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Research Article / Araştırma Makalesi

B-Hücreli Non-Hodgkin Lenfoma Tanılı Hastalarda Subkutan Rituksimab Tedavi Sonuçlarının Değerlendirilmesi:

Evaluation of Subcutaneous Rituximab Treatment Results in Patients with B-Cell Non-Hodgkin Lymphoma: A Single Center Experience

Hava Üsküdar Teke, Fatih Yaman, Neslihan Andıç, Eren Gündüz

Eskişehir Osmangazi Universitesi, Tıp Fakültesi Hematoloji Bilim Dalı, Eskişehir, Türkiye

Özet

Non-Hodgkin Lenfoma (NHL), en sık görülen hematolojik malignitedir. Diffüz Büyük B Hücreli Lenfoma (DBBHL) en sık görülen histolojik tiptir ve prognoz değişkenlik gösterir. Rituksimab+CHOP standart tedaviyi oluşturmaktadır. İntravenöz rituximab (IV Rtx) doz uygulaması uzun infüzyon süresine (90 dk ile 5-8 saat) sahip iken aynı etkinliğe sahip subkutan rituksimabın uygulaması ise 5-7 dk arasındadır. Amacımız, DBBHL veya foliküler lenfoma tanısı olup IV Rtx sonrası subkutan Rtx kullanan hastalarımızın demografik özelliklerini, klinik bulgularını, tedavi yanıtlarını, varsa yan etkileri ve hastaların memnuniyetini retrospektif olarak değerlendirerek az sayıdaki gerçek yaşam verileri ile karşılaştırmaktır. ESOGÜTF Hematoloji Bilim Dalında takip ve tedavileri yapılan, DBBHL veya foliküler lenfoma tanısı olan, Ocak.2018-Haziran.2021 tarihleri arasında en az 1 doz IV Rtx sonrası SC Rtx alan 28 hasta çalışmaya dahil edildi. Hastaların demografik özellikleri, klinik bulguları, tedavi yanıtları, varsa yan etkileri ve hastaların memnuniyeti kaydedildi. Yirmi sekiz hastanın 16'sı (%57) erkek olup yaşları ortalama 53,8±13,5 (26-78) yıl idi. 19 (%68) hastanın tanısı DBBHL iken, 9'u (%32) foliküler lenfoma tanılı idi. 22 hasta R-CHOP, 3 hasta R-COP, 3 hasta R-Bendamustin tedavisi almıştı. Hastaların hepsine hem IV hem de subkutan Rtx öncesi premedikason uygulanmıştı. 4 hastada nötropeni gözlenmedi. 17 hastada (%60.7) IV Rtx sonrası, 4 (%14.3) hastada SC Rtx sonrası, 3 (%10.7) hastada ise hem IV hem de SC Rtx sonrası nötropeni gelişmişti. IV Rtx alan hiçbir hastada infüzyon ilişkili reaksiyon gelişmedi. Subkutan Rtx uygulanan hastalarda grade 3-4 uygulama ilişkili reaksiyon (ARR) gelişmedi. Lokal reaksiyon olarak enjeksiyon bölgesinde kızarıklık, hafif ödem ve ağrı dışında yan etki gözlenmedi. IV Rtx dozu ortalama 685.2±63,5 (580±790) mg, uygulanan SC Rtx sayısı hasta bazında 3.53±1.37 (1-5) doz, hastaların takip süresi 20±8.2 (7-39) ay idi. BSA düşük, orta ve yüksek olarak sınıflandırıldığında etkinlik açısından fark saptanmadı (p>0.05) Rituximab, CD20 pozitif B hücreli lenfomanın tedavisinde standart bir tedavidir. IV Rtx ile aynı etkinliğe sahip olan SC rituksimabın uygulaması ise 5-7 dk arasında olup daha kolay bir uygulama yolu sağlamakta, klinikte uygulama sürelerini kısaltmakta, hastanın memnuniyetini artırmakta ve hastanede kalış süresi ile ilgili maliyetleri azaltmaktadır Düşük, orta ve yüksek vücut yüzey alanı (BSA) olanlarda fix doz SC Rtx ile yan etki ve etkinlik açısından fark saptanmamıştır. Hiçbir hastada SC Rtx'a bağlı lokal reaksiyon dışında yan etki görülmedi. Hastaların hepsi SC Rtx kullanımından rahat ilaç uygulaması, daha az duygusal sıkıntı, daha az enjeksiyon ağrısı ve günlük yaşam hareketine daha fazla etki en önemlisi de zaman tasarrufu nedeniyle memnun idi. SC Rtx, hem hekim, hem hasta hem de tedaviyi uygulayan hemşireler açısından zaman tasarrufu, uygulama kolaylığı, hasta memnuniyeti, ilaç uygulama konforu sağlamakta hem de IV form gibi etkinlik ve güvenlilik göstermektedir.
Anahtar Kelimeler: B hücreli lenfoma, rituksimab, subkutan

Abstract

Non-Hodgkin Lymphoma (NHL) is the most common hematological malignancy. Diffuse Large B-Cell Lymphoma (DLBCL) is the most common histological type and the prognosis is variable. Rituximab+CHOP constitutes the standard treatment. Intravenous rituximab (IV Rtx) dosing has a long infusion time (90 minutes to 5-8 hours), while subcutaneous rituximab administration with the same efficacy is between 5-7 minutes. Our aim is to retrospectively evaluate the demographic characteristics, clinical findings, treatment responses, side effects, if any, and patient satisfaction of our patients with DLBCL or follicular lymphoma using subcutaneous Rtx after IV Rtx, and compare them with a small number of real-life data. Who were followed up and treated in ESOGÜTF Hematology Department, diagnosed with DLBCL or follicular lymphoma, and received SC Rtx after at least 1 dose of IV Rtx between January 2018-June 2021 28 patients were included in the study. Demographic features, clinical findings, treatment responses, side effects, if any, and patient satisfaction were recorded. Sixteen (57%) of 28 patients were male, with a mean age of 53.8±13.5 (26-78) years. While 19 (68%) patients were diagnosed with DLBCL, 9 (32%) patients were diagnosed with follicular lymphoma. 22 patients received R-CHOP, 3 patients R-COP, 3 patients R-Bendamustine treatment. Premedication was administered to all patients before both IV and subcutaneous Rtx. Neutropenia was not observed in 4 patients. Neutropenia developed after IV Rtx in 17 patients (60.7%), after SC Rtx in 4 (14.3%) patients, and after both IV and SC Rtx in 3 (10.7%) patients. No infusion-related reaction developed in any patient receiving IV Rtx. Grade 3-4 ARR did not develop in patients who received subcutaneous Rtx. As a local reaction, no side effects were observed except redness, mild edema and pain at the injection site. The mean dose of IV Rtx was 685.2±63.5 (580±790) mg, the number of SC Rtx administered was 3.53±1.37 (1-5) doses on a patient basis, and the follow-up period of the patients was 20±8.2 (7-39) months. There was no difference in efficacy and side effects when BSA was classified as low, medium and high (p>0.05). Rituximab is standard therapy for the treatment of CD20-positive B-cell lymphoma. The administration of SC rituximab, which has the same efficacy as IV Rtx, takes 5-7 minutes, provides an easier way of administration, shortens the time of application in the clinic, increases patient satisfaction and reduces the costs associated with the hospital stay. There was no difference in terms of side effects and efficacy with fixed dose SC Rtx in those with low, medium and high body surface area (BSA). No side effects were observed in any of the patients except for the local reaction related to SC Rtx. All of the patients were satisfied with the use of SC Rtx due to comfortable drug administration, less emotional distress, less injection pain and more effect on daily life activities, most importantly time saving. In conclusion, SC Rtx provides time saving, ease of application, patient satisfaction, drug administration comfort in terms of both physicians, patients and nurses applying the treatment, as well as showing efficacy and safety like the IV form.
Keywords: B-cell lymphoma, rituximab, subcutaneous

Correspondence:
Hava ÜSKÜDAR TEKE
Eskişehir Osmangazi Üniversitesi,
Tıp Fakültesi Hematoloji Bilim Dalı,
Eskişehir, Türkiye.
e-mail: havaus@yahoo.com

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1. Giriş

Non-Hodgkin Lenfoma (NHL), en sık görülen hematolojik malignitedir. NHL, pek çok değişik alt tipi içermektedir. Diffüz Büyük B Hücreli Lenfoma (DBBHL) en sık görülen histolojik tip olmakla birlikte, her sene yeni tanı konulan olguların %30'unu oluşturmaktadır. 2.sıklıkta ise folliküler lenfoma görülmektedir. (1). ABD'de insidansı 100.000 kişide senede 7 vakadır (2). Avrupa'da ise insidansı 100.000 kişide yıllık 4.92 hastadır (3). Çoğu NHL gibi erkek predominansı vardır ve hastaların %55'i erkektir. İnsidans yaş ile artar; tüm hastalarda ortanca tanı yaşı 64'tür. (4). DBBHL, ileri yaş hastalığıdır ve bu yönü ile, yaşlı hastaların tedavisi, hastalığın yönetimi açısından önem kazanmaktadır. DBBHL hastalarında prognoz değişkenlik gösterir. Rituksimab çağında DBBHL hastalarında, standart tedavi ile 4 yıllık genel sağkalım, standart IPI risk ayrıştırması ile %59 ile %82 arasında değişmektedir (4). Rituksimab+CHOP tedavisi standart tedaviyi oluşturmaktadır. İntravenöz rituximab (IV Rtx) doz uygulaması uzun infüzyon süresi (375 mg/m2 olup infüzyon süresi 90 dk ile 5-8 saat), infüzyonla ilişkili reaksiyonları da içeren yan etkiler yanında hastaların rahatsız olduğu invazif prosedürleri de içermektedir (5). Aynı etkinliğe sahip olan subkutan rituksimabın uygulaması ise 5-7 dk arasında olup daha kolay bir uygulama yolu sağlamakta, klinikte uygulama sürelerini kısaltmakta, hastanın memnuniyetini artırmakta ve hastanede kalış süresi ile ilgili maliyetleri azaltmaktadır (6-9).

Çalışmamızın amacı, diffüz büyük B Hücreli lenfoma veya folliküler lenfoma tanısı olup intravenöz rituksimab sonrası subkutan rituksimab kullanan hastalarımızın demografik özelliklerini, klinik bulgularını, tedavi yanıtlarını, varsa yan etkileri ve hastaların memnuniyetini retrospektif olarak değerlendirerek az sayıdaki gerçek yaşam verileri ile karşılaştırmaktır.

2. Materyal ve Metod

Eskişehir Osmangazi Üniversitesi Tıp Fakültesi (ESOGÜTF) Hematoloji Bilim Dalında takip ve tedavileri yapılan, folliküler lenfoma veya diffüz büyük B hücreli NHL tanısı olan, Ocak.2018-Haziran.2021 tarihleri arasında en az 1 doz IV Rtx sonrası SC Rtx alan 28 hasta çalışmaya dahil edildi. Hastaların demografik özellikleri, klinik bulguları, tedavi yanıtları, varsa yan etkileri ve hastaların memnuniyeti kaydedildi.

Çalışma için Eskişehir Osmangazi Üniversitesi Girişimsel Olmayan Etik Kurul'undan 2021-339 numaralı onay alındı.

İstatistiksel analiz

Elde edilen veriler SPSS 21.0 sürümünde analiz edildi. Ölçüm değişkenleri ortalama ± SD (standart sapma) olarak sunulmuştur. Normallik varsayımları Shapiro Wilk testi ile test edildi. Normal dağılan verilerle parametrik testler, normal dağılmayan verilerle parametrik olmayan testler yapıldı. İstatiksel değerlendirmede $p<0.05$ anlamlı kabul edildi

3. Bulgular

Çalışmaya toplam 28 hasta alındı. Hastaların 16'sı (%57) erkek, 12'si (%43) ise kadın olup, yaşları 53,8±13,5 (26-78) yıl idi. 19 (%68) hastanın tanısı DBBHL iken, 9'u (%32) folliküler lenfoma tanılı idi. Evre dağılımına bakıldığında 5 hasta (%17.9) evre 1, 10 hasta (%35.7) evre 2, 6 hasta (%21,4) evre 3 ve 7 hasta (%25) evre 4 idi. 28 hastanın 4'ü (%14.3) takiplerde ex olmuştu. 14 hastanın (%50) en az bir kronik hastalığı mevcuttu. Hastaların 21'inde (%75) ECOG performansı 0 iken, 7'sinde (%25) ECOG 1 idi. 1 hastanın (%3.6) HBsAg pozitifliği mevcutken, 12 hastanın (%42.9) antiHBc-total pozitifliği mevcut olup bu nedenle Rtx öncesi antiviral tedavi başlandı. Hastaların demografik ve laboratuvar bulguları tablo 1'de verilmiştir. 3 hastanın ara yanıt değerlendirmesinde kısmı yanıttan fazla yanıt mevcut olup, tedavi sonu yanıt değerlendirmesinde 1 hastada progrese hastalık saptandı, diğer hastalar ise tam yanıtlı idi. Hastaların hepsine hem IV hem de subkutan Rtx öncesi premedikason uygulanmıştı. 17 hastada (%60.7) IV Rtx sonrası, 4 (%14.3) hastada SC Rtx sonrası, 3 (%10.7) hastada ise hem IV hem de SC Rtx sonrası nötropeni gelişmişti. 4 hastada nötropeni gözlenmedi. 1 hastada pnömoni, 4 hastada febril nötropeni (FEN) gelişti. IV Rtx ilk dozu tüm hastalarda 8 saatte infüze edildi.

IV Rtx alan hiçbir hastada infüzyon ilişkili reaksiyon gelişmedi. Subkutan Rtx uygulanan hastalarda grade 3-4 ARR gelişmedi. Lokal reaksiyon olarak enjeksiyon bölgesinde kızarıklık, hafif ödem ve ağrı dışında yan etki gözlenmedi. Hastalar vücut yüzey alanlarına göre (BSA) düşük (≤1.73), orta (≥1.74, ≤1.92) ve yüksek (≥1.93) olarak 3 gruba ayrıldığında hastaların 10'u (%35,7) düşük, 9'u (32.1) orta, 9'u (%32.7) ise yüksek grubunda idi. Hastaların boyu 165.4±7.3 (150-177) cm, kilo 76.2 ±14.7 (55-106) kg, m2 ise 1.84±0.19 (1.52±2.20)idi. IV Rtx dozu ortalama 685.2±63,5 (580±790) mg, uygulanan SC Rtx sayısı hasta bazında 3.53±1.37 (1-5) doz, hastaların takip süresi ise 20±8.2 (7-39) ay idi.

Tablo 1. İntravenöz rituksimab sonrası subkutan rituksimab tedavisi alan hastaların demografik ve laborutavar bulguları

Klinik ve laboratuvar değişkenler		
Cinsiyet, n, %	Kadın/Erkek	12 (%43)/16 (%57)
Yaş/yıl ort±SS (min-max)		53,8±13,5 (26-78)
Lenfoma tipi, n, %	DBBHL	19 (%68)
	FL	9 (%32)
Evre, n, %	Evre I	5 (%17,9)
	Evre II	10 (%35,7)
	Evre III	6 (%21,4)
	Evre IV	7 (%25)
IPI skoru, n, %	**0 puan**	7 (%36,8)
	1 puan	1 (%5,3)
	2 puan	8 (%42,1)
	3 puan	3 (%15,8)
FLIPI skoru, n, %	**0 puan**	1 (%11,1)
	1 puan	3 (%33,3)
	2 puan	2 (%22,2)
	3 puan	3 (%33,3)
ECOG performansı, n, %	**0**	21 (%75)
	1	7 (%25)
Kemoterapi protokolleri, n, %	R-CHOP	22 (%78,5)
	R-COP	3 (%10,7)
	R-Bendamustin	3 (%10,7)
BSA, n, %	düşük (≤1.73)	10 (%35,7)
	orta (≥1.74, ≤1.92)	9 (%32,1)
	yüksek (≥1.93)	9 (%32,1)
IV Rtx, mg, ort±SS (min-max)		685.2±63,5 (580±790)
Hasta başına SC Rtx doz, n, ort±SS (min-max)		3.53±1.37 (1-5)
Mortalite, n, %		4 (%14,3)
LDH U/L, ort±SS (min-max)		282.3±133.1(144-677)
AST U/L, ort±SS (min-max)		19.6±7.3 (9-37)
ALT U/L, ort±SS (min-max)		22.4±15.1 (5±67)
Ürik asit mg/dl, ort±SS (min-max)		4.8±1.5 (2.10±8.80)
Total protein mg/dl, ort±SS (min-max)		7±0.5 (6-8.18)
Albümin g/dl, ort±SS (min-max)		4.2±0.5 (2,92-5,29)
ESH mm/h, ort±SS (min-max)		34,6±30,4 (4-105)
CRP mg/dl, ort±SS (min-max)		37,8±65,4 (0.32-254,8)
Hemoglobin g/dl, ort±SS (min-max)		12,6±2,1 (6.3-16)
Lökosit /mm3, ort±SS (min-max)		10370.7±12356.9 (3300-71680)
Platelet /mm3, ort±SS (min-max)		334964.2±164277.4 (71000±708000)

IV; intravenöz, Rtx; rituksimab, SC; subkutan, BSA; vücut yüzey alanı, LDH; laktat dehidrogenaz, AST; aspartat aminotransferaz, ALT; alanin aminotransferaz, ESH; eritrosit sedimentasyon hızı, CRP; c-reaktif protein

4. Tartışma

Rituximab, CD20 pozitif B hücreli lenfomanın tedavisinde standart bir tedavidir. İntravenöz rituximab (IV Rtx) doz uygulaması uzun infüzyon süresi (375 mg/m2 olup infüzyon süresi 90 dk ile 5-8 saat), infüzyonla ilişkili reaksiyonları da içeren yan etkiler yanında hastaların rahatsız olduğu invazif prosedürleri de içermektedir (5). Aynı etkinliğe sahip olan subkutan rituksimabın uygulaması ise 5-7 dk arasında olup daha kolay bir uygulama yolu sağlamakta, klinikte uygulama sürelerini kısaltmakta, hastanın memnuniyetini artırmakta ve hastanede kalış süresi ilgili maliyetleri azaltmaktadır (6,7). SABRINA çalışması rituksimab aktivitesinin uygulama yolundaki değişiklikten etkilenmediğini göstermektedir. SC Rtx ve IV Rtx'nin güvenlilik profilleri benzer bulunmuş ve klinik olarak önemli yeni güvenlilik sinyalleri tanımlanmamıştır. SC Rtx ile ortaya çıkan ARR'lerde artış görülmüş olup, bu ARR'ler çoğunlukla derece 1–2 lokal enjeksiyon yeri reaksiyonlarından oluşmuştur (7). Subkutan Rtx'ın fix doz olması nedeniyle zayıf hastalarda yan etkinin fazla olabileceği, kilolu hastalarda ise etkinliğin yetersiz olabileceği akla gelebilen sorulardandır. Yapılan çalışmalarda düşük, orta ve yüksek vücut yüzey alanı (BSA) olanlarda fix doz SC Rtx kullanımı ile, düşük BSA olanlarda daha yüksek bir yan etki gözlenmemiştir. BSA düşük, orta ve yüksek olarak sınıflandırıldığında ise etkinlik açısından da fark saptanmamıştır (7,8). Bizim çalışmamızda da düşük, orta ve yüksek vücut yüzey alanı (BSA) olanlarda fix doz SC Rtx ile yan etki ve etkinlik açısından fark saptanmamıştır. Hiçbir hastada SC Rtx'a bağlı lokal reaksiyon dışında yan etki görülmedi. Hastaların hepsi SC Rtx kullanımından rahat ilaç uygulaması, daha az duygusal sıkıntı, daha az enjeksiyon ağrısı ve günlük yaşam hareketine daha fazla etki en önemlisi de zaman tasarrufu nedeniyle memnun idi.

Sonuç olarak; SC Rtx, hem hekim, hem hasta hem de tedaviyi uygulayan hemşireler açısından zaman tasarrufu, uygulama kolaylığı, hasta memnuniyeti, ilaç uygulama konforu sağlamakta hem de IV form gibi etkinlik ve güvenlilik göstermektedir.

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Clinical and Survival Outcomes in Patients with Supra-Diaphragmatic Vs Infra-Diaphragmatic Diffuse Large B Cell Lymphoma

Supra-Diyafragmatik ve İnfra-Diyafragmatik Diffüz Büyük B Hücreli Lenfoma Hastalarında Klinik ve Sağkalım Sonuçları

[1]Utku Iltar, [1]Unal Atas, [1]Ece Vural, [1]Fadime Nurcan Alhan, [1]Orhan Kemal Yucel, [1]Ozan Salim, [1]Levent Undar, [2]Burak Deveci

[1]Akdeniz University, Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Antalya, Turkey.

[2]Medstar Antalya Hospital, Clinic of Hematology, Antalya, Turkey

Correspondence:
Utku ILTAR,
Akdeniz University, Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Antalya, Turkey
e-mail: utq_07@hotmail.com

Abstract

Limited-stage diffuse large B-cell lymphoma (DLBCL) accounts for approximately 30% of all DLBCL cases. This study aimed to investigate the impact of the lymphoma involvement side relative to the diaphragm on clinical and survival outcomes in patients with limited-stage DLBCL treated with first-line rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Data from 93 patients with limited-stage DLBCL between 2010 and 2019 receiving R-CHOP were retrospectively analyzed. Patients were divided into two subgroups according to the side of the diaphragm: 29 patients with infradiaphragmatic (InD) and 64 patients with supradiaphragmatic (SpD). There were no significant differences in survival outcomes [5-year PFS rate of SpD and InD groups, 76.7% and 85.7%, respectively (P =0.553); 5-year OS rates of SpD and InD groups, 82.1% and 89.1%, respectively (P = 0,524)] and clinical characteristics, except that extra nodal involvement was dominant in the InD group and the SpD group had a higher IPI. In conclusion, in early-stage DLBCL, extra nodal involvement is expected more if the primary involvement area is below the diaphragm, however whether the primary involvement area is below or above the diaphragm has no effect on survival outcomes. The results of this study need to be confirmed by further studies with a larger case group.

Keywords: Infradiaphragmatic, supradiaphragmatic, diffuse large B-cell lymphoma, prognosis.

Özet

Erken evre diffüz büyük B hücreli lenfoma (DBBHL), tüm DBBHL olgularının yaklaşık %30'unu oluşturur. Bu çalışma, birinci basamak rituksimab, siklofosfamid, doksorubisin, vinkristin ve prednizon (R-CHOP) ile tedavi edilen erken evre DBBHL tanılı hastalarda diyaframa göre lenfoma tutulum tarafının klinik ve sağkalım sonuçları üzerine etkisini araştırmayı amaçladı. 2010 ve 2019 yılları arasında R-CHOP alan erken evreli 93 DBBHL tanılı hastadan veriler geriye dönük olarak analiz edildi. Hastalar diyafram tarafına göre iki alt gruba ayrıldı: 29 infradiyafragmatik (InD) ve 64 supradiyafragmatik (SpD) hasta. Sağkalım sonuçlarında anlamlı bir fark yoktu [SpD ve InD gruplarının 5 yıllık PFS oranı, sırasıyla %76.7 ve %85.7 (P =0.553); SpD ve InD gruplarının 5 yıllık OS oranları, sırasıyla %82.1 ve %89,1 (P = 0,524)]. Ayrıca, klinik özellikler açısından InD grupta ekstra nodal tutulumun baskın olması ve SpD grupta daha yüksek IPI mevcut olması dışında anlamlı farklılık yoktu. Sonuç olarak, erken evre DBBHL'de, tutulum alanı diyaframın altındaysa ekstra nodal tutulum daha fazla beklenir, ancak tutulum alanının diyaframın altında veya üstünde olmasının sağkalım sonuçları üzerine etkisi yoktur. Bu sonuçlarının daha geniş bir hasta grubuyla yapılacak yeni çalışmalarla doğrulanması gerekmektedir.

Anahtar Kelimeler: İnfradiyafragmatik, supradiyafragmatik, diffüz büyük B hücreli lenfoma, prognoz.

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1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL). The staging of DLBCL is based on the Lugano modification of the Ann Arbor system[1]. This staging system focuses on the extent of tumor spread. For example, stage I refers to lymphoma found in 1 lymph node region or lymphoma invading 1 extralymphatic organ or site but not any lymph node regions. Stage II refers to lymphoma in 2 or more lymph node regions on the same side of the diaphragm. However, it does not consider whether it is above or below the diaphragm.

It was previously suggested that there may be differences in patient characteristics and treatment outcomes depending on whether the lymphoma involvement site is above or below the diaphragm, and some studies have addressed this point. Most of the studies reporting comparisons of patient characteristics and treatment outcomes between the supradiaphragmatic (SpD) and infradiaphragmatic (InD) lesion groups were in Hodgkin lymphoma (HL)[2–5]. According to previous reports, patients with infradiaphragmatic HL have been shown to present with an unfavorable risk profile, including older age, predominantly male sex and unfavorable histological subtypes, and involvement of >3 lymph node areas. Additionally, some reports suggested a poor outcome in HL patients with InD lesions[4]. However, some other reports showed no significant differences in outcomes between these 2 groups[2,6]. While much more literature data are available for Hodgkin's disease on this topic, only few data are available for DLBCL thus far, which is inconsistent with previously reported HL data [7]. Regarding the prognostic significance of the involvement side relative to the diaphragm, new studies are needed in limited-stage DLBCL patients. To compare the pretreatment patient characteristics and survival outcomes of two cohorts of SpD and InD DLBCL patients, we conducted a retrospective study of de novo DLBCL patients treated with immunochemotherapy.

2. Patients and Methods

Data source and patient selection

A retrospective analysis was conducted in 93 patients with limited-stage DLBCL who were treated with front-line rituximab, cyclophosphamide, adriamycin, vincristine and prednisone (R-CHOP) or R-CHOP-like regimens at our institution between 2010 and 2019. Upfront radiation therapy was not performed for any patients. Patients were excluded if they had evidence of a coincident or prior indolent lymphoma, received only palliative management, or had another malignancy that was uncontrolled. Patients with primary testicular, primary central nervous system (CNS), primary mediastinal B cell, primary cutaneous diffuse large B-cell lymphoma leg type and intraocular lymphoma were excluded due to the unique biology and established poorer outcome of these entities. The baseline characteristics of all patients were documented. Baseline clinical, laboratory, pathology, and imaging information for each patient were obtained from their paper and/or electronic medical records. PET-CT scans and bone marrow biopsies were routinely performed for staging purposes. Clinical staging was performed according to the Ann Arbor system using data obtained from physical examination records, whole-body PET/CT, bone marrow aspiration, and biopsy. Official approval from the institutional review board was obtained before the start of the study.

Definition of variables

The database contains variables including age at diagnosis, year of diagnosis, treatment initiation date, sex, presence of B symptoms, Eastern Cooperative Oncology Group (ECOG) performance status (PS), clinical stage, primary site of involvement, serum lactate dehydrogenase level, outcome and survival time. Limited (early) stages were defined as stage I or II based on the Ann Arbor system. We classified the patients into a supradiaphragmatic (SpD) lesion group and an infradiaphragmatic (InD) lesion group according to the location of the lesions. The presence of extranodal involvement and, if

present, the location of extranodal areas was noted. Bulky disease was defined as a lymph node mass greater than 7,5 cm in diameter[8]. If data were available, we used Hans' algorithm requiring three antibodies [CD10, multiple myeloma oncogene 1 (MUM1), and polyclonal B-cell lymphoma 6 (BCL6)] to classify DLBCL into GCB and non-GCB (ABC) subtypes[9]. Follow-up information, including details on relapse and death, was also obtained. Overall survival was calculated from the date of the initiation of R-CHOP therapy to the date of the last follow-up or death. PFS was calculated from the date of the initiation of R-CHOP therapy to the date of progression, death, or last contact, whichever occurred first.

Statistical analysis

Continuous data were presented with mean±standard deviation (SD) or median (IQR: Q1-Q3). Categorical variables were presented with frequency (n) and percentage (%) and analyzed with Pearson chi-square, Fisher's Exact test and Fisher-Freeman-Halton test. The normality assumptions were controlled by the Shapiro-Wilk test. Mann-Whitney U test and Independent t-test were used for analysis of non-normally and normally distributed numerical data, respectively. Survival curves were generated by the Kaplan–Meier method and the log-rank test was performed to compare overall and progression-free survival between the InD and SpD groups. Cox proportional hazards model was used to estimate HRs. Hazard ratio (HR), with corresponding 95% confidence intervals (95% CIs), was reported. Statistical analysis was made using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). Two-sided p-value less than 0.05 was considered statistically significant.

3. Results

Of 93 patients with stage I and II DLBCL, 64 presented with supradiaphragmatic DLBCL, and 29 presented with infradiaphragmatic DLBCL. The clinical characteristics of the patients according to the primary site of disease are listed in Table 1. Patient characteristics were comparable between the two cohorts, although patients with SpD lesions exhibited a higher stage (p=0.04) and patients with InD lesions exhibited a higher rate of extra-nodal lesions (p=0.002).

Table 1. Baseline characteristics of 93 patients according to the primary site of limited stage diffuse large B-cell lymphoma

Variables	Infradiaphragmatic (n=29)	Supradiaphragmatic (n=64)	*p*
Age (years), ***Mean±SD***	58.59±11.07	52.75±16.56	[a]*0.087*
Gender, ***n (%)***			
Male	19(65.5)	36(56.3)	[c]*0.400*
Female	10(34.5)	28(43.8)	
Stage, ***n (%)***			
I	14(48.3)	17(26.6)	[c]***0.040***
II	15(51.7)	47(73.4)	
IPI, ***Median (Q1-Q3)***	1(1-2)	1(0-2)	[b]*0.197*
Unknown	6(20.7)	19(29.7)	[d]*0.138*
Low	12(41.4)	26(40.6)	
Low-Int	4(13.8)	14(21.9)	
High-Int	7(24.1)	4(6.3)	
High	0(0)	1(1.6)	
''B'' symptom, ***n (%)***	10(34.5)	15(23.4)	[c]*0.266*

LDH, *Median (Q1-Q3)*	232(192-307)	231(189-297.5)	[b]*0.842*
ECOG PS, *n (%)*			
0-1	26(89.7)	55(85.9)	[e]*0.748*
≥2	3(10.3)	9(14.1)	
GIS involvement, *n (%)*	12(41.4)	3(4.7)	[e]***<0.001***
Bulky lesion, *n (%)*	4(13.8)	8(12.5)	[e]*0.999*
Extra-nodal lesions, *n (%)*	18(62.1)	18(28.1)	[c]***0.002***
Ocular	0(0)	1(1.6)	[e]*0.999*
Thyroid	0(0)	2(3.1)	[e]*0.999*
Colon	4(13.8)	1(1.6)	[e]***0.032***
Pleura	0(0)	3(4.7)	[e]*0.549*
Gastric	10(34.5)	3(4.7)	[e]***<0.001***
Pulmonary	0(0)	4(6.3)	[e]*0.306*
Bone	1(3.4)	2(3.1)	[e]*0.999*
Cell of origin, *n (%)*			
GBC	6(35.3)	8(19.5)	[e]*0.311*
ABC	11(64.7)	33(80.5)	

[a]Independent t-test; [b]Mann-Whitney U Test; [c]Pearson Chi-Square Test; [d]Fisher Freeman Halton Test; [e]Fisher's Exact Test; ABC, activated B-cell; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GCB, germinal center B-cell; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

No significant difference was detected in PFS or OS between patients with SpD and InD groups. 5-year PFS rate of patient with InD group was 85.7% and mean PFS was 107.81 months (95% CI: 92.42-123.21); 5-year PFS rate of patient with SpD group was 76.7% and mean PFS was 103.42 months (95% CI: 90.89-115.95); Log-rank=0.352, p=0.553; **Fig. 1(A)**. 5-year OS rate of patient with InD group was 89.1% and mean OS was 107.1 months (95% CI: 91.17-123.03); 5-year OS rate of patient with SpD group was 82.1% and mean OS was 104.31months (95% CI: 92.03-116.58); Log-rank=0.405, p=0.524; Fig. 1(B).

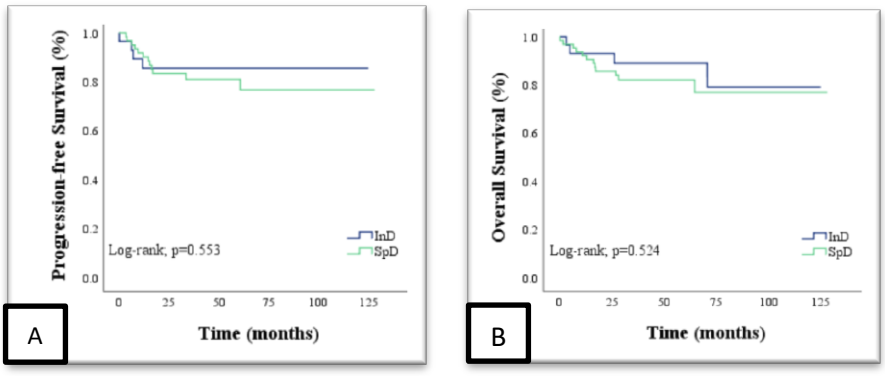

Figure 1. Survival curves of the two groups were compared using the log rank test. **A.** Progression-free survival (PFS) of patients with supradiaphragmatic (green line) and infradiaphragmatic (blue line) nodal disease. **B.** Overall survival (OS) of patients with supradiaphragmatic (green line) and infradiaphragmatic (blue line) nodal disease.

An IPI of 2 (P = 0.002), advanced age (P = 0.012), high LDH (P = 0.010) and performance status ≥ 2 (P = 0.004) were the clinical factors associated with poor 5-year PFS in univariate analysis (Table 2). With regard to 5-year OS, performance status ≥ 2 (P<0.001), advanced age (P<0.001), high LDH (P = 0.019), B symptom (P = 0.008), and higher IPI (P<0.001) were significant adverse prognostic factors in univariate analysis (Table 3). Multivariate Cox regression analysis of these risk factors revealed that OS was significantly worse in patients with advanced age.

Table 2. Cox regression analysis for progression free survival

Variables	Relapse		Univariate		Multivariate	
	No (n:77)	Yes (n:16)	HR (95% CI)	p	HR (95% CI)	p
Age						
Mean±SD	52.88±15.03	62.69±14.01	1.052(1.011-1.094)	***0.012***	1.048(0.999-1.099)	*0.057*
Gender						
Male	45(58.4)	10(62.5)	Reference			
Female	32(41.6)	6(37.5)	0.772(0.28-2.128)	*0.617*		
Group						
İnfradiaphragmatic	25(32.5)	4(25)	Reference			
Supradiaphragmatic	52(67.5)	12(75)	1.408(0.453-4.378)	*0.555*		
Stage						
I	29(37.7)	2(12.5)	Reference		Reference	
II	48(62.3)	14(87.5)	4.097(0.931-18.035)	*0.062*	3.753(0.8-17.61)	*0.094*
IPI						
Median (Q1-Q3)	1(0-2)	2(1-2)	1.901(1.197-3.017)	***0.006***	1.101(0.547-2.218)	*0.788*
LDH						
Median (Q1-Q3)	224(183-295)	260.5(214.5-403.5)	1.003(1.001-1.005)	***0.010***	1.003(0.999-1.006)	*0.122*
ECOG PS						
0-1	70(90.9)	11(68.8)	Reference		Reference	
≥2	7(9.1)	5(31.3)	4.779(1.635-13.968)	***0.004***	0.951(0.16-5.646)	*0.951*
Extra-nodal lesion						
No	46(59.7)	11(68.8)	Reference			
Yes	31(40.3)	5(31.3)	0.712(0.247-2.051)	*0.530*		
Cell of origin						
GBC	13(28.9)	1(7.7)	Reference			
ABC	32(71.1)	12(92.3)	4.467(0.579-34.446)	*0.151*		
Bulky lesion						
No	68(88.3)	13(81.3)	Reference			
Yes	9(11.7)	3(18.8)	1.611(0.459-5.658)	*0.456*		

''B'' symptom						
No	59(76.6)	9(56.3)	Reference		Reference	
Yes	18(23.4)	7(43.8)	2.559(0.951-6.883)	*0.063*	0.949(0.262-3.441)	*0.937*
GIS involvement						
No	64(83.1)	14(87.5)	Reference			
Yes	13(16.9)	2(12.5)	0.693(0.158-3.053)	*0.628*		

ABC, activated B-cell; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GCB, germinal center B-cell; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

Table 3. Cox regression analysis for overall survival

Variables	**Mortality**		**Univariate**		**Multivariate**	
	No (n:77)	**Yes (n:16)**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age						
Mean±SD	51,86±14,29	67,63±13,11	1,094(1,044-1,146)	***<0,001***	1,057(1,002-1,116)	***0,043***
Gender						
Male	46(59,7)	9(56,3)	Reference			
Female	31(40,3)	7(43,8)	0,984(0,364-2,658)	*0,975*		
Group						
İnfradiaphragmatic	25(32,5)	4(25)	Reference			
Supradiaphragmatic	52(67,5)	12(75)	1,442(0,464-4,48)	*0,527*		
Stage						
I	31(40,3)	0(0)	Reference			
II	46(59,7)	16(100)	41,93(0,604-2909,349)	*0,084*		
IPI						
Median (Q1-Q3)	1(0-2)	2(1-3)	2,553(1,578-4,132)	***<0,001***	1,068(0,503-2,269)	*0,864*
LDH						
Median (Q1-Q3)	230(184-291)	260,5(196-412,5)	1,003(1,001-1,005)	***0,019***	1,001(0,998-1,005)	*0,363*
ECOG PS						
0-1	73(94,8)	8(50)	Reference		Reference	
≥2	4(5,2)	8(50)	11,551(4,242-31,452)	***<0,001***	4,177(0,659-26,482)	*0,129*
Extra-nodal lesion						
No	47(61)	10(62,5)	Reference			
Yes	30(39)	6(37,5)	0,995(0,361-2,739)	*0,992*		
Cell of origin						
GBC	13(29,5)	1(7,1)	Reference			
ABC	31(70,5)	13(92,9)	6,035(0,772-47,181)	*0,087*		
Bulky lesion						

No	67(87)	14(87,5)	Reference			
Yes	10(13)	2(12,5)	0,985(0,224-4,341)	*0,984*		
''B'' symptom						
No	61(79,2)	7(43,8)	Reference		Reference	
Yes	16(20,8)	9(56,3)	3,801(1,411-10,241)	***0,008***	0,886(0,216-3,635)	*0,867*
GIS involvement						
No	64(83,1)	14(87,5)	Reference			
Yes	13(16,9)	2(12,5)	0,755(0,171-3,325)	*0,710*		

ABC, activated B-cell; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GCB, germinal center B-cell; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

4. Discussion

In our study, we found that patients with InD and SpD lesions have similar PFS and OS and similar distributions of clinical features. Among the two groups classified by primary site, only extranodal disease and stage were different. The SpD group contained a predominance of stage II. The InD group contained a predominance of extranodal disease. To date, only one study has specifically evaluated the prognostic impact of primary regions by location in the InD region versus the SpD region in limited-stage DLBCL. As found in our study, Nakajima et al.[7] reported that patients with InD and SpD lesions treated with R-CHOP therapy have similar PFS and OS in limited-stage DLBCL. Additionally, Nakajima et al. reported a similar distribution between these two groups regarding the clinical features; only B symptoms presented more frequently in the InD group.

In addition, Abdulla et al.[10] reported a study that provides data on InD DLBCL. Patients with abdominal lymph node involvement were compared with those without abdominal lymph node involvement; however, all stages of DLBCL were included in the study. The clinical characteristics and survival outcomes of the patients were evaluated. Patients with abdominal lymph node involvement more often had bulky disease, B symptoms, a higher age-adjusted IPI, a higher stage and more frequent double expression of MYC and BCL2 than patients with no lymph node involvement in the abdomen. Patients with abdominal lymph node involvement had significantly inferior lymphoma-specific survival compared to patients without abdominal lymph node involvement, while there were no significant differences in OS or PFS between these two groups. However, abdominal lymph node involvement did not remain an independent prognostic factor in multivariate survival analyses.

Since, by definition, there is involvement above and below the diaphragm in advanced-stage DLBCL, especially in stage 3, abdominal involvement is expected in the majority of this patient group. Therefore, when comparing patients with and without abdominal involvement, regardless of the lymphoma stage, investigating advanced stage and high IPI in patients with abdominal involvement may introduce a bias. In other words, since patients with abdominal involvement have an extra involvement area compared to those without abdominal involvement, advanced stage and therefore high IPI can be expected to occur more frequently. Therefore, we included only limited stage patients in the analysis to avoid selection bias from using data from all patients, including advanced stage patients.

Extranodal disease was more common in the InD group. In particular, GIS involvement was prominent among extranodal areas ($P<0.001$). Due to the widespread lymphoid structure around the GIS and its own structure, extranodal tissue invasion may be a possible reason, which is easier in the GIS. Many other studies investigating extranodal

disease have similarly reported that extranodal involvement is more common in the GIS[5,11,12].

The InD group accounted for 31.5% of all cases of clinical stage I/II DLBCL, a finding comparable with other studies. While approximately 5-10% of patients with early-stage HL present with InD disease at initial diagnosis, Nakajima et al. [7] and Abdulla et al. [10] reported this rate in DLBCL as 39% and 22%, respectively. Compared to HL, a higher rate of InD lesions has been reported in DLBCL patients. Unlike NHL, HL commonly spreads through contiguous groups of lymph nodes[13]. Since the patterns of disease spread in HL and NHL are different, it is not surprising that the incidence of isolated InD involvement is higher in patients with DLBCL.

Retrospective design and limited patient number of the study which possibly limit the relevance of the results however, the long follow-up time and the homogeneity of selected patients according to stage and management gave reliability to our results. Nevertheless, additional examination of a larger set of cases is necessary in order to assess the prognostic relevance of the involvement side relative to the diaphragm in limited-stage DLBCL patients.

5. Conclusion

SpD localization was associated with a higher stage and InD localization with a higher rate of extra-nodal lesions. Even if these few differences in clinical presentation exist between SpD and InD limited-stage DLBCL, SpD or InD localization had no effect on PFS or OS.

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Research Article / Araştırma Makalesi

Clinical Manifestations of COVID-19 in Children at a Pediatric Tertiary Center in Turkey

Pediatrik COVID-19 Vakalarının Klinik Değerlendirilmesi: 3. Basamak Tek Merkez Deneyimi

[1]Yalcın Kara, [1]Mahmut Can Kizil, [2]Ebru Kacmaz, [2]Mehmet Ozgur Arslanoglu, [2]Eylem Kiral, [2]Gurkan Bozan, [1]Omer Kilic, [3]Sabiha Sahin, [4]Tercan Us, [4]Gul Durmaz, [2]Ener Cagri Dinleyici

[1]Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Infectious Diseases, Eskişehir,Turkey

[2]Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Intensive Care, Eskişehir, Turkey

[3]Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Emergency Care, Eskişehir, Turkey

[4]Eskişehir Osmangazi University Faculty of Medicine, Department of Microbiology, Eskişehir, Turkey

Abstract

Limited studies have been published on practices and management of coronavirus disease-2019 (COVID-19) in children from the beginning of the pandemic. With this study, we aimed to share the clinical and epidemiological characteristics of infection in pediatric patients and our experiences. COVID-19 Polymerase Chain Reaction (PCR) test positive pediatric patients we followed up in our hospital between March to December 2020 were included in the study. The epidemiological, laboratory, radiological, and clinical data of the patients were analyzed retrospectively. During the study period, 246 test positive pediatric patients were admitted. The median age was 9 years (2 months-17 years), girls accounted for 53,7%, and 76 (31%) patients were asymptomatic. The cough was the predominant symptom (48%), followed by fever (43%) and sore throat (15%). There was a household contact in 199 (81%) of all cases and 32 (12%) patients had comorbidity and chronic illness. The most common laboratory findings; lymphopenia (26%), eosinopenia (21%), monocytosis (18%), high C-reactive protein (20%). Distribution according to case classes; asymptomatic (32,2%), mild (52,4%), moderate (13,8%), severe (1.2%), critical (0.4%). Of all cases, 48 (19.5%) were inpatients and 11 (4.5%) were in intensive care. Chest tomography was performed in 25 (10%) patients and 10 (4%) were abnormal. As a treatment, 22 (8%) patients received favipiravir, 1 (0.4%) lopinavir-ritonavir, 16 (%6) antibiotics, 4 (1.6%) methylprednisolone and 3 (1.2%) low molecular weight heparin. COVID-19 is often asymptomatic and mild in children, it may rarely have a severe course. More caution should be exercised in children under 1 year of age and patients with comorbidities.
Keywords: COVID-19, child, pandemics

Özet

Pandeminin başlangıcından itibaren çocuklarda COVID-19 tanı, klinik bulguları ve yönetimi hakkında sınırlı sayıda çalışma yayınlanmıştır. Bu çalışma ile çocuk hastalarda COVID-19 enfeksiyonun klinik ve epidemiyolojik özelliklerini ve deneyimlerimizi paylaşmayı amaçladık. Mart 2020 -Aralık 2020 tarihleri arasında hastanemizde takip ettiğimiz COVID-19 polimeraz zincir reaksiyon testi pozitif çocuk hastalar çalışmaya dahil edildi. Hastaların epidemiyolojik, laboratuvar, radyolojik ve klinik verileri geriye dönük olarak incelendi. Çalışmaya 246 çocuk hasta kabul edildi. Hastaların, %53'ü kızdı ve ortanca yaşı 9'du (2 ay-17 yıl) ve 76'sı (%31) asemptomatikti. En sık semptomlar, öksürük (%48), ateş (%43) ve boğaz ağrısıydı (%15). Olguların 199'unun (%81) ailesinde temas öyküsü mevcuttu ve 32'sinin (%12) kronik hastalığı vardı. En sık görülen laboratuvar bulguları; lenfopeni (%26), eozinopeni (%21), monositoz (%18), yüksek C-reaktif protein (%20) di. Vakaların %32'si asemptomatik, % 52'si hafif, %14'ü orta, %1,2'si şiddetli (%1.2), %0,4'ü kritik sınıftaydı. Hastaların 48'i (%19,5) hastaneye yatırıldı, 11'i (%4,5) yoğun bakımda takip edildi. Hastaların 25'ine (%10) akciğer tomografisi çekildi ve 10'unda (%4) anaormal bulgular mevcuttu. Tedavi olarak 22 (%8) hastaya favipiravir, 1 (%0,4) lopinavir-ritonavir, 16 (%6) antibiyotik, 4 (%1,6) steroid ve %3 (1,2) düşük molekül ağırlıklı heparin verildi. COVID-19, çocuklarda sıklıkla asemptomatik ve hafif olmasına rağmen, nadiren şiddetli seyredebilir. Özellikle bir yaşın altındaki çocuklarda ve komorbiditesi olan hastalarda daha dikkatli olunmalıdır.

Anahtar Kelimeler: COVID-19, çocuk, pandemi

Correspondence:
Yalçın KARA
Eskisehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Infectious Diseases, Eskişehir,Turkey
e-mail: dryalcinkara@hotmail.com

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1. Introduction

In December 2019, many atypical pneumonia cases were detected in Wuhan, China, and spread rapidly to the World (1). This epidemic has been linked to a new coronavirus called Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19), respectively. On March 11, 2020, the World Health Organization (WHO) announced a COVID-19 Pandemic (2).

The first COVID-19 case in our country was reported on March 11, 2020. In phylogenetic analysis, SARS-CoV-2 is included in the beta coronavirus family with the largest positive-polar RNA genome. (3) Droplets are the most common way for respiratory secretions to transfer pathogens from person to person, with an average incubation period of 1-14 days. It causes symptoms ranging from mild upper respiratory tract symptoms to severe respiratory failure in adult patients. In the early days of the COVID-19 pandemic, there were very few pediatric patients and children were thought not to be susceptible to this infection. A 10-year-old boy living in Shenzhen, China, was reported as the first pediatric case of COVID-19 in the literature on January 20, 2020. (4) Pediatric cases continued to be reported from many centers afterward. The clinical and laboratory manifestations of COVID-19 in children differ from those in adults, and the disease had a mild form in children than in adults. (5). However, it has also been reported that COVID-19 can be severe, especially in children with underlying chronic diseases (6). Despite the numerous studies, the COVID-19 course in children has not been fully elucidated. This study was carried out to shed light on the epidemiology, laboratory, and clinical course of COVID-19 in pediatric patients.

2. Materials and Methods

Between March 2020 and December 2020, children with positive COVID-19 PCR test results were enrolled in this study at Eskişehir Osmangazi University Medical Faculty Hospital, Department of Pediatrics. The study was sent for approval to the Ministry of Health's COVID-19 Scientific Research Assessment Commission and the Eskişehir Osmangazi University Faculty of Medicine Ethics Committee (decision number,161618). Children aged 0 to 18 years old were included in the study if their combined nasopharyngeal swab sample was positive for COVID-19 PCR (confirmed by our hospital's microbiology and genetic laboratory using the Bio-Speedy Double Gene test kit). The hospital automation system was used to access the details of these patients, and the research was performed retrospectively. Patients who were negative for COVID-19 PCR and whose COVID-19 PCR test was found to be positive in other health institutions were not included in the study. The diagnosis, treatment, and follow-up of the cases were arranged according to the Ministry of Health COVID-19 Pediatric Patient Guide and the World Health Organization data. The data belong to cases; epidemiological and demographic data, age, gender, contact and transmission history, presence of accompanying chronic disease and risk factors, symptoms and signs, laboratory and radiological findings (hemogram, CRP, procalcitonin, erythrocyte sedimentation rate, AST, ALT, urea, creatinine, LDH, triglyceride, D-dimer, INR, ferritin, chest radiography, chest computed tomography), echocardiography findings, service, and intensive care admission history, disease severity (asymptomatic, mild, moderate, severe, critical), treatments (favipiravir, hydroxychloroquine, lopinavir, steroid, antibiotic, oxygen support), treatment duration, disease course, etc. were evaluated. The classification of the disease degree was classified according to the COVID-19 guidelines of the Ministry of Health and the classification made by Dong et al, which is accepted in the literature (6). Patients were divided into 5 groups as asymptomatic, mild, moderate, severe, and critical illness, according to the clinical, laboratory findings, radiological findings, oxygen, and intensive care needs of the patients.

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) version 21.0 software. Numerical properties

were compared with the Mann – Whitney U test, and the relationships between numerical properties were analyzed by correlation analysis. The compatibility of the variables to normal distribution was examined using the Kolmogorov-Smirnov / Shapiro-Wilk tests. Descriptive analysis for normally distributed variables; The mean, standard deviation, and the median (minimum-maximum) for non-normally distributed variables were given. Categorical variables were expressed as "%". p <0.05 was considered statistically significant.

3. Results

Between March 2020 and December 2020, combined nasopharyngeal swab samples were taken from 2225 pediatric patients for suspicion of COVID-19 infection, and 246 (10.2%) patients were found to be positive for COVID-19. In patients with positive COVID-19 PCR test, 132 were girls (53.7%). The median age was 9 years (min: 2 months, max: 17 years). The cases were divided into five age groups, with approximately half of the cases (55%) being children over the age of ten. There was a household contact in 199 (81%) of all cases. A total of 32 cases had comorbid diseases, with the most common being a chronic hematological disease in 6 patients, chronic kidney disease in 4 four patients, chronic lung disease in 3 patients, chronic heart disease in 2 patients, and obesity in 4 patients (Table-1). While 76 of all cases were asymptomatic, the most common symptom was cough (48%), followed by fever (43%), sore throat (15%), shortness of breath (12%), myalgia (11%) (Table 1). Chest X-ray was taken in 66 patients and 6 of them had infiltration and consolidation. Lung tomography was performed in 25 (10.2%) patients, 10 (4.1%) patients had ground-glass opacity, consolidation, and infiltration. In four patients who were found to be normal on chest X-ray, ground-glass opacity and infiltration were found in lung tomography (Table-2). The most common laboratory findings; lymphopenia in 66 (26.8%), eosinopenia in 53 (21.5%), elevated CRP in 48 (20%), monocytosis in 45 (18.3%), leukopenia in 20 (8.1%), leukocytosis in 15 (6.1%) (Table 1). Elevated CRP, LDH, and ferritin levels were prominent in the inpatient group compared to outpatients (p: 0.01) (Table-2).

Table 1. Demographic and clinical features of patients with COVID-19

Factors	All patients (n:246)(%)	Outpatient (n:198)(%)	Inpatient (n:48)(%)	p
Sex				0,342
Girl	132 (54)	108 (81)	24 (19)	
Boy	114 (46)	90 (79)	24 (21)	
Age (year)	9,4 (2 month-17)	9,7 (2month-17)	8,1(2month-16)	**0,006**
<1	18 (7)	8 (44)	10 (56)	
1-5	53 (21)	44 (83)	9 (17)	
6-10	37 (15)	32 (87)	5 (13)	
11-15	77 (31)	61 (79)	16 (21)	
>15	61 (24)	53 (87)	8 (13)	
Symptoms				
Asymptomatic	76 (31)	76(100)	0(0)	
Cough	120 (48)	87 (73)	33 (27)	**0,002**
Fever	107 (43)	64 (60)	43 (40)	**0,001**
Sore throat	38 (15)	29 (76)	9 (23)	0,300
Shortness of breath	30 (12)	10 (33)	20 (67)	**0,001**
Myalgy	28 (11)	18 (64)	10 (36)	**0,025**
Chest Pain	12 (5)	3 (25)	9 (75)	**0,001**
Vomiting	9 (3,7)	1 (11)	8 (89)	**0,001**
Headache	9 (3,7)	5 (63)	3 (37)	0,192
Diarrhea	7 (2,9)	5 (71)	2 (29)	**0,411**
Abdominal pain	4 (1,5)	1 (25)	3 (75)	**0,024**
Neurological sign	5 (2)	0 (0)	5 (100)	**<0,001**
Accompanying diseases				**0,001**
Lung diseases	3 (1,2)	2 (67)	1 (33)	

Congenital heart Disease	2 (0,8)	2 (100)	0 (0)	
Renal disease	4 (1,6)	4 (100)	0 (0)	
Romatological diseases	3 (1,2)	2 (67)	1 (33)	
Hemato-Oncological diseases	6(2,4)	3 (50)	3 (50)	
Gastrointestinal diseases	5 (2)	4 (80)	1 (20)	
Neurological disease	2 (0,8)	0 (0)	2 (100)	
Immun deficiency	2 (0,8)	2 (100)	0 (0)	
Tip-1 DM	1 (0,4)	0 (0)	1 (100)	
Obesity	4 (1,6)	0 (0)	4 (100)	
History of Contact				
Housohold contact	199 (81)	163 (82)	36 (18)	0,300
School contact	6 (4)	5 (83)	1 (17)	
No contact	39 (15)	27 (71)	11 (29)	

Table 2. Laboratory and radiolocigal findings of patients with COVID-19

Laboratory	All patients (n:246)(%)	Outpatients (n:198)(%)	Inpatients (n:48)(%)	P
Leucocyt	8162(1310-62910)	1550(1550-17400)	9254(1310-62910)	
Leucocytosis	15 (14,7)	6 (5,9)	9 (8,8)	0,504
Leucopenia	20 (19)	11 (10)	9 (9)	0,500
Lymphocyte	3119 (400-60420)	2358(400-7420)	4140(410-60720)	
Lymphopenia	66 (64,7)	38(37,3)	28 (27,5)	0,504
Eosinophils	134(0-4700)	98 (0-800)	182(0-4700)	
Eosinopenia	53(52)	27 (26,5)	26(25,5)	0,146
Monocytes	815 (70-2730)	798 (70-1960)	836 (150-2730)	
Monocytosis	45 (43,7)	23 (22,3)	22(21,4)	0,180
CRP	13(1-181)	10 (1-119)	16 (1-181)	
Crp ↑	45(48,4)	23 (24,7)	22 (23,7)	0,184
D-dimer	1,2 (0,1-26)	0,6(0,1-6)	1,7(0,2-26)	
D-dimer ↑	27(40,3)	9 (13,4)	18 (26,9)	**0,018**
LDH	284 (125-1500)	257(125-780)	324(132-1500)	
LDH ↑	29(34,1)	14(16,5)	15(17,6)	0,117
Ferritin	118(4-857)	68(4-344)	180(28-857)	
Ferritin ↑	7 (13,7)	1(2)	6(11,8)	**0,027**
ProBNP	251 (8-3671)	86 (10-570)	8 (89)	
ProBNP ↑	5 (20)	2 (8)	3 (12)	0,230
Chest X-ray	66 (26,8)	38(15,4)	28(11,4)	**0,001**
Normal	60(24,4)	36(14,6)	24 (9,9)	
Consolidation+Infiltration	6 (2,4)	2(0,8)	4 (1,6)	
Chest tomography	25 (10)	13(5,3)	12 (4,8)	**0,001**
Normal	15 (6,1)	9 (3,7)	6(2,4)	
Abnormal	10(4,1)	4(1,6)	6 (2,4)	
Treatment				
Supportive	221 (89)	188 (76)	33 (13)	**0,001**
Favipiravir	22(8,9)	8 (3,3)	14(5,7)	**0,001**
Lopinavir-ritonovir	1 (0,4)	1(0)	1 (0,4)	0,195
Steroid	6 (2,4)	2 (0,8)	4(1,6)	**0,004**
LMWH	3 (1,2)	0(0)	3 (1,2)	**0,001**
Antibiotics	16 (6,5)	2 (0,8)	14 (5,7)	**0,001**
Ventilation support				**0,001**
Noninvasive ventilation	4 (1,6)	0 (0)	4 (100)	
Invasive ventilation	1(0,4)	0 (0)	1 (18)	

Distribution according to case classes; Asymptomatic 79 (32,2%), mild 129 (52,4%), moderate 34 (13.8%), severe 3 (1.2%), critical 1 (0.4%) patient were observed. Of all cases 198 were followed up as outpatients, 48 as inpatients, and 11 as intensive care patients.

While the morbidity rate was very low in our study, there was no mortality. The mean length of stay in the hospital was 6.9 days (Table-3). Patients who received favipiravir 22(8%), lopinavir-ritonavir 1(0.4%), antibiotics 16(6.5%), methylprednisolone 4(1.6%), and low molecular weight heparin 3(1.2 %). Thirty-nine patients received oxygen therapy via mask and nasal cannula, four received noninvasive ventilation, and one received invasive ventilation (Table-3).

Table 3. Treatment and clinical classification of patients with COVID-19

	Asymptomatic	Mild	Moderate	Severe-Critic	Total	P
Age						**0,008**
<1 age	3 (1,2)	9 (3,7)	5 (2)	1 (0,4)	18 (7,3)	
2-5 age	16 (6,5)	33 (13,4)	4 (1,6)	0 (0)	53 (21,5)	
6-10 age	10 (4,1)	24 (9,8)	3 (1,2)	0 (0)	37 (15)	
11-15 age	28 (11,4)	37 (15)	9 (3,7)	3 (1,2)	77 (31,3)	
>15 age	22 (8,9)	26 (10,6)	13 (5,3)	0 (0)	61 (24,8)	
Total	79 (32,2)	129 (52,4)	34 (13,8)	4 (1,6)	246 (100)	
Treatment						**0,001**
Favipiravir	0 (0)	1 (0,4)	17 (6,9)	4 (1,6)	22 (8,9)	
Lopinavir-Ritonovir	0 (0)	0 (0)	0(0)	1 (0,4)	1 (0,4)	
Steroid	0 (0)	0 (0)	3 (1,2)	3 (1,2)	6 (2,4)	
DMAH	0 (0)	0 (0)	0 (0)	3 (1,2)	3 (1,2)	
Antibiotics	0 (0)	5 (2)	7 (2,8)	4 (1,6)	16 (6,5)	
Oxigen support						**0,001**
Noninvazive ventilation	0 (0)	0 (0)	0 (0)	4 (1,6)	4 (1,6)	
İnvazive ventilation	0 (0)	0 (0)	0 (0)	1 (0,4)	1 (0,4)	

4. Discussion

After the World Health Organization declared COVID-19 a pandemic in March 2020, the entire world has struggled to control and treat this pandemic. While data on pediatric patients was limited at the start of the pandemic, data were updated on a daily basis with the participation of all countries and centers. In this study, we looked at the epidemiological, laboratory, and clinical data of 246 COVID-19 PCR positive pediatric patients who were followed up on at our center. Although COVID-19 is seen in children of all ages, it progresses with milder clinical findings than in adults (6,7). In our study, appropriate to the literature, 79 (32,2%) of the cases were asymptomatic and 129 (52,4%) had mild symptoms. Observation of children who have milder symptoms than adults; Children with lower expression of ACE-2 cell receptors and S-proteins involved in coronavirus pathology, as well as a more active natural immune system as a result of previous viral infections, are thought to have a better response to COVID-19 (8-10). In our study, 53,7 percent of COVID-19 -PCR positive pediatric patients were girls, with median age of 9 years. While the majority of cases were over ten years old, there were only 18 cases that were under than 1-year-old. While the number of cases increased with age, the rate of hospitalization was higher in children under the age of one year. According to Dong et al. boys are more affected than girls. According to the same study, COVID-19 has a more severe course in those under the age of one year and those with concurrent chronic diseases (6). In our study, however, there was no significant difference between boys and girls in terms of both disease onset and progression. The rate of hospitalization was higher in children under the age of one year. This can be explained by the higher number of hospitalizations (unrelated to clinical severity) for follow-up and surveillance in children under the age of one year. In our study, 32 of the cases also had chronic diseases. The most common symptoms of COVID-19 in children in studies

with large case numbers were fever, cough, shortness of breath, chest pain, sore throat, but other system findings such as headache, diarrhea, vomiting, and abdominal pain have also been shown to cause less frequently (6, 11-13). Similar to the literature, the most common symptoms at presentation in our study were cough, fever, sore throat, and shortness of breath. Patients who presented with dyspnea, chest pain, or neurological findings were more likely to be hospitalized. The majority of pediatric cases were infected through household contacts. A study found that this rate was 94 percent (7). There was a history of household contact in 81% of our cases. According to clinical and laboratory findings, COVID-19 positive cases were classified as asymptomatic, mild, moderate, severe, or critical in the study by Dong et al (6). 4.4 percent of the cases were asymptomatic, 50.9 percent were mild, 38.8 percent were moderate, 52 percent were severe, and 0.6 percent were critical. Similarly, in our study, the distribution of cases was as follows: asymptomatic 32,2%, mild 52,4%, moderate 13,8%, severe 1,2%, and critical 0,4%. The number of asymptomatic cases was higher than expected based on the literature. This can be explained by the early screening of parent-positive family members. The most frequently reported laboratory findings were lymphopenia, elevated CRP, elevated LDH, elevated D-dimer, and normal procalcitonin levels (14-16). The most common laboratory findings in our study included lymphopenia, eosinopenia, monocytosis, and elevated CRP levels. D-dimer and ferritin levels were higher in hospitalized patients and moderate-to-severe patients.

Although COVID-19 causes some changes in the lung, such as consolidation, infiltration, and ground-glass opacity, chest radiography may be normal in the early stages of the disease, lung tomography is more sensitive. However, radiation exposure from tomography in childhood should be considered (17-18). Chest radiography was performed on 66 patients in our study, and lung tomography was performed on 25 patients. Consolidation, infiltration, and ground-glass opacity were found in ten of the twenty-five patients who underwent lung tomography. The frequency of lung tomography was lower than in the literature, and in four patients with normal chest radiography, a ground-glass opacity and infiltration were detected in lung tomography.

There is no established common treatment protocol for COVID-19 in pediatric patients. Supportive therapies, antiviral treatments, antibiotic therapy, oxygen support, steroid low molecular weight heparin, intravenous immunoglobulin, remdesivir, tocilizumab, and plasma therapy are all used (19-27). In our study, 22 patients received favipiravir, one patient received lopinavir-ritonavir, and three patients received low molecular weight heparin treatment. In none of our patients did we use hydroxychloroquine or oseltamivir treatment.Four patients received noninvasive ventilation, while one received invasive ventilation support. Favipiravir is typically used in moderate-to-severe and hospitalized patients, whereas low molecular weight heparin and steroids are typically used in severe and critical cases.

Our study had some limitations, including the use of observational data from a single center with a small sample size. There were only four serious and critical patients in our study. As a result, the small sample size may have prevented some analyses from reaching definitive conclusions. Despite these limitations, this study is important because it is one of the few reports on the characteristics of confirmed pediatric COVID-19 cases in Turkey. The study provides valuable data on pediatric cases because COVID-19 is a novel disease with limited data, particularly in the pediatric population.

As a result; Although COVID-19 is often asymptomatic and mild in children, it should be kept in mind that it can be severe and critical. In children under 1 year of age and patients with comorbidities, more care should be taken in the follow-up of the disease. The vast majority of pediatric patients are infected indoors, so children from families with positive parents should be closely monitored in terms of symptoms and signs. Larger and multi-center clinical studies are needed for the follow-up and treatment of COVID-19 in children.

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Research Article / Araştırma Makalesi

Comparison of Exercise-Physical Activity Consciousness and Fear Avoidance Beliefs in Inflammatory Rheumatological Diseases

İnflamatuar Romatizmal Hastalıklarda Egzersiz-Fiziksel Aktivite Bilinç Düzeyi ve Korku Kaçınma İnanışlarının Karşılaştırılması

[1]Hanife Doğan, [2]Özlem Balbaloğlu

[1]Yozgat Bozok University, Sarıkaya School of Physiotherapy and Rehabilitation, Yozgat, Turkey

[2]Yozgat Bozok University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Yozgat, Turkey

Abstract

The aim of this study was to compare the quality of life, fear avoidance beliefs, physical activity levels, exercise and physical activity consciousness status of Ankylosing spondylitis (AS), Rheumatoid Arthritis (RA) and healthy individuals and to investigate the relationship between disease activity level with these parameters in AS and RA. AS (n=27), RA (n=28), and healthy (n=28) individuals were included in this study. Participants' disease activity levels, physical activity levels (Short form-International Physical Activity Questionnaire, IPAQ-7), fear avoidance beliefs (Fear-Avoidance Beliefs Questionnaire), FABQ), physical activity and exercise awareness (Exercise and Physical Activity Consciousness Questionnaire, EPACQ), and quality of life (Short form-36, SF-36) were evaluated. AS and RA groups; IPAQ-7, EPACQ and SF-36 scores were similar and lower than healthy group ($p<0.05$). FABQ scores of the AS and RA groups were higher than the healthy individuals ($p<0.05$). There was a negative correlation between disease activity and UFAA-7 and SF36 scores ($p<0.05$); A positive correlation was found between the disease activity and FABQ scores in the AS and RA groups ($p<0.05$). These results may indicate that patients with RA and AS may have similar disease burden and may have false beliefs that exercise and physical activity will increase the disease burden in these patients.

Keywords: rheumatology, arthritis, exercise, fear, movement, quality of life.

Özet

Bu çalışmanın amacı, Ankilozan spondilit (AS), Romatoid Artrit (RA) ve sağlıklı bireylerin yaşam kalitesi, korku kaçınma inançları, fiziksel aktivite düzeyleri, egzersiz ve fiziksel aktivite bilinç durumlarını karşılaştırmak ve hastalık aktivitesi ile bu parametreler arasındaki ilişkisini araştırmaktı. Bu çalışmaya AS (n=27), RA (n=28) ve sağlıklı (n=28) bireyler dahil edildi. Katılımcıların hastalık aktivite düzeyleri, fiziksel aktivite düzeyleri (Kısa form-Uluslararası Fiziksel Aktivite Anketi, UFAA-7), korku kaçınma inanışları (Korku-Kaçınma İnançları Anketi, KKİA), fiziksel aktivite ve egzersiz farkındalığı (Egzersiz ve Fiziksel Aktivite Bilinci Anketi, EFBA) ve yaşam kalitesi (Kısa form-36, SF-36) değerlendirildi. AS ve RA grupları; UFAA-7, EFBA ve SF-36 skorları açısından benzer ($p>0.05$) ve sağlıklı gruba göre düşüktü ($p<0.05$). AS ve RA gruplarının KKİA puanları sağlıklı bireylerden daha yüksekti ($p<0.05$). Hastalık aktivitesi ile UFAA-7 ve SF36 skorları arasında negatif yönde ($p<0.05$); AS ve RA gruplarında hastalık aktivite skoru ile KKİA arasında pozitif yönde ilişki bulundu ($p<0.05$). Bu sonuçlar, RA'daki ve AS'deki hastaların hastalık yükünün benzer olabileceğini ve bu hastalarda egzersiz ve fiziksel aktivitenin hastalık yükünü artıracağına dair yanlış inançlara sahip olabileceğini gösterebilir.

Anahtar Kelimeler: romatoloji, artrit, egzersiz, korku, hareket, yaşam kalitesi.

Correspondence:
Hanife DOĞAN
Yozgat Bozok University, Sarıkaya School of Physiotherapy and Rehabilitation, Yozgat, Turkey,
e-mail: hanife_dogan@yahoo.com.tr

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1. Introduction

Ankylosing spondylitis (AS) and Rheumatoid arthritis (RA) are progressive type of chronic inflammatory diseases that can cause joint damage and loss of function in organs. AS is often characterized by spinal and sacroiliac joint involvement. In RA, peripheral joint involvement is usually prominent, but atlantooccipital and sacroiliac joint involvement can also be seen (1). Although these inflammatory disorders are characterised by different clinical, laboratory and imaging markers, symptoms such as pain, loss of function and fatigue are similar (2). In AS and RA, the most common symptom is chronic pain. It is thought that chronic pain in the musculoskeletal system creates a feeling of fear and avoidance in some individuals (3,4,5). Although there are studies indicating that both AS and RA patients experience fear of movement separately, there is a need for studies examining factors such as disease activity and exercise consciousness level.

When the medical treatment options of individuals with AS and RA are examined, it has been shown that no treatment option has a completely curative effect on the disease. The treatment goals of patients with AS and RA are to prevent structural damage, alleviate remission, and improve patients' quality of life. (5,6). It is known that physical activity and exercise contribute greatly to remission in these patients (7,8). Determining the knowledge and awareness levels of individuals with low physical activity levels and participation in exercise is important in terms of gaining exercise habits. As far as we know, there is no study comparing AS and RA patients and healthy individuals in terms of fear of movement beliefs, physical activity and exercise consciousness (9). In addition, there is no study examining the relationship between disease activity and these parameters in patients with AS and RA. Therefore, the aim of our study was to compare AS, RA and healthy individuals in terms of quality of life, fear avoidance beliefs, physical activity level, exercise and physical activity consciousness status, and to investigate the relationship between disease activity and these parameters in AS and RA.

2. Material and Methods

Research Design

This prospective controlled study was conducted on individuals aged 18-65 years who applied to Yozgat Bozok University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, diagnosed with AS or RA (who have been followed up regularly for at least 1 year and have not undergone any change in their treatment for the last 3 months) and healthy individuals (without inflammatory rheumatic disease and meeting the exclusion criteria).

Those with cognitive problems, cardiovascular and respiratory problems, neurological diseases, musculoskeletal deformities, surgical operations in the last 6 months, pregnant women and those using any psychiatric medication were not included in the study.

Data Collection

In the socio-demographical data form; Participants' age, height, body weight, gender, use of medical or herbal medicines, surgeries, marital status and smoking were questioned. Body Mass Index (BMI) of the participants was calculated with the formula weight/height^2.

Disease Activity: Disease activity of patients with AS was evaluated by BASDAI (Bath Ankylosing Spondylitis Disease Activity Index). BASDAI questions the patient's level of weakness/fatigue, spinal pain, joint pain/swelling and sensitivity to touch, morning stiffness and duration in the past week. BASDAI consists of 6 questions. The questions are evaluated by the patient with a 10 cm Visual Analogue Scale (VAS) (0→None, 10→Very severe). The score of the first four questions is added to the average of the scores of the last two questions questioning morning stiffness, and the total score is obtained (10). Turkish validity and reliability study Akkoç et al. (11). A higher score indicates increased disease activity, while a score of 4 or higher indicates higher disease activity. Disease activity in patients

with RA was evaluated with DAS-28 (Disease Activity Score-28). The number of evaluated joints is 28. These are bilaterally shoulder, elbow, wrist, MCP, PIF in the hand and knee joints. The number of swollen and painful joints was determined by clinical examination (12,13).

Physical Activity Level: International Physical Activity Questionnaire-Short form (IPAQ-7) was used to evaluate the physical activity levels of all individuals. IPAQ-7 evaluates the physical activity participation of individuals in the last 7 days. This questionnaire includes the sum of duration (minutes) and frequency (days) of walking, moderate and vigorous activity. The energy expenditure of individuals related to their physical activities for the last 7 days is converted to Metabolic activity (MET). The MET score represents each type of activity with energy expenditure and is calculated using 1 MET for sitting, 3.3 METs for walking, 4 METs for moderate-intensity activity, and 8 METs for intense activity (14).

Fear-Avoiding Beliefs: The Fear Avoidance Beliefs Questionnaire (FABQ) was used to evaluate the participants' fear-avoidance beliefs related to the effects of their problems (such as pain and activity limitation) on physical activity and work situations. FABQ consists of 16 questions and 2 parts. The first part includes physical activity and the second part includes beliefs about work. It consists of physical activity (5 questions) and division of labor (11 questions) sub-dimensions. The Physical Activity section is scored between 0-24 and the Labor section is scored between 0-36. Turkish version study Özcan Bingül et al. (15).

Quality of Life: The overall health-related quality of life of all individuals was assessed with the Short Form-36 (SF-36). The SF-36 assesses functionality and well-being. SF-36 consists of 36 questions and has 8 sub-dimensions. The sub-dimensions in this scale are; physical function (10 items) (SF36-I), role limitation due to physical problems (4 items) (SF36-II), role limitation due to emotional problems (4 items) (SF36-III), mental health perception (5 items) (SF36-IV), social function (2 items) (SF36-V), general health perception (5 items) (SF36-VI), body pain (2 items) (SF36-VII) and energy (4 items) (SF36- VIII). Each of the subscales is calculated over 0-100 points. “0: lowest, “100: highest” indicates quality of life The higher the total score, the higher the quality-of-life level (16)

Exercise and Physical Activity Awareness Level: The Health Exercise/Physical Activity Awareness Questionnaire (Turkish version developed by Tuncel et al (17)) was used to evaluate the exercise knowledge and consciousness levels of all participants. The scale consists of 82 items. Of the 82 items, 31 are for personal information, 51 for regular exercise and physical activity awareness. In this study, the 51-item regular exercise and physical activity awareness section of the scale was used. The reliability coefficient of 51 items for regular exercise and physical activity awareness is 0.95. Each item is scored as “I know very well” (3 points), “I have heard” (2 points), “I have no idea” (1 point). The total score of the survey is averaged. An increase in the score obtained means that the level of awareness about exercise and physical activity increases (18).

Ethical approval

The study Yozgat Bozok University was approved by the Faculty of Medicine, Clinical Research Ethics Committee. (Decision No: 2017-KAEK-189_2020.10.14_07). Informed consent forms were obtained from individuals who agreed to participate in the study.

Statistical Analysis

SPSS 21 program (IBM SPSS Statistics 21 software /Armonk, NY: IBM Corp.) was used for data analysis. The conformity of the data to the normal distribution was examined by histogram and Kolmogrov-Smirnov test. Continuous variables in the data were expressed as minimum-maximum values, and categorical variables were expressed as numbers and percentages. Chi-square test was used to compare categorical variables. In the comparisons between groups,

Kruskall Wallis test was used for data that was not normally distributed for continuous

variables, and the One-way Anova test was used for parameters suitable for normal distribution. The Mann Whitney U test was used for pairwise comparisons to determine between which groups the significant difference was in the data not normally distributed. For normally distributed data, Gabriel Test, one of the post-Hoc tests, was used after the Anova test. "Spearman correlation coefficient" was used to evaluate the relationship of two different measurements in independent groups. In all analyzes, p value of <0.05 was considered statistically significant.

3. Results

The study was completed with AS (n=27), RA (n=28) and healthy individuals (n=28). The comparison of demographic information and disease activity levels of the groups is given in Table 1. There was no difference in demographic characteristics (age, gender, BMI, education and marital status), disease activity scores (in RA and AS groups) and duration of diagnosis (in RA and AS groups) of the participants (p>0.05). There was a difference between the disease activity levels of the AS and RA groups. The disease activity level of the AS group was higher (p<0.05) (Table 1).

Table 1. Comparison of demographic information and disease-related status of the groups

	AS groups (n=27)	RA groups (n=28)	Healthy groups (n=28)	p
Age (years)	49 (36-57)	49.5(21-58)	50(38-59)	0.458[a] (X^2 =1.449)
BMI (kg/m^2)	27.7±4.5	29±4.4	26.5±5.4	0.152[b] (F= 1.929)
Marital status				
married	24 (88.9%)	23 (82.14%)	25 (89.3%)	0.677[c] (X^2=0.781)
single	3 (11.1%)	5 (17.6%)	3 (10.7%)	
Gender				
Female	17 (62.97%)	19 (67.86%)	19 (67.86%)	0.907[c] (X^2=0.195)
Male	10 (37.03%)	9 (32.14%)	9 (32.14%)	
Education				
Primary school	12 (44.44%)	17 (60.72%)	9 (32.14%)	0.276[c] (X^2=5.11)
High school	8 (29.63%)	5 (17.85%)	8 (28.57%)	
Graduate	7 (25.93%)	6 (21.43	11 (39.29%)	
Disease activity level				
Low	14 (51.85%)	12 (42.86%)	----	
Middle	-	16 (57.14%)		**0.00[c]** (X^2=29.145)
High	13 (48.14%)	-		
Disease activity score	3.1 (2.6-5.2)	3.43 (2.6-5)	----	0.736[d] (z=358)
Diagnosis time (y)	10 (5-20)	10 (3-20)	----	0.387[d] (z=327)

a: Kruskal Wallis Test, b: One way Anova, c=Pearson Kikare, d=Mann Whitney U

The comparison of the participants' IPAQ-7 total score, SF-36 total and sub-parameters, exercise and physical activity awareness score, total and sub-dimensions of FABQ are given in Table 2. The IPAQ-7 total scores of the AS group and the RA group were similar (p>0.05), while the IPAQ-7 total score of the healthy group was higher than the other groups (p<0.05). The mean total score of FABQ and the mean of physical activity sub-dimension of FABQ were similar in AS and RA groups and higher than the healthy group (p<0.05). The mean scores of SF36-I and SF36-VII were higher in the healthy group than in the other groups (p<0.05). The mean EPACQ total score was similar in the RA and AS groups (p>0.05), while the mean score of the healthy group was statistically higher than the other groups (p<0.05). (Table 2). The relationship between the disease activity score and physical activity level, fear avoidance beliefs, quality of life, and exercise and

physical activity awareness level of the AS and RA groups are given in Table 3. In the RA group, a low-level positive and significant correlation (r=0.389, p= 0.041) was found between the disease activity score and the FABQ-work sub-dimension. In addition, a low negative correlation was found between IPAQ-total score and disease activity score (r= -0.458, p<0.05) (Table 3). In the AS group, the difference between disease activity score and IPAQ-total (r=-0.437), SF36-II (r= -0.464), SF36-VI (r= -0.386), SF36-VIII (r= -0.418) was low; high level between disease activity score and SF36-III (r= -0.802), SF36-IV (r= -0.781), SF36-V (r= -0.802); moderate level between SF36-VII (r= -0.633) was found to be negatively correlated. A high positive correlation (r= 0.752) was found between the disease activity score and FABQ-physical activity (Table 3).

Table 2. Comparison of IPAQ-7, SF-36, EPAQ, FABQ scores of the groups

	(A) AS groups (n=27)	(R) RA groups (n=28)	(H) Healthy groups (n=28)	p
IPAQ-7total	990 (396-1668)	1386 (198-2772)	1584 (396-2826)	**0.002**[a] (H-R, H-A)
FABQ-total	25.92±14.45	25.39±12.72	14.18±12.69	**0.002**[b] (A-H, R-H)
FABQ-P	12 (0-24)	14.5 (0-24)	5 (0-20)	**0.000**[b] (A-H, R-H)
FABQ-W	7 (0-29)	10.5 (0-30)	6 (0-23)	0.136[a]
SF36-I	55 (35-75)	55 (5-80)	80 (25-100)	**0.000**[a] (A-H, R-H)
SF36-II	100 (0-100)	100 (0-100)	100 (0-100)	0.388[a]
SF36-III	100 (0-100)	100 (0-100)	75 (0-100)	0.266[a]
SF36-IV	50±22.49	39.11±16.83	46.96±21.36	0.295[b]
SF36-V	59.89±16.80	53.07±15.29	56.5±16.08	0.178[b]
SF36-VI	75 (22.5-100)	100 (25-100)	75 (25-100)	0.248[a]
SF36-VII	55 (20-80)	55 (22-77)	67.5 (25-100)	**0.035**[a] (A-H, R-H)
SF36-VIII	50 (10-80)	35 (15-70)	47.5 (15-100)	0.061[a]
EPACQ-total	86 (68-147)	90 (57-134)	141.5 (57-153)	**0.005**[a] (H-A, H-R)

a: Kruskal Wallis Test, b: One way Anova, IPAQ: International Physical Activity Questionnaire, FABQ-P: Fear Avoidance Beliefs Questionnaire-Physical Activity, FABQ-W: Fear Avoidance Beliefs Questionnaire-Work, SF36: Short Form 36, I: physical Function, II: Role limitation due to physical problems, III: role limitation due to emotional problems, IV: mental health perception, V: social Function, VI: general health perception, VII: pain in the body, VIII: vitality, EPACQ: Exercise and Physical Activity Consciousness Questionnaire.

Table 3. The relationship between disease activity score and IPAQ-7, FABQ, SF36, EPACQ scores

		RA (n=28)	AS (n=27)
		Disease activity Score (DAS-28)	**Disease activity Score (BASDAI)**
IPAQ-total	r	-0.458	-0.437
	p	**0.014***	**0.023***
FABQ-total	r	0.257	0.465
	p	0.187	0.015
FABQ-P	r	0.035	0.752
	p	0.859	**0.000***
FABQ-W	r	0.389	0.115
	p	**0.041***	0.567
SF36-I	r	-0.182	
	p	0.353	-0.291
			0.141
SF36-II	r	-0.315	-0.464
	p	0.103	**0.015***
SF36-III	r	-0.090	-0.802
	p	0.649	**0.000***

SF36-IV	r		
	p	-0.177 0.366	-0.781 **0.000***
SF36-V	r	-0.090	-0.802
	p	0.649	**0.000***
SF36-VI	r	0.021	-0.386
	p	0.916	**0.047***
SF36-VII	r	-0.202	-0.633
	p	0.302	**0.000***
SF36-VIII	r	-0.348	-0.418
	p	0.070	**0.030***
EPACQ-total	r	-0.015	-0.002
	p	0.938	0.993

*r: Spearman Correlation Coefficient , *: p<0.005 statistical significance , DAS-28: Disease Activity Score-28, BASDAI: Bath Ankylosing Spondylitis Disease Activity*

4. Discussion

Our study revealed that physical activity levels, exercise and physical activity awareness levels of AS and RA groups were similar and lower than healthy individuals. Fear avoidance beliefs (related to physical activity) were higher in individuals with RA and AS than healthy individuals. In addition, a relationship was found between disease activity and physical activity, quality of life, and fear avoidance beliefs. To the best of our knowledge, our study was the first to compare individuals with AS, RA, and healthy individuals in terms of fear-avoidance beliefs, exercise, and physical activity awareness levels.

In addition to symptomatic treatment in inflammatory rheumatic diseases, the anti-inflammatory effects of physical activity and exercise have been reported. The mechanism of this effect is realized by the release of IL-6 cytokine from muscle tissue due to exercise, showing an anti-inflammatory feature and inhibiting TNF-a (pro-inflammatory cytokine) via a different receptor pathway (19). In this way, it reduces muscle and joint damage due to chronic inflammation. The importance of exercise and physical activity, which has been reported to reduce the inflammatory process in this way, is still not fully understood. (8,20,21). In order to understand the importance of exercise and physical activity, it is very important to investigate the knowledge and consciousness on this subject. There is limited literature on the perceived benefits of exercise and the barriers to exercise. We found two studies investigating knowledge and thoughts about exercise and physical activity in rheumatic diseases. The first study investigated beliefs and thoughts about the disease in inflammatory rheumatic diseases. They found 35.5% of the patients who thought that physical activity triggered the exacerbations of the disease and 36.5% of those who advocated that it reduced them (22). In another study, the attitudes of adults with AS towards physical activity and exercise were investigated and it was determined that individuals with AS had low motivation to exercise and do physical activity. (20). Our three groups had similar education levels; but the physical activity level, exercise and physical activity awareness of individuals with AS and RA were considerably lower than healthy individuals. This may be due to the fact that individuals cannot gain enough exercise habits in their environment or that individuals think that they will not benefit from exercise in recovery.

Most of the studies conducted in the last decade have reported that most of the inflammatory rheumatic patients have low physical activity levels. (8,20,21). In our study, the physical activity level of both inflammatory rheumatic patient groups was low. These results may be due to the fact that the importance of physical activity and exercise is still not known and is not seen as a need.

Löof et al. (3) was the first to investigate the levels of fear of movement in patients with RA and found that patients with high levels of fear of movement had low levels of physical activity. The patient's ability to perform activities in daily life is an important goal of treatment. Therefore, any effort to improve patients' fear of movement can play an important role in treatment and improve functional outcomes. The most important parameter that prevents rheumatological patients from being physically active during daily activities is chronic pain (4,5). Patients with chronic pain often believe that their ability to control their pain is limited, and such negative beliefs can inhibit health-promoting behaviors. While negative beliefs can reinforce inactivity, decreased physical activity can lead to increased perception of pain, negative expectations, and increased avoidance. Therefore, appropriate belief assessment is advocated (3). Tezcan et al. (4) evaluated the fear-avoidance (FA) beliefs of patients with hand osteoarthritis (OA), rheumatoid arthritis (RA) and fibromyalgia (FM) and found that fear avoidance beliefs were higher in RA patients. In our study, we found that participants with RA and AS had similar fear avoidance beliefs (mostly in the physical activity sub-dimension) but higher than healthy individuals. This may indicate that patients with inflammatory rheumatism may show similar results in terms of fear of movement despite different involvement and forms. Individuals with rheumatic diseases experience more fear of movement than healthy individuals, the reason of this may be their negative prejudices (about physical activity can increase their current symptoms).

It has been reported in systematic studies that RA and AS have a significant effect on quality of life. Regular assessment of quality of life is very important for effective management of the disease (23,24). In our study, in accordance with the literature, the quality of life of the AS and RA groups was similar and lower than that of healthy individuals (SF36 pain and physical function sub-dimensions). This result may show that the most important parameters affecting the quality of life in inflammatory diseases are pain and physical function.

Due to the heterogeneity in the characteristics of inflammatory rheumatic diseases, it is expected that there may be differences between RA and AS in terms of disease burden. Zink et al. (25) reported that patients with RA, PsA, and AS had a comparable disease burden. In a study, the disease burden of RA, spondyloarthriopathy (SA) and psoriotic arthritis (PA) patients were compared and the disease activity of SA and PA patients was found to be higher than those of RA patients (26). In our study, the disease activity level of the AS group was higher than that of RA. Pain mechanisms in RA and AS may be different because the inflammatory process in AS often involves enthesitis and the spine. In addition, there were individuals with high disease activity in the AS group. Our study is similar to the studies shown previously and, it confirms the comparability of AS and RA.

In our study, when the relationships between the disease activity level and quality of life, fear avoidance beliefs and physical activity level of the AS and RA groups were examined; It was determined that fear avoidance beliefs (physical activity sub-dimension) and quality of life (physical, emotional and social sub-dimension) were highly correlated with disease activity. This may indicate that as the burden of disease increases, physical deformity and mental problems increase, leading to a sedentary lifestyle.

Some limitations of this study should be considered when interpreting the results. The appropriate sample used may have caused selection bias; Participants presenting to a physical medicine and rehabilitation clinic at a university hospital may not be representative of all adults with AS and RA. In addition, the majority of the participants had a low level of education, this issue can be investigated in individuals with inflammatory diseases (at different educational levels).

Despite these limitations, one of the strengths of the research is that it determines the level of consciousness of the participants about exercise and physical activity and gives an idea about the level of exercise programs that can be planned in the future. Another strength

is that the comparison of these parameters with the healthy control group at the same education level can provide information about which need is more in rehabilitation.

5. Conclusion

This study showed that inflammatory rheumatic patients had higher fear of movement and lower quality of life, physical activity and exercise awareness than healthy individuals. At the same time, disease activity may negatively affect quality of life, physical activity, and fear beliefs in RA and AS. Considering that inflammatory chronic diseases continue for life, exercise and physical activity counselors taking a more active role in developing appropriate coping strategies may facilitate the management of the disease. Exercise and physical activity practices (goal-directed therapy) can increase the remission rate and assist to cope with fear avoidance beliefs. In future studies, the effects of different exercise practices on these parameters in different rheumatic patients can be compared.

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Research Article / Araştırma Makalesi

Effects of the COVID-19 Pandemic on the Orthopedic Trauma Practice: Experiences From A University Hospital in Turkey

COVID-19 Pandemisinin Ortopedik Travma Pratiğine Etkileri: Türkiye'de Bir Üniversite Hastanesinin Deneyimi

[1]Mustafa Kavak, [2]Muzaffer Bilgin,[1]Ulukan Inan

[1]Eskisehir Osmangazi University Faculty of Medicine, Department of Orthopedics and Traumatology, Eskisehir, Turkey

[2] Eskisehir Osmangazi University Faculty of Medicine, Department of Biostatistics, Eskisehir, Turkey

Correspondence:
Mustafa KAVAK
Eskisehir Osmangazi University Faculty of Medicine, Department of Orthopedics and Traumatology, Eskisehir, Turkey
e-mail: kavak.m@gmail.com

Abstract

After a new type of coronavirus in Wuhan, China was found to cause deadly pneumonia, the World Health Organization declared the disease caused by the virus a pandemic on March 11, 2020. This situation led to the effectuation of some social restrictions that radically changed our daily lives in our country and across the world. This comprehensive change in social life also affected the daily practices in all branches of medicine as well as orthopedic trauma practice. The aim of this study was to evaluate the incidence, location, and treatment methods of the fractures seen in the pediatric and adult population during the pandemic period, and to investigate their differences with the pre-pandemic period. Our study was designed as a retrospective cohort study comparing the acute fractures admitted to our center during the pandemic period and the fractures that occurred before the pandemic. Patients who presented with a new fracture to our emergency ward or outpatient clinic between March 16, 2020, and December 30, 2020, when social restrictions were in effect in our country, were identified. Patients who applied to our center with a new fracture within the same date range in 2019 and 2018 were also identified. The patient group was determined by scanning the International Classification of Diseases code and orthopedic consultation charts on the database. After removing the duplicate records, the radiological examinations of all patients were evaluated by the researchers. The data regarding patients' age, gender, fracture location, treatment types, length of hospital stay, and in-hospital mortality were recorded. The patients were divided into two groups: the pediatric group (16 years and younger) and the adult group (over 16 years). The total number of fractures in the pandemic period was significantly less than in the non-pandemic period ($p<0.001$). Although the number of fractures decreased significantly in both groups ($p<0.001$), there was no significant difference between the pandemic and non-pandemic period data regarding the age groups ($p=0.771$). The most common fracture sites were the distal radius (20% and 19.4%) and the ankle (8, 45% and 8.54%) in the non-pandemic period, while the distal radius (21.5%) and the proximal femur (10.8%) were the most involved sites in the pandemic period. The percentage of surgically treated fractures among all fractures was 49.6%, 46.6%, and 39.4% for 2018, 2019, and 2020, respectively. Although the prevalence of surgical treatments was lower in the pandemic period, the difference was not statistically significant ($p=0.089$). The mean length of hospital stay for the surgically treated fractures for all groups was 5.36±2.79, 5.78±2.41, and 4.10±1.62 days for the years 2018, 2019, and 2020, respectively. The decline in the length of stay during the pandemic period was found to be significant ($p<0.001$). We experienced some difficulties and confusion due to our lack of previous experience in orthopedic daily practices under the extraordinary conditions brought by the pandemic. We have seen how necessary and important previous experience can be in such extraordinary situations. The main motivation for us to carry out this study was to contribute to the knowledge in the literature. We observed a 26% decrease in the prevalence of fractures during the pandemic period. Although the indications for surgical treatment have not changed, we observed that the changes in the patient population and trauma mechanism also changed the treatment type.
Keywords: COVID-19, epidemiology, fracture, pandemic, trauma.

Özet

Wuhan-Çin'deki yeni bir tür corono virüsün ölümcül pnömoniye neden olduğu tespit edildikten sonra Dünya Sağlı Örgütü 11 Mart 2020'de pandemi ilan etti. Bu durum tüm dünyada olduğu gibi ülkemizde de günlük hayatı kökten değiştiren bir takım sosyal kısıtlamalar uygulanmasına neden oldu.(1) Sosyal hayattaki bu kapsamlı değişiklik tüm tıp dallarındaki günlük pratikleri etkilediği gibi ortopedik travma pratiğini de etkiledi. Bu çalışmanın amacı, pandemi döneminde pediatrik ve erişkin popülasyonda görülen kırık insidansını, lokalizasyon dağılımlarını ve tedavilerini değerlendirmek ayrıca pandemi olmayan dönem ile farklılıklarını araştırmaktır. Çalışmamız, COVID-19 pandemisi nedeniyle yaygın sosyal kısıtlamaların uygulandığı dönemde merkezimize başvuran akut kırıklar ile pandemi öncesi döneme ait kırıkları karşılaştıran, retrospektif bir kohort çalışması olarak tasarlanmıştır. Ülkemizde sosyal kısıtlamaların uygulandığı 16 Mart 2020 ile 30 Aralık 2020 tarihleri arasında yeni kırık ile merkezimize acil servis ve ya poliklinik aracılığı ile başvuran hastalar hastane veri tabanı sistemi aracılığı ile belirlendi. Ayrıca 2019 ve 2018 yılında aynı tarih aralığında merkezimize yeni kırık ile başvuran hastalar belirlendi. Veri tabanı üzerinden ICD 10 kod ile ve ortopedik konsültasyon chartları taranarak hasta grubu belirlendi. Dublikasyonlar ve tekrar eden kayıtlar çıkartıldı. Ardından araştırmacılar tarafından tüm hastaların radyolojik tetkikleri incelendi. Ardından hastaların başvuru sırasındaki yaşları, cinsiyetleri, kırık lokalizasyonları, tedavi tipleri, hastanede yatış süreleri ve hastane içi mortalite verileri kayıt altına alındı. Hastalar pediatric grup (16 yaş ve altı) ile yetişkin grup (16 yaş üstü) olarak iki gruba ayrıldı. 2018,2019 ve 2020 yılına ait veriler karşılaştırıldı. Pandemic perioddaki toplam kırık sayısının nonpandemic döneme göre anlamlı derecede az olduğu görüldü. ($p<0.001$) Her ne kadar her iki grupta kırık sayısı anlamlı derecede ($p<0.001$) azalsa da oransal olarak yaş dağılımına göre pandemic period ile non pandemic arasından anlamlı fark bulunmadı. ($p=0.771$) En sık görülen kırık lokalizasyonları pandemik dönemde distal radius (21,5%) ve proksimal femur (10,8%) iken non-pandemik dönemde 2018 ve 2019 yıllarında distal radius (20% ve 19,4%) ve ayak bileği (8,45% ve 8,54%) olduğu görüldü. Cerrahi tedavi edilen kırıkların toplam kırıklara oranı 2018,2019 ve 2020 yılları için sırasıyla 49,6%, 46,6% ve 39,4% olduğu görüldü. Pandemik denemde cerrahi tedavi oranları düşük bulunsa da istatisliksel olarak anlamlı değildi. ($p=0.089$) Tüm gruplar için cerrahi olarak tedavi edilen kırıklarda hastanede yatış süreleri 2018,2019 ve 2020 yılları için sırasıyla ortalama 5.36 ± 2.79, 5.78± 2.41 ve 4.10 ± 1.62 gündür. Pandemic periodda yatış sürelerindeki azalma anlamlı bulunmuştur. ($p<0.001$) Pandeminin getirdiği olağanüstü şartlarda ortopedi günlük uygulamaları konusunda daha önce tecrübemiz olmaması nedeniyle bazı zorluklar ve kafa karışıklıkları yaşadık. Fakat dünya genelinde ortopedik cerrahların konu ile ilgili deneyimlerini hızla paylaşması sonucunda günlük uygulamalarımız kanıta dayalı olarak netleşti. Bu gibi olağan dışı durumlarda önceki tecrübelerin ne kadar gerekli ve önemli olabileceğini gördük. Bu çalışmayı yapmamızdaki temel motivasyon literatürdeki bu bilgi birikimine katkı sağlamaktı. Pandemi döneminde kırık sayısında 26% oranında azalma gözlemledik. Her ne kadar cerrahi tedavi endikasyonları değişmese de hasta popülasyonu ve travma mekanizmasındaki değişikliklerin tedavi tiplerini değiştirdiğini gözlemledik.
Anahtar Kelimeler: Varfarin; oral antikoagulasyon; kanama riski, kanama risk skorları

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1. Introduction

After a new type of coronavirus in Wuhan, China was found to cause deadly pneumonia, the World Health Organization declared the disease caused by the virus (COVID-19) a pandemic on March 11, 2020. This situation led to the effectuation of some social restrictions that radically changed our daily lives in our country and across the world (2). This comprehensive change in social life also affected the daily practices in all branches of medicine as well as orthopedic trauma practice (2).

The most common etiology of fractures are falls from height, simple falls in the elderly, after-school activities of children, sports injuries, and traffic accidents (3, 4). The incidence of fractures, as well as the etiology of fractures, has changed due to the extraordinary conditions faced during the pandemic period, such as quarantines, travel restrictions, distant education, and flexible and remote working practices (5-7). Similarly, we also observed changes in the type and number of fractures encountered in both adult and pediatric patients in our daily practices. In addition, the extraordinary conditions brought by the pandemic have revealed the necessity and importance of our previous orthopedic experiences in our daily practices. Studies on the incidence and prevalence of health services such as fracture surgery, which could not be interrupted or cancelled even during the pandemic period, will also be a reference in the management of health resources in possible similar future scenarios. Although orthopedics and trauma interventions do not appear at the forefront in the fight against COVID-19, they require good planning in terms of human resources and management since there are many orthopedic trauma cases that need to be dealt with urgently.

We believe that keeping records of the orthopedic trauma practices during the pandemic period in our center, where trauma patients are treated intensively, and comparing them to those of the pre-pandemic period sheds an important light on future studies. For this reason, the aim of this study was to evaluate the incidence, location, and treatment methods of the fractures seen in the pediatric and adult population during the pandemic period, and to investigate their differences with the pre-pandemic period.

2. Patients and Methods

This study was carried out with the approval of the local ethics committee. (no.29, date: Dec 30, 2020). Our study was designed as a retrospective cohort study comparing the acute fractures admitted to our center during the period of widespread social restrictions due to the COVID-19 pandemic and the fractures that occurred before the pandemic. Patients who presented with a new fracture to our emergency ward or outpatient clinic between March 16, 2020, and December 30, 2020, when social restrictions were in effect in our country, were identified. Patients who applied to our center with a new fracture within the same date range in 2019 and 2018 were also identified and compared to the former group of patients, who were considered to present during the ‘pandemic period’.

The patient group was determined by scanning the International Classification of Diseases, ICD-10 code, and orthopedic consultation charts on the database. After removing the duplicate records, the radiological examinations of all patients were evaluated by the researchers. Patients with conflicting data from ICD-10 diagnoses, orthopedic consultation charts, and radiological images were also excluded (total 17 patients). As a result, a total of 1,267, 1,370, and 963 fracture cases from the years 2018, 2019, and 2020 were included in the study. Then, data regarding patients’ age, gender, fracture location, treatment types (conservative vs surgical), length of hospital stay (if treated surgically), and in-hospital mortality (if deceased) were recorded. The patients were divided into two groups: the pediatric group (16 years and younger) and the adult group (over 16 years).

Statistical analysis

The continuous data were expressed as mean ± standard deviation and the categorical data as percentage (%). The Shapiro-Wilk test was

used to investigate the normality of the data. In comparing the normally distributed groups, independent samples t-test was used for comparing the cases with two groups, while one-way ANOVA was utilized when comparing the cases with three or more groups. As for the cases that were not normally distributed, the Mann-Whitney U test was used when comparing two groups and the Kruskal-Wallis H test when comparing three or more groups. Pearson's chi-square and Pearson's exact chi-square analyses were employed in analyzing the created cross tables. The IBM SPSS v.21.0 software (IBM Corp., Armonk, NY, USA) was used in all analyses. A p value less than 0.05 was accepted for statistical significance.

3. Results

The total number of fractures in the pandemic period was significantly less than in the non-pandemic period (p<0.001). The number of fractures in the pediatric group by years and its ratio to the total number of fractures in the same year were 447 (35.3%), 465 (33.9%), and 333 (34.6%) for the years 2018, 2019, and 2020, respectively. As for the adult group, the number and percentage of the fractures by years were 820 (64.7%), 905 (66.1%), and 630 (65.4%) for 2018, 2019, and 2020, respectively. Although the number of fractures decreased significantly in both groups (p<0.001), there was no significant difference between the pandemic and non-pandemic period data regarding the age groups (p=0.771). The mean age of the patients based on the years investigated was 35.5±26.3, 36.3±26.4, and 36.9±27.0 years for 2018, 2019, and 2020, respectively. There was no significant difference between the mean ages in the pandemic group and the non-pandemic group (p=0.478). As for gender distributions, we found that 43.8%, 44%, and 42.2% of the patients were females for the years 2018, 2019, and 2020, respectively (p=0.639). The number of fractures, age distributions, and gender distributions by years are presented in Tables 1 and 2.

Table 1. Distribution of the number of fractures and the mean age data in the pediatric and adult groups by year.

	Number of fractures			Mean age±SD
	Pediatric group (≤16 years old)	Adult group (>16 years old)	Total	
2018	447 (35.3%)	820 (64.7%)	1,267	35.5±26.3
2019	465 (33.9%)	905 (66.1%)	1,370	36.3±26.4
2020	333 (34.6%)	630 (65.4%)	963	36.9±27.0
p	<0.001	<0.001	<0.001	0.478

Table 2. Distribution of the fractures based on gender, age groups, fracture sites, and length of hospital stays by year.

	2018	2019	2020	p
	(n=1,267)	(n=1,370)	(n=963)	
Gender				
Male	712 (56.2%)	767 (56.0%)	557 (57.8%)	0.639
Female	555 (43.8%)	603 (44.0%)	406 (42.2%)	
Age group				
Pediatric	447 (35.3%)	465 (33.9%)	333 (34.6%)	0.771
Adult	820 (64.7%)	905 (66.1%)	630 (65.4%)	
Fracture location				
Clavicle	85 (6.7%)	89 (6.5%)	53 (5.5%)	
Scapula	33 (2.6%)	40 (2.9%)	13 (1.4%)	
Proximal humerus	72 (5.7%)	76 (5.5%)	52 (5.4%)	
Humerus shaft	14 (1.1%)	16 (1.2%)	13 (1.3%)	
Distal humerus	104 (8.2%)	116 (8.5%)	68 (7.1%)	

Proximal radius-ulna	46 (3.6%)	49 (3.6%)	36 (3.7%)	
Radius-ulnar shaft	64 (5.1%)	67 (4.9%)	57 (5.9%)	
Distal radius-ulna	**253 (20.0%)**	**266 (19.4%)**	**207 (21.5%)**	
Carpal	10 (0.8%)	12 (0.9%)	6 (0.6%)	
Metacarpal	26 (2.1%)	28 (2.0%)	18 (1.9%)	
Finger	**88 (6.9%)**	**100 (7.3%)**	**47 (4.9%)**	
Pelvis	**41 (3.2%)**	**48 (3.5%)**	**19 (2.0%)**	0.419
Acetabulum	11 (0.9%)	11 (0.8%)	4 (0.4%)	
Proximal femur	**90 (7.1%)**	**94 (6.9%)**	**104 (10.8%)**	
Femoral shaft	17 (1.3%)	17 (1.2%)	17 (1.8%)	
Distal femur	14 (1.1%)	15 (1.1%)	15 (1.6%)	
Patella	25 (2.0%)	28 (2.0%)	14 (1.5%)	
Proximal tibia	30 (2.4%)	31 (2.3%)	21 (2.2%)	
Tibia shaft	29 (2.3%)	31 (2.3%)	21 (2.2%)	
Ankle	107 (8.4%)	117 (8.5%)	79 (8.2%)	
Calcaneus-talus	33 (2.6%)	35 (2.6%)	26 (2.7%)	
Metatarsal	57 (4.5%)	64 (4.7%)	51 (5.3%)	
Toe	**18 (1.4%)**	**20 (1.5%)**	**22 (2.3%)**	
Length of hospital stay (days)	5.36±2.79	5.78±2.41	4.10±1.62	p<0.001

Items with significant p values are written in bold.

The most common fracture sites were the distal radius (20% and 19.4%) and the ankle (8, 45% and 8.54%) in the non-pandemic period, while the distal radius (21.5%) and the proximal femur (10.8%) were the most involved sites in the pandemic period. Proximal femur fractures accounted for 7.1% and 6.86% of all fractures in the non-pandemic and 10.8% of all fractures in the pandemic period. Pelvic fractures constituted 3.24% and 3.5% of all fractures in the non-pandemic period, whereas this rate was 1.97% in the pandemic period. Finger fractures were observed to have a prevalence of 6.95% and 7.3% in the non-pandemic period and 4.88% in the pandemic period, while toe fractures were encountered with prevalences of 1.42%, 1.46%, and 2.28% for the respective periods. The differences between fracture locations in the non-pandemic and pandemic periods were not statistically significant (p=0.419). The distribution of the fracture types by year is given in Table 2.

The percentage of surgically treated fractures among all fractures was 49.6%, 46.6%, and 39.4% for 2018, 2019, and 2020, respectively. Although the prevalence of surgical treatments was lower in the pandemic period, the difference was not statistically significant (p=0.089). The distribution of the age groups, gender, and fracture locations according to treatment type and years are presented in Table 3. An individual evaluation of fracture locations demonstrated that the surgical treatment rates varied significantly in clavicular, proximal humeral, distal radial, proximal femoral, calcaneal-talar, and metatarsal fractures. While 38.8% of the clavicle fractures in 2018 and 37.1% in 2019 were treated surgically, surgical treatment was applied to only 5.7% of those in the pandemic period (p<0.001). As for the proximal humerus fractures, 47.2% in 2018, 44.7% in 2019, and 15.4% in the pandemic period were treated surgically (p<0.001). The surgical treatment rates in distal radius fractures were 39.5%, 38%, and 9.7% for the same periods (p<0.001). The surgical treatment rates in proximal femur fractures were 81.1% and 79.8% in the non-pandemic period, however, the rate increased to 96.2% in the pandemic period (p=0.001). As for calcaneus-talus fractures, 45.5% and 45.7% of those in the non-pandemic period and 80.8% in the pandemic period received surgical treatment (p=0.009). The surgical treatment rates in metatarsal fractures were 33.3% and 31.3% in the non-pandemic period, whereas this rate decreased to 9.8% in the pandemic period (p=0.008). There was no significant difference regarding the rates of the treatment types of other fracture locations when compared based on years. The rates of the treatment types according to fracture locations and their distributions by years are shown in Table 4.

Table 3. Distribution of the treatment types based on gender, age groups, and fracture locations by year.

	2018		2019		2020	
	Surgery	Conservative	Surgery	Conservative	Surgery	Conservative
Gender						
Male	348 (55.3%)	364 (57.1%)	353 (%55.2)	414 (56.6%)	234 (61.7%)	323 (55.3%)
Female	281 (44.7%)	274 (42.9%)	286 (44.8%)	317 (43.4%)	145 (38.3%)	261 (44.7%)
Age group						
Pediatric	178 (28.3%)	269 (42.2%)	174 (27.2%)	291 (39.8%)	81 (21.4%)	252 (43.2%)
Adult	451 (71.7%)	369 (57.8%)	465 (72.8%)	440 (60.2%)	298 (78.6%)	332 (56.8%)
Fracture location						
Clavicle	33 (5.2%)	52 (8.2%)	33 (5.2%)	56 (7.7%)	3 (0.8%)	50 (8.6%)
Scapula	5 (0.8%)	28 (4.4%)	6 (0.9%)	34 (4.7%)	0 (0%)	13 (2.2%)
Proximal humerus	34 (5.4%)	38 (6.0%)	34 (5.3%)	42 (5.7%)	8 (2.1%)	44 (7.5%)
Humerus shaft	6 (1.0%)	8 (1.3%)	6 (0.9%)	10 (1.4%)	9 (2.4%)	4 (0.7%)
Distal humerus	55 (8.7%)	49 (7.7%)	55 (8.6%)	61 (8.3%)	34 (9.0%)	34 (5.8%)
Proximal radius-ulna	20 (3.2%)	26 (4.1%)	20 (3.1%)	29 (4.0%)	10 (2.6%)	26 (4.5%)
Radius-ulnar shaft	34 (5.4%)	30 (4.7%)	34 (5.3%)	33 (4.5%)	18 (4.7%)	39 (6.7%)
Distal radius-ulna	100 (15.9%)	153 (24.0%)	101 (15.8%)	165 (22.6%)	20 (5.3%)	187 (32.0%)
Carpal	5 (0.8%)	5 (0.8%)	5 (0.8%)	7 (1.0%)	1 (0.3%)	5 (0.9%)
Metacarpal	14 (2.2%)	12 (1.9%)	14 (2.2%)	14 (1.9%)	6 (1.6%)	12 (2.1%)
Finger	45 (7.2%)	43 (6.7%)	45 (7.0%)	55 (7.5%)	22 (5.8%)	25 (4.3%)
Pelvis	16 (2.5%)	25 (3.9%)	16 (2.5%)	32 (4.4%)	4 (1.1%)	15 (2.6%)
Acetabulum	6 (1.0%)	5 (0.8%)	6 (0.9%)	5 (0.7%)	3 (0.8%)	1 (0.2%)
Proximal femur	73 (11.6%)	17 (2.7%)	75 (11.7%)	19 (2.6%)	100 (26.4%)	4 (0.7%)
Femoral shaft	14 (2.2%)	3 (0.5%)	14 (2.2%)	3 (0.4%)	16 (4.2%)	1 (0.2%)
Distal femur	13 (2.1%)	1 (0.2%)	14 (2.2%)	1 (0.1%)	12 (3.2%)	3 (0.5%)
Patella	10 (1.6%)	15 (2.4%)	11 (1.7%)	17 (2.3%)	7 (1.8%)	7 (1.2%)
Proximal tibia	22 (3.5%)	8 (1.3%)	22 (3.4%)	9 (1.2%)	17 (4.5%)	4 (0.7%)
Tibia shaft	24 (3.8%)	5 (0.8%)	25 (3.9%)	6 (0.8%)	13 (3.4%)	8 (1.4%)
Ankle	61 (9.7%)	46 (7.2%)	62 (9.7%)	55 (7.5%)	45 (11.9%)	34 (5.8%)
Calcaneus-talus	15 (2.4%)	18 (2.8%)	16 (2.5%)	19 (2.6%)	21 (5.5%)	5 (0.9%)
Metatarsal	19 (3.0%)	38 (6.0%)	20 (3.1%)	44 (6.0%)	5 (1.3%)	46 (7.9%)
Toe	5 (0.8%)	13 (2.0%)	5 (0.8%)	15 (2.1%)	5 (1.3%)	17 (2.9%)
Total	629 (49.6%)	638 (50.4%)	639 (46.6%)	731 (53.4%)	379 (39.4%)	584 (60.6%)

Table 4. Distribution of the treatment types based on fracture locations by year.

	2018		2019		2020		p
	Surgery	Conservative	Surgery	Conservative	Surgery	Conservative	
Fracture location							
Clavicle	**33 (38.8%)**	**52 (61.2%)**	**33 (37.1%)**	**56 (62.9%)**	**3 (5.7%)**	**50 (94.3%)**	**<0.001**
Scapula	5 (15.2%)	28 (84.8%)	6 (15.0%)	34 (85.0%)	0 (0%)	13 (100%)	0.325
Proximal humerus	**34 (47.2%)**	**38 (52.8%)**	**34 (44.7%)**	**42 (55.3%)**	**8 (15.4%)**	**44 (84.6%)**	**<0.001**
Humerus shaft	6 (42.9%)	8 (57.1%)	6 (37.5%)	10 (62.5%)	9 (69.2%)	4 (30.8%)	0.203
Distal humerus	55 (52.9%)	49 (47.1%)	55 (47.4%)	61 (52.6%)	34 (50.0%)	34 (50.0%)	0.720
Proximal radius-ulna	20 (43.5%)	26 (56.5%)	20 (40.8%)	29 (59.2%)	10 (27.8%)	26 (72.2%)	0.310
Radius-ulnar shaft	34 (53.1%)	30 (46.9%)	34 (50.7%)	33 (49.3%)	18 (31.6%)	39 (68.4%)	0.035
Distal radius-ulna	**100 (39.5%)**	**153 (60.5%)**	**101 (38.0%)**	**165 (62.0%)**	**20 (9.7%)**	**187 (90.3%)**	**<0.001**
Carpal	5 (50%)	5 (50%)	5 (41.7%)	7 (58.3%)	1 (16.7%)	5 (83.3%)	0.407
Metacarpal	14 (53.8%)	12 (46.2%)	14 (50.0%)	14 (50.0%)	6 (33.3%)	12 (66.7%)	0.380
Finger	45 (51.1%)	43 (48.9%)	45 (45.0%)	55 (55.0%)	22 (46.8%)	25 (53.2%)	0.696
Pelvis	16 (39.0%)	25 (61.0%)	16 (33.3%)	32 (66.7%)	4 (21.1%)	15 (78.9%)	0.389
Acetabulum	6 (54.5%)	5 (45.5%)	6 (54.5%)	5 (45.5%)	3 (75.0%)	1 (25.0%)	0.748
Proximal femur	**73 (81.1%)**	**17 (18.9%)**	**75 (79.8%)**	**19 (20.2%)**	**100 (96.2%)**	**4 (3.8%)**	**0.001**
Femoral shaft	14 (82.4%)	3 (17.6%)	14 (82.4%)	3 (17.6%)	16 (94.1%)	1 (5.9%)	0.516
Distal femur	13 (92.9%)	1 (7.1%)	14 (93.3%)	1 (6.7%)	12 (80.0%)	3 (20.0%)	0.430
Patella	10 (40.0%)	15 (60.0%)	11 (39.3%)	17 (60.7%)	7 (50.0%)	7 (50.0%)	0.782
Proximal tibia	22 (73.3%)	8 (26.7%)	22 (71.0%)	9 (29.0%)	17 (81.0%)	4 (19.0%)	0.711
Tibia shaft	24 (82.8%)	5 (17.2%)	25 (80.6%)	6 (19.4%)	13 (61.9%)	8 (38.1%)	0.181
Ankle	61 (57.0%)	46 (43.0%)	62 (53.0%)	55 (47.0%)	45 (57.0%)	34 (43.0%)	0.793
Calcaneus-talus	**15 (45.5%)**	**18 (54.5%)**	**16 (45.7%)**	**19 (54.3%)**	**21 (80.8%)**	**5 (19.2%)**	**0.009**
Metatarsal	**19 (33.3%)**	**38 (66.7%)**	**20 (31.3%)**	**44 (68.8%)**	**5 (9.8%)**	**46 (90.2%)**	**0.008**
Toe	5 (27.8%)	13 (72.2%)	5 (25.0%)	15 (75.0%)	5 (22.7%)	17 (77.3%)	0.935

Items with significant p values are written in bold.

The mean length of hospital stay for the surgically treated fractures for all groups was 5.36±2.79, 5.78±2.41, and 4.10±1.62 days for the years 2018, 2019, and 2020, respectively. The decline in the length of stay during the pandemic period was found to be significant ($p<0.001$). Lengths of hospital stays are shown in Table 2. All patients who were planned to receive surgical treatment during the pandemic period were screened with the polymerase chain reaction (PCR) test before hospitalization. In this period, 13 patients with positive results were treated in clinics with COVID-19 isolation measures, after consulting with infectious diseases specialists. Nine patients for whom surgical treatment could be delayed were operated on after COVID-19 treatments. Four patients aged 60 years and older who had hip fractures and tested positive for COVID-19 were operated on under maximum infection precaution measurements. Of them, one died due to respiratory failure on the sixth postoperative day.

4. Discussion

As a result of the decrease in people's mobility due to social isolation and quarantine practices effectuated during the pandemic period, a decrease in the incidence of fractures has been observed. These obligatory changes in the lifestyle of the society also changed the injury mechanisms, which in turn led to striking changes in fracture locations and types we encounter in clinical practice. The results of this study, in which we analyzed the changes observed in our daily practice, we noticed a 26% decrease in the incidence of fractures during the pandemic period compared to the pre-pandemic period. Other studies also reported similar decreases in the incidence of fractures during the pandemic period (5-14).

Turgut et al. (5) reported that the number of fractures decreased to one third during the pandemic period, while Bram et al. (6) reported a 2.5-fold decrease in pediatric fractures. Kalem et al. (7) reported that the incidence of fractures almost halved during the pandemic, and Hernigou et al. (8) stated that with the curfew, trauma rates in France decreased by 32% compared to previous years. In our study, we did not observe any difference between the pandemic and pre-pandemic period in terms of age distributions and mean age. Both Turgut et al. (5) and Bram et al. (6) showed that the mean age in the pediatric group decreased significantly during the pandemic period and associated this decline to the adolescent group's refrain from contact sports due to the closing of the schools and gyms and curfew measures. Although this inference seems logical, when the same scenario is considered for the adult group, it would be expected that the mean age in the adult group would increase after active adults' refrain from contact sports. In addition, the proportional increase in geriatric hip fractures should also cause an increase in the average age in the adult group. Ishii et al. reported that the mean age of the patients during the pandemic period was higher (14). We associate these differences with the patient population differences in the centers where the studies were conducted. Therefore, we believe that more accurate results can be achieved with meta-analyses.

We found that the most common fracture site was the distal radius, similar to the pre-pandemic period. Turgut et al. also reported in their study that the most common fractures during the pandemic and non-pandemic periods were distal radius fractures (5). We also found that the second most common fracture site was the ankle in the pre-pandemic period and the proximal femur in the pandemic period. Although the ratio of ankle fractures to all fractures did not change during the pandemic period, both the number and percentage of proximal femur fractures have increased. Kalem et al. examined the fracture mechanisms during the pandemic period and reported that 64.5% of the fractures were encountered at home and 73.9% were due to low-impact injuries (7). The increase in proximal femur fractures, which mostly occur as a result of domestic falls in geriatric patients, in comparison to the decrease in fracture incidence in the young population due to social restrictions during the pandemic period is an expected outcome. However, despite the decrease in the overall fracture incidence, the number of proximal femur fractures has increased. Contrary to our study, there are studies in the literature

reporting no change in the number of adult hip fractures during the pandemic period (7-10). On the other hand, Ishii et al. (14) reported an increase in the number of hip fractures during the pandemic period, similar to our study. In our country, during the pandemic period, social restrictions were implemented for a longer period of time to people aged 65 and over, who were considered a high-risk group. We believe that this practice increases immobilization in the geriatric population, and therefore may lead to an increase in osteoporotic fractures.

The overall rate of surgical treatment did not change compared to the pre-pandemic period. However, when we evaluated the fracture location individually, we observed that the surgical treatment rates changed in some fracture types. The rate of surgical treatment of clavicle fractures has decreased during the pandemic period. When we investigated the reason behind this, we noticed that the majority of the clavicle fractures during the pandemic period were in the pediatric group. The conservative treatment of the majority of pediatric clavicle fractures explains this decrease in the surgical treatment rates during the pandemic period. Similarly, we observed that the surgical treatment rates in proximal humeral fractures also decreased during the pandemic period. We believe that this is because most of the proximal humerus fractures in the pandemic period have occurred as a result of falling at home in geriatric patients and that conservative treatment was more prominent in geriatric proximal humerus fractures. We observed that the changes in the patient population were the reason for the decrease in the rate of surgical treatment of distal radius fractures during the pandemic period. We have seen that the majority of distal radius fractures in the pandemic period have occurred in pediatric and geriatric patients after a low-energy trauma such as falling indoors. The surgical treatment rates of proximal femur fractures increased during the pandemic period. While almost all of the proximal femur fractures in the pandemic period were in geriatric patients, we saw that the prevalence of these fractures was increased in pediatric patients in the pre-pandemic period. We believe that this difference explains the increase in the surgical treatment rate. In the evaluation of the increase in the surgical treatment rate of calcaneus-talus fractures during the pandemic period, we observed no difference among the patients in terms of age and fracture mechanism. The effect of fracture type and patient comorbidities on the treatment plan may have caused this situation. We have seen that the reason for the decrease in the surgical treatment rate of metatarsal fractures was that most of the fractures during the pandemic period were caused by in-home low-energy traumas. Although surgical treatment indications have not changed, we observed that the changes in the patient population and trauma mechanism also changed the treatment type. On the other hand, Turgut et al. (5) reported that the rate of surgical treatment in the pediatric age group doubled during the pandemic period. The authors asserted that the reason for this might be that the families of the patients with minor traumas avoided presenting to the hospital during the pandemic period and that other centers referred fractures that required surgery to the authors' institution. Similarly, Kalem et al. reported that although there was a decrease in the number of patients admitted to the hospital due to trauma, there was an increase in the number of patients who underwent surgical treatment (7). In our study, we did not find any difference in the overall surgical treatment rates compared to the pre-pandemic period. However, we saw some differences in fracture location and associated this with the differences in the patient population and fracture types. During the pandemic period, different practices were carried out in the provision of health services in different cities and centers, according to local needs. We believe that these different practices are the reason for the differences between the studies.

In our study, there was a significant decrease in the length of hospital stays of the patients treated surgically during the pandemic period compared to the pre-pandemic period. Similarly, Turgut et al. reported a significant decrease in the duration of hospitalization (5), contrary to Kalem et al. who stated that there was no change in the duration of hospitalization during the pandemic period

compared to the previous period (7). We believe that the main reason for the decrease in the length of hospital stays is the risk of transmission of COVID-19, which is a common concern of patients and surgeons.

Although we conducted this study in a trauma center with a high volume of patients, this may not reflect the general trend since it is a single-center study. Another important limitation to our study was its retrospective design. On the other hand, in our study, fractures were evaluated within a period of approximately nine months. Considering the shorter periods in similar studies, this long period can be considered an advantage of our study. Another strength of our study was the elimination of possible errors owing to the examination of the radiological images of each patient, as well as using the ICD-10 codes during the identification of fracture patients.

In conclusion, we experienced some difficulties and confusion due to our lack of previous experience in orthopedic daily practices under the extraordinary conditions brought by the pandemic. However, as orthopedic surgeons around the world quickly shared their experiences on the subject, our daily practices became clear based on evidence. We have seen how necessary and important previous experience can be in such extraordinary situations. The main motivation for us to carry out this study was to contribute to the knowledge in the literature. We observed a 26% decrease in the prevalence of fractures during the pandemic period. Although the indications for surgical treatment have not changed, we observed that the changes in the patient population and trauma mechanism also changed the treatment type. Further multicenter and national studies are required to shed light on orthopedic practices in extraordinary situations such as a pandemic which we might probably encounter in the future

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Research Article / Araştırma Makalesi

Erişkin Başlangıçlı İmmunglobulin (Ig)-A Vaskülitinde Ayrıntılı Renal Tutulum Sonuçları ve Prognoz

A Detailed Analysis of Renal Involvement and Prognosis in Adult-Onset Immunglobulin (Ig)-A Vasculitis

[1]Reşit Yıldırım, [2]Sedanur Oğuzman, [1]Döndü Üsküdar Cansu, Mustafa Dinler, [1]Cengiz Korkmaz

[1]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Romatoloji Bilim Dalı, Eskişehir, Türkiye

[2]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi İç Hastalıkları Anabilim Bilim Dalı, Eskişehir, Türkiye

Abstract

İmmunglobulin-(Ig) A vasküliti çocukluk çağında daha sık ve benign seyir gösterirken, erişkin başlangıç daha nadirdir ve ağır seyretmektedir. Amacımız, merkezimizdeki IgA vaskülitli erişkin hastaların ayrıntılı klinik özellikleri, uzun dönem renal tutulum sonuçlarını ve prognozlarını retrospektif olarak belirlemekti. Çalışmaya IgA vasküliti tanı kriterlerini karşılayan 52 hasta alındı. Hastaların çoğunluğu erkek (37 vs 15, %71,2 vs %28.8) ve ortalama yaş 45 ± 18 yıl olarak bulundu. Renal tutulumu olan 20 hastanın, 12'sine (%23,1) renal biyopsi yapılmış ve IgA nefropatisi ile uyumlu saptanmıştır. 5 hastada kronik renal yetmezlik (KRY) gelişti ve bunların 3'ünde hemodiyaliz desteğinin en az bir kez gerektiği görüldü. 9 (%17,3) hastada relaps gözlendi (5'i renal, 3'ü cilt ve 1'i gastrointestinal). İleri yaş (>65) olanlarda başvuru sırasında akut böbrek yetmezliği (%50 vs %10 p:0,002) ve nefrotik düzeyde proteinüri (%75 vs %32,5 p:0,028) daha yüksek oranda tespit edildi. Bu grupta KRY gelişme riski (%33,3 vs %2,5 p<0,001) ve ölüm oranı (%41,7 vs %5 p:0,001) daha yüksekti. Takipleri sırasında 7 hasta ölmüştü. Bu hastaların başvuru semptomları incelendiğinde başvuru anında 5'inde (%71,4) akut böbrek yetmezliği mevcuttu (%71,4 vs %11,1 p<0,001). Sonuç olarak çalışmamızda ileri yaş (>65) ve renal tutulum, KRY gelişimi ve ölüm için önemli bir kriter olarak tespit edilmiştir. Bu nedenle ileri yaşta başlayan ve renal tutulumu olan hastalar KRY gelişimi ve kötü prognoz açısından dikkatle takip edilmelidirler.

Anahtar Kelimeler: IgA vasküliti, renal tutulum, ileri yaş, prognoz

Özet

Immunglobulin (Ig)- A vasculitis is seen more common in children characterized with benign course, whereas adult-onset form is relatively rare but may be associated with severe organ involvement and worse prognosis. Our aim in this study is to retrospectively evaluate clinical features, detailed analysis of renal involvement, longterm renal outcome and overall prognosis in adult-onset IgA vasculitis patients followed in our center. 52 cases fullfilling selection criterias were included in this study. Majority of patients were male (37 vs 15, 71,2% vs 28.8%) and mean age was calculated 45 ± 18 years. Among 20 patients who had renal involvement, renal biopsy was performed in 12 (23,1%), consistent with IgA nephropathy. Chronic kidney disease (CKD) developed in 5, and among those, hemodialysis was needed in 3 at least once through entire following period. Relaps was seen in 9 (17,3%) with the sites of distribution as following; 5 renal, 3 skin and 1 gastrointestinal. Acute kidney injury (50% vs 10% p:0,002) and nephrotic range proteinuria (75% vs 32,5% p:0,028) at admission were found significantly higher in patients at advanced age (>65). CKD development (33,3% vs 2,5%, p<0,001) and overall mortality were also higher (41,7% vs 5% p:0,001) in this group. Mortality was seen in 7 patients and 71,4% of them had acute kidney injury at the time of first admission (p<0,001). In our study, we have found that advanced age (>65) and renal involvement seem to be significant risk factors for the development of CKD and overall mortality, consistent with the literature. Therefore, these patients should be monitored closely.

Keywords: IgA vasculitis, renal involvement, advanced age, prognosis

Correspondence:
Reşit YILDIRIM
Eskişehir Üniversitesi Tıp Fakültesi Romatoloji Bilim Dalı, Eskişehir, Türkiye
e-mail: celeng18@gmail.com

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1. Giriş

İmmunoglobulin (Ig)-A vasküliti, IgA içerikli immun komplekslerin cilt, eklem, böbrek ve gastrointestinal sistem gibi organlardaki küçük çaplı damarlarda depolanması sonucu ortaya çıkan bir vaskülittir (1). Hastalığın patogenezi tam olarak bilinmemektedir. Etyoloji genellikle idiyopatik olmakla beraber enfeksiyonlar, ilaçlar, aşılar, toksinler gibi nedenlerin tetikleyici faktörler olarak rol oynadığı düşünülmektedir (2). Hastalık, çocukluk çağında daha sık görülmekte ve benign seyir gösterirken, erişkin başlangıçlı olgular daha az sıklıkta görülür ve ağır seyredebilmektedir (3). Olguların çoğunluğunda hastalık kendini sınırlar ancak gastrointestinal ve ciddi renal etkilem varlığında immünsüpresif tedavi ihtiyacı olmaktadır (3). Bugüne kadar yapılan pek çok çalışma erişkin populasyonda renal tutulum sıklığının daha sık ve prognozun daha kötü olduğunu göstermektedir. Bu çalışmada, merkezimizde IgA vasküliti tanısı konan ve takibi yapılan erişkin hastaların demografik ve klinik özellikleri, tedavi yanıtları ve uzun dönem renal tutulum sonuçları ve ileri yaş hasta populasyonundaki farklılıklar değerlendirilecektir. Literatürle olan farklılıklar ve benzerlikler tartışılacak, renal tutulum ile ilgili veriler detaylı olarak analiz edilecektir.

2. Gereç ve Yöntemler

Hasta seçimi

Çalışmamız ile ilgili Eskişehir Osmangazi Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu tarafından 15.06.2021 tarih ve 31 numaralı karar ile etik kurul onayı alınmıştır.

Eskişehir Osmangazi Üniversitesi Romatoloji Bilim dalı'nda 2000 ile 2020 yılları arasında klinik ve/veya histopatolojik olarak IgA vasküliti tanısı ile takip ve tedavisi yapılan 18 yaş ve üzerindeki hastaların dosyaları retrospektif olarak incelendi. IgA vaskülit tanı kriterleri olarak PRINTO kriterleri kullanıldı (4). Bu tanı kriterlerini karşılayan 52 hasta çalışmaya dahil edildi. Hastalarin demografik bilgileri, hastaneye ilk başvuruları sırasındaki klinik özellikleri (cilt, renal, muskuloskeletal, gastrointestinal ve diğer), takip ve tedavi süreleri boyunca yeni gelişen organ tutulumları, klinik semptomları nedeniyle ilk başvurdukları merkez (acil servis, aile hekimliği, iç hastalıkları, romatoloji ve dermatoloji), ilk başvuru sırasındaki laboratuvar bulguları (tam kan sayımı, serum kreatin düzeyi, serum IgA seviyesi, serum C-reaktif protein (CRP) ve eritrosit sedimentasyon hızı (ESH), idrarda hematuri varlığı, spot ve 24 saatlik idrar örnekleri ile ölçülmüş proteinuri düzeyi, idrar mikroskopik incelemesi), tanı sonrası aldıkları 1.basamak tedavi rejimleri, takip sırasında eklenen immunsupresif tedaviler, relaps sayısı ve relaps gelişen organlar, uzun dönem renal prognoz (kronik renal yetmezlik gelişimi, hemodiyaliz verileri ve renal transplantasyon gelişimi) ve tüm nedenlere bağlı mortaliteye dair veriler elektronik dosya arşivinden elde edildi. Klinik remisyon; hastalığa sekonder tutulan cilt, eklem ve gastrointestinal şikayetlerinin tamamen gerilemesi ve muayenede patoloji saptanmaması olarak, renal tutulumu olanlarda ise hematürinin idrar tetkikinde <5 eritrosit olacak şekilde gerilemiş olması ve proteinürinin <300 mg/gün olması şeklinde tanımlandı (5). Hastaların böbrek fonksiyon testleri, Kronik böbrek yetmezliği National Kidney Foundation - Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) tarafından hazırlanan 2002 yılı Kronik Böbrek Hastalığı Değerlendirme ve Sınıflama Kılavuzundaki tanıma göre belirlendi. Bu tanıma uygun olarak glomerüler filtrasyon hızının 3 ay veya daha uzun süredir 60 ml/dk/1,73 m²'den daha düşük olması kronik böbrek yetmezliği (KRY) olarak değerlendirilmiştir (6).

İstatistiksel analiz

Verilerin tanımlayıcı istatistiklerinde sürekli veriler medyan olarak, kategorik veriler ise yüzde (%) olarak verilmiştir. Oluşturulan çapraz tabloların analizinde Pearson Ki-Kare, Fisher's Kesin (Exact) Ki-Kare ve Pearson Kesin (Exact) Ki-Kare analizleri kullanılmıştır. Analizlerin uygulanmasında IBM SPSS Statistics 23.0 programından yararlanılmıştır. İstatistiksel önemlilik için $p<0.05$ değeri anlamlı kriter olarak kabul edilmiştir.

3. Bulgular

Hastaların büyük çoğunluğu erkek (37 vs 15, %71,2 vs %28.8) ve ortalama yaş 45 ± 18 yıl olarak saptandı. Hastaların 19'unda (%36,5) semptomlardan önceki son bir ay içerisinde geçirilmiş enfeksiyon öyküsü, 15'inde (%28,8) ilaç kullanım öyküsü, 3'ünde (%5,7) ise aşı öyküsü mevcuttu. Hastaların 32'sinde (%61,5) eklem tutulumu, 20'inde (%38,5) renal tutulum mevcuttu. 28 (%53,8) hastada karın ağrısı mevcuttu ve bunların 5'inde (%9,6) ishal eşlik ediyordu. Başvuru anında hastaların 8'inde (%15,4) üst ve 3'ünde (%5,8) alt gastrointestinal sistem kanaması vardı. Hastaların başvuru anındaki laboratuvar verileri incelendiğinde 17'sinde (%32,7) anemi, 23'ünde (%44,2) lökositoz, 3'ünde (%5,8) trombositoz, 9'unda (%17,3) kreatin yüksekliği, 39'unda (%75) sedimentasyon yüksekliği, 24'ünde (%46,2) CRP yüksekliği, 13'ünde (%25) IgA yüksekliği, 6'sında (%11,5) anti-nükleer antikor (ANA) pozitifliği, 1'inde (%1,9) anti-nötrofilik sitoplazmik antikor (ANCA) pozitifliği, 9'unda (%17,5) kompleman düşüklüğü tespit edildi. Başvuru anında bakılan medyan sedimentasyon değeri 35 mm/saat , serum C-reaktif protein (CRP) değeri 4,6 mg/dl olarak hesaplandı (Hastaların demografik, klinik özellikleri ve laboratuvar bulguları Tablo 1'de özetlenmiştir.). Hastaların 40'ına (%76,9) cilt biyopsisi yapılmıştı ve tümü IgA vasküliti ile uyumlu idi. Gastrointestinal tutulumu olan hastaların 2'sinde endoskopik biyopside IgA vasküliti tutulumu gösterildi

Tablo 1. IgA vaskülit tanılı tüm hastaların demografik, klinik ve laboratuvar özellikleri

Parametre	Sayı/yüzde (%)
Erkek /Kadın, %	37/15 (%71,2/%38,8)
Ortalama yaş, yıl	45 ± 18
Tetikleyici etken	
Enfeksiyon	19 (%36,5)
İlaç	15 (%28,8)
Aşı	3 (%5,7)
Bilinmeyen	15 (%28,8)
Klinik bulgular	
Cilt	52 (%100)
Muskuloskeletal	32 (%61,5)
Renal	20 (%38,5)
Gastrointestinal	11 (%21)
Diğer	0
Laboratuvar bulguları	
Anemi	17 (%32,7)
Lökositoz	23 (%44,2)
Trombositoz	3 (%5,8)
Kreatin yüksekliği (yeni gelişen)	9 (%17)
ESH yüksekliği	39 (%75)
CRP yüksekliği	24 (%46,2)
Serum IgA yüksekliği	13 (%25)
ANA pozitifliği	6 (%11,5)
Medyan takip süresi, ay	21
Relaps	9 (%16)
Mortalite	7 (%12)

İlk başvuru yeri verisine ulaşılabilen 20 hasta incelendiğinde 11 (%21,2) hastanın acil servise, 6 (%11,5) hastanın dermatolojiye, 3 (%5,8) hastanın genel dahiliyeye başvurduğu görüldü. Hastaların romatoloji bölümüne medyan ulaşım süresi 10 gün, semptomların başlaması ile cilt biyopsisine kadar geçen medyan süre 12 gün olarak hesaplandı. Renal tutulumu olanlarda semptomların başlaması ile renal biyopsi yapılana kadar geçen medyan süre 20 gün olarak hesaplandı. Kas iskelet sistemi tutulumun eşlik ettiği hastaların, etmeyenlere göre romatoloji bölümüne ulaşım süresinin istatistiksel olarak daha kısa olduğu

izlendi (8,5 gün ve 17,5 gün p:0,026). Romatoloji uzmanına ulaşım süresi medyanları kıyaslandığında, takiplerinde ölen ve hayatta kalan gruplar arasında anlamlı farklılık saptanmadı (9 gün ve 10 gün).

Yatış sırasında bakılan spot idrarda protein kreatin oranı veya 24 saatlik idrarda proteinuri oranı incelendiğinde 19 (%36,5) hastada 1 gramın üzerinde olduğu, 7 (%13,5) hastada 300 mg ile 1 gram arasında olduğu tespit edildi. Hastaların yatışları sırasında bakılan idrar sedimentleri incelendiğinde 14 (%27) hastada dismorfik eritrosit saptandı. Tüm hastalar içerisinde 20 hastada renal tutulum vardı, 12 (%23,1) hastaya renal biyopsi yapılmış ve IgA vasküliti ile uyumlu saptanmıştır. Renal biyopsiler incelendiğinde; 4'ünde kresent, 8'inde skleroz, 9'unda selülarite, 6'sında fibröz yapılar izlendi. Renal tutulumu olan 20 hastanın prognozları incelendiğinde 5'inde KRY geliştiği ve bunların 3'ünde hemodiyaliz desteğinin en az bir sefer gerektiği tespit edilidi (Renal tutulumun özellikleri ve uzun dönem prognoz verileri Tablo 2'de verilmiştir). Takipleri sırasında 5 hastada KRY gelişmiş olup, bu hastaların hepsinde başvuru esnasında hematüri veya proteinüri mevcuttu (p:0,15). Takiplerinde HD desteği gereken 3 hastanın hepsinin KRY'ye ilerlediği izlendi (p<0,001). Takipleri sırasında ölen 7 hastanın başvuru semptomları incelendiğinde başvuru anında 5'inde (%71,4) akut böbrek yetmezliği mevcuttu ve hayatta kalan popülasyonla kıyaslandığında istatistiksel olarak anlamlı bulundu (%71,4 vs %11,1 p<0,001).

Tablo 2. Renal tutulumun özellikleri ve uzun dönem prognoz verileri

a. Başvuru anında Proteinuri	
<1 gram	7 (%13,5)
>1 gram ve üzeri	19 (%36,5)
Kreatin yüksekliği	9 (%17)
İdrar mikroskopisinde dismorfizm	14 (%27)
b. Renal biyopsi	12
c. Patoloji	
• Kresent	4
• Selülarite	9
• Fibroz	6
• Skleroz	8
d. Prognoz	
Renal fonksiyonlarda düzelme	10 hafta
Kronik renal hastalık	5
Hemodiyaliz ihtiyacı	3

Yaşları 65 yaş ve üstü olan hastalar ile 65 yaştan küçük olan yetişkinler kıyaslandı (12 ve 40). Semptomların çıkmasından bir ay önceki süreçte enfeksiyon öyküsü yaşlı olan grupta gençlere kıyasla daha azdı (%16,7 ve %42,5 p:0,03). Kas-iskelet sistemi tutulum oranları kıyaslandığında yaşlılarda gençlere göre daha az izlendi (%25 ve %72,5 p:0,012). Yaşı ileri olan grupta başvuru anında akut böbrek yetmezliği varlığı (%50 ve %10 p:0,002), yatışları sırasında nefrotik düzeyde proteinüri düzeyi (%75 ve %32,5 p:0,028), renal biyopsi yapılma oranı (%50 ve %15 p:0,012), takiplerinde KRY gelişme oranı (%33,3 ve %2,5 p<0,001) diğer gruba göre daha yüksek bulunmuştur. Tüm nedenlere bağlı mortalite de ileri yaşlı olan grupta yüksek saptandı (%41,7 ve %5 p:0,001) (Renal tutulum özellikleri, tedavi yaklaşımları ve mortalite ile ilgili bilgiler Tablo 3'de verilmiştir).Hastaların birinci basamak tedavileri incelendiğinde 7 (%13,5) hastaya yalnızca steroid, 25 (%48,1) hastaya steroid ve kolşisin kombinasyonu verildiği görüldü. Steroide ek olarak 17 (%32) hastaya azatioprin, 4 (%7,6) hastaya siklofosfamid tedavisi eklendiği görüldü. 11 (%21,2) hastada relaps veya birinci basamak tedaviye direnç nedenli ikinci basamak tedavi ihtiyacı olmuştur (steroid: 3, azatiyoprin: 3, mikofenolat mofetil: 2 ve siklofosfamid: 2). Birinci basamak tedavide immünsüpresif tedavi (azatiyoprin, mikofenolat mofetil, siklofosfamid) alan hastalar ile almayan

hastalar kendi aralarında kıyaslandı. İmmünsüpresif tedavi alanlarda, başvuru esnasında akut böbrek yetmezliği mevcudiyeti daha fazlaydı (%40 ve %6,3 p :0,003). Başvuru anındaki beş faktör (5F) skorları kıyaslandığında immünsüpresif tedavi alanlarda skoru ≥2 olan kişi sayısı daha fazlaydı (%55 ve %3,1 p<0,001). İmmünsüpresif tedavi alan ve almayan gruplar bir yıl takibin sonunda remisyona girme açısından kıyaslandığında aralarında istatistiksel olarak anlamlı bir sonuç bulunamadı (p:0,072). Hastaların medyan takip süresi 21 ay olarak hesaplandı. 13 (%25) hastanın takiplerine gelmediği, gelen hastalar arasında cilt lezyonlarının medyan iyileşme süresi 8 hafta, renal tutulumu olanlarda renal fonksiyonların normale döndüğü medyan süre 10 hafta ve hastalığın her açıdan remisyona girdiği medyan süre 26 hafta olarak saptandı. Takiplerine devam eden hastalar incelendiğinde 9 (%17,3) hastada relaps tespit edildi ve bu hastaların 4'ünde iki ve üzerinde çoklu relaps izlendi. Relaps yerleri incelendiğinde 5'inin renal, 2'sinin cilt, 1'inin gastrointestinal sistem olduğu görüldü. Takipleri sırasında 7 hastanın vefat etti ve medyan ölüm yaşı 66 olarak hesaplandı.

Tablo 3. Renal tutulum özellikleri, tedavi tercihi ve mortalite

Yaş	>65	<65	P değeri
Hasta sayısı	12	40	
Başvuru kreatin yüksekliği	%50	%10	0.002
Nefrotik proteinuri oranı	%75	%32,5	0.028
Renal biyopsi	%50	%15	0.012
Kronik renal yetmezlik gelişimi	%33	%2,5	<0.001
1.basamak tedavi yaklaşımı			
Steroid	3 (%25)	4 (%10)	
Steroid + Kolşisin	3 (%25)	22 (%55)	
Steroid + Azatioprin	4 (%33)	12 (%30)	
Steroid + Siklofosfamid	2 (%16)	2 (%5)	0.02
Mortalite	%41,7	%5	0.001

4. Tartışma

Literatürde erişkin başlangıçlı IgA vasküliti ile ilgili yapılan çalışmalarda belirgin bir homojenisite yoktur. Her çalışmada farklı sekonder sonlanım hedefleri konulması nedeniyle farklı sonuçlar elde edilmiştir. Biz çalışmamızı temel olarak aşağıdaki 5 soru çerçevesinde dizayn ettik ve cevapları aramaya çalıştık.

1-Hastaların ilk başvuru yerleri farklı mıdır ? Başvurudaki gecikmenin prognoz üzerine etkisi var mıdır?

Literatürde bu hususta yeterli veri bulunmamakla beraber, hastaların klinik prezentasyon şekline göre başvurdukları klinikler değişkenlik göstermektedir. Cilde sınırlı IgA vaskülit tanılı hastalar genellikle dermatoloji takip ve tedavisine devam ederken, kas-iskelet sistemi, gastrointestinal ve renal tutulumu olması durumunda romatolojiye ve nefrolojiye başvurmaktadır. Ülkemizde bu konuda henüz bir çalışma yapılmamıştır. Çalışmamızda ilk başvuru yerleri incelendiğinde 11 (%21,2) hastanın acil servise, 6 (%11,5) hastanın dermatolojiye, 3 (%5,8) hastanın genel dahiliyeye başvurduğu görüldü. Kas-iskelet sistemi tutulumu olması halinde romatoloji'ye başvuru sıklığında artış olduğunu tespit ettik. Hastaların romatoloji uzmanına medyan ulaşım süresi 10 gün, semptomların başlaması ile cilt biyopsisine kadar geçen medyan süre 12 gün, renal tutulumu olanlarda semptomların başlaması ile renal biyopsi yapılana kadar geçen medyan süre ise 20 gün olarak hesaplandı. Ancak bu sürenin renal prognoz üzerine etkisi olmadığını tespit ettik. Erken tanı ve tedavi yaklaşımı konusunda da romatoloji uzmanına ulaşma süresi açısından yaptığımız değerlendirmede, süre ile hastalık prognozu arasında anlamlı bir ilişki bulamadık. Ancak toplam hasta sayısı ve bu veri için bilgisine ulaşılan hasta sayısındaki

azlık bu istatistiği değerlendirmede göz ardı edilmemelidir.

2- Hastalıkta uzun dönemde relaps oranı nedir ve relaps görülen organlar nelerdir?

Yapılan çalışmalarda hastaların yaklaşık üçte ikisinde relaps, bunların %27'sinin çoklu relaps olduğu bildirilmektedir. En çok relaps gözlenen organlar sırasıyla cilt ve böbrektir (7). Bir başka çalışmada tanıdan sonraki 1.yılda hastaların %42'sinde tam, %32'sinde parsiyel remisyon, %10'unda yanıtsızlık, %5'inde relaps ve %12'sinde ölüm bildirilmiştir (8). Çalışmamızda her ne kadar materyal ve metod kısmında belirtilmiş olsa da veri eksikliği nedeniyle remisyon oranları net hesaplanamamıştır. Relaps ise hastaların %17,3'ünde görülmüş ve en sık relaps yeri olarak böbrekler tespit edilmiştir.

3- Renal tutulum özelliklerinin uzun dönem renal prognoz üzerine etkisi nedir?

Hastalığın en önemli morbidite göstergelerinden biri de renal tutulumdur. Yetişkinlerde, tanı anında böbrek yetmezliği yaklaşık %30 oranında görülürken, çocuklarda böbrek yetmezliği daha nadirdir. Glomerulonefrit, nefrotik sendrom görülme sıklığı ve renal yetmezlik gelişimi erişkin populasyonda daha sık görülmektedir (8, 9, 10). Çalışmamızda başvuru anında hastaların %17'sinde akut renal yetmezlik, %36,5'inde nefrotik sendrom mevcut idi. Renal yetmezlik nedeniyle hastaların bir kısmının nefroloji kliniği tarafından takibe alınması bu farklılığı açıklayabilir. Yapılan çalışmalarda başvuru anında proteinuri varlığı ve düzeyi (>1 gr/gün) kötü renal prognoz ile ilişkili olarak bulunmuştur (11, 12). Çalışmamızda böyle bir ilişki tespit edemedik.

IgA vaskülitinde uzun dönemde KRY gelişimi hakkında farklı prevalans verileri mevcuttur (7, 11, 12). Villatoro ve ark. yaptığı çalışmada KRY gelişimi 1.yıl ve 5.yıl sonunda sırasıyla %10 ve %15 olarak bildirilmiştir (8). Çalışmamıza katılan hastaların medyan takip süreleri 21 ay olup bu süre sonunda %9,6'sında KRY, %5,7'sinde uzun dönem hemodiyaliz ihtiyacı olmuştur. Ek olarak 65 yaş ve üzeri hasta grubunda proteinuri, akut renal yetmezlik ve kronik renal yetmezlik gelişiminin diğer gruba göre daha yüksek oranda olduğunu saptadık. Histopatolojik karakteristik özelliklerin (kresent, skleroz, fibroz) renal prognoz üzerine olan etkisine dair farklı çalışma sonuçları mevcuttur. Yakın zamanda yapılmış bir çalışmada kresent veya proliferatif glomerulonefrit varlığının renal tam yanıt veya relaps açısından herhangi bir fark yaratmadığı bildirilmiştir (8). Biz de çalışmamızda renal yetmezlik gelişimi ile histopatolojik veriler arasında anlamlı bir ilişki bulamadık. Ancak hasta sayımızdaki kısıtlılık göz ardı edilmemeli, veriler bu açıdan dikkatle değerlendirilmelidir.

4-İmmünsüpresif tedavi yaklaşımları nelerdir ve prognoz üzerine etkisi var mıdır?

Çocukluk çağındaki IgA vaskülit'inde hastalık kendini sınırlaması nedeniyle nadiren immunsupresif tedavi ihtiyacı olmaktadır. Erişkin populasyonda ise renal tutulumun daha yoğun olması ve uzun dönem prognoz verileri dikkate alındığında organ tehdit edici durumlar varlığında (renal ve gastrointestinal tutulum) kortikosteroid tedavisine ek olarak immunsupresif ajanlar (azatiyoprin, mikofenolat mofetil, siklofosfamid, rituksimab) tedaviye eklenmektedir. Hangi ajanın ne zaman tercih edileceği ve ne kadar süre kullanılacağı konusunda net bir görüş mevcut değildir (13). İmmunsupresiflerin (steroid dışı) organ prognozları üzerine etkinliği ile ilgili pek çok farklı çalışma mevcuttur. Bu çalışmaların çoğunda immunsupresif tedavinin remisyon, organ prognozlarını iyileştirme gibi sonlanımlarda etkili olduğu gösterilememiştir (7, 14, 15). Biz de çalışmamızda immunsupresif alan hastalar ile almayanlar arasında birinci yılda remisyona girme açısından farklılık tespit edemedik. Ancak yukarıda belirttiğimiz gibi remisyon verilerine sahip olduğumuz hasta sayısının düşük olması göz ardı edilmemelidir. Bu hususta IgA vaskülitinde immunsupresif tedavilerin etkinliğini gösterecek, iyi kategorize edilmiş randomize kontrollü çalışmalara ihtiyaç vardır.

5-İleri yaş populasyonda mortalite farklı mıdır?

Yapılan pek çok retrospektif gözlemsel çalışma ileri yaş ile renal tutulum, renal prognoz ve mortalite arasında ilişki olduğunu bildirmektedir (8, 12). Ancak bu çalışmalarda temel alınan yaş sınırı farklılıklar göstermektedir. Villatoro ve ark. yaptığı çalışmada 51 yaş ve üzerindeki IgA vaskülit tanılı hastalarda normal populasyona göre mortalite riski 7 kat artmış olarak tespit edilmiştir ($p<0.001$) (8). Çalışmamızda 65 yaş ve üzeri populasyonda tüm nedenlere bağlı mortalite 65 yaş

ve altındaki populasyona göre belirgin olarak yüksek saptandı (%41,7 ve %5, $p<0.001$). Ancak çalışmamaızda her iki grup arasında hasta sayısı bakımından (12 ve 40) belirgin bir farklılık olduğu unutulmamalıdır.

Çalışmamızda bazı sınırlılıklar mevcuttur. Öncelikle retrospektif olması nedeniyle verilerin kaybının söz konusu olması kaçınılmazdır. Bunun dışında, sadece romatoloji kliniğinde tanı ve takibi yapılan IgA vaskülitli hastaları içermesi ve göreceli hasta sayısının azlığı sonuçların yorumlanması üzerinde etkili olmuş olabilir. Bu nedenle renal ve gastrointestinal tutulum oranları literatüre kıyasla farklı saptanmış olabilir. Hastaların komorbidite verilerinde kayıp olması nedeniyle tüm nedenlere bağlı mortalite üzerine olan etkileri hakkında öngörüde bulunamadık. Renal tutulumu olan hastaların bir kısmına biyopsi yapılamaması nedeniyle histopatolojik özelliklerin renal prognoz üzerine etkisi istatistiksel açıdan anlamlılığa ulaşmamış olmasını açıklayabilir.

5. Sonuç

Tek merkez romatoloji ünitesinden yapılan bu çalışmada renal tutulum erişkin başlangıçlı IgA vaskülitinin en sık üçüncü organ tutulumu idi. Hastalığın prognozunu belirleyen en önemli faktörlerden biri ilk başvuru anındaki renal tuıtulumdu. İleri yaşta başlayan ve renal tutulumu olan IgA vaskülitli hastalar KRY'ye gidiş ve prognoz açısından dikkatle takip edilmelidirler.

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Research Article / Araştırma Makalesi

Evaluation of the Citalopram Levels on Qtc Interval in Rats Using with Radio-Telemetry

Sıçanlarda Sitalopram Düzeylerinin Qtc Aralığı Üzerine Etkilerinin Radyo-Telemetri Yöntemi ile Değerlendirilmesi

[1]Nusin Harmanci, [2]Cigdem Toprak, [1]Zuhal Kaltus, [1]Semra Yigitaslan,[1]Basar Sirmagul

[1]Eskisehir Osmangazi University, Faculty of Medicine, Department of Pharmacology, Eskisehir, Turkey

[2]Bursa Uludag University, Vocational School of Health Services, Bursa, Turkey

Abstract

Long QT syndrome is an arrhythmogenic disease characterized by prolonged QT interval. Citalopram (CIT) was reported to prolong QT interval dose-dependently. Omeprazole (OMP), inhibits CIT metabolizing enzyme CYP2C19, thereby increases serum concentrations which may increase the risk of QT prolongation. These are commonly co-prescribed and recent studies have raised the safety concerns about. We aimed to investigate the dose dependent effects of citalopram alone and in combination with OMP. Forty male, Sprague Dawley rats were divided into 5 groups (n=8). CIT (10 mg/kg or 30 mg/kg) was given for 2 weeks alone or in combination with OMP (100 mg/kg) starting from the 2nd week. ECG recordings and blood samples were collected. QT interval significantly increased in all groups compared to control. The plasma level of CIT in the CIT30 group was significantly higher than CIT10 group ($p<0.01$) and was significantly higher in the CIT10+OMP group than that of the CIT10 group ($p<0.01$). In treatment groups, the increase in plasma citalopram level correlated positively with the increase in QT ($r=0.844$, $r2=0.713$). It was determined that CIT caused prolongation of QT interval, the addition of OMP increased QT interval more, and these increases correlated positively with CIT plasma concentration. Therefore, it would be appropriate to routinely measure CIT plasma levels in addition to ECG, particularly in patients with additional risk factors for QT prolongation.

Keywords: Citalopram, electrocardiography, long qt syndrome, radiotelemetry, therapeutic drug monitoring

Özet

Uzun QT sendromu, senkop ve ani ölüme neden olabilen QT aralığında uzama ile karakterize aritmojenik bir hastalıktır. Seçici serotonin geri alım inhibitörü olan sitalopram (CIT), en çok reçete edilen antidepresanlardan biridir. CIT'nin doza bağlı olarak QT aralığını uzattığı bildirilmektedir. Bir proton pompası inhibitörü olan omeprazol (OMP), CIT metabolize edici enzim CYP2C19'u inhibe eder, böylece CIT'nin serum konsantrasyonunu artırır ve bu da QT uzaması riskini artırabilir. CIT ve OMP genellikle birlikte reçete edilir ve son çalışmalar CIT ile OMP'nin birlikte kullanılmasıyla ilgili güvenlik endişelerini ortaya çıkarmıştır. Bu çalışmanın amacı, sıçanlarda sitalopramın tek başına ve OMP ile kombinasyon halinde QT aralığı üzerine olan etkilerini doza bağlı olarak araştırmaktır. Kırk adet erkek, Sprague Dawley sıçan 5 gruba ayrıldı (n=8). CIT 10 mg/kg ve 30 mg/kg 2 hafta süreyle oral gavaj yoluyla verildi, 2. haftadan itibaren de iki gruba OMP (100 mg/kg) ile kombine olarak verildi. Kontrol grubu sadece serum fizyolojik aldı. Birinci haftanın ve ikinci haftanın sonunda EKG kayıtları yapıldı ve kan örnekleri alındı. QT aralığı tüm gruplarda kontrol grubuna göre anlamlı olarak arttı. CIT30 grubundaki ilaç plazma düzeyi, CIT10 grubundan önemli ölçüde daha yüksekti ($p<0.01$). CIT10 + OMP grubunda CIT10 grubuna göre anlamlı derecede yüksekti ($p<0.01$). Tedavi gruplarında, plazma sitalopram düzeyindeki artış, QT aralığındaki artışla pozitif korelasyon gösterdi ($r = 0.844$, $r2 = 0.713$). Sitalopramın sıçanlarda QT aralığının uzamasına neden olduğu, metabolizma inhibitörü OMP eklenmesinin ise ilaç plazma düzeyini daha da arttırdığı. dolayısıyla QT aralığını da daha fazla arttırdığı gösterildi. Ek olarak QT aralığındaki artışların CIT plazma düzeylerindeki artışlar ile pozitif korelasyon gösterdiği belirlendi. Bu nedenle, özellikle QT uzaması için ek risk faktörleri olan hastalarda EKG takibinin ve CIT plazma düzeylerinin rutin olarak ölçülmesinin uygun olacağı görüşündeyiz.

Anahtar Kelimeler: Elektrokardiyografi, radyotelemetri, sitalopram, terapötik ilaç düzeyi izlemi, uzun qt sendromu

Correspondence:
Nuşin HARMANCI
Eskisehir Osmangazi University, Faculty of Medicine, Department of Pharmacology, Eskisehir, Turkey,
e-mail: nusinharmanci@yahoo.com

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1. Introduction

The QT interval is measured from the beginning of the QRS complex to the end of the T wave and it refers to ventricular depolarization and repolarization (1, 2). LQTS is an arrhythmogenic disease characterized with QT prolongation that can cause syncope and sudden cardiac death secondary to cardiac arrhythmias (3). LQTS is usually caused by mutations in genes that encode ion channels in the heart, however, some drugs, like selective serotonin reuptake inhibitors (SSRIs) can also lead to LOTS (4, 5). One of the most common reasons for the withdrawal of drugs or the restriction of use in recent years has been the prolongation of the QT interval (6, 7). Due to serious drug-induced arrhythmias, regulatory authorities require investigation of the possible risks of drugs to QT interval prolongation (8, 9). Selective serotonin reuptake inhibitors (SSRIs) are similar in efficacy to tricyclic antidepressants, but have high selectivity and low risk of side effects (10, 11). In recent years, some SSRIs have drawn attention due to their arrhythmogenic effects resulting in LOTS (12-15). Citalopram is one of the most frequently used is reported to alter the electrical activity of the heart, causing abnormal heart rhythm (12, 16). Citalopram is metabolised via CYP2C19 and Omeprazole (OMP), a proton pump inhibitor (PPI), can inhibit CYP2C19 (17). Omeprazole has shown to increase citalopram concentrations in humans (14). A study examining geriatric inpatient health records has reported that citalopram and omeprazole were commonly co-prescribed in this age-group which resulted in significant interactions causing QT interval prolongation of individuals (18).Moreover, a recent cohort study has reported that citalopram and omeprazole use increased incidence of sudden cardiac arrest in an Asian population as compared with non-users and this risk was also more pronounced in concomitant use (19). The radio-telemetry system is a method for evaluating the arrhythmogenic effects of drugs. The advantages of the system are that biological parameters can be measured in the closest conditions to physiological conditions, there are no time-dependent limitations, more than one biological parameter can be recorded simultaneously and continuously, there is no stress related to movement restriction or the physiological response due to general anesthesia is not suppressed, and the number of animals used can be reduced (20). In this study, we aimed to evaluate the effects of citalopram alone and in combination with omeprazole on QT interval using radio-telemetry method and relation of QT interval to plasma levels of citalopram in rats.

2. Material and Methods

Ethical Statement

This study was approved by the Local Ethical Committee for Animal Experimentation (Approval no: (25.01.2018/517).

Animals

Forty male, Sprague Dawley rats (250-300g, n=8 per group) were purchased from Medical and Surgical Research Center of our university and housed in a temperature (20–25°C) controlled room with a 12:12-h light-dark cycle with food and water ad libitum.

Experimental Procedures

Rats received 10 mg/kg or 30 mg/kg citalopram alone (Sigma-Aldrich, USA) for 2 weeks (CIT10 and CIT30 groups) or in combination with OMP (100 mg/kg, Sigma-Aldrich, USA) starting from 2nd week (CIT10+ OMP and CIT30+ OMP groups) via daily oral gavage at same time (10:00 am). Control rats received vehicle saline.At the end of the first week, the radio-telemetry transmitters (C50-PXT or F40 model, DSI, St. Paul, MN, USA, Ponemah software v6.50) were implanted as previously described(21) to perform electrocardiography (ECG) recordings in conscious freely moving rats (22). Briefly, transmitters were placed into the peritoneal cavity and electrodes were placed subcutaneously at the forefoot level under ketamine (80 mg/kg) and xylazine (10 mg/kg) anesthesia (20). Rats received intraperitenoal tramadol hydrochloride (25 mg/kg) for postoperative analgesia. After surgery, rats were housed individually. During one-week recovery period, Citalopram alone treated rats continued to receive citalopram

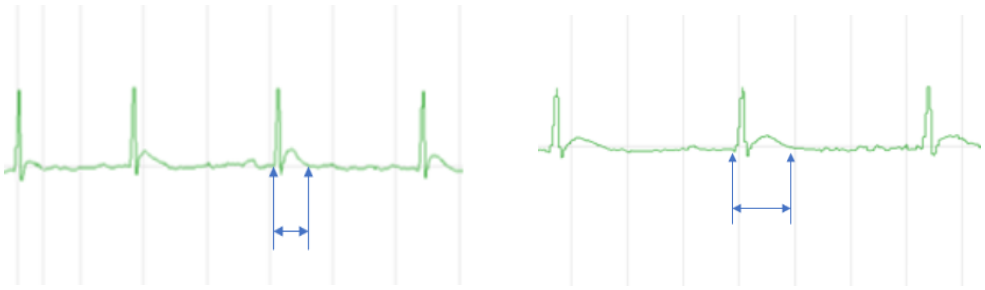
and omperazol combination groups of citalopram started to receive omperazol (CIT10+OMP and CIT30+OMP groups). ECG data were collected at 1000 Hz in 6 consecutive periods, each consisting of 10 min (at the and of first and second week). Bazett's equation is used for correction of prolongation of QT (23-25). Corrected QT interval (QTc) was to compare QT values according to heart rates and evaluate the risk of arrhythmia (26, 27). Plasma citalopram levels were measured at the end of the first week of treatment in the omeprazole-added groups and end of the second week of treatment in the all treatment groups. Blood samples were collected from the tail vein by using a strainer. The level of citalopram in plasma was measured by LC-MS/MS method. At the end point, rats were euthanized with high dose anesthetic and cervical dislocation.

Statistical Analysis

SPSS 21.0 (IBM SPSS Corp.; Armonk, NY, USA) was used to analyze the data. Measurement data were expressed as mean ± SEM. Data were analyzed by the One-Way ANOVA test followed by posthoc analyses with Tukey test. Regression correlation analysis was performed for the relationship between drug levels and QT intervals. $p < 0.05$ was considered statistically significant.

3. Results

All recordings (normal and prolonged QT intervals) were made by the radio telemetry system both as ECG image and numerically (Fig.1).



Normal QT (220ms) **Prolonged QT (255 ms)**

Fig 1. ECG images of normal and prolonged QT interval recorded by radiotelemetry system

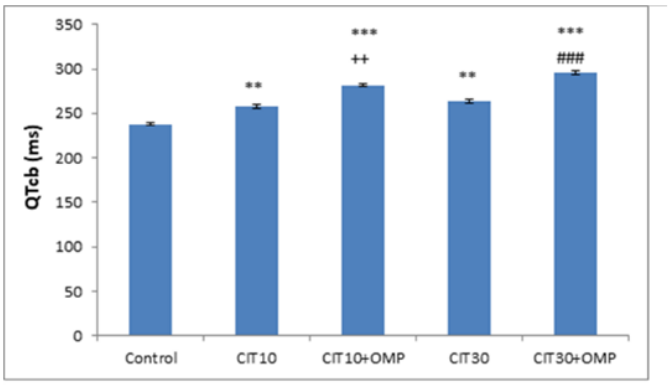


Fig 2. QT interval measurements in control and treatment groups(ms).
***p<0.01, *** p<0.001; vs. control group*
++ p<0.01; vs. CIT10 group
p<0.001; vs. CIT30 group;

QT interval was 237.91 ± 1.89 ms in the control group and 257.70 ± 2.18 ms in the CIT10 group; 281.84 ± 1.89 ms in the CIT10 + OMP group; It was increased to 264.06 ± 2.02 ms in the CIT30 group and 295.38 ± 2.18 ms in the CIT30 ± OMP group. Briefly, QT interval in CIT10, CIT10+OMP, CIT30 and CIT30+OMP groups was significantly increased compared to the control group ($p<0.01$, $p<0.001$, $p<0.01$ and $p<0.001$, respectively). On the other hand, addition of omeprazole increased the QT interval significantly in CIT10-treated and CIT30-treated animals ($p<0.01$ and $p<0.001$, respectively) (Fig.2).

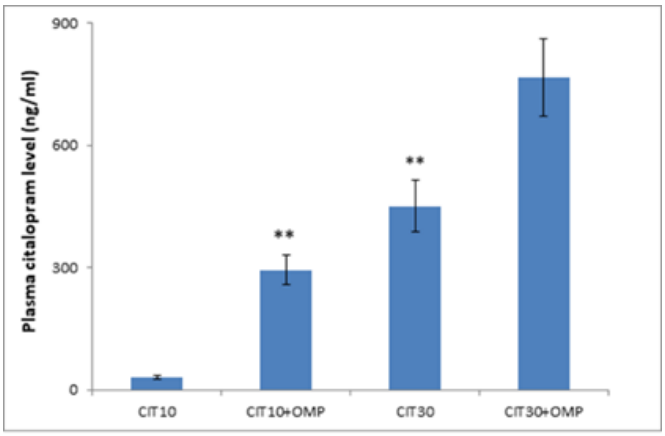


Fig. 3. Citalopram plasma levels (ng / ml) measured in treatment groups
**; $p<0.01$ vs. CIT10 group

Plasma citalopram level was measured in the treatment groups and a statistically significant difference was observed between the groups. Accordingly, citalopram plasma level in the CIT30 group was significantly higher than in the CIT10 group (451.00 ± 63.90 vs 30.79 ± 4.51 ng / ml) ($p<0.01$). Citalopram plasma level was also significantly higher in the CIT10 + OMP group compared to the CIT10 group (293.71 ± 36.09 vs 30.79 ± 4.51 ng / ml) ($p<0.01$). Although the citalopram plasma level in the CIT30 + OMP group increased slightly compared to the CIT30 group, this difference was not statistically significant (765.57 ± 94.77 vs 451.00 ± 63.90 ng / ml) ($p>0.05$) (Fig. 3).

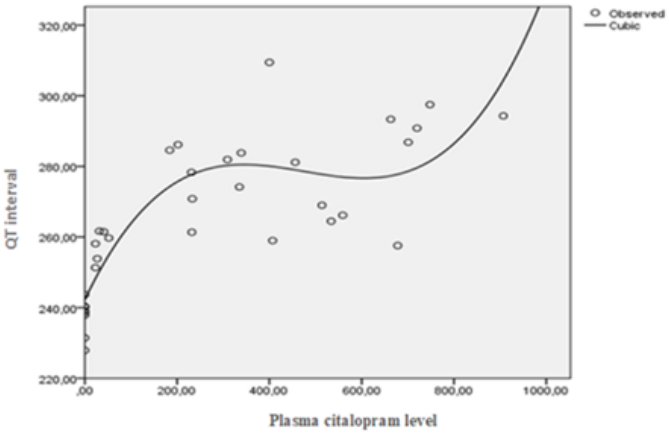


Fig. 4. Relationship between Citalopram plasma levels and QT interval values
($r = 0.84$, $r^2 = 0.713$)

The increase in citalopram plasma level in the treatment groups was positively correlated with the increase in QT interval value in the same groups (r = 0.844, r2 = 0.713) (Fig. 4).

4. Discussion

In our study, two different doses of citalopram (10 and 30 mg/kg) were given to rats alone or in combination with omeprazole (100 mg/kg) and QT interval were evaluated by telemetric method and plasma drug levels were measured.

As a result, citalopram plasma level increased according to the dose and QT interval prolonged in correlation with this. The addition of omeprazole to the treatment also resulted in a greater increase in both plasma drug level and QT interval compared to citalopram-alone administration. Accordingly, in a retrospective study, citalopram produced a dose-dependent increase in QT interval compared to baseline ECG results. The authors have recommended taking caution and frequent ECG follow-up visits during high dose citalopram use particularly in elder and high-risk patients with arrhythmia (28). In 2011, the FDA reported that citalopram doses should be limited to 40 mg/day as well as should be contraindicated in LQTS patients (21). Thereafter, in 2012, the FDA changed the definition of contraindications from not recommended to an absolute contraindication in patients with QT interval of over 500 ms (29). These warnings are based on a randomized, double-blind, placebo-controlled multicenter study (12). In addition, some studies with high doses use and some case studies with therapeutic doses has also reported prolongation of the QT interval (30-36). On the other hand, there are also some studies showing no negative effect on QT interval (37, 38). Mechanism of prolonging the QT interval has been suggested to be associated with direct blocking of cardiac potassium channels encoded by the human ether related gene (hERG) (39) and blocking of α L-type calcium channels (40-42). LQTS may be congenital or acquired abnormality and risk factors for acquired have been identified. For instance, female sex, advanced age, hypokalemia and hypomagnesemia; also combination with hepatic enzyme inhibitors (43-45). In our study, QT interval was significantly prolonged in omeprazole-added groups compared to citalopram-alone groups. So, FDA recommended limiting the maximum dose of citalopram to 20 mg/day in patients taking the CYP2C19 inhibitor (12). Accordingly, in our study, concurrent use of omeprazole and citalopram increased plasma citalopram level as well as QT interval. In a study reported that there was a significant increase in citalopram plasma levels when used with PPIs, and that a dose reduction of up to 50% may be required in patients (14). In a study conducted in healthy volunteers, omeprazole administration resulted increase citalopram concentration (46). In our study, increased doses caused an increase in both QT interval and plasma citalopram level with a positive correlation between these two parameters. This correlation was evaluated in order to determine whether routine plasma citalopram level measurement is required in patients using citalopram, particularly in those at high-risk for QT prolongation. There is no recommended drug plasma concentration range that can be used to evaluate the clinical response to citalopram treatment (47, 48), with only one case report suggesting that there may be a therapeutic window for citalopram in some patients (49). However, according to the results of our study, the increase in the dose of citalopram was directly related to both plasma drug level and QT interval. Therefore, we believe that monitorization of plasma level may be useful when used in combination with ECG follow-up in patients. Determination of a therapeutic window for citalopram plasma level may enable us to predict the high-risk patients before occurance of arrythmic ECG changes and to timely reduction of citalopram dose in this group of patients.

There are some limitations that need to be addressed in this study. Although the animals used were similar in terms of age and body weight, the basal heart rate, QT interval, electrolyte levels, and liver and kidney function were not evaluated. However, since young adult healthy male animals were used, it can be assumed that they did not have an

additional risk factor for QT prolongation in terms of these parameters.

In conclusion, in our study, it was found that 10 mg/kg and 30 mg/kg citalopram use caused prolongation of QT interval in rats, addition of omeprazole to the treatment further increased QT interval and these increases were positively correlated with citalopram plasma level. Therefore, we believe that it is appropriate to measure citalopram plasma level in combination with ECG recording routinely, particularly in patients with additional risk factors for QT prolongation. In the light of these results, further and larger animal and even human studies on the relationship between the QT interval and citalopram plasma level may provide stronger evidence about the necessity of measuring citalopram level.

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Ethical Statement

All experiments were performed with the permission of Eskisehir Osmangazi University Animal Experiments Local Ethics Committee (25.01.2018/517).

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Research Article / Araştırma Makalesi

Evaluation of Total Oxidant and Total Antioxidant Status in Patients with Acne Vulgaris

Akne Vulgarisli Hastalarda Total Oksidan ve Total Antioksidan Durumun Değerlendirilmesi

[1]Ersoy Acer, [1]Hilal Kaya Erdogan, [2]Evin Kocaturk, [3]Esra Agaoglu, [1]Nurhan Saracoglu, [4]Muzaffer Bilgin

[1]Eskişehir Osmangazi University Faculty of Medicine, Department of Dermatology, Eskisehir, Turkey

[2]Eskişehir Osmangazi University Faculty of Medicine Department of Medical Biochemistry, Eskisehir, Turkey

[3]Kars Harakani State Hospital, Department of Dermatology, Kars, Turkey

[4]Eskişehir Osmangazi University Faculty of Medicine Department of Biostatistics, Eskisehir, Turkey

Abstract

Acne vulgaris is a common skin disease and has a complex pathogenesis. There is no enough data related with oxidative stress in acne vulgaris. We purposed to assess total oxidant and total antioxidant status in acne vulgaris. We included 32 acne patients and 35 healthy controls in this study. Global Acne Grading System (GAGS) scores were calculated. Serum total oxidant status (TOS) and total antioxidant status (TAS) levels were evaluated and oxidative stress index (OSI) was calculated by proportion of the TOS to the TAS. Mean GAGS scores of acne patients were 14.08 ± 5.72. Mean disease duration of acne patients was 33.97 ± 25.99 months. TAS, TOS and OSI were significantly higher in acne patients (p=0.010, p=0.021, p=0.015, respectively). TAS, TOS and OSI were not correlated with disease duration and GAGS scores (p>0.05). Both oxidant and antioxidant status increased in acne patients. The study showed that oxidative stress may play a role in pathogenesis of acne but it isn't exactly known that is a cause or a result of acne. Advanced studies especially comparing mild to moderate and severe acne patients are required. In addition we consider that antioxidant agents may be beneficial in the treatment of acne.

Keywords: Acne vulgaris; total oxidant status; total antioxidant status; oxidative stress

Özet

Akne vulgaris sık görülen bir deri hastalığıdır ve karmaşık bir patogeneze sahiptir. Literatürde, akne vulgarisde oksidatif stresin durumu ile ilgili yeterli veri yoktur. Bu çalışmada akne vulgarisli hastalarda total oksidan ve total antioksidan seviyenin değerlendirilmesi amaçlandı. Bu çalışmaya 32 akne vulgarisli hasta ve 35 sağlıklı kontrol dahil edildi. Global akne skorlama sistemi (GASS) skorları hesaplandı. Serum total oksidan seviye (TOS), total antioksidan seviye (TAS) ölçüldü ve TOS, TAS'a bölünerek oksidatif stres indeksi (OSİ) hesaplandı. Akne hastalarının ortalama GASS skoru 14.08 ± 5.72 idi. Akne hastalarının ortalama hastalık süresi 33.97 ± 25.99 ay idi. Akne hastalarında TAS, TOS ve OSİ daha yüksekti (p=0.010, p=0.021, p=0.015, sırasıyla). TAS, TOS ve OSİ ile hastalık süresi ve GASS skoru arasında bir ilişki yoktu (p>0.05). Bu çalışmada akne hastalarında oksidan ve antioksidan seviye yüksekti. Bu sonuç oksidatif stresin akne patogenezinde bir rolü olabileceğini düşündürmektedir. Ancak oksidatif stres aknenin nedeni mi yoksa sonucu mu olduğu tam olarak bilinmemektedir. Özellikle hafif-orta ve şiddetli akne hastalarında oksidatif stres durumunu karşılaştıran ileri çalışmaların yapılmasına ihtiyaç vardır. Ayrıca akne tedavisinde antioksidan ajanların faydalı olabileceğini düşünmekteyiz.

Anahtar Kelimeler: Akne vulgaris; total oksidan durum; total antioksidan durum; oksidatif stres

Correspondence:
Ersoy ACER
Eskişehir Osmangazi University Faculty of Medicine, Department of Dermatology and Venereal Diseases, Eskisehir, Turkey
e-mail: ersoyacer@hotmail.com

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1. Introduction

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit. It is very frequent in adolescent with psychosocial and socioeconomic effects (1,2). Acne lesions are characterized by noninflammatory (open and closed comedones) and inflammatory (papules and pustules) lesions (2). Hyperseborrhoea, abnormal follicular keratinization, follicular colonization with Propionibacterium acnes (P. acnes) and inflammation are suggested as major factors of acne vulgaris pathogenesis (1,3). Moreover, oxidative stress may contribute to pathogenesis of acne vulgaris (4).

Oxidative stress in acne was evaluated by some oxidative stress markers such as catalase (CAT), malondialdehyde (MDA) and superoxide dismutase (SOD) in literature (5-8). These markers do not show total evaluation of oxidative stress. However, total oxidant status (TOS) and total antioxidant status (TAS) allow total evaluation of oxidative stress (9,10). In recent years, TOS and TAS were assessed in various dermatological diseases such as warts, pityriasis rosea, premature hair graying, androgenetic alopecia and rosecea too (11-15). In this study, we aimed to evaluate the TOS and TAS levels in acne patients.

2. Materials and Methods

We enrolled 36 acne vulgaris patients and 35 healthy controls aged between 18-25 years. Participants with any systemic diseases, metabolic syndrome, smoking, drinking, pregnancy and breast feeding were excluded. Using any medications and antioxidant nutritions in the last one month were other exclusion criterions. All individuals signed the informed consent form. Sociodemographic data of the volunteers were recorded. Global Acne Grading System (GAGS) was used to evaluate of acne severity. GAGS points are discounted by region of lesion' factor coefficients (forehead: 2, left cheek: 2, right cheek: 2, nose: 1, chin: 1 and neck, chest and back: 3) multiplying by lesion points (no lesion: 0, comedone: 1, papule: 2, pustule: 3, nodule: 4) and scores of each area are accumulated. Finally intensity of acne is categorized as no (0 point), mild (1-18 points), moderate (19-30 points), severe (31-38 points) and very severe (>39) (16).

Ten cc of venous blood samples were taken from all participants. The blood samples were centrifugated at 1500 g, 10 minutes and their sera were separated. Then the serum samples were preserved at -40°C (maximum 2 months) until TOS and TAS evaluations were taken colorimetrically by Cobas 8000 auto-analyser (Roche Diagnostics, Mannheim, Germany). TOS and TAS levels were evaluated by utilizing commercial kits of Rel Assay (Rel Assay Kit Diagnostics, Turkey). The analysis of TOS was adjusted with hydrogen peroxide (H2O2). The outcomes were stated as micromolar H2O2 equivalent per liter. The assay of TAS was adjusted with a stable antioxidant solution is conventionally referred to Trolox Equivalent which is a vitamin E analogue. TAS level stated as mmol Trolox equiv./lt. OSI level was computed by the method; OSI = [TOS (µmol H2O2 equiv./lt) / TAS (µmol Trolox equiv./lt)] X 100. To make the calculation, TAS valuations transformed to µmol/lt. OSI level showed as an arbitrary unit (17).

The Local Ethics Committee (14/03/19, decision no: 14) accepted the research protocol.

Statistical Analysis

IBM SPSS Statistics 21.0 programme was utilized. Constant data was showed as mean ± standard deviation and median. Categorical data was showed in percentage (%). Pearson's Chi-Square, Independent samples t test and The Spearman Correlation test were utilized. $p<0.05$ was admitted statistically significant.

3. Results

Of acne vulgaris patients, 33.3% (n=12) were male and 66.6% (n=24) female. 42.8% (n=15) of the control group were male, and 47.2% (n=20) were female. Mean age was 20.80 ± 2.30 years in acne group and was 20.91 ± 1.86 years in control group. Acne patients and controls were similar by distribution of sex and age ($p>0.05$). Mean GAGS scores of acne patients was 14.08 ± 5.72 (4-27) so participants had mild-moderate acne. Mean

disease duration of acne patients was 33.97 ± 25.99 months (1-96 months) (Table 1).

Mean TAS, TOS and OSI values were higher in acne group compared to control group (p=0.010, p=0.021, p=0.015, respectively) (Table 2). However, TAS, TOS and OSI were not related with disease duration and GAGS scores in acne group (Table 3).

Table 1. Characteristics in acne patient and control groups

Characteristics		Patients Mean ± SD, % (n)	Controls Mean ± SD, % (n)	p
Gender	Male	33.3% (n=12)	42.8% (n=15)	p>0.05
	Female	66.6% (n=24)	47.2% (n=20)	
Mean age		20.80 ± 2.30 year	20.91 ± 1.86 year	p>0.05
Mean GAGS score		14.08 ± 5.72		
Mean disease duration		33.97 ± 25.99 month		

(GAGS: Global acne grading system)

Table 2. Comparison of TAS, TOS and OSI levels in control and acne patient groups

Characteristics	Controls Mean ± SD	Patients Mean ± SD	p
TAS	2.47 ± 0.14	2.56 ± 0.17	0.021
TOS	3.21 ± 1.70	4.62 ± 2.65	0.010
OSI	129.02 ± 65.93	181.02 ± 105.45	0.015

**Independent Samples Test, (Standard deviation: SD, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index)*

Table 3. Correlation between TAS, TOS and OSI levels and GAGS scores and disease duration in acne group

	TAS	TOS	OSI
Disease duration (r;p)	-0.04; 0.798	0.11; 0.488	0.17;0.323
GAGS scores (r;p)	0.24; 0.159	-0.07; 0.654	-0.09; 0.601

**Spearman's Correlation Test, (GAGS scores: Global acne grading system scores, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index)*

4. Discussion

In present study, we detected oxidative stress was higher in acne patients. The pathogenesis of acne vulgaris is complex including P. acnes colonization, increased sebum generation and hypercornification of the pilasebaceous duct and inflammatory response. Furthermore, it is tought that oxidative stress may play a role in pathogenesis of acne (1,3,4). Previous studies showed that oxidative stress was higher in acne patients too (5-8). However it isn't exactly known either oxidative stress is a cause of acne or a result of inflammatory response. Acne is considered as a primarily inflammatory disease (18). P. acnes takes part in cutaneous flora, has a beginning role in inflammation of acne. It produces chemotactic factors therefore neutrophils collect at the site. Neutrophils release inflammatory factors such as lysosomal enzymes and generate reactive oxygen species (ROS). They injury the follicular epithelial tissue (4,19). Sebum secretion increase in acne vulgaris too. In addition, balance of sebum production changes contribute to inflammation of acne

(20). Linoleic acid has inhibitive impacts on ROS. Squalene's lipid peroxidation products cause comedogenic impacts. The linoleic acid decreases but squalene levels increase in acne (20,21).

The other major factor of oxidative stress is antioxidant capacity. The organisms have antioxidant defense systems such as SOD, CAT which restrain production of ROS. If ROS levels increase or antioxidant levels decrease, oxidative stress rise (8). Extravagant production of ROS cause damage to structures of cell such as proteins, lipids and nucleic acids (8,22). Oxidative stress involves in etiopathogenesis of various skin illnesses and it may be also in acne vulgaris (5,21,23). Akamutsu H et al showed increased H2O2 generation by neutrophils in acne inflammation and suggested that the production of ROS by neutrophils is an significant factor in pathogenesis of acne (19). In our study TOS levels of acne patients were high too. In the literature, higher oxidant status markers such as MDA, H2O2 and carbonyl contents (biomarker of protein oxidation) and lower antioxidant status markers such as CAT and SOD in serum and scraping samples of acne patients were reported (5-8,22,24,25). But these markers don't show completely oxidant and antioxidant status. Therefore we evaluated TOS and TAS levels which reflect globally total oxidant and antioxidant status in serum of acne patients. In our study, TOS, OSI and TAS were higher in acne patients. These results showed that both oxidant and antioxidant status increase acne. Antioxidant status may have increased response to increased oxidative stress in our study.

In a recent study, Abdel Fattah NS et al. showed that no important difference in MDA and SOD levels in tissue and blood between acne patients and healthy controls. But they detected mild acne patients had higher SOD levels, severe acne patients had lower SOD and higher MDA levels. Moreover, the authors reported a negative correlation between SOD and MDA levels (21). Similarly a negative correlation between MDA and CAT levels in severe acne patients was reported by Al-Shobaili et al. They suggested that high serum levels of MDA may be a result of tissue injury by causing ROS (7).

TAS, TOS and OSI were not related with acne severity and disease duration in our study. Similarly, it was reported that there was no significant differences between oxidant status and antioxidant status markers and acne severity and disease duration in literature (6,21,22). However, Akamutsu et al showed that inflamed acne patients demostrated a significant H2O2 production by neutrophils than comedonal acne patients and controls (19). In another study, a significant correlation were detected between the carbonyl contents levels and GAGS scores. Moreover, as acne severity increased, MDA levels increased and SOD levels decreased were reported (8). However, both TOS and TAS were high in acne patients in our study. This may have been caused by participants had mild to moderate disease (mean GAGS scores of acne patients were 14.08 ± 5.72) so TAS may have been rised in response to high oxidant status. Consequently, it may be suggested that first, oxidant status increase and then antioxidant status increase in response to high oxidative stress in mild to moderate acne. After then, antioxidant status decreases by increase of severity of acne. Antioxidant capacitiy may be exhausted while reducing high oxidative stress.

Study Limitations

Limitation of study was relatively small sample size. Another limitation was absence of participants with severe acne.

5. Conclusions

Both total oxidant and total antioxidant status was higher in mild to moderate acne vulgaris. Oxidative stress may contribute to pathogenesis of acne vulgaris but it isn't exactly known that is a cause or a result of acne. Advanced studies especially comparing mild to moderate and severe acne patients are required to illuminate this situtation. In addition, we consider that antioxidant agents may be beneficial in the treatment of acne.

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Research Article / Araştırma Makalesi

Gender Gap in the Authorship of Gynecology and Obstetrics Literature in Turkey: An Evaluation From 1995 to 2020

Türkiye Kadın Hastalıkları ve Doğum Alanyazını Makale Yazarlığı Cinsiyet Trendleri: 1995-2020 Yılları Arası Bir Değerlendirme

[1]Imran Gokcen Yilmaz Karaman, [2]Gülhan Sagiroglu Muslu, [3]Ayşe Betul Albayrak Denizli,

[1]Eskisehir Osmangazi University, Faculty of Medicine, Department of Psychiatry, Eskişehir, Turkey

[2]Diako Flensburg Hospital, Gynecology and Obstetrics Clinic Flensburg, Germany

[3]S.B.Ü Zeynep Kamil Gynecology and Pediatrics Training and Research Hospital, Istanbul, Turkey

Abstract

Although it is not the only output of academic productivity and representation, authorship can be considered as an important outcome. The present study aims to explore obstetrics and gynecology literature in Turkey, to assess the representation of women in academic journals as the author, of the male gender, and the inter-annual variation of article types. The journals which were indexed in the Scientific and Technological Research Council of Turkey, National Academic Network and Information Center's Turkish journal index in 2020, were included in the study. The volumes of the journals in 1995, 2000, 2005, 2010, 2015, and 2020, investigated online. Year of the articles, gender of the first author, gender of the last author, gender of corresponder author, number of female authors, number of male authors were coded.The variables of year, first author gender, last author gender, correspondent author gender, number of female authors, number of male authors were coded. A total of 1312 articles from 7 journals were analyzed. The gender inequality in the position of the first writer has been closed by years, and the gender inequality in the position of the writer responsible for correspondence has disappeared; however, there was no statistically significant change in the position of the last author from 1995 to 2020. In order to eliminate the current inequality in leadership positions, the clinical and educational work should be shared among the academicians in a balanced way, work environments where work life balance can be achieved should be created, sexual harassment and gender-based discrimination should not be tolerated.

Keywords: ITP, fragility, treatment outcomes, older adults

Özet

Makale yazarlığı akademik üretkenliğin ve temsiliyetin tek çıktısı olmamakla birlikte, önemli bir çıktısı olarak değerlendirilebilir. Çalışmamız Türkiye'de kadın hastalıkları ve doğum akademik dergilerinde kadın ve erkek cinsiyetlerinin yazar olarak temsiliyetini ve makale türünün yıllar arası değişimini araştırmayı amaçlamaktadır. 2020 yılında Türkiye Bilimsel ve Teknolojik Araştırma Kurumu Ulusal Akademik Ağ ve Bilgi Merkezi tarafından oluşturulan Türkçe dergi dizininde yer almış dergilerin 1995, 2000, 2005, 2010, 2015 ve 2020 yıllarında yayınlanmış sayılarından çevrimiçi ulaşılabilenler çalışmamıza dâhil edilmiştir. Makalelerin yıl, ilk yazar cinsiyeti, son yazar cinsiyeti, yazışmadan sorumlu yazar cinsiyeti, kadın yazar sayısı, erkek yazar sayısı değişkenleri kodlanmıştır Toplam 7 dergiden 1312 makale incelenmiştir. İlk yazar konumundaki cinsiyet eşitsizliğinin yıllara göre kapandığı, yazışmadan sorumlu yazar konumundaki cinsiyet eşitsizliğinin kaybolduğu; ancak son yazar konumunda 1995 yılından 2020 yılına dek istatistiksel olarak anlamlı bir değişme olmadığı görülmüştür. Liderlik konumlarındaki mevcut eşitsizliğin giderilebilmesi için akademisyenler arasında klinisyenlik ve eğitim görevlerinin dengeli bir biçimde paylaştırılması, iş ve özel hayat dengesinin sağlanabileceği çalışma ortamlarının yaratılması, cinsel tacize ve cinsiyete dayalı ayrımcılığa tolerans gösterilmemesi önerilmektedir.

Anahtar Kelimeler: cinsiyet eşitliği, toplumsal cinsiyet, yazarlık, kadın hastalıkları, doğum

Correspondence:
İmran Gökçen YILMAZ KARAMAN
Eskisehir Osmangazi University, Faculty of Medicine, Department of Psychiatry, Eskişehir, Turkey,
e-mail: gokcenylmz@yahoo.com

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1. Introduction

Social expectations based on biological sex are defined as gender. Physicians, as individuals, cannot be free from the social structures they live in, and they may have a gender-biased perspective both towards their colleagues and patients in their work environment and their private lives. This situation causes an asymmetry between women and men in terms of clinical and academic career opportunities (1).

Gender inequality has been continuing to negatively affect women's science careers for centuries. While achieving the right to education was a priority problem in the past, today there is an imbalance between women and men against women in terms of holding leadership positions. In America, a similar number of women and men earn doctoral degrees, while the majority of the faculty members are men. It is also known that female academicians who are in the same position as men and doing the job receive lower wages (2).

The representation of women on an equal basis with men in medical academic publications and medical research is important for patients, science, and general public health (3). The way to eliminate inequality in these areas is to be aware of the inequality. Gender distributions in important areas such as awards and appointments in institutions should be published consistently and transparently (4). Thus, it can contribute to the creation of a positive corporate culture in the context of gender equality.

Although it is not the only outcome of academic productivity and representation, academic publishing can be considered an important outcome. As a matter of fact, it is stipulated by universities for first appointments and reappointments (5).

Having a female patient, as a rule, obstetrics and gynecology practices are especially important for women's health and structural health equity. Regarding gender inequality and racism have similar social dynamics, research shows patients from ethnic minorities may get better treatment outcomes with the doctors from ethnic minorities (6). Women can be considered as the biggest minority of the world: not because of their number, but because they do not have equal power, rights, and opportunities with men (7). We think it is important to assess women's contribution to academic publishing in the area which focuses on women.

In this context, our study aims to investigate the trends in the representation of female and male genders as authors and the article type in academic journals of obstetrics and gynecology in Turkey.

2. Materıals and Method

In 2020, the journals included in the Turkish journal index created by the Scientific and Technological Research Council of Turkey (TÜBİTAK) National Academic Network and Information Center (ULAKBİM) were included in our study. In the search engine of the directory at https://app.trdizin.gov.tr/statistics/listAcceptedJournals.xhtml, by selecting "subject area" and "journal name", a total of 6 calls were made. General medical journals and journals that were not published in 2020 were eliminated from the results, and a total of 7 journals were reached (See Table 1). The online issues of the journals published in 1995, 2000, 2005, 2010, 2015, and 2020 were included in our study. Congress special supplements and correction notes (erratum) of journals were excluded from the study. Published CVs were excluded from the study. The variables of year, first author gender, last author gender, responsible author gender, number of female authors, number of male authors were coded by two gynecologists and obstetricians. Articles other than obstetrics and gynecology were excluded from the study (for example, articles focusing on the field of pediatrics).

Table 1. Journals included in the study, the number of articles that can be accessed online

Journal Order Number	Journal Name	Year of publication	Number of publications/ year	Number of articles available online					
				1995	2000	2005	2010	2015	2020
1	*Zeynep Kamil Tıp Bülteni*	1969	4	-	-	21	21	20	25
2	*Journal of Clinical Obstetrics & Gynecology*	1991	4	52	58	72	77	56	18
3	*Perinatoloji Dergisi*	1993	3	35	26	41	22	34	24
4	*Gynecology Obstetrics & Reproductive Medicine*	1995	3	-	-	62	46	44	42
5	*Journal of the Turkish-German Gynecological Association*	2000	4	-	-	60	56	39	39
6	*Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi*	2004	4	-	-	-	-	45	53
7	*Turkish Journal of Obstetrics and Gynecology*	2004	4	-	-	68	60	55	41
Total number of articles evaluated by years				87	84	324	282	293	242

In the process of determining the gender of the authors, female names or male names (for example Mary or James, for the English language) were coded directly, for names suitable for both genders (for example Kerry, for the English language), the websites of the authors' institutions and the photographs of the authors on social media accounts such as ResearchGate or LinkedIn were examined. For some authors, when gender information could not be reached with these methods, coding was made by searching for the name on the website https://genderize.io/ and by looking at which gender the name is most likely.

Since there were no human participants in our study, ethics committee approval was not required considering other bibliometric studies in the literature. Data were collected between January 1, 2021, and January 31, 2021.

Statistical analysis

IBM SPSS 22.0 version was used for data analysis. One-way analysis of variance (One-way ANOVA) was used to compare continuous variables by years, and the chi-square test was used for the analysis of categorical variables. When the column proportion is 0-1%, the data is automatically excluded from the analysis by the program used, Bonferroni correction is used for paired comparisons.

3. Results

A total of 1312 articles published in 1995, 2000, 2005, 2010, 2015, and 2020 were included in the study (Table 1). The number of female and male authors could not be determined in a 1995 article in which only the surnames of the authors other than the first author were specified. In another article published in 1995, only the surnames of all authors were specified, so the gender of the first author, the last author, and the author responsible for the correspondence, the total number of female authors and the total number of male authors could not be determined. Incomplete data of these two articles were excluded from the analysis.

As stated in Table 2; a trend that resulted in equality in the ratio of the first authorship of the genders and the ratio of correspondence authorship from 1995 to 2020 were

determined. However, there was no change in the final authorship rates between genders. In terms of article type, it was seen that the rates of research articles were in a downward trend from 1995 to 2010, and then increased to the levels in 1995. Complementary with this trend, the rate of case reports increased from 1995 to 2010, after which it started to decline.

As can be seen in Table 3, the ratio of female authors among the total authors has increased from 1995 to 2020.

Table 2. Gender ratio of authors by position, article type and article subject in all articles

		1995	2000	2005	2010	2015	2020	Dual comparison	Chi-square	p
First author gender	Male (%)	76.7	77.4	65.1	58.9	51.2	50.0	1995-2010, 1995-2015, 1995-2020, 2000-2010, 2000-2015, 2000-2020, 2005-2015, 2005-2020	43.477	<0.001
	Female (%)	23.3	22.6	34.9	41.1	48.8	50.0			
Last author gender	Male (%)	69.4	72.6	71.9	73.8	68.3	64.0	-	7.240	0.203
	Female (%)	30.6	27.4	28.1	26.2	31.7	36.0			
Gender of the corresponding author	Male (%)	76.7	77.4	65.1	58.9	51.2	50.0	1995-2010, 1995-2015, 1995-2020, 2000-2010, 2000-2015, 2000-2020, 2005-2015, 2005-2020	43.477	<0.001
	Female (%)	23.3	22.6	34.9	41.1	48.8	50.0			
Article type	Research (%)	72.4	66.7	52.8	48.9	56.7	74.4	1995-2005, 1995-2010, 2005-2020, 2010-2020, 2015-2020	93.982	<0.001
	Case report (%)	25.3	20.2	30.9	41.1	28.3	11.2	1995-2020, 2000-2010, 2005-2020, 2010-2015, 2010-2020, 2015-2020		
	Review (%)	2.3	8.3	12.7	7.4	10.6	11.2	-		
	Letter to editor (%)	0	0	0.6	1.8	2.0	2.5	-		
	Editorial (%)	0	4.8	3.1	0.7	2.4	0.8	-		

Table 3. Percentage of female authors in all articles by year

Year	Percentage of female authors (%)	Comparison between groups	Dual comparison (year- year: p score)
1995	20.69 ± 24.34	F= 15.010	1995-2005: 0.005 1995-2010: <0.001 1995-2015: <0.001 1995-2020: <0.001 2000-2010: 0.041
2000	25.39 ± 28.54		
2005	33.78 ± 29.04		

2010	36.48 ± 29.58	p<0.001	2000-2015: <0.001 2000-2020: <0.001 2005-2015: 0.004 2005-2020: <0.001 2010-2020: 0.004
2015	42.56 ± 30.56		
2020	46.02 ± 31.53		

4. Discussion

In our study, academic journals on obstetrics and gynecology in Turkey have been examined at 5-year intervals since 1995. In this process, it is stated that the gender inequality in the position of the first author has been closed by years, and the gender inequality in the position of the writer responsible for correspondence disappeared; however, it was observed that there was no statistically significant change in the position of the last author from 1995 to 2020.

In the United States, the rate of women among residents who received training in obstetrics and gynecology increased from 12% in 1980 to 77% in 2006 (8). The reflection of this increase in leadership positions is weak: women constitute 20.4% of presidents in administrative positions, 36.1% of vice presidents, and 29.6% of department heads. It has been reported that gender inequality is observed especially in the field of gynecological oncology (9).

The final author position is an authorship position with senior academics and leaders. The fact that no change has been observed between years in the last authorship can be interpreted as the glass ceiling effect. The term "glass ceiling" defines the inability of women to take leadership positions, even though they have no apparent handicaps. It is thought to have been first brought up by Marilyn Loden. Tesch and Nattinger, on the other hand, as a result of their interviews with doctors of similar seniority, suggested that there were similar invisible obstacles for women to be promoted, and they suggested the term "sticky base" (10). In summary, in the period examined in our study, no rule or law prevents women from receiving medical education and becoming researchers or academics. However, in practice, there is no change in the representation of women in leadership roles.

One of the reasons for this is the asymmetrical distribution of academic time. It has been revealed that women are clinicians and educators rather than research and publication. Some authors have described this situation as “corporate housework” (10, 11). Due to the asymmetrical use of time, women lag behind men in productivity measured by publishing. Another reason is that women care more or have to care more about the balance of work and private life due to their social roles. For example, when a woman or a man has a child, their work-life is not equally affected. The work environment and relationships with colleagues can also influence academic leadership positions. It can be predicted that women will stay more frequently and for a longer period in work environments that are free from discrimination, sexual harassment is not experienced, and where women are respected during periods of maternity and breastfeeding (11). In general, it is beneficial to have a balanced workforce of men and women in all branches of medicine (8).

Study Limitations

Our study was conducted through retrospective records, and the researchers directly coded the commonly used single-sex names. This application method has a certain margin of error. However, since it was not appropriate to state the gender by the author in practice, it was thought that the possible error remained within acceptable limits. Another limitation is that the archive was scanned intermittently, that is, not all publications were examined.

In our study, gender inequality has been taken into consideration. However, the hierarchical patriarchal structure dominates all individuals

except heterosexual men. Therefore, in an ideal study, homosexual, bisexual, transgender, and non-binary should be stated whether individuals are also properly represented in academic publications. This is not possible with the research method we use.

Regarding the limitations of the present study, it is the first study to examine gender inequality in gynecology and obstetrics academic publications in Turkey.

5. Conclusion

Similar to the examples in the world, there is no gender difference in representation measured by academic publications in Turkey, but women are not sufficiently represented in leadership positions. Having a balanced male and female workforce is important in terms of the quality of the health service provided and the reduction of gender bias in the knowledge constructed.

To eliminate the current inequality in leadership positions, it is recommended that the clinical and educational duties be shared among academics in a balanced manner, that work environments can be created in which work and private life can be balanced, and that sexual harassment and gender-based discrimination are not tolerated.

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Research Article / Araştırma Makalesi

Kist Hidatik Ön Tanılı Hasta Serumlarında ELISA ve Western Blotting Yöntemleriyle Ekinokok Antikor Varlığının Araştırılması

Investigation of the Echinococcus Antibodies in Sera of Patients with Pre-Diagnosed Hydatid Cyst Using ELISA and Western Blot Methods

[1]Ahsen Çifci, [2]Nihal Doğan

[1]Kahramanmaraş Afşin Devlet Hastanesi, Kahramanmaraş, Türkiye

[2]Eskişehir Osmangazi Tıp Fakültesi, Tıbbi Mikrobiyoloji Anabilim Dalı, Eskişehir, Türkiye

Özet

Kist hidatik(KH) dünyada ve ülkemizde önemli zoonotik enfeksiyonlardan biridir. Bu çalışmada; KH ön tanısı ile girişimsel radyoloji bölümünden perkütan aspirasyonla alınan kist sıvıları Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Tıbbi Mikrobiyoloji Laboratuvarı'nda direkt mikroskobik inceleme ile değerlendirilmiştir. Değerlendirme sonrası, KH hastalığı ile uyumlu yapıların görüldüğü hastalardan serum örnekleri istenerek, ELISA ve Western Blotting testleriyle *Echinococcus granulosus*' a karşı antikor varlığı araştırılmıştır. KH hastalığının laboratuvar tanısında ELISA ve Wetern Blotting serolojik tanı yöntemlerinin birbirleriyle ve direkt mikroskobik incelemeyle karşılaştırılması amaçlanmıştır. Girişimsel Radyoloji Polikliniği'nden gönderilen 16 aspire kist sıvısı direkt mikroskobik inceleme ile değerlendirilmiştir. Bu hastalara ait 16 serum örneği çalışma grubuna alınmış, bu serum örneklerinde ELISA ve Western Blotting yöntemleriyle antikor varlığı araştırılmıştır. Kontrol grubu olarak da kist hidatik ön tanısı ya da şüphesi olmayan, paraziter enfeksiyon bulgusu olmayan, 10 sağlıklı gönüllü serumunda serolojik testlerle *E. granulosus*'a karşı antikor varlığı araştırılmıştır. 16 serum örneğinin 8'inde ELISA IgG pozitif, 3'ünde şüpheli pozitif, 5'inde negatif bulunmuştur. 16 serumun 14'ünde Western Blotting testi ile pozitif, 2'si negatif sonuçlanmıştır. Direkt mikroskobik incelemenin altın standart olarak değerlendirildiği çalışmamızda ELISA testinin direkt mikroskobik inceleme ile uyumu %53.3, Western Blotting testinin uyumu %93.3 oranında bulunmuştur. KH hastalığının serolojik tanısında Western Blotting yönteminin daha güvenilir olduğu ve mümkünse birden fazla serolojik yöntemin kombine edilmesinin tanıya katkı sağlayacağı düşünülmüştür.

Anahtar Kelimeler: Kist hidatik, *Echinococcus granulosus*, kistik ekinokokkoz,tanı

Abstract

Hydatid cyst (CH) is one of the important zoonotic infections in the world and in our country. In this study; cyst fluids taken by percutaneous aspiration from the interventional radiology department with a preliminary diagnosis of CH were evaluated by direct microscopic examination in Eskişehir Osmangazi University Medical Faculty of Microbiology Laboratory. After the evaluation, serum samples were requested from patients with structures compatible with CH disease, and the presence of antibodies against *Echinococcus granulosus* was investigated by ELISA and Western Blotting tests. It is aimed to compare ELISA and Western Blotting serological diagnosis methods with each other and with direct microscopic examination in the laboratory diagnosis of CH disease. 16 aspirated cyst fluids were evaluated by direct microscopic examination which sent from the Interventional Radiology Outpatient Clinic. 16 serum samples taken from the same patients were included in the study group and the presence of antibodies in these serum samples was investigated by ELISA and Western Blotting methods. As a control group, the presence of antibodies against *E. granulosus* was investigated by serological tests in the sera of 10 healthy volunteers who had no prediagnosis or suspicion of hydatid cyst and no signs of parasitic infection. According to serological test results, ELISA IgG was positive in 8 of 16 serum samples, suspiciously positive in 3, and negative in 5 of them. Of the 16 sera, 14 were positive by Western Blotting and 2 were negative. In our study, in which direct microscopic examination was evaluated as the gold standard, the compatibility of the ELISA test with the direct microscopic examination was found to be 53.3%, and the Western Blotting test was 93.3%. It was thought that Western Blotting method was more reliable in the serological diagnosis of CH disease and that combining more than one serological method, if possible, would contribute to the diagnosis.

Keywords: Hydatid cyst, *Echinococcus granulosus*, cystic echinococcosis, diagnosis

Correspondence:
Nihal DOĞAN
Eskişehir Osmangazi Tıp Fakültesi, Tıbbi Mikrobiyoloji Anabilim Dalı, Eskişehir, Türkiye
e-mail: nihaldogan42@gmail.com

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1. Giriş

Kist hidatik (KH) erişkini köpek ve kurt gibi karnivorların ince bağırsağında yaşayan; *Echinococcus granulosus* başta olmak üzere, *Echinococcus* türlerinin metasestodunun insan ve diğer arakonaklarda oluşturduğu paraziter bir enfeksiyondur (1,2). *Echinococcus* türlerinin kesin konakları köpek, kurt, çakal gibi karnivorlar; ara konakları ise insan dahil çeşitli memelilerdir (3). KH, insanda her yaş ve cinsiyette görülmekle birlikte, yaşla insidansın arttığı ve 20-40 yaş arasında daha sık rastlandığı bilinmektedir. Sosyo-ekonomik düzeyi düşük toplumlarda hastalığın görülme oranı daha yüksektir (4). Dünyanın pek çok yerinde önemli bir halk sağlığı sorununu oluşturan KH, yurdumuzun çeşitli bölgelerinde gerek kasaplık hayvanlarda gerekse insanlarda sıkça rastlanılan ve morbidite ve mortaliteye neden olan önemli paraziter etkenlerin başında gelmektedir.

Tanıda, ultrasonografi (USG), bilgisayarlı tomografi (BT) ve manyetik rezonans (MR) gibi görüntüleme yöntemlerinin yanı sıra; direkt mikroskobik inceleme, serolojik yöntemler, moleküler testler gibi mikrobiyolojik tanı yöntemleri de kullanılmaktadır. Direkt mikroskobik inceleme ile kist sıvısı aspirasyon örneklerinde, kistlerin kendiliğinden yırtılması durumunda safra, balgam, dışkı veya idrarda karakteristik protoskoleks veya çengel yapılarının görülmesiyle doğrudan tanı konabilir. KH hastalığında serolojik tanı yöntemleri ise esas olarak klinik tanının doğrulanmasında, cerrahi veya antimikrobiyal tedavi sonrası takip ve prognozun değerlendirilmesinde, seroprevelans çalışmalarında kontrol yöntemlerinin etkinliğinin değerlendirilmesinde kullanılmaktadır. Serolojik tanıda kullanılan çoğu test hasta serumunda spesifik antikorların aranması esasına dayanmaktadır. Spesifik antikorların araştırıldığı yöntemlerde ortaya çıkabilen yalancı negatif ve pozitif sonuçların en aza indirilebilmesi için konfirmasyonu sağlayan yöntemlerle çalışılması gerekli olarak görülmektedir (5,6,7).

Çalışmamızda; girişimsel radyoloji kliniğinden KH ön tanısıyla gönderilen aspire kist sıvısı örneklerinde, direkt mikroskopi ile protoskoleks ve çengel varlığı saptanan hastaların serumlarında Enzyme-Linked ImmunoSorbent Assay (ELISA) ve Western Blotting (WB) yöntemleriyle *E. granulosus*'a karşı oluşan antikor varlığının araştırılması planlanmıştır. Bu sonuçların değerlendirilmesi doğrultusunda ELISA ve WB testlerinin sonuçlarının karşılaştırılması ve direkt mikroskobik inceleme sonuçlarıyla uyumunun araştırılması amaçlanmıştır.

2. Gereç ve Yöntemler

Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Hastanesi'nde 2016-2019 yılları arasında klinik ve radyolojik tetkikler sırasında/sonrasında kist hidatik ön tanılı hastalardan Girişimsel Radyoloji Polikliniği'nde perkütan aspirasyon yapılarak Tıbbi Mikrobiyoloji Anabilim Dalı Laboratuvarı'na gönderilen 15 aspire kist sıvısı ve bu hastalara ait 16 serum örneği çalışma grubuna alınmıştır. Kontrol grubu olarak da kist hidatik ön tanısı ya da şüphesi olmayan, paraziter enfeksiyon bulgusu olmayan, 10 sağlıklı gönüllü serumunda serolojik testlerle antikor varlığı araştırılmıştır. Çalışma öncesi laboratuvarımıza gönderilen tüm kan örnekleri 3000 devir/dakika santrifüj edilerek serumları ayrılmış ve ayrılan serumlar deneylerde kullanılıncaya kadar -20°C'de saklanmıştır. Çalışmada; direkt mikroskopi, ELISA, Western Blotting tanı yöntemlerinin birbirleri ile performansı karşılaştırılmıştır.

Direkt mikroskobik inceleme

Girişimsel Radyoloji Polikliniği'nde ultrasonografi eşliğinde alınan ponksiyon materyali ışık mikroskobunda x10'luk ve x40'lık mikroskobik büyütme ile incelenerek çengel, protoskoleks yapılarının varlığı araştırılmıştır.

ELISA

Hasta serumları, ticari bir ELISA kiti ile (Vircell Microbiologist, Spain, Hydatidosis IgG ELISA) üretici firma prosedürlerine göre çalışılmıştır. Testin prensibi insan serumunda hidatoza karşı oluşan total IgG antikor

varlığını araştıran dolaylı immunoenzim testi olup, sonuçlar 450 nm'de Bio-Tek cihazı ile okunmuştur. "Cut-off" optik dansitesi, kontrol serumlarına göre çıkarıldıktan sonra, antikor indeksi (Aİ) hesaplanıp (Aİ= Örnek OD/"cut-off" OD x 10) Aİ 11'in üzerinde olan serumlar pozitif, 9'un altında olan serumlar ise negatif olarak değerlendirilmiştir. Aİ 9-11 arasında olan serumlar şüpheli olarak değerlendirilip tekrar çalışmaya alınmıştır.

Western Blotting

Serumda *Echinococcus*'a karşı antikor oluşumunu saptayan; Em18, Em95, EgAgB antijenlerini içeren, Anti-Echinococcus Euroline WB (EUROIMMUN Medizinische Labordiagnostika AG, Germany) ticari Western Blot kiti kullanılmıştır. Test prosedürüne göre; kontrol bandı ve IgG bandında mor renkli boyanma gerçekleşmesi, *Echinococcus* antijenlerine karşı IgG sınıfı antikorların olduğunu göstermektedir. Test şeritleri tarayıcıda tarandıktan sonra Tablo 1, Tablo 2, Tablo 3 ve Tablo 4'teki kit prosedürlerine göre değerlendirilmiştir.

Tablo 1. Test şeritleri üzerindeki antijenlerin spesifitesi.

Bant	Antijen	Spesifiklik
24-26 kDa	p25/26	Nonspesifik
21 kDa	p21	Ekinokok veya diğer parazitler için spesifik
16-18 kDa	p16/18	Ekinokok için spesifik
7 kDa	P7	Ekinokok için spesifik
Em 95	Em 95	*E.multilocularis* için spesifik
Em 18	Em 18	*E.multilocularis* için spesifik
EgAgB	EgAgB	Ekinokok için spesifik

Tablo 2. Kit prosedürüne göre, bantlar üzerindeki antijen kategorileri.

Kategori	Antijen
1	Antijen: p25/26
2	Genus-spesifik *Echinococcus* antijen: EgAgB
3	*Echinococcus* antijen: p21
4	*Echinococcus* antijen: p7 ve p16/18
5	*E.multilocularis* antijen: Em18 ve Em95

Tablo 3. Test prosedürüne göre sonuçların değerlendirilmesi

Sonuç	Yorum
Negatif	Band yok/kategori 1'de 1 pozitif antijen bandı/kategori 2'de 1 borderline antijen bandı
Borderline	Kategori 2'de pozitif antijen bandı/kategori 3, 4 ya da 5'ten en az birinde 1 borderline antijen bandı Taze örnek alınması ve birkaç hafta sonra testin tekrarlanması önerilir
Pozitif	Kategori 3, 4 ya da 5'in en az birinde pozitif antijen bandı Kategori 3'ün bir antijen bandı, tek başına veya kategori 1'in bir antijen bandı ile birlikte pozitif ise, bir Ascaris veya Anisakis enfeksiyonu nedeniyle çapraz reaktivite meydana gelmiş olabilir

Tablo 4. Test prosedürüne göre *E. granulosus* ve *E.mutilocularis* ayrımı.

E. granulosus	**Kategori 2'deki pozitif antijen bandı ve ilaveten kategori 3 veya 4'ün en az bir pozitif antijen bandı**
E. multilocularis	5. kategorideki en az bir pozitif antijen bandı Ayrıca diğer kategorilerden de pozitif antijen bandı eşlik edebilir

İstatistiksel analiz

İstatistiksel analizler için Cohen kappa uyum testi kullanılmıştır.

3. Bulgular

Çalışma kapsamına Girişimsel Radyoloji Kliniği'nden KH şüphesiyle gönderilen toplam 16 hastanın serumu ve bu hastalardan perkütan aspirasyonla alınan 15 aspire kist sıvısı alındı. Bir hasta örneğinde ise radyolojik tetkikler sonrası kistin kalsifiye olduğunun saptanması nedeniyle perkütan aspirasyon ve cerrahi müdahale yapılamadığından bu hastanın aspire kist sıvısı değerlendirilemedi. 16 hastadan ve 10 sağlıklı bireyden alınan serum örneklerinde ELISA ve Western Blotting yöntemleriyle anti-Echinococcus IgG antikorları araştırıldı. Hasta grubun kist sıvıları mikroskobik olarak incelendi(Tablo5).

Çalışma grubunu oluşturan 16 hastanın 11'i (%68.7) erkek, 5'i (%31.3) kadın, kontrol grubunun ise, 7'si (%70) erkek, 3'ü (%30) kadın gönüllülerden oluşmaktaydı. Hastaların yaş aralığı 5-79 arasında ve yaş ortalaması 31.75 olarak belirlendi. 15 aspire kist sıvısının 15'inde direkt mikroskobik inceleme ile *Echinococcus*'a ait çengel ve/veya protoskoleks yapıları görüldü. Hasta grubuna ait 16 serum örneğinin 8'inde ELISA IgG pozitif, 3'ünde şüpheli pozitif, 5'inde negatif bulundu. ELISA testinde şüpheli pozitiflik tanımlanan örneklerde test tekrarı yapıldı ve 3 serum örneği aynı şekilde şüpheli pozitif olarak sonuçlandı. 16 serumun 14'ünde Western Blot testi ile *Echinococcus*'a karşı spesifik antikor varlığı saptandı, 2 tanesinde antikor tespit edilmedi.

Western Blot ile pozitif sonuç veren 14 örneğin 13'ünde kategori 2 (genus-spesifik *Echinococcus* antijen: EgAgB) antijen bandı saptandı. Bu hastalarda Kategori 2 ye ilave olarak Kategori 3 veya 4'ün en az birinde pozitif antijen bandı eşlik etmekteydi. Buna göre 13 hastanın sonucu *E. granulosus* olarak yorumlandı. Kalan 1 örnekte ise Kategori 3 ve 4'te pozitif bant saptandı, fakat *E. granulosus* ve *E. multilocularis* ayrımı yapılamadı. Bu hastanın akciğerde kisti olduğu ve görüntüleme yöntemleriyle E.multilocularis le uyumlu görüntüleme bulgularının olduğu hasta dosya notlarından öğrenildi. 15 hastanın kistinin karaciğerde, 1'inin akciğerde olduğu radyolojik görüntüleme yöntemleriyle tespit edilmiştir.

Kontrol grubundaki 10 hastaya ait serumun hiçbirinde ELISA ve Western Blot ile seropozitiflik saptanmadı. ELISA ile pozitif ve şüpheli pozitif olarak sonuçlanan örnekler Western Blot ile de pozitif olarak tespit edildi . Western Blot ve ELISA ile negatif sonuç alınan hastalardan 1'inin kist sıvısından yapılan direkt mikroskobik incelemede protoskoleks yapıları görüldü. ELISA ile negatif sonuç alınan serumlardan 3 tanesinde Western Blot ile pozitiflik saptandı (Tablo 6).

Tablo 5. Hasta grubunda test sonuçlarının karşılaştırılması

	Direkt mikroskopi	ELISA	WB
Pozitif	15	8	14
Negatif	0	5	2
Şüpheli	0	3	0
Toplam	15	16	16

** ELISA: Enzyme-Linked ImmunoSorbent Assay, WB: Western Blotting*

Tablo 6. Hasta grubunda test sonuçlarının ayrıntılı incelenmesi

	Direkt mikroskopi	ELISA	WB
1	Pozitif	Şüpheli pozitif	Pozitif
2	Örnek yok	Negatif	Negatif
3	Pozitif	Pozitif	Pozitif
4	Pozitif	Şüpheli pozitif	Pozitif
5	Pozitif	Pozitif	Pozitif
6	Pozitif	Negatif	Pozitif
7	Pozitif	Şüpheli pozitif	Pozitif
8	Pozitif	Negatif	Negatif
9	Pozitif	Pozitif	Pozitif
10	Pozitif	Pozitif	Pozitif
11	Pozitif	Negatif	Pozitif
12	Pozitif	Pozitif	Pozitif
13	Pozitif	Negatif	Pozitif
14	Pozitif	Pozitif	Pozitif
15	Pozitif	Pozitif	Pozitif
16	Pozitif	Pozitif	Pozitif

Hastalara ait serum ve aspirasyon materyali örneklerinde, 8 olguda her üç yöntemle de pozitiflik bulundu. Direkt mikroskobisi pozitif bulunan 2 hasta örneğinde ELISA ve Western Blot testiyle negatif sonuç alındı. Western Blot testi ile pozitif olarak değerlendirilen altı serum örneğinde, ELISA testiyle üç örnekte şüpheli pozitiflik, üç örnekte de negatiflik tanımlandı (Tablo 6).

Çalışmamızda Direkt mikroskobik inceleme altın standart olarak değerlendirildi. Buna göre; ELISA testinin direkt mikroskobi ile uyumu %53.3 olarak belirlendi. WB testinin direkt mikroskobik inceleme yöntemi ile uyumu ise %93.3 olarak saptandı. ELISA ve WB testlerinin uyumluluk oranı %45.1 olarak belirlendi (Cohen Kappa=0.451).

4. Tartışma ve Sonuç

KH hastalığında şüphenin doğrulanması, genellikle noninvaziv görüntüleme yöntemlerinin kullanımını gerektirmekte; bununla birlikte kistin tümör, apse, basit kist gibi diğer yer kaplayan lezyonlarla ayırıcı tanısının yapılabilmesi ve cerrahi sonrası nükslerin daha sağlıklı bir şekilde değerlendirilebilmesi için radyolojik tanının serolojik tanı yöntemleriyle desteklenmesi gerekmektedir (8,9). Ayrıca KH'te uygulanan tedavinin takibinde de serolojik test sonuçlarının değerli olması nedeniyle kullanılan bu testlerin duyarlılık ve özgüllüklerinin ve test sonuçlarını etkileyen faktörlerin bilinmesi son derece önem taşımaktadır. Halen KH tanısında standart, yüksek duyarlılık ve özgüllüğe sahip serolojik tanı testi bulunmamaktadır. İmmünolojik tanının duyarlılık ve özgüllüklerinin artırılmasını sağlamak ve en güvenilir sonuçları elde etmek için aynı serumun birden fazla serolojik yöntemle test edilmesi önerilmektedir (10, 11, 12).

Çalışmamızda serolojik testlerin birbirleriyle karşılaştırılması ve direkt mikroskobik tanı sonuçlarının serolojik test sonuçlarıyla uyumunun araştırılması hedeflenmiştir. Yazar ve ark. tarafından yapılan bir çalışmada kist hidatik şüpheli 221 hastada Indirect Hemagglutination (IHA) ve ELISA yöntemleriyle anti-*E. granulosus* IgG antikorları araştırılmış ve 153 hasta serumunda (%69.2) ELISA pozitifliği saptanmıştır. Aynı çalışmada ELISA testi ile cerrahi olarak KH olduğu doğrulanmış 150 hastanın 145'inde (%96.7) pozitif sonuç alınmıştır (13). Akısü ve ark. (14), cerrahi olarak akciğer KH tablosu olan 31 hasta ile akciğer KH'i dışında diğer akciğer hastalığı tanısı alan 18 hasta ve 10 sağlıklı insan olmak üzere toplam 59 olguda IHA, ELISA ve WB testlerini kullanmışlardır. Buna göre IHA, ELISA ve WB testlerinin duyarlılığı sırasıyla %96.7, %87.1 ve %100 olarak bulunurken, bu testlerin özgüllükleri %82.2, %89.2 ve %85.7 olarak saptanmıştır. Delibaş ve ark. (15), KH şüphesiyle başvuran 465 hastayı ELISA ve IHA yöntemleriyle değerlendirmişler, hastaların %17'sinde ELISA ile pozitiflik saptamışlardır. KH ön tanısı alan hastalardan

serolojik doğrulama amacıyla 186 hastadan örnek gönderilen bir başka çalışmada ise ELISA ile %35.5 oranında anti-Echinococcus IgG seropozitifliği saptanmıştır (16).

Western Blot yöntemiyle duyarlılık, çapraz reaksiyonlar ve *E.granulosus - E. multilocularis* ayrımını değerlendirmek için yapılan bir çalışmada (17) testin duyarlılığı %97 olarak saptanmıştır.

Yazar ve ark. (17) Kayseri'de 2242 kişi üzerinde yapmış oldukları seroepidemiyolojik bir çalışmada ise; ELISA ile %2.72, Western Blot yöntemiyle %0.94 seropozitiflik saptanmıştır.

Cezayir'de kist hidatik ön tanısıyla opere edilen 78 hastanın kist sıvısı direkt mikroskobik inceleme ile değerlendirilerek kist hidatik olduğu doğrulanan bir çalışmada, bu hastalara ait serum örneklerinde WB, ELISA ve IHA testleriyle antikor varlığı araştırılmıştır. Çalışmada 66 hasta serumunda WB, 54 hasta serumunda ise ELISA testi ile çalışılmış ve WB testi ile %68.1, ELISA testi ile % 75.9 oranında pozitiflik saptanmıştır (18).

Direkt mikroskobik incelemenin altın standart olarak değerlendirildiği çalışmamızda; 16 serum örneğinin 8'inde ELISA Ig G pozitif, 3'ünde şüpheli pozitif, 5'inde negatif bulunmuştur. ELISA sonuçlarındaki şüpheli pozitif olgular dışlandığında, ELISA testi için duyarlılık % 53.3 saptanmıştır. Literatürde ELISA testi için değişen oranlarda duyarlılık saptanmasına karşın, KH tanısı doğrulanmış hastalarda yapılan çalışmalara göre, bizim bulduğumuz duyarlılığın düşük olduğu görülmüştür. Bu durumun kısıtlı örnek sayısına ve ticari testin içeriğindeki antijene bağlı olabileceği düşünülmüştür.

Çalışmamızda, Western Blot testi ile hasta serum örneklerinden 14 tanesinde *Echinococcus'*a karşı IgG antikor varlığı saptanmıştır. Bir hastaya ait kist sıvısında ise direkt mikroskobik incelemede parazite ait yapılar görülmesine rağmen WB testi ile negatif sonuç alınmıştır. Western Blot testinin direkt mikroskobi ile uyumu % 93.3 olarak belirlenmiştir. Bizim sonuçlarımız literatürdeki WB duyarlılık sonuçlarıyla benzer olup, daha geniş hasta popülasyonunda yapılacak in vitro çalışmalarda daha yüksek duyarlılık sonuçları alınabileceği düşünülmektedir. Buna göre, ELISA testinin kist hidatik tanı veya ön tanılı hastalarda ve hastaların tedavi sonrası takibinde tek başına yeterli olmayacağı, WB testinin tanıda ve tedavinin takibinde daha değerli bir serolojik yöntem olduğu düşünülmüştür. WB testinin doğrulama yöntemi olarak kullanılabileceği görülmüştür.

Sonuç olarak; kist hidatik mikrobiyolojik tanısı ve tedavi sonrası takibinde birden fazla serolojik yöntemin beraber uygulanmasının tanı ve takip açısından fayda sağlayacağı, mümkünse bu serolojik yöntemlerden birinin WB olmasının uygun olacağı kanısına varılmıştır. Bununla birlikte, çalışmamız sınırlı sayıda örnek içerdiğinden daha fazla sayıda örnek içeren çalışmalarla desteklenmesi gerekmektedir.

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Lower Urinary Tract Symptoms in Obese Children

Obez Çocuklarda Alt Üriner Sistem Semptomları

[1]Nuran Cetin, [2]Nadide Melike Sav, [3]Gonca Kilic Yildirim

[1]Department of Pediatric Nephrology, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey.

[2]Department of Pediatric Nephrology, Faculty of Medicine, Düzce University, Düzce, Turkey.

[3]Department of Pediatric Nutrition and Metabolism, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

Abstract

Lower urinary tract symptoms (LUTS) is very common in childhood. We aimed to investigate the frequency of LUTS in obese, overweight and normal children using voiding dysfunction symptom score validated for Turkish children by Akbal and et al. The children older than five-years-old who were followed in Pediatric Nutrition and Metabolism Outpatient Clinic were included. Children with a body mass index above the 95th percentile were classified as obese. The symptom score was administered face to face to each child and their mothers together. A score ≥9 was defined as lower urinary tract dysfunction (LUTD). A 164 children (62 obese, 52 overweight, 50 normal) were included. Symptom score was significantly higher in obese children than in overweight and normal weight children. (p=0.004, p=000, respectively). Overweight children had higher symptom score than in normal weight children (p=0.037). The frequency of daily urinary incontinence was higher in obese than overweight and normal weight children (p=0.041, p=0.000, respectively). The both obese and overweight children had higher frequencies of urgency and increased urinary frequency than in children with normal weight (p=0.002, p=0.021 for urgency, p=0.000, p=0.037 for increased urinary frequency, respectively). The frequencies of voiding postponement and constipation were higher in the obese children than those of overweight and normal weight (p=0.000, p=0.000 for voiding postponement, p=0.031, p=0.028 for constipation respectively). Obesity is a significant risk factor for LUTD. The questioning LUTS using questionnaire validated by Akbal et al in obese children can help in the early diagnosis of LUTD.

Keywords: Children, lower urinary tract symptoms, obesity, voiding dysfunction symptom score

Özet

Alt üriner sistem semptomları (AÜSS) çocukluk çağında oldukça yaygındır. Biz Akbal ve arkadaşları tarafından Türk çocukları için valide edilmiş işeme disfonksiyonu semptom skorunu kullanarak obez, fazla ve normal kilolu çocuklarda AÜSS sıklığını araştırmayı amaçladık. Çocuk Beslenme ve Metabolizma Polikliniği'nde takip edilen beş yaş üstü çocuklar çalışmaya dahil edildi. Vücut kitle indeksi 95 persentilin üzerinde olan çocuklar obez olarak sınıflandırıldı. Semptom skoru her çocuğa ve annesine yüz yüze birlikte uygulandı. Semptom skoru ≥9 olması alt üriner sistem disfonksiyonu (AÜSD) olarak tanımlandı. Çalışmaya 164 çocuk (62 obez, 52 kilolu, 50 normal) dahil edildi. Obez çocuklarda semptom skoru, aşırı kilolu ve normal kilolu çocuklara göre anlamlı olarak daha yüksekti (sırasıyla p=0,004, p=000). Fazla kilolu çocukların semptom skoru normal kilolu çocuklara göre daha fazla idi (p=0.037). Obezlerde günlük idrar kaçırma sıklığı fazla kilolu ve normal kilolu çocuklara göre daha yaygındı (sırasıyla p=0,041, p=0,000). Hem obez hem de fazla kilolu çocuklarda normal kilolu çocuklara göre daha yüksek aciliyet sıklığı ve artmış idrar sıklığı vardı (sırasıyla, aciliyet için p=0,002, p=0,021, idrar sıklığı artışı için p=0,000, p=0,037). İşemeyi erteleme ve kabızlık sıklıkları obez çocuklarda fazla kilolu ve normal kilolu çocuklara göre daha yüksek bulundu (sırasıyla p=0.000, p=0.000 işemeyi erteleme, p=0.031, p=0.028 kabızlık). Obezite AÜSD için önemli bir risk faktörüdür. Obez çocuklarda Akbal ve arkadaşları tarafından doğrulanan anket kullanılarak AÜSS'nin sorgulanması AÜSD'nin erken teşhisine yardımcı olabilir.

Anahtar Kelimeler: Çocukluk, alt üriner sistem semptomları, obezite, işeme disfonksiyonu semptom skoru.

Correspondence:
Nuran ÇETİN
Department of Pediatric Nephrology, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey.
e-mail: nurancetin17@hotmail.com

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1. Introduction

Lower urinary tract symptoms are common in childhood. Children with lower urinary tract symptoms may develop emotional and behavioral problems, and their quality of life may be reduced[1]. The disorders associated with voiding behavior can lead to an increased risk of recurrent urinary tract infection[2]. Using scoring systems in children with voiding problems is highly useful for both diagnosing and monitoring the response to treatment. Akbal et al. (2005) validated the voiding dysfunction symptom score (VDSS) for Turkish children. A score of more than 8.5 points had a sensitivity and specificity of 90% in detecting lower urinary tract dysfunction (LUTD)[3].

Obesity and being overweight are common and growing social health problems in children. In recent years, a relationship has been found between obesity and lower urinary tract symptoms [4]. In this study, we investigated the frequency of lower urinary tract symptoms in obese, overweight, and normal-weight children using the VDSS validated by Akbal et al.

2. Materials and Methods

This work is a cross-sectional study investigating lower urinary tract symptoms in obese, overweight, and normal-weight children. Consecutive children older than five years old who were followed up at our Pediatric Nutrition and Metabolism Outpatient Clinic between January 2011 and May 2016 were eligible to enroll in this study. Patient information was accessed from electronic records. Children who previously did not consult a doctor about their urinary symptoms and who were not tested for this purpose were included in this study. Children with congenital anomalies of the kidney and urinary tract, as well as neurological, endocrinological, and gastrointestinal anomalies, were excluded.

The mothers of the children were called and invited to participate in the study. They were informed about a voiding diary and asked to make a three-day voiding diary for their children during their first visit. A detailed physical examination, urinalysis, and urine culture were conducted on the children. Patients with abnormal urinalysis or those who were unable to complete their three-day voiding diary were excluded.

Height measurements were taken, with the child standing barefoot. Body weights were measured using a digital scale. Body mass index (BMI) was calculated by dividing weight (kg) by height (m^2) squared. BMI percentiles were determined based on the reference values of Turkish children[5]. Children with a BMI of 85^{th}–95^{th} percentile on gender and age were classified as overweight. Children with a BMI above the 95^{th} percentile were classified as obese.

The VDSS was administered face-to-face to each child and his/her mother together at the second visit. The VDSS developed for Turkish children by Akbal et al. is shown in Figure 1[3]. The scoring system consisted of 13 items. Items 1 and 2 are related to daytime incontinence, items 3 and 4 to nocturnal enuresis, items 5–9 to daytime urination characteristics, item 10 to urgency, item 11 to holding maneuver, item 12 to urine leakage before reaching the toilet, and constipation to item 13. In our study, 13 items were used for scoring. A score ≥ 9 was defined as LUTD. Urination of > 7 times per day was considered increased urinary frequency, and urination < 4 times per day and habitual delay of micturition were defined as urinary incontinence with voiding postponement. Painful and interrupted urination was considered a sign of dysfunctional voiding[6]. Nocturnal enuresis was defined as bedwetting while asleep in children older than five years. Monosymptomatic enuresis was defined as enuresis without any other lower urinary tract symptoms. Patients with secondary nocturnal enuresis were not included. Constipation was defined using the Rome III questionnaire[7].

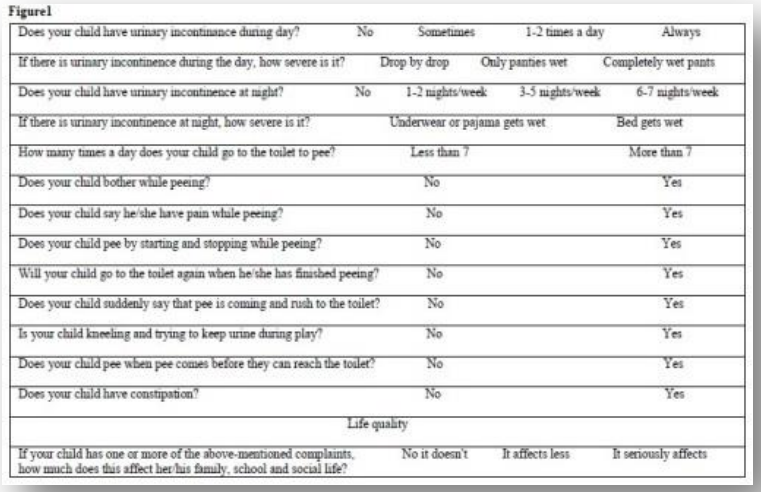


Figure1

Does your child have urinary incontinance during day?	No	Sometimes	1-2 times a day	Always
If there is urinary incontinence during the day, how severe is it?		Drop by drop	Only panties wet	Completely wet pants
Does your child have urinary incontinence at night?	No	1-2 nights/week	3-5 nights/week	6-7 nights/week
If there is urinary incontinence at night, how severe is it?		Underwear or pajama gets wet		Bed gets wet
How many times a day does your child go to the toilet to pee?		Less than 7		More than 7
Does your child bother while peeing?		No		Yes
Does your child say he/she have pain while peeing?		No		Yes
Does your child pee by starting and stopping while peeing?		No		Yes
Will your child go to the toilet again when he/she has finished peeing?		No		Yes
Does your child suddenly say that pee is coming and rush to the toilet?		No		Yes
Is your child kneeling and trying to keep urine during play?		No		Yes
Does your child pee when pee comes before they can reach the toilet?		No		Yes
Does your child have constipation?		No		Yes
Life quality				
If your child has one or more of the above-mentioned complaints, how much does this affect her/his family, school and social life?		No it doesn't	It affects less	It seriously affects

Figure 1. The Voiding Dysfunction Symptom Score which was developed for Turkish children by Akbal et al.

In addition, the following questions about how the existing complaints affect the family, school, and social life of the child were asked: 1) To what extent do bladder problems affect parents and children in their choice of sport or activity?, 2) Does waking up due to bedwetting during sleep tire parents and children, or does it affect their daily activities?, 3) Is the child's friendships and participation in group activities affected?, 4) Is the child teased in class when he/she asks for permission to go to the toilet?, and 5) Do the child's complaints lead to learning difficulties or academic failure? The answers to the quality of life items were grouped under four headings: 0–it has no effect, 1–it has a slight effect, 2–it has a moderate effect, and 3–it has a serious effect.

The study was approved by the institutional research ethics committee and was conducted in accordance with the principles set forth in the Helsinki Declaration (protocol number: 80558721/g-179; date of approval: 05.30.2016). Written informed consent was obtained from the mothers of the children.

Statistical analysis

Statistical analysis was performed using SPSS 11.0 (SPSS Inc., Chicago, IL, USA). The values were expressed as the mean and standard deviation for continuous variables and as the median (interquartile range) for non-normally distributed variables. The Kolmogorov–Smirnov test was used to determine the normality of data. The means were compared using a one-way analysis of variance for the normally distributed data and the Kruskal–Wallis test for the non-normally distributed data. The categorical variables were compared using the chi-square test. A binary logistic regression analysis was performed to determine the association between obesity and lower urinary tract symptoms. A p value < 0.05 was considered statistically significant.

3. Results

Data from 369 patients older than 5 years of age were analyzed based on electronic records. Fifty-six patients had previously been examined for urinary symptoms. The mothers of seventy-nine patients indicated their refusal to participate in the study when spoken to by phone. Thirty-eight children had neurological, endocrinological, or gastrointestinal anomalies.

A total of 196 patients and their mothers were interviewed face-to-face. Twelve of the

patients interviewed face-to-face were excluded due to abnormal urinalysis at the first visit. Twenty of the remaining 184 patients did not complete their voiding diaries.

A total of 164 children who met the inclusion criteria (62 obese, 52 overweight, and 50 normal) were included in this study. No difference was found in gender or age between the groups (p = 0.253, p = 0.586, respectively). The symptom score was significantly higher in obese children than in overweight and normal-weight children (p = 0.004, p = 000, respectively, Figure 2). Overweight children had a higher symptom score than normal-weight children (p = 0.037). Based on the VDSS validated by Akbal et al., 36 (21.9%) patients had LUTD. The frequency of LUTD was more common in obese children than in overweight and normal-weight children (p = 0.001, p = 0.000, respectively). Although the frequency of LUTD was higher in overweight children than in normal-weight children, no statistically significant difference was found (p = 0.051). The frequency of urinary incontinence during daytime was higher in obese children than in overweight and normal-weight children and also in overweight children than in normal-weight children (p = 0.041, p = 0.000, p = 0.001, respectively). The findings on the severity of urinary incontinence during daytime are shown in Table 1. Both obese and overweight children had a higher frequency of urgency and an increased urinary frequency than normal-weight children (p = 0.002, p = 0.021 for urgency, p = 0.000, p = 0.037 for increased urinary frequency, respectively). Increased urinary frequency was higher in obese children than in overweight children (p = 0.045). The frequencies of voiding postponement and constipation were higher in obese children than in overweight and normal-weight children (p = 0.000, p = 0. 0.000 for voiding postponement, p = 0.031, p = 0.028 for constipation, respectively, Table 1). No statistically significant differences were found in the frequencies of voiding postponement and constipation between overweight and normal-weight children (p = 0.072, p = 0.296, respectively).

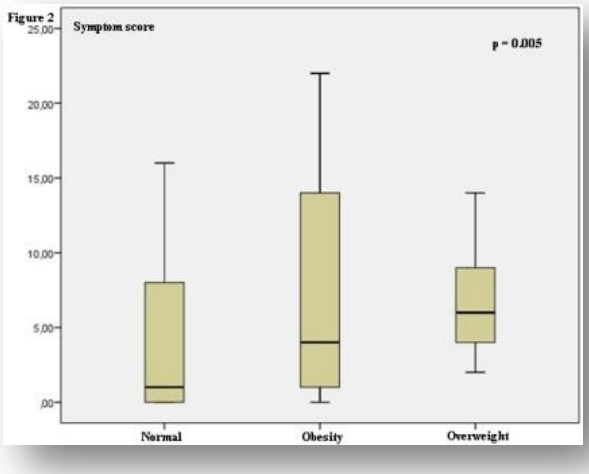


Figure 2. Symptom score was significantly higher in obese children than in overweight and normal weight children (p = 0.005).

Table 1. The features of the study groups.

	Obesity (n=62)	Overweight (n=52)	Normal (n=50)	p
Gender (female)	34 (54.8)	22 (42.3)	26 (52)	p1 = 0.153 p2 = 0.365 p3 = 0.098
Age (years)	11.67±3.17	10.48±3.38	12.2±1.86	p1 = 0.321 p2 = 0.439 p3 = 0.248
Weight (kg)	59.2±18.81	44.3±15.17	34.9±12.41	p1 = 0.031 p2 = 0.002 p3 = 0.008
Height (cm)	150.2±16.07	152.4±14.56	141.3±18.16	p1 = 0.387 p2 = 0.283 p3 = 0.402
Body mass index (kgm-2)	25.6±3.38	20.5±2.76	16.2±1.37	p1 = 0.036 p2 = 0.000 p3 = 0.043
Urinary incontinence during the day	19 (30.6)	9 (17.3)	4 (8)	p1 = 0.041 p2 = 0.000 p3 = 0.001
Urinary incontinence during the day severity				
Drop by drop	8 (12.9)	4 (7.7)	3 (6)	p1 = 0.048 p2 = 0.036 p3 = 0.098
Only panties wet	10 (16.1)	5 (9.6)	1 (2)	p1 = 0.034 p2 = 0.005 p3 = 0.000
Completely wet pants	1 (1.6)	-	-	
Urgency	28 (45.2)	19 (36.5)	8 (16)	p1 = 0.058 p2 = 0.002 p3 = 0.021
Increased urinary frequency	21 (33.9)	12 (23.1)	5 (10)	p1 = 0.045 p2 = 0.000 p3 = 0.037
Voiding postponement	33 (53.2)	9 (17.3)	7 (14)	p1 = 0.000 p2 = 0.000 p3 = 0.072
Painful and interrupted urination	6 (9.7)	4 (7.7)	2 (4)	p1 = 0.309 p2 = 0.097 p3 = 0.237
Symptom score	11 (4-18)	6 (3-9)	1 (0-8)	p1 = 0.004 p2 = 0.000 p3 = 0.037
Constipation	18 (29)	7 (13.5)	8 (16)	p1 = 0.031 p2 = 0.028 p3 = 0.296
Lower urinary tract dysfunction	20 (32.3)	9 (17.3)	7 (14)	p1 = 0.001 p2 = 0.000 p3 = 0.051
Monosymptomatic enuresis	7 (12.9)	4 (7.7)	4 (8)	p1 = 0.097 p2 = 0.165 p3 = 0.235

Values were expressed as mean ± SD or median (interquartile range) and number (percentage). UTI; urinary tract infection. A p value <0.05 was considered significant. P1; between obese and overweight patients, P2; between obese and normal weight patients, P3; between overweight and normal weight patients.

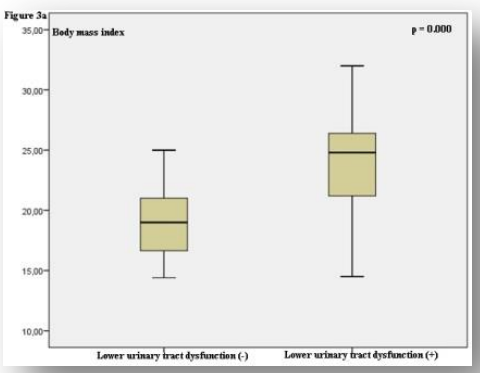
The results of the logistic regression analysis showing the association between lower urinary tract symptoms and obesity are shown in Table 2. Obesity was significantly associated with urgency, increased urinary frequency, voiding postponement, and constipation (p = 0.024, p = 0.031, p = 0.001, p = 0.024, respectively).

Table 2. The results of logistic regression analysis showing associations between obesity and lower urinary tract symptoms

	Odds ratio	%95 confidental interval	p
Urgency	1.352	1.141-3.910	0.024
Increased urinary frequency	1.226	1.219-1.769	0.031
Voiding postponement	1.726	1.387-2.918	0.001
Painful and interrupted urination	0.389	0.243-0.912	0.714
Constipation	1.551	1.112-2.151	0.024

A p value <0.05 was considered significant

Children with LUTD had a higher BMI than those with a symptom score < 9 (23.9 ± 4.06/20.2 ± 4.45 kgm-2, respectively, p = 0.000, Figure 3a). The BMI showed a sensitivity of 71.8% and a specificity of 64.9% for LUTD, with a cut-off of 23.7 kgm-2 (area under the curve [AUC ± SE]: 0.741 ± 0.049, confidence interval [CI]: 0.644–0.838, p = 0.000, Figure 3b).



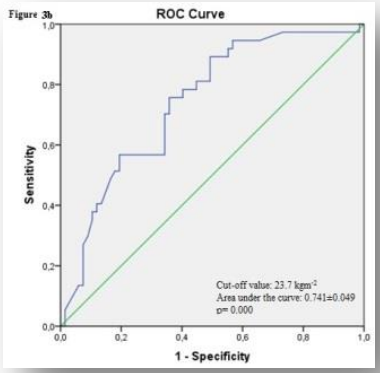


Figure 3a. The children with lower urinary tract dysfunction had higher body mass index than those of symptom score <9 (p = 0.000), **3b**. Body mass index showed a sensitivity of 71.8% and specificity of 64.9% for lower urinary tract dysfunction with a cut-off of 23.7 kgm-2 (area under the curve [AUC ± SE]: 0.741 ± 0.049, p = 0.000).

The answers to the quality of life items were compared among obese, overweight, and normal-weight children. The mothers of 29 (46.8%) obese children stated that lower urinary tract symptoms had no effect on their children's social and school lives, 12 (19.4%) had a slight effect, 16 (25.8%) had a moderate effect, and 5 (8%) had a serious effect. The mothers of 32 (61.5%) overweight children with LUTD stated that their complaints had no effect on their children's social and school lives, 10 (19.2%) had a slight effect, 8

(15.5%) had a moderate effect, and 2 (3.8%) had a serious effect. The mothers of 35 (70%) normal-weight children with LUTD revealed that their complaints had no effect on their children's social and school lives, 10 (20%) had a slight effect, and 5 (10%) had a moderate effect. The "it has a serious effect" response was greater in obese children than in overweight children ($p = 0.041$). The "it has no effect" response was less in obese children than in overweight and normal-weight children ($p = 0.036$, $p = 0.029$, respectively).

4. Discussion

We investigated the frequency of lower urinary tract symptoms using the VDSS validated by Akbal et al. in obese and overweight children who previously did not consult a doctor for urinary symptoms and were not tested for this purpose. The results of the study revealed that symptom scores were significantly higher in obese children than in overweight and normal-weight children. The frequencies of urgency and increased urinary frequency were higher in obese and overweight children than in children of normal weight. Obese children had higher frequencies of voiding postponement and constipation.

Children with lower urinary tract symptoms have an increased risk of recurrent urinary tract infections and permanent renal damage. Therefore, the early recognition of these symptoms and the planning of treatment are of great importance[8]. Several questionnaire forms have been developed to determine the presence and severity of lower urinary tract symptoms and to evaluate the response to treatment[3, 9]. Many studies have been conducted on symptom scoring associated with voiding problems in children. The Pediatric Lower Urinary Tract Scoring System is superior to the bladder volume wall index in distinguishing children with lower urinary tract symptoms from those without lower urinary tract symptoms[1]. The VDSS validated by Akbal et al. is significantly associated with doctors' clinical impressions about lower urinary tract symptom severity[10]. Using Akbal's questionnaire, the frequency of LUTD in schoolchildren was 9.3% in this study[11]. The frequency of LUTD was found to be 21.8% in healthy schoolchildren from Brazil using modified voiding symptom scores[8]. In our study, the frequency of LUTD was 21.9%. This high frequency may be due to the fact that our study included obese and overweight children.

Recently, obesity and being overweight have been considered risk factors for LUTD. One-third of children with daytime urinary incontinence are found to be obese[12]. Obesity leads to a decrease in functional bladder capacity by increasing intravesical and intra-abdominal pressure[13]. To date, only a few studies have investigated scoring systems for obese children. A study examining the presence and severity of LUTD using a modified version of the Dysfunctional Voiding Scoring System questionnaire (Brazilian Portuguese) showed higher median scores in obese children[14]. Another study found that obese children had higher symptom scores than normal-weight children with non-neurogenic LUTD [4]. In the present study, which used the VDSS validated by Akbal et al., the results showed that obese children had the highest symptom scores and that obesity was a risk factor for LUTD.

Urinary incontinence during the day is common in childhood. The prevalence of daytime urinary incontinence varies from 2.1% to 30.7%[15–18]. Urinary incontinence may be caused by increased intra-abdominal pressure in obese children[19]. Our study revealed that the frequency of urinary incontinence during daytime was 19.5%. Obese and overweight children had a higher frequency of urinary incontinence than normal-weight children.

Overactive bladder (OAB) is defined as urgency and increased daytime frequency, with or without urinary incontinence, in the absence of urinary tract infection or other pathological or neurological factors. Urinary urgency is the main sign of the OAB[20]. Obesity has been noted to increase OAB symptoms and to be an independent risk factor for OAB[21]. Although the relationship between obesity and disease is not clear, it is considered that the negative effects on bladder functions and the pressure on the pelvic organs due to changes in body structure are

responsible[22]. The risk of urgency was higher in obese children than in non-obese children[23]. In a study of Taiwanese children, urgency symptom scores were higher in obese children, and obesity was found to be a significant risk factor for OAB[24]. In this study, obesity was a significant risk factor for increased urinary frequency and urgency, which are symptoms of OAB. Our results highlighted the importance of questioning OAB symptoms in obese children.

Voiding postponement is observed by parents or carers as a urine-holding maneuver and delayed micturition[25]. Children with voiding postponement have an increased risk of recurrent urinary tract infections due to poor fluid intake, decreased voiding frequency, and urine stasis[26]. Behavior disorders and attention deficits are common among children with voiding postponement[27]. We found a significant association between obesity and voiding postponement. Obesity can lead to changes in children's psychological, emotional, and behavioral characteristics[28]. In addition, watching television may be the cause of obesity, leading to reduced activity and, therefore, reduced energy consumption[29]. Accordingly, we considered that obesity could be a risk factor for voiding postponement due to prolonged watching of TV, playing computer games, or accompanying behavioral disorders.

Constipation is a common complaint in childhood. The frequency of constipation and chronic diseases, such as hypertension and type 2 diabetes mellitus, have increased in obese children[30, 31]. Several studies have reported that obese children have a higher prevalence of functional constipation[32, 33]. Similar to the literature, our results demonstrate that obesity is a significant risk factor for constipation. This significant relationship may be due to poor nutrition, less physical activity, impaired production of hormones, such as motilin and pancreatic polypeptide, and autonomic dysfunction in obese children[34–36].

Urinary incontinence negatively affects children's social activities, behaviors, and emotions[37]. Children who are allowed to leave the classroom because of incontinence problems are often considered "different" or are ridiculed[38]. LUTD is also associated with a lower self-image and a lower quality of life in children[39, 40] The vast majority of children with symptoms have learning difficulties in school[41]. In our study, quality of life was affected at different degrees in more than half of the obese children and nearly half of the overweight children.

This study has several limitations. First, this study had a small sample size. Second, symptom scoring was performed based on the mothers' memories and answers. Third, lower urinary tract symptoms were evaluated in obese, overweight, and normal-weight children, and radiological findings and urodynamic results were not included in the assessment.

In conclusion, children who were not taken to the doctor because of urinary problems were included in the study. One-fifth of the children were found to have LUTD. This indicates that children who come to the outpatient clinic should be questioned about lower urinary tract symptoms, even if they do not report complaints about urination. According to the results of our study, obesity is a significant risk factor for LUTD. Lower urinary tract symptoms can be detected in obese children using the VDSS questionnaire validated by Akbal et al. Our results can serve as a basis for further investigations of obese children.

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Research Article / Araştırma Makalesi

Prenatal Sitogenetik Anormallikler ve Ultrasonografik olarak Saptanan Fetal Anomalilerin Korelasyonu

Prenatal Cytogenetic Abnormalities and the Correlation of Ultrasonographically Detected Fetal Anomalies

[1]Emine İkbal Atlı, [1]Engin Atlı, [1]Sinem Yalçıntepe, [1]Çisem Mail, [1]Selma Demir, [1]Hakan Gurkan, [2]Gülizar Füsun Varol

[1]Trakya Üniversitesi Tıp Fakültesi Tıbbi Genetik Ana Bilim Dalı, Edirne, Türkiye

[2]Trakya Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı

Özet

Bu çalışmada, Trakya Üniversitesi Tıp Fakültesi Hastanesi'nde 8 yıllık süreçte anormal ultrasonografi bulguları ile gelen 141 adet amniyosentez, 9 koryon villus ve 5 fetal kan örneği sitogenetik olarak analiz edilmiştir. Amacımız ultrasonografi taramasında anomali riski öngörülen gebeliklerdeki karyotipik anormalliklerin korelasyonunu belirlemekti. Amniyosentez, koryon villus ve kordosentez örnekleri ile yapılan hücre kültürlerinden elde edilen karyotipler değerlendirilmiştir. Ayrıca hızlı tanı için interfaz nukleuslarında X,Y,13, 18,21 kromozomları için floresan insitu hibridizasyon yöntemi ile anöploidi taraması yapılmıştır. Anormal ultrasonagrafi bulgusu ile refere edilen 155 hastadan 23 tanesinde (%14.83) kromozom anomalisi saptanmıştır. NT artışı en sık tespit edilen ultasonografi bulgusuydu. Kromozom anomalilerinden 2 tanesi yapısal kromozom anomalisi olarak değerlendirildi. Geriye kalan 21 hastada saptanan anomaliler sayısal kromozom anomalisiydi. Bu 21 sayısal anomaliden 5 tanesi trizomi 13, 3 tanesi trizomi 18, 13 tanesi trizomi 21'dir. Trizomi 21 vakalarından 1 tanesi kordosentez materyalinden, 1 tanesi ise CVS materyalinden elde edilmiştir. Sonuçlarımız, yüksek riskli bir populasyonda kromozom anomalileriyle, ultrasonografik bulgular arasındaki ilişkinin anlamlı olduğunu ortaya çıkarırken, seçilen ultrasonografik belirteçlerin fetüsteki anöploidiyi saptamadaki geçerliliğini doğrulamaktadır.

Anahtar Kelimeler: Sitogenetik, Prenatal Tanı, Ultrasonografi

Abstract

In this study, 141 amniocentesis, 9 chorionic villus and 5 fetal blood samples, which come with abnormal ultrasonography findings representing 8 years of experience in Trakya University Medical Faculty Hospital, were analyzed cytogenetically. Our aim is to determine the correlation of karyotypic abnormalities detected by ultrasonography for the detection of fetal anomalies in prenatal diagnosis.Karyotypes in metaphases obtained from amniocentesis, chorionic villus and cordocentesis samples were evaluated. For rapid diagnosis, fluorescent in situ hybridization was performed in the interphase nuclei specific to X, Y, 13,18, 21 chromosomes. Chromosome anomalies were found in 23 (14.83%) out of 155 patients referred with abnormal ultrasound findings. NT increase is the most common abnormal fetal ultrasonography finding. Two of the chromosomal anomalies were evaluated as structural chromosome analysis. Anomalies detected in the remaining 21 patients were numerical chromosome anomalies. Of these 21 numerical anomalies, 5 are trisomy 13, 3 are trisomy 18, 13 are trisomy 21. One of the 21 trisomy cases was obtained from cordocentesis material and 1 was obtained from CVS material. Our results present that the relationship between fetal chromosomal anomalies and ultrasonographic findings is significant in a high-risk population, while verifying the validity of selected ultrasonographic markers in detecting aneuploidy in the fetus.

Keywords: Genetic Diagnosis, Prenatal Diagnosis, Ultrasonography

Correspondence:
Emine İkbal ATLI
Trakya Üniversitesi Tıp Fakültesi Tıbbi Genetik Ana Bilim Dalı, Edirne, Türkiye
e-mail: emine.ikbal@gmail.com

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1. Giriş

Prenatal tanı, doğum öncesi bakımın temel bir parçasıdır, çünkü fetüste hafif ila şiddetli anormalliklerin tanımlanmasını sağlar. Bu, sayede mevcut ve gelecekteki gebeliğin uygun şekilde planlanmasına ve yönetilmesine izin verir.

Anöploidi, prenatal tanı ile saptanan en yaygın genetik anormalliktir. Fetal kromozom anomalileri, birinci ve ikinci trimesterde, canlı doğan bebeklerden daha yaygındır, çünkü bu fetüsler hamilelik boyunca yüksek oranda spontan kayba uğrar. Buna ek olarak etkilenen gebeliklerin sona erdirilmesi de burada rol oynar. Fetal anöploidinin antepartum tespiti prenatal tarama programlarının ana hedeflerinden biridir. Sonografik inceleme yararlıdır çünkü anormal karyotipleri olan fetüslerde genellikle anatomik değişiklikler veya anomaliler vardır (1,2).

Ultrason, fetal anormallikleri tespit etmek için hamilelik boyunca kullanılabilir. İlk trimester ultrasonografik taraması nukal saydamlık ve diğer tarama testleri ile birlikte giderek daha fazla kullanılmaktadır. Birinci trimesterdeki ultrasonagrafinin, trizomi 21 gibi anöploidi durumlarının taranmasında etkili olduğu gösterilmiştir. İlk trimesterdeki 3 mm veya daha büyük bir orandaki nukal kalınlık ölçümünün yüksek bir duyarlılığa sahip olduğu ve kromozom anomalileri için risk altındaki hamileliklerin belirlenmesinde özgüllük taşıdığı bildirilmiştir (3,4).

Ek olarak, erken anatomik araştırmaların deneyimli bir sonografi uzmanı tarafından yürütüldüğünde, fenotipik yapının iyi tespit edildiği gösterilmiştir. Picklesimer ve ark. anöploidi taşıyıcısı fetusların retrospektif bir kohort çalışmasında, ultrasonagrafinin anındaki gebelik yaşının anöploidinin ultrasonagrafik belirteçlerinin saptanması üzerindeki etkisini araştırmıştır. Bu çalışmadaki fetal ultrasonagrafiler 14 ila 32 haftalık gebelikler arasında gerçekleştirilmiştir ve araştırmacılar anöploidinin sonografik belirteçlerinin tüm gebelik yaşlarında mevcut olduğunu göstermiştir. Daha erken gebelik yaşlarında, soft marker ve yapısal olmayan anormalliklerin saptanması daha sonraki gebelik yaşlarında ise majör anormalliklerin saptanmasına doğru bir kayma göstermiştir (5-7). Soft marker'lar belirsiz önemi olan ultrasonografi bulgularıdır. Genellikle normal fetuslarla (yani normal varyantlarla) ilişkilidir, klinik sekelleri yoktur ve geçicidir. İlerleyen gebelikle veya doğumdan sonra bu bulgularda gerileme görülür. Bununla birlikte, fetal anöploidi için artmış bir risk taşırlar ve hastanın biyokimyasal risk durumu ile birlikte değerlendirilmelidir. Bu marker'lar;

Artmış nukal kalınlık,

Nazal kemik yokluğu,

Ekojenik bağırsak,

Pyelektazi,

Uzun olması gereken kemiklerde kısalık (humerus, femur),

Ekojenik intrakardiyak odak,

Koroid pleksus kistleridir.

Tüm gebe kadınların ikinci trimesterde fetal anatomik bir araştırmaya tabi tutulması tavsiye edilir. Fetal anatomi yaklaşık 18 hafta sonra ultrasonografi yoluyla sistematik olarak değerlendirilir. Standart fetal anatomik değerlendirmelerin özellikleri Amerikan Ultrason Enstitüsü Tıp uygulama kılavuzlarında ayrıntılı olarak açıklanmıştır.

İlk trimester ultrasonografisi büyük ölçüde kromozomal hastalık riskini belirlemede ense kalınlık ölçümüne odaklanır; ancak, ikinci trimester ultrasonu farklı genetik sendromlar için ayrı bir paterni takip eden spesifik kusurları tanımlayabilir (7,8).

Üçüncü trimester ultrasonografisi, tanımlanan fetal anormalliklerin evrimini takip etmek için ikinci trimester taramasına ek olarak da kullanılabilir. Bununla birlikte, fetal genetik hastalıklar için bir tarama aracı olarak üçüncü trimester ultrasonografisi sınırlı faydaya sahiptir. 2008 yılında, Cochrane ve ark.'nın çalışmasında, seçili olmayan bir populasyonunda üçüncü trimester ultrasonografi taramasının rutin kullanımının fayda sağlamadığı sonucuna varılmıştır (9).

Doğru bir doğum öncesi tanının anahtarı, fetüsün dikkatli bir şekilde taranması ve sonografi uzmanı tarafından anormalliklerin belirlenmesidir. Kromozom anomalili bir fetüsün klasik sonografik bulguları artmış ense kalınlığı, yaygın fetal ödem, septasyonlu kistik higroma, böbrek ve kalp anomalileri vb. içerir. Bu ultrasonografi bulguları fetüste anomali teşhisine güvenilir ve özgül mü, bu doğrultuda Trakya Üniversitesi Tıp Fakültesi Tıbbi Genetik ABD 'da retrospektif bir çalışma yapılmıştır. Karyotipleme altın standart olsa da, sonografinin fetüste anomali tanısının neresinde olduğunun belirlemesi amaçlanmıştır.

Klasik yöntemlerle uygulanmakta olan fetal karyotip elde etme süresi 10-17 gün arasında sürmektedir. Bu bekleme süresi içinde aile, önce amniyosentez işlemi sırasında bir stres yaşamakta buna ek olarak bekleme süreci boyunca stresi artmaktadır. Bu durum karyotiplemenin yanı sıra, anöploidi taraması için rutin olarak uygulanmakta olan Floresan İn-Situ Hibridizasyon Yöntemi (FISH) ile kültür yapılmamış amniyon hücreleri kullanılarak aşılmıştır. FISH ile klasik sitogenetik yöntemde görülen kromozomların yerine, genetik materyal olarak hücre içinde bulunan yoğunlaşmamış kromatin yapısı kullanılmaktadır. FISH ile anöploidi taraması sırasında 13, 18, 21, X ve Y kromozomlarına ait anöploidiler sık rastlanıldığı için bu kromozomları yansıtan problar kullanılır. Genelde bu kromozomların dışında olan anöploidiler, gebeliğin erken haftalarında kaybedilmektedir. FISH'in prenatal tanıda sadece sayısal anomalileri göstermesi, yöntemin bir kısıtlılığı olarak bilinmektedir. Bu nedenle diğer kromozom anomalilerini elimine etmek için bu olgularda klasik karyotipleme de yapılmaktadır. Ayrıca FISH çalışmalarında maternal kontaminasyon üzerinde durulması gereken bir durumdur. Yöntem, kendi içindeki sınırlılıklarına rağmen güvenilirliği kanıtlanmış bir ön tarama ve tanı yöntemidir. FISH ile sonuca ulaşma süresi 24 saat sürmekte ve çabuk verilen ön-sonuç aileyi oldukça rahatlatmaktadır.

2. Gereç ve Yöntem

Temmuz 2012 ile Mayıs 2020 arasında doğum öncesi tanı merkezimizde değerlendirilen gebelerden prenatal ön tanısında anormal USG bulguları olan, 18 yaşında veya daha büyük, 14 ila 24 haftalık gebelikler arasında 155 hasta bu çalışmaya dâhil edildi. USG muayenelerinin belgelenmiş bilgileri baş (beyin ve yüz) boyun, göğüs boşluğu kalbi, karın boşluğu, ekstremiteler (eller ve ayaklar) mesane, omurga ve genital bölgeyi içeriyordu. Tüm hastalara ve eşlerine girişimsel işlem uygulanmadan önce uygulama tekniği ve fetal kayıp oranları başta olmak üzere, işlemin riskleri ve komplikasyonları hakkında detaylı bilgi verilerek bilgilendirilmiş onam alınmıştır.

Bu çalışmada, Trakya Üniversitesi Tıp Fakültesi Hastanesi'nde 8 yıllık tecrübeyi temsil eden anormal USG bulguları ile gelen 141 adet amniyosentez (AC), 9 koryon villus (CVS) ve 5 fetal kan örneği sitogenetik olarak analiz edilmiştir. Amniyosentez için 16.-20. gebelik haftalarında gebelik haftası başına 1 cc amniyon sıvısı örneği alınmıştır. Tek seferde amniyosentez işlemi gerçekleştirilemeyen hastalara maksimum iki kez girişim denenmiştir ve tüm hastalarda başarılı olunmuştur. Uygulama esnasında uygun sıvı cebinde fetal kısım ve kordon bulunmamasına dikkat edilmiştir, transplasental geçişin zaruri olduğu durumlarda plasenta yüzeyine dik olarak geçilmiştir. Amniyon sıvısı 20 ml'lik enjektörle negatif basınç uygulanarak aspire edilmiştir.

Koryon villus örneklemesi işlemi 11.-14. gebelik haftaları arasında yapılmıştır. Transabdominal yolla, 20 ml'lik enjektör yardımıyla, 10 mg kadar fetal doku negatif basınç yardımıyla alınarak transport medyumuna aktarılmıştır. Transservikal yolla hiç koryon villus örneklemesi yapılmamıştır. Koryon villus örneklemesi yapılan hastaların tümünde tek seferde işlem başarılı olmuş ve hepsinden yeterli fetal doku elde edilmiştir.

Kordosentez girişimleri gebeliğin 15-38 haftalarında, aynı hekimler tarafından, serbest el tekniğiyle yapıldı. Girişim yeri olarak plasental insersiyon veya kordonun serbest parçası hedeflendi. Kordosentez, plasentanın yerleşimine bağlı olarak, uygun olgularda transplasental geçilerek kord insersiyon yerinden, plasentanın posterior yerleşimli

olduğu olgularda ise transamniotik geçilerek serbest kordondan veya kordonun plasentaya giriş noktasının 1-2 cm uzağından umbilikal venden heparinli enjektör içerisinde 1-5 cc kadar kan örneği alınarak yapıldı.

Amniyositler ve koryon villus örnekleri, 3 ml AmnioGrow (Cytogen GmbH, Bienenweg, Almanya) ve Chang Medium-D (Irvine Scientific, Santa Ana, CA, ABD) içeren iki veya üç farklı flaskta kültüre edildi. Fetal kan örneklerinden kısa süreli hücre kültürü (72 saat) yapıldı. Fetal kan örnekleri için maternal kontaminasyon olasılığı Apt testi ile ekarte edildi. CVS örnekleri için maternal kontaminasyon olasılığı STR analizi ile ekarte edildi. Kültür sonrasında harvest işlemleri tamamlanan örneklerden preparasyon sonrasında Leishmann-Pankreatin (GPL) ve C bantlama teknikleri ile boyanarak elde edilen metafazlar analize alındı. Her örnek için en az 25 metafaz alanı sayısal ve yapısal kromozom anomalileri açısından incelenerek, sonuçlar ISCN nomenklatürüne uygun raporlandı.

FISH çalışması: Sitogenetik amaçlı yapılan amniyosentez için 0.5-4 ml kordosentez için 0.5-1 ml CVS materyalinden ≈ 2mg direk FISH çalışması için ayrılmıştır. Fikse edilerek lam üzerinde FISH çalışması için hibridizasyona uygun hale getirilen hücreler için AneuVysion EC DNA prob kiti (Vysis 30-161-075) kullanılmıştır. Cytovision Image Analyser sistemi ile uygun filtreler kullanılarak X, Y, 18 için minimum 50 nükleus, 13, 21 nolu kromozomlar için minimum 50 nükleus analiz edilmiş ve görüntüleri dijital ortama aktarılmıştır. Mozaik bulunan olgularda analiz edilen nukleus sayısı 200'e çıkarılmıştır. Tüm analizler iki ayrı kişi tarafından eş zamanlı ve kontrollü olarak tamamlanmıştır. Olgularda yapılan klasik sitogenetik analiz, FISH analizini yapan gruptan bağımsız ve körleme tekniği kullanılarak gerçekleştirilmiştir.

3. Bulgular

Temmuz 2012 ile Mayıs 2020 arasında yapılan bir veri tabanı araştırmasında, perinatoloji kliniğinden anormal USG bulgusu ile yönlendirilmiş 155 prenatal tanı vakası dâhil edildi. Gebe kadınların yaşı 19 ila 40 yaşları arasında ve gebelik yaşı (GA) 9 ila 32 hafta arasında değişmekteydi. Olguların ortalama gebelik sayısı 2.57±1.24 ortalama doğum sayısı 1.05±1.23 ortalama abortus sayısı 0.23±1.12 ortalama yaşayan çocuk sayısı 1±0.51idi. Daha önce amniyosentez, koryonik villus veya kordosentez örneklemesi yapılmış, majör konjenital malformasyonlu bir fetusu olan veya pozitif maternal serum tarama testi gibi başka bir risk faktörü olan kadınlar çalışma dışı bırakıldı. İkiz gebeliği olan kadınlar da homojen bir populasyonu korumak için dışlandı. Daha önce kromozomal anormalliği olan bir çocuğu olan kadınlar da USG bulgularına bakılmaksızın invaziv prenatal tanı önerildiği için çalışma dışı bırakıldı. USG de anomali belirteci bulunan tüm kadınlar anöploidili fetüs taşıyor olma olasılığı hakkında bilgilendirilmiştir (Tablo 1).

Tablo 1. Ultrasonda saptanan anomaliye bağlı olarak anöploidi riski

Marker	Anöploidi riski	Referanslar
Artmış nukal kalınlık	Oranı 18.6 kez (ortalama %2.5; yaşla birlikte değişir)	10-12
Nazal kemik hipoplazisi	Burun kemiği uzunluğunda her 1 mm'lik azalma ile 2.4 kat arttı	10, 11,13
Hafif ventrikülomegali (atriyal kalınlık 10–14 mm)	%4	10, 11,14
Ekojenik bağırsak	%1.4	10, 11,15
Kalpteki ekojenik odak/odaklar	%1	10, 11, 16-18
İzole koroid pleksus kisti	%0.36 (anne <35 yaş) %2.4 (anne >35 yaş)	10, 11, 19
Tek umblikal arter	İzole ise <%1	10,11
Kısa humerus/femur	%0.3	10, 11, 20
İzole renal piyelektazi (33 haftadan önce ≥4 mm/33 hafta sonra ≥7 mm)	%0.33 (anne <36 yaş) %2.22 (anne >36 yaş)	10,21

Anormal ultrasonografi bulgusu ile refere edilen 155 hastadan 23 tanesinde (%14.83) kromozom anomalisi saptanmıştır. NT artışı en sık tespit edilen anormal fetal ultrasonografi bulgusuydu (Tablo 2). Kromozom anomalilerinden 2 tanesi yapısal kromozom anomalisi olarak değerlendirildi. Geriye kalan 21 hastada saptanan anomaliler sayısal kromozom anomalisiydi. Bu 21 sayısal anomaliden 5 tanesi trizomi 13, 3 tanesi trizomi 18, 13 tanesi trizomi 21'dir. Trizomi 21 vakalarından 1 tanesi kordosentez materyalinden, 1 tanesi ise CVS materyalinden elde edilmiştir. Yapısal kromozom anomalilerinden 1 tanesi CVS materyalinden elde edilen metafazlarda saptanmıştır. Fetüste 46,--,inv(2)(p15q11.2) karyotipi elde edilmiştir. Diğer yapısal anomali amniyosentez materyalinden 46,--,dup(1)(q21;q31) olarak saptanmıştır (Tablo 3).

Tablo 2. Prenatal tanı olgularında saptanan ultrasonografik anomalilerin dağılımı

USG anomali bulgusu	Olgu sayısı	USG anomali bulgusu	Olgu sayısı
Hidrosefali	3	Ekstremite anomalisi	8
Ventrikülomegali	10	Diafragma hernisi	7
NT artışı	48	Osteokondroplazi	1
Koroid pleksus kisti	20	Araknoid kist	1
Hipoplastik sol kalp	1	Multiple konjenital anomali	15
Kalpte ekojen odak	10	Omfalosel	1
Kistik higroma	22	Hidrops fetalis	1
Korpus Kallosum agenezisi	3	ARSA	1
Orofasial defekt	1	Kraniyal ventrikülomegali	1
Toplam= 155 olgu			

Tablo 3. Hastalarda saptanan kromozomal anomalilerin USG bulguları ile ilişkisi.

Anomali çıkan hasta sayısı	Kromozom anomalisi	USG anomalileri
13 (%8.38)	47,--,+21	NT kalınlığı, multipl anomali, ARSA, nazal hipoplazi, kalpte ekojen odak, koroid pleksus kisti, kistik higroma
5 (%3.22)	47,--,+13	Kalpte ekojen odak, NT artışı, diafragma hernisi, ventrikülomegali
3 (%1.93)	47,--,+18	Hidrops fetalis, kistik higroma, VSD, omfalosel
1 (%0.64)	46,--,inv(2)(p15q11.2)	Ventrikülomegali, kistik higroma
1 (%0.64)	46,--,dup(1)(q21;q31)	Ekstremite anomalisi, NT artışı
Toplam: 23 (%14.83)		

4. Tartışma

Çoğu gelişmiş ülkede fetal yapısal anormalliklerin tespiti için ultrasonografi doğum öncesi taramanın ayrılmaz bir parçası haline gelmiştir. Halk sağlığı açısından, fetal anormallikler için ultrasonografi taramasının potansiyel faydaları ve sınırlamaları kapsamlı bir şekilde tartışılmıştır. Bugüne kadar, seçilmemiş populasyonlar arasında hem ölümcül hem de ölümcül olmayan anormalliklerin saptanması için ultrasonografi taramasının faydaları hakkındaki raporlar sonuçsuz kalmaktadır. Randomize kontrollü çalışmalar yapılmış ancak sonuç değişkenleri olarak perinatal mortalite ve morbidite kullanılmıştır. Dahası, araştırma ortamlarında, sonografi uzmanlarının uzmanlık seviyelerinde büyük farklılıklar vardır. Araştırma bulgularının yorumlanması, yapılan çalışmaların zaman dilimi tarafından engel oluşturmuş ve günümüzde ultrasonografi mekaniği geçmişe göre daha ileridir. Bu metodolojik problemler; konjenital anormalliklerin tespitinde bildirilen genel duyarlılığın, %14 ila 96 arasında değişen muazzam bir varyasyon olarak yansıma gösterir. Bu metodolojik kusurların yanı sıra, perinatal mortalitenin kullanımı ve morbidite en önemli sonuç değişkenleri olarak sorgulanabilir (22,23).

Ultrasonografi taraması, kromozom anormallikleri olan fetüslerde morfolojik

anormalliklerin saptanması için iyi bir araçtır. Anöploidilerde yapısal kusurları ve yapısal olmayan bulguları (sonografik belirteçler) belirleyebiliriz. Fetal anöploidinin sonografik belirteçleri (SMFA'lar) genellikle önemsizdir, çünkü spesifite göstermezler ve sıklıkla geçicidirler. Sonografinin bu anormallikleri tespit etme duyarlılığı bir dizi faktöre göre değişir: kromozomal anormallik tipi, gebelik yaşı, sonografi kalitesi ve sonografi uzmanının deneyimi. İlk üç aylık dönemde anöploidili fetüs taşıyan gebeliklerde sadece SMFA tanımlanabilir. İkinci üç aylık dönemde, trizomi 21'li fetüslerin % 20'sinde, trizomi 13 ve 18'li fetüslerin çoğunda majör/yapısal anormallikler gözlenmiştir. SMFA ve yapısal kusurları birleştirerek sonografi; trizomi 21'li fetusların %50'sini, trizomi 18'li fetüslerin % 80'ini ve trizomi 13'lü fetüslerin %90'ını tanımlamayı sağlar (24,25). Şener ve ark.'nın yaptıkları çalışmada 98 anormal fetal ultrasonografi bulgusu olan olguların 6'sında (%6,1) kromozomal anomali tespit edilmiştir. Araştırmacılar, klasik trizomi 13, 18, 21 kromozom kuruluşu saptanmışlar haricinde USG anomalisi olan diğer gebelikler arasında; kısa femur nedeni ile kordosentez yapılan bir olguda 47,XX, t(8;14)(p22;q21),+der(14)(8;14) karyotipi saptanmıştır. Fetal USG de tek umblikal arter nedeni ile kordosentez yapılan bir olguda 46,XX, del(3)(p25pter) karyotipi saptanmıştır (26).

M. Erdemoğlu ve ark.'nın yaptıkları çalışmada Fetal patolojisi olan grupta kromozom anomalisi oranı %9,8 olarak saptandı. Tüm anomalilerin 8(%62) tanesi trizomi 21, 18, 13 idi Geriye kalan bir olgu 46,XY (9p inversiyonu), bir olgu 47,XX,+22 (22. kromozom fazla), bir olgu 46,XX, 22p+ ve bir olgu da 46,XY,+14,rob(14;21) idi (27).

Diğer bir çalışmada Dağlar ve ark 268 olguyla yaptıkları çalışmada sadece 2 anormal USG bulgusu olan hasta bulunmaktadır. Bunun sebebi periferdeki il ve ilçelerdeki hastanelerde bulunan ultrason cihazlarının ölçümler için yetersiz olması olabilir. Değerlendirilen bu 2 hastadan 1 tanesinde 45,X kromozom kuruluşu saptanmıştır (28).

Yüce ve ark.'nın yaptığı çalışmada 356 olgunun retrospektif analizinde anormal USG bulgusu endikasyonu olan 25 olgunun sadece birinde kromozom anomalisi (trizomi 21) saptandı. Bu olgunun 16.haftada yapılan USG değerlendirmesinde polihidoamnios, fetal batında asit ve femur uzunluğunda kısalık mevcuttur (29).

5. Sonuç

Sonuçlarımız, yüksek riskli bir populasyonda fetal kromozomal anomalilerle ultrasonografik bulgular arasındaki ilişkinin anlamlı olduğunu sunarken, seçilen ultrasonografik belirteçlerin fetüsteki anöploidi saptamadaki geçerliliğini doğrulamaktadır.

Sonuç olarak, ultrasonografik bulgular ile ilişkili kromozomal anormalliklerin saptanması, hem invaziv girişim gerekliliği açısından hem de uygun genetik danışmanlıkta perinatolog ve genetikçiler için çok önemlidir.

Etik Kurul Onayı

Çalışma protokolü Trakya Üniversitesi Tıp Fakültesi Bilimsel Araştırmalar Etik Kurulu, Edirne tarafından onaylandı.

Hasta Onayı

Tüm katılımcılar çalışmaya katılmayı kabul etti ve her katılımcının yasal vasisinden yazılı bilgilendirilmiş onam alındı.

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Research Article / Araştırma Makalesi

Sacral Epidural Laser Discectomy Efficacy in Non-Operated Lumbar Disc Herniation-A Single Center Experience

Non-Opere Lomber Disk Herniasyonlu Hastalarda Sakral Epidural Lazer Diskektomi Etkinliği-Tek Merkez Deneyimi

[1]Derya Guner, [2]Gungor Enver Ozgencil, [3]Burak Erken, [2]Ibrahim Asik

[1]Izmir University of Health Sciences Tepecik Training and Research Hospital, Algology/Pain Department Izmir,Turkiye

[2]Ankara University Faculty of Medicine, Algology/ Pain Department, Ankara,-Turkiye

[3]Basaksehir Cam ve Sakura City Hospital, Algology / Pain Department, İstanbul,-Turkiye

Abstract

Sacral Epidural Laser Discectomy (SELD) which is an effective and minimally invasive procedure for the direct visualization and therapeutic treatment of pain due to spinal disorders. The aim of this study is to share the effect of SELD on clinical findings and pain. 43 patients who had not undergone back surgery and were found to have lumbar intervertebral disc herniation at L4-5 or L5-S1 level without any indication for back surgery, and who underwent SELD for the treatment patients with low back and/or radicular pain were evaluated. Physical examination findings (the straight leg raising test (SLR) <45 degrees positive(+), SLR >45 degrees negative(-) test were accepted) and visual pain scale (VAS) values were evaluated at admission, on the same day of post-op, 1st and 6th months. Disc herniation was observed at L4-5 level in 27 patients (62.79%) and at L5-S1 level in 16 patients (37.21%). 31 patients (72.09%) benefited from SELD treatment, while surgery was recommended for 10 patients (23.26%). With SELD procedure no permanent complication was observed. The clinical response of SELD according to the lumbar disc level, a more significant improvement was found in both physical examination and VAS scores in patients with disc herniation at the L5-S1 level ($p<0.001$). There was no statistically significant relationship between the SLR (+) side and the outcome. SELD is a more effective option, especially in patients with good physical examination findings at admission and mild-to-moderate soft disc herniation at the L5-S1 level.

Keywords: Sacral epidural laser discectomy, back pain, radicular pain, disc herniation, epidural discectomy, minimal invasive surgery

Özet

Sakral Epidural Lazer Diskektomi (SELD) omurga hastalıklarına bağlı ağrıda doğrudan görüntüleme ve tedavi olanağı sağlayan minimal invaziv bir yöntemdir. Bu çalışmanın amacı SELD tedavisinin klinik bulgular ve ağrı üzerine etkinliğini değerlendirmektir. Omurga cerrahisi geçirmemiş ve cerrahi endikasyonu olmayan L4-5 veya L5-S1 düzeyinde lomber intervertebral disk herniasyonu nedeniyle SELD uygulanmış 43 hasta çalışmaya dahil edildi. Tüm hastalarda başvuru şikayeti olarak bel ve/veya radiküler ağrı mevcuttu. Hastaların başvuru, post-op aynı gün, 1. ve 6.ay kontrollerinde fizik muayene bulguları (düz bacak kaldırma testi (SLR) <45 derece pozitif(+), SLR>45 derece negatif(-) test kabul edildi) ve görsel ağrı skalası (VAS) skorları değerlendirildi. 27 hastada (%62.79) L4-5 düzeyinde, 16 hastada (%37.21) L5-S1 düzeyinde lomber disk hernisi gözlendi. SELD tedavisinden 31 hasta (%72.09) klinik olarak fayda görürken, 10 hastaya (%23.26) omurga cerrahisi önerildi. SELD prosedürü ile hiçbir hastada kalıcı bir komplikasyon gözlenmedi. L5-S1 düzeyinde disk hernisi olan hastalarda SELD hem fizik muayene hem de VAS skorlarında daha anlamlı düzelme sağladı($p<0.001$). SLR (+) tarafı ile klinik yanıt arasında istatistiksel olarak anlamlı bir ilişki saptanmadı. SELD, özellikle başvuru sırasında fizik muayene bulguları iyi olan ve L5-S1 düzeyinde hafif-orta derecede yumuşak disk hernisi olan hastalarda daha etkili bir tedavi seçeneğidir.

Anahtar Kelimeler: Sakral epidural lazer diskektomi, bel ağrısı, radiküler ağrı, lomber disk hernisi, ağrı tedavisi

Correspondence:
Derya GÜNER
Izmir University of Health Sciences Tepecik Training and Research Hospital, Algology/Pain Department Izmir,Turkiye
e-mail: guner.derya@yahoo.com

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1. Introduction

Epiduroscopy, also known as epidural spinal endoscopy, is the percutaneous minimally invasive examination of the epidural space by entering the sacral hiatus with the aid of a flexible endoscope. With the developing technology, since the 2000s, the trans-sacral epiduroscopic decompression (SELD) technique has been developed to treat symptomatic pathologies of the lumbosacral spine, with small-caliber flexible optical and light sources, video-guided catheters and video systems, and laser technology (1). The SELD technique not only demonstrates epidural space pathologies, but also enables the diagnosis and treatment of lesions that cannot be detected even with MRI, by directly seeing them (2). SELD is a very successful method in the treatment of chronic low back and/or radicular pain due to spinal disorders. It provides treatment by eliminating the pathology in the epidural space (such as protruded disc material or epidural adhesion and fibrosis around nerve roots)(3-12). The aim of this study is to share our SELD experience for the treatment of patients with mild to moderate soft lumbar disc herniation with low back and/or radicular pain who have not had low back surgery and have no back surgery indication.

2. Material and Methods

Patient Selection

Between January 2016 and January 2017, the files of 43 patients who applied to Ankara University Faculty of Medicine, İbni Sina Hospital Pain outpatient clinic, who had not undergone back surgery and were found to have lumbar intervertebral disc herniation without any indication for back surgery, and who underwent SELD for the treatment of patients with low back and/or radicular pain were evaluated. Ethical approval of our study was obtained from the ethics committee of Ankara University Faculty of Medicine (ethics committee approval number: 02-56-17). Physical examination findings and visual pain scale (VAS) values were evaluated at admission, on the same day of post-op, 1st and 6th months. For physical examination the straight leg raise test (SLR) was performed all patients in a supine position. The examiner gently raised the patient's leg by flexing the hip with the knee in extension, and the test was considered positive when the patient experiences pain along the lower limb in the same distribution of the lower radicular nerve roots (usually L5 or S1). Furthermore, a positive SLR test was determined when pain was elicited by lower limb flexion at an angle lower than 45 degrees. Complications that developed were recorded. Indications for SELD are mild to moderate soft disc herniation confirmed by magnetic resonance imaging (MRI) consistent with clinical symptoms, low back pain and/or radicular leg pain that causes limitation of daily living activities despite adequate conservative treatment. Contraindications for SELD are cauda equina syndrome or severe paresis (motor grade 3 or less), hard disc, foraminal disc herniation inaccessible using SELD, advanced spinal stenosis or instability, infection, bleeding coagulation disorder, and anatomical abnormalitiessuch as sacral hiatus anomaly or peridural cyst are inaccessible catheterization. Patients with multiple disc herniation, previous history of lumbar surgery, patients with insufficient follow-up period or incomplete information were not included in the study.

Technic

The SELD procedure is performed under operating room conditions with sedoanalgesia and local anesthesia and does not require hospitalization. First, the patient is placed on the operating table in the prone position, and an elevation is placed under the abdomen to exclude the lumbar lordosis and reveal the sacral hiatus. The patient's vital signs are monitored, after sterile cleaning and dressing of the sacral region, local anesthesia with 1% lidocaine and a 5 mm skin incision is applied to the sacral hiatus. A fluoroscopically-guided trocar is passed through the sacrococcygeal ligament. After advancing the trocar to the S2-3 level, a 3.2 mm diameter video-guided catheter (Spinaut V, Imedicom Inc., Seoul, Korea) containing two 1.2 mm diameter lumens is inserted into the trocar towards the target site. The video-guided catheter is advanced to the target level using

bidirectional guidance features and injected radio-opaque through an infusion port, fluoroscopic imaging is performed to confirm the position of the catheter in the ventral epidural space, to detect the outline of the herniated disc and opaque flow obstruction caused by adhesion around the pathological site. A 1.0 mm diameter flexible epiduroscope (Spinaut S, Imedicom Inc., Seoul, Korea) and a 550 µm diameter Holmium YAG flexible laser are advanced to the tip of the catheter via the video-guided catheter to visualize the epidural space and clarify the pathological lesion. Irrigation with saline is applied to sharpen the endoscopic video image and cool the ablation site. Epiduroscopy visualizes herniated disc material, adhesive bands, inflammation tissue, fibrotic connective tissue, and adipose tissue around the dura and nerve root. After confirming with flexible epiduroscopic imaging that the catheter tip is inferior to the herniated disc covered by the posterior longitudinal ligament, laser ablation (power range 2.5 W-5W) is applied to the herniated disc material and adhesive bands. First, the posterior longitudinal ligament bulging material is ablated with Holmium YAG 2.5 W laser , looking at the patient's response. After the patient tolerates the low-grade laser, the posterior longitudinal ligament is penetrated using a 5 W (0.5 J and 10 Hz) laser. Then, the herniated disc under the posterior longitudinal ligament is shrunk with an 8–10 W (0.8–1.0 J and 10 Hz) high-energy laser, until decompression is observed in the thecal sac and nerve root. As the herniated disc shrinks, the epidural space between the dura and the pathological lesion widens. After adequate decompression with repeated epidurograms, a flattened line and free flow should be observed in the target area. After ablation, if adhesion and/or fibrosis is observed, 1500 units of hyaluridase are applied, if not, 16 mg of dexamethasone is injected, the procedure is terminated by removing the epiduroscopic catheter. The skin is closed with sutures, all procedures are applied by the same pain physician.

Statistics

SPSS statistical package program SPSS version 23.0 was used in the study. Categorical candidates were considered as percentage and continuous standards were 'mean± deviation'. Frequency analysis, single Anova test, test and time graphs were used in the analysis. A p value of <0.05 was accepted.

3. Results

A total of 43 patients, 22 (51.16%) female and 21 (51.16%) male, were included in our study. The mean age of the patients was 43.23 ± 12.50, and no statistically significant difference was found between male and female patients (p>0.05) (Table 1). It was evaluated on which side the straight leg raising test (SLR) was positive due to low back and radicular pain at the time of admission. SLR <45 degrees positive and SLR >45 degrees negative test were accepted. Accordingly, at the time of admission, 39.53% of our patients (17 patients) had SLR positive in both legs, while 32.56% (14 patients) had SLR positive in the left leg and 27.91% (12 patients) in the right leg. Disc herniation was observed at L4-5 level in 62.79% (27 patients) of our patients, and at L5-S1 level in 37.21% (16 patients). The SLR degree, which was 45.00 ± 15.96 before SELD, ranged from 76.86 ± 13.18 in the post-op period, 78.95 ± 12.70 at the first month, and 79.30 ± 12.79 at the sixth month. It was found that the SLR value increased as time progressed. A statistically significant difference was found between the patient's pre-SELD, post-op, 1st month and 6th month SLR values (p<0.001). Patients with disc herniation at the L5-S1 level have higher mean SLR averages than patients with disc herniation at L4-5 level, while their mean increase in SLR is similar to each other (Figure 1).

The VAS score, which was 8.02 ± 0.59 in the initial evaluation before SELD, was 5.44 ± 0.90 in the postoperative period, 4.33 ± 1.14 in the first month, and 2.86 ± 1.75 in the sixth month. It was determined that the VAS score decreased in the follow-up. In addition, a statistically significant difference was found between VAS scores according to measurement times (p<0.001). When the VAS scores are evaluated according to the disc herniation level; patients with disc herniation at L4-5 level had higher values than patients

with disc herniation at L5-S1 level. However, although VAS scores were similarly decreased in follow-up evaluations, it is observed that patients with disc herniation at the L5-S1 level experienced a faster decrease in VAS scores (Figure 2). In our study, 72.09% (31 patients) of our patients benefited from SELD treatment, while surgery was recommended for 23.26% (10 patients).In addition, complications were observed in 4.65% (2 patients) of our patients. Transient headache was observed in 1 patient, dural puncture was observed in 1 patient, no permanent complication was observed. When we evaluated the clinical responses obtained from SELD treatment according to sex, 14 of our female patients (63.6%) benefited from the treatment, while 17 (80.9%) of 21 of our male patients benefited from the treatment. However, no relationship was found between the rates of clinical responses and sex (p:0.393). Disc herniation levels and clinical response rates are shown in Table 2. In Table 3, the initial SLR values and outcome status of our patients are compared. Accordingly, 16 out of 27 patients with a baseline SLR value below 45 degrees benefited, while 15 out of 16 patients with a baseline SLR value above 45 degrees benefited from treatment. In Table 4, the SLR side of our patients and their outcome were compared. Accordingly, 8 out of 12 patients with SLR (+) on the right and 11 out of 14 patients with SLR(+) on the left benefited from treatment, while 12 out of 17 patients with bilateral SLR (+)benefited from treatment. In addition, whether there is a relationship between the SLR (+) side and the result was tested with the chi-square relationship test and the chi-square value was found to be 2.24, and the corresponding p value was found to be 0.692. In other words, there was no statistically significant relationship between the SLR (+) side and the outcome.

Table 1. Analysis of Age Distribution of Our Patients by sex

Sex	Mean ± Standard Deviation	P value
Female	46.64 ± 13.52	0.067
Male	39.67 ± 10.49	
TOTAL	43.23 ± 12.50	

Table 2. Comparison of Level of disc herniation and Outcomes of Our Patients

Outcome	Level of disc herniation		TOTAL
	L4-5	L5-S1	
Surgery recommended	10	0	10
Benefited	15	16	31
Complication has developed	2	0	2
TOTAL	27	16	43

Table 3. Comparison of initial SLR Value and Outcome Conditions

Initial SLR Value	Outcome			TOTAL
	Surgery recommended	Benefited	Complication has developed	
<45 Degree	9	16	2	27
>45 Degree	1	15	0	16
TOTAL	10	31	2	43

Table 4. Comparison of SLR Side and Outcome Situations of Our Patients

Side	Outcome			TOTAL
	Surgery recommended	Benefited	Complication has developed	
Right SLR+	3	8	1	12
Left SLR+	2	11	1	14
Bilateral SLR+	5	12	0	17
TOTAL	10	31	2	43

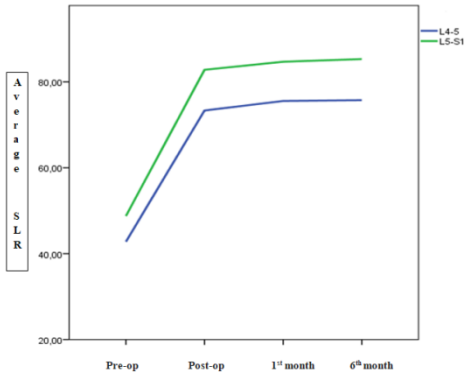

Figure 1. Change of SLR Value Averages According to Disc Hernia Levels of our Patients

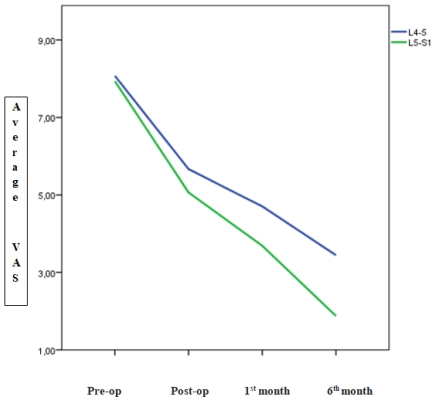

Figure 2. Change of VAS Value Averages According to Disc Hernia Levels of our Patients

4. Discussion

SELD; is an interventional treatment method used in the treatment of chronic low back and/or radicular pain due to spinal disorders like intervertebral disc herniation, fibrosis, spinal stenosis or failed back surgery syndrome. Compared to other conventional algological interventional treatment options (such as drug injection, epiduroscopic adhesiolysis, and neuroplasty), laser ablation with SELD has a higher rate of permanent benefit because it can shrink the disc material(13-16). In a double-blind randomized study comparing caudal injection and epiduroscopic drug injection into the target nerve root in chronic sciatic pain, it was found that the two methods were not superior to each other (17). In a study comparing the clinical efficacy and safety of percutaneous epidural neuroplasty (PEN) and SELD in the treatment of lumbar disc herniation, SELD was found to be more effective and superior to PEN(18).In line with this information, SELD stands out as an optimal treatment option for patients with mild or moderate soft disc herniation (18,19).In many previous studies SELD stands out as a very effective treatment with significant improvement in the pain and quality of life indexes of patients, and it shows rapid efficacy (20,21).However, this may be due to the short follow-up patients and the lack of data reliability. In our study, we evaluated our patients with a control period of 6 months. Although a significant decrease in VAS score and improvement in physical examination were observed in 31 patients (72.09%), surgery was required in 10 patients (23.26%) during the follow-up period.In addition, complications that did not cause permanent damage developed in 4.65% (2 patients) of our patients.In the study of 82 patients by Son et al., patients were followed for 6 months, similar to our study, and clinical

results were not positive in all patients.As the reasons for this situation; It has been suggested that laser ablation may show a lower than expected decompression effect and although reduction in disc material is observed with ablation during the procedure, this may not be reflected as an objective reduction in MR imaging (23,24).In addition, the late effects of laser ablation and dehydration of herniated soft disc may cause various clinical responses in patients(25). Although SELD is an easier procedure than other endoscopic surgical procedures, it requires access through the sacral hiatus, safe entry into the ventral epidural space, reaching the target area with a flexible endoscope, and the ability to use a very narrow and enlarged endoscopic view. In a study evaluating the effectiveness of SELD learning curve and surgical adequacy on clinical response, depending on the operation time and results, the learning curve of SELD is not as difficult as other minimally invasive spinal surgeries and the procedure time gets shorter as the number of operations increases found to have no effect (22).Many factors such as demographic and ethnic characteristics of the patients, the level of the disc, the degree of degeneration and the morphology of the pathology affect the clinical response variability of the patients (23).Although no significant difference was found in terms of efficacy in a study comparing SELD at the L5-S1 level with the microscopic open interlaminar approach, SELD seems to be more advantageous because it provides healing without scar tissue and a quick return to daily life(26).At the L5-S1 level, the location of the epiduroscope is more advantageous than other anatomical levels, it is closer to the sacral hiatus and has a wider disc space. At other anatomical levels (L1-L5), the epiduroscope has to pass through multiple intervertebral structures (26). In our study, when we evaluated the clinical response of SELD according to the lumbar disc level, a more significant improvement was found in both physical examination and VAS scores in patients with disc herniation at the L5-S1 level. In addition, none of the patients with disc herniation at the L5-S1 level required surgery. We found that L5-S1 level discs can be treated more effectively during the SELD procedure. Therefore, we think that further case-controlled studies are needed to investigate the effectiveness of SELD according to the level of disc herniation. We know that SELD is an effective treatment especially for central extruded discs (26). But we did not include only patients with central hernia in our study. SLR positivity side gave us information about the patient's disc herniation area. The SLR test also called the Lasegue test, is a fundamental neurological maneuver during the physical examination of the patient with lower back pain aimed to assess the sciatic compromise due to lumbosacral nerve root irritation. This test can be positive in a variety of conditions (facet joint cyst or hypertrophy) being lumbar disc herniation the most common. Overall, this test is one of the most commonly performed maneuvers across clinical practice and provides important information when making the clinical decision to refer a patient to a specialist as well as among spinal surgeons to guide therapeutic decision-making. Sciatic pain is radiating pain from the buttocks to the leg and is frequently associated with low back pain. In this regard, the neurological examination is fundamental in discriminating patients with isolated lower back pain from those with associated radiculopathy. Consequently, early recognition of radiculopathy allows a targeted treatment and diminishes disability. The specificity of the straight leg raise test has been reported to be low, making the diagnosis accuracy limited. However, the clinical usefulness of this test remains important both for general practitioners as for spine surgeons and should still be considered a relevant component of the physical examination that, associated with proper imaging studies can lead to an accurate diagnosis and treatment (27). In our study in epiduroscopic imaging; right-sided herniation was observed in patients with right SLR(+), left-sided herniation in patients with left SLR (+) and central herniation was observed in patients with bilateral SLR (+). Accordingly, SLR positivity side and SELD efficiency were evaluated in the admission examinations of the patients, but no statistically significant difference was found. In our study, it was found that patients who have worse pre-SELD examination findings (SLR <45 degree) benefited less from SELD than patients with

good initial examination findings (SLR >45 degree).SELD treatment was an effective method in our patients in accordance with the literature. The limitations of our study are that it is retrospective, the number of cases is small and there is no control group. And no scale was used for clinical evaluation, except for physical examination and VAS. SELD, which is an effective and minimally invasive procedure in patients with low back and radicular pain unresponsive to conservative treatment and without an indication for operation, is an effective treatment option as well as surgical methods with the right patient selection. Additionally, SELD proved to be advantageous, with significantly shorter hospital stays. Many factors such as demographic and ethnic characteristics of the patients, the level of the disc, the degree of degeneration and the morphology of the pathology affect the clinical response variability of the patients. SLR test is a physical examination method that is frequently used in daily practice and guides patients with low back and radicular pain in making treatment decisions. We evaluated SELD treatment as a more effective option, especially in patients with good physical examination findings (SLR >45 degrees) at admission and mild-to-moderate soft disc herniation at the level of L5-S1. We think that further case-controlled studies are needed to evaluate the clinical efficacy of SELD treatment.

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Research Article / Araştırma Makalesi

Öz Bildirim Ölçeği'nin 18 ve Üzeri Genç Yaş Grubunda Türkçe Geçerlik ve Güvenirliği

Turkish Validity and Reliability of the Self Reporting Questionnaire in the Young Age Group of 18 and Over

Tuğçe Arslan Torba, Sevil Aydoğan Gedik, Ayşegül Mutlu, Sevda Sungur, Mine Tepetaş, Didem Arslantaş, Alaettin Ünsal

Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Halk Sağlığı Dalı, Eskişehir, Türkiye

Özet

Ruhsal bozuklukların taranması amacıyla DSÖ tarafından geliştirilen Öz Bildirim Ölçeği'nin 18 yaş ve üzeri genç grupta Türkçe geçerlik ve güvenirliğini test etmek amaçlanmıştır. Çalışma, Eylül-Ekim 2021 tarihinde, Eskişehir Osmangazi Üniversitesi Tıp Fakültesi'nde öğrenim görmekte olan 18-25 yaş arası öğrencilerde yapılan metodolojik tipte bir araştırmadır. SRQ-20, üç yabancı dil uzmanı tarafından çeviri-geri çeviri yöntemiyle Türkçe'ye çevrildi. Yapı geçerliği için açımlayıcı faktör analizi(AFA), doğrulayıcı faktör analizi (DFA) ve ayırt edici geçerlik test edildi. Ölçüt geçerliği için Genel Sağlık Anketi (GSA) kullanıldı. Güvenirliği değerlendirmek için Cronbach Alfa ve madde toplam korelasyon katsayısı hesaplandı. Test-tekrar test yöntemiyle ölçeğin kararlılığı değerlendirildi. Madde ayırt ediciliğini değerlendirmek için alt-üst %27'lik gruplara ait madde puanları karşılaştırıldı. Çalışma grubunu 164 kadın (%50,5) ve 161 erkek (%49,5) olmak üzere 325 kişi oluşturdu. Yaş ortalamaları 21,2±2,1 yıldı. SRQ-20'nin Türkçe versiyonun üç alt boyuttan oluştuğu görüldü. Faktör yükleri 0,408-0,779 arasında idi. Toplam açıklanan varyans %44,2 bulundu. Uyum iyiliği indekslerinden Ki-kare/SD=1,58, SRMR=0,08, RMSEA=0,042, CFI=0,971 ve NNFI=0,967 bulundu. Cronbach Alfa ölçeğin geneli için 0,875 bulundu. Madde toplam korelasyon katsayıları 0,323-0,613 arasında değişmekteydi. Alt-üst %27'lik grupların SRQ-20'den aldıkları puanlar arasında fark tespit edildi. SRQ-20 ve GSA arasında pozitif yönde kuvvetli bir korelasyon tespit edildi. Hekim tanılı ruhsal bir bozukluğu olduğunu bildiren öğrencilerin SRQ-20'den aldıkları puanlar diğerlerine göre daha yüksek bulundu. Test-tekrar test uygulaması sonucu iki uygulamadan elde edilen SRQ-20 puanları arasındaki Spearman korelasyon katsayısı 0,792 olarak bulundu. SRQ-20'nin ruhsal bozuklukların taranması amacıyla Türk toplumunda 18 ve üzeri genç yaş grubunda kullanılabilecek geçerli ve güvenilir bir ölçek olduğu sonucuna ulaşıldı.

Anahtar Kelimeler: Ruh sağlığı, SRQ-20, Türkçe, geçerlik, güvenirlik

Abstract

It was aimed to test the Turkish validity and reliability of the Self Reporting Questionnaire-20 (SRQ-20) developed by WHO in order to scan the mental disorders in the young group aged 18 years and over. The study is a methodological type research conducted on students between the ages of 18-25, who are studying at Eskişehir Osmangazi University Faculty of Medicine, in September-October 2021. SRQ-20 was translated into Turkish by three foreign language experts using the translation-back translation method. Exploratory factor analysis (EFA), confirmatory factor analysis (CFA), and discriminant validity were tested for construct validity. General Health Questionnaire (GHQ) was used for criterion validity. To assess reliability, Cronbach's Alpha and item-total correlation coefficient were calculated. The stability of the scale was evaluated with the test-retest method. The item scores of the lower and upper 27% groups were compared to evaluate item discrimination. The study group consisted of 325 people, including 164 women (50.5%) and 161 men (49.5%). The mean age was 21.2±2.1 years. It was seen that the Turkish version of SRQ-20 consisted of three sub-dimensions. The factor loads were between 0.408 and 0.779. The total explained variance was 44.2%. Chi-square/SD=1.58, SRMR=0.08, RMSEA=0.042, CFI=0.971 and NNFI=0.967 were found among the goodness-of-fit indices. It was found 0.875 for the overall Cronbach Alpha scale. Item-total correlation coefficients ranged from 0.323 to 0.613. There was a difference between the scores of the lower and upper 27% groups from the SRQ-20. A strong positive correlation was detected between SRQ-20 and GSA. It was found that students who reported that they had a physician-diagnosed mental disorder had higher scores on the SRQ-20 than the others. As a result of test-retest application, the Spearman correlation coefficient between the SRQ-20 scores obtained from the two applications was found to be 0.792. It was concluded that the SRQ-20 is a valid and reliable scale that can be used in the young age group of 18 and over in the Turkish population in order to scan the mental disorders.

Keywords: Mental health, SRQ-20, Turkish, validity, reliability

Correspondence:
Tuğçe ARSLAN TORBA
Eskişehir Üniversitesi Tıp Fakültesi Halk Sağlığı Anabilim Dalı, Eskişehir, Türkiye
e-mail: dr.tugce.arslan@gmail.com

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1. Giriş

Ruh sağlığı, bireyin yeteneklerini fark ettiği, hayatın olağan stresleriyle baş edebildiği, verimli çalışabildiği ve içinde bulunduğu topluma katkı sağlayabildiği bir iyilik halidir (1). Ruhsal bozukluklar ise ruhsal, biyolojik ya da gelişimsel süreçlerde işlevsellikte bir bozulma olması ile karakterizedir (2). Ruh sağlığı bozuklukları, artık tüm dünyada halk sağlığının önemli bir sorunudur (3).

Ruhsal bozukluklar, hastalık yükünün önde gelen nedenlerinden birisidir. Küresel hastalık yükü araştırmasının bulgularına göre ruhsal bozukluğa sahip tahmini birey sayısı 1990 yılında 654,8 milyon iken 2019 yılında %48,1 artarak bu sayı 970,1 milyona ulaşmıştır. Ruhsal bozukluklara bağlı yükün 2019 verilerine göre %80,6'sı çalışma çağındaki (16-65 yaş arası) bireylerden oluşmaktadır. En yaygın iki ruhsal bozukluk depresif bozukluklar ve anksiyete bozukluklarıdır. Ruhsal bozukluk DALY'lerinin en büyük kısmını 2019'da depresif bozukluklar oluşturmuştur (%37,3), bunu anksiyete bozuklukları (%22,9) ve şizofreni izlemiştir. Küresel olarak, ruhsal bozukluklar 1990'da DALY'lerin 13. önde gelen nedeni iken 2019'da yedinci önde gelen nedeni olmuştur. Ayrıca ruhsal bozukluklar hem 1990 hem de 2019'da dünya çapında YLD'nin ikinci önde gelen nedeni olmuştur (4).

Ruhsal bozukluklar, tüm toplumlarda gençlerdeki hastalık yükünün de büyük bir bölümünü oluşturmaktadır. Ruhsal bozuklukların çoğu gençlik (12-24 yaş) döneminde başlar, ancak genellikle yaşamın sonraki dönemlerinde saptanırlar (1, 5). Zayıf ruh sağlığı, özellikle düşük okul başarısı, madde bağımlılığı, şiddet gibi diğer sağlık ve gelişim kaygılarıyla güçlü bir şekilde ilişkilidir. Bu yaş grubundaki ruhsal bozuklukların bir kısmına yönelik bazı müdahalelerin etkililiği kanıtlanmıştır (5); ancak öncelikle ruhsal bozukluğa sahip olan gençlerin belirlenmesi gerekmektedir. Dünya Sağlık Örgütü (DSÖ)'ne göre, ülkelerin %27'sinden fazlasının ruh sağlığı hakkında veri toplama ve raporlama sistemi bulunmamaktadır (3). Ruh sağlığı sorunlarının oluşumu, risk faktörleri ve risk grupları hakkında daha fazla bilgiye ihtiyaç vardır. Bu amaçla çeşitli ölçekler geliştirilmiştir (6-8). Bunlardan biri ruhsal bozuklukların taranması amacıyla DSÖ tarafından geliştirilen Öz Bildirim Ölçeği'dir (Self Reporting Questionnaire-20, SRQ-20). Pek çok ülkede geçerlik ve güvenirlik çalışmaları yapılmış olan SRQ-20'nin Türkçe geçerlik ve güvenirlik çalışmasına rastlanmamıştır (3, 9-11). Bu çalışmada SRQ-20'nin 18 üzeri genç yaş grubunda Türkçe geçerlilik ve güvenilirliğinin değerlendirilmesi amaçlandı.

2. Gereç ve Yöntem

Çalışma, Eylül-Ekim 2021 tarihinde, Eskişehir Osmangazi Üniversitesi Tıp Fakültesi'nde öğrenim görmekte olan 18-25 yaş arası öğrencilerde yapılan metodolojik tipte bir araştırmadır. SRQ-20'nin Türkçe diline çevrilebilmesi için ölçeğin yazarı Beusenberg'den izin alındı. Çalışmanın yapılabilmesi için gerekli idari izinler ve etik kurul onayı (28.09.2021/24) alındı.

Çalışmanın amacına uygun olarak literatürden faydalanılarak bir anket formu hazırlanmıştır (12-15). Anket formu üç bölümden oluşmaktadır. Formun birinci bölümü katılımcıların bazı sosyodemografik özellikleri (yaşı, cinsiyeti, sınıfı, aile tipi, aile gelir durumu, kimlerle yaşadığı) ve ruhsal bozukluklarla ilişkili olduğu düşünülen bazı değişkenleri (ruhsal hastalık öyküsü, çevreden alınan sosyal desteğin yeterli olup olmadığı, hekim tanılı kronik hastalık varlığı, hayatını etkileyen büyük bir travma yaşama durumu) ikinci bölümü SRQ-20, üçüncü bölümü ise Genel Sağlık Anketi-12 (GSA-12) sorularını içermektedir.

SRQ-20, DSÖ tarafından, özellikle gelişmekte olan ülkelerde psikiyatrik rahatsızlıkları taramak için 1994 yılında tasarlanmıştır. SRQ-20, katılımcıların son 30 gün içindeki durumlarına göre evet veya hayır olarak yanıtlanan 20 sorudan oluşmaktadır ve ''hayır'' seçeneği 0, ''evet'' seçeneği 1 olarak puanlanmıştır. Alınan puan arttıkça spesifik olmayan bir ruhsal bozukluğa sahip olma olasılığı artmaktadır (15).

GSA-12, Goldberg ve Blackwell tarafından 1970'de geliştirilmiştir. GSA'nın 12, 28, 30 ve 60 maddelik formları bulunmaktadır. Türkçe geçerlik ve güvenirlik çalışması 1996'da Kılıç tarafından yapılmıştır. GSA-12 anksiyete ve depresyon belirtilerinin daha yoğunlukta olduğu maddelerden oluşur. Çizelgedeki sorulara verilen yanıtlar "her zamankinden daha iyi, her zamanki kadar, her zamankinden az ve her zamankinden çok daha az" gibi maddenin içeriğine göre hazırlanmış ve sırayla "0, 0, 1, 1" olarak puanlanmıştır. Her puan bir belirtiyi göstermektedir ve alınabilecek maksimum puan 12'dir. Puan arttıkça muhtemel ruhsal sorunlara işaret etmektedir (16, 17).

Hazırlanan anket form, "Google Formlar" çevrimiçi platformuna yüklendi. Daha sonra whatsapp, facebook, bip, telegram gibi sosyal medya uygulamaları ile online olarak öğrencilere ulaştırıldı. Anket formlarının girişinde öğrencilere çalışmanın konusu, amacı, katılımın gönüllülük esasına dayalı olduğu, toplanan verilerin bilimsel bir çalışma için kullanılacağı ve gizliliği hakkında bilgilere yer verildi.

Geçerlik ve güvenirlik çalışmalarında minimum örneklem hacmi için, madde sayısının yaklaşık 5-10 katına ulaşılması veya genellikle 300 kişinin üzerinde bir örneklemde çalışılmasının önerilmesi sebebiyle, çalışmamızda minimum 300 kişiye ulaşılması hedeflendi (18). Çalışma grubunu 325 kişi oluşturdu.

SRQ-20'nin dil geçerliliğinin sağlanabilmesi için ölçek üç yabancı dil uzmanı tarafından çeviri-geri çeviri yöntemi kullanılarak Türkçe'ye çevrildi. Ölçeğin yapı geçerliği için açımlayıcı faktör analizi (AFA), doğrulayıcı faktör analizi (DFA) ve ayırt edici geçerlik test edildi. AFA'da temel bileşenler analizi kullanıldı. Rotasyon yöntemi olarak direct oblimin yöntemi kullanıldı. Faktör sayısını belirlerken öz değerin 1'den büyük olması ve ortaya çıkan faktörlerin mantıken anlamlı olmasına dikkat edildi. Faktör yükü sınır değeri olarak 0,40 kabul edildi. DFA'da, diagonal en küçük kareler yöntemi ile analiz yapıldı. Eş zamanlı ölçüt geçerliği için GSA-12 ile SRQ-20 arasında Spearman korelasyon katsayısı hesaplandı. Ölçeğin güvenirliğini değerlendirmek için Cronbach Alfa güvenirlik katsayısı ve madde toplam korelasyon katsayısı hesaplandı. Ayrıca test tekrar test yapılarak Spearman korelasyon katsayısı hesaplandı. Madde ayırt ediciliğini değerlendirmek için alt ve üst %27'lik gruplara ait madde puanları karşılaştırıldı. Analizler SPSS (versiyon 15.0) ve R (versiyon 4.0.3) istatistik paket programları ile yapıldı. Grupların karşılaştırmasında Mann-Whitney U ve Kruskal Wallis H testi kullanıldı. İstatistiksel anlamlılık düzeyi $p<0,05$ kabul edildi.

3. Bulgular

Çalışma grubunu 164 kadın (%50,5) ve 161 erkek (%49,5) olmak üzere toplam 325 kişi oluşturdu. Yaşları 18-25 arasında değişmekte olup ortalaması 21,2±2,1 yıldı.

SRQ-20 -Ölçeği'nin Geçerlilik Analizleri

1.Açımlayıcı Faktör Analizi (AFA)

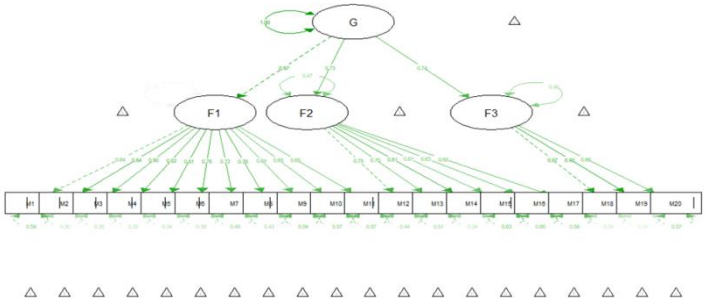
Faktör analizi yapmak için örneklemin yeterli büyüklükte olup olmadığını gösteren KMO değeri 0,88, Bartlett's testi $\chi 2$:1833,45, df:190, $p<0,001$ olarak bulundu. Bu sonuçlara bakılarak verinin faktör analizine uygun olduğu görüldü ve AFA yapıldı. AFA sonunda SRQ-20'nin Türkçe versiyonun üç alt boyuttan oluştuğu görüldü. Ölçeğin faktör yükleri 0,408 ile 0,779 arasında idi. Toplam açıklanan varyans %44,2 bulundu (1.Faktör %30,0, 2.Faktör %7,7, 3.Faktör %6,5). SRQ-20 ölçeğinin AFA sonuçları Tablo 1'de verildi.

Tablo 1. Son elde edilen faktör deseni, faktör özdeğerleri, ortak faktör varyansları ve maddelerin faktör yükü değerleri

Faktörler	Maddelerin Faktör Yükü Değerleri		
Faktör 1 Başlangıç Özdeğeri: 6,001 Ortak Faktör Varyansı: 30,003			
12.Karar vermekte zorlanıyor musunuz?	0,713		
15.Bir şeylere olan ilginizi kaybettiniz mi?	0,704		
6.Sinirli, gergin ya da endişeli hissediyor musunuz?	0,670		
8. Düşüncelerinizi toparlamakta zorlanıyor musunuz?	0,668		
9. Kendinizi mutsuz hissediyor musunuz?	0,633		
18. Kendinizi sürekli yorgun hissediyorsunuz musunuz?	0,622		
13. Günlük işlerinizi yaparken zorlanıyor musunuz?	0,600		
11. Günlük aktivitelerinizden zevk almakta zorlanıyor musunuz?	0,590		
4. Kolayca her şeyden korku duyar mısınız?	0,501		
10. Her zamankinden daha fazla ağlıyor musunuz?	0,477		
20. Kolay yorulur musunuz?	0,431		
Faktör 2 Başlangıç Özdeğeri: 1,543 Ortak Faktör Varyansı: 7,717			
19. Midenizde yanma, kramp, ağrı gibi şikayetleriniz oluyor mu?		0,747	
2. İştahsızlık yaşıyor musunuz?		0,684	
7. Hazımsızlık şikayeti yaşıyor musunuz?		0,669	
3. Uyku problemi yaşıyor musunuz?		0,597	
5. Elleriniz titriyor mu?		0,442	
1. Sıklıkla baş ağrısı şikayeti yaşıyor musunuz?		0,408	
Faktör 3 Başlangıç Özdeğeri: 1,305 Varyansı: 6,527			
16. Değersiz bir insan olduğunuzu düşünüyor musunuz?			0,779
14. Hayatta faydalı olmadığınızı düşünüyor musunuz?			0,638
17. Hayatınıza son vermeyi düşündünüz mü?			0,612
Toplam Açıklanan Varyans: 44,247			

2. Doğrulayıcı Faktör Analizi (DFA)

SRQ-20 Ölçeği'nin faktör yapısını doğrulamak amacıyla yapılan DFA sonucunda ölçeğin orijinal halindeki faktör yapısıyla yeterli uyuma sahip bulunduğundan yapıda herhangi bir madde değişikliğine gerek görülmedi. DFA sonucunda uyum iyiliği indekslerinden $\chi 2/SD$ 1,58, SRMR 0,08, RMSEA 0,042, CFI 0,971 ve NNFI 0,967 olarak bulundu. Tüm uyum indekslerine göre yeterli model-veri uyumunun sağlandığı tespit edildi. SRQ-20 ölçeğinin uyum iyiliği indeksleri değerleri Tablo 2'de verildi. SRQ-20 Ölçeği'nin DFA sonucunda elde edilen diyagram Şekil 1'de verildi.



Şekil 1. Model yapısının ve standart regresyon katsayılarının gösterildiği path diyagramı

Tablo 2. SRQ-20'nin uyum iyiliği indeksleri değerleri

Uyum İyiliği İndeksleri	Değer	Kabul Edilebilir Değer	Yorum
χ2	263,954	-	
p	<0,001	-	
χ2/SD	1,580	<5	Çok iyi
CFI	0,971	>0,90	Çok iyi
TLI (NNFI)	0,967	>0,95	Çok iyi
RMSEA	0,042	<0,08	Çok iyi
SRMR	0,080	<0,08	Çok iyi

3. SRQ-20 Ölçeği'nin madde ayırt ediciliği

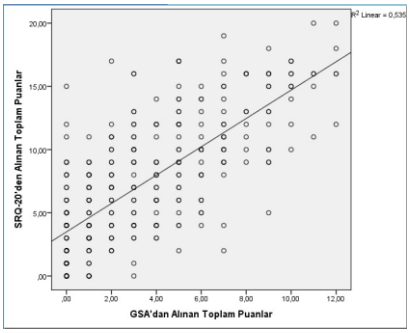
Alt ve üst %27'lik grupların SRQ-20'den aldıkları puanlar arasında anlamlı fark tespit edildi. Ayrıca madde bazında yapılan karşılaştırmada da alt ve üst %27'lik gruplar arasında da fark olduğu görüldü (her biri için p<0,001). SRQ-20'nin her bir maddesinin ve ölçeğin tamamının madde ayırt ediciliğinin olduğu, ruhsal bozukluk olma ihtimalini ayırt edebildiği kabul edildi. SRQ-20'den alınan toplam puanların üst ve alt %27'lik gruplara göre dağılımı Tablo 3'te verildi.

Tablo 3. SRQ-20'den alınan toplam puanların üst ve alt %27'lik gruplara göre dağılımı

Gruplar	SRQ-20 Puanı		z; p
	Ortalama±SS	Ortanca (min-max)	
Alt %27	1,43±1,13	1,00 (0-3)	11,519; <0,001
Üst %27	13,9±2,38	13,50 (10-20)	
Toplam	7,29±5,01	7,00 (0-20)	

4. SRQ-20 Ölçeği'nin Eşdeğer Ölçüt Geçerliliği

SRQ-20 Ölçeği'nin eş değer ölçüt geçerliliği için GSA ile korelasyonunu değerlendirmek amacıyla yapılan Spearman korelasyon analizi sonucuna göre alınan puanlar arasında pozitif yönde kuvvetli düzeyde bir korelasyon tespit edildi (r=0,729, p<0,001). SRQ-20 Ölçeği'nden alınan puanlar ile GSA'dan alınan puanların dağılımını gösteren serpilme diyagramı Şekil 2'de verildi.



Şekil 2. SRQ-20 ölçeğinden alınan puanlar ile GSA'dan alınan puanların dağılımını gösteren serpilme diyagramı

5. Ayırt Edici Geçerlik

Çalışmaya katılan öğrencilerden kadın olanların, aile gelir durumunu kötü olarak bildirenlerin, hekim tanılı ruhsal bozukluğu olanların ve hayatını etkileyen büyük bir travma yaşadığını belirtenlerin SRQ-20'den aldıkları puanlar diğerlerine göre daha yüksek bulundu. Öğrencilerin bazı sosyodemografik özelliklere göre SRQ-20'den aldıkları puanların dağılımı Tablo 4'te verildi.

Tablo 4. Öğrencilerin bazı sosyodemografik özelliklere göre SRQ-20'den alınan puanların dağılımı

	n (%)	SRQ-20 Puanı		z; p
		Ortalama±SS	Ortanca (min-max)	
Cinsiyet				
Kadın	164 (50,5)	8,43±5,02	8,0 (0-20)	
Erkek	161 (49,5)	6,13±4,73	6,0 (0-18)	4,115;<0,001
Toplam	325 (100,0)	7,29±5,01	7,0 (0-20)	
Aile Gelir Durumu				
İyi	56 (17,2)	6,19±5,41	4,5 (0-20)	
Orta	248 (76,3)	7,37±4,88	7 (0-20)	7,084;<0,029
Kötü	21 (6,5)	9,28±4,89	9 (0-17)	
Toplam	325 (100,0)	7,29±5,01	7 (0-20)	
Hekim Tanılı Ruhsal Bozukluk				
Yok	301 (92,6)	6,99±4,90	6,0 (0-20)	
Var	24 (7,4)	11,17±4,92	12,0 (0-18)	3,766; <0,001
Toplam	325 (100,0)	7,29±5,01	7,0 (0-20)	
Hayatını Etkileyen Büyük Bir Travma Yaşama Durumu				
Evet	236 (72,6)	9,10±4,61	9,0 (0-20)	
Hayır	89 (27,4)	6,61±4,99	6,0 (0-20)	4,162;<0,001
Toplam	325 (100,0)	7,29±5,01	7,0 (0-20)	

SRQ-20 Ölçeği'nin Güvenirlik Analizleri

1. SRQ-20'nin iç tutarlılığı

Cronbach Alfa katsayısı ölçeğin geneli için 0,875 olarak bulundu (1.Faktör 0,850, 2.Faktör 0,696, 3.Faktör 0,662). Ölçek maddelerinden herhangi birinin silinmesi durumunda Cronbach Alfa değeri 0,864-0,874 arasında değişmekteydi. Madde toplam korelasyon katsayıları 0,323 ile 0,613 arasında değişmekteydi. SRQ-20'nin iç tutarlığının

yeterli olduğu kabul edildi. Faktörler kendi içlerinde değerlendirildiklerinde tüm faktörlerin iç tutarlılıklarının yeterli olduğu sonucuna varıldı. SRQ-20 Ölçeği'nin madde analizi sonuçları Tablo 5'te verildi. Her bir faktörün Cronbach Alfa katsayısı ve madde toplam korelasyon katsayısı ise Tablo 6'da verildi.

Tablo 5. SRQ-20'nin madde analizi sonuçları

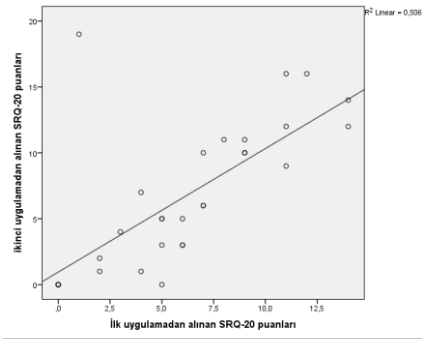
Maddeler	Madde-Toplam Korelasyon Katsayısı	Madde Silindiğindeki Cronbach Alfa
1	0,366	0,873
2	0,402	0,872
3	0,364	0,874
4	0,424	0,871
5	0,369	0,873
6	0,582	0,866
7	0,476	0,870
8	0,613	0,864
9	0,589	0,865
10	0,435	0,871
11	0,542	0,867
12	0,440	0,871
13	0,502	0,869
14	0,492	0,869
15	0,582	0,866
16	0,46	0,87
17	0,323	0,874
18	0,582	0,866
19	0,433	0,871
20	0,482	0,869

Tablo 6. Her bir faktörün Cronbach Alfa katsayısı ve madde toplam korelasyon katsayısı

	Cronbach Alfa	Madde Silindiğindeki Cronbach Alfa	Madde-Toplam Korelasyon Katsayısı
Faktör 1			
12	0,844	0,835	0,486
15		0,823	0,613
6		0,824	0,600
8		0,823	0,612
9		0,823	0,605
18		0,828	0,559
13		0,831	0,519
11		0,828	0,552
4		0,840	0,407
10		0,838	0,433
Faktör 2			
19	0,696	0,622	0,525
2		0,639	0,480
7		0,627	0,514
3		0,675	0,377
5		0,682	0,339
1		0,685	0,330
Faktör 3			
16	0,662	0,405	0,585
14		0,495	0,525
17		0,725	0,334

2. SRQ-20 Ölçeği'nin test - tekrar test güvenilirliği

SRQ-20 Ölçeği'nin test - tekrar test güvenilirliği için araştırmaya katılan 31 kişi SRQ-20 Ölçeği'ni iki hafta sonra yeniden yanıtladı. Söz konusu katılımcıların birinci değerlendirmelerindeki ortanca (min - max) puanları 6 (0-14) olup, ikinci değerlendirmelerindeki ortanca (min - max) puanları 5 (0 – 19) idi. Test-tekrar test uygulaması sonucu iki uygulamadan elde edilen SRQ-20 puanları arasında pozitif yönlü güçlü bir korelasyon saptandı (r=0,792, p<0,001). SRQ-20 Ölçeği'nin test - tekrar test puanlarının serpilme diyagramı Şekil 3'te verildi.



Şekil 3. İlk uygulamadan ve ikinci uygulamadan elde edilen toplam SRQ-20 puanlarının dağılımı

4. Tartışma

Çalışmada, SRQ-20 Ölçeği'nin 18-25 yaş grubundaki öğrencilerde Türkçe geçerlik ve güvenirliğinin ölçülmesi değerlendirildi. Çalışmanın sonuçlarına göre SRQ-20 Ölçeği Türk toplumunda, 18-25 yaş grubunda ruhsal bozuklukların taranmasında kullanılabilecek geçerli ve güvenilir bir ölçektir.

Çalışmada elde edilen verilerin AFA yapmak için uygunluğu Kaiser-Meyer-Olkin (KMO) ve Bartlett testi ile değerlendirilir. Bartlett testi ile korelasyon matrisinin tümel anlamlılığı incelenir ve p değerinin 0.05'ten küçük olması korelasyon matrisinin faktör analizi yapmak için uygun olduğunu gösterir. KMO ölçüsü, 0 ile 1 arasında değişir ve iyi bir faktör analizi için bu değerin 0,80'den fazla olması beklenir (19). Çalışmada, KMO 0,88 ve Bartlett testi p değeri p<0,001 olarak bulundu ve verilerin AFA yapılmasına uygun olduğuna karar verildi.

AFA, ölçeklerin alt boyutlarını ortaya çıkarmayı amaçlamaktadır. AFA, veri matrisindeki maddelerin puan değerleri arasındaki ilişkilerden faydalanarak daha az sayıda faktöre indirgemeyi amaçlayan bir analizdir (20). Faktör yüklerinin en az 0,30 olması gerekirken, 0,70 den büyük yük değerlerinin yapıyı iyi açıkladığı söylenebilir. Çalışmada, ölçeğin faktör yükleri 0,408 ile 0,779 arasında bulundu. Döndürme (rotasyon) yöntemlerinden direct oblimin yöntemi kullanılarak üç faktörlü yapı oluştuğuna karar verildi. Ayrıca, üç faktör için açıklanan varyans 1. Faktör için %30,0, 2. Faktör için %7,7 ve 3. Faktör için %6,5 olmak üzere toplam %44,2 bulundu. Sosyal bilimlerde açıklanan toplam varyansın %40-60 arasında olması yeterli kabul edilmektedir (19). Scholte ve arkadaşlarının Ruanda'da yaptığı bir çalışmada toplam varyansın %38,0'ını açıklayan beş faktör bulunduğu bildirilmiştir (21). Eritre'de yapılan bir çalışmada faktör analizi sonucunda ölçekte toplam varyansın %31,2'sini açıklayan iki faktör olduğu bulunmuştur (22). Ventevogel ve arkadaşlarının yaptığı çalışmada, toplam varyansın %39'unu açıklayan iki faktörlü bir model ortaya çıktığı rapor edilmiştir (23). Chen ve arkadaşlarının Çin'de yaptığı bir çalışmada ise, toplam varyansın %54,17'sini oluşturan üç faktör bulunduğu bildirilmiştir (24). Çalışmalardaki bu farklılıkların sebebi ölçeğin uygulandığı popülasyonların kültürel farklılarından kaynaklanıyor olabilir.

Doğrulayıcı faktör analizinde ise AFA ile belirlenen yapıların uygunluğu test edilir (19). Uyum indekslerinden $\chi 2/SD$'nin 0-2, CFI ve NNFI'nın 0,97-1,00, RMSEA ve SRMR'nin 0-0,05 aralığında olması iyi uyum olarak değerlendirilir (25). Çalışmada, uyum indeks değerlerinin hepsinin iyi uyum gösterdiği bulundu. Tüm bu sonuçlara göre ölçeğin yapı geçerliğini sağladığını söyleyebiliriz. SRQ-20 ölçeği'nin Ruanda'da yapılan geçerlik ve güvenirlik çalışmasında da benzer bulgular elde edildiği raporlanmıştır (21).

Ölçülmek istenen özelliğe sahip olanlarla olmayanları ölçüm aracının ayırt etmesi istenir ve buna madde ayırt ediciliği denir (26). Bunu hesaplamak için ölçekten alınan toplam puanlar büyükten küçüğe sıralanıp üst ve alt %27'lik gruplara ayrılır. Her iki grubun ortalamaları/ortancaları karşılaştırılır ve aralarında istatistiksel olarak bir fark olması gerekir (19). Çalışmada yapılan Mann Whitney U analizine göre alt ve üst %27'lik gruplar arasında anlamlı bir fark bulundu ($p<0,001$). SRQ-20 Ölçeği'nin Ruhsal bozukluk olma ihtimalini ayırt edebildiği kanısına varıldı.

Bir özelliğe sahip olduğu bilinen bir grubun, o özelliği ölçen başka bir ölçekten yüksek puan alması beklenmektedir (19). Bu nedenle ölçüt geçerliliği için GSA ile SRQ-20 Ölçeği'nin korelasyonuna bakıldı. Her iki ölçek arasında pozitif yönde kuvvetli bir korelasyon bulundu ($r=0,729$, $p<0,001$). Mari ve arkadaşlarının yaptığı çalışmada da SRQ-20 ve GSA arasında pozitif yönde kuvvetli bir korelasyon olduğu bildirilmiştir ($r=0,720$) (10).

Çalışmada kurulan hipoteze göre, ruhsal bir bozukluğu olanların SRQ-20'den daha yüksek puan alması beklenmekte idi. Analizler sonucunda da, beklendiği üzere hekim tanılı ruhsal bir bozukluğu olduğunu beyan edenlerin SRQ-20'den aldıkları puanların daha yüksek olduğu saptandı. Bu durum ölçeğin ayırt edici geçerliği sağladığını göstermektedir. Scholte ve arkadaşlarının yaptığı bir çalışmada da hekim tanılı ruhsal bozukluğu olan katılımcıların SRQ-20 Ölçeği'nden aldıkları puanların daha yüksek bulunduğu bildirilmiştir (21).

Güvenirliği tahmin etmek için çeşitli yollar vardır. Bunlardan biri ölçme aracıyla yapılan tek ölçümün kendi içerisinde tutarlılığının bir göstergesi olan Cronbach tarafından geliştirilen alfa katsayısı yöntemidir. Cronbach alfa katsayısı, ölçekte yer alan k maddenin varyansları toplamının genel varyansa oranlanması ile bulunur. Cronbach alfa katsayısının 0,60 ile 0,90 arasında olması oldukça güvenilir olarak değerlendirilmektedir (27, 28). Çalışmada, Cronbach alfa katsayısı ölçeğin geneli için 0,875 bulunarak oldukça güvenilir olarak değerlendirildi (1.Faktör 0,850, 2.Faktör 0,696, 3.Faktör 0,662). Literatüre baktığımızda Cronbach alfa katsayısının 0,784 ile 0,900 arasında değiştiği görülmektedir (17, 21, 24, 29). Ölçekte bulunan maddelerden herhangi birisi silindiğinde Cronbach alfa katsayısının anlamlı düzeyde yükselmediği saptandı (0,864-0,874). Eğer tüm katılımcılar, maddelere, benzer tepkiler veriyorsa o maddeden alınan puanlar dizisi arasında pozitif ve yüksek korelasyon göstermesi beklenir ve bunun için madde toplam korelasyon katsayısı hesaplanır. Bu katsayının 0,30 ve üzerinde olması maddelerin iyi maddeler olduğunu belirtir (28). Çalışmada, madde toplam korelasyon katsayıları 0,323 ile 0,613 arasında değişmekteydi.

Güvenirliği test etmek için bir diğer yöntem de aynı testi belli bir süre süre sonunda aynı kişilere tekrar uygulamaktır. Ölçeğin kararlılığı test – tekrar test yöntemiyle değerlendirilebilir. İki test arası süre uygulanacak testin özelliğine göre değişmekle birlikte psikolojik testler için 10-15 günün yeterli olduğu bildirilmiştir. Her iki ölçüm arasındaki korelasyon katsayısının en az 0,70 olması gerekmektedir. Korelasyon katsayısı yükseldikçe ölçeğin kararlığı artar (19, 30, 31). Çalışmada iki hafta arayla 31 kişi ye yeniden aynı test uygulandı ve korelasyon katsayısı $r=0,792$ olarak hesaplandı. Buna göre ölçeğin kararlılığının yeterli olduğu kabul edildi.

5. Sonuç ve Öneriler

Yapılan analizler neticesinde SRQ-20'nin ruhsal bozuklukların taranması amacıyla Türk toplumunda 18 ve üzeri genç yaş grubunda

kullanılabilecek geçerli ve güvenilir bir ölçek olduğu sonucuna ulaşıldı. Ölçeğin, daha farklı gruplarda da geçerlik ve güvenirliğinin test edilmesinin ve kestirim puanının hesaplanmasının faydalı olacağı kanısına varıldı.

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Demographic, Epidemiological and Etiological Characteristics of Fungal Keratitis Cases in Southern Anatolia Tertiary Eye Care Center

Güney Anadolu Üçüncül Göz Sağlığı Merkezinde Fungal Keratit Olgularının Demografik, Epidemiyolojik ve Etiyolojik Özellikleri

[1]Ayse Idil Cakmak, [2]Meryem Cetin, [3]Yasemin Oz, [4]Necip Kara

[1]Hatay Mustafa Kemal University Tayfur Ata Sokmen Medical School Department of Ophthalmology, Hatay, Turkey

[2]Amasya University Medical School Department of Microbiology, Amasya, Turkey

[3]Eskişehir Osmangazi University Medical School Department of Microbiology, Eskişehir, Turkey

[4]Gaziantep University Medical School Department of Ophthalmology, Gaziantep, Turkey

Abstract

To evaluate the demographic, epidemiological and etiological characterisitics of fungal keratitis cases in our tertiary eye care center located in the Eastern Mediterraen coast of South Anatolia.A retrospective review of all culture-proven fungal keratitis seen from May 2017 to May 2019 was performed. The demographic features, predisposing factors, associated systemic and ocular characteristics, and microbiological analysis results of cases were evaluated. The mean age of 15 cases with fungal keratitis was 46±7 years (range: 19-77 years) with a male-to-female ratio of 4:1. The majority of the occupations of the cases were agricultural workers or farmers (73%). The etiology was predominantly trauma mostly with an environmental origin (93.3%). Fungal growth was detected in 15 eyes (38.5%) in a total of 39 microbial positive corneal cultures. Filamentous fungi were responsible for all cases, including Fusarium sp. in 8 eyes (53.3%) and Aspergillus sp. in 7 eyes (46.7%). Species of Fusarium were determined in 4 eyes, namely F. Aquaeductus, F. Chlamydosporum, F. oxysporum and F. solani; whereas species of Aspergillus were determined in 3 eyes, namely A. niger and A. flavus. Bacterial and fungal coinfection was shown in two eyes (Aspergillus sp. with Gram (+) beta hemolytic streptococcus; Fusarium sp. with Pseudomonas orzyihabitans). The results of this study, which determines the characteristics of fungal keratitis cases encountered in the Eastern Mediterranean coasts of Southern Anatolia may be useful in the early diagnosis of the disease, in the timely and appropriate empirical treatment of the patients living in this region.

Keywords: Fungal keratitis, ocular microbiology, filamentous fungi, fusarium, aspergillus

Özet

Güney Anadolu Doğu Akdeniz kıyısında yer alan üçüncü basamak göz sağlığı merkezimizde fungal keratit olgularının demografik, epidemiyolojik ve etiyolojik özelliklerini değerlendirmek. Mayıs 2017'den Mayıs 2019'a kadar görülen, kültürle kanıtlanmış tüm mantar keratitleri retrospektif olarak değerlendirildi. Olguların demografik özellikleri, predispozan faktörleri, ilişkili sistemik ve oküler özellikleri ve mikrobiyolojik analiz sonuçları incelendi. Fungal keratitli 15 olgunun ortalama yaşı 46±7 yıl (19-77 yıl arasında) idi ve erkek/kadın oranı 4:1 idi. Vakaların çoğunluğunu tarım işçileri veya çiftçiler oluşturuyordu (%73). Etyoloji ağırlıklı olarak çevre kaynaklı travmaydı (%93.3). Toplam 39 mikrobiyal pozitif kornea kültüründe 15 gözde (%38.5) mantar üremesi tespit edildi. Fusarium sp. dahil tüm vakalardan filamentöz mantarlar sorumlu olup 8 gözde (%53.3) Fusarium türleri ve 7 gözde (%46.7) Aspergillus türleri saptandı. Fusarium türleri F. Aquaeductus, F. Chlamydosporum, F. oxysporum ve F. solani olmak üzere 4 gözde; Aspergillus türleri ise 3 gözde A. niger ve A. flavus olarak belirlendi. İki gözde bakteriyel ve fungal koenfeksiyon gösterildi (Gram (+) beta hemolitik streptokokla beraber Aspergillus türü; Pseudomonas orzyihabitans ile beraber Fusarium türü). Güney Anadolu'nun Doğu Akdeniz kıyılarında karşılaşılan fungal keratit vakalarının özelliklerini belirleyen bu çalışmanın sonuçları, bu bölgede yaşayan hastaların hastalığın erken teşhisinde ve zamanında ve uygun ampirik tedavisinin başlanmasında faydalı olabilir.

Anahtar Kelimeler: Fungal keratiti, oküler mikrobiyoloji, filamentöz mantarlar, fusarium, aspergillus

Correspondence:
Ayşe İdil ÇAKMAK
Hatay Mustafa Kemal University
Tayfur Ata Sokmen Medical School
Department of Ophthalmology,
Hatay, Turkey
e-mail: idilayse@yahoo.com

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1. Introduction

Fungal keratitis, also known for keratomycosis, is the inflammation of the cornea that results from fungal infection. It accounts for more than 50% of cases with corneal ulcers, in especially tropical areas of the world [1]. Classification according to fungal genera was basically made in two groups, filamentous fungi and yeast or yeast-like fungi [2]. The epidemiological and etiological factors differ from country to country and even from region to region throughout the country [3]. Numerous studies have reported that filamentous fungi, particularly *Fusarium sp., Aspergillus sp.* and *Curvularia sp.*, are the main causes of mycotic keratitis worldwide [1]. It has been also shown that fungal keratitis infected with these species is more common in tropical and subtropical regions, while yeasts such as *Candida sp.* have been isolated in cases of fungal keratitis mostly in temperate climates [1-3].

Predisposing factors that contribute to the occurence of fungal keratitis also vary around the world. While corneal trauma with vegetative material was reported most frequently, immunosuppression, contact lens wear and ocular surface disorders were reported as other predisposing factors [3,4].

Typical pesentation of fungal keratitis consists of suppurative and ulcerative lesions, which may progress to corneal perforations and endophthalmitis if the stromal inflammation is not taken under control [4]. Therefore, fungal corneal infections require urgent recognition to initiate appropriate antimycotic therapy and prevent permanent vision loss [5].

Knowing the underlying causes and predisposing factors of fungal keratitis in a specific geographical region would help clinicians living in the same area to make the diagnosis and apply the right treatment in a timely manner [4]. Therefore the present study aimed to evaluate the demographic, epidemiological and etiological characteristics of fungal keratitis cases in our tertiary eye care center located in the Eastern Mediterranean coast of Southern Anatolia.

2. Methods

The design of the study was retrospective and cross-sectional that was conducted in accordance with the principals of the Declaration of Helsinki. Approval was obtained from the University Research and Ethics Committee. The files of 39 patients who applied to the tertiary eye care center with corneal ulcer between May 2017 and May 2019 were reviewed and analyzed.

The demographic features, predisposing factors, associated systemic and ocular characteristics, and microbiological analysis results of cases diagnosed with fungal keratitis were evaluated. Patients with viral keratitis, bacterial keratitis and neurotrophic keratitis, and patients with corneal ulcers that did not show any fungi in cytological samples were excluded from the study.

Microbiological investigations

The base and edges of corneal ulcers were scrapped by a spatula under local anesthesia. Microscopical examination was performed for all corneal scraping specimens after staining by Gram, Giemsa, and calcofluor white with 10% potassium hydroxide. A part of each specimen was also inoculated onto blood agar, brain-heart infusion agar and Sabouraud glucose-neopepton agar plates which were incubated for up to 6 weeks at 30◦C and 37◦C under appropriate atmospheric conditions [6]. All culture plates were examined daily for fungal or bacterial growth. Fungal growth in culture was deemed significant if:

1. it was correlated with the clinical presentation, or

2. the growth of the same fungus was demonstrated on two or more solid culture media in the absence of fungus in smears, or

3. there was a semiconfluent growth at the site of inoculation on one solid medium, or

4. there was growth in the liquid media, consistent with microscopy [6].

Re-scraping was performed in case of insufficient material, or suspicion of

contaminated material, or adverse results unrelated to clinical properties. After growth on media the isolated fungi were identified according to their macroscopic and microscopic features. The identification of filamentous fungal colonies was made by conventional methods; microscopically (features of conidiogenous cells and conidiophores, production, morphology and organization of conidia, macro-microconidia and blastoconidia, presence or absence of chlamydospores) and macroscopically (structures and colors of colonies) morphological characteristics, rates and temperatures of growth. [7]. Antibiotic susceptibility testing was performed according to CLSI M38-A2, broth microdilution method for molds.

3. Results

We identified 39 cases with culture positive microbial keratitis, where a fungal cause was isolated from corneal scraping samples of 15 eyes (38.5%) of 15 cases. Hyphae were observed in 17 samples out of 17 cases with keratitis on microscopy; however, no fungal growth was shown in two. The remainder were cases of bacterial keratitis (61.5%).

The age of cases with microbiologically proven fungal keratitis ranged from 19 to 77 years with a mean of 46 ± 7 years. Of the 15 patients, 12 (80%) were men and the male / female ratio was 4:1. There were 1 scrap seller (6.7%), 1 undergraduate student (6.7%), 2 construction workers (13.3%) and 11 agricultural workers (9 farm workers and 2 farm owners) (73.3%). Corneal contact with a herbal material was recorded in 10 cases; the others were soil in 4 patients; lime powder in 1 patient and a metal rod in 1 patient. The undergraduate student who had a history of scratching her eyes while working in a garden was the only case who wore soft contact lenses. None of the cases had a previous history of topical or systemic steroid use.

The genera isolated were *Aspergillus* in 7 eyes (47%) and *Fusarium* in 8 eyes (53%). Among the *Fusarium* species isolated cases, *F. Aquaeductus, F. Chlamydosporum, F. oxysporum and F. solani* were detected from 4 samples (Fig.1). Among the Aspergillus species, *A. niger* (2 samples) and *A. flavus* (1 sample) were isolated. The demographic, etiological characteristics and microbiological spectrum of fungal keratitis cases are shown in Table 1.

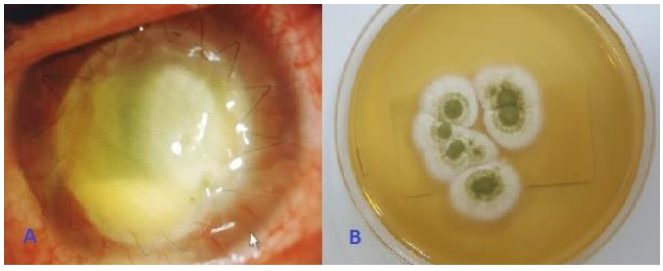

Figure 1. A. Fungal keratitis in the cornea of the left eye of an agricultural worker who underwent penetrating keratoplasty surgery 5 years ago. **B.** Aspergillus flavus growth was seen in the culture of corneal scraping sample.

Table 1. The demographics, epidemiological and etiological features of the fungal keratitis cases

Age / Gender	Occupation	Eye contact	Associated conditions	Fungus
20 / F	Undergrad-gardening	soil	Soft contact lens use	*Aspergillus sp.*
57 / M	Agricultural worker	tree branch	Diabetes mellitus	*Aspergillus sp.*
55 / M	Agricultural laborer	onion skin	-	*Aspergillus sp.*
51 / F	Agricultural worker	tree branch	Diabetes mellitus	*Aspergillus sp.**
35 / M	Agricultural worker	tree branch	-	*Aspergillus niger*
77 / M	Farmer	leaf	Pseudophakia	*Aspergillus niger*

32 / M	Agricultural worker	soil	Keratoplasty	*Aspergillus flavus*
50 / M	Agricultural worker	tree branch	Diabetes mellitus, hypertension, stroke	*Fusarium oxysporium*
57 / M	Agricultural worker	tree branch	-	*Fusarium chlamydosporum*
38 / M	Agricultural worker	tree branch	-	*Fusarium aquaeductum*
19 / M	Agricultural worker	bush	-	*Fusarium solani*
70 / F	Farmer	tree branch	-	*Fusarium sp.*
49 / M	Construction worker	metal rod	-	*Fusarium sp.*
25 / M	Construction worker	lime powder	-	*Fusarium sp.*
50 / M	Scrap dealer	wooden object	-	*Fusarium sp.* †

M: male; F: Female
** Fungal keratitis coinfected with gram(+) beta hemolytic streptococci.*
† Fungal keratitis coinfected with Pseudomonas oryzihabitans.

Antibiotic susceptibility testing of the identified species are given in Table 2. In vitro test results of Caspofungin and Anidulafungin MIC values against *Aspergillus sp.* were found to be very low, while they were found high against *Fusarium sp.* in general.

Table 2. Broth microdilution antifungal susceptibility test results.

Isolates	**MIC values of antifungal drugs (µg/mL)**				
	AmphotericinB	Voriconazole	Posaconazole	Caspofungin	Anidulafungin
A. flavus	1.5	0.5	0.5	0.064	0.003
A. niger* – 1	0.12 g/L	1	0.06	≤0.03	≤0.03
***A. niger* – 2 †**	0.25 g/L	0.5	0.06	≤0.03	≤0.03
F.aquaeductum	1	1	>16	16	>16
F.chlamydosporum	2	4	>16	16	2
F.oxysporum	0.25	8	>16	4	1
F. solani	16	8	>16	16	16

A. Aspergillus; F. Fusarium
** A. niger–1: identified from the corneal sample of the 35-year- old male*
† A. niger–2: identified from the corneal sample of 77-year-old male.

Bacterial and fungal coinfection was shown in two eyes (13.3%). *Aspergillus sp.* and *Gram (+) beta hemolytic streptococci* co-infection was detected in a 51-year-old diabetic agricultural worker who was admitted to the hospital with a diagnosis of both keratitis and endophthalmitis with findings of proliferative diabetic retinopathy observed on fundoscopy. The other was *Fusarium sp.* and *Pseudomonas oryzihabitans* co-infection detected in a 50-year-old male. He was a scrap dealer with a corneal ulcer injured by a wooden object.

Among the known systemic factors, diabetes mellitus type II was reported in three patients (20%). A history of hypertension and stroke was determined in a 50-year-old diabetic male agricultural worker. Two patients had previous ocular surgery (13%). One of them was a 77-year-old rancher who had bilateral cataract surgery for senile cataracts 6 years ago. His right cornea was injured by an orange leaf from which *Aspergillus niger* was isolated. The other was an agricultural worker who had penetrating keratoplasty due to trauma 5 years ago. He had a history of soil-related corneal injury while working in a cotton field. *Aspergillus flavus* was isolated from the patient's corneal sample. (Fig.1)

4. Discussion

The results of this study covering a period of two years showed that filamentous fungi were the main etiology in cases with fungal keratitis. *Fusarium* was the most isolated filamentous fungus, followed by *Aspergillus*. Most of the cases had been associated with outdoor activities, where trauma with a herbal substance was the leading susceptibility factor, with structural materials in the second place. It was also observed that the number of affected males was significantly higher than females.

Epidemiological studies have shown that the microorganisms that cause keratitis may vary according to the geographical features and climatic conditions of the countries. Filamentous fungi are the predominant pathogens that have been widely proven to be associated with fungal keratitis in humid and warm climates [1,8]. Provinces of Southern Anatolia are located in the far east of the Mediterranean coast. The climate here is Mediterranean, characterized by hot and humid summers and humid subtropical climate ranging from cold to mild winters [9]. The main pillars of the economy in this region are agriculture and industry [10].

Studies have reported that ocular trauma is the predominant risk factor for fungal keratitis [1-6]. In a 10-year study by Gopinathan et al, it was found that males were affected 2.5 times more than females, and trauma was the etiological factor in more than 50% of infected eyes [6]. Corneal trauma with an organic or herbal substance has been considered the predominant predisposing factor affecting 40-60% of patients with mycotic keratitis [2,11-13]. In line with these facts, Bharathi et al noted in a retrospective review that the highest prevalence of culture-proven cases of fungal keratitis was observed during the South Indian harvest season between June and September [14]. They determined that 92% of patients with fungal keratitis had ocular trauma and 61% of cases were injured by a herbal substance.

In the etiology of corneal damage that causes keratomycosis, leaves, rice grain, cow tail, tree branch, soil and metal objects have been described in various studies [14,15]. Similarly, Ebadollahi-Natanzi et al found that corneal ulcers caused by fungal microorganisms are most common among farmers and construction workers in rural, structural, and roofless areas [16]. In parallel with various studies in the literature, it has been reported that men over the age of 15, especially those working outdoors, are more frequently affected [8,16-19]. Also, in regions where agriculture is the main economy, the highest fungal keratitis is analyzed to be associated with *Fusarium* and *Aspergillus* species [16].

Filamentous fungi, inhabitants of the environment, are widely associated with keratitis caused by ocular trauma, especially in tropical areas containing organic matter [1,8,17]. In some countries with tropical or subtropical regions such as Singapore, Hong Kong, China, East India, South Florida, East Africa, and Northern Tanzania, the filamentous species were mostly isolated fungi and it was *Fusarium sp*. identified as the primary cause, followed by *Aspergillus sp.* [14,18-26]. Similarly, studies from Ghana, Australia, Iran, Brazil, Tunisia, Thailand, Taiwan, Northern China and South India found *Fusarium* to be the most commonly identified species isolated from fungal keratitis cases. On the other hand, studies from India and the rest of Bangladesh showed that *Aspergillus sp.* was the major species detected in cases of fungal keratitis [3].

Epidemiological studies of fungal keratitis cases in the Eastern Mediterranean Coast of Southern Anatolia have not been conducted yet. Therefore, this study has been compared with studies conducted in other regions of Anatolia where geographical and demographic factors are similar. The available data obtained are similar to these studies in some respects. For instance, in a study conducted in a province of Southern Anatolia, 11 out of 20 fungal keratitis cases had a history of trauma due to plant or soil material [27]. In this 3-year retrospective study, there were five patients with a previous history of topical steroid use, but similarly, the cases were predominantly male, and filamentous pathogens were seen in the microscopy of all corneal scrapings. In another study

retrospectively investigating the etiological factors and clinical features of microbial keratitis cases admitted in Western Anatolia over a 16-year period, it was found that approximately half of the eyes had a history of ocular trauma with herbal substance. The fungal pathogens isolated from these traumatized eyes were found to be predominantly filamentous and 43.5% of fungal keratitis cases were agricultural workers or farmers [28]. Unlike our study, it was determined that corticosteroid therapy was the second most common risk factor for fungal keratitis. *Fusarium sp* were identified as the most isolated fungal species but different from our study they were followed by *Candida sp*.

Unlike filamentous fungi, it has been reported that corneal infections with *Candida sp.* are more common in temperate climates and are less associated with vegetative matter and trauma. In a large analysis conducted in New York, *Candida sp.* was found to be the most common fungal agent (48%) among 5083 cases with keratitis [29]. Ocular surface diseases such as dry eye syndrome and corneal ulcer, systemic immunosuppressive diseases such as diabetes mellitus and the use of steroids and broad-spectrum antibiotics have been shown to be important predisposing factors for *Candida*-induced keratitis [1,17,18,29]. In addition, previous ocular surgeries, especially penetrating keratoplasty, a pre-existing epithelial defect due to herpes keratitis and contact lens abrasions have been also found as risk factors for *Candida* keratitis [1,29]. In the present study, there were cases with diabetis mellitus, previous history of ocular surgery and contact lens use, however, *Candida sp.* was not isolated from any of them. It may be because all of these cases had a history of corneal contact with an environmental agent.

There are extensive retrospective studies defining contact lens use as an important predisposing risk factor for fungal keratitis in studies where fungal etiologies differ by species [18,21-24]. Filamentous fungi have been reported as one of these etiological factors for contact lens-associated keratitis [30]. In this study, *Aspergillus sp.* grew up in a corneal scraping culture of a case using contact lenses and she had a history of scratching her eye while working in a garden. In a 5-year hospital-based retrospective study in which the microbial and clinical characteristics of cases with fungal keratitis were determined in Singapore, where the climate is warm and tropical, 2 cases using contact lenses were reported. Similar to the current study, more than half of the patients in this study had trauma and *Fusarium sp.* was the leading cause of fungal keratitis, followed by *Aspergillus* [22].

When compared to the studies on antibiotic susceptibility of fungal pathogens isolated from patients with keratitis in the literature, the lower number of Fusarium and Aspergillus species in the present study limits the evaluation of this study in this respect. For example, drug susceptibility differences between Fusarium and Aspergillus species were similar in our study compared to the study of Lalitha et al. [31]. However, unlike our study, the sensitivity of fungal agents to different drugs such as Natamycin and Itraconazole was also investigated in the study of Lalitha et al. , which had a much larger sample size (41 Aspercillus spp and 38 Fusarium spp).

The most significant limitations of the present study were the retrospective design and relatively small number of patients. In addition, there were cases where subspecies could not be detected. Adding to this, the inclusion of only culture-positive cases of fungal keratitis may have led to a biased prevalence. That is, there may be some patients with high suspicion of fungal keratitis where fungal growth was not demonstrated in cultures of corneal specimens and microbiological studies were not repeated enough. Furthermore, although important information was provided to guide the treatment of fungal keratitis, the clinical picture, treatment methods and responses to these treatments were not included due to the lack of follow-up information of the patients. For this reason, the current study chose to focus more on the predisposing and etiological factors of the cases with fungal keratitis.

5. Conclusions

Our study, despite all its limitations, provides reliable preliminary information on this subject, showing that agricultural activity and associated eye trauma are the main cause of fungal keratitis caused by filamentous fungi in the Eastern Mediterranean coast of South Anatolia. Since corneal infections need to be recognized urgently to prevent permanent vision loss by facilitating complete recovery, the characteristics of fungal keratitis cases described in this retrospective review may be helpful in early diagnosis of the disease and initiating appropriate early empirical treatment by clinicians working in this geaographic region.

Ethical Approval

All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (ethics committee approval date-decision number: 23/05/2019-10).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

The authors affirm that human research participants provided informed consent for publication of the images in Figures 1A and 1B.

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Araştırma Makalesi / Research Article

A Single-Center Experience in the Diagnosis and Treatment of Subacute Thyroiditis: Should Steroids Always Be the First Choice?

Subakut Tiroidit Tanı ve Tedavisinde Tek Merkez Deneyimi: Steroidler Her Zaman İlk Seçenek mi Olmalıdır?

Melisa Sahin Tekin, Goknur Yorulmaz

1Eskişehir Osmangazi University, Faculty of Medicine, Department of Internal Medicine, Eskişehir, Turkey

2Eskişehir Osmangazi University, Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism, Eskişehir, Turkey

Abstract

We aimed to evaluate the clinical and laboratory findings of our patients with subacute thyroiditis (SAT) and their responses to the treatments given. Twenty SAT patients and 31 healthy controls were included in this retrospective case-control study. The clinical and laboratory data were obtained from the file records. The patient group consisted predominantly of women. The thyroid function tests and acute phase reactants of the patient group were different than the controls, as expected. The platelet count and alkaline phosphatase levels were found to be significantly higher in the patient group. Remission was achieved in 17 patients with non-steroidal anti-inflammatory drug (NSAID) treatment, five of the patients were administered steroid treatment in another center, and switched to NSAIDs by us. Only one patient switched from NSAIDs to steroids. Two patients were switched to acetylsalicylic acid treatment due to moderate transaminase elevation. One of the patients was in the 16th week of pregnancy and took NSAID treatment due to her appropriate trimester. Remission was achieved in all patients with the treatments we administered, and no recurrence was observed in any patient. SAT may be encountered by clinicians from different specialties in daily practice. Referral of the patient to an internist or an endocrinologist is important in terms of timely diagnosis and right treatment. Since SAT shows a self-limiting feature, clinicians should not be in a hurry to administer steroids, NSAID option should always be considered.

Keywords: Subacute thyroiditis; non-steroidal anti-inflammatory drug treatment; permanent hypothyroidism; acetylsalicylic acid; pregnancy

Özet

Subakut tiroiditli (SAT) hastalarımızın klinik ve laboratuvar bulgularını ve verilen tedavilere yanıtlarını değerlendirmeyi amaçladık. Bu retrospektif vaka kontrol çalışmasına 20 SAT hastası ve 31 sağlıklı kontrol dahil edildi. Klinik ve laboratuvar veriler dosya kayıtlarından elde edildi. Hasta grubu ağırlıklı olarak kadınlardan oluşuyordu. Hasta grubunun tiroid fonksiyon testleri ve akut faz reaktanları beklendiği üzere kontrol grubundan farklıydı. Hasta grubunda trombosit sayısı ve alkalen fosfataz düzeyleri anlamlı olarak yüksek bulundu. Non-steroid antiinflamatuar ilaç (NSAİİ) tedavisi ile 17 hastada remisyon sağlandı, hastaların beşine başka bir merkezde steroid tedavisi başlanmıştı ve tarafımızca NSAİİ'lere geçildi. Sadece bir hasta NSAİİ tedaviden steroide geçti. İki hastada orta derecede transaminaz yüksekliği nedeniyle asetilsalisilik asit tedavisine geçildi. Hastalardan biri gebeliğinin 16. haftasındaydı ve uygun trimester nedeniyle NSAİİ tedavisi aldı. Uyguladığımız tedaviler ile tüm hastalarda remisyon sağlandı ve hiçbir hastada nüks görülmedi. SAT, günlük pratikte farklı uzmanlıklardan klinisyenlerin karşısına çıkabilir.Hastanın iç hastalıkları veya endokrinoloji uzmanına sevki zamanında tanı ve doğru tedavi açısından önemlidir. SAT kendi kendini sınırlayıcı bir özellik gösterdiğinden klinisyenlerin steroid tedavisi konusunda aceleci olmaması gerekir, NSAİİ tedavi seçeneği her zaman düşünülmelidir.

Anahtar Kelimeler: Subakut tiroidit; non-steroid antiinflamatuar ilaç tedavisi; kalıcı hipotiroidi; asetilsalisilik asit; gebelik

Correspondence:
Melisa ŞAHİN TEKİN
Eskişehir Osmangazi University, Faculty of Medicine, Department of Internal Medicine, Eskişehir, Turkey
e-mail: melisasahin@gmail.com

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1. Introduction

Subacute thyroiditis (SAT) is a self-limiting inflammatory disease of the thyroid gland. Its prevalence has been reported as 24-35/100000 (1,2). The diagnosis is made by clinical features, and laboratory and imaging studies. In cases where the diagnosis is uncertain, fine needle aspiration biopsy (FNAB) shows infiltration with neutrophils, lymphocytes, histiocytes, and giant cells, deterioration in the structure of thyroid follicles, and necrosis in thyroid follicular cells. However, the FNAB is generally rarely used. After the thyroiditis resolves fibrosis may occur, but gland histology mostly returns to normal (3).

It is thought that SAT is not associated with thyroid autoimmunity. Human leukocyte antigen (HLA)-B*35 positivity had been found higher in patients with SAT than in the general population, thus it can be said that cellular immunity is predominant in SAT (4). In the etiology of the disease, it is thought that viral antigens or antigens resulting from virus-caused tissue damage bind to the HLA-B*35 molecule in macrophages, and cytotoxic T lymphocytes are activated thereafter. Thyroiditis is triggered when activated cytotoxic T lymphocytes target thyroid follicle cells with similar antigenic structure. Histopathological absence of viral inclusion bodies in the thyroid tissue suggests immunological damage rather than direct viral invasion (3).

Inflammation of the thyroid gland in SAT causes damage to the thyroid follicles and proteolysis of the thyroglobulin stored in the follicles. As a result, uncontrolled large amounts of thyroxine (T4) and triiodothyronine (T3) enter the systemic circulation and cause thyrotoxicosis. The state of hyperthyroidism continues until the thyroglobulin stores are depleted, and because of the high thyroid hormone concentration in the peripheral circulation, thyrotropin (TSH) is suppressed by the feedback mechanism, and new hormone synthesis pauses. As the inflammation subsides, the thyroid follicles regenerate and thyroid hormone synthesis and release begin again. Before thyroid hormone secretion returns to normal, there may be a transient period of hypothyroidism and associated increased TSH secretion. In addition, hypothyroidism may be permanent in 15% of the patients (1,5).

The patients' complaints at presentation are mostly neck pain, tenderness in the thyroid lodge, and symptoms related to thyrotoxicosis. Fatigue, weakness, anorexia, and myalgia are common. Usually, both thyroid lobes are affected, but unilateral involvement can also be seen. In some patients, the inflammation may start on one side and then spread to the other side. About half of the patients have symptoms and signs of hyperthyroidism, and fever may also be present. In addition, an increased erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level is typical in laboratory investigation. A low uptake of radioiodine in the scintigraphic evaluation helps confirm the diagnosis. Thyroid ultrasonography (USG) may be useful in distinguishing cystic and/or solid lesions in clinically atypical patients. Demonstration of decreased blood flow during the hyperthyroid phase of SAT with color Doppler sonography is very useful in distinguishing it from Graves' disease (2,3,6). Patients' complaints at the beginning can be confusing for the clinician, and if the preliminary diagnosis of SAT does not come to mind, it can easily be missed, and the patients could take unnecessary medication. The main element of the treatment is non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), or corticosteroid drugs to suppress inflammation. Also, antithyroid treatment is useless in SAT, so if the etiology of hyperthyroidism in a patient is not well defined it can result in unnecessary antithyroid use. In the treatment period, the patients should be well managed in terms of the effectiveness of the treatments and the problems encountered during the treatment.

In this study, we aimed to evaluate the clinical and laboratory findings of patients presenting with SAT and their responses to different treatments given.

2. Materials and Methods

Study population

The current study is a retrospective observational study. Twenty patients with SAT, diagnosed in the Internal Medicine and Endocrinology outpatient clinics, and 31 healthy control subjects were included. The demographic characteristics of the patients, their complaints at presentation, conditions that cause delay in diagnosis, laboratory and imaging tests, treatments given, response to treatment, relapse, and permanent hypothyroidism situations were evaluated from the file records. In addition, the laboratory findings of the patients at admission were compared with the data of the healthy control group.

The study was approved by the Eskisehir Osmangazi University Ethics Committee (Approval No: 40, dated 15 Feb 2022). The study was carried out in accordance with the statement of the Helsinki Declaration. Informed consent was obtained from each participant.

Laboratory measurements

Complete blood count parameters were determined on a Sysmex XN 9100 (Sysmex Corporation, Kobe, Japan) hematology analyzer. Erythrocyte sedimentation rate (ESR) was studied in a fully automated Vacuplus ESR-120 (Ankara, Turkey) analyzer by the Westergren method. Serum C-reactive protein (CRP) levels were measured by immunoturbidimetric method, thyrotropin (TSH), free triiodothyronine (fT3), free thyroxine (fT4), anti-thyroglobulin antibodies (TgAb), and anti-thyroid peroxidase antibodies (TPOAb) were analyzed by electrochemiluminescence immunoassay (ECLIA) in a Cobas 8000 (c702 and e801) autoanalyzer (Roche Diagnostics, Mannheim, Germany).

Statistical Analysis

Statistical analyses of the data were performed with the IBM SPSS Statistics 21.0 package program. The relevance of data to normal distribution was surveyed with the Shapiro-Wilk test. Continuous data were presented as mean± standard deviation. Categorical data were presented as percentage (%) values. Between-group comparisons of normally distributed continuous variables were made with Student's t-test, and non-normally distributed variables with the Mann-Whitney U test. For the categorical variables, Fisher's exact test was used. P values lower than 0.05 were considered statistically significant.

3. Results

The patient group consisted of 5 men (25%) and 15 women (75%), and the control group consisted of 8 men (25.8%) and 23 women (74.2%). The mean ages of the groups were 44.9±8.22 and 44.3±11.17, respectively. There were no differences between the groups in terms of age and gender distribution ($p>0.05$ for both). Serum TSH, fT4, fT3, ESR, and CRP values in the patient group were significantly different from the control group depending on the SAT diagnosis. In the comparison of thyroid autoantibodies, no difference was found between the groups in terms of TgAb and TPOAb positivity.

While there was no difference between the groups in terms of leukocyte count and leukocyte subgroups in the evaluation of hemogram parameters, the platelet count was found to be significantly higher in the patient group than in the control group. In biochemical tests, alanine aminotransferase (ALT) levels were similar between groups, while alkaline phosphatase (ALP) levels were found to be significantly higher in the patient group than in the control group. There was no difference between the groups in terms of 25-hydroxy vitamin D levels. The comparison of demographic characteristics and laboratory parameters of the patient and control groups is given in Table 1.

Table1. The demographic characteristics and laboratory parameters of the patient and control groups

	Patients (n:20)	Healthy Controls (n: 31)	p
Age (year)	44.9±8.22	44.3±11.17	>0.05
Gender (male/female)	5/15	8/23	>0.05
TSH (uIU/mL)	0.05±0.014	1.66±0.5	**<0.001**
fT3 (pg/mL)	6.77±3.86	3.24±0.14	**<0.001**
fT4 (ng/dL)	3.84±1.6	1.19±0.17	**<0.001**
ESR (mm/h)	70.1±20.3	12.5±5.4	**<0.05**
CRP (mg/L)	54.4±14.2	1.2±0.72	**<0.001**
TPOAb positivity	3/20	1/31	>0.05
TgAb positivity	6/20	5/31	>0.05
Leukocyte (10^3/uL)	7.95±2.99	7180±2200	>0.05
Thrombocyte (10^3/uL)	355±107	272±74	**<0.01**
ALT (U/L)	25±14	21±14	>0.05
ALP (U/L)	91.3±29.3	59±33.8	**<0.001**
25-hydroxy vitamin D (ng/ml)	23±17	16.4±6.6	>0.05

**TSH: thyrotropin, fT3: free triiodothyronine, fT4: free thyroxine, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, TPOAb: anti-thyroid peroxidase antibodies, TgAb: anti-thyroglobulin antibodies, ALT: alanine aminotransferase, ALP: alkaline phosphatase*

When we evaluated the treatments our patients had, remission was achieved in 12 patients with NSAID treatment. Six of our patients received steroid treatment. 5 of these patients were given steroid treatment in another center and applied to our clinic with SAT activation. NSAID treatment was administered to these patients, steroid treatment was discontinued, and no recurrence was observed in the follow-up after remission was achieved. In one of our patients, NSAID was given initially, but due to severe symptoms while using NSAIDs, it was necessary to switch to steroid therapy. No recurrence was observed in the follow-up of this patient after remission was achieved with steroids and treatment was discontinued. Moderate elevation of transaminases occurred in two of the patients treated with NSAIDs, and therefore remission was achieved by switching to ASA treatment.

One of our patients was in the 16th week of pregnancy at the time of admission. After diagnosing this patient with SAT, NSAID treatment was administered due to the appropriateness of the patient's trimester for safe use, and it was immediately discontinued after symptomatic improvement was achieved. No obstetric problems were encountered in the peripartum and postpartum follow-ups of the patient who gave birth at term. The patient is still being followed as euthyroid without recurrence.

The mean time from symptom onset to remission of the patients was 52 days.

4. Discussion

In this study, we compared the laboratory characteristics of our 20 SAT patients with the control group and evaluated the treatments and treatment responses of the patients. SAT is a rare thyroid disease, but it is the leading cause of painful thyrotoxicosis. The most important symptoms are pain in the thyroid lodge in the neck and tenderness on palpation. Since SAT is not a very common disease, the probability of misdiagnosis is high. In these cases, patients presenting with SAT findings can be treated with empirical antibiotics with a preliminary diagnosis of a bacterial infection or get treatment due to tachycardia (5,6). All of our patients had anterior neck pain. In 20% of our patients, there was a history of empirical antibiotic therapy before the diagnosis of SAT was clear. It was observed that these patients could not be relieved with the empirical treatment given and applied to our clinic which is a tertiary center. 15% of our patients were those treated with tachycardia and referred to us with newly diagnosed hyperthyroidism while being investigated. In summary, 35% of the patients had delays in the diagnoses and treatments because the diagnosis of SAT was not considered.

In the laboratory evaluation, thyroid function tests, ESR, and CRP levels of our patients were found to be consistent with SAT, and different compared to the control group. When thyroid autoantibodies were examined, TPOAb was positive in 15% of the patient group, and 3% in the control group; TgAb was positive in 30% of the patient group and 16% in the control group. Although there was no statistically significant difference between the groups in terms of autoantibody positivity, positivity rates were higher in the patient group. Transient positivity in thyroid autoantibodies can be seen in SAT, as there is antigenic stimulation with the destruction of thyroid follicles (7). In a recently published study, it was revealed that most of these antibodies are of the IgM type and increase the thyroglobulin clearance, and show a protective feature against the formation of a permanent autoimmune thyroid response (8). Based on this point, it can be predicted that the risk of developing permanent hypothyroidism may be lower in SAT patients who develop a transient autoantibody response.

While no difference was found between the patient and control groups in terms of leukocyte count and leukocyte subgroups in hemogram evaluations, the platelet count, another hemogram parameter indicating inflammation, was found to be significantly higher in the patient group than in the control group. In inflammation, platelet count increases probably secondary to the expansion of megakaryocyte number due to inflammatory cytokines (9). We evaluated the platelet elevation in our patients in favor of reactive thrombocytosis.

ALP levels of our patients were significantly higher than the control group. Thyroid hormone receptors are abundant on osteoblast-like cells and stimulate late expression of receptor activator of nuclear factor kappa-B ligand (RANKL) on cell surfaces. RANKL on osteoblasts binds to the RANK receptor expressed on osteoclast progenitor cells and induces their differentiation into multinucleated osteoclasts. This leads to increased bone resorption, followed by bone formation. ALP is an ectoenzyme that binds to the cell membrane and is released into the bloodstream in response to various stimuli (10). An in vitro study showed that T3 has a stimulating effect on membrane-bound ALP release by osteoblastic cells (11). Although more significant ALP elevation is expected in Graves' disease, we associated the elevation of the ALP levels of the patients with thyrotoxicosis in our study.

Vitamin D deficiency is quite common in endocrine diseases and its replacement is considered to have a beneficial effect (12). In a study conducted with patients with SAT, vitamin D levels were found to be low (13). In the current study, we could not find a statistically significant difference between vitamin D levels in the comparison of the patient and control groups.

Treatment of patients with SAT should be directed towards relieving the pain and the tenderness in the thyroid lodge; and improving symptoms of hyperthyroidism, if present. To date, there are no randomized controlled trials evaluating optimal treatment in SAT. Treatment strategies are based on observational data and clinical experience (3). While some patients do not require treatment, clinical relief can be achieved with NSAID or ASA treatment in mild cases (14). If initial treatment is not sufficient or severe symptoms occur, it may be necessary to switch to steroid therapy (15). With steroid treatment, symptoms are usually relieved within the first 24 hours, but the course of the disease does not change. The inflammatory response is suppressed, but the pathological event continues subclinically. There are different treatment protocols with high or low steroid doses (16). Re-exacerbation can be seen after discontinuation or dose-reduction of steroid treatment in 20% of patients (17). In the event of an exacerbation, it is recommended to increase the dose of steroid therapy to the initial dose or to the previous dose at which the patient's symptoms do not recur. Such situations result in the patient becoming dependent on steroids for a long time. In a study evaluating the recurrence rate with NSAID and steroid use, the total recurrence rate was found 19.8%, and recurrences were observed more frequently in patients receiving only steroid therapy than in patients treated

with NSAID only (23% vs. 10.5% p:0.04) (18). Five of our patients had been initiated steroid treatment in another center and they applied to us because of the exacerbation of the disease after the reduction of the steroid dose. Since their symptoms were not very severe, we tapered and discontinued steroid treatment and gave NSAIDs to these patients during the exacerbation period. Symptom control was achieved in approximately 2 weeks in these patients. Only one of our patients received steroid therapy because of severe symptoms and insufficient control with NSAID therapy. We did not detect exacerbation or recurrence in the 1-year period in any of our patients.

While receiving NSAID treatment two of our patients developed moderate transaminase elevation. They were switched to ASA therapy, and after that, both patients' transaminases returned to normal and did not rise again. Although it is not preferred in the first place in providing symptom control, ASA should also be kept in mind in the management of SAT. In the initial phase of thyrotoxicosis, beta-adrenergic blockers are useful in symptomatic treatment. Since three of our patients had adrenergic symptoms, we also gave propranolol treatment to these patients.

In the follow-up of SAT patients, thyroid function tests should be monitored every two to eight weeks to confirm resolution of hyperthyroidism and subsequent return of thyroid function to normal, and to detect possible development of hypothyroidism. The mean time to remission in our patients was 52 days. If the patients enter the hypothyroid phase after acute inflammation, administration of thyroid hormones may be necessary. Due to the high incidence of transient hypothyroidism, it should not be thought that levothyroxine replacement therapy should be continued for life. During the follow-ups, five of our patients developed hypothyroidism, and levothyroxine replacement was started. Two of these patients were those who switched to NSAID treatment by us after receiving steroid treatment from an external center, and three of them were those who only used NSAIDs in the treatment. In the follow-ups, the need for levothyroxine disappeared in two of these five patients. Statistical comparison was not made because the number of samples was small between the groups in terms of the frequency of development of permanent hypothyroidism in patients receiving NSAID or steroid treatment. In recent years, studies have been published showing that persistent hypothyroidism is more common in SAT patients receiving steroid therapy (18). In a retrospective study of 252 patients with SAT, it was concluded that 5.9% of them developed permanent hypothyroidism, and all of them had bilateral hypoechogenic areas on thyroid ultrasound at first admission, which may be a useful prognostic marker for the development of potential thyroid dysfunction after SAT (19). Bilateral involvement was present in 65% of our patients. On the other hand, 80% of the patients who developed permanent hypothyroidism had bilateral involvement. Since the number of patients was small, a statistical comparison could not be made.

We diagnosed one of our patients with SAT at the 16th week of pregnancy. The patient had anterior neck pain, hyperthyroidism, elevated acute phase response, and classical ultrasonographic findings. Thyroid scintigraphy was not performed because there was no hesitation in the diagnosis and it was contraindicated in pregnancy. In the literature, there are case reports stating that treatment-free follow-up, or treatment with paracetamol or steroids (20). We started NSAID treatment, which was safe for our patient during her current gestational week. After symptomatic relief, we terminated the treatment in the 3rd week. Thyroid functions returned to normal in the 5th week after the initiation of treatment, and the patient did not have a recurrence during her pregnancy. No obstetric problems were encountered in the peripartum and postpartum follow-ups of the patient who gave birth at term. She is still being followed as euthyroid without recurrence.

In conclusion, although SAT is not a very common disease, it may be encountered by clinicians from different specialties in daily practice. The correct interpretation of the symptoms and the referral of the patient to an internist or an endocrinologist by the clinicians are important in terms of timely diagnosis of the patient and not being exposed

to unnecessary treatments. We think that clinicians should not act in a rush in initiating steroid therapy in order to provide rapid symptomatic relief in patients after the diagnosis of SAT. Since SAT shows a self-limiting feature, this will be an important approach to protect the patient from steroid dependency and side effects due to long-term steroid use, as well as the risk of recurrence, which has been demonstrated by previous studies. Internal medicine and endocrinology specialists have important duties in this regard.

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Olgu Sunumu / Case Report

The Efficacy and Tolerability of Xeliri-Aflibercept Combination in A Metastatic Colorectal Cancer Patient After 5-Fu- Induced Symptomatic Bradycardia: A Case Report and A Brief Review of Literature

5-Fluorourasil İlişkili Semptomatik Bradikardi Gelişen Bir Metastatik Kolorektal Kanser Hastasında XELİRİ-Aflibercept Kombinasyonunun Etkinlik ve Tolerabilitesi: Bir Olgu Sunumu ve Kısa Literatür Derlemesi

Lutfiye Demir, Mustafa Ersoy

Eskisehir Osmangazi University, Faculty of Medicine, Department of Medical Oncology, Eskisehir, Turkey

Abstract

5-Fluorouracil (5-FU) and oral fluoropyrimidines are the backbone of colorectal cancer (CRC) chemotherapy, but these have many traditional and cardiotoxic side effects. Rechallenge is usually not recommended due to high mortality rates after ischemic symptoms and other cardiac side effects, but replacing these drugs with another fluropyrimidine, or bolus 5-FU, can be considered for some patients. Aflibercept combined with a FOLFIRI regimen is an accepted second-line therapy for metastatic colorectal cancer (mCRC) patients. XELIRI is another effective and feasible irinotecan and fluoropyrimidine combination, which is more toxic than the FOLFIRI regimen and is not routinely recommended. However, modified doses of XELIRI (mXELIRI) were found to be non-inferior to FOLFIRI. The efficacy of the mXELIRI and aflibercept combination has not investigated yet. We present a patient with infusional 5-FU-induced sinus bradycardia that we could not continue FOLFIRI-aflibercept due to this cardiac side effect. We replaced infusional 5-FU with reduced dosages of capecitabine and irinotecan as in the mXELIRI regimen and combined those with aflibercept. The patient tolerated this regimen well without cardiac or severe gastrointestinal side effects, and had 12 months of progression-free survival. Replacing capecitabine with infusional 5-FU might be an option for some patients experiencing 5-FU-related sinus bradycardia. However, oncologists should arrange the treatment plan according to the risk/benefit ratio. Aflibercept combined with mXELIRI may be an alternative regimen for patients who refuse port catheter placement or who are not able to receive infusional-5-FU due to adverse side effects.

Keywords: XELIRI; Aflibercept; Bradycardia; 5-Fluorouracil; Capecitabine

Özet

5-Fluorouracil (5-FU) ve oral floropirimidinler kolorektal kanser (CRC) kemoterapisinde temel yapıtaşı ilaçlardan olmasına rağmen, bu ilaçların pek çok geleneksel ve kardiyotoksik yan etkileri bulunmaktadır. Oluşabilecek yüksek mortalite riskinden dolayı genellikle iskemik belirtiler ve diğer kardiyak yan etkilerden sonra bu ilaçların yeniden kullanımları önerilmemekle birlikte, bazı hastalarda başka bir floroprimidin ya da bolus 5-FU ile devam edilmesi düşünülebilir. Aflibercept ve FOLFIRI rejimi kombinasyonu metastatik kolorektal kanserli (mCRC) hastaların ikinci basamak tedavisinde kullanılan onaylı bir tedavidir. XELIRI, bir başka etkili ve kullanılması kolay bir irinotekan ve floropirimidin kombinasyonu rejimi olmasına rağmen FOLFIRI rejiminden daha toksik oldğundan artık rutin olarak önerilmemektedir. Buna rağmen, XELIRI rejiminin modifiye doz formunun (mXELIRI), FOLFIRI ile kıyaslandığında daha az etkin olmadığı ve tolerabl olduğu saptanmıştır. Ancak henüz mXELIRI ve aflibercept kombinasyonunun etkinliği araştırılmamıştır. Bu yazıda infüzyonel 5-FU sonrası semptomatik sinüs bradikardisi gelişen ve bu kardiyak yan etki nedenli FOLFIRI-aflibercept rejimine devam edilemeyen bir hasta sunulmuştur. Hastada infüzyonel 5-FU yerine azaltılmış doz kapesitabin ve irinotekan ile mXELIRI rejimi şeklinde verilmiş ve aflibercept ile kombine edilmiştir. Hasta bu tedaviyi kardiyak ya da ciddi gastrointestinal yan etkiler olmadan iyi bir şekilde tolere etmiş, ve 12 aylık progresyonsuz sağkalım süresi sağlanmıştır. İnfüzyonel 5-FU ilişkili sinüs bradikardisinde, infüzyonel 5-FU yerine kapesitabin kullanmak bazı hastalar için bir seçenek olabilir. Ancak, yine de onkoloji uzmanları bu durumlarda mutlaka tedavi planını yarar/zarar oranına göre düzenlemelidir. Aflibercept ve mXELIRI kombinasyonu port katater takılmasını istemeyen ya da yan etki nedenli infüzyonel 5-FU alamayan hastalarda alternatif bir rejim olabilir.

Anahtar Kelimeler: XELİRİ; Aflibercept; Bradikardi; 5-Fluorourasil; Kapesitabin

Correspondence:
Lütfiye DEMİR
Eskisehir Osmangazi University, Faculty of Medicine, Department of Medical Oncology, Eskisehir, Turkey
e-mail: demir.lutfiye77@gmail.com

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1. Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths worldwide. Approximately 20% of CRC patients are diagnosed with stage IV disease and the 5-year survival rates is approximately 15% for these patients.[1] Until the late 1990s, 5-FU combined with leucovorin (LV) was the only effective combination for treating CRC.[2] However, approval of the two drugs, irinotecan and oxaliplatin respectively, and the addition of each drug to standard 5-FU/LV-based chemotherapy improved survival of CRC patients compared to 5-FU/LV only.[3,4] In addition, after realizing the significance of molecular targets such as vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR), new targeted therapies have become valuable in the treatment of metastatic CRC. The addition of either anti-EGFR or anti-VEGF monoclonal antibodies (bevacizumab) to 5-FU-LV/ irinotecan or oxaliplatin combinations increased median survival to 25 months.[5,6]

In 2012, the approval of two targeted agents aflibercept, in second-line and regorafenib, in third-line treatments resulted in a 5-month gain in median survival of mCRC patients.[7,8] Furthermore, personalized therapy was replaced with standard therapy after recognizing the predictive value of driver RAS mutations, the effect of tumor sidedness and the prognostic role of BRAF mutation in CRC.[9,10]

Aflibercept is a recombinant fusion protein containing VEGF-binding proteins from the extracellular domains of human VEGF receptors 1 and 2 that is fused to the Fc portion of human immunoglobulin G1. Aflibercept blocks the activity of VEGFA, VEGFB, and placental growth factor by acting as a high-affinity ligand trap to prevent the ligands from binding to their endogenous receptors.[11] Based on the results of the phase III VELOUR (Aflibercept Versus Placebo in Metastatic Colorectal Cancer After Failure of an Oxaliplatin-Based Regimen) study, Aflibercept was approved in combination with the conventional FOLFIRI regimen (infusional-5-FU, LV, irinotecan) as second-line treatment for patients who have progressed on an oxaliplatin-containing regimen.[7] XELIRI is another irinotecan and oral 5-FU derived combination used in the treatment of CRC. A modified form of the XELIRI regimen (mXELIRI) was recently compared to the FOLFIRI regimen and was found to be non-inferior in a phase III study.[12] However, there is lack of randomized studies about the use of aflibercept in combination with XELIRI.

Fluoropyrimidines (5-FU, capecitabine) are antimetabolites that frequently cause many side effects similar to those of other chemotheurapeutics, such as diarrhea, emesis, stomatitis and cytopenia. Besides these traditional side effects, 5-FU and its derivates are also related to carditoxicity. The relationship between 5-FU and cardiotoxicity was first reported in 1962,[13] followed by several case reports and retrospective studies thar reported different 5-FU and other fluoropyrimidine-related cardioxicity incidence and mortality rates ranging between 1-34 % and 0-13%, respectively.[14-19] The most frequent symptoms and manifestations are coronary vasospasm and ischemic electrocardiography (ECG) changes, myocardial infarction, arrhythmias, cardiac failure and ECG abnormalities. Sinus bradycardia is a relatively rare complication of 5-FU.[20] After experiencing 5-FU induced cardiotoxicity, experts usually recommend that patients discontinue therapy; however, as 5-FU is the major component of chemotherapy combinations for many cancers, such as mCRC, decision should not be made until after weighing the risks and benefits.[21]

In this report, we present a case of an mCRC patient with infusional 5-FU induced bradycardia, in whom capecitabine rechallenge was well-tolerated without cardiotoxicity. Moreover, the patient received a combination of aflibercept with XELIRI with manageable side effects and a long PFS.

2. Case Presentation

In March 2017, a 54-year-old female patient was admitted to the out-patient clinic of our hospital's surgery department with complaints of abdominal pain and constipation. Due to these symptoms, a colonoscopy was performed, and an obstructive mass with malign appearence in the sigmoid colon was observed. The biopsy taken from this mass was compatible with adenocarcinoma. Computed tomography (CT) screening was immediately performed and multiple metastatic lesions were detected; the one with largest diameter (3 cm) was found in the liver, and multiple paraaortic lymph nodes were also found. The surgeons decided to open a stoma through colostomy due to the risk of intestinal obstruction during treatment, and after the operation, they directed the patient to the Department of Medical Oncology. The presence of the NRAS codon 61 mutation was determined by genetic analysis of primary tumor. The basal carcinoembryonic antigen (CEA) level was 11 ng/ml. The ECOG performance score was 1, and the patient had no limiting comorbid diseases except hypotiroidism from a thyroidectomy, for which she was receiving thyroid hormone replacement therapy.

In April 2017, we initiated mFOLFOX6(modified FOLFOX6-oxaliplatin, infusional 5FU, leucovorin) and bevacizumab combination treatment for first-line therapy. After three months of treatment, a significant increase in the level of CEA (25.9 ng/ml) and progression of liver metastases was observed. Therefore, we decided to start second-line therapy as FOLFIRI-aflibercept, however, the patient quit follow-up, but she came back with abdominal pain, rectal bleeding and fatique in October 2017. Contol CEA was 117 ng/ml. The number and size of liver metastases were significantly increased, and newly developed para-aortic lymph nodes were detected on CT imaging. The patient performance status was ECOG 2 at that time, liver and renal function tests were still within normal ranges. However, she had grade II anemia due to rectal bleeding, so we could not start the second-line FOLFIRI-aflibercept treatment per our planning. We referred the patient to the Department of Radiation Oncology, where they decided to initiate radiotherapy to the primary lesion for bleeding control and restore anemia. After 10 fractions of radiotherapy, bleeding was controlled. Subsequently, the FOLFIRI regimen was started. On the second day of the first cycle, the patient experienced hypotension and bradycardia (Figure 1). We discontinued 5-FU infusion, symptomatic bradycardia lasted approximately for 6 hours and we tried to continue 5-FU infusion again, however symptomatic bradycardia and hypotension reappeared and we had to apply atropin 0.5 mg IV twice. Thyroid function tests and cardiac markers were all within normal ranges, and normal ejection fraction was observed on echocardiogram. We concluded that symptomatic bradycardia was due to 5-FU infusion, and we considered changing to bolus 5-FU. However, as side effects such as diarrhea and neutropenia are seen much more frequently with bolus 5-FU, we rescheduled the treatment as XELIRI, and we combined this regimen with aflibercept. Aflibercept was administered at the same dosage (4 mg/kg), but in three weekly cycles. Irinotecan was administered at 200 mg/m^2, and capecitabine was administered at 800 mg/m^2 twice per day for a two weeks on-one week off regimen (mXELIRI dosage). Due to the government policies, we requested permission from the Health of Ministry for the usage of this treatment combination and after getting the permission, The first XELIRI-aflibercept regimen was initiated in the hospital due to the possibility of bradycardia, bleeding and other complications. The patient hospitalized for one week; however no bradycardia, hypotension and bleeding were observed. The patient was carefully warned about serious adverse events, and the other cycles were given in an out-patient chemotherapy clinic. After one cycle of FOLFIRI and three cycles of mXELIRI-aflibercept, response evaluation was performed. CEA levels decreased to 22 ng/ml and partial response was observed in liver lesions (Figure 2a-2b). We reduced irinotecan dosage to 180 mg/m^2 due to grade II neutropenia/leucopenia and diarrhea after the second cycle, and then, she had no further dose-limiting adverse events. We observed grade I fatigue, diarrhea, and grade II hypertension, which was manageable with

amlodipine. Partial response proceeded on the six-month radiologic evaluation, and a stabile response was observed on the ninth month evaluation, at which time CEA level was 30 ng/ml. Unfortunately, in January 2019, one year after initiation of this regimen, liver lesions progressed, a new perihepatic fluid and periportal multiple lymph nodes were observed on CT imaging (Figure 2c), and the serum CEA level had increased to 234 ng/ml. The patient was tired and her ECOG performance score was 3 upon physical examination. After a one-month hiatus from treatment, she was reevaluated at outpatient clinic. She was quite well compared to her condition a month ago, and her liver function tests were still within normal ranges. We started Regorafenib at 80 mg, and planned to increase the dosage after the second week of examination. However, the patient had fatique, and grade I stomatitis, so we decided to continue with the same dosage (three weeks on, one week off). After three months of regorafenib, she visited the hospital with ascites and jaundice, and one month later, on June 8, 2019, 27 months after intial diagnosis, she died.

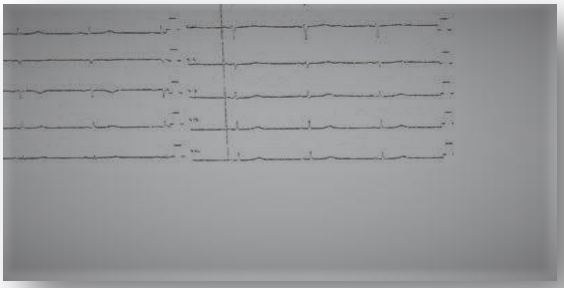

Figure 1. Electrocardiography of the patient during infusional 5-FU, sinus bradycardia; heart rate:46/minute

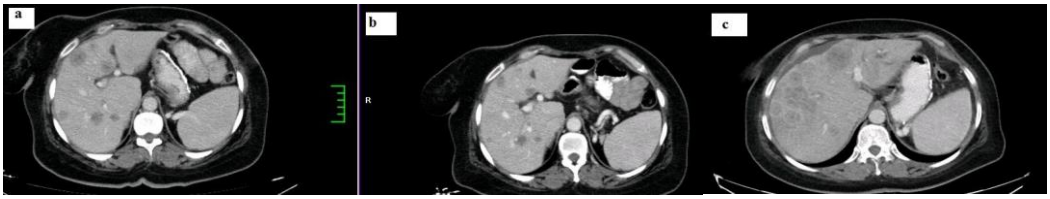

Figure 2. Liver metastases during patient follow-up a. before XELIRI-aflibercept b. Partial response in liver lesions after sixth month. C. Progression of liver metastases before regorafenib.

3. Discussion

We decided to report this case to focus on two topics. First, to discuss 5-FU-induced symptomatic bradycardia that did not occur after replacing infusional 5-FU/LV with another fluoropyrimine, capecitabine; and second, to discuss the combination of XELIRI with aflibercept, for which no randomized data regarding tolerability and efficacy were found in the literature.

Several retrospective and prospective studies have examined the link between 5-FU and cardiotoxicity. One of the larger studies involved 644 patients who were enrolled by Kosmas et al. [22] Among patients treated with infusional 5-FU/LV, the cardiotoxicity rate was 12.5%, it was 2.4% in bolus 5-FU/LV-treated patients, and 5.5% in capecitabine-treated patients.[22] Deboever et al. also reviewed the incidence of cardiotoxicity, which varied between 2.5% and 8.5% for the De Gramont's schedule, 3%–9% for capecitabine, 1.6%–3% for intravenous bolus regimens, and 5.3%–12.5% for high-dose and continuous infusion schedules of 5-FU.[21] Although capecitabine is also related to

cardiotoxicity in many reports, the fact that we did not observe toxicity after capecitabine treatment in our patient could be due to fluoropyrimidine metabolism. About 10% of 5-FU is cleared by renal excretion, and the remainder is deactivated to dihydrofluorouracil (DHFU) by dihydropyrimidine dihydrogenase (DPD).[23] The DPD activity and metabolism of 5-FU may become saturated at higher levels, and the tolerated daily dose of 5-FU decreases as the length of infusion increases.[23] However, the metabolism of oral fluoropyrimidines (and capecitabine) is different from infusional 5-FU. They undergo more diverse metabolism in the gastrointestinal system and in the liver through the action of multiple enzymes.

Sinus bradycardia is termed as a heart rate under 50 beats/minute, with otherwise normal function of the sinoatrial node and conduction systems and is an unusual presentation of 5-FU cardiotoxicity. Kosmas et al.[22] found that only four of their 26 patients developed bradycardia; three of these were due to a complete atrioventricular block, and only one, as in the case we describe here, was sinus bradycardia (50 beats/min). Hafeez et al.[24] investigated the effect of 5-FU on the sinoatrial node and conduction system of the heart. They observed ECG changes in 25 patients during 5-FU infusion. Sinus bradycardia was seen in 8% of patients, who were receiving continuous 5-FU infusion.[24] They also reported that heart rates increased to normal rates after intervention with atropine in those patients and concluded that 5-FU bradycardia might be a hypervagotonia, as vagolytics abolished it in a previous report.[24,25] In our case, we also observed that the patient's heart rate increased to normal ranges after atropine injection, so hypervagotonia may be the reason.

5-FU-related cardiotoxicity is more frequent during the first treatment cycle.[26] However, our patient had not experienced any cardiac side effects while she was receiving the mFOLFOX6 regimen; nor was bradycardia observed with capecitabine treatment. It is possible that the changes in the activity of the DPD enzyme could play a role in this situation. Another point to consider is that the autonomic imbalance of 5-FU is triggered by irinotecan, which is a well-known chemotherapeutic agent that induces cholinergic effects.[27] Apart from all these hypotheses, capecitabine may be a safer fluoropyrimidine than continuous infusion of 5-FU.

We previously mentioned that this is also the first case report about the efficacy and tolerability of the XELIRI-aflibercept combination, which was not tested before in phase II-III trials. In our case, after failure of FOLFOX-bevacizumab treatment, aflibercept-FOLFIRI therapy was planned, but could not be given due to serious symptomatic bradycardia.

Although XELIRI is an effective regimen for the treatment of mCRC, standard XELIRI regimen was found to be associated with high grades of gastrointestinal toxicity and lower PFS times compared to FOLFIRI in phase III BICC-C trials.[28] Following these results, standard XELIRI was not a recommended alternative to the FOLFIRI regimen. In contrast, a phase III second-line AXEPT trial demonstrated that mXELIRI with or without bevacizumab was non-inferior to FOLFIRI and was well-tolerated. In the AXEPT trial, mXELIRI included reduced irinotecan and capecitabine dosages, as irinotecan and capecitabine were administered in doses of 200 mg/m^2 and 1600 mg/m^2, respectively. Therefore, in contrast to XELIRI regimen, the mXELIRI regimen could be an alternative to the standard FOLFIRI as a second-line backbone therapy for metastatic colorectal cancer.[12]

A clinical trial with XELIRI-aflibercept therapy is not yet available. However, a phase I study recently evaluated the combination of capecitabine and aflibercept as three weekly cycles among refractory mCRC patients. They reported two-month PFS rates as 72% and defined this combination as tolerable and efficacious.[29] Similarly, the addition of irinotecan to capecitabine-aflibercept doublet did not increase serious adverse events in our patient and disease control was successfully provided during a significantly longer period. A progression-free survival time of 12 months in our patient was a respectable result and

mXELIRI-aflibercept combination seems to be an alternative regimen for CRC patients.

In conclusion, this is the first case report that shows replacing capecitabine with infusional 5-FU might be an option for some patients experiencing 5-FU-related sinus bradycardia. However, oncologists should arrange the treatment plan according to the risk/benefit ratio after cardiac side effects. Aflibercept may be combined with an mXELIRI regimen and may be an alternative for patients who refuse port catheter placement or who are not able to receive infusional-5-FU due to adverse side effect

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Olgu Sunumu / Case Report

IL-12Rβ1 Deficiency Presenting with BCG Lymphadenitis: A Case Report

BCG Lenfadeniti ile Başvuran Kalıtsal IL-12Rβ1 Eksikliği; Olgu Sunumu

[1]Yalcın Kara, [1]Seher Tekeli, [1]Mahmut Can Kızıl, [2]Sumeyye Koc, [3]Serkan Belkaya, [4]Sabiha Sahin, [2]Koray Harmanci, [1]Omer Kilic, [5]Ener Cagri Dinleyici

[1]Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Infectious Diseases, Eskişehir, Turkey

[2]Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Immunology and Allergy Diseases, Eskişehir, Turkey

[3]Bilkent University, Department of Molecular Biology and Genetics, Ankara, Turkey

[4]Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Emergency Care, Eskişehir, Turkey

[5]Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Intensive Care, Eskişehir, Turkey

Abstract

Mendelian susceptibility to mycobacterial disease (MSMD) is a primary immunodeficiency disease characterized by a greater propensity for infection development with weakly-virulent mycobacterial strains and various intracellular pathogens including salmonella. After receiving the Bacille-Calmette-Guérin (BCG) vaccine, patients typically present to clinics with local or widespread mycobacterial infections, recurrent moniliasis, and salmonella infections. The pathogenesis of the disease is caused by a decrease in interferon-gamma production or an inadequate response to interferon-gamma release. The most common genetic deficiency in MSMD is interleukin-12 receptor deficiency. In this report we describe the case of an 11-month-old boy presenting with suppurative lymphadenitis after BCG vaccination who was found to have interleukin-12 receptor β1 deficiency by mutation analysis. We emphasize that MSMD should be investigated in patients who develop local or systemic mycobacterial infections after receiving the BCG vaccine.

Keywords: BCG lymphadenitis, mycobacterial infection, primary immune deficiency

Özet

Mikobakteri enfeksiyonlarına karşı Mendelyan yatkınlık, zayıf virülan mikobakteri suşları ve Salmonella gibi çeşitli hücre içi patojenlere duyarlılık ile karakterize bir primer immün yetmezlik hastalığıdır. Hastalar genellikle Bacille Calmette-Guerin aşısı sonrası gelişen lokal veya yaygın mikobakteri infeksiyonları, tekrarlayan moniliazis ve salmonella infeksiyonları ile kliniklere başvururlar. Hastalığın patogenezinden azalmış interferon gama üretimi yada interferon gamaya yetersiz yanıt sorumludur. İnterlökin-12 reseptör β1 eksikliği mikobakteri enfeksiyonlarına karşı Mendelyan yatkınlıkta en sık görülen genetik eksikliktir. Burada Bacille Calmette-Guerin aşısı sonrası süpüratif lenfadenit gelişen ve mutasyon analizi ile interlökin-12 reseptör β1 defekti saptanan 11 aylık bir olgu sunulmaktadır. Bacille Calmette-Guerin aşısı sonrası gelişen lokal veya sistemik mikobakteri infeksiyonlarında IL-12 reseptör β1 eksikliği göz önünde bulundurulmalıdır.

Anahtar Kelimeler: BCG, IL-12Rβ1, lenfadenit, mikobakter

Correspondence:
Yalçın KARA
Eskisehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Infectious Diseases, Eskişehir,Turkey
e-mail: dryalcinkara@hotmail.com

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1. Introduction

Mendelian susceptibility to mycobacterial disease (MSMD) was clinically defined in the 1950s as a rare disease, and its genetic etiology was discovered in 1996. The pathogenesis of the disease is associated with decreased interferon (IFN) production or insufficient response to its release. A mutation in any of the genes encoding the essential proteins of the type 1 cytokine cascade may lead to the development of this deficiency [1]. So far, nine autosomal (IFNGR1, IFNGR2, IL-12B, IL-12R1, STAT1, IRF8, ISG15, TYK2, and RORC) and two X-linked (NEMO, CYBB) genes have been identified as culprits of MSMD [2-5]. Interleukin (IL) - 12 is a cytokine that promotes the production of IFNs from T cells and natural killer cells, which boost immunity against intracellular bacteria, such as *mycobacteria and salmonella*. Therefore, the IL-12/IFN-axis is critical in human immunity against *mycobacteria* [6-7]. In such cases, infections with weakly-virulent non-tuberculosis *mycobacteria and salmonella* strains are possible [8-9]. Following the administration of the Bacille-Calmette-Guérin (BCG) vaccine, various adverse events may occur, ranging from regional reactions (such as lymphadenitis) to disseminated BCG infection [2]. The most common genetic deficiency in MSMD has been identified as IL-12R1 deficiency. We present a case of lymphadenitis development following BCG vaccination and the ensuing investigation of its cause, which ultimately yielded IL-12R1 deficiency–discovered through mutation analysis.

2. Case Report

An 11-month-old girl was brought in with complaints of swelling, redness, and discharge under her left armpit. The BCG vaccine had been applied when she was 2 months old (as per the routine schedule), and the complaints of armpit swelling had developed at 6 months of age. She was given oral antibiotic treatment when she first applied to a healthcare facility, with a diagnosis of acute lymphadenitis, but the symptoms did not improve with said treatment. Our physical examination identified a BCG vaccination scar on the left arm and a 2x2 cm ulcerated, draining, painless lymphadenopathy in the anterior axillary region on the same side (Figure 1). Other system examinations were unremarkable. The tuberculin skin test measured 11 mm of induration. In the laboratory analyses, Hb was 11.3 g/dL, leukocyte count was 9.450 / mm3 (neutrophil 2660 / mm3, lymphocyte 5.830 / mm3) and platelet count was 299.000 / mm3 Other viral and bacterial tests, including Human Immunodeficiency Virus (HIV) were negative. Chest radiography and abdominal ultrasonography revealed no apparent pathologies. The lymph node was biopsied using fine needle aspiration, and acid-resistant bacteria were not found in the biopsy material when stained with Erlich-Ziehl-Nielsen. The polymerase chain reaction for *mycobacterium tuberculosis* was negative, and there was no growth in the culture performed with Löwenstein–Jensen medium. A lymph node histopathological examination revealed several lymphoid tissue fragments and lymphoid cells. Immunoglobulin G, A, M, E levels and immunodeficiency features in lymphocyte subgroups were all within reference ranges for age. Nitroblue tetrazolium (NBT) was normal. A mutation in the IL12R1 gene was discovered with a sequence analysis to assess MSMD (Figure 2). The parents were third-degree consanguineous, and the mother had no known medical history other than Familial Mediterranean Fever. During the patient's six-month follow-up, ulceration and lymphadenopathy in the skin above the lymph node regressed without anti-tuberculosis treatment (Figure 3), and no additional problems were observed.

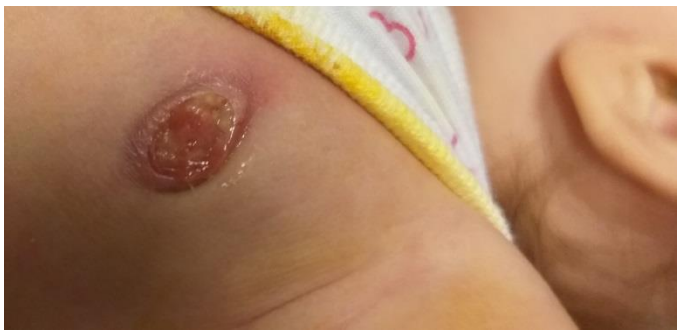

Figure 1. Ulcerated lymphadenopathy in the anterior axillary region

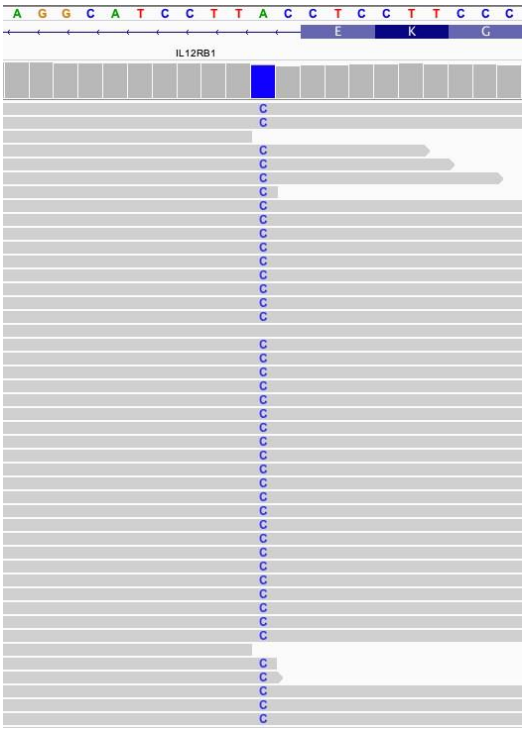

Figure 2. Genetic Sequence Analysis

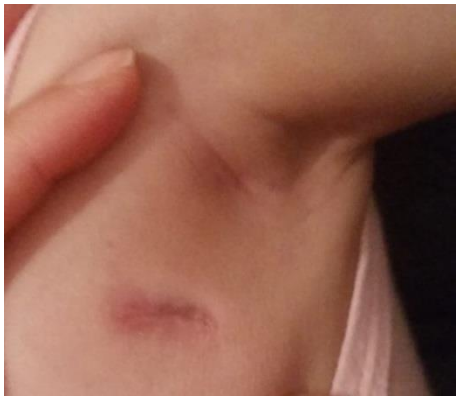

Figure 3. Post Treatment Picture of Axillary Lymphadenopathy

3. Discussion

The BCG vaccine is one of six vaccines included in the World Health Organization's expanded vaccination program. BCG, the origin of the vaccine, is a *mycobacterial* member of the *mycobacterium tuberculosis* complex. This vaccine is currently being used actively in Turkey, similar to many other countries. It is known that the incidence of significant side effects is very low in individuals with healthy immune systems, barring the relatively higher frequency of local reactions, such as cellulitis, abscess, and rarely, suppurative lymphadenitis. Regional lymphadenitis (BCG-itis) or widespread infection involving lymph nodes, lungs, kidneys, spleen and other organs (BCG-osis) may develop after BCG vaccination in patients with underlying cellular immune deficiency [10]. BCG lymphadenitis is a common development in MSMD patients in countries where the vaccine is administered [6,11]. In a large study of 141 patients with IL-12R1 deficiency from 30 countries, it was discovered that 84 of the 108 patients who had received the BCG vaccine had developed BCG-related infection, with 17 of the cases being local infections [2]. In our case, the BCG vaccine was administered according to the routine vaccination schedule (in the second month), and regional suppurative lymphadenitis developed approximately 4 months after. Infection with *mycobacterium tuberculosis* has been observed in a small number of MSMD patients, as have infections with candida, *klebsiella, nocardia, paracoccidioidomyces, histoplasma and leishmania*, which are microorganisms with pathogenesis similar to that of mycobacteria [2, 12–13]. In contrast to *Salmonella* infections, *mycobacteria* infections do not reoccur. A BCG vaccination study conducted by Fieschi et al., infection was reported in 36 of 63 patients diagnosed with IL-12R1 deficiency after the vaccination, but no mycobacterial infection was observed in any of these patients. However, *mycobacterial* infections were later reported in 12 of the 27 patients who had not developed an infection immediately after BCG vaccination [14]. BCG vaccine or previous disease has been shown to protect against mildly-virulent *mycobacterial* infections [2,3]. As per the last follow-up, our patient, who was 18 months old at the time of writing, did not develop any *mycobacterial* infections. With early diagnosis and treatment, patients with IL-12R1 deficiency have good clinical prognosis. Diagnosis of IL-12R1 deficiency, the most common genetic defect in MSMD can be made by determination of IL-12R1 expression on the peripheral blood lymphocyte surface (less than 1%) by flow cytometry after in-vitro stimulation with phytohemagglutinin. However, it is critical to perform mutation analysis in order to both identify the disease and provide genetic counseling to the family [15]. In our patient, whose mother and father were third-degree relatives, homozygous NM 005535.3: c.1791 + 2T> G: p. Ala573Leufs * 22 mutations in the IL-12RB1 gene were discovered as a result of whole-exome sequencing analysis. Many studies have found that this essential splice site mutation is pathogenic, causing genetic susceptibility *to mycobacteria, salmonella and klebsiella* infections [2]. New mutations and clinical diversity of the disease make genetic investigations crucial in societies where consanguineous marriage is common, as is the case in our country [16].

Patients with local or widespread mycobacterial infections that have developed after BCG vaccination should be evaluated for immune deficiency. As awareness of the clinical features of IL-12R1 deficiency increases, these patients will be diagnosed earlier and easier, especially in countries where consanguineous marriage is prevalent and BCG vaccine is routinely administered.

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Olgu Sunumu / Case Report

Erişkin Hastada Meckel Divertikülüne Bağlı İnce Barsak Volvulusu: Olgu Sunumu

Small Intestine Volvulus Due to Meckel's Diverticulum in an Adult Patient: A Case Report

[1]Bilal Turan, [1]Bülent Sultanoğlu, [2]Mehmet Zafer Sabuncuoğlu

[1]Dr. Ersin Arslan Eğitim ve Araştırma Hastanesi Genel Cerrahi Kliniği, Gaziantep, Türkiye

[2]Süleyman Demirel Üniversitesi Tıp Fakültesi Genel Cerrahi Anabilim Dalı, Isparta, Türkiye

Özet

Erişkinlerde ince bağırsak volvulusu (İBV) çok nadir görülen bir hastalıktır ve hayatı tehdit eden bir cerrahi acildir. Bu nedenle İBV'nin erken teşhisi ve tedavisi önemlidir. Meckel divertikülü sindirim sisteminin en sık görülen malformasyonudur. Gastrointestinal kanama, Meckel divertikülünün çocuklarda %40,2'ye varan insidansı ile en sık görülen prezentasyonudur. Bununla birlikte, bağırsak tıkanıklığı yetişkinlerde en sık görülen belirtidir ve semptomatik Meckel divertikülü vakalarının %14 ila %40'ını oluşturur. Meckel divertikülüne sekonder ince barsak volvulusu ise nadirdir. İBV ve özellikle meckel divertikülüne sekonder İBV ile ilgili bazı makaleler yayınlanmış olsa da bunların çoğu vaka raporlarıdır. Bu sunumda, daha önce cerrahi öyküsü olmayan ve ileus tablosuyla acil ameliyata alınan ve eksplorasyonda Meckel divertikülü nedeniyle ince barsak volvulusuna sekonder barsak obstrüksiyonu olduğu görülen 40 yaşında bir kadın hastayı sunuyoruz. Ayrıca bu vakada meckel divertikülü uterusa yapışık ve sağ over kisti ve inflame tuba mevcuttu. İnce barsak volvulusuna ovaryan yapıların etyoloji olarak gösterildiği literatürde bir vaka tespit edildi. Amaç, tanı ve klinik yönetimi tanımlamak ve literatürü gözden geçirmektir.

Anahtar Kelimeler: İleus, meckel divertikülü, over kisti, volvulus

Abstract

Small bowel volvulus (SBV) in adults is a very rare disease and it is a life-threatening emergency that requires surgery. Therefore, early diagnosis and treatment of SBV is important. Meckel's diverticulum is the most common malformation of the digestive tract. Gastrointestinal bleeding is the most common presentation of Meckel's diverticulum with an incidence of up to 40.2% in children. However, intestinal obstruction is the most common symptom in adults, accounting for 14% to 40% of symptomatic Meckel's diverticulum cases. Small bowel volvulus due to Meckel's diverticulum is rare. Although some articles have been published about SBV secondary to meckel's diverticulum, most of them are case reports. We present a 40-year-old female patient who had no previous surgical history and underwent emergency surgery due to ileus and had a bowel obstruction secondary to small bowel volvulus due to Meckel's diverticulum on exploration. In this case, Meckel's diverticulum was attached to the uterus, and the patient had right ovarian cyst and inflamed tuba on exploration. One case in which ovarian structures were shown as the etiology of small bowel volvulus was reported in the literature. The aim of this case report is to describe the diagnosis and clinical management and to review the literature.

Keywords: Ileus, Meckel's diverticulum, ovarian cyst, volvulus

Correspondence:
Bilal TURAN
Dr. Ersin Arslan Eğitim ve Araştırma Hastanesi Genel Cerrahi Kliniği, Gaziantep, Türkiye
e-mail: bturan117@gmail.com

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1. Giriş

Erişkinlerde ince bağırsak volvulusu (İBV) çok nadir görülen bir hastalıktır ve hayatı tehdit eden bir cerrahi acildir. Bu nedenle İBV'nin erken teşhisi ve tedavisi önemlidir. (1).

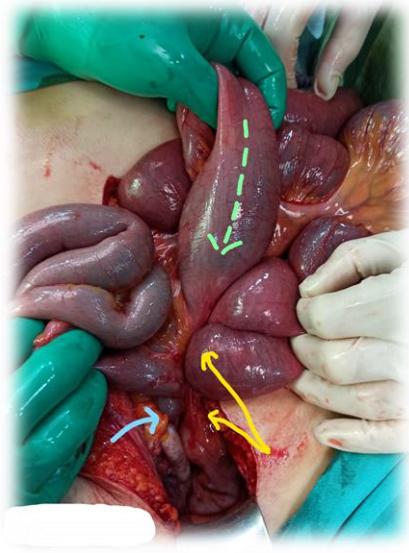
Meckel divertikülü sindirim sisteminin en sık görülen malformasyonudur. Gastrointestinal kanama, Meckel divertikülünün çocuklarda %40,2'ye varan insidansı ile en sık görülen prezentasyonudur. Bununla birlikte, bağırsak tıkanıklığı yetişkinlerde en sık görülen belirtidir ve semptomatik Meckel divertikülü vakalarının %14 ila %40'ını oluşturur. Diğer komplikasyonlar divertikülit, perforasyon ve tümördür. Genel popülasyonda Meckel divertikülünün prevalansı %0,3 ile %2,9 arasında değişse de, gecikmiş bir tanı yaşamı tehdit eden olaylara yol açar. (2,3).

Meckel divertikülüne sekonder ince barsak volvulusu ise nadirdir. İBV ve özellikle meckel divertikülüne sekonder İBV ile ilgili bazı makaleler yayınlanmış olsa da bunların çoğu vaka raporlarıdır.(1,4,5).

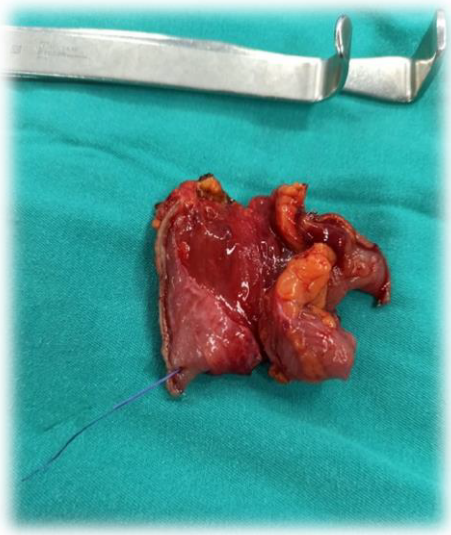
Bu sunumda, daha önce cerrahi öyküsü olmayan ve ileus tablosuyla acil ameliyata alınan ve eksplorasyonda Meckel divertikülü nedeniyle ince barsak volvulusuna sekonder barsak obstrüksiyonu olduğu görülen 40 yaşında bir kadın hastayı sunuyoruz. Ayrıca bu vakada meckel divertikülü uterusa yapışık ve sağ over kisti ve inflame tuba mevcuttu. İnce barsak volvulusuna ovaryan yapıların etyoloji olarak gösterildiği literatürde bir vaka tespit edildi.(6). Amaç, tanı ve klinik yönetimi tanımlamak ve literatürü gözden geçirmektir.

2. Olgu Sunumu

40 yaşında kadın hasta 1 gündür ani başlangıçlı karın ağrısı, karında şişlik, bulantı ve kusma şikayetleri acil servise başvurdu. Biline sistemik bir hastalığı yoktu ve daha önce geçirilmiş cerrahi öyküsü yoktu. Başvuru sırasında nabzı dakikada 100 atış, kan basıncı 128/74 mmHg ve vücut ısısı 36.7°C idi. Fizik muayenesinde batında distansiyon, alt kadranlarda belirgin olmak üzere yaygın hassasiyet, rebound ve defansı vardı. Rektal tuşede rektum boş olarak tespit edildi. Laboratuvar incelemesinde lökositoz saptandı (19.9 × 10 9/L). Hemoglobin 9,2 g/dL, kreatin 2,21 mg/dL, C-reaktif protein konsantrasyonu 166,5 mg/ml . İlk bakıda acil serviste çekilen bilgisayarlı tomografide (BT) ince barsak anslarında uzun segment genişleme ve hava sıvı seviyesi izlendi. İnce barsak ansı en geniş yerinde 41 mm çapında ölçüldü. Geçiş zonu ve kitle ayırt edilemedi. Mevcut bulgularla hastaya laparotomi yapıldı.



Resim 1. Mavi ok: Over kisti ve inflame tuba, Sarı ok: Uterus ve uterusa yapışık meckel divertikül segmenti, Yeşil ok: Dilate, volvule olan ince barsak segmenti ve mezosu-eksplorasyon esnasında ve resimlemek için kısmen açılmış vaziyette-



Resim 2. Meckel divertikülü ile birlikte kombine segmenter ince barsak rezeksiyonu materyali

Laparatomide uzunluğu 5 cm, genişlemiş, kalın duvarlı, iskemik ve etrafında aksiyel torsiyonel ince barsak segmenti yer alan Meckel divertikülünün ileoçekal valvden 80 cm uzaklıkta olduğu görüldü. Ayrıca meckel divertikülü uterusa yapışık ve sağ over kisti ve inflame tuba mevcuttu. (Resim 1, Resim 2). Segmenter ince barsak rezeksiyonu ile kombine divertikülektomi gerçekleştirildi. histolojik incelemede Meckel divertikülünde ince barsak mukozası ve süpüratif inflamasyon saptandı. Hasta postoperatif 1 hafta komplikasyonsuz taburcu edildi. Hastanın kısa poliklinik takibinde takibinde herhangi bir komplikasyon olmadı.

3. Tartışma ve Sonuç

İnce barsak volvulusu, barsak anslarının kendi mezenteri ekseni etrafında anormal bir şekilde bükülmesi sonucu mezenterik damarların bükülmesine ve tıkanmasına neden olarak barsak tıkanıklığı, venöz kanlanma bozukluğu, iskemi, nekroz ve perforasyona neden olur. İnce barsak volvulusu yenidoğanlarda ve genç erişkinlerde daha sık görülür ve erişkinlerde çok nadirdir. (7,8).

İnce bağırsak volvulusu, etiyolojisine göre primer ve sekonder olarak ikiye ayrılır Primer İBV, altta yatan herhangi bir belirgin neden olmaksızın mezenter temelinde ince barsak segmentinin torsiyonu olarak tanımlanır. Sekonder SBV, konjenital malrotasyon, postoperatif yapışıklıklar, tümörler, gebelik ve divertiküler hastalık gibi edinilmiş bir durumun varlığında ortaya çıkar. (1). Herhangi bir spesifik semptom, klinik bulgu veya anormal laboratuvar bulgusu yoktur. Obstruksiyon bulguları, ince bağırsak volvulusunun en yaygın klinik belirtisidir. Görüntüleme yöntemleri de her zaman tanı için yeterli bilgi sağlayamadığından tanıda hayati tehlike oluşturabilecek gecikmeler olabilir. (6,7). Yüksek morbidite ve mortalite ile ilişkili olan ince bağırsakta iskemiyi önlemek için erken tanı ve hızlı cerrahi şarttır. Aslında, literatürde daha önce hiçbir rapor İBV vakalarında nekroz ile ilişkili risk faktörlerini tanımlamamıştır. (1,4,5).

Karın bulguları ile başvuran jinekolojik patoloji, ayaktan hastalarda yaklaşık %1.5 ve acil serviste %5 civarındadır. Over kistini komplikasyonuna bağlı bağırsak tıkanıklığı nadirdir ve genellikle yenidoğanlarda (%3) görülür, yenidoğanlarda 19 vaka ve yetişkinlerde 2 vaka bildirilmiştir. Bağırsak komplikasyonları esas olarak yumurtalık kistinin boyutu 10 cm'den fazla olduğunda ortaya çıkar ve bu da acil cerrahi gerektirir. Bağırsak komplikasyonlarının nedeni olarak iki mekanizma öne sürülmüştür. Bunlardan birincisi, torsiyona neden olan yapışıklıklar ve ikincisi, büyük kistlerin basınç etkileridir. Over kisti ve meckel divertikülünün birlikte olduğu ince barsak volvulusu bir vakada bildirilmiş olup, bu vakada 10 cm lik dev over kistinin internal herniasyonundan

bahsedilmektedir. (6). Bizim vakamızda meckel divertikülü uterusa yapışık ve inflame tuba ve küçük over kisti mevcuttu ve İBV bu yapışık alandan kaynaklanmaktaydı.

Meckel divertikülünün ortalama uzunluğu 2,9 cm olup, meckel divertikülüne sekonder İBV vaka raporlarında meckel divertikülünün 10 cm ve üzeri olduğu görülmektedir. (2). Bizim vakamızda meckel divertikülü 4 cm olarak ölçüldü.

Hastalığın sonucu esas olarak erken tanı ve müdahaleye dayanmaktadır. Mortalite, nekroze olmayan ince bağırsak volvulusunda yaklaşık %5.8-8'dir ve nekroze bağırsakta büyük ölçüde %20-100'e yükselir. Ameliyat sonrası kısa bağırsak sendromuna yol açan kangreni önlemek için ince bağırsak volvulusunda erken tanı ve laparotomi ile müdahale son derece önemlidir. Daha önce geçirilmiş cerrahisi olmayan ve ileus tablosu ile başvuran hastalarda meckel divertikülü akılda tutulmalıdır. Vakamızda görüldüğü gibi meckel divertikülü ve ovaryan yapıların kompleks olması ve buna sekonder İBV görülmesi gibi sürpriz sonuçlar uç nokta da olsa göz ardı edilmemelidir.

- *30 Kasım - 4 Aralık 2021 tarihlerinde Antalya'da Susesi Kongre Merkezi'nde düzenlenen 1. Uluslararası Türk Kolorektal Cerrahi&18.Türk Kolon ve Rektum Kongresi'nde O-190 bildiri numarası ile Sözel Bildiri olarak sunulmuştur.*

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Derleme / Review

Çocuklarda Yeşil Çay Kullanımının Dental ve Periodontal Sağlığa Etkileri

Effects of Green Tea Use on Dental and Periodontal Health in Children

Handan Vural, Sacide Duman

İnönü Üniversitesi Diş Hekimliği Fakültesi Pedodonti Anabilim Dalı, Malatya, Türkiye

Abstract

Oral hygiene is essential for prevention of dental caries and periodontal diseases. If mechanical cleaning cannot be performed, mouthwashes, which have antimicrobial, anti-inflammatory and antiplaque effects, are of great importance in providing oral hygiene. The healing effects of polyphenols in content of green tea, which is a common beverage, have been reported in many studies. Epigallocatechin-3-gallate (EGCG) is major polyphenol found in green tea. It is most biologically active with its antioxidant, antiinflammatory, antibacterial and anticarcinogenic properties.In this review, current literature information has been compiled dental and periodontal effects of green tea use in children. Green tea; Chlorhexidine etc. features such as wide age range in its use, mostly no side effects, no limited usage period, no harm in swallowing. are its main advantages over mouthwashes. Green tea, an easy-to-find, low-cost herb for oral healthy can be a beneficial agent.

Keywords: Child, Dentistry, Mouthwash, Green tea

Özet

Diş çürüğü ve periodontal hastalıkların önlenmesinde öncelikle iyi bir oral hijyen gereklidir. Antimikrobiyal, antienflamatuar ve antiplak özellikli gargaralar mekanik temizleme yapılamadığı durumlarda oral hijyen sağlamada büyük öneme sahiptir. Yaygın bulunan bir içecek olan yeşil çayın içeriğindeki polifenollerin iyileştirici etkileri birçok çalışmada bildirilmiştir. Epigallokateşin gallat (EGCG), yeşil çayda bulunan başlıca polifenoldür. Antioksidan, antienflamatuar, antibakteriyel ve antikanserojenik özellikleriyle biyolojik olarak en aktif olanıdır. Yeşil çayın ağız ve diş sağlığına etkilerine yönelik birçok çalışma yapılmıştır. Bu derlemede yeşil çayın çocuklarda kullanımının dental ve periodontal sağlığa etkileriyle ilgili güncel literatür bilgileri derlenmiştir. Kullanımında yaş aralığının geniş olması, çoğunlukla herhangi bir yan etkisinin olmaması, sınırlı kullanım süresinin olmaması, yutulmasında bir sakınca olmaması gibi özellikler yeşil çayın klorheksidin vb. gargaralara karşı başlıca avantajlarıdır. Kolay bulunabilen, düşük maliyetli bir bitki olan yeşil çay sağlıklı bir ağız için faydalı bir ajan olabilir.

Anahtar Kelimeler: Çocuk, Diş Hekimliği, Gargara, Yeşil çay

Correspondence:
Handan VURAL
İnönü Üniversitesi Diş Hekimliği Fakültesi Pedodonti Anabilim Dalı, Malatya, Türkiye
e-mail: handan.yildar@gmail.com

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1. Giriş

Bitkiler, uygarlık tarihinin ilk zamanlarından beri hastalıkları tedavi etmekte yaygın olarak kullanılmıştır. 21. yüzyılda ekonomik, sosyal ve çevresel değişimlerle beraber bitkisel ürünlere ilgi giderek artmaktadır. Dünya Sağlık Örgütü'ne göre, dünya nüfusunun %80'inden fazlası, temel sağlık ihtiyaçlarında başta bitkiler olmak üzere, geleneksel ilaçlara daha sık güvenmektedir (1). Uzun zamandır bitkiler ve doğal maddeler terapötik ilaç kaynağı olarak, ağrı kesici, ateş düşürücü, antimikrobiyal, antiinflamatuar, antikanser vb. özellikleriyle fitofarmakoljide kullanılmaktadır. Kurkumin, yüksük otu, aleo vera, tarçın, çemen otu, Yerbe Mate, tarhun, kekik, yeşil çay gibi pek çok bitkinin genel sağlığa olan katkıları bilimsel olarak kanıtlanmıştır (1).

Dental ve periodontal doku proflaksisinin en başında ağız hijyeni gelmektedir. Tek başına düzenli ve doğru fırçalamayla çürük ve periodontal hastalık insidansı ciddi düzeyde gerilemektedir. Ancak fırçalamanın etkinliğinde fırçadan macuna, fırçalama süresinden fırçalama tekniğine, kişinin motor becerisine kadar birçok faktör etkilidir. Özelikle çocuklarda, mental ya da bedensel engelli bireylerde temel fırçalama etkililiğini sağlamak çok daha zordur. Bu durumda fırçalamayla beraber yardımcı metotlar da önem kazanmaktadır. Kimyasal ajanlar, mekanik plak kontrolünün etkisini arttırmak için giderek daha fazla kullanılmaktadır. Doğal içerikli ağız sağlığı ürünlerinin kullanıma hazır ambalajlı olarak doğrudan tüketiciye sunulması, sentetik ürünlere kıyasla bitkisel/doğal ürünlere talebi arttırmıştır.

Günümüzdeki doğal olana karşı artan bu ilgi, bilimsel çalışmaların yol göstericiliğinde desteklenmeli ve denetlenmelidir. Çağdaş bilimsel çalışmalar, antik ve geleneksel tıbbın bilgilerinin doğruluğunu ve güvenilirliğini aydınlatırken, bilinen bitki ve karışımlarının farklı kullanım alanlarındaki etkilerini ve etki mekanizmalarını da ortaya koymaktadır. Bu şekilde şifalı bitkiler başta olmak üzere birçok medikal bitkinin etkinliği, toksisitesi, etkin konsantrasyonları vb özellikleri açıklanabilmektedir.

Bu makalenin amacı bilimsel popülerliği hızla artan yeşil çayın çocuklarda kullanımının dental ve periodontal sağlığa etkileriyle ilgili güncel literatür bilgilerini derlemektir.

Yeşil Çay

Çay (Camellia sinesis), yaz, kış her dem yeşil ağaç ya da çalı toplulukları olan Theaceae familyasının alt türüdür. Camellia sinesis (C. sinesis), Hindistan, Çin, Sri Lanka, Japonya, Endonezya, Pakistan, Türkiye, Kenya, Malawi ve Arjantin'de yetiştirilen, çoğunlukla soğuğa dayanıklı yüksek yerlerde ve tropik iklimlerde yetişen bir bitkidir (2, 3). C. sinesis'in yapraklarından hazırlanan çaylar, yaprakların işlenme yöntemine veya hasat edilen yaprakların bulundukları gelişim aşamasına göre siyah (fermente edilmiş), yeşil (fermente edilmemiş) ve oolong (yarı fermente edilmiş) çayları olarak farklı türlere ayrılmıştır. Dünya çapında üretilen ve tüketilen çayın yaklaşık %77'si siyah, %21'i yeşil ve %2'ye yakını oolong'dur (4).

Yeşil çayın kuru ağırlığının yaklaşık %20'sini proteinler , %7'sini karbonhidratlar (selüloz, pektin, glikoz, fruktoz) %2,5 aminoasitler, ve %5'ini ise mineral ve diğer elementler (yağlar, vitaminler [B,C,E], sterol, ksantik bazlar [kafein, theophylline], pigmentler ve uçucu bileşikler) oluşturmaktadır (5).

Yeşil çay, içerisinde bulunan polifenollerin alt grubu olan flavonoidler özellikle kateşinler ve kateşin türevlerinden zengindir. Yeşil çay, siyah çay ve oolong çayından daha fazla kateşin içerir. Yeşil çay kateşinleri toplam kuru çay ağırlığının yaklaşık %33'ünü oluşturur. Epigallokateşin gallat (EGCG), epigallokateşin (EGC), epikateşin (EC) ve epikateşin gallat (ECG), yeşil çayda bulunan başlıca kateşinlerdir. EGCG antioksidan, antitümörijenik, antienflamatuar ve antianjiyojenik özellikleri nedeniyle oldukça dikkat çekmiştir (6). Ayrıca yeşil çayda en çok bulunan kateşindir (7). EGCG, kateşinler içinde en yüksek antioksidan etkiye sahip bileşiktir (8).

Yeşil Çayın Genel Sağlığa Etkileri

Yapılan birçok çalışmanın ortak noktası, yeşil çayın sağlığa potansiyel faydalarının çoğunun içeriğindeki polifenollerden kaynaklandığı yönündedir. Hayvan deneyleri, yeşil çay kateşinlerinin dejeneratif hastalıklara karşı koruyuculuğunu göstermektedir (9).

Çayın başlıca sağlığa etkileri şu şekilde sıralanabilir:

Antioksidan etkiye sahiptir (3,10,11). Çayın bu etkisi sayesinde çeşitli kardiovasküler hastalıklarda (Örn; ateroskleroz) önleyici özelliği olduğu iddia edilmiştir (11,12). ABD, Avrupa ve Birleşik Krallık'a ait çalışmaları inceleyen bir meta analizde günde üç fincan çay tüketiminin miyokard enfarktüs insidansını %11 azalttığını bildirmektedir (13).

Antiülseratiftir. Takabayashi ve ark.(14) kemirgenler ile yaptıkları çalışmada yeşil çay kateşinlerinin helicobacter pylori üzerinde inhibitör etkisi olduğu sonucuna varılmıştır. Yeşil çay ve kateşinlerinin helicobacter pylori enfeksiyonlarını azalttığını bildiren çalışmalar da vardır (14,15).

Antikarsinojen etkiye sahiptir. Kanser insidansını ve çeşitliliğini etkileye bilirliği, spesifik kanser türlerine ait klinik, epidemiyolojik ve hayvansal çalışmalarla desteklenmiştir (16-20).

Çağımızın en büyük problemlerinden biri olan obezitenin önlenmesinde yeşil çay tüketiminin etkili olduğu bilinmektedir. Düzenli çay tüketimi vücut yağ oranını, kolesterol seviyelerini düşürürken aynı zamanda antidiabetik ve antihipertansif etki de göstermektedir (21).

Antimikrobiyal ve antiviral etkileri vardır. Yapılan çalışmalar mikrobiyal ve viral enfeksiyonlarda yeşil çayın hem önleyici hem de tedavi edici potansiyelinin olduğunu göstermiştir (22).

Yeşil Çayın Ağız Sağlığına Etkileri

Çay katekşinlerinin antimikrobiyal, antioksidan vb. etkileri, yeşil çayın oral sağlık üzerine de etkinliğinin araştırılmasına kaynak olmuştur. Son yıllarda bitkisel/doğal ürünlere artan taleple beraber yeşil çay özütlü gargaralar, macunlar, oral spreyler gibi birçok dental bakım ürünü üretilmiştir.

Diş Çürüğü ve Dental Plak Üzerine Etkisi: Çayın bileşenindeki kateşinler, Streptococcus mutans (S. mutans) bakterileri tarafından üretilen, sükrozu glukana dönüştüren glukoziltransferaz enzimlerinin aktivitesini inhibe eder. Böylelikle S. mutans tarafından kolayca fermente edilen karbonhidrat (maltoz) oluşumunu engeller. Dolayısıyla bakteri üremesi ve asit üretimi engellenmiş olur (23,24).

Periodontal Dokularda Etkisi: Çay antimikrobiyal, antioksidan ve antikollogenaz etkileriyle periodontal dokularda iyileştirici özelliğe sahiptir (24-26). Ayrıca EGCG, osteoblastlarda bazı matriks metalloproteinazların ekspresyonunu azaltıp, osteoklast oluşumunu engelleyerek, periodontal hastalığı olan bireylerde alveolar kemik rezorpsiyonunu önleyebilir (26).

Halitozisde Etkisi: Yeşil çayın gargara olarak uzun süre kullanımı ağız kokusuna temelde sebep olan uçucu sülfür bileşiklerinin (VSC) seviyesini azaltır (27). EGCG ve yeşil çay ekstratları VSC üreten gram pozitif anaerobik Solobacterium moorei bakterisini inhibe ederek ve oral epitele yapışmasını engelleyerek ağız kokusunu azaltmaya yardımcı olur (28).

Oral Malignitelede Potansiyel Kemopreventif Etkisi: Yeşil çay ve EGCG sahip oldukları antioksidan, antianjiogenez, , antimikrobiyal aktivite, radyasyonun etkilerini azaltma, apoptozis ve hücre döngüsü regülasyonu özelliklerinin tümü sayesinde kemopreventif etki göstermektedir (29). Squamoz hücreli karsinomlarda yeşil çay ve EGCG'nin kanserli hücreleri inhibe ettiği sonucuna varılmıştır (30,31).

Diş Sert Dokusu Üzerine Koruyucu ve Onarıcı Etkisi: C. sinensis gibi Theaceae familyasındaki bitkiler, yapraklarında ve infüzyonlarında yüksek konsantrasyonlarda florür içerir (32). Yeşil çay, diş çürüklerini önlemek için topikal florür kaynağı olarak faydalıdır (33).

Yan Etkileri

Yeşil çay tüketiminin belirgin bir yan etkisi olmamakla beraber çeşitli minerallerin

metabolizmasını etkilemesi, hepatotoksisite ve aşırı tüketiminde kafein içeriğine bağlı yan etkilerinden söz edilebilir (34).

Yeşil çay bazı metal iyonlarının emilimini etkileyebilir (35). Uzun süre yeşil çay tüketimi demir emilimini azaltır ve bu durumdan özellikle "hem" olmayan demir etkilenir (36). Çinko emilimini azaltırken magnezyumun emilimini arttırır ve bakır emilimini görünür oranda değiştirmez (37).

Hayvan deneylerinde oral yoldan verilen yeşil çay ekstresinin (%85 EGCG içeren) median letal dozu yaklaşık 3-5 g/kg'dır (38). Yeşil çay ekstraktlarının hepatotoksiteye ilişkin riskleri hala tam olarak netleşmemiştir. 2008-2015 yılları arasını kapsayan bir meta analizin sonucunda yeşil çayın tek başına hepatotoksisiteye neden olduğuna dair kesinliğin olmadığı ancak çok yüksek dozlarda ve uzun süre yeşil çay ekstraktlarının kullanımının hepatotoksisite açısından riskli olduğu sonucuna varılmıştır (39).

Avrupa Gıda Güvenliği Otoritesi (EFSA) yayınladığı raporda "geleneksel şekilde hazırlanan yeşil çay infüzyonundan elde edilen kateşinler ve geleneksel yeşil çay infüzyonlarına eşdeğer bir bileşime sahip sulandırılmış içecekler, güvenlik varsayımına göre genel olarak güvenli kabul edilir" ifadeleriyle yeşil çayın tüketim güvenilirliği açıklanmıştır (39).

Çocuklarda Yeşil Çay Kullanımı

Klorheksidin (CHX) kimyasal etkinliği kanıtlanmış, en yaygın kullanılan antigingivit ve antiplak ajandır. CHX uzun etki süresi sayesinde tükürükteki mikroorganizma sayısını %90 oranında düşürmektedir. Fakat CHX!in uzun süre kullanımına bağlı olarak ağız dokularını boyama, tat kaybı, diş taşı oluşumu, tek taraflı veya çift taraflı parotis bezi şişmesi, mukozal ülserasyonlar, uzun dönemde oral florada değişim gibi bazı yan etkileri bulunmaktadır (40). C.sinensis, fitokimyasal ve farmakolojik özellikleriyle gargaralarda aktif bileşen olarak kullanılmaya mükemmel bir adaydır (41). Yeşil çayın ideal bir gargara olabileceği yönündeki düşünceler in vivo çalışmalarla da desteklenmiştir (42-44).

Yeşil çayla ilgili çocukların katılımcı olduğu çalışmalar çoğunlukla son 5-6 yıl içerisinde yoğunlaşmıştır. Güncel çalışmalara dair bilgiler Tablo 1'de sunulmuştur. İncelenen çalışmaların hiçbirinde kullanımına bağlı yan etkilerden bahsedilmemiştir.

Tablo 1. Çocuklarda yeşil çayla ilgili yapılan çalışmalara ait bilgiler

YAZAR VE YIL	HEDEF	KULLANILAN AJANLAR	KATILIMCI	SÜRE-MİKTAR	SONUÇLAR
Abdülmecid ve ark./2015(58)	Yeşil çay (Y.Ç) ve bal solüsyonlarının tükürükteki Streptococcus mutans (S.mutans) düzeyi üzerindeki etkisini değerlendirmek	Y.Ç Bal (gargara)	7-10 yaş 30 çocuk	Tek seferlik uygulama (2 dk)	Bal ve Y. Ç solüsyonları tükürük S. mutans sayısını etkili bir şekilde azalttı ($P < 0.05$).
Hambire ve ark./2015(56)	Y.Ç, sodyum florür (NaF) ve Klorheksidin (CHX) glukonat gargaralarının plak önleyici etkinliğini karşılaştırmak	%0.5 Y.Ç ekstresi, %0.05 NaF %0.2 CHX glukonat (gargara)	9-14 yaş 60 çocuk	2 hafta boyunca günde 2 kez (1 dk)	Plak ve diş eti skorları, deney gruplarında azaldı. Plak önleyici etkinlik tüm gruplarda gözlendi, en yüksek etki Y.Ç grubundaydı ($P < 0.05$). CHX glukonat ve çay, diş eti skorunda NaF'den daha iyi etkinlik gösterdi ($P < 0.05$). Tükürük pH artışı NaF ve Y.Ç'da CHX'den daha yüksek ve anlamlıydı. %0.5 C. sinensis özütünün etkinliği, %0.05 NaF ve %0.2 CHX glukonat ağız gargaralarına kıyasla daha fazladır.

Thomas ve ark./2016(46)	Y.Ç ve CHX gargaralarının antimikrobiyal etkinliğini S.mutans , Lactobacilli spp. Ve Candida Albicans'a karşı değerlendirmek ve karşılaştırmak .	%0.5 Y.Ç %0.2 CHX (gargara)	4-6 yaş 30 çocuk	2 hafta boyunca günde 1 kez	S. mutans sayısındaki azalmada, Y.Ç >CHX Lactobacilli spp.'de CHX> Y. Ç C. Albicans'a karşı ise istatistiksel anlamlı fark yok.
Ali ve ark./2019(43)	Y.Çın ağız gargarasının antimikrobiyal etkinliğini S. mutans ve Lactobacilli spp.'ye karşı CHX ile karşılaştırmak	(% 0.125) CHX Renkli su (%0,5) Y.Ç (gargara)	60 -71 ay 42 çocuk	2 hafta boyunce günde 1 kez	Hem cHX hem de Y. Ç ağız çalkalama suları, S. mutans ve Lactobacilli spp. koloni sayılarında istatistiksel olarak anlamlı bir düşüş gösterdi . (P< 0,001 ve <0,001),
Goyalve ark./2017(49)	Y.Ç kateşininin çocuklarda koloni sayısı S. mutans üzerindeki antimikrobiyal etkinliğini değerlendirmek	%0.25 w/v kateşin çözeltisi (gargara)	7-12 yaş 30 çocuk	2 hafta boyunca günde 2 kez	Y. Ç kateşinin S. mutans'a karşı ağız yıkamada etkili olduğunu (p <0,001) ve tükürüğe kıyasla plakta daha iyi etki.
Rahul J Hegde , Shamika Kamath/2017(44)	Streptococcus mutans ve Lactobacillus'un tükürük sayısını azaltmada CHX ve kombinasyon (CHX ve NaF) agargarasının etkinliğini Y.Ç özütü (%0,5) ile karşılaştırmak	CHX (%0,12) CHX ve NaF Y.Ç özütü (%0,5) (gargara)	8-12 yaş 75 ç	2 hafta boyunca günde 1 kere	Üç çalışma grubunun tümünde S. mutans ve lactobacilli sayısında istatistiksel olarak anlamlı bir azalma var. CHX daha fazla azalma kombinasyon ve Y. Ç arasında anlamlı fark yok
Kamalaksharappa ve ark./2018(54)	Probiyotik ve yç gargaralarının tükürük ph'sı üzerindeki etkilerinin değerlendirmek	Probiyotik Y.Ç (garagara)	6-8 yaş 40 çocuk	1 ay boyunca günde 1 kez	Her iki guruptada ph alkali yöne doğru artmıştır.
Ahmadi ve ark./2019(59)	Y.Ç jeli ve gargarasının S.mutans ve Lactobacillus'un tükürük seviyesi üzerindeki etkinliğini karşılaştırmak.	%0.5 Y.Ç gargarası Jel %0.5 Y.Ç jeli ile dişlerini fırçalamaları istendi.	12-18 yaş 30 çocuk	2 hafta boyunca günde iki kez	Y. Ç ağız gargarası ve jelinin, bir dizi tükürük S. mutans kolonisinde önemli bir azalma ile sonuçlandığını göstermiştir . Y. Ç ağız gargarası jelden daha etkiliydi. Ancak aradaki fark istatistiksel olarak anlamlı değildi.
Salama ve Alsughier /2019(50)	Okul öncesi çocuklarda Y.Ç gargarasının S. mutans'ın tükürük seviyesi üzerindeki etkinliğini değerlendirmek	Y.Ç (gargara)	4-5 yaş 40 çocuk	4hafta boyunca günde 2 kez	Çalışma grubu, S. mutans sayılarında kontrol grubuna göre daha yüksek bir düşüş gösterdi . p <0,001
Manikandan ve ark../ 2020(55)	Probiyotik ve Y.Ç ağız gargarasının tükürük ph'ı üzerindeki etkinliğini değerlendirmek	Probiyotik Y.Ç (garagara)	6-8 yaş 40 çocuk	1 ay boyunca günde 1 kez	Her iki guruptada ph alkali yöne doğru artmıştır.
Vilela ve ark../2020(24)	EGCG ve yeşil çayın (Y.Ç) antimikrobiyal etkinliğini değerlendirerek CHX ve distile su ile karşılaştırmak	4000 Ug/Ml EGCG Yeşil Çay (Y.Ç) %0.12 Alkolsüz CHX Distile Su (gargara)	5-12 47 çocuk	Tek sefer (1dk)	Başlangıçtaki S.mutans streptokoklar azalma yüzdesi: CHX>ECGC>Y.Ç>Distile su .Lactobasillusl azalma yüzdesi: EGCG>Y.Ç>CHX>Distile su
Deshpande, ve ark./2021(57)	Y.Ç (YÇ), YÇ artı zencefil (Y + Z) ve CHX gargaranın (CHX) çocuklarda plak ve diş eti iltihabı önleyici etkilerini karşılaştırma	%0,2 alkolsüz chx %5 YÇ YÇ + Z (gargara)	10-14 yaş 60 çocuk	1 ay boyunca günde 2 kez	Y.Ç artı zencefil içeren gargara, ardından Y.Ç ve CHX içeren gargara kullandıktan sonra çocuklarda plak skoru ve dişeti indeksi skorunda önemli bir azalma.

Ferrazzano/2021 (48)	Tükürükteki S. mutans ve Lactobasillus düzeylerini düşürmede deneysel bir Y.Ç ekstratının etkinliğini in vivo olarak test etmekti	Y.Ç ekstresi Plasebo (gargara)	12-18 yaş 66 çocuk	haftada üç kez 1 dakika boyunca	Y. Ç ekstraktının karyojenik oral floraya karşı etkindir. Deney grubu, kontrol grubuna göre S.mutans ve Lactobasillus koloni sayılarında istatistiksel olarak anlamlı bir azalma gösterdi
Sajadi ve ark./2021(47)	CHX, florür ve Y.Ç'ın çocuklarda tükürük S. mutans ve Lactobacillus üzerindeki etkilerini araştırmak NaF ve Y.Ç ağız	%5 Y.Ç jel, %2 CHX jel %0.2 florür jel	4-6 yaş 60 çocuk	Tek seferlik uygulama (5dk)	Her üç jel tipinin uygulanmasından 1 hf sonra karyojenik bakterileri azaltmada Y. Ç ekstresi jeli, florür ve CHX jele kıyasla daha uzun süre etkiliydi.
Tahrani ve ark./2021(45)	gargaralarının çocukların tükürük S. mutans ve Lactobacillus seviyeleri üzerindeki etkisini karşılaştırmak	%0.05 NaF %0.5 Y.Ç (gargara)	8-12 yaş 60 çocuk	2 hafta boyunca günde 2 kez	Y. Ç ağzı çalkalamanın , NaFlü ağız çalkalama ile karşılaştırılabilir tükürük S. mutans ve Lactobacillus koloni sayısında önemli bir azalma ile sonuçlandığını göstermiştir .

Yeşil çay gargaralarının sodyum florür (NaF) veya CHX gargaralarıyla karşılaştırıldığı in vivo çalışmalarda S.mutans ve Lactobasillus sayılarında kullanımdan hemen sonra azalma olmuş ve kullanmaya devam ettikçe de azalma devam etmiştir (24,42-48). 2017 yılında yapılan çalışmada yeşil çay kateşinleriyle hazırlanan gargaranın tükürükteki S. mutans miktarı üzerine olan etkisinin plaktaki S. mutans miktarına olan etkisinden daha fazla olduğu bildirilmiştir (49,50).

CHX'in jel ve gargara formları arasındaki etkinliği karşılaştıran sistematik derlemede jel formunun plak büyümesini bir dereceye kadar engellediğini, ancak gargara formunun daha etkili olduğu sonucuna varmıştır. Yeşil çay jeli ve gargarası arasında benzer bir karşılaştırmayı Ahmedi ve ark.(52) 2019 yılına ait çalışmalarında yapmış ve gargaranın daha etkili olduğunu bildirmiştir.

Çayın Candida Albicans'a karşı etkisini inceleyen birçok çalışma, yeşil çay ve polifenollerinin tükürükteki, biofilmdeki veya akrilik protezlerdeki C. albicans sayısını azalttığını söylemiştir (51, 52). Çayın antifungal etkisi; polifenoller tarafından proteazomal aktivitenin bozulması, biyofilm oluşumunun inhibisyonunu ve hücresel yapı ve metabolizma bozulmasının hızlandırılması olarak açıklanmıştır (53). Dört ila altı yaş arası çocuklara 2 hafta süreyle her gün 1 dk boyunca 5 ml yeşil çay gargarası kullandırılan çalışmada S. mutans ve Lactobasillus sayılarıyla beraber C. albicans miktarında azalma olduğu bildirilmiştir (46).

Yetişkinlerde yapılanların aksine çocuklarda tükürük ve periodontal durum üzerine yapılan çalışmalar oldukça sınırlıdır. Yapılan çalışmalarda tükürük ph'sını alkali yönde arttırdığı(54-56) ve plak ve gingivit önleyici özelliğinin olduğu sonucuna varılmıştır (56,57).

2. Sonuç

Yeşil çay ve polifenollerinin antimikrobiyal, antigingivit, antiplak ve antiasit özellikleri çocuklarla yapılan çalışmalarda bir kez daha desteklenmiştir. Yeşil çay, mevcut özellikleriyle, ayrıca; çocuklar tarafından kabul edilebilir tadı, uygun maliyeti, bilinen yan etkisinin ve belirli bir kullanım süresi olmaması gibi diğer gargaralara karşı avantajlarıyla piyasada bulunan gargaralara ek olarak kullanılabilir. Özellikle erken çocukluk çağı çürüğüne sahip çocuklarda, mental yahut bedensel rahatsızlıkları nedeniyle düzenli fırçalama yapamayan çocuk ve yetişkinlerde diş hekimleri tarafından gargara olarak önerilebilecek güvenli bir ürün olabilir. Tüm bunların yansıra örneklem büyüklüklerinin daha geniş olduğu, konsantrasyon ve dozlarının kar-zarar oranına göre belirlendiği, uzun süreli kullanımına ilişkin sonuçların bulunduğu çalışmalara ihtiyaç vardır.

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