is a rare benign tumor, originating from the anterior mediastinum. It accounts for 2-9% of all thymus neoplasms. It is composed of fat tissue, epithelium, and the lymphoid tissue of the thymus. The etiology of the disease has not been completely clarified yet [1-3]. Thymolipoma was first described by Hall in 1948 [4]. Thymolipoma is mostly diagnosed incidentally. Thymolipoma is composed of mature adipose tissue and thymus tissue histopathologically. Fat tissue is composed of mature adipocytes, without showing atypia. Thymus tissue consists of atrophic thymic epithelium and areas of thymus parenchyma containing Hassall's corpuscles [1-2]. In most cases, calcification of Hassall's corpuscles and areas of cystic degeneration can be observed [1,2,5]. The histopathological differential diagnosis of thymolipoma should include thymic hyperplasia, lipoma, and well-differentiated liposarcoma [1-2]. The histopathological differential diagnosis of thymolipoma is summarized in Table 1 [1-2]. Thymolipoma may rarely contain thymoma or a carcinoid tumor. An immunohistochemical examination is usually not required for diagnosis [1].

Case presentation

A 35-year-old male patient presented to our hospital with the complaint of shortness of breath lasting for one month. The patient's medical history informed that he smoked 20 packs of cigarettes per year and had a diagnosis of ankylosing spondylitis. The family history was non-specific. We were informed that the patient was an engineer and had no exposure to asbestos. In the physical examination; blood pressure was 120/85 mmHg, pulse rate was 82/minute, and the respiratory rate was 18/minute. The respiratory system examination revealed dullness to percussion over the right hemithorax and decreased respiratory sounds. The results of hemogram, biochemistry tests, and urinalysis were within normal limits and the viral markers were negative. The chest radiography and ultrasound (US) examination of the thorax showed that, in line with the findings of the physical examination, the costodiaphragmatic recess was blunted and a massive amount of pleural fluid was present.

Corresponding author / Sorumlu yazar:
Zeynep Bayramoğlu
Address / Adres: Konya Eğitim ve Araştırma Hastanesi, Patoloji Bölümü Meram, Konya, Türkiye
e-Mail: drzeynepbayramoglu@hotmail.com

Informed Consent: The author stated that the written consent was obtained from the patient presented in the study.
Hasta Onamı: Yazar çalışmada sunulan hastadan yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş tarihi: 03.01.2019
Accepted / Kabul tarihi: 04.03.2019
Published / Yayın tarihi: 05.03.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite / Atıf için: Bayramoğlu Z, Ömeroğlu E, Ünlü Y. Thymolipoma with massive pleural effusion: A case report. J Surg Med. 2019;3(3):276-277.

Table 1: Histopathological differential diagnosis of thymolipoma [1-2].

Thymolipoma	• Consists of small amounts of mature adipose tissue and thymic tissue residues • Fat tissue consists of mature adipocytes that do not show atypia • Contains thymic tissue component • Calcification and cystic degeneration can be observed • There are no germinal centers
Thymus Hyperplasia	• Normal thymic structure • Adipose tissue is not seen too much • Germinal centers are available
Lipoma	• Thymic tissue is not detected • Nuclear atypia non-observed lipocytes
Well-differentiated liposarcoma	• Nuclear atypia and lipoblasts are observed. • Thymic epithelium is not detected • Positive reaction with immunohistochemical MDM-2 may support the diagnosis of well-differentiated liposarcoma

The pleural fluid was drained and its volume was determined to be 800 cc. Computed tomography (CT) of the thorax showed a large mass of 7.5x5x5 cm in the anterior mediastinum, containing fat tissue, calcifications, fine bands, and vascular structures (Figure 1). The levels of blood gases were not abnormal. A right thoracotomy was performed for the treatment and to make a definite diagnosis. The mass originating from the anterior mediastinum was excised completely and it was submitted for pathological examination. In the macroscopic examination, the mass was 10x7x5 cm in size, slightly lobulated, and in yellow-to-white color. The cross-sections of the mass were observed in yellow-grey color, containing calcifications and hard nodules. The microscopic examination revealed a mature fat tissue, containing Hassall's corpuscles, thymus tissue, and calcifications (Figure 2). A thymolipoma diagnosis was made based on the histopathological finding. The patient consent was taken before writing this case report.

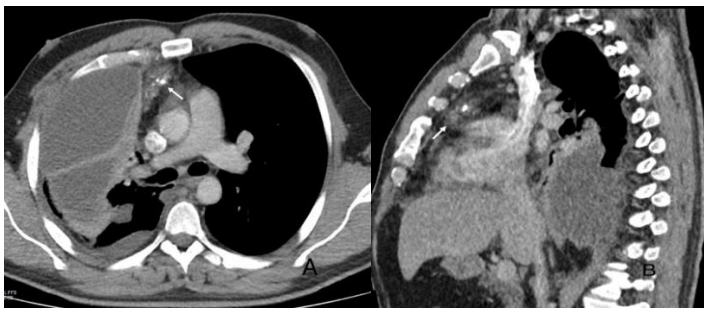

Figure 1: A: Axial contrast-enhanced computed tomography image shows a hyperdense lesion with calcifications within the anterior mediastinum, B: Sagittal contrast-enhanced computed tomography image shows a hyperdense lesion with calcifications within the anterior mediastinum

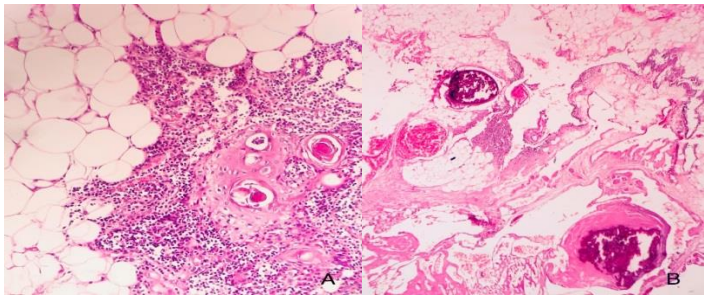

Figure 2: A: Thymus tissue and fat tissue at small magnification (H & E 20X), B: Thymus tissue and fat tissue containing calcification areas at small magnification (H & E 10X)

Discussion

Thymolipoma is a rare and benign lesion originating from the anterior mediastinum [1-2]. The etiology of thymolipoma has not been completely explained yet, however, there are several suggestions for its clarification. It was preliminarily suggested that these lesions were lipomas in the thymus tissue. After noticing that the amount of the thymus tissue itself was also increased significantly, this point of view was abandoned. Then, it was considered that these lesions represented a co-existence of lipoma and thymoma, however, this point of view was also abandoned as thymus tissue was normal histologically. Another argument was that the tumor initially began to develop as real thymic hyperplasia and then degenerated into fat tissue [1-3].

Thymolipoma is usually diagnosed incidentally. Local symptoms may also occur including a cough, dyspnea, chest pain, and cyanosis in symptomatic cases. Myasthenia gravis is also commonly seen. In rare cases; aplastic anemia, erythrocytic hypoplasia, and hypogammaglobulinemia may develop [6-12].

Thoracic CT and / or MRI in the radiological diagnosis of thymolipoma support the diagnosis by showing the fat content of the tumor. In the radiological differential diagnosis, the lesions involving the anterior mediastinum should be considered. Germ cell tumors, thymic hyperplasia, lipoma, liposarcoma, lymphoma, mediastinal fat pad, diaphragmatic herniation, lymphangioma, hemangioma are included in the differential diagnosis of thymolipoma. The wide range of radiological differential diagnosis necessitates histopathological evaluation [13-14]. In this article, we reported a patient with thymolipoma presenting with massive pleural effusion, as this clinical condition is rare.

Acknowledgements

We thank Dr. Vefa Öner from Konya Training and Research Hospital for radiological images.

References

1. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. Introduction to the 2015 World Health Organization classification of tumors of the lung, pleura, thymus, and heart. Journal of Thoracic Oncology. 2015;1240-2.
2. Husain A. Thoracic Pathology E-Book: A Volume in the High Yield Pathology Series. Elsevier Health Sciences; 2012.
3. Haynes BF. Human thymic epithelium and T cell development: current issues and future directions. Thymus. 1990;16(3-4):143-57.
4. Hall GFM. A case of thymolipoma. With observations on a possible relationship to intrathoracic lipomata. British Journal of Surgery. 1949;36(143):321-4.
5. Moran CA, Rosado-de-Christenson M, Suster S. Thymolipoma: clinicopathologic review of 33 cases. Modern Pathology. 1995;8(7):741-4.
6. Roque C, Rodríguez P, Quintero C, Santana N, Hussein M, Freixinet J. Timolipoma gigante. Archivos de Bronconeumología. 2005;41(7):402-3.
7. Carillo GAO, Fontán EMG, Carretero MÁC. Timolipoma gigante: presentación de un caso de tumor mediastínico inusual. Archivos de Bronconeumología. 2014;50(12):557-9.
8. Alban T, Tekin M, Yurttaş M. Asemptomatik dev timolipoma (Olgu sunumu). Tüberküloz ve Toraks Dergisi. 2000;48(1):70-2.
9. Ramos Filho J, Melo RF, Macedo MD, Fiorelli LA, Costa A, Isolatto RB. Chest pain due to right atrial compression caused by a thymolipoma. Arquivos brasileiros de cardiologia. 2004;82(5):481-3.
10. Halkos ME, Symbas JD, Symbas PN. Acute respiratory distress caused by massive thymolipoma. Southern medical journal. 2004;97(11):1123-6.
11. Rosado-de-Christenson ML, Pugatch RD, Moran CA, Galobardes J. Thymolipoma: analysis of 27 cases. Radiology. 1994;193(1):121-6.
12. Hayashı A, Takamorı S, Tayama K, Mıtsuoka M, Ohtsuka S, Aoyama Y, Shırouzu K. Thymolipoma: Clinical an Pathological Features. Kurume Med J. 1997;44(2):141-6.
13. Maki, H. Imaging findings of fat containing mediastinal lesions. European Congress of Radiology 2016.
14. Miranda A, Marques J, Ferreira J, Cunha F, Ribeiro M, Ruivo R. Persistent radiologic thoracic hypotransparency: A case report and review of the literature. Archives de Pédiatrie. 2018;25(8):489-92.

J Surg Med. 2019;3(3):278-279.
DOI: 10.28982/josam.538939

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Pseudo-septic arthritis developed after hyaluronic acid injection: A case report

Hylarunoik asid enjeksiyonu sonrası gelişen psödo-septik artrit: Olgu sunumu

Özlem Karataş [1], Tiraje Tuncer [2]

[1] University of Health Sciences, Antalya Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Antalya, Turkey
[2] Department of Physical Medicine and Rehabilitation, Akdeniz University School of Medicine, Antalya, Turkey

ORCID ID of the author(s)
ÖK: 0000-0003-3053-9333
TT: 0000-0001-8654-0603

Abstract
One of the most frequent causes of knee pain is knee osteoarthritis. Intra-articular hyaluronic acid (HA) injection is one of the preferred treatment methods. Although, systemic side effects are not seen, rarely local side effects as pain and swelling can be seen. Following HA injection, some cases with pseudo-septic manifestations unrelated to crystal formation have been reported. In this case report, a patient with knee pain which aggravated with medial tibio-femoral osteoarthritis refractory to conservative treatment methods including administration of non-steroidal anti-inflammatory drugs and others is presented. After intra-articular HA injection, her preexisting knee pain worsened, and swelling, and increase in local temperature were added to the clinical picture. Based on clinical, and laboratory examinations, and analysis of synovial fluid, diagnosis of pseudo- septic arthritis which mimicked manifestations of septic arthritis was made. Clinical, and laboratory improvement was achieved with early treatment. If following intra-articular HA injection, knee pain of the patient aggravates suddenly with local swelling and heat, then the possibility of pseudo-septic arthritis of the affected knee should be always kept in mind.
Keywords: Knee, Pseudo-septic arthritis, Hyaluronic acid, Knee osteoarthritis

Öz
Diz ağrısının en sık nedenlerinden biri diz osteoartritidir. İntraartiküler hyaluronik asit (HA) enjeksiyonları sık tercih edilen tedavi yöntemlerinden biridir. HA enjeksiyonlarından sonra sistemik yan etkiler neredeyse hiç görülmemekle birlikte, seyrek olarak ağrı ve şişlik gibi lokal yan etkiler görülebilmektedir. HA enjeksiyonu sonrası, kristal oluşumuna bağlı olmayan pseudoseptik artrit tablosu literatürde çok az sayıda olguda bildirilmiştir. Bu olguda medial tibia-femoral osteoartrite bağlı yürümekle şiddetlenen, nonsteroidal antiinflamatuar ve diğer konservatif tedavi yöntemlerine yanıtsız diz ağrısı olan ve intraartiküler HA enjeksiyonu uygulandıktan sonra dizinde mevcut olan ağrının artması, şişlik ve ısı artışı eklenmesi nedeniyle yapılan klinik muayene, laboratuvar tetkikleri ve sinoviyal sıvı analizi sonucu hastaya septik artrit tablosunu taklit eden psödoseptik artrit tanısı kondu. Erken tedavi ile klinik ve laboratuvar iyileşme sağlandı. Dize intraartiküler HA enjeksiyonu sonrası bir hastada aniden diz ağrısında artma, şişlik ve ısı artışı olursa, etkilenen eklemde psödoseptik artrit olasılığı her zaman akılda tutulmalıdır.
Anahtar kelimeler: Diz, Psödoseptik artrit, Hyaluronik asit, Diz osteoartrit

Corresponding author / Sorumlu yazar:
Özlem Karataş
Address / Adres: Antalya Eğitim ve Araştırma Hastanesi, Sağlık Bilimleri Üniversitesi, Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, Antalya, Türkiye
e-Mail: ozlemkaratas@outlook.com

Informed Consent: The author stated that the written consent was obtained from the patient presented in the study.
Hasta Onamı: Yazar çalışmada sunulan hastadan yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş tarihi: 12.03.2019
Accepted / Kabul tarihi: 14.03.2019
Published / Yayın tarihi: 15.03.2019

Copyright © 2019 The Author(s)
Published by JOSAM
This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Introduction

Nowadays, in knee pains associated with osteoarthritis (OA) intraartiular hyaluronic acid (HA) injection is one of the preferred treatment methods. As its mechanism of action improvement of viscoelastic properties of the synovial fluid, and its anti-inflammatory, and anti-nociceptive characteristics have been proposed [1]. The guideline for the treatment of knee OA formulated by TIAR indicated its potential usefulness in mild, and moderate knee OA unresponsive to pharmacological, and non-pharmacological treatment modalities [2]. Development of pseudo-septic arthritis is rarely seen following HA injection, and very few relevant case reports have been indicated in the literature [3-5]. In this paper, a rarely seen case with acute monoarticular pseudo-septic arthritis developed 2 days after intra-articular HA injection in a patient with knee osteoarthritis has been presented.

Case presentation

A 67-year-old female patient consulted to our outpatient clinic with knee pain related to medial tibio-femoral osteoarthritis which worsened while walking, and did not respond to nonsteroidal anti-inflammatory drugs, and other conservative treatment methods. A single intra-articular dose of HA (Monovisc®) was applied. Before injection the region to be intervened was firstly wiped with iodine-based antiseptic solution, and then left to dry. The procedure was performed with extreme care paid to sterility. Two days after the procedure, the patient reapplied to our output clinic with swollen and severely painful knee.

On physical examination of the patient, marked effusion, increased local temperature, and restricted range of motion of the knee which received HA injection were detected. The patellar effusion was aspirated, and clinical sample aspirated with sterile injector was inoculated on culture media for bacteriologic culture. On microscopic examination of the synovial fluid leukocytosis (37.000 cells/mm3) (PNL, 70 %, and lymphocyte, 30 %) was detected. Any bacterial growth was not detected on cultures. Fluid sample obtained was analyzed under polarized light microscope, and any crystal formation was not encountered. Some laboratory findings were also measured. Routine hematological, and biochemical values were within normal limits. Erythrocyte sedimentation rate (ESR: 62 mm/hr), and C-reactive protein (120 mg/dL) levels were also measured. Since clinical findings mimicked those of septic arthritis, ampicillin at daily doses of (1.5 g qid) was started till culture results of the synovial fluid were obtained. Antibiotherapy was terminated after negative culture results were obtained, and suspicion of septic arthritis was discarded. The patient was followed up with nonsteroidal anti-inflammatory drugs. Complaints of the patient, and adverse laboratory test results regressed completely within nearly 15 days. In this case we use Naranjo Adverse Drug Reaction Probability Scale Worksheet and calculated +6 point. This result is considered probably drug adverse reaction and this adverse reaction also reported Monovisc® Company. The patient's consent was taken for this case report.

Discussion

Intra-articular hyaluronan injection draws considerable attention as an alternative OA treatment in patients with osteoarthritic knee who did not benefit from other treatment options. Its mechanism of action has been suggested to relate to its anti-inflammatory, anabolic, local analgesic, and chondro protective effects [6]. The aim in OA is to improve impaired viscoelastic properties of the synovial fluid in OA. Although after intra-articular HA injections systemic side effects are almost never seen, rarely local adverse effects as local pain, and swelling can be seen. In very few cases cited in the literature, manifestations of aseptic arthritis after HA injection unrelated to crystal formation have been reported [7,8].

Pseudo-septic arthritis has been described in only 2 cases after injection of sodium hyaluronan (Ostenil®), and in all remaining cases it was described following injection of hylane GF-20 (Synvisc®) [7,9]. However, in the literature any case developed related to cross-linked sodium hyluronate (Monovisc®) injection has not been reported so far. This case we presented with this respect is the only case reported developed after cross-linked sodium hyluronate injection. Pseudo-septic arthritis is generally seen within 24-72 hours after intra-articular injection [10]. Also in our case, similarly, pseudo-septic arthritis developed within 48 hours after injection.

Synovial fluid typically has inflammatory characteristics. Symptoms, and clinical findings regress completely with non-steroidal drugs, and corticosteroids within 3-21 days [7,9,10]. Our case we have presented was followed up with nonsteroidal anti-inflammatory treatment, and within nearly 6 days nearly complete cure was achieved. Because of severity of clinical manifestations, and their occurrence following injection, it mimics acute septic arthritis. However, nonobservance of pathogens in direct microscopy of synovial fluid, rapid onset of symptoms within a short time after injection, dramatic, and faster response to anti-inflammatory drugs, and corticosteroids discriminate pseudo-septic arthritis from septic arthritis. Blood culture should be and absolutely obtained to exclude septic arthritis which might develop due to infectious causes. Besides, synovial fluid should be obtained through arthrosynthesis for direct examination, and culture, and then empirical IV treatment should be initiated.

Although the mechanism of pseudo-septic arthritis is not fully understood, the current emphasis is on the production of proinflammatory cytokines, and inflammatory process induced by HA degradation products. In addition to this hypothesis, it has been indicated that inhibition of flow of synovial fluid with inappropriate injection technique may contribute to the development of pseudo-septic arthritis [11].

In conclusion, severe joint involvement which mimics acute septic arthritis may develop following intra-articular HA injections. We, the physicians, should keep this clinical picture in mind, perform diagnostic laboratory examinations, and administer rapid, and effective treatment.

References

1. Wen DY. Intra-articular Hyaluronic Acid Injections for Knee Osteoarthritis. Am Fam Physician. 2000;62:565-70.
2. Tuncer T, Çay HF, Kaçar C, Altan L, Atik OŞ, Aydın AT, et al. Evidence-based recommendations for the management of knee osteoarthritis: A consensus report of the turkish league against rheumatism. Turk J Rheumatol. 2012;27(1):1-17.
3. Tahiri L, Benbouazza K, Amine B, Hajjaj-Hassouni N. Acute pseudo-septic arthritis after viscosupplementation of the knee: a case report. Clinical Rheumatology. 2007;26(11):1977-9.
4. Brandt Kenneth D, Gerald NS, Simon LS. Intra-articular injection of hyaluronan as treatment for knee osteoarthritis. Arthritis Rheum. 2000;43(6):1132-203.
5. Goldberg, Victor M., and Richard D. Coutts. Pseudo-septic reactions to hylan visco supplementation: diagnosis and treatment. Clinical Orthopaedics and Related Research. 2004;419:130-7.
6. Wen DY. Intra-articular hyaluronic acid injections for knee osteoarthritis. Am Fam Physician. 2000;62(3):565-70,572.
7. Leopold SS, Warme WJ, Pettis PD, Shott S. Increased frequency of acute local reaction to intra-articular hylan GF-20 (synvisc) in patients receiving more than one course of treatment. J Bone Joint Surg Am. 2002;84-A(9):1619–23.
8. Puttick MP, Wade JP, Chalmers A, Connell DG, Rangno KK. Acute local reactions after intra-articular hylan for osteoarthritis of the knee. J Rheumatol. 1995;22(7):1311–4.
9. Idrissi Z, Benbouazza K, Fourtassi M, Raissouni H, El Aadmi M, Zanat F, Hajjaj-Hassouni N. Acute pseudo-septic arthritis following viscosuplementation of the knee. Pan African Medical Journal. 2012;12(1):44.
10. Roos J, Epaulard O, Juvin R, Chen C, Pavese P, Brion JP. Acute pseudo-septic arthritis after intra-articular sodium hyaluronan. Joint Bone Spine. 2004;71(4):352–4.
11. Michou L, Job-Deslandre C, de Pinieux G, Kahan A. Granulomatous synovitis after intra-articular Hylan GF-20: A report of two cases. Joint Bone Spine. 2004;71(5):438–40.