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Faks/Fax: +90 (212) 621 99 27
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Amaç ve Kapsam

Haseki Tıp Bülteni, S.B.Ü. Haseki Eğitim ve Araştırma Hastanesi'nin süreli yayın organı olup, genel tıp içerikli, yayın dili Türkçe ve İngilizce olan, bağımsız ve önyargısız hakemlik ilkelerine dayanan uluslararası periyodik bir dergidir. Haseki Tıp Bülteni Mart, Haziran, Eylül, Aralık aylarında olmak üzere yılda dört sayı çıkmaktadır.

Haseki Tıp Bülteni'nin hedefi uluslararası düzeyde nitelikli, sürekli ve genel tıp konusunda özgün, periyodik olarak klinik ve bilimsel açıdan en üst düzeyde orijinal araştırmaları yayınlamaktır. Bununla birlikte eğitim ile ilgili temel yenilikleri kapsayan derlemeler, editöre mektuplar, olgu sunumları da yayınlar.

Haseki Tıp Bülteni, **Emerging Sources Citation Index (ESCI), Index Copernicus, EBSCO Database, Turkish Medline-National Citation Index, Excerpta Medica/EMBASE, SCOPUS, TÜBİTAK/ULAKBİM Türk Tıp Dizini, CINAHL, DOAJ, Hinari, GOALI, ARDI, OARE, AGORA, ProQuest, ROOT INDEXING, British Library, J-Gate, IdealOnline ve Türkiye Atıf Dizini** tarafından indekslenmektedir.

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Açık Erişim, "[hakem değerlendirmesinden geçmiş bilimsel literatürün], İnternet aracılığıyla; finansal, yasal ve teknik engeller olmaksızın, serbestçe erişilebilir, okunabilir, indirilebilir, kopyalanabilir, dağıtılabilir, basılabilir, taranabilir, tam metinlere bağlantı verilebilir, dizinlenebilir, yazılıma veri olarak aktarılabilir ve her türlü yasal amaç için kullanılabilir olması"dır. Çoğaltma ve dağıtım üzerindeki tek kısıtlama yetkisi ve bu alandaki tek telif hakkı rolü; kendi çalışmalarının bütünlüğü üzerinde kontrol sahibi olabilmeleri, gerektiği gibi tanınmalarının ve alıntılanmalarının sağlanması için, yazarlara verilmelidir.

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The Medical Bulletin of Haseki

Aims and Scope

The Medical Bulletin of Haseki is the official scientific journal of the University of Health Sciences Haseki Training and Research Hospital. It covers subjects on general medicine, published both in Turkish and English, and is independent, peer-reviewed, international periodical and is published quarterly (March, June, September and December).

The aim of The Medical Bulletin of Haseki is to publish original research papers of highest scientific and clinic value on general medicine. Additionally, educational material reviews on basic developments, editorial short notes and case reports are published.

The Medical Bulletin of Haseki is indexed in **Emerging Sources Citation Index (ESCI), Index Copernicus, EBSCO Database, Turkish Medline-National Citation Index, Excerpta Medica/EMBASE, SCOPUS, TÜBİTAK/ULAKBİM Türk Tıp Dizini, CINAHL, DOAJ, Hinari, GOALI, ARDI, OARE, AGORA, ProQuest, ROOT INDEXING, British Library, J-Gate, IdealOnline ve Türkiye Atıf Dizini** databases.

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Secretariat of The Medical Bulletin of Haseki
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Phone: +90 212 529 44 00/1874
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Yazarlara Bilgi

Haseki Tıp Bülteni, genel tıp alanlarını ilgilendiren tüm konulardaki yazıları yayınlar. Dergide orijinal makalelerin dışında derleme yazıları, orijinal olgu sunumları, editöre mektuplar, ve kongre/toplantı duyuruları da yayınlanır.

Dergide yayınlanacak yazıların seçimine temel teşkil eden hakem heyeti, dergide belirtilen danışmanlar ve gerekirse yurt içi/dışı otörler arasından seçilir.

Yazılarda Türk Dil Kurumu'nun Türkçe Sözlüğü ve Yazım Kılavuzu temel alınmalıdır. İngilizce yazılan yazılar özellikle desteklenmektedir.

Editör veya yardımcıları tarafından, etik kurul onayı alınması zorunluluğu olan klinik araştırmalarda onay belgesi talep edilecektir. Yazıların içeriğinden ve kaynakların doğruluğundan yazarlar sorumludur.

Yazarlar, gönderdikleri çalışmanın başka bir dergide yayınlanmadığı ve/veya yayınlanmak üzere incelemede olmadığı konusunda garanti vermelidir. Daha önceki bilimsel toplantılarda 200 kelimeyi geçmeyen özet sunumlarının yayınları, durumu belirtilmek koşulu ile kabul edilebilir. Tüm otörler bilimsel katkı ve sorumluluklarını bildiren formu doldurarak yayına katılmalıdırlar.

Tüm yazılar, editör ve ilgili editör yardımcıları ile en az üç danışman hakem tarafından incelenir. Yazarlar, yayına kabul edilen yazılarda, metinde temel değişiklik yapmamak kaydı ile editör ve yardımcılarının düzeltme yapmalarını kabul etmiş olmalıdırlar.

Makalelerin formatı 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication' (http://www.icmje.org) kurallarına göre düzenlenmelidir.

Anahtar kelimelerin Türkiye Bilim Terimleri (http://www.bilimterimleri.com)'nden seçilmelidir.

Dergi kaynaklarda kullanılırken Med Bull Haseki şeklinde kısaltılmalıdır.

Haseki Tıp Bülteni makale başvuru ücreti veya makale işlem ücreti uygulamamaktadır.

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Yazılar sadece online olarak kabul edilmektedir. Yazarların makale gönderebilmesi için web sayfasına (http://hasekitip.dergisi.org) kayıt olup şifre almaları gereklidir. Bu sistem on-line yazı gönderilmesine ve değerlendirilmesine olanak tanımaktadır.

Makale gönderimi yapılırken sorumlu yazarın ORCID (Open Researcher ve Contributor ID) numarası belirtilmelidir. http://orcid.org adresinden ücretsiz olarak kayıt oluşturabilir.

Bu sistem ile toplanan makaleler ICMJE-www.icmje.org, Index Medicus (Medline/PubMed) ve Ulakbim-Türk Tıp Dizini kurallarına uygun olarak sisteme alınmakta ve arşivlenmektedir. Yayına kabul edilmeyen yazılar, sanatsal resimler hariç geriye yollanmaz. Dergide yayınlanmak üzere editöre gönderilen yazılar A4 sayfasının bir yüzüne 12 punto, çift aralıkla, arial/times new roman karakteri ve kenarlarda 2,5 cm boşluk bırakılarak yazılmalıdır. Kullanılan kısaltmalar yazı içerisinde ilk geçtikleri yerde, parantez içinde, açık olarak yazılmalı, özel kısaltmalar yapılmamalıdır. Yazı içindeki 1-10 arası sayısal veriler yazıyla (Her iki tedavi grubunda, ikinci gün), 10 ve üstü rakamla belirtilmelidir. Ancak, yanında tanımlayıcı bir takısı olan 1-10 arası sayılar rakamla (1 yıl) cümle başındaki rakamlar da (Onbeş yaşında bir kız hasta) yazıyla yazılmalıdır. Yazının tümünün 5000 kelimeden az olması gerekmektedir. İlk sayfa hariç tüm yazıların sağ üst köşelerinde sayfa numaraları bulunmalıdır. Yazıda, konunun anlaşılmasında gerekli olan sayıda ve içerikte tablo ve şekil bulunmalıdır.

Başlık sayfası, kaynaklar, şekiller ve tablolar ile ilgili kurallar bu dergide basılan tüm yayın türleri için geçerlidir.

Hastalar mahremiyet hakkına sahiptirler. Belirleyici bilgiler, hasta isimleri ve fotoğraflar, bilimsel olarak gerekli olmayan durumlarda ve hasta (ebeveyn veya koruyucu) tarafından yayınlanmasına yazılı olarak bilgilendirilmiş bir onay verilmediği sürece yayınlanmamalıdır.

Bu amaçla, bilgilendirilmiş onay, hastanın yayınlanacak belirli bir taslağı görmesini gerektirir. Eğer gerekli değilse hastanın belirleyici detayları yayınlanmayabilir. Tam bir gizliliği yakalamak oldukça zordur ancak eğer bir şüphe varsa, bilgilendirilmiş onay alınmalıdır. Örneğin, hasta fotoğraflarında göz bölgesini maskelemek, yetersiz bir gizlilik sağlanmasıdır.

Haseki Tıp Bülteni'ne yayınlanmak amacıyla gönderilen ve etik kurul onayı alınması zorunluluğu olan deneysel, klinik ve ilaç araştırmaları için uluslararası anlaşmalara ve 2013'de gözden geçirilmiş Helsinki Bildirisi'ne uygun etik kurul onay raporu gereklidir (http://www.wma.net/en/30publications/10policies/b3/). Deneysel hayvan çalışmalarında ise "Guide for the care and use of laboratory animals (https://oacu.oir.nih.gov/regulations-standards) doğrultusunda hayvan haklarını koruduklarını belirtmeli ve kurumlarından etik kurul onay raporu almalıdırlar. Etik kurul onayı (onay numarası ile birlikte) ve "bilgilendirilmiş gönüllü olur formu" alındığı araştırmanın "Yöntemler" bölümünde belirtilmelidir. Yazarlar, makaleleriyle ilgili çıkar çatışması ve maddi destekleri bildirmelidirler.

Orijinal Makaleler

1) Başlık Sayfası (Sayfa 1): Yazı başlığının, yazar(lar)ın bilgilerinin, anahtar kelimelerin ve kısa başlıkların yer aldığı ilk sayfadır.

Türkçe yazılarda, yazının İngilizce başlığı da mutlaka yer almalıdır; yabancı dildeki yayınlarda ise yazının Türkçe başlığı da bulunmalıdır. Türkçe ve İngilizce anahtar sözcükler ve kısa başlık da başlık sayfasında yer almalıdır.

Yazarların isimleri, hangi kurumda çalıştıkları ve açık adresleri belirtilmelidir. Yazışmaların yapılacağı yazarın adresi de ayrıca açık olarak belirtilmelidir. Yazarlarla iletişimde öncelikle e-posta adresi ve mobil telefon kullanılacağından, yazışmaların yapılacağı yazara ait e-posta adresi ve mobil telefon mutlaka belirtilmelidir. Buna ek olarak sabit telefon ve faks numaraları da bildirilmelidir.

Çalışma herhangi bir bilimsel toplantıda önceden bildirilen koşullarda tebliğ edilmiş ya da özeti yayınlanmış ise bu sayfada konu ile ilgili açıklama yapılmalıdır.

Yine bu sayfada, dergiye gönderilen yazı ile ilgili herhangi bir kuruluşun desteği sağlanmışsa belirtilmelidir.

2) Özet (Sayfa 2): İkinci sayfada yazının Türkçe ve İngilizce özetleri (her biri için en fazla 200 sözcük) ile anahtar sözcükler belirtilmelidir.

Özet Bölümü: Amaç, Yöntemler, Bulgular, Sonuç şeklinde alt başlıklarla düzenlenir. Derleme, olgu sunumu ve eğitim yazılarında özet bölümü alt başlıklara ayrılmaz. Bunlarda özet bölümü, 200 kelimeyi geçmeyecek şekilde amaçlar, bulgular ve sonuç cümlelerini içermelidir.

Özet bölümünde kaynaklar gösterilmemelidir. Özet bölümünde kısaltmalardan mümkün olduğunca kaçınılmalıdır. Yapılacak kısaltmalar metindekilerden bağımsız olarak ele alınmalıdır.

3) Metin (Özetin uzunluğuna göre Sayfa 3 veya 4'den başlayarak)

Genel Kurallar bölümüne uyunuz.

Metinde Ana Başlıklar Şunlardır: Giriş, Yöntemler, Bulgular, Tartışma, Çalışmanın Kısıtlılıkları ve Sonuç.

Giriş bölümü çalışmanın mantığı ve konunun geçmişi ile ilgili bilgiler içermelidir. Çalışmanın sonuçları giriş bölümünde tartışılmamalıdır.

Yöntem bölümü çalışmanın tekrar edilebilmesi için yeterli ayrıntılar içermelidir. Kullanılan istatistik yöntemler açık olarak belirtilmelidir.

Bulgular bölümü de çalışmanın tekrar edilebilmesine yetecek ayrıntıları içermelidir.

Tartışma bölümünde, elde edilen bulguların doğru ve ayrıntılı bir yorumu verilmelidir. Bu bölümde kullanılacak literatürün, yazarların bulguları ile direkt ilişkili olmasına dikkat edilmelidir.

Çalışmanın Kısıtlılıkları bölümünde çalışma sürecinde yapılamayanlar ile sınırları ifade edilmelidir. Sonuç bölümünde çalışmadan elde edilen sonuç, gelecek çalışmalara ilişkin öneriler ile vurgulanmalıdır.

Teşekkür mümkün olduğunca kısa tutulmalıdır. Çalışma için bir destek verilmişse bu bölümde söz edilmelidir. (Teşekkür yalnızca "Başlık Sayfası" içerisinde gönderilmelidir.)

Metinde fazla kısaltma kullanmaktan kaçınılmalıdır. Tüm kısaltılacak terimler metinde ilk geçtiği yerde parantez içinde belirtilmelidir. Özette ve metinde yapılan kısaltmalar birbirinden bağımsız olarak ele alınmalıdır. Özet bölümünde kısaltması yapılan kelimeler, metinde ilk geçtiği yerde tekrar uzun şekilleri ile yazılıp kısaltılmalıdırlar.

4) Kaynaklar: Kaynakların gerçekliğinden yazarlar sorumludur.

Kaynaklar metinde geçiş sırasına göre numaralandırılmalıdır. Kullanılan kaynaklar metinde parantez içinde belirtilmelidir.

Kişisel görüşmeler, yayınlanmamış veriler ve henüz yayınlanmamış çalışmalar bu bölümde değil, metin içinde şu şekilde verilmelidir: (isim(ler), yayınlanmamış veri, 19..).

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a) Standart Makale: Intiso D, Santilli V, Grasso MG, Rossi R, Caruso I. Rehabilitation of walking with electromyographic biofeedback in foot-drop after stroke. Stroke 1994;25:1189-92.

b) Kitap: Getzen TE. Health economics: fundamentals of funds. New York: John Wiley & Sons; 1997.

c) Kitap Bölümü: Porter RJ, Meldrum BS. Antiepileptic drugs. In: Katzung BG, editor. Basic and clinical pharmacology. 6th ed. Norwalk, CN: Appleton and Lange; 1995. p. 361-80.

Birden fazla editör varsa: editors.

d) Toplantıda Sunulan Makale: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. North-Holland; 1992. p. 1561-5.

e) Elektronik Formatta Makale: Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis [serial online] 1995 1(1):[24 screens]. Available from:s URL:http://www/cdc/gov/ncidoc/EID/eid.htm. Accessed December 25, 1999.

f) Tez: Kaplan SI. Post-hospital home health care: the elderly access and utilization (thesis). St. Louis (MO): Washington Univ; 1995.

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Editor of The Medical Bulletin of Haseki
Haseki Training and Research Hospital, Department of Nephrology
Adnan Adıvar Caddesi, 34906 Haseki-Aksaray-İstanbul-Turkey
Phone: +90 212 529 44 00/1874
Fax: +90 212 530 84 23
Web Page: www.hasekidergisi.com
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Original Article / *Özgün Araştırma*

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Fetal Biometry: Is it Same in African Population? Are There Racial Differences?

Afrika Popülasyonunda Fetal Biyometrik Ölçümler Aynı mı? Etnik Farklılık Var mıdır?

Özer Birge, Mehmet Sait Bakır*

Somali Turkey Recep Tayyip Erdoğan Training and Research Hospital, Clinic of Gynaecology and Obstetrics, Mogadishu, Somali
**Akdeniz University Faculty of Medicine, Department of Gyneacologic Oncology, Antalya, Turkey*

Abstract

Aim: Our study aims to investigate whether there is a difference between the African pregnant population at 14-42 weeks of gestation and standard ultrasonographic fetal biometric measurements.

Methods: This study was carried out at Mogadishu Somali Turkey Recep Tayyip Erdoğan Training and Research Hospital, Hodan District, Mogadishu, Somalia from July 2018 to September 2018. Four hundred and eighty-six females at 14-42 weeks' gestation were evaluated. Obstetrical ultrasound was done using a 3.5 MHz convex transducer on Toshiba Aplio XG Ssa-790a. Biparietal diameter (BPD), head circumference (HC), femur length (FL), and abdominal circumference (AC) were identified and measured.

Results: The median maternal age in the study sample was 26 years with the mode value of 30 years. The highest number of participants were in 38 weeks (31, 6.4%) and the lowest number of participants were in weeks 15 and 18 with 1 in each (0.2%). BPD gradually increased from a minimum of 26.0 mm at week 14 to a maximum of 95.9 mm. HC gradually increased from a minimum of 101.1 mm at week 14 to a maximum of 95.9 mm at week 42. AC increased gradually from a minimum of 76.6 mm at week 14 to a maximum of 369.2 mm at week 42. FL increased gradually from a minimum of 15.0 mm at week 14 to a maximum of 79.1 mm at week 42.

Conclusion: The frequently used parameters of fetal biometry along with ultrasonographic appearance and measurements in our local population are in agreement with international studies except for HC which was lower than the Hadlock's measurement by an average of 7.8 mm.

Keywords: Fetal biometry, biparietal diameter, head circumference, femur length, abdominal circumference, African population, ethnicity

Öz

Amaç: 14-42 gebelik haftasındaki Afrikalı gebe popülasyonu ile standart ultrasonografik fetal biyometrik ölçümler arasındaki farkı araştırmaktır.

Yöntemler: Bu çalışma Somali Hodan Eyaleti Mogadişu'daki, Somali-Türkiye Eğitim ve Araştırma Hastanesi'nde Temmuz ve Eylül 2018 ayları arasında yapıldı. Gestasyonel haftası 14-42 arasında olan 486 hamile kadın muayene edildi. 3,5 MHz probu olan Toshiba Aplio XG Ssa-790a marka obstetrik usg cihazı kullanıldı. Bipariatal çap (BPD), baş çevresi (HC), femur uzunluğu (FL) ve karın çevresi (AC) tanımlanıp ölçüldü.

Bulgular: Çalışma örneğinin maternal ortalama yaşı 26 yıl idi. Ortanca yaş 26, mod yaşı 30 idi. En yüksek katılımcı sayısı 38 haftada 31 kişi (%6,4), en düşük katılımcı sayısı 15 ve 18. haftalarda 1 kişi (%0,2) idi. BPD ölçümleri sırasıyla 14. haftada minimum 26,0 mm'den maksimum 95,9 mm aralığında ölçüldü. HC ölçümleri sırasıyla 14. haftada minimum 101,1 mm'den maksimum 95,9 mm aralığında ölçüldü. AC 14. haftada minimum 76,6 mm'den 42. haftada maksimum 369,2 mm'ye kadar ölçümlerin olduğu görüldü. FL 14. haftada minimum 15,0 mm'den maksimum 79,1 mm'ye 42. haftada ölçüldü.

Sonuç: Bizim ölçüm yaptığımız lokal popülasyonda sık kullanılan fetal biyometrik ölçümler uluslararası çalışmalarla uyumlu görülürken, sadece Hadlock'un HC ölçümlerine göre ortalama olan 7,8 mm den küçük ölçüldü.

Anahtar Sözcükler: Fetal biyometrik, bipariatal çap, baş çevresi, femur uzunluğu, karın çevresi, Afrika popülasyonu, etnisite

Address for Correspondence/Yazışma Adresi: Özer Birge, Somali Turkey Recep Tayyip Erdoğan Training and Research Hospital, Clinic of Gynaecology and Obstetrics, Mogadishu, Somali
Phone: +24 996 184 70 56 E-mail: ozbirge@gmail.com ORCID: orcid.org/0000-0002-1939-3743
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Introduction

With the introduction of obstetric ultrasonography (USG) in the early 1970s, it has been the most widely used method of fetal weight estimation. So many estimation models are evaluated. These models are based on evaluating fetal measurements. However, fetal growth differs by race/ethnicity, environment, and area. It is hard to apply an estimated fetal weight model made for a community to other communities. Thus, most researchers suggest analysing suitability of the model for that community before its clinical use. They also suggest that data specific for each community should be used, especially in undeveloped countries (1-4).

Methods

This was a prospective cross-sectional study carried out in Mogadishu, the capital city of Somalia. All pregnant mothers at 14-42 weeks' gestation and having a viable single baby who attended the obstetrics and gynecology outpatient clinic at Mogadishu Somali Turkey Recep Tayyip Erdoğan Training and Research Hospital from July 7, 2018, to September 5, 2018 were included in the study. Mothers with multiple gestations, mothers with less than 14 weeks of gestation, mothers with pregnancy complicated disorders (e.g. pre-eclampsia, bleeding), mothers with known fetal anomalies, pregnant women with concomitant disease possibly affecting fetal growth (e.g. diabetes mellitus, asthma, hypertension, renal disease, thyroid disease) were the exclusion criteria. Simple random sampling was used in this study. Data were collected using a specially made questionnaire. All the fetal biometry measurements were performed by the investigator using a Toshiba Aplio XG Ssa-790a USG machine equipped with a 3.5 MHz transducer. Fetal head measurements were made in an axial plane at the level where the continuous midline echo is broken by the cavum septum pellucidum in the anterior third and that includes the thalamus. This transverse section should demonstrate an oval symmetrical shape. Measurement of biparietal diameter (BPD) was from the outer edge of the closest temporomandibular bone to the outer edge of the opposite temporomandibular bone. Head circumference (HC) was measured around the calvarium from the same axial image as for the BPD. Abdominal circumference (AC) was measured through the transverse section of the fetal abdomen at the level of the stomach and bifurcation of the main portal vein into its right and left branches. Femur length (FL) was measured from the greater trochanter to the lateral condyle, with both ends clearly visible and at a horizontal angle <450. All measurements were expressed in millimeters. Estimated fetal weight was calculated in grams by the formulae described by Shepard and Filly, as these are included in the software of most commercially available USG scanners (5). To enable appropriate statistical comparison of data, only studies with the number of examined fetuses indicated were included since many studies do not indicate the number of fetuses and are reported in graphic rather than tabular forms.

The study was approved by the ethics committee of the hospital and before the inclusion of the patients, informed consent was obtained (Mogadishu Somalia Turkey Recep Tayyip Erdoğan Training and Research Hospital, date: 26.06.2018, decision no: 45).

Statistical Analysis

The data analyzed manually and then presented using tables and graphs which are designed in SPSS and Excel.

Results

The median maternal age of the study sample was 26 years (range: 16-43) with the mode value of 30 years.

The number of deliveries in the pregnant women was classified from 0 (primigravida/nullipara) to 16 (multipara) with multiparas constituting 77.8% of the participants who were scanned followed by nulliparas 22.2%. This figure revealed that multiparas were the highest in number in the study sample (77.8%). As the parity increased, the number of women who were scanned dropped. Again, it showed that there were women who delivered 16 times during their reproductive life.

The number of participants who did not know their last menstrual period (LMP) was 299 (61.5%) and those who knew it was 187 (38.5%). Due to this fact, most of the participants came to the clinic to find out their gestational age (GA).

Among participants in this study, the minimum GA was 14 weeks and the maximum was 42 weeks. The median GA was 29.9 weeks. Week 38 was the highest number of participants documented with 31 (6.4%) followed by weeks 39 and 32 with 27 in each (5.6%).

To the analysis of fetal biometric parameters;

The highest number of participants were in 38 weeks with 31 (6.4%) and the lowest number of participants were in weeks 15 and 18 with 1 in each (0.2%).

BPD measurements gradually increased from a minimum of 26.0 mm at week 14 to a maximum of 95.9 mm at week 42 as shown in Table 1. In comparison with Hadlock's study, we found out that there was a close relationship except in weeks 16-20; the mean BPD in this study was higher than in Hadlock's study. In the following weeks, it was almost the same mean BPD with fluctuation of 0.3 mm as shown in Figure 1.

HC measurements gradually increased from a minimum of 101.1 mm at week 14 to a maximum of 95.9 mm as shown in Table 2. In comparison with Hadlock's study and we found out that the mean HC in this was lower than

in Hadlock's study starting from week 17 to week 42 as shown in Figure 2.

AC increased gradually from a minimum of 76.6 mm at week 14 to a maximum of 369.2 mm at week 42 as shown in Table 3. In comparison with Hadlock's study, we found out that the mean AC was higher in weeks 17-22 and weeks 33-42 and lower in weeks 23-32 (Figure 3).

FL increased gradually from a minimum of 15.0 mm at week 14 to a maximum of 79.1 mm at week 42 as shown in Table 4. In comparison with Hadlock's study, we found out that the mean FL was similar to that in Hadlock's study with +0.2/-0.2 mm differences between the studies (Figure 4).

Table 1. Frequency distribution table of fetal biparietal diameter measurements showing gestational age in weeks, number of participants, their mean and percentiles from 14-42 weeks gestation

GA in WKS	No of participants	Mean BPD (mm)	Percentiles		
			5th	50th	95th
14 to 14+6	2	26.0	25.01	26.00	26.99
15 to 15+6	1	33.6	33.60	33.60	33.60
16 to 16+6	8	34.6	30.30	34.05	40.70
17 to 17+6	11	37.1	32.95	37.20	41.50
18 to 18+6	1	40.8	40.80	40.80	40.80
19 to 19+6	18	46.5	40.23	44.20	58.18
20 to 20+6	15	50.2	36.72	46.90	75.31
21 to 21+6	10	49.1	40.07	50.00	54.48
22 to 22+6	19	53.4	49.45	53.20	58.45
23 to 23+6	18	55.9	50.54	55.60	59.72
24 to 24+6	17	60.0	54.84	58.90	68.10
25 to 25+6	16	62.4	59.18	62.15	65.70
26 to 26+6	20	65.7	61.51	65.75	70.41
27 to 27+6	23	67.9	61.24	67.80	71.99
28 to 28+6	17	69.1	61.66	69.50	74.56
29 to 29+6	23	72.6	67.56	72.70	78.54
30 to 30+6	24	76.4	72.18	75.95	82.33
31 to 31+6	20	78.8	73.56	78.90	85.26
32 to 32+6	27	80.7	77.09	80.90	83.30
33 to 33+6	25	83.1	79.42	83.20	87.08
34 to 34+6	19	85.5	81.30	85.50	88.98
35 to 35+6	21	86.7	83.70	86.20	90.80
36 to 36+6	19	88.1	84.06	88.70	90.90
37 to 37+6	25	89.6	85.00	90.60	94.02
38 to 38+6	31	94.2	91.30	94.20	98.15
39 to 39+6	27	93.9	90.35	94.40	99.71
40 to 40+6	21	94.9	87.30	95.40	100.00
41 to 41+6	5	96.8	93.12	97.10	100.76
42 to 42+6	3	95.9	92.51	96.20	99.08

GA: Gestational age, WKS: Weeks, BPD: Biparietal diameter

Discussion

Sonographic estimation of GA, especially when based on the measurements of multiple fetal parameters and obtained under research conditions during the antepartum period, provides reliable and clinically useful information for most of the patients.

Since GA is still determined by LMP in some places, the chances of error increase, therefore, USG investigation is highly recommended as the only measuring tool for GA determination.

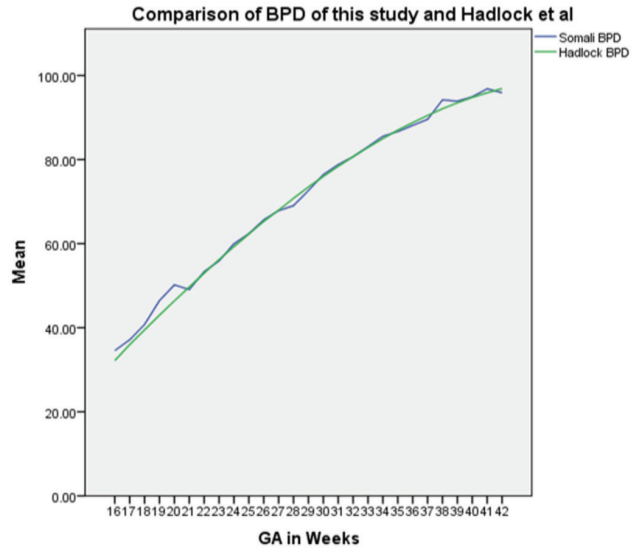

Figure 1. Line chart showing the comparison of BPD of this study and hadlocks
GA: Gestational age, BPD: Biparietal diameter

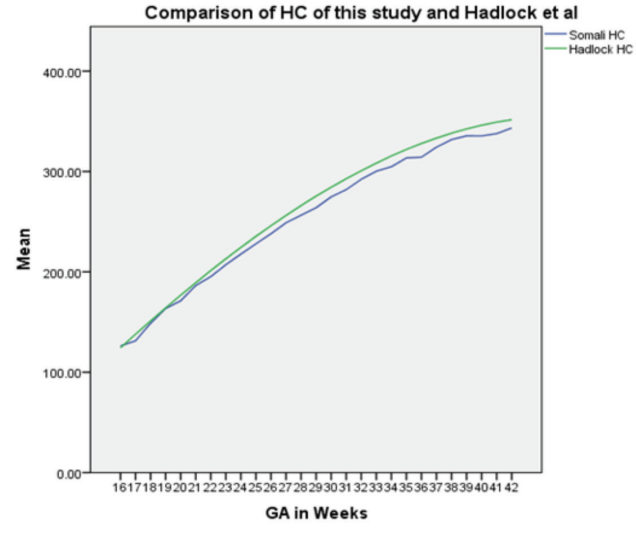

Figure 2. Line chart showing the comparison of HC of this study and hadlocks
GA: Gestational age, HC: Head circumference

Also, since USG has pre-embedded equations to GA from the different fetal biometry measurements, there will be ethnic differences. Most of the USG machines have multiple equations based on different ethnicities that were collected by examining normal antepartum data from many participants. Each ethnicity has its own charts that correspond with their growth.

USG was first used to diagnose brain tumors and to measure the dimensions of the brain ventricles in 1942 by a neurologist, Dussik from Vienna (6). The possible existence of high frequency sounds which we can not hear was suggested by Spallanzini in 1974 after his studies on bats. Piezoelectricity is found by Curries in 1880. Thirty-five years later, ultrasonic energy was first used. At the beginning of 1990s the basics of USG are found (7).

Currently available sonographic growth standards for fetal head size, abdominal size, and limb length are based primarily on studies from white populations. There is not much data from the black population in underdeveloped countries. To determine if these published standards are

Table 2. Frequency distribution table of fetal head circumference measurements showing gestational age in weeks, number of participants, their mean and percentiles from 14-42 weeks gestation

			Percentiles		
GA in WKS	No of participants	Mean HC (mm)	5th	50th	95th
14 to 14+6	2	101.1	97.59	101.10	104.61
15 to 15+6	1	119.3	119.30	119.30	119.30
16 to 16+6	8	126.2	116.80	125.70	137.85
17 to 17+6	11	131.4	115.30	135.90	146.00
18 to 18+6	1	148.8	148.80	148.80	148.80
19 to 19+6	18	163.6	147.42	163.40	175.77
20 to 20+6	15	171.2	142.29	175.20	187.71
21 to 21+6	10	186.4	177.01	187.25	196.65
22 to 22+6	19	195.3	183.71	193.10	210.94
23 to 23+6	18	207.1	185.89	207.30	224.38
24 to 24+6	17	217.7	205.62	218.20	232.02
25 to 25+6	16	227.9	215.58	228.65	242.43
26 to 26+6	20	238.0	211.88	238.55	258.89
27 to 27+6	23	248.9	225.53	247.40	275.43
28 to 28+6	17	256.4	229.48	258.70	276.04
29 to 29+6	23	263.9	242.98	266.20	282.63
30 to 30+6	24	274.7	254.48	275.05	291.63
31 to 31+6	20	282.0	264.26	281.20	308.39
32 to 32+6	27	292.2	278.10	292.20	304.55
33 to 33+6	25	300.3	284.18	300.30	313.72
34 to 34+6	19	304.8	290.66	305.30	316.32
35 to 35+6	21	313.5	300.00	316.20	325.90
36 to 36+6	19	314.3	303.06	313.50	325.77
37 to 37+6	25	324.3	313.80	324.30	334.64
38 to 38+6	31	331.8	322.35	331.50	341.80
39 to 39+6	27	335.5	317.61	337.70	359.84
40 to 40+6	21	335.4	314.70	339.80	347.60
41 to 41+6	5	337.8	326.50	337.00	349.76
42 to 42+6	3	343.4	334.30	345.10	351.40

GA: Gestational age, WKS: Weeks, HC: Head circumference

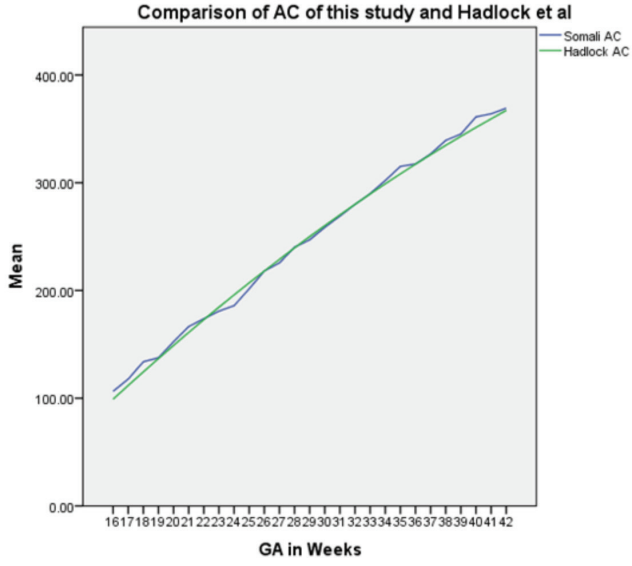

Figure 3. Line chart showing the comparison of AC of this study and hadlocks
GA: Gestational age, AC: Abdominal circumference

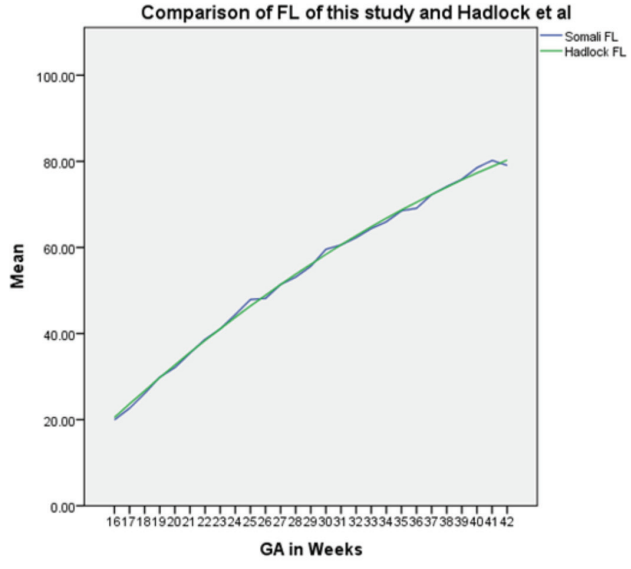

Figure 4. Line chart showing the comparison of FL of this study and hadlocks
GA: Gestational age, FL: Femur length

appropriate for a racially mixed, indigent population. we compared our published data which is generated from a black African population examined at a training and research hospital in Mogadishu Somalia, with international Hadlocks USG data.

In their study investigating racial differences in humerus length, Mastrobattista et al. (8) found a difference between Asian and Afro-Americans at all GAs. When Caucasians and Afro-Americans were compared, it was observed that the humerus length of Afro-American fetuses were longer at all GAs. In addition, Caucasian fetuses had consistently longer humerus length than Asians.

Hadlock at al. (9) examined the relation between FL and menstruation age and concluded that fetal FL could be used as an adjunct in estimating menstrual age. In Chitty and Altman's study, the femur and humerus measurements were longer for GA compared to that in our study (10). In our study, we used Hadlock's formula, so we did not measure humerus length. There was no difference in FL according to Hadlocks score.

In their study measuring fetal BPD by USG in 558 Nigerian women, Ayangade and Okonofua (11). reported a curve similar to those reported from Caucasian populations but with much less flexion in the later weeks

Table 3. Frequency distribution of fetuses scanned by abdominal circumference: frequency distribution table of fetal abdominal circumference measurements showing gestational age in weeks, number of participants, their mean and percentiles from 14-42 weeks gestation

GA in WKS	No of Participants	Mean AC (mm)	Percentiles		
			5th	50th	95th
14 to 14+6	2	76.6	73.36	76.60	79.84
15 to 15+6	1	101.3	101.30	101.30	101.30
16 to 16+6	8	106.5	102.00	105.20	112.68
17 to 17+6	11	117.8	109.10	119.90	127.10
18 to 18+6	1	133.9	133.90	133.90	133.90
19 to 19+6	18	137.5	125.42	138.90	146.32
20 to 20+6	15	152.5	135.07	150.20	171.42
21 to 21+6	10	166.5	156.10	163.10	183.45
22 to 22+6	19	173.7	162.25	174.10	183.50
23 to 23+6	18	180.9	169.59	180.55	192.07
24 to 24+6	17	185.9	143.12	190.10	206.56
25 to 25+6	16	201.5	180.50	203.30	225.10
26 to 26+6	20	218.1	199.50	220.45	228.81
27 to 27+6	23	225.6	188.40	228.90	244.92
28 to 28+6	17	240.2	219.70	240.90	254.80
29 to 29+6	23	247.1	228.43	247.50	263.59
30 to 30+6	24	258.7	247.85	259.30	274.29
31 to 31+6	20	269.1	242.69	268.15	295.02
32 to 32+6	27	279.9	265.10	281.00	293.87
33 to 33+6	25	289.9	273.66	289.60	301.58
34 to 34+6	19	302.1	275.91	304.60	317.49
35 to 35+6	21	315.2	300.90	312.70	345.30
36 to 36+6	19	317.4	296.98	321.90	328.55
37 to 37+6	25	326.8	314.84	327.00	339.46
38 to 38+6	31	339.3	322.85	337.20	364.85
39 to 39+6	27	345.2	331.42	345.00	371.38
40 to 40+6	21	361.2	341.40	361.10	378.50
41 to 41+6	5	364.0	346.18	359.90	383.90
42 to 42+6	3	369.2	367.28	368.00	371.96

GA: Gestational age, WKS: Weeks, AC: Abdominal circumference

Table 4. Frequency distribution of fetuses scanned by femur length: frequency distribution table of fetal femur length measurements showing gestational age in weeks, number of participants, their mean and percentiles from 14-42 weeks gestation

GA in WKS	No of Participants	Mean FL (mm)	Percentiles		
			5th	50th	95th
14 to 14+6	2	15.0	14.19	15.00	15.81
15 to 15+6	1	17.2	17.20	17.20	17.20
16 to 16+6	8	20.0	16.70	20.25	22.80
17 to 17+6	11	22.7	19.25	23.10	25.60
18 to 18+6	1	26.1	26.10	26.10	26.10
19 to 19+6	18	29.9	26.89	29.55	32.51
20 to 20+6	15	32.1	29.29	31.20	35.64
21 to 21+6	10	35.5	34.04	35.70	37.17
22 to 22+6	19	38.7	35.25	38.70	42.11
23 to 23+6	18	41.1	37.78	40.95	45.30
24 to 24+6	17	44.4	40.08	43.70	49.00
25 to 25+6	16	47.9	44.03	47.15	51.03
26 to 26+6	20	48.2	41.30	49.10	51.64
27 to 27+6	23	51.4	48.04	51.60	55.53
28 to 28+6	17	53.1	50.70	52.80	57.30
29 to 29+6	23	55.6	50.97	56.40	60.04
30 to 30+6	24	59.6	54.70	58.85	62.38
31 to 31+6	20	60.6	56.50	60.70	64.77
32 to 32+6	27	62.3	58.73	62.50	65.10
33 to 33+6	25	64.4	58.76	65.10	69.74
34 to 34+6	19	66.0	62.47	65.50	71.39
35 to 35+6	21	68.5	65.70	68.80	73.10
36 to 36+6	19	69.1	66.06	69.30	72.84
37 to 37+6	25	72.3	68.94	72.20	75.24
38 to 38+6	31	74.2	68.65	73.70	79.60
39 to 39+6	27	75.8	71.78	76.20	80.06
40 to 40+6	21	78.5	74.20	79.00	81.70
41 to 41+6	5	80.2	78.82	80.90	81.20
42 to 42+6	3	79.1	76.97	80.30	80.30

GA: Gestational age, WKS: Weeks, FL: Femur length

of pregnancy. The BPD values per week were also lower in this study group. The reasons for these differences need to be discussed.

Muñoz et al. (12) reported that the smaller BPD in late pregnancy could be explained by the head's shape and concluded that new charts were valuable in assessing fetal growth in African blacks.

Van Bogaert (13) reported in their study from South Africa that there was no significant difference between customized gravidogram for African population and intrauterine fetal growth curve charts established for Caucasians.

Hadlock et al. (14) analyzed if the accuracy of fetal weight estimation increases with FL added to head and body parameters and developed an estimation model which is based on AC and FL when cephalometric measurements undoable. They found no statistically significant differences for any of the following fetal sonographic parameters (20 to 41 weeks): nBPD, HC, AC and FL.

The HC was lower than in Hadlock's study. Variations in head size and brain volume are genetic and since the times of Galton, it has been customary to associate the size of the head (and size of the brain), as measured by HC, with intelligence. Even the genes responsible for brain size (which is directly related to HC, cranial capacity, occipitofrontal diameter, etc.) have been identified even though they vary from one continent to another and require to be mapped out. Studies using brain imaging techniques such as magnetic resonance imaging reported that there was a 40% correlation between head size and intelligence quotient. Small brain size is said to be positively correlated with memory retention in old age and onset of dementia. It has also been shown that HC was strongly correlated with brain volume which presumably determines intelligence. Racial studies have shown a relationship between brain size and adult intelligence but we do not have enough data to determine what the situation of things is before birth which is different from what obtains after birth (14).

A Nigerian study provides extensive data for HC of 13,740 African (Nigerian) fetuses and suggests that early maturation of HC in African children vis-à-vis European, is a genetic rather than nutritional factor. Postnatal development, however, is probably dependent on nutrition and environment rather than gene. USG measurement of BPD in Nigerian fetuses showed a linear correlation between BPD and GA as well as BPD and fetal weight in normal fetuses (15).

In this study, particular attention was paid to the methodology used to construct these new ranges, doing our best to follow the recommendations made by the authors of previous methodological reviews (16-20). The BPD values and centiles in this study were significantly lower than those in the Western population (21,22). The only time that our values were significantly higher was from 15-16 weeks gestation. This finding is contrary to the one reported (23). This difference may be attributed to the claim that there is a systematic difference in the USG data sets collected before and after 1974, probably due to the differences that exist in the scanner resolutions before and after that period, and the later introduction of grayscale imaging (23).

The analytical method followed standard recommendations strictly. In the discussion, we classified the findings into maternal characteristics and fetal biometrics.

The study showed that, according to age group, higher number of participants (51,10.5%) were aged 30 years and the least number of participants (3, 0.6%) were aged 40, 41 and 43. The youngest was aged 16 years and the oldest was 43 years. The study also showed that according to parity, the highest number of participants were multiparas (378, 77.8%) followed by nulliparas (108, 22.2%). When the participants were asked about their LMP 299 (61.5%) did not know it and 187 (38.5%) knew their LMP.

Study Limitations

Before utilizing the results of this study with any pregnant woman, the following limitations must be noted:

1. The study population was selected from pregnant women who attended and had an USG scan at Mogadishu Somali Turkey Recep Tayyip Erdoğan Training and Research Hospital only. These women may not be representative of the general population.

2. A lot of rejections about the research have forced us to leave out many candidates with our limited time. Therefore, as health professionals, we must be gentle in convincing and potential participants incoming research and clear the misconceptions about any research in our community which has finished a civil war that devastated the country.

Conclusion

The study concludes that; further studies should examine and assess the HC of Somali fetuses and should use a large sample size to enable the generalization of the findings.

However at this level, we recommend consideration of the findings of this study to obstetricians practicing in Mogadishu, Somalia. To the obstetrician, normal values for the parameters of fetal BPD, HC, AC, and FL from Somali fetuses in Mogadishu between 14 and 42 weeks of gestation will be so useful such that the obstetrician who uses USG routinely in ante-natal care can screen for

congenital anomalies in the fetus during the period of gestation using ratios of anthropometric measurement as described above in this environment.

We highly recommend awareness of LMP at the national level. As more than half of our participants did not know their LMP and it can be used to verify the GA determined by USG which currently uses an embedded equation from other ethnicities.

It can be used as a guideline for predicting GA fetal biometry measurements, in order to ascertain the degree of risk, to encourage mothers to improve their fetus's health and to come for follow-up.

It can be used for further studies in related fields.

The study has shown a detailed report of USG assessment of fetal biometry studies in Somali fetuses in Mogadishu using a very large sample size.

This study has identified that our HC was lower than in Hadlock's study while other parameters were closely related, which requires to be pursued by future investigators.

This study has provided a standard against which to compare size in individual fetuses in our environment.

Authorship Contributions

Concept: Ö.B., M.S.B. Design: Ö.B. Data Collection or Processing: Ö.B. Analysis or Interpretation: Ö.B., M.S.B. Literature Search: Ö.B., M.S.B. Writing: Ö.B., M.S.B.

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Ameliorative Effect of Alpha Lipoic Acid on Endometriosis: An Experimental Model in Rats

Alfa Lipoik Asidin Endometriozis Üzerindeki İyileştirici Etkisi: Sıçanlarda Deneysel Model

Taylan Onat, Murat Çakır*

Yozgat Bozok University Faculty of Medicine, Department of Gynecology and Obstetrics Yozgat, Turkey
**Yozgat Bozok University Faculty of Medicine, Department of Physiology, Yozgat, Turkey*

Abstract

Aim: This study aims to evaluate the effects of alpha lipoic acid (ALA), which is a strong antioxidant, on endometriosis (EMS).

Methods: Thirty sexually-mature, female Wistar albino rats weighing 180-220 grams were separated into three groups: sham (n=10), EMS (n=10) and EMS + ALA (n=10). Blood samples were taken from the rats and were centrifuged and stored at -80 °C before forming the experimental EMS model. ALA at a dose of 50 mg/kg was orally administered to EMS + ALA group. At the end of this procedure, blood samples were taken again and were centrifuged and stored at -80 °C. Plasma total antioxidant status (TAS), plasma total oxidant status, oxidative stress (OS) index and cancer antigen 125 were studied from these samples.

Results: There were no differences between the groups in terms of baseline results. According to the second blood test results, all parameters in the sham group and all parameters other than plasma TAS in EMS + ALA group were statistically different than in EMS group ($p<0.05$). Considering the 1st and 15th day changes in the parameters of the groups, it was observed that ALA had positive effects.

Conclusion: ALA reduces OS in EMS; thus, may have a positive effect on the severity and stage of the illness and reduce recurrence after treatment.

Keywords: Endometriosis, oxidative stress, alpha lipoic acid

Öz

Amaç: Bu çalışma güçlü bir antioksidan olan alfa lipoik asitin (ALA) endometriozis (EMS) üzerine etkilerini değerlendirmeyi amaçlamaktadır.

Yöntemler: Otuz adet, 180-220 gram ağırlığında, seksüel matür, dişi Wistar albino rat üç gruba ayrılmıştır: Sham, EMS grubu ve EMS + ALA grubu. Deneysel EMS modeli oluşturulmadan ratlardan kan örnekleri alındı ve santrifüj edilerek -80 °C'de saklandı. EMS + ALA grubuna 15 gün, 50 mg/kg dozda, oral yoldan alfa lipoik asit verildi. Bu sürenin sonunda ratlarda tekrar kan örnekleri alındı ve santrifüj edilerek -80 °C'de saklandı. Bu örneklerden plazma total antioksidan status (TAS), plazma total oksidan status, oksidatif stres (OS) indeks ve kanser antijen 125 çalışıldı.

Bulgular: Grupların başlangıç sonuçları arasında farklılık yoktu. İkinci alınan kan sonuçlarında sham grubu bütün parametrelerde, EMS + ALA grubu ise plazma TAS dışındaki bütün parametrelerde EMS grubundan istatiksel olarak farklıydı ($p<0,05$). Gruplarda parameterelerin 1.-15. gün değişimine baktığımızda ALA'nın olumlu etkilerini saptadık.

Sonuç: ALA, EMS'de OS'yi azaltarak hastalığın şiddeti ve evresi üzerinde olumlu etki gösterebilir, ayrıca tedavi sonrası nüksleri azaltabilir.

Anahtar Sözcükler: Endometriozis, oksidatif stress, alfa lipoik asit

Address for Correspondence/Yazışma Adresi: Taylan Onat, Yozgat Bozok University Faculty of Medicine, Department of Gynecology and Obstetrics Yozgat, Turkey
E-mail: onat.taylan@gmail.com ORCID: orcid.org/0000-0002-8920-1444
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Introduction

Endometriosis (EMS) is a common estrogen-dependent gynecological disease defined by the presence of endometrial-like glands and stroma outside the uterine cavity. EMS is observed in 10% of women of reproductive age, and 35-50% of women with pelvic pain and/or infertility are diagnosed with EMS (1). Considering that EMS diagnosis requires histopathological verification, its frequency might be higher. It negatively affects women's health with its primary symptoms such as chronic pelvic pain, dyspareunia, dysmenorrhea and infertility. Although it mostly settles in the pelvic peritoneum, its involvement in the ovary and rectovaginal septum is considerably frequent. The risk of recurrence after treatment is quite high in the first stage of EMS (2). EMS was first defined in 1,860 but its etiopathogenesis has still not been clarified (3). The most popular theory among the various proposed theories is the theory of retrograde menstruation (Sampson) (4). However, although 90% of women have retrograde menstruation, the fact that EMS is observed to a lesser extent suggests that additional factors such as inflammatory and immune factors are effective in the development of the disease (5).

Oxidative stress (OS) is oxidant-antioxidant imbalance in favor of the oxidants. Antioxidant system consists of enzymatic (e.g. catalase, superoxide dismutase) and non-enzymatic (e.g. vitamin C and selenium) substances. Recent findings have shown that OS has a key role in the development of EMS and spread of the endometrial tissue (6,7). The idea that OS may trigger inflammation in EMS, which is a chronic inflammatory disease, is gaining currency. OS may also cause inflammation with the changes it causes in endothelial cells (increased permeability and adhesion molecule expression in endothelial cells) (6). It was found that there was a correlation between the severity of EMS and lipid peroxide activity in blood and peritoneal fluid (8). Moreover, another study determined that low GSH peroxidase and high malondialdehyde levels were found in ectopic endometrial tissue (9). In this case, it increases the possibility of using antioxidant agents in the treatment of EMS. Antioxidant agents have been used for EMS treatment in human studies and animal experiments (9-11).

Alpha lipoic acid (ALA) is a powerful antioxidant found naturally inside every cell of the human body. It has an important role in metabolism due to the fact that it is the cofactor for various mitochondrial enzymes (12). Besides its antioxidant properties, ALA helps regenerate other endogenous antioxidants such as GSH (13). Protective effect of ALA has been investigated in experimental ischemia/reperfusion (I/R) injuries (14,15). To the best of our knowledge, there has been no study examining the ameliorative effect of ALA on EMS. This study aims to examine the effects of ALA on EMS in which there are robust findings indicating that OS plays a role in its etiopathogenesis.

Methods

This study was carried out in the Saki Yenilli Production and Application Laboratory. The study was conducted in accordance with the Animals Research: Reporting of *in vivo* Experiments (ARRIVE) guidelines after obtaining approval from the Ethics Committee of the same center (no: 01.03.01, date: 06/01/2020). Since the experimental nature of the study, informed consent was not obtained.

Thirty sexually-mature, female Wistar albino rats weighing 180-220 grams were used in this experiment. The rats were monitored for a few days before the first phase of the experiment and were determined to be healthy.

The rats were randomly dived in three groups: sham (n=10), EMS (n=10) and EMS + ALA (EMS + ALA, n=10). A combination of 7 mg/kg xylazine hydrochloride (Bayer, Turkey) and 50 mg/kg ketamine hydrochloride (Eczacıbası, Turkey) was intraperitoneally injected for anesthesia. Before starting surgical procedure, approximately 1 mL of intravenous blood was taken from all rats. These samples were centrifuged at 4,000 rpm for 10 minutes. Serums were stored at -80 °C for biochemical evaluation. The rats were put on surgical platform in the supine position. After shaving the abdominal area and cleaning with 10% povidone-iodine, approximately 2-3 cm long vertical incision was made. In the sham group, abdomen was closed with a 4/0 Vicryl Rapide Polyglactin 910 suture (Ethicon Inc., Somerville, NJ). The EMS model was formed within the frame of a procedure determined by Uygur et al. (16) in EMS and EMS + ALA groups. Skin closure was done using 4/0 Vicryl Rapide Polyglactin 910 suture. The EMS + ALA group was started ALA (Sigma-Aldrich, Darmstadt, Germany) at a dose of 50 mg/kg by oral administration using a gavage one day after the procedure, and the treatment was continued for 15 days. At the end of 15 days, second blood samples taken from the rats under anesthesia were centrifuged and stored at -80 °C.

Plasma total antioxidant status (TAS) measurement was made according to the Erel (17) method using a commercial kit (REL Assay Diagnostics, Gaziantep, Turkey). The basis of the method is the reduction of the dark blue-green ABTS radical into colorless ABTS form through antioxidant substances in the samples. 18 µL of plasma was added over 300 µL of reactive (acetate buffer 0.4 mol/L, pH=5.8) solution. The measurement was made at 660 nm wavelength after 30 seconds using a spectrophotometer device (Shimadzu UV-1800, Kyoto, Japan). Then, reactive

2 (prochromogen ABTS 30 mmol/L) solution was added and kept at 37 °C for 5 minutes and spectrophotometric measurements were made at 660 nm. For the calculation of the measurements, the absorbance change was calculated by deducting the first measurement value from the second measurement value. Then, the calculation was made according to the formula using the absorbance changes: TAS=ΔAbs H_2O - ΔAbs sample/ΔAbs H_2O - ΔAbs standard. The results were presented as mmol Trolox equivalent/L.

Plasma plasma total oxidant (TOS) measurement was made according to the Erel (18) method using the commercial kit (REL Assay Diagnostics, Gaziantep, Turkey). Oxidants in the sample oxidize the ferrous ion-chelator complex into ferric ions. Color intensity is related to the oxidant molecule amount. The measurement was made in line with the measurement protocol included in the kit. 45 µL plasma was added over 300 µL tampon solution (H_2SO_4 25 mM pH=1.75). The measurement was made at 530 nm wavelength with spectrophotometer after 30 seconds. Then, 15 µL substrate solution was added and waited for 5 minutes at 37 °C, and the measurement was repeated with the spectrophotometer device at 530 nm wavelength. For the calculation of the measurements, the absorbance change was calculated by deducting the first measurement value from the second measurement value. Calculations were made according to formula included in the kit: TOS=ΔAbs sample/ΔAbs standard x10. The results were presented as µmol H_2O_2 equivalent/L.

Oxidative stress index (OSI) was calculated using TAS and TOS results according to the following formula (19): OSI (arbitrary unit) = TOS (µmol H_2O_2 equivalent/L)/TAS (µmol Trolox equivalent/L) ×100.

Plasma cancer antigen 125 (Ca 125) level was measured by enzyme-linked immunosorbent assay using a commercial kit (Shanghai SunRed Biological Company, Catalogue no: 201-11-0448).

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS Inc; Chicago, IL, USA) version 20.0. Normality of the variables was analyzed using the Shapiro-Wilk test. Numerical data were presented as mean ± standard deviation. Intergroup differences of the numerical data were evaluated with One-Way ANOVA test. The Bonferroni test was used for the post-hoc analysis. A p value of less than 0.005 was considered statistically significant.

Results

During this procedure, in each group, one rat died. The evaluation of the blood samples taken at the beginning of the procedure (1st day) showed that there were no significant differences between the groups in terms of Ca 125, TAS, TOS and OSI values (Table 1).

Evaluation of the blood samples taken in the 15th day of the procedure showed that there was a significant difference in Ca 125, TOS and OSI values between sham and EMS + ALA groups and EMS group, and in TAS value between sham group and EMS group (Table 2).

Figure 1 and Table 3 show the comparisons of Ca 125, TAS, TOS and OSI values in the 1st and 15th days of the procedure. All parameters in EMS group showed statistically significant differences between the 1st and 15th days ($p<0.05$). There was a significant difference between Ca 125, TOS and OSI values on the 1st day and those on the 15th day in EMS + ALA group, but the difference was not as significant as in EMS group.

Discussion

This study investigates the effects of ALA treatment and the relationship between EMS and OS in an experimental rat EMS model. The study determined that ALA had positive effects on EMS through biochemical indicators. TOS, OSI and Ca 125 values were found to be significantly different in EMS + ALA group compared to EMS group.

EMS etiology is still not clear despite growing information. OS is the imbalance between free radicals such as reactive oxygen species (ROS) and antioxidant defense system. OS is thought to have a role in the

Table 1. Comparison of biochemical parameters of the groups in the 1st day

	Sham (n=10)	EMS (n=10)	EMS + ALA (n=10)	p value
Ca125	1.19±0.09	1.22±0.07	1.18±0.12	0.611
TAS	1.95±0.36	1.73±0.40	1.87±0.23	0.364
TOS	14.06±2.26	14.39±3.24	14.12±3.59	0.968
OSI	7.39±1.69	8.42±1.48	7.73±2.37	0.467

One-Way ANOVA test. Ca 125 (U/mL), TAS (mmol Trolox equivalent/L), TOS (µmol H_2O_2 equivalent/L) and OSI (arbitrary unit).
EMS: Endometriosis, ALA: Alpha lipoic acid, TAS: Total antioxidant status, TOS: Total plasma oxidant, OSI: Oxidative stress index, n: Number

Table 2. Comparison of biochemical parameters of the groups in the 15th day

	Sham	EMS	EMS + ALA	p value
Ca 125	1.25±0.16	1.62±0.15	1.32±0.16	<0.001[a,c]
TAS	1.88±0.39	1.32±0.27	1.62±0.34	0.005[a]
TOS	14.59±1.61	18.69±2.63	15.61±3.15	0.003[a,c]
OSI	8.12±2.09	13.14±2.55	9.93±2.55	<0.001[a,c]

One-Way ANOVA test. Post-hoc analysis Bonferroni test was applied. Ca 125 (U/mL), TAS (mmol Trolox equivalent/L), TOS (µmol H_2O_2 equivalent/L) and OSI (arbitrary unit).
[a]Significantly different in sham group compared to EMS group.
[b]Significantly different in sham group compared to EMS + ALA group.
[c]Significantly different in EMS group compared to EMS + ALA group.
EMS: Endometriosis, ALA: Alpha lipoic acid, TAS: Total antioxidant status, TOS: Total plasma oxidant, OSI: Oxidative stress index

Table 3. Comparison of the 1st and 15th day levels of the biochemical indicators of groups

Groups	Parameters	Mean	SD	p value
Sham	TAS(1)-TAS(2)	0.07	0.66	0.733
	TOS(1)-TOS(2)	-0.52	1.07	0.157
EMS	OSI(1)-OSI(2)	-0.73	3.15	0.481
	Ca 125(1)-Ca 125(2)	-0.05	0.15	0.273
	TAS(1)-TAS(2)	0.41	0.13	<0.001
	TOS(1)-TOS(2)	-4.30	2.93	0.001
	OSI(1)-OSI(2)	-4.72	2.40	<0.001
	Ca 125(1)-Ca 125(2)	-0.39	0,167	<0.001
	TAS(1)-TAS(2)	0.24	0.40	0.089
EMS+ALA	TOS(1)-TOS(2)	-1.48	1.68	0.021
	OSI(1)-OSI(2)	-2.20	2.79	0.034
	Ca 125(1)-Ca 125(2)	-0.13	0.15	0.019

Paired t test. Ca 125 (U/mL), TAS (mmol Trolox equivalent/L), TOS (μmol H_2O_2 equivalent/L) and OSI (arbitrary unit).
(1): 1st day level, (2): 15th day level
EMS: Endometriosis, ALA: Alpha lipoic acid, TAS: Total antioxidant status, TOS: Total plasma oxidant, OSI: Oxidative stress index, SD: Standard deviation

development of EMS as in numerous diseases (20-22). ROS in oviductal fluid affects the reproductive system at various levels from ovulation to implantation. Additionally, ROS molecules may cause damage by adhering to various structures in the cell. Cellular debris in oviductal fluid and erythrocytes forms a source for OS reactions. Erythrocytes are likely to release pro-oxidant and proinflammatory factors, such as heme and iron, into the peritoneal cavity. These factors play an important role in the formation of ROS if not properly cleaned from the environment (23). On the other hand, OS increases the growth and implantation of endometrial cells in the peritoneal cavity. Thus, a vicious cycle forms between EMS and OS. Jamali et al. (9) compared eutopic and ectopic endometrial cells and found that malondialdehyde (MDA) levels increased in ectopic endometrial cells while glutathione (GSH) levels decreased. Turgut et al. (22) conducted a study with 72 women who were operated for different indications and divided the patients into groups based on EMS diagnosis. While the level of OS indicators such as copper, ceruloplasmin and TAS was high in EMS group, the TAS was significantly low. Amreen et al. (8) revealed a

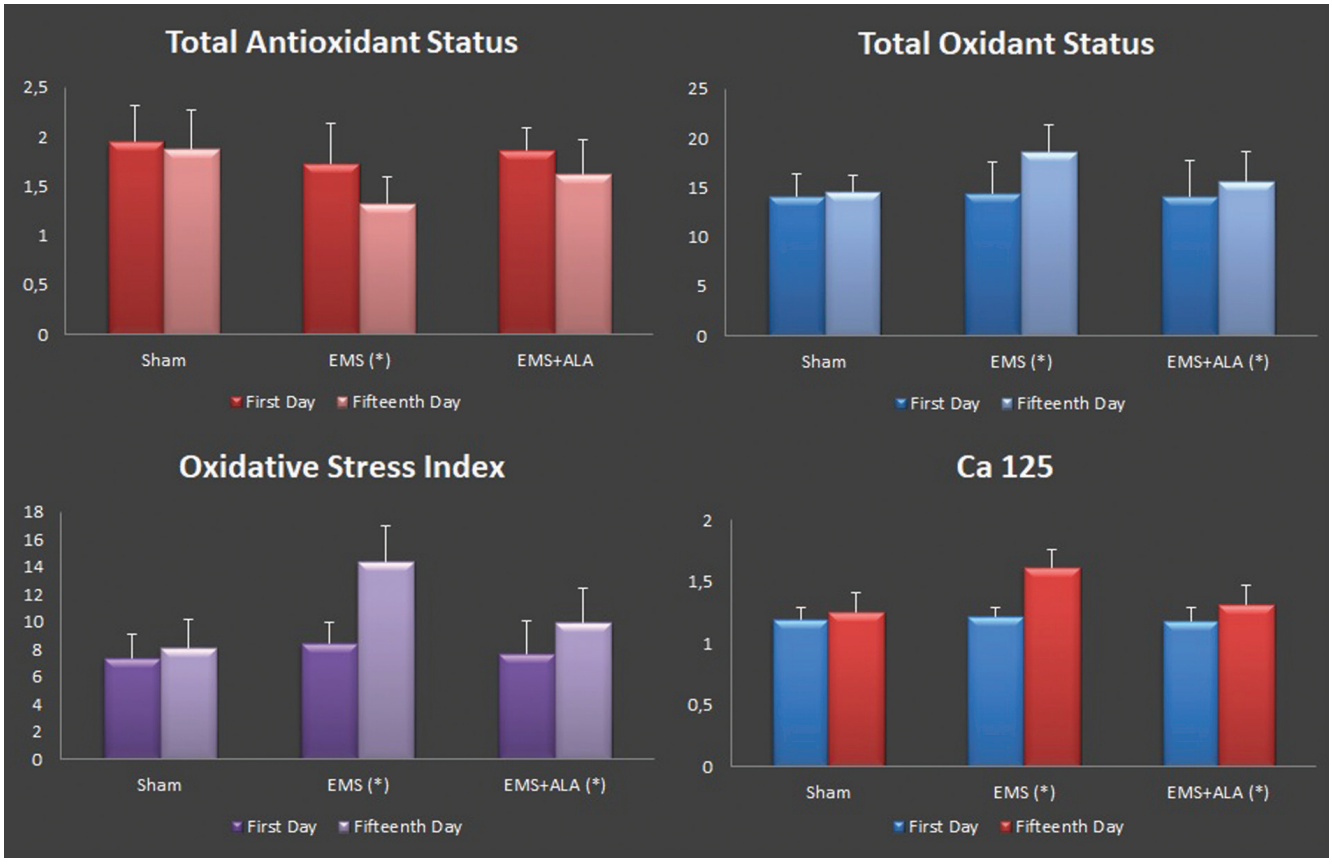

Figure 1. Comparison of the 1st and 15th day levels of the biochemical indicators of groups. [(*): The change of the biochemical indicator is statistically significant]
EMS: Endometriosis, ALA: Alpha lipoic acid

relationship between OS and disease severity. The present study found a significant correlation between EMS and OS, in line with the literature.

Ca 125, an indicator in the glycoprotein structure, is used for the evaluation of ovarian masses. However, its diagnostic value is low, similar to other cancer indicators (24). Studies showed that Ca 125 increases in various malign and benign conditions such as chronic liver diseases, EMS, pelvic inflammatory disease, ovarian, endometrium and gastrointestinal tract cancers (25-29). Studies also showed that Ca 125 level which is known to increase in EMS is correlated with the stage of illness (27). Oliveira et al. (30) revealed that Ca 125 measurement made in mid-cycle was more effective in EMS diagnosis. In the present study, we used CA 125 level to verify EMS diagnosis and found that elevated Ca 125 increased the probability of the diagnosis. Additionally, the study found that ALA treatment significantly decreased the Ca 125 level.

Cells try to be freed from oxidant stress with enzymatic and non-enzymatic antioxidant mechanisms. Numerous antioxidant substances have been used against OS in non-enzymatic chol (9-12,14). Erten et al. (11) examined the effects of vitamin C on endometriotic implants and found that vitamin C suppressed the growth of endometrial implants and reduced the size of these implants. Another study found that caffeic acid may decrease EMS-related complications by reducing OS (9). Resveratrol has been used to reduce the effects of OS and similar results obtained (31). Additionally, antioxidants have been found to be effective in reducing EMS-related pain (32). ALA is a powerful antioxidant that is a cofactor for disulfide structures and is synthesized within a number of tissues including the liver (13). 20-40% of orally taken ALA get into circulation and reach to the highest plasma concentrations within 30-120 minutes (33). A study examining the effects of ALA on intestinal I/R damage determined that there was a statistically significant difference in MDA and GSH levels between ALA-treated and nontreated rats (34). Deng et al. (35) determined that ALA in myocardial I/R had a positive effect on heart functions after I/R by reducing necrosis, apoptosis and inflammation in cardiomyocytes. As we mentioned above, there is a vicious circle between EMS and OS. We think that ALA neutralizes ROS and reduces the effects of these molecules such as inflammation, angiogenesis, adhesion and endometriotic cell differentiation. If we consider the relationship between EMS and OS, it can be said that ALA had a positive effect on EMS in our study.

Study Limitations

The limitations of this study were that EMS was evaluated with only biochemical methods, and histopathological verification was not done. Another limitation is that the verification rate of the study results in humans is low due to the fact that it was an animal study.

Conclusion

EMS is a chronic disease that tends to relapse despite various treatments. ALA with proven antioxidant effect reduces OS in EMS; thus, may positively affect the severity and stage of illness and reduce recurrence after treatment. In order to confirm our results, studies including histopathological evaluation are needed.

Authorship Contributions

Concept: T.O., M.Ç., Design: T.O., M.Ç., Data Collection or Processing: T.O., M.Ç., Analysis or Interpretation: T.O., M.Ç., Literature Search: T.O., M.Ç., Writing: T.O., M.Ç.

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Clinical and Radiological Early Results of Acetabulum Fractures Operated with the Modified Stoppa Approach

Modifiye Stoppa Yöntemiyle Yaptığımız Asetabulum Kırıklarının Erken Dönem Klinik ve Radyolojik Sonuçları

Nevzat Gönder, Günhan Karakurum*, Burçin Karslı*, Toktamış Savaş**, Nurcihan Yavuz Savaş***

İslahiye State Hospital, Clinic of Orthopedics and Traumatology, Gaziantep, Turkey

**Gaziantep University Faculty of Medicine, Şahinbey Training and Research Hospital, Clinic of Orthopedics and Traumatology, Gaziantep, Turkey*

***Ceylanpınar State Hospital, Clinic of Orthopedics and Traumatology Şanlıurfa, Turkey*

****Ceylanpınar State Hospital, Clinic of Radiology, Şanlıurfa, Turkey*

Abstract

Aim: To evaluate the follow-up results of patients hospitalized for acetabular fractures and treated with the modified Stoppa approach.

Methods: Records of fifty-two Acetabula from 48 patients who were followed up for at least six months between 2016 and 2019 were retrospectively analyzed. All fractures were classified according to the Judet-Letournel classification along with direct X-rays and 3D computed tomography findings. The postoperative reduction quality and radiological assessments during follow-up visits were evaluated according to Matta's reduction quality criteria and Matta's radiological scoring system. The clinical outcomes were analyzed using the modified Merle d'Aubigné scoring system.

Results: The mean follow-up period of 48 patients included in the study was 9.72 (6-26) months. Excellent clinical results were obtained in 38 acetabula (73%). A significant correlation was found between the reduction quality assessment performed on the postoperative X-rays and the clinical outcome (p=0.002). At the same time, there was a significant correlation between Matta's radiological criteria and clinical outcomes (p<0.001).

Conclusion: This study shows that reduction quality in acetabular fractures and anatomical reduction done with stable fixation under optimal conditions is strongly associated with clinical outcomes.

Keywords: Acetabulum, pelvis, traumatology

Öz

Amaç: Asetabulum kırığı nedeniyle yatırılan ve modifiye Stoppa yöntemiyle tedavi edilen hastaların takip sonuçlarını değerlendirmektir.

Yöntemler: Çalışmaya 2016-2019 yılları arasında en az altı ay izlemi olan 48 hastanın 52 asetabulumu dahil edildi. Veriler retrospektif olarak analiz edildi. Kırıkların tümü elde edilen direk grafi ve üç boyutlu bilgisayarlı tomografi bulguları ile Judet-Letournel sınıflamasına gore sınıflandırıldı. Hastaların postoperative redüksiyon kalitesi ve takiplerdeki radyolojik değerlendirmeleri Matta'nın redüksiyon kalitesi ve Matta'nın Radyolojik Evreleme sistemine göre yapıldı. Klinik sonuçlar Modifiye Merle D'Aubigne Değerlendirme ölçeği'ne göre değerlendirildi.

Bulgular: Çalışmaya dahil edilen 48 hastanın ortalama takip süresi 9,72 (6-26) ay idi. Otuz sekiz asetabulumda (%73) mükemmel klinik sonuç elde edildi. Hastaların postoperatif röntgenlerinde yapılan redüksiyon kalitesi değerlendirmesi ile klinik sonuç arasında anlamlı bir korelasyon bulundu (p=0,002). Aynı zamanda Matta'nın radyolojik kriterleri ile klinik sonuçlar arasında anlamlı bir korelasyon vardı (p<0,001).

Sonuç: Bu çalışma bize asetabulum kırıklarında redüksiyon kalitesinin, optimum şartlarda stabil fiksasyonla yapılan anatomic redüksiyonun klinik sonuçlarla kuvvetli ilişkili olduğunu göstermektedir.

Anahtar Sözcükler: Asetabulum, pelvis, travmatoloji

Address for Correspondence/Yazışma Adresi: Nevzat Gönder, İslahiye State Hospital, Clinic of Orthopedics and Traumatology, Gaziantep, Turkey
E-mail: n_gonder_02@hotmail.com ORCID: orcid.org/0000-0003-0691-1289

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Introduction

The incidence of high-impact injuries has increased due to increased vehicle use and hectic pace of working and social life. As a result, the number of patients who suffer from acetabular fractures is also increasing. The treatment of acetabular fractures still remains a major issue due to the complex anatomy of the acetabular region, challenges with reaching the fracture site, its rarity compared to other injuries, the complex nature of surgical procedures, and potential complications (1).

Studies have shown that as with all intra-articular fractures, ensuring anatomical reduction, stable internal fixation and early joint movement are important for acetabular fractures; and that the primary factor influencing the clinical outcome is reduction quality (1-5). For this reason, surgical treatment aims to prevent and delay posttraumatic arthrosis, which is the most important late-stage complication of acetabular fractures (6).

The modified Stoppa approach has recently become more popular. The advantages of the modified Stoppa method include easy access to the quadrilateral surface, possibility to perform direct and indirect reduction, less invasiveness and less damage to the soft tissue. In this study, we aimed to compare clinical and radiological findings of patients with acetabular fractures, who were treated with the modified Stoppa approach and followed up adequately, with other studies in the literature.

Methods

Study Design

This clinical trial was performed after obtaining approval from Gaziantep University Clinical Research Ethics Committee (decision no: 2019/256, date: 19.06.2019).

The study population comprised of 48 patients (52 acetabula) who were treated in the orthopedics and traumatology clinic at Gaziantep University Faculty of Medicine due to acetabular fracture between 2016 and 2019 and followed up for at least six months following treatment and volunteered to participate in the study.

Exclusion Criteria:

a. Patients not followed up sufficiently
b. Fractures of the isolated posterior acetabulum
c. Those with a previous history of peritonitis or pelvic inflammatory diseases
d. Those who had pelvic surgery such as C-section, hysterectomy, and bladder surgery
e. Pathological fractures
f. Open fractures
g. Patients followed up conservatively

Clinical Evaluation

The data collection flow was carried out as follows: Orthopedic and general systemic examinations of all patients admitted were performed in the emergency room. Standard X-rays of the anterior and posterior pelvis and the obturator-iliac oblique were taken apart from direct X-rays performed due to additional findings during the examination of patients. Firstly, the patients were stabilized; afterwards, a 3-dimensional pelvic computed tomography was taken as a standard procedure. All patients were applied skeletal traction on the femoral supracondylar region. All patients had urinary catheter inserted as a precaution against injuries of the urogenital system; hematuria was monitored, and urological consultation was requested. For cases of abdominal sensitivity, chest trauma and head trauma, the relevant departments were asked for a consultation. The patients were operated on the 2nd day of the trauma at the earliest, and on the 24th day of the trauma at the latest. Antimicrobial prophylaxis with 1,000 mg cefazolin was administered before surgery and continued for at least 24 hours afterwards. For prophylaxis against heterotopic ossification, the patients received 75 mg/day indomethacin for eight weeks postoperatively. A treatment regimen with low molecular weight heparin was given for prophylaxis against deep vein thrombosis (DVT) until the end of the first postoperative month after patients were hemodynamically stabilized. The patients were prescribed passive exercises in bed on the first operative day, to the extent they tolerated. Depending on their clinical condition, they practiced active exercises from the days 2 or 3 and were mobilized with crutches to prevent strains on the operated joints. The sutures were removed on the 15th day after discharge, and the patients were invited for a follow-up visit after an average of four weeks. Standard X-rays of the anterior and posterior pelvis, iliac and obturator oblique were taken during the follow-up visit. The patients were mobilized with partial weight bearing on the week 6th on average and full weight bearing on the week 10th. Fifty-two acetabula of 48 patients who were followed up for at least six months for a thorough final assessment were included in the study.

Clinical assessment of patients during their final follow-up visit was made according to the Modified Merle d'Aubigne clinical evaluation criteria. According to this scoring system, 18 points are interpreted as "excellent", 15-17 points "good", 12-14 points "average" and 3-11 points "poor" (7).

Postoperative reduction quality was evaluated according to Matta's reduction quality criteria and early postoperative X-rays. A maximum residual displacement level of 0-2 mm was considered anatomical, 2-3 mm - fair and >3 mm was graded as poor. X-rays of the anterior

and posterior pelvis, iliac and obturator oblique were taken during final follow-up visit. X-rays of the anterior and posterior pelvis, iliac and obturator oblique were taken on the same day as the surgery if patients' general condition was good; or after improvement of their general condition if patients' general condition was poor. The reduction quality was assessed and analyzed according to the X-rays. On the basis of the X-rays, a classification was done according to Matta's radiological scoring system (8).

All preoperative, intraoperative and postoperative complications and findings were recorded. Any additional injury was also recorded.

Surgical technique

All patients were placed supine on the operating table so that Anteroposterior and Judet images could be taken after the stabilization of the posterior component of the fracture. The extremity on the same side and the operating area were covered with a drape. The broken side was slightly flexed to relax the hip and knee, the iliopsoas, external iliac neovascular bundle and the obturator neovascular bundle. The patients had a Foley catheter inserted to monitor fluid balance during surgery and to avoid bladder damage. The surgeon started the operation on the opposite side of the broken side. Using the modified Stoppa approach, surgical penetration was performed 2 cm proximal to the pubic symphysis with a 12 cm transverse incision. The linea alba was dissected vertically; the bone was reached by loosening the rectus abdominis on its point of attachment to the pubis. The corona mortis was dissected in all patients and attached with a medium sized clip. The obturator was preserved by locating the neurovascular bundle. The fracture was reduced and fixed with a 3.5 mm pelvic reconstruction plate and 3.5 mm cortical screws. In the present study, the lateral window of the ilioinguinal approach was used additionally only for patients with two-column fractures.

Statistical Analysis

Continuous variables are presented as mean and standard deviation, and categorical variables are presented as absolute numbers and percentages. The Shapiro-Wilk test was used for testing the normality of numerical data. Spearman's rank correlation coefficient was used to test the relationships between numerical variables. The relationship between categorical variables was analyzed by the chi-square test. The SPSS 22.0 software package was used for the analyses. For all analyses, a p value of <0.05 was considered statistically significant.

Results

Fifty-two acetabula from 48 patients who were followed up for at least six months were studied within the scope of the study. The mean age of the subjects was 40.75 (15-80 years) and the mean follow-up time was 9.72 months (6-26 months). Forty (83.3%) patients were male and eight (16.7%) were female. The mean time interval between injury and surgery was 5.02 days (2-24 days). Table 1 illustrates the demographic data of the patients included in the study.

The patients had other fractures accompanying their acetabular fractures. Table 2 illustrates these in terms of numbers and percentages.

An examination of the 52 acetabula of 48 patients according to the Judet-Letournel classification showed that the anterior wall fracture was the most frequent form of fracture affecting 16 acetabula (30.7%), while the least common type of fracture was the anterior column fracture affecting one acetabulum (1.9%) (Figure 1).

The modified Gibson incision and trochanteric osteotomy were preferred for one (2%) patient due to the accompanying fracture of the femoral head. In four (8.3%) patients with sacroiliac separation, stabilization was performed with a 3.5 mm reconstruction plate for the sacrum from the posterior aspect. Following the surgeries, X-rays were taken and the postoperative reduction

Table 1. Demographic data of patients

Characteristic	Number of patients (%)
Age (years)	**40.75 (15-80)**
Sex	
Male	40 (83.3%)
Female	8 (16.7%)
Follow-up time (months)	9.72 (6-26)
Surgical approach	
Modified Stoppa	10 (20.8%)
Modified Stoppa + KL	33 (68.7%)
Modified Stoppa + lateral window	3 (6.2%)
Modified Stoppa + KL + lateral window	1 (2%)
Modified Stoppa + modified Gibson	1 (2%)
Trauma etiology	
Fell from height	20 (41.7%)
Pedestrian injury	17 (35.4%)
Motor vehicle injury	10 (20.8%)
Gunshot wound	1 (2.1%)

KL: Kocher Langenbeck, n: Number

Table 2. Fractures accompanying acetabular fractures

Accompanying fracture site	Pelvis	Humerus	Femur	Vertebra	Scapula	Tibia	Clavicula	Radius, ulna	Other
Number of accompanying fractures	11 (22%)	3 (6%)	4 (8%)	3 (6%)	3 (6%)	10 (20%)	2 (4%)	7 (14%)	7 (14%)

quality was evaluated according to Matta's reduction quality criteria. Accordingly, 29 (60.4%) patients had an anatomical reduction, 14 (29.1%) a fair reduction and five (10.4%) a poor reduction. On the basis of Matta's radiological scoring system evaluation made with standard X-rays of the anterior and posterior pelvis, follow-up X-rays were very good in 26 acetabula (50%), good in 11 (21.2%), fair in nine (17.3%), and poor in six (11.5%). No significant difference was observed between Matta's radiological criteria and reduction quality criteria values. (p=0.112).

Clinical assessment of patients during the final follow-up visit was made according to the Modified Merle d'Aubigne clinical evaluation criteria. According to these criteria, excellent clinical results were obtained in 38 acetabula (73%), fair in seven (13.5%) and poor in seven (13.5%). A significant correlation was found between the reduction quality assessment performed on the postoperative X-rays and the clinical outcomes (p=0.002). At the same time, there was a significant correlation between Matta's radiological criteria and clinical outcomes (p<0.001). While there was no significant correlation between modified Merle d'Aubigne score and age (r=-0.260, p=0.075), there was a moderately negative correlation between length of hospital stay and score (r=-0.486, p=0.005).

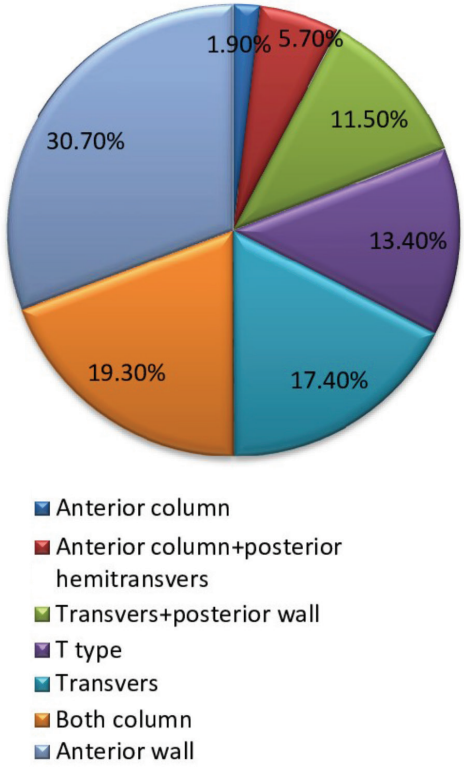

Figure 1. Distribution of fracture types according to the Judet-Letournel classification

In this study, two patients had to undergo surgery again due to failure of the first procedure. In one of the patients, an implant failure was noticed during a postoperative follow-up visit; the patient was reoperated and fixation was attempted, but the implant was removed and a conservative treatment was decided because the intra-op bone was osteoporotic. One patient underwent a total hip arthroplasty due to osteolysis of the femoral head and severe hip pain observed during a follow-up examination. In our study, two preoperative patients had total sciatic damage and two patients had peroneal damage. In one postoperative patient, iatrogenic peroneal nerve injury developed and in the postoperative follow-up at month five, it completely resolved. In our series, one (2%) patient developed surgical site infection that required debridement. Recovery was achieved after debridement and antibiotherapy during patient follow-up.

Discussion

Acetabular fractures may cause serious limitations and disabilities that can seriously affect daily life activities, work and social life. The main cause of the condition is traffic accidents at a rate of 50-70% (9). An investigation of the causes of the acetabular fractures in the study revealed that 20 patients (41.7%) fell from height, 17 patients (35.4%) had a pedestrian injury, ten patients (20.8%) had a motor vehicle injury (driver/passenger), and one patient (2.1%) developed an acetabular fracture following a gunshot injury. Acetabular fractures usually occur after high-impact traumas. For this reason, it is often accompanied by other musculoskeletal and visceral injuries (10,11). In our study, 28 patients (58.3%) had a concomitant fracture in their extremities. In a series by Matta (3), it was reported that extremity injuries accompanied acetabular fractures in 35% of patients.

In our study, anterior wall fracture was the most frequent form of fracture affecting 16 acetabula (30.7%), while the least common type of fracture was the anterior column fracture affecting one acetabulum (1.9%). According to the literature, the most common type of fracture is two-column fracture as reported in 33.3% of cases in a study by Matta (2), and posterior wall fracture as reported in 23.6% of cases in a study by Giannoudis et al. (9). The rarest type of fracture in all studies was anterior wall fracture. The reason why the most common fracture in our study was anterior wall fracture may be the inclusion of patients using the modified Stoppa method. When this method is used, all fractures involving isolated posterior components are excluded from the study.

Determining the time of surgery is important. Many authors have advocated surgery within two to eight days following trauma. In the present study, the mean time to

surgery was 5.02 (±3.72) days. According to our clinical experience, surgery should be performed shortly after stabilization of comorbid conditions that prevent surgery and once the patient is stable hemodynamically. According to the data obtained in the present study, the patients' condition worsened according to Merle d'Aubigne criteria as the length of hospital stay was extended for any reason. In our study, the modified Stoppa method was used for all patients. It has been reported that better reduction, fewer complications, shorter operative time, less neurovascular damage and intraoperative blood loss were observed in patients managed with the modified Stoppa method (12,13).

The modified Stoppa approach is also an alternative to the ilioinguinal approach (14,15). In this study, the modified Stoppa approach was combined with the lateral window in four (8.3%) patients. The combined lateral window approach was used for patients with two column fractures. In a patient series, it was reported that this combination was required in 34 (60%) of 57 patients for fracture reduction and/or fixation (16). In our opinion, the combination of the modified Stoppa approach with lateral window approach is appropriate for patients with a column fracture or an additional iliac wing fracture. Its routine use is not necessary.

In our study, we achieved excellent and good clinical outcomes in 73% of patients. Of the authors who provided an assessment of clinical outcomes after surgical treatment, Matta (2) and Letournel (4) reported a success rate of 87% and 84%, respectively. Ruesch et al. (16) reported acceptable results in 81% of cases (4). Meir Liebergall et al. (17) reported a success rate of 77%.

Clinical outcomes of older patients with acetabular fractures are worse in comparison to younger ones (18,19). In contrast to other studies in the literature, we found no significant difference between patients above 45 and those under 45 years of age in terms of post-operative clinical outcomes, regardless of factors such as fracture type and reduction quality.

The results of hip arthroplasty performed after conservatively treated acetabular fracture or after open reduction procedures are worse in comparison to primary arthroplasty for arthrosis on non-traumatic areas (20,21).

One of the patients in our study underwent total hip arthroplasty due to development of avascular necrosis in the femoral head and hip pain during post-op follow-up. Severe ossification in as many as 50% of cases has been reported in some patient groups (22). No heterotopic ossification leading to a significant loss of function was found in patients included in our study. Letournel and Judet (23) reported 13 cases of death after acetabular fracture surgery, four of which were due to massive pulmonary thromboembolism. More than 75% of the cases of pulmonary thromboembolism occur due to DVT in the lower extremities (24). In our study, no patients had symptoms of DVT.

Study Limitations

First of all, this study is a retrospective study that investigates acetabular fracture treated by modified Stoppa incision. The fracture types are heterogeneous; all fracture types of acetabulum were analyzed. So, we did not evaluate a single fracture group. Our study includes short-term results of acetabulum fractures. On the other hand, we do not know if additional injuries affected the results or not. Also, additional injuries were classified, but we do not know which of them affected results more, for example in the literature it is stated that whether there is an additional fibula fracture with a tibial fracture that could affect the healing time, but in our study, we only investigated whether the patients had additional injuries or not'.

Conclusion

The modified Stoppa approach may be an alternative to other surgical methods because of less soft tissue damage, effective reduction and stabilization of the fracture, bilateral access through a single incision, less likelihood of damage to the neurovascular bundles, and faster recovery in the postoperative period. It might also be acknowledged as a routine procedure in the future.

Authorship Contributions

Concept: G.K. Design: G.K. Data Collection or Processing: N.G., T.S. Analysis or Interpretation: N.G., G.K., B.K., T.S., N.Y.S. Literature Search: N.G. Writing: N.G., G.K.

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Altmış Beş Yaş ve Üzeri Bireylerde Dünya Sağlık Örgütü Tarafından Önerilen Aşılardan İnfluenza, Pnömokok, Herpes Zoster ve Tetanoz Aşıları Hakkındaki Bilme Düzeyi ve Bu Aşıları Yaptırma Düzeyini Belirleme Çalışması

A Study on Determining the Level of Knowledge about Influenza, Pneumococcal, Herpes Zoster, and Tetanus Vaccines among the Vaccines Recommended by the World Health Organization and the Level of Vaccination in Individuals Sixty-Five Years Old and Over

Alpay Medetalibeyoğlu, Elif Ezirmik*

İstanbul Üniversitesi, İstanbul Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, İstanbul, Türkiye
**İstanbul Üniversitesi, İstanbul Tıp Fakültesi, Halk Sağlığı Anabilim Dalı, İstanbul, Türkiye*

Öz

Amaç: Bu araştırmada 65 yaş ve üzeri bireylerde Dünya Sağlık Örgütü'nün (DSÖ) önerdiği aşılardan influenza, pnömokok, herpes zoster ve tetanoz aşılarını bilme ve yaptırma düzeyi ile bu düzeyi etkileyen faktörlerin belirlenmesi amaçlandı.

Yöntemler: Araştırma İstanbul Üniversitesi İstanbul Tıp Fakültesi Hastanesi İç Hastalıkları Polikliniği'ne başvuran 65 yaş ve üzerindeki 147 kişi ile yapıldı. Yirmi bir soruluk anket formu yüz yüze görüşme tekniği kullanılarak kişilere uygulandı.

Bulgular: Araştırmaya katılan yaşlıların %53,7'si aşı yaptırmıştı. İnfluenza aşısı en fazla bilinen (%56,5), tetanoz aşısı ise en fazla yaptırılmış olan (%32,7) aşı idi. Yaşlıların 65-74 yaş grubu referans alındığında; 75 yaş ve üstü olanlarda aşılanmama 2,56 kat [güven aralığı (GA): 1,20-5,44; p=0,014], aşı hakkında bilgi almış olanlar referans alındığında; bilgi almamış olanlarda aşılanmama 2,48 kat (GA: 1,19-5,18; p=0,016), kronik hastalığı olanlar referans alındığında; kronik hastalığı olmayanlarda aşılanmama 6,30 kat (GA: 1,60-24,85; p=0,009) daha fazla olup bu değişkenler yaşlılarda aşı yaptırmayı etkileyen faktörler olarak belirlendi.

Sonuç: Yaşlı nüfusun DSÖ'nün önermiş olduğu aşıları yaptırmasında, sağlık çalışanlarının aşılar hakkında kişileri bilgilendirmesi ve bu aşıları tavsiye etmesi önem taşımaktadır. Yetmiş beş yaş ve üzeri kişilerin bağışıklanması konusunda yeni

Abstract

Aim: We investigated the level of knowledge about influenza, pneumococcal, herpes zoster and tetanus vaccines recommended by the World Health Organization (WHO) for individuals aged 65 and over.

Methods: A total of 147 patients aged 65 and over who attended to the Internal Diseases Outpatient Clinic in İstanbul University Faculty of Medicine Hospital were included in this study. A 21-item questionnaire was administered to the participants.

Results: Fifty-three point seven percent of the elderly who participated in the study had been vaccinated. Influenza vaccine was the most known (56.5%), and tetanus vaccine was the most commonly used (32.7%) vaccine. When the 65-74 age group was taken as a reference, the percentage of adults aged 75 years and older who were not vaccinated was 2.56 times higher [confidence interval (CI): 1.20-5.44; p=0.014]; when those who received information about the vaccines were taken as a reference, in those who did not receive information, the percentage of adults who were not vaccinated was 2.48 times higher (CI: 1.19-5.18; p=0.016); when patients with chronic diseases were taken as reference, in patients without any chronic disease, the percentage of individuals who were not vaccinated was 6.30 times higher (CI: 1.60-24.85; p=0.009).

Yazışma Adresi/Address for Correspondence: Alpay Medetalibeyoğlu, İstanbul Üniversitesi, İstanbul Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, İstanbul, Türkiye
Tel.: +90 212 414 20 00 E-posta: alibeyoglualpay@gmail.com ORCID: orcid.org/0000-0002-5829-9186
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Öz

düzenlemeler yapılmalıdır. Bu kapsamda aile hekimleri tarafından bu yaş grubunun bağışıklanma durumunun özel olarak takip edilmesi veya evde sağlık hizmetleri çerçevesinde bu kişilere bağışıklama hizmetlerinin verilmesi önerilebilir.

Anahtar Sözcükler: Yaşlı, influenza aşısı, pnömokok aşısı, herpes zoster aşısı, tetanoz aşısı

Abstract

Conclusion: It is important for the elderly population to have vaccines recommended by WHO, healthcare professionals to inform people about vaccines and to recommend these vaccines. New regulations should be made for the immunization of people aged 75 and over. In this context, family physicians may be recommended to follow the immunization status of this age group specifically or to provide immunization services to these people within the framework of home health services.

Keywords: Elderly, influenza vaccine, pneumococcus vaccine, herpes zoster vaccine, tetanus vaccine

Giriş

Nüfusların yaşlanması, demografik geçiş sürecinin bir sonucu olarak karşımıza çıkmaktadır. Sağlık sistemlerinin ve sağlık hizmetlerinin gelişmesine paralel olarak dünya genelinde yüksek ölüm oranlarının azalması ve doğurganlık düzeyindeki azalma ile birlikte yaşam süreleri uzamış, doğumda beklenen yaşam süresi artmıştır (1). Doğumda beklenen yaşam süresinin artması, Dünya Sağlık Örgütü'nün (DSÖ) "yaşlı" olarak tanımladığı 65 yaş ve üstü nüfus oranlarının artması anlamına da gelmektedir (1-3). Dünya genelinde 2000-2016 yılları arasında doğumda beklenen yaşam süresi 5,5 yıl artış göstererek 72,0 yıl olmuştur (4). DSÖ'ye göre 2015 yılında %12 olan 60 yaş üstü nüfus oranının 2050'de %22'ye yükselmesi beklenmektedir (5). Ülkemizde de demografik açıdan dünyadakine benzer bir süreç meydana gelmiştir. Türkiye İstatistik Kurumu 2016-2018 verilerine göre ülkemizde beklenen yaşam süresi 78,3 yıldır (6,7). Yaşlı nüfus oranı 2010 yılında %7,2 iken, 2019 yılında %9,1 olmuştur. Bu oranın 2030'da %13'e, 2050'de ise %20,8'e yükselmesi beklenmektedir (8). Türkiye'de 2019'da 7,5 milyon olan 65 yaş ve üstü nüfusun, 2050 yılında 20,8 milyon olması öngörülmektedir (9).

Artan yaşlı nüfusla birlikte artan sağlık sorunları da önem taşımaktadır. Yaşlılara yönelik "hastalıkların önlenmesi" anlamı taşıyan koruyucu sağlık hizmetlerinden bir tanesi de aşılama/bağışıklama hizmetleridir. Aşılama/bağışıklama yaşlılık döneminde bulaşıcı hastalıklardan korunmak amacıyla önerilmektedir (10).

Yaşa bağlı olarak immün sistemde değişiklikler olur. "İmmünosens" olarak adlandırılan bu değişiklikler artan morbidite ve mortaliteden de sorumlu tutulmaktadır. Yaşlılık hem doğal hem de edinsel immün sistemi etkilese de, edinsel immünite üzerinde daha ciddi değişiklikler meydana getirmektedir. T-lenfosit fonksiyonunda azalma, B-lenfosit uyarılması, immünglobülin üretimi ve aşı yanıtında azalma klinikte etkili olan edinsel immün sistem değişiklikleridir (11). Tüm bunlara bağlı olarak immün cevap artan yaşla birlikte duyarsızlaşır. Bu durum aşıların yaşlılarda gençler kadar koruyucu olmamasını açıklar (12).

Günümüzde yaşlılarda bağışıklama uygulamalarının en önemli gerekçesi bu yaş grubunda mortalite ve morbidite sebebi olan durumlardan hastayı korumaktır. Bu nedenle de ülkemizde 65 yaş ve üzeri grup için genel ve özel bağışıklama seçenekleri vardır. İnfluenza, pnömokok hastalıkları, tetanoz, herpes zoster yaşlıları etkileyebilecek aşı ile önlenebilir hastalıklardandır (12).

İnfluenza, *Orthomyxoviridae* ailesinde yer alan, negatif zincirli, zarflı bir RNA virüsünün neden olduğu, tüm dünyada önemli morbidite ve mortalite nedeni olan akut solunum yolu enfeksiyonudur (13,14). DSÖ'ye göre dünyada her yıl 3-5 milyon kişi influenzaya yakalanmakta ve 290.000-650.000 arasında influenza ile ilişkili ölüm meydana gelmektedir (15). Amerika Birleşik Devletleri (ABD) Hastalık Kontrol ve Önleme Merkezi verilerine göre, mevsimsel griple ilişkili ölümlerin %70-85'i 65 yaş ve üzeri kişilerde meydana gelmektedir. Benzer şekilde mevsimsel griple ilgili hastaneye yatışların %50-70'ini 65 yaş ve üzeri kişiler oluşturmaktadır. Yaşlılar için oldukça ciddi olabilen influenzadan ve ciddi komplikasyonlarından korunmanın en iyi yolu ise grip aşısıdır (16). Grip aşısının kontrendikasyonu olmayan bütün erişkinlere yılda 1 kez yapılması önerilir. DSÖ önerilerine paralel olarak ülkemizde de grip aşısı öncelikli tanımlanan gruplara ücretsiz olarak sağlanmaktadır; 65 yaş ve üzerindeki kişiler de bu gruptadır. Yüksek doz aşılar, klasik aşıya göre dört kat daha fazla antijen içerir ve özellikle aşıya yanıtın daha düşük olduğu bilinen 65 yaş ve üstü kişilere önerilmektedir (17).

Pnömokokal enfeksiyonlar, *Streptococcus pneumonia*'nın neden olduğu menenjit, sepsis ve pömoni gibi ciddi hastalıkların yanı sıra sinüzit ve otitis media gibi daha hafif ancak daha yaygın hastalıkları içerir (18). ABD'de 2011 yılında 35.000'den fazla invazif pnömokok olgusu, bu olgulara bağlı 4.200'den fazla ölümün meydana geldiği tahmin edilmektedir. Bu olguların yarısından fazlasının

pnömokok polisakkarit aşısı endikasyonu olan yetişkinlerde meydana geldiği düşünülmektedir (19). Pnömokokal hastalık insidansı ve mortalitesi 50 yaş üzerinde, belirgin olarak da 65 yaş üzerinde artış gösterir. Bu nedenle 65 yaş ve üzeri bireylere pnömokok aşısı yapılması önerilmektedir.

Varicella zoster virüsü (VZV), genellikle çocuklarda görülen suçiçeği ve dorsal kök ganglionlarında latent kalan virüsün reaktive olmasıyla görülen herpes zoster (zona) olmak üzere 2 klinik tabloya neden olur. İmmünosense bağlı hücresel bağışıklığın azalması yaşlıları VZV reaktivasyonuna daha yatkın hale getirir ve bu nedenle herpes zoster insidansı yaşla birlikte artar (20). Herpes zoster aşısı 60 yaş üzerindeki immünokompetan erişkinlere, herpes öyküsü olup olmamasına bakılmaksızın, herpes zoster ve post-herpetik nevraljiden koruma amacıyla tek doz olarak önerilmektedir.

Tetanoz, zorunlu anerob bir bakteri olan *Clostridium tetani*'nin neden olduğu, tetanospazmin toksini ile sinir sistemini etkileyen akut ve genellikle ölümcül bir hastalıktır. DSÖ'ye göre 2018 yılında dünya genelinde bildirilen 15.103 yeni tetanoz olgusu olmuştur. Olguların tamamına yakını hiç aşılanmamış ya da aşının rapel dozlarını yaptırmamış kişilerdir (21,22). DSÖ, bir bireyin 6 doz (3 doz primer, 3 doz rapel) tetanoz aşısı almasını önerir (22). İleri yaşlarda tetanoz antikorlarının çok azaldığı hatta kaybolduğu bilinmekte ama yaşlı nüfusun tetanoz aşılaması ihmal edilmektedir.

Bu araştırmanın amacı, 65 yaş ve üzeri bireylerde DSÖ'nün önerdiği aşılardan influenza, pnömokok, herpes zoster ve tetanoz aşılarını bilme ve yaptırma düzeyi ile bu düzeyi etkileyen faktörlerin belirlenmesidir.

Yöntemler

Bu araştırma 01.09.2020-01.10.2020 tarihleri arasında İstanbul Üniversitesi İstanbul Tıp Fakültesi Hastanesi İç Hastalıkları Polikliniği'ne başvuran 65 yaş ve üzeri kişilerle yapılmış tanımlayıcı tipte bir araştırmadır. Belirtilen tarihler arasında iç hastalıkları polikliniğine başvuran, 65 yaş ve üzeri olan, çalışmaya katılmayı kabul eden kişiler araştırmaya dahil edildi. Bu kriterleri karşılayan 147 kişinin tamamı çalışmaya alınarak herhangi bir örneklem hesabı/seçimi yapılmadı.

Verilerin toplanmasında literatür desteği ile hazırlanan 21 soruluk anket formu kullanıldı. Form yaşlıların sosyodemografik, sosyoekonomik ve kişisel özelliklerini sorgulayan sorular, aşıları bilme ve aşılama durumu ile ilgili bilgileri içermekteydi. Veriler yüz yüze görüşme tekniği kullanılarak toplandı. Aşı yaptırma durumu araştırmanın bağımlı değişkeni iken; aşı bilgisi, sosyoekonomik, sosyodemografik ve kişisel özellikler ise araştırmanın bağımsız değişkenleri olarak belirlendi.

Araştırmanın etik kurul izni 31.08.2020 tarih ve 13074 sayı ile İstanbul Üniversitesi İstanbul Tıp Fakültesi Klinik Araştırmalar Etik Kurulu'ndan alındı.

İstatistik Analiz

Verilerin analizinde kategorik veriler sayı ve yüzdelerle birlikte sunuldu. Kategorik verilerin karşılaştırılmasında ki-kare ve Fisher's Exact test kullanıldı. Tek değişkenli analizde anlamlı çıkan bağımsız değişkenler çok değişkenli analize dahil edildi. Aşı yaptırmama durumu üzerine etkisi olduğu belirlenen bağımsız değişkenlerin etkilerini beraber değerlendirmek için lojistik regresyon analizi yapıldı.

İstatistiksel anlamlılık için %95 güven aralığında, 0,05'in altında bulunan p değerleri anlamlı kabul edildi. İstatistiksel analizler için İstanbul Üniversitesi tarafından lisanslı IBM SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) programının 21.0 versiyonu kullanıldı.

Bulgular

Araştırmaya katılan yaşlıların (n=147); yaş ortalaması 72,58±6,43 (ortanca: 72,0, minimum: 65,0, maksimum: 92,0) idi. Üçte ikisi 65-74 yaş aralığında, %53,1'i kadın, %72,1'i evliydi. %91,2'si il/ilçe merkezinde yaşamaktaydı ve %74,8'i ilkokul ve üstü öğrenim düzeyine sahipti. Katılımcıların %60,3'ü bir sağlık kuruluşu ya da doktor tarafından aşılama hakkında bilgi almamıştı. %86,4'ü ailesine ait bir evde yaşıyordu, %87,1'i yalnız yaşamıyordu. %96,6'sının sosyal güvencesi vardı ve sosyal güvencesi olanların da %95,8'inin sosyal güvencesi Sosyal Güvenlik Kurumu idi. %76,9'unun algılanan gelir durumu yeterli idi. %91,8'i sigara içmiyor, %95,2'si alkol kullanmıyordu ve %89,1'inin bilinen kronik hastalığı vardı (Tablo 1).

Yaşlıların %53,7'si influenza, pnömokok, herpes zoster veya tetanoz aşılarından en az bir tanesini yaptırmıştı, %46,3'ü bu aşılardan hiçbirini yaptırmamıştı. Araştırmaya dahil edilen hastalar, bu dört aşıdan en az birini yaptırmış olanlar ve hiçbirini yaptırmamış olanlar olarak iki gruba ayrıldı. Aşı yaptıran ve yaptırmayan grupların; yaş grupları, aşı hakkında daha önce bilgi alma durumu ve kronik hastalık varlığı arasında istatistiksel olarak anlamlı fark saptandı (p=0,003, p=0,003, p=0,003) (Tablo 1).

Tablo 1'de istatistiksel olarak anlamlı farklılık gösteren bağımsız değişkenler lojistik regresyon analizine dahil edildi. Bu analiz sonuçlarına göre 65-74 yaş grubu referans alındığında; 75 yaş ve üstü olanlarda aşılanmama 2,56 kat [güven aralığı (GA): 1,20-5,44; p=0,014], aşı hakkında bilgi almış olanlar referans alındığında; bilgi almamış olanlarda aşılanmama 2,48 kat (GA: 1,19-5,18; p=0,016), kronik hastalığı olanlar referans alındığında; kronik hastalığı olmayanlarda aşılanmama 6,30 kat (GA: 1,60-24,85; p=0,009) daha fazla olup bu değişkenler yaşlılarda aşı yaptırmayı etkileyen faktörler olarak belirlendi (Tablo 2).

Araştırmada kronik hastalığı olan 131 kişi vardı ve bu kişilere ait toplam 325 tanı mevcuttu. Kişilere kronik

hastalıkları sorulup verdikleri yanıtlar sistemlere göre gruplandığında; en fazla tanının kalp damar sistemi hastalıklarına (%52) ait olduğu, bunu da sırasıyla endokrin sistem hastalıkları (%23,7), solunum sistemi hastalıkları (10,2) ve ürogenital sistem hastalıklarının (%9,2) izlediği görüldü (Tablo 3).

Katılımcılara, "yaşlılık döneminde önerilen aşılardan bildiğiniz var mı?" diye sorulduğunda %56,5'i influenza (grip) aşısı, %8,8'i pnömokok (zatürre) aşısı, %5,4'ü herpes zoster (zona) aşısı yanıtını vermiştir.

Araştırmaya katılan 147 yaşlının; %32,7'si tetanoz aşısı, %31,3'ü influenza aşısı, %8,8'i pnömokok aşısı, %2,7'si herpes zoster aşısı yaptırmıştı (Tablo 4). Tetanoz aşısı yaptıran yaşlıların (n=48), %35,4'ü tetanoz aşısını son 10 yıl içinde yaptırmıştı.

Yaşlıların %87,1'i doktoru önerirse bu aşıları yaptıracağını, %12,9'u ise doktor önerisine rağmen bu aşıları yaptırmayacağını ifade etti. Tablo 5'te aşı yaptırmayacağını belirten kişilerin yüzdesi ve aşı yaptırma nedenleri yer almaktadır (Tablo 5).

Tablo 1. Yaşlıların aşı yaptırma durumu ile aşı bilgisi, sosyodemografik, sosyoekonomik ve kişisel özellikleri arasındaki ilişki

		*Aşı yaptıran	Aşı yaptırmayan	Toplam	p
		Sayı (%)	Sayı (%)	Sayı (%)	
Yaşanılan yer	İl/ilçe merkezi	75 (56)	59 (44)	134 (91,2)	0,082
	Köy/belde	4 (30,8)	9 (69,2)	13 (8,8)	
Yaş	65-74 yaş	61 (62,2)	37 (37,8)	98 (66,7)	**0,003**
	≥75 yaş	18 (36,7)	31 (63,3)	49 (33,3)	
Cinsiyet	Kadın	43 (55,1)	35 (44,9)	78 (53,1)	0,720
	Erkek	36 (52,2)	33 (47,8)	69 (46,9)	
Aşı hakkında bilgi alma[a]	Evet	40 (69)	18 (31)	58 (39,7)	**0,003**
	Hayır	39 (44,3)	49 (55,7)	88 (60,3)	
Medeni durum	Evli	57 (53,8)	49 (46,2)	106 (72,1)	0,990
	Bekar	22 (53,7)	19 (46,3)	41 (27,9)	
Öğrenim durumu	İlkokul altı	16 (43,2)	21 (56,8)	37 (25,2)	0,139
	İlkokul ve üstü	63 (57,3)	47 (42,7)	110 (74,8)	
Ev durumu	Kira	10 (50,0)	10 (50,0)	20 (13,6)	0,718
	Ailesine ait	69 (54,3)	58 (45,7)	127 (86,4)	
Birlikte yaşama	Yalnız	9 (47,4)	10 (52,6)	19 (12,9)	0,550
	Yalnız değil	70 (54,7)	58 (45,3)	128 (87,1)	
Ailedeki kişi sayısı	≤4	72 (54,1)	61 (45,9)	133 (90,5)	0,768
	>4	7 (50,0)	7 (50,0)	14 (9,5)	
Sağlık güvencesi[b]	SGK	77 (56,6)	59 (43,4)	136 (95,8)	0,406
	Yeşil kart	2 (33,3)	4 (66,7)	6 (4,2)	
Algılanan gelir durumu	Yetersiz	16 (47,1)	18 (52,9)	34 (23,1)	0,373
	Yeterli	63 (55,8)	50 (44,2)	113 (76,9)	
Sigara[c]	İçmiyor	73 (54,1)	62 (45,9)	135 (91,8)	0,786
	İçiyor	6 (50)	6 (50)	12 (8,2)	
Alkol[c]	Kullanmıyor	77 (55)	63 (45)	140 (95,2)	0,250
	Kullanıyor	2 (28,6)	5 (71,4)	7 (4,8)	
Kronik hastalık	Yok	3 (18,8)	13 (81,3)	16 (10,9)	**0,003**
	Var	76 (58)	55 (42)	131 (89,1)	
Toplam		79 (53,7)	68 (46,3)	147 (100)	

SGK: Sosyal Güvenlik Kurumu
*İnfluenza, pnömokok, herpes zoster veya tetanoz aşılarından herhangi birini yaptırmış olanlar
[a]Katılımcıların bir sağlık kuruluşu ya da doktor tarafından aşılama hakkında bilgi alıp almadığı
[b]Bu analize sağlık güvencesi olmayan 5 kişi dahil edilmedi
[c]Önceki duruma bakılmaksızın, sigara veya alkol alışkanlığının devam edip etmediği

Tablo 2. Altmış beş yaş ve üstü kişilerde influenza, pnömokok, herpes zoster veya tetanoz aşılamasını etkileyen faktörleri içeren lojistik regresyon analizi sonuçları

Bağımsız Değişkenler		B	S.E.	Wald	OR	%95 GA	p
Yaş	65-74 yaş				Referans		
	≥75 yaş	0,941	0,385	5,992	2,56	1,20-5,44	**0,014**
Aşı hakkında bilgi alma	Evet				Referans		
	Hayır	0,908	0,376	5,832	2,48	1,19-5,18	**0,016**
Kronik hastalık	Var				Referans		
	Yok	1,841	0,700	6,919	6,30	1,60-24,85	**0,009**

R^2=0,150 (Cox & Snell) 0,201 (Nagelkerke), χ^2 =23,757, p=0,000
B: Beta katsayısı, SE: Standart hata, OR: Odds oranı, GA: Güven aralığı

Tablo 3. Kişilerin kronik hastalık tanılarının sistemlere göre dağılımı

	Sayı	Yüzde
Kalp-damar sistemi hastalığı	171	52,6
Endokrin sistem hastalığı	77	23,7
Solunum sistemi hastalığı	33	10,2
Ürogenital sistem hastalığı	30	9,2
Kas-iskelet sistemi hastalığı	7	2,2
Sindirim sistemi hastalığı	4	1,2
Sinir sistemi hastalığı	3	0,9
Toplam	325	100,0

Tablo 4. Altmış beş yaş ve üstü kişilerde influenza, pnömokok, herpes zoster ve tetanoz aşılarının bilinmesi ve bu aşıları yaptırmış olma oranları

		Sayı (%)
İnfluenza aşısı (kendiliğinden)	Evet	83 (56,5)
	Hayır	64 (43,5)
İnfuluenza aşısı (okunduğunda)	Evet	119 (81,0)
	Hayır	28 (19,0)
İnfluenza aşısı yaptırmış olma	Evet	46 (31,3)
	Hayır	101 (68,7)
Herpes zoster (kendiliğinden)	Evet	8 (5,4)
	Hayır	139 (94,6)
Herpes zoster (okunduğunda)	Evet	78 (53,1)
	Hayır	69 (46,9)
Herpes zoster aşısı yaptırmış olma	Evet	4 (2,7)
	Hayır	143 (97,3)
Pnömokok aşısı (kendiliğinden)	Evet	13 (8,8)
	Hayır	134 (91,2)
Pnömokok aşısı (okunduğunda)	Evet	86 (58,5)
	Hayır	61 (41,5)
Pnömokok aşısı yaptırmış olma	Evet	13 (8,8)
	Hayır	134 (91,2)
Tetanoz aşısı yaptırmış olma	Evet	48 (32,7)
	Hayır	99 (67,3)
Toplam		147 (100)

Araştırmamızdaki yaşlılar, son 3 ay içinde %85,7 oranında aile sağlığı merkezine (ASM), %81,6 oranında üniversite hastanesine, %61,9 oranında devlet hastanesine, %14,3 oranında özel hastaneye veya muayenehaneye başvurduğunu, %8,8 oranında 112 acil sağlık hizmetlerinden, %4,1 oranında ise evde sağlık hizmetlerinden faydalandığını belirtti. Hastaların %27,2'si son 3 ay içinde hastanede yatarak tedavi hizmeti aldığını ifade etti.

Tartışma

Araştırmamıza katılan 147 yaşlının, influenza, pnömokok, herpes zoster ve tetanoz aşılarından en az birini yaptırma oranı %53,7 idi. Erdoğdu ve ark.'nın (23) Türkiye'nin kuzeydoğusunda yer alan TRA2 bölgesinde (Kars, Ağrı, Iğdır, Ardahan) 65 yaş ve üzeri kişilerle yapmış olduğu çalışmada; influenza, pnömokok ve herpes zoster aşılarından en az birini yaptırma yüzdesi %12,5 idi. Bal ve ark.'nın (24) Mersin'de yapmış olduğu çalışmada, 65 yaş ve üzeri kişilerin aşı yaptırma oranı %30,4 idi. İstanbul'da Uzuner ve ark.'nın (25) 18 yaş üstü erişkinlerle yapmış olduğu çalışmada, katılımcıların %57,9'u hayatında en az 1 kez erişkin aşısı yaptırdığını belirtti. Antalya'da Aşık'ın (26) erişkinlerle yapmış olduğu bir çalışmada ise en az bir erişkin dönem aşısını yaptırmış olanların oranı %59'du. Avrupa'da 24 ülkenin sonuçlarını içeren büyük ölçekli çok merkezli ADVICE araştırmasında ise, aşı yaptırma oranı medyan değeri %44,7 (minimum: %1, maksimum: %77,4) olarak bildirilmiştir. Bu araştırmaya göre aşılama oranlarının en yüksek olduğu Avrupa ülkeleri Hollanda ve Birleşik Krallık'tır (27). Çalışmamızdaki aşılama oranları da literatür ile benzer sonuçlar göstermektedir.

Araştırmamızda kronik hastalığı olan 131 kişi vardı ve bu kişilere ait 325 tanının yarısı kalp damar sistemi hastalıklarına (%52,6) aitti; bunu da sırasıyla endokrin sistem hastalıkları (%23,7), solunum sistemi hastalıkları (%10,2) ve ürogenital sistem hastalıkları (%9,2) izledi. Bal ve ark.'nın (24) Mersin'de 65 yaş ve üstü kişilerle yaptığı çalışmada ise kalp damar sistemi hastalıkları (%82,6), endokrin sistem hastalıkları (%46,3), solunum sistemi

hastalıkları (%10,9) ve kas-iskelet sistemi hastalıkları (%10,0) oranında bulunmuş ve bizim araştırmamızdakiyle benzer bir sıralama göstermiştir.

Araştırmamızda aşı yaptıran ve yaptırmayan gruplar arasında kronik hastalık varlığı açısından istatistiksel olarak anlamlı fark saptandı (p=0,003). Kronik hastalığı olmayan grupta aşılanmama, kronik hastalığı olan gruba göre 6,3 kat daha fazlaydı (p=0,009). Kronik hastalığı olanların aşı yaptırma oranı %58; kronik hastalığı olmayanların aşı yaptırma oranı %18,8'di. Bu durumun, kronik hastalığı olmayan yaşlıların aşılar ile ilgili yeterince bilgilendirilmemesi ile ve bu kişilerin kendini sağlıklı gördüğü için aşı yaptırmaması ile ilgili olabileceği düşünüldü. Bal ve ark.'nın (24) 65 yaş ve üzeri kişilerle yaptığı çalışmada kronik hastalığı olanların %81'i aşılarını yaptırdığını belirtmişti. Gorska-Ciebiada ve ark.'nın (28) Polonya'da diyabetli yaşlılarla yapmış olduğu çalışmada komorbidite sayısı; influenza aşısını [Odds oranı (OR)=1,351, p=0,004] ve pnömokok aşısını (OR=2,778, p=0,000) yaptırma üzerinde etkili bulunmuştur (28).

Araştırmamızda aşı yaptıran ve yaptırmayan grupların yaş grupları arasında istatistiksel olarak anlamlı fark saptandı (p=0,003). Yetmiş beş yaş ve üzeri grupta aşılanmama, 65-74 yaş grubuna göre 2,56 kat daha fazlaydı (p=0,014). Bal ve Borekci'nin (24) yaptığı çalışmada da yaş grupları ile aşı yaptırma durumu arasında anlamlı fark vardı (p=0,001). Ancak Erdoğdu ve Çatak'ın (23) ve Vural ve ark.'nın (29) yaptığı çalışmalarda aşılanma durumu ile yaş grupları arasında istatistiksel olarak anlamlı fark bulunmamıştı. Yapılan çalışmalarda 75 yaş ve üzeri bireylerin hem aile hekimine hem de acil servise başvurularının 65-74 yaş grubuna göre daha az olduğu, bu yaş grubunda artan yaşla birlikte kronik hastalık sayısının ve yatağa bağımlılığın arttığı gösterilmiştir (30,31). Araştırmamızda 75 yaş ve üstü bireylerin aşı yaptırmama oranlarının 65-74 yaş grubuna göre yüksek olmasının; bu yaş grubunun sağlık hizmeti almak için hastaneye veya aile hekimine daha az başvurmaları ve yaşla birlikte artan yatağa bağımlılık oranlarıyla ilişkili olabileceği düşünüldü.

Tablo 5. Doktorları tarafından influenza, pnömokok, herpes zoster ve tetanoz aşıları önerilse aşı yaptırmak istemeyen kişilerin oranı aşı yaptırmama nedenleri

Cevaplar	Sayı (%)
İstemiyorum	9/147 (6,12)
Zararlı olduğunu düşünüyorum	5/147 (3,40)
Neden belirtmedi	2/147 (1,36)
Çok hastalığım olduğu için istemiyorum	1/147 (0,68)
Doktora gitmek istemiyorum	1/147 (0,68)
Şikayetim olmadığı için düşünmüyorum	1/147 (0,68)
Toplam sayı (%)	19/147 (12,92)

Araştırmamızda, daha önceden sağlık kuruluşundan ya da doktordan aşılama hakkında bilgi alanların oranı %39,7 idi. Aşı yaptıran ve yaptırmayan grupların aşı hakkında bilgi alma durumları arasında istatistiksel olarak anlamlı fark saptandı (p=0,003). Aşı hakkında bir sağlık kuruluşundan ya da doktordan bilgi almamış olan kişilerde aşılanmama, bilgi almış olanlara göre 2,48 kat daha fazlaydı (p=0,014). Erdoğdu ve Çatak'ın (23) yapmış olduğu çalışmada aşı hakkında bilgi alma oranı %5,5'ti. Bilgi almamış olanlarda aşılanmama, bilgi almış olanlara göre 6,6 kat daha fazla bulunmuştur (p=0,001). Bu sonuç araştırmamızı destekler niteliktedir. Aşık'ın (26) yaptığı çalışmada aşılama hakkında doktor/eczacı tarafından bilgilendirilmiş olma oranı %27 idi. Ancak bu çalışmada aşılama durumu ile bilgi alma durumu arasında anlamlı fark saptanmamıştı (p>0,05). Araştırmamızdaki katılımcıların bilgi almış olma oranları bu çalışmalardaki oranlara göre daha yüksektir.

Araştırmamızda katılımcıların influenza, pnömokok ve herpes zoster aşılarını bilme oranları sırasıyla %56,5, %8,8 ve %5,4 olarak; tetanoz, influenza, pnömokok ve herpes zoster aşısını yaptırma oranları sırasıyla %32,7, %31,3, %8,8 ve %2,7 olarak bulundu. Ünal ve ark.'nın (32) Denizli'de yaptığı, 80.047 kişiye ait aşılanma verilerinin incelendiği çalışmaya göre son 5 yılda yaşlı popülasyonun sadece %11,6'sı pnömokok aşısı olmuştu. Erer ve ark.'nın (33) İzmir'de kronik obstrüktif akciğer hastalığı tanılı hastalarla yaptığı çalışmada influenza ve pnömokok aşılarını bilme oranları %49 ve %12; bu aşıları yaptırma oranları ise %40 ve %10'dur. Aşık'ın (26) Antalya'da erişkin aşılamalarını araştırdığı çalışmada en fazla bilinen aşı influenza (%32); en fazla yapılan aşı ise tetanoz aşısı (%45,7) olmuştur. Doherty ve ark'nın (34) ABD'de yaptığı çalışmaya göre 65 yaş ve üzeri kişilerin influenza aşısı yaptırma oranı %67, tetanoz ve pnömokok aşılama oranları %55-60; 60 yaş ve üzeri herpes zoster aşı yaptırma oranı ise %24'tü ve bu oranlar düşük olarak yorumlanmıştı. Bu çalışma sonuçlarına kıyasla ülkemizdeki aşılama oranları ABD'ye göre oldukça düşüktür. Çalışmamızdaki aşılama oranları Türkiye'de yapılan diğer çalışma sonuçlarıyla benzerlik gösterse de, bu durum ülkece 65 yaş ve üzeri kişilerde aşılanma düzeyimizin düşük olduğunu göstermektedir.

Araştırmamızda doktoru önerse de aşıları yaptırmayacağını belirten 19 yaşlı (%12,9) vardı. Neden olarak ise en sık verilen yanıtlar "Aşı yaptırmak istemiyorum" (%6,12) ve "Aşının zararlı olduğunu düşünüyorum" (%3,40) olmuştur. Erdoğdu ve Çatak'ın (23) yaptığı çalışmada en sık neden "yan etki korkusu" (%6,3) ve "sağlıklı olduğum için aşı yaptırmayı düşünmüyorum" (%5,5) olarak belirtilmiştir. Bal ve Borekci'nin (24) yaptığı çalışmada ise aşı yaptırmayan

kişiler, en sık aşı hakkında bilgisi olmadığı için (%69,1) ve aşının gerekli olduğunu düşünmediği için (%24,3) aşı yaptırmadığını ifade etmiştir. Uzuner ve ark.'nın (25) yaptığı çalışmada ise kişilere eksik aşıları varsa neden yaptırmadığı sorulmuş ve katılımcıların %47,1'i konu hakkında bilgilendirilmediğini, %43,2'si ise aşıları yaptırmaya gerek duymadığını belirtmiştir. Tüm bu yanıtlar kişilerin aşılar ve aşılama hakkında yeterince bilgi sahibi olmadığını göstermektedir. Sağlık çalışanları tarafından bu aşıların önerilmesi ve kişilerin bu aşılar hakkında bilgilendirilmesi; erişkin aşılamaları konusunda ciddi önem taşımaktadır. Beş Avrupa ülkesinde 12.036 kişiyle yapılan influenza aşılamasının sorgulandığı bir çalışmada aile hekimi ya da hemşire gibi bir sağlık çalışanının aşıyı önermesinin influenza aşılamasında en önemli teşvik edici faktör olduğu ortaya konmuştur (35).

Çalışmanın Kısıtlılıkları

Çalışmamızın kısıtlılığı, çalışmanın tek merkezli olması ve örneklem sayısının küçük olmasıdır.

Sonuç

Kişilere yönelik koruyucu sağlık hizmetlerinin sunumunda birinci basamak sağlık hizmetleri önemli yer tutmaktadır. Aile hekimleri, sadece kendisine kayıtlı kişilere hizmet sunduğu için hastalarını daha iyi tanıma olanağı vardır. Bu durum da hizmet kalitesini ve verimliliğini olumlu yönde etkilemektedir (36). Araştırmamızdaki yaşlıların %85,7'si son 3 ay içinde ASM'ye başvurmuştu. ASM'ler çalışmamızdaki yaşlıların son 3 ay içinde en yüksek oranda başvurduğu sağlık kuruluşu olmuştur. Aşılama konusunda sağlık çalışanlarının verdiği bilginin aşı yaptırma üzerindeki etkisi düşünüldüğünde yaşlıların en çok başvuru yaptığı aile hekimlerinin koruyucu sağlık hizmetlerinin sunumundaki rolü bir kez daha ortaya çıkmaktadır. Bu amaçla aile hekimleri kendisine yapılan her başvuruyu aşılama için yakalanmış bir fırsat olarak görmelidir. Ünal ve ark.'nın (32) Denizli'de yapmış olduğu bir çalışmada aile hekimlerine aşılama ile ilgili verilen eğitimin pnömokok aşılama oranları üzerindeki etkisi değerlendirilmiştir ve eğitim öncesinde yaşlılarda %11,6 olan pnömokok aşılanma oranı %47,9 artış göstererek eğitim sonrası 8. ayda %59,5'e ulaşmıştır. Buna göre aile hekimleri başta olmak üzere tüm sağlık çalışanlarına; aşı ile önlenebilir hastalıkların epidemiyolojisi ve immünopatogenezi, aşıların etkileri, olası yan etkileri ve önerilen aşılamanın optimal zamanlaması gibi konuları içeren eğitimler verilmesi önerilmekte ve bu eğitimlerle yaşlılarda aşılama oranlarının artırılması beklenmektedir.

Yazarlık Katkıları

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Analysis of Stroke Patients Requiring Re-hospitalisation for Rehabilitation

Rehabilitasyon için Tekrar Hastaneye Yatış Gereken İnme Hastalarının Analizi

Tuğba Aydın, Fatma Nur Kesiktaş, Mustafa Çorum

İstanbul Physical Medicine and Rehabilitation Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, İstanbul, Turkey

Abstract

Aim: The aim of this study is to investigate the pure rate of rehospitalisation in stroke patients hospitalised for rehabilitation purpose only.

Methods: Patients hospitalised according to International Statistical Classification of Diseases and Related Health Problems 10 (ICD 10) code with the following conditions are included in the study: flaccid hemiplegia (G81.0), spastic hemiplegia (G81.1), hemiplegia unspecified (G81.9). The study is conducted with two groups: patients hospitalised once (n=290) and patients re-hospitalised for stroke rehabilitation purposes (n=38).

Results: The mean stroke duration is 12.3±23.5 months. The rate of rehospitalisation is 11.6%. The mean length of hospital stay is 41.4±22.1 days in the hospitalised once group and 40.0±20.1 days in the rehospitalisation group. There are no significant differences between the re-hospitalised and hospitalised once groups in stroke duration, length of hospital stay, Brunnstrom recovery stages for the upper and lower extremities, functional ambulation score and vitamin B12 and D levels.

Conclusion: The pure rehospitalisation rate is unknown due to the many different comorbid diseases included in the rehospitalisation rate for stroke patients. Our study provides the rate of rehospitalisation for rehabilitation purposes only. Indeed, the rehospitalisation rate is low in stroke patients hospitalised for rehabilitation purposes only.

Keywords: Stroke, hospitalization, rehabilitation

Öz

Amaç: Bu çalışmanın amacı, sadece rehabilitasyon amacıyla hastaneye yatırılan inmeli hastaların yeniden hastaneye yatış oranlarını araştırmaktı.

Yöntemler: Hastalıkların ve İlgili Sağlık Sorunlarının Uluslararası İstatistiksel Sınıflaması 10 (ICD 10) koduna göre flaksid hemipleji (G81.0), spastik hemipleji (G81.1) ve hemipleji tanımlanmamış (G81.9) tanısı ile hastanemize yatırılan hastalar çalışmaya dahil edildi. Çalışmaya alınan hastalar iki gruba ayrıldı; birinci grup rehabilitasyon için sadece bir kez hastaneye yatırılan hastaları (n=290), diğer grup ise aynı hastalardan rehabilitasyon amacıyla yeniden hastaneye yatırılan hastaları (n=38) içermekteydi.

Bulgular: Hastaların inmeden sonra geçen süresi ortalama 12,3±23,5 aydı. Yeniden yatış oranı %11,6 idi. Hastanede kalış süresi sadece bir kez hastaneye yatırılan grupta 41,4±22,1 gün, yeniden yatış grubunda ise 40,0±20,1 gün idi. Ortalama inme süresi, hastanede yatış süresi, Brunnstrom'un üst ve alt ekstremite skoru, fonksiyonel ambülasyon skoru, B12 vitamini ve D vitamini düzeyleri arasında anlamlı fark yoktu.

Sonuç: Literatürde inme hastalarında yeniden yatış oranları değerlendirilirken komorbid hastalıklar nedeni ile olan yatışlar da bu orana dahil edildiğinden sadece rehabilitasyon için gerçek yeniden yatış oranları bilinmemektedir. Yalnızca rehabilitasyon amacıyla hastaneye yatırılan inme hastalarında rehabilitasyon nedenli yeniden hastaneye yatış oranı daha düşük bulunmuştur.

Anahtar Sözcükler: İnme, hospitalizasyon, rehabilitasyon

Address for Correspondence/Yazışma Adresi: Tuğba Aydın, İstanbul Physical Medicine and Rehabilitation Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, İstanbul, Turkey
E-mail: drtugbaaydin@gmail.com ORCID: orcid.org/0000-0002-0298-1485
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Introduction

Each year, approximately fifteen million people suffer stroke worldwide. Of these, approximately five million die and another five million require rehabilitation due to morbidity and disability. Considering the social and economic burden associated with stroke, the aim of rehabilitation should be decreasing disability and it should, moreover, be cost-effective (1).

Length of hospital stay for post-stroke rehabilitation varies from country to country, and it is affected by various factors, such as stroke severity, patient age, patient functional capacity, comorbid disease, rehabilitation success and healthcare funding. The average reported rehabilitation length of hospital stay is 17 days in the United States, 35 days in Canada and 75 days in England. Indeed, the length of hospital stay for stroke rehabilitation is generally quite long and expensive compared with other non-stroke diseases (2).

The rehospitalisation rate in patients who have experienced stroke varies from 20% to 27% in epidemiological studies (3). The cause of re-hospitalisation for patients suffering stroke is related to a number of other factors, such as respiratory tract infections and electrolyte disorders (3). Overall, 13% of all treatment costs are due to rehospitalisation in stroke patients (4), and the leading cause of re-hospitalisation is early discharge from hospital (2,5). In the existing literature, the rehospitalisation rate includes stroke-rehabilitation purposes as well as other comorbid diseases. Accordingly, the aim of this study is to investigate stroke patients re-hospitalised for stroke rehabilitation only.

Methods

Ethical approval of the Ethics Committee of the Bakırköy Dr. Sadi Konuk Training and Research Hospital (number: 2018-449) was granted. This was a retrospective descriptive study. The unique protocol IDs were IstPMRTRH-449 and NCT03927469, which were obtained from ClinicalTrials.gov. According to International Statistical Classification of Diseases and Related Health Problems 10 (ICD 10) code, the patients included in the study were hospitalised between January 2015 and January 2019 due to hemiplegia (G81), flaccid hemiplegia (G81.0), spastic hemiplegia (G81.1) and hemiplegia unspecified (G81.9). The patients were selected by scanning the hospital database.

Overall, three hundred eight stroke patients who had no traumatic injury, no intracranial cancer and no intracranial surgery were included in the study. The first group, called the 'no rehospitalisation group', included patients who were hospitalised only once. The second group, called the 'rehospitalisation group', included 38 patients who were re-hospitalised for stroke rehabilitation only. The following factors were evaluated: age, sex, hemiplegia aetiology, season of admission, hemiplegia duration, 25(OH) vitamin D levels, vitamin B12 levels, Brunnstrom recovery stages (upper extremity, lower extremity and hand) and Functional Ambulation Classification (FAC).

In particular, Brunnstrom's staging was used to evaluate the motor development of stroke patients in six stages. The flask phase without the any voluntary movement was stage 1, whereas the presence of isolated movements was stage six (6). FAC is defined in five stages according to the basic motor skills required for functional ambulation. FAC stage 0 is used to indicate non-functional ambulation and stage 5 is used to indicate independent walking at each speed and on ground (7).

Statistical Analysis

The mean, standard deviation, median, range, frequency and ratio values were used in the descriptive statistics of the data. The Kolmogorov-Smirnov test was used to evaluate the distribution of the variables. The Mann-Whitney U test was used to analyse the quantitative independent data, and the chi-square test was used in the analysis of qualitative independent data. In addition, the Wilcoxon test was used in the analysis of quantitative dependent data. Spearman's correlation coefficient was used to identify correlative relationships. The Statistical Package for the Social Sciences version 22.0 software was also used in the analysis.

Results

Statistical analysis was conducted with a total of 328 patients. The mean age of the patients was 65.2±12.9 years. Of these patients, 35.1% (n=115) were female and 64.9% (n=213) were male. The mean stroke duration was 12.3±23.5 months. Overall, 17.1% (n=56) of the patients had haemorrhagic stroke and 82.9% (n=272) had ischaemic stroke. The no re-hospitalisation group included 290 (88.4%). The re-hospitalisation group included 38 patients (11.6%). The mean of 25(OH) vitamin D level was 16.8±14.1 ng/mL and the mean of vitamin B12 level was 398.1±276 pg/mL (Table 1).

Age, sex, stroke duration, seasonal distribution and stroke aetiology were statistically similar between the no rehospitalisation group and the rehospitalisation group ($p>0.05$). The mean length of hospital-stay was 41.4±22.1 days in the no rehospitalisation group and 40.0 ± 20.1 days in the rehospitalisation group (Table 2).

Brunnstrom upper extremity scores, lower extremity scores and hand scores increased significantly in both groups upon discharge ($p<0.05$). Indeed, there were no significant differences in Brunnstrom upper and lower extremity scores between the groups at admission and discharge ($p>0.05$). In addition, there were no significant

differences between the groups for Brunnstrom hand scores during admission (p>0.05). However, Brunnstrom hand scores at discharge were significantly lower in the rehospitalisation group compared with the no rehospitalisation group (p<0.05) (Table 2).

There was no significant difference in FAC scores at admission and discharge between the groups (p>0.05). FAC scores increased significantly in both groups upon discharge compared with admission scores (p<0.05) (Table 2). There was no significant difference in vitamin B12 and vitamin D levels between the groups (p>0.05) (Table 2).

There was no significant correlation between stroke duration and 25(OH) vitamin D levels, lower extremity Brunnstrom scores and FAC scores (p>0.05). A significant negative correlation was observed between the duration of hemiplegia and vitamin B12 levels (p<0.05). There was a significant positive correlation between stroke duration and Brunnstrom upper extremity scores and hand scores (p<0.05). A significant positive correlation was observed between vitamin B 12 and 25(OH) vitamin D levels (p<0.05). There was no significant correlation between 25(OH) vitamin D and FAC and Brunnstrom hand, upper and lower extremity scores (p>0.05) (Table 3).

Discussion

The length of hospital-stay is longer, more expensive and mortality rate is higher in stroke patients than in those with other medical diagnoses. In addition, stroke patients have higher rehospitalisation rate than patients with other diseases (8). Unfortunately, relatively few studies exist about rehospitalisation rates in stroke patients (9,10), and the studies that do exist are not restricted to stroke, but, rather, include other comorbid diseases, such as diabetes and pneumonia. In other words, the number of studies investigating the rates of re-hospitalisation for strictly rehabilitation purposes is limited. Accordingly, we designed this study to understand the factors related to rehospitalisation for rehabilitation only.

In the literature, the incidence of stroke is higher in men than in women, which is consistent with our study since 64.9% of patients were male. In our study, ischaemic strokes accounted for 82% of cases (32% large vessel occlusion/infarction, 32% embolism and 18% small vessel occlusion) and haemorrhagic strokes accounted for 18% (11% intracerebral haemorrhage and 7% subarachnoid haemorrhage) (11,12). Indeed, the ischaemic/haemorrhagic rates are similar to those in the literature.

In the literature, the rate of rehospitalisation of stroke patients varies depending on age, time since discharge, stroke severity and impairment type. In a study by Johansen et al. (13), stroke patients were examined over a year. Here in, re-hospitalisation rates including all comorbid diseases were found to be between 25% and 37% (13). In a study by Tseng and Lin (14), 49.5% of stroke patients were re-hospitalised within one year for stroke and other comorbid diseases. The rate of rehospitalisation in our study was relatively low at 11.6%, which can be attributed to the acceptance of patients who were eligible for only rehabilitation. In other words, patients with other life-threatening diseases, such as acute stroke, cardiac problems, electrolyte disorders and pneumonia, were not accepted for rehabilitation in our study.

Ottenbacher et al. (3) examined 80-180 days' worth of data of 15,992 stroke patients after discharge, finding no relationship between gender and age with regard to the rehospitalisation rate. We did not find any study that compared stroke duration with re-hospitalisation rates in the literature search. In our study, contrary to expectations,

Table 1. Descriptive data of the study

		Min-max			Median	Mean ± SD (n, %)
Age		16.0-90.0			65.0	65.2±12.9
Sex	Female		-		-	115±35.1
	Male					213±64.9
Side	Right		-		-	152±46.3
	Left					176±53.7
Stroke duration (month)		1.0-165.0			3.0	12.3±23.5
Etiology	Haemorrhagic		-		-	56±17.1%
	Ischemic					272±82.9%
Re-hospitalization	(-)		-		-	290±88.4%
	(+)					38±11.6%
25(OH) vitamin D (ng/mL)		3.0-70.0			13.0	16.8±14.1
Vitamin B12 (pg/mL)		7.0-2000.0			322.0	398.1±276.0

SD: Standard deviation, n: Number, min: Minimum, max: Maximum

Table 2. Comparison of the no re-hospitalization and re-hospitalization groups							
		No re-hospitalization group		Re-hospitalization group		p	
		Mean ± SD (n, %)	Median	Mean ± SD (n, %)	Median		
Age		65.2±13.1	65.0	65.5±11.3	65.0	0.951	m
Sex	Female	102±35.2%		13±34.2%		0.907	χ^2
	Male	188±64.8%		25±65.8%			
Stroke duration (month)		10.9±20.6	3.0	20.6±36.0	7.5	0.068	m
Duration of initial hospital stay (days)		41.4±22.1	42.0	40.0±20.1	40.0	0.823	m
Season	Spring	62±21.4%		8±21.1%		0.799	χ^2
	Summer	68±23.4%		7±18.4%			
	Autumn	60±20.7%		7±18.4%			
	Winter	100±34.5%		16±42.1%			
Etiology	Haemorrhagic	52±17.9%		4±10.5%		0.254	χ^2
	Ischemic	238±82.1%		34±89.5%			
Brunnstrom's upper extremity							
Admission score		2.8±1.9	2.0	2.2±1.4	2.0	0.068	m
Discharge score		3.4±1.7	3.0	2.8±1.5	2.0	0.125	m
p		**0.000[w]**		**0.000[w]**			
Brunnstrom's hand							
Admission score		2.8±2.0	2.0	2.1±1.5	1.0	0.062	m
Discharge score		3.4±1.7	3.0	2.7±1.5	2.0	0.041	m
p		**0.000[w]**		**0.000[w]**			
Brunnstrom's lower extremity							
Admission score		3.1±1.7	3.0	2.9±1.6	3.0	0.671	m
Discharge score		3.8±1.5	4.0	3.6±1.5	3.0	0.426	m
p		**0.000[w]**		**0.000[w]**			
FAC							
Admission score		1.4±1.3	1.0	1.2±1.2	1.0	0.614	m
Discharge score		2.5±1.6	2.0	1.9±1.2	2.0	0.084	m
p		**0.000[w]**		**0.000[w]**			
25(OH) vitamin D (ng/mL)		16.9±14.3	13.0	15.9±13.4	10.0	0.622	m
Vitamin B 12 (pg/mL)		398.3±284.8	320.0	396.9±216.8	325.0	0.619	m

[m]Mann-Whitney U test, χ^2 Chi-squared test, [w]Wilcoxon test, FAC: Functional ambulation classification, SD: Standard deviation, n: Number

Table 3. Correlation of data, admission scores, and levels								
		Stroke duration (months)	Vitamin B12	Vitamin D	Brunnstrom's upper extremity	Brunnstrom's hand	Brunnstrom's lower extremity	FAC
Stroke duration (months)	r	-	-0.174	0.018	0.153	0.159	-0.002	0.101
	p	-	**0.022**	0.807	**0.034**	**0.028**	0.980	0.207
Vitamin B12	r	-		0.163	-0.039	-0.187	-0.113	-0.082
	p	-		**0.029**	0.609	0.613	0.135	0.320
25(OH) vitamin D	r	-			-0.084	-0.081	-0.118	-0.068
	p				0.256	0.273	0.111	0.395

Spearman correlation, FAC: Functional ambulation classification

stroke duration was not statistically significant for the no rehospitalisation group and re-hospitalisation group.

Ottenbacher et al. (3) considered the most important factor in the rehospitalisation of patients to be a short initial hospital stay (25.3±14.7 days). In contrast to Ottenbacher et al.'s study (3), the length of initial hospital-stay for our patients was long in the re-hospitalisation group (40.0±20.1 days). In addition, no significant differences were identified between the no rehospitalisation group and the re-hospitalisation group, suggesting that a long initial hospital stay upon admission does not positively affect the rehospitalisation rate.

In another study by Ottenbacher et al. (15), stroke patients were examined for rehospitalisation rate for three months, finding that stroke aetiology (haemorrhagic and ischaemic) is not a significant variable in the rehospitalisation rate, which is consistent with the findings of our study.

In our study, the upper-extremity motor levels, lower-extremity motor levels and ambulation levels increased significantly in both groups after rehabilitation. However, hand-motor healing was lower in the rehospitalisation group compared with the no re-hospitalisation group. In addition, hand recovery was lower in patients with hand paralysis and no measurable grasp strength in the fourth week (12). Although there was no statistically significant difference in the stroke duration, long hemiplegia duration resulted in less hand healing in the re-hospitalisation group. In our study, the mean duration of hemiplegia was 20 months in the re-hospitalisation group. Indeed, it was important to be careful when planning hand rehabilitation during admission for the re-hospitalisation group, because hand-rehabilitation healing was minimal in our study.

The low functional status of patients has been shown to be the most important factor in increased rehospitalisation rates with respect to studies investigating rehospitalisation causes (15,16). Functional ambulation status was investigated using the Functional Ambulation Categories (FAC) scale in our study. Indeed, the functional ambulation levels of the patients were not statistically significant between the two groups; however, there was a significant improvement after rehabilitation when compared with the initial scores.

In studies investigating low 25(OH) vitamin D levels in stroke patients, low levels were associated with an increased risk of hip fracture, cardiovascular disease and sarcopenia (among others) (17,18). In our study, the average value of the 25(OH) vitamin D levels was 16.8 ng/mL, constituting a deficiency level for both groups. Indeed, the majority of researchers agree that a 25(OH) vitamin D level above 30 ng/mL (75 nmol/L) is sufficient, between 20 and 30 ng/mL (50-75 nmol/L) is insufficient, and below 20 ng/mL (50 nmol/L) is deficient (19,20). We found no significant differences in the 25(OH) vitamin D levels between the no re-hospitalisation and re-hospitalisation groups. Moreover, levels of 25(OH) vitamin D were not associated with the season of hospitalisation, which can be explained by low ambulation scores (mean FAC score was 1 in the no rehospitalisation group), indicating that the patients were dependent on other people for mobility and, therefore, mostly resided in non-solar closed areas.

In the literature, high serum vitamin B12 levels in hemiplegia patients have been associated with optimal functional outcomes (16). Indeed, many studies have reported that vitamin B12 deficiency increases the risk of stroke (17,18). Generally, vitamin B12 levels higher than 400 pg/mL are classified as sufficient, between 150-399 pg/mL as insufficient and below 150 pg/mL as deficient (21). The mean vitamin B12 level in our patients was 398.1 pg/mL. Moreover, we found no significant difference between the no rehospitalisation group and the rehospitalisation group.

Although 25(OH) vitamin D level was found to be low in our study, this situation was not associated with stroke duration. Indeed, 40% of stroke patients experienced dysphagia and 16% experienced malnutrition (22,23). This information explains the negative correlation between vitamin B12 levels and stroke duration, which can be attributed to malnutrition.

In our study, the Brunnstrom upper extremity and hand scores had positive correlations with stroke duration. This situation can be explained by motor-level rehabilitation, which is worse in the acute period after stroke (12).

Study Limitations

Many comorbid diseases were included in the re-hospitalisation rates in stroke patients in the literature. The real rates of rehospitalisation are not well-known in patients admitted for rehabilitation purposes only. Unlike the literature, our study provides pure re-hospitalisation rates for rehabilitation purposes only.

Conclusion

In the literature, pure re-hospitalisation rates are unknown. Accordingly, in this study, pure re-hospitalisation rates for rehabilitation purposes only are examined. Indeed, the re-hospitalisation rate was low in stroke patients who were hospitalised for rehabilitation purposes only. Moreover, re-hospitalisation rates were not associated with length of initial hospital-stay, stroke duration and FAC.

Authorship Contributions

Concept: F.N.K., Design: F.N.K., T.A., Data Collection or Processing: T.A., Analysis or Interpretation: F.N.K., T.A, M.Ç., Literature Search: T.A., M.Ç., Writing: T.A.

Conflict of Interest: This study was conducted as a master's thesis. The authors confirm that this article's content has no conflicts of interest.

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Effect of Renal Vein Variations on Apparent Diffusion Coefficient in Asymptomatic Patients

Asemptomatik Hastalarda Renal Ven Varyasyonlarının Böbrek Görünür Difüzyon Katsayısı Değerlerine Etkisi

Elif Gündoğdu, Emre Emekli, Mehmet Oğuzman, Mahmut Kebapçı

Eskişehir Osmangazi University Faculty of Medicine, Department of Radiology, Eskişehir, Turkey

Abstract

Aim: The aim of this study was to investigate whether renal vein variations had an effect on apparent diffusion coefficient (ADC) values in diffusion magnetic resonance imaging (MRI).

Methods: Images of 958 patients who underwent MRI between January 2017 and October 2018 were retrospectively evaluated for renal vein variations based on the records obtained from the image archive. Forty-six patients with renal vein variations and thirty patients of similar age and gender as the control group enrolled in the study. The ADC values of both kidneys were measured at low-high b values.

Results: The ADC values in the left kidney were lower than in the right kidney in both groups ($2.04x10^{-3}$± $0.22x10^{-3}$ mm^2/sec, $1.96x10^{-3}$±$0.17x10^{-3}$ mm^2/sec, for the renal vein variation group; p=0.008 and 2.08x10-3±$0.13x10^{-3}$ mm^2/sec, $1.94x10^{-3}$±$0.11x10^{-3}$ mm^2/sec, for the control group; p=0.0001). However, no significant difference was found between the renal vein variation and control groups in terms of the ADC values in both kidneys.

Conclusion: Renal vein variations had no effect on renal ADC values in asymptomatic patients. Further studies can provide additional information for symptomatic patient groups.

Keywords: Renal vein variations, diffusion magnetic resonance imaging, ADC

Öz

Amaç: Bu çalışmanın amacı, renal ven varyasyonlarının difüzyon ağırlıklı manyetik rezonans görüntülemede (MRG) görünür difüzyon katsayısına (GDK) etkisinin olup olmadığını araştırmaktadır.

Yöntemler: Ocak 2017 ile Ekim 2018 tarihleri arasında abdominal MRG çekilmiş 958 hastanın tetkikleri renal ven varyasyonları açısından hastane görüntü arşivinden retrospektif olarak incelendi. Renal ven varyasyonu olan 46 hasta ve 30 hastadan oluşan kontrol grubunda yüksek ve düşük b değerlerinde her iki böbreğin GDK değerleri ölçüldü.

Bulgular: Renal ven varyasyonu olan grupta ve kontrol grubunda sağ ve sol böbrek GDK değerleri arasında fark saptandı [$2,04x10^{-3}$±$0,22x10^{-3}$ mm^2/sec, $1,96x10^{-3}$±$0,17x10^{-3}$ mm^2/sec; p=0.008 (varyasyonu olan grupta sağ ve sol böbrek, sırasıyla), $2,08x10^{-3}$±$0,13x10^{-3}$ mm^2/sec, $1,94x10^{-3}$±$0,11x10^{-3}$ mm^2/sec; p=0,0001, kontrol grubunda sağ ve sol böbrek, sırasıyla]. Sol böbrek GDK değerleri her iki grupta da sağ böbrekten daha düşüktü. Her iki böbrek GDK değerleri renal ven varyasyonu olan grupta ve kontrol grubunda benzerdi.

Sonuç: Renal ven varyasyonu asemptomatik hastalarda böbrek GDK değerleri üzerinde herhangi etki göstermemektedir. Gelecekte semptomatik hasta gruplarıyla yapılacak çalışmalar ek bilgi verebilir.

Anahtar Sözcükler: Renal ven varyasyonları, difüzyon manyetik rezonans görüntüleme, GDK

Address for Correspondence/Yazışma Adresi: Emre Emekli, Eskişehir Osmangazi University Faculty of Medicine, Department of Radiology, Eskişehir, Turkey
Phone: +90 222 229 39 79 E-mail: emreemekli90@gmail.com ORCID: orcid.org/0000-0001-5989-1897
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Introduction

Left renal vein and inferior vena cava variations are relatively frequent compared to those of the right renal vein due to the complexity of embryological development (1). The most common left renal vein variations are observed in the retroaortic and circumaortic renal veins. Renal vein variations are generally asymptomatic and frequently discovered incidentally (1,2). However, in some cases, increased venous pressure due to compression between the vertebrae and the aorta may cause symptoms, such as left side pain, hematuria, and proteinuria (3,4). It has also been reported that renal vein variations may be associated with left-sided varicoceles, pelvic congestion syndrome, dyspareunia, and dysmenorrhea (5,6). Recently, the prevalence of incidentally detected renal vein variations has increased due to the increased use of imaging techniques.

Magnetic resonance imaging (MRI) can noninvasively assess the kidney structure and function in a single screening session. It is possible to evaluate the microstructure of the kidney using diffusion-weighted imaging (DWI), which evaluates the Brownian motion of water molecules in the tissue and allows the quantification of motion based on the apparent diffusion coefficient (ADC) (7,8). There are many human studies concerning the use of DWI in diffuse renal pathologies (9). There are also studies conducting DW MRI in patients with acute renal failure, acute pyelonephritis, acute graft dysfunction, polycystic disease, amyloidosis, diabetes, various glomerulonephritis, obstruction, renal artery stenosis, and other various etiologies (10). These studies revealed changes in renal parenchyma, such as edema and fibrosis using DW MRI and ADC values.

It is suggested that renal vein variations can cause venous hypertension, which may also be responsible for symptoms. If venous hypertension due to venous variation causes changes in the kidney ADC values, this parameter can be used in the diagnosis and follow-up of these patients. In this study, we aimed to evaluate whether left renal vein variations caused changes in the kidney ADC values.

Methods

Study Subjects

Ethics committee approval was obtained from Eskişehir Osmangazi University Faculty of Medicine (date: 27.11.2018, no: 25403353-050.99-E.128703) and the study was conducted in accordance with the Declaration of Helsinki. The study involved retrospective reevaluation of the upper abdominal MRI recorded between January 2017 and October 2018, obtained from the hospital image archive. Upper abdominal MRI performed in patients with non-urinary system indications (chronic liver parenchymal disease, focal lesion in liver parenchyma, choledocholithiasis, adrenal lesion, pancreatic lesions, etc.) were included in the study. Patients with renal dysfunction and solitary kidneys, and those with images that could not be evaluated for technical reasons (motion artefacts, MRI without diffusion examination at an appropriate value of b) were excluded from the study. As a result, the MRI images of 958 patients, comprising 498 (52%) females and 460 (48%) males were evaluated. The flowchart is presented in Figure 1.

None of the patients had any urinary symptom or pathological finding in urinalysis. Their serum urea and creatinine values were also normal. The presence and type (circumaortic, retroaortic) of left renal vein variations were recorded. Thirty patients of similar age and gender without renal vein variations were selected to form the control group. Renal function values were normal in the control group. The serum urea and creatinine values and urine analysis were also within the normal range.

Magnetic Resonance Imaging

MRI was performed using a 3-Tesla (General Electric, Milwaukee, WI) device. In all examinations, a 48-channel body coil was used. T2-weighted axial and coronal plane images, T1-weighted axial plane images, and diffusion-weighted echo planar images (DW-EPI) were obtained in each patient. The DW sections were obtained in the axial

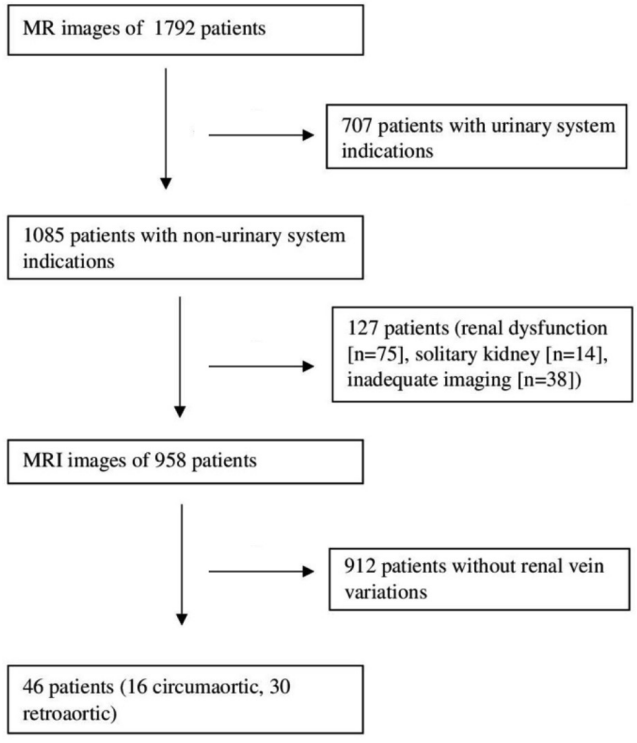

Figure 1. Recruitment schema of the participants
MR: Magnetic resonance

plane using the DW-EPI sequence at low (b=0 s/mm^2) and high (b=1000 s/mm^2) gradient values without breath-holding. The imaging parameters of the DW-EPI sequence were as follows: TR/TE, 9231/64.1; slice thickness, 5 mm; field of view, 42 cm; and matrix size; 98x128. The ADC value was automatically calculated by the device simultaneously. To prevent bowel movements causing artefacts, MRI was performed after four to six hours of fasting. However, the patients were not given any anti-spasmolytic.

Analysis of Images

The images of the patients with renal vein variations and the control group were evaluated using the dedicated workstation (GE, Advantage Workstation 4.3, USA) by two radiologists (one experienced in abdominal imaging) based on consensus. The T1- and T2-weighted images were evaluated for focal kidney lesions. There was no solid renal tumor in patients with renal vein variations. In patients with simple cysts, the levels including the cysts were not included in the measurement. The circular-shaped regions of interest (ROI) with a diameter of 1 cm were placed in the corticomedullary area in both renal parenchyma (Figure 2, 3). Circular ROI was placed in three regions in the upper, middle and lower sections of the posteromedial of both kidneys. All measurements were undertaken by a single radiologist experienced in abdominal imaging. The measurements were performed twice, and the mean ADC values were used for further evaluation. The diameter of the left renal vein in both the control and renal vein variation groups was measured by the same radiologist based on the midpoint between the abdominal aorta and the left renal hilum in the axial plane (Figure 4, 5).

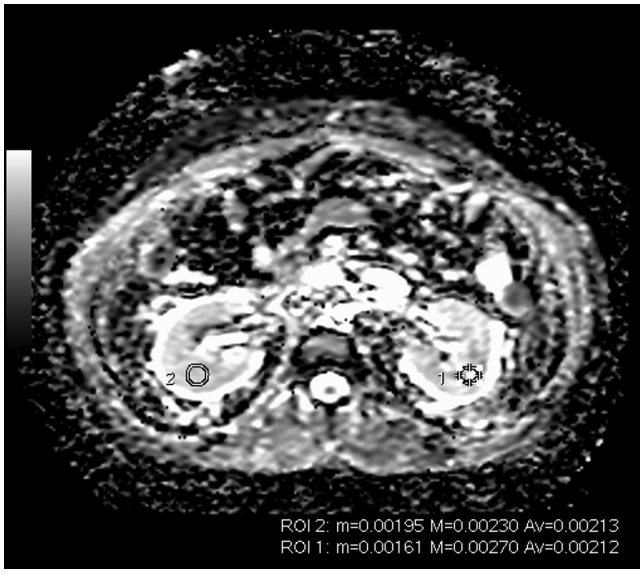

Figure 2. ADC maps (b=1000 s/mm^2) in of a 52-year-old male in the control group. Regions of interest for the ADC measurements of the right and left kidneys are indicated by white circles
ADC: Apparent diffusion coefficient

Statistical Analysis

SPSS software v.22.0 (Chicago, IL) was used for statistical analysis. The Shapiro-Wilk test was used for normality testing. Quantitative variables were shown as arithmetic mean ± standard deviation, and qualitative variables as numbers and percentages. The right and left kidney ADC values in both the control and renal vein variation groups were compared using the Student's t-test. The same test was used to compare the left renal vein diameter between the two groups. The paired samples t-test was used to investigate whether there

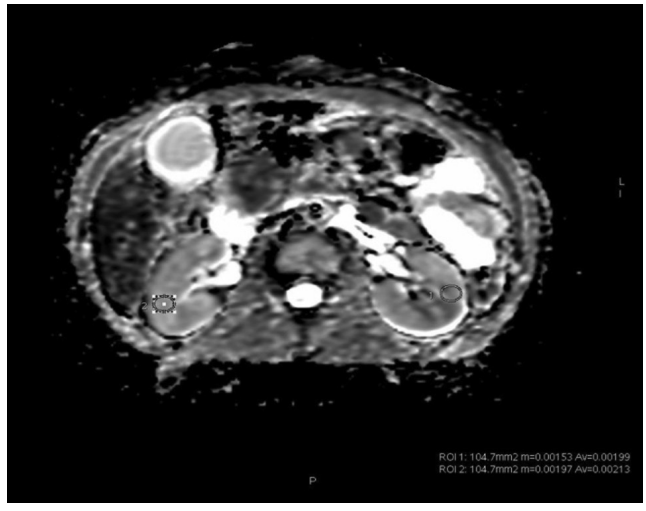

Figure 3. ADC maps (b=1000 s/mm^2) of a 61-year-old male in the renal vein variation group. Regions of interest for the ADC measurements of the right and left kidneys are indicated by white circles
ADC: Apparent diffusion coefficient

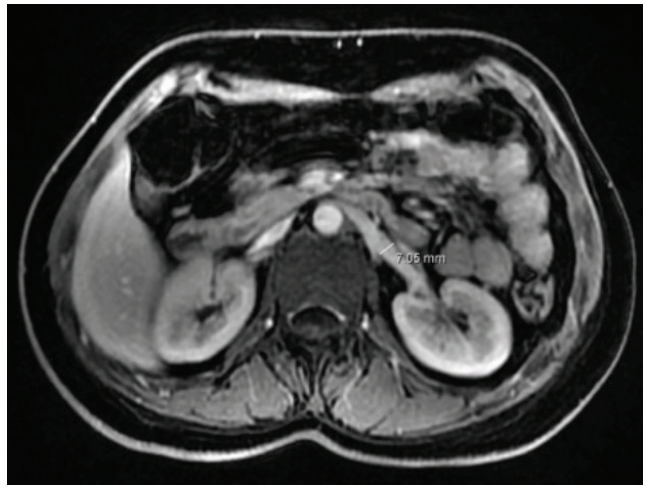

Figure 4. Measurement of the left renal vein diameter on the axial plane images in a 45-year-old female in the control group

was a difference in the right and left kidney ADC values between the two groups.

Results

Left renal vein variations were found in 46 (4.80%) of 958 patients [circumaortic in 16 (Figure 6a and 6b) and retroaortic in 30 (Figure 7)]. There were 24 women (age range: 23-88 years; mean age: 58.1±14.6 years) and 22 men (age range: 30-92 years; mean age: 57.7±16.8 years) with renal vein variations and 18 women (age range: 27-69 years; mean age: 56.2±13.6 years), 12 men (age range: 34-77 years; mean age: 60.5±14.3 years) in the control group. There was no difference in age between the groups.

Table 1 presents the comparison of the data between the two groups. The mean ADC of the left kidney was lower than that of the right kidney in control group p=0.0001). The mean ADC of the left kidney was lower than that of the right kidney in renal vein variation group (p=0.008). In the comparison of the right and left kidney ADC values between the renal vein variation and control groups, no significant difference was found.

Table 1. Comparison of data belonging to groups

Parameters	Renal vein variations group	Control group	p value
Number of patients (n)	46	30	-
Male age/ female age (years)	57.7±16.8/58.1±14.6	60.5±14.3/56.2±13.6	0.12
Male/female (n)	22/24	12/18	-
ADC of right kidney (mm^2/ sec)	$2.04x10^{-3}$±$0.22x10^{-3}$	$2.08x10^{-3}$±$0.13x10^{-3}$	0.26
ADC of left kidney (mm^2/ sec)	$1.96x10^{-3}$ ± $0.17x10^{-3}$	$1.94x10^{-3}$±$0.11x10^{-3}$	0.71
Left renal vein diameter (cm)	7.39±0.90	7.32±0.81	0.75

ADC: Apparent diffusion coefficient, n: Number

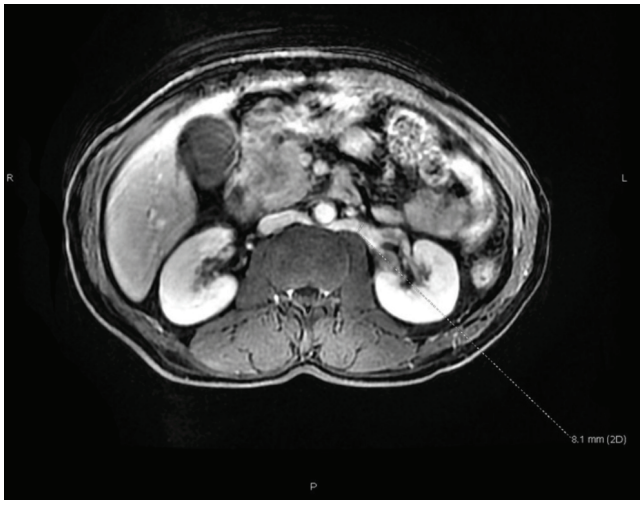

Figure 5. Measurement of the left renal vein diameter on the axial plane images in a 61-year-old male with (retroaortic) renal vein variations

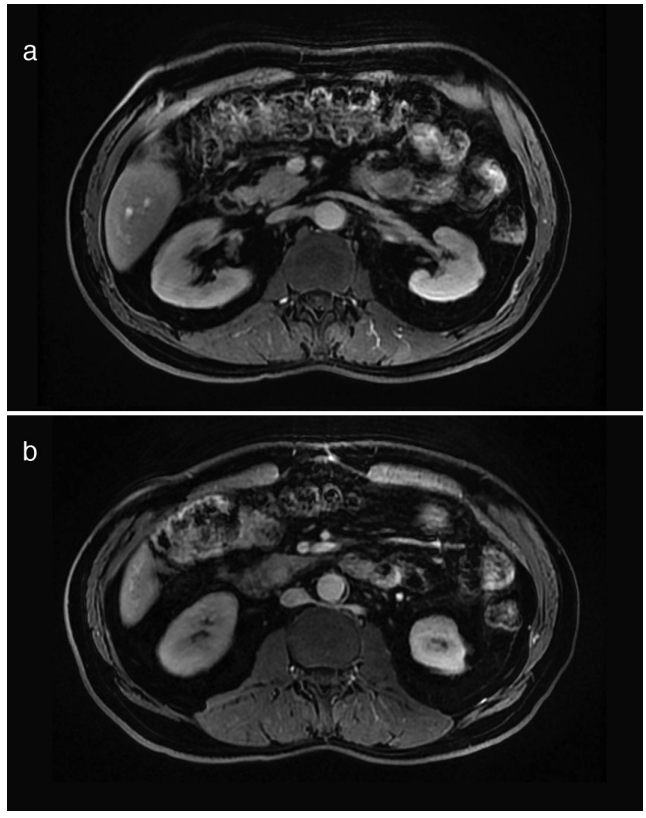

Figure 6. Axial plane MRI showing the circumaortic position of the left renal vein. The left renal vein reaches both the anterior **(a)** and posterior **(b)** of the abdominal aorta
MRI: Magnetic resonance imaging

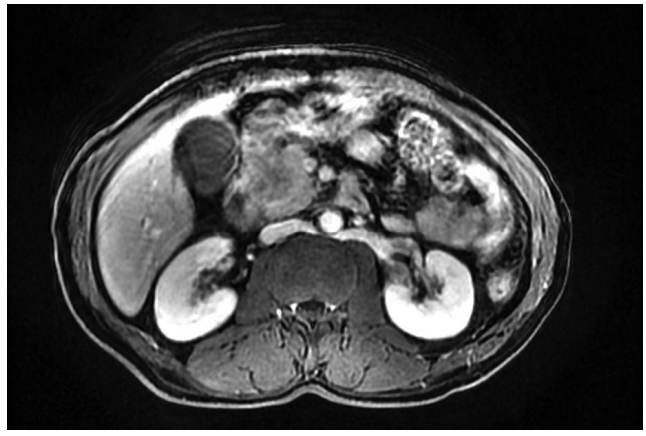

Figure 7. Axial plane MRI showing the retroaortic position of the left renal vein
MRI: Magnetic resonance imaging

Lastly, the mean left renal vein diameter in the renal vein variation group did not differ from that of the control group.

Discussion

Numerous radiological (with computed tomography or MRI), surgical and post-mortem studies have been conducted to investigate renal vein variations. In these studies, the incidence of retroaortic and circumaortic renal vein variations was reported to be 0.5-17% and 0.3-6.8%, respectively (3). In the current study, the incidence of left renal vein variations was similar to the values reported in previous studies.

In recent years, DWI has gained increased interest in the evaluation of chronic kidney disease due to the correlation between reduced tissue water diffusion and fibrosis development (11-14). There are many studies in the literature on the ADC values obtained from both patients with diffuse renal parenchymal diseases and individuals with normal renal parenchyma. These studies generally showed that the ADC values in patients with diffuse renal diseases were decreased, and the glomerular filtration rate and renal ADC values were positively correlated in patients with renal dysfunction (15-17). In patients with both acute and chronic renal failure, ADC values are known to decrease. The relationship between reduced ADC and pathological fibrosis development seems to primarily relate to the renal cortex (11-14). Although the literature contains several studies on the renal functions and diffusion values in patients with diffuse renal diseases, to the best of our knowledge, no study has been undertaken to evaluate the effect of renal vascular structures and renal anomalies on ADC values. Therefore, our study is the first and will contribute to the literature in this regard.

In the literature, different ADC values for the right and left kidneys were found in normal kidneys in studies using different devices with different magnetic field strength (1.5 and 3 Tesla) (18-22). However, in some of these studies, the right and left kidney values were not separately reported (19). Kim et al. (18) found that the ADC values of the left kidney were lower than those of the right kidney at high b values using 3 Tesla MRI devices. However, the authors did not provide any information on whether these differences were statistically significant. Similar to our study, Yoshikawa et al. (22) found that the left kidney ADC values were lower than the right kidney values using a1.5 Tesla MRI device. However, they did not present any information about the statistical significance of their results. In contrast, Song et al. (23) determined that the ADC values of the left kidney were higher than those of the right kidney in individuals with healthy renal function. In our study, a difference was found between the right and left kidney ADC values in both the control and renal vein variation groups. However, similar ADC results between these two groups led us to conclude that renal vein variations had no effect on kidney ADC values.

Variations do not cause pressure changes in the renal vein as long as they are asymptomatic. Therefore, we may not have detected the differences in the ADC value between the control and renal vein variation groups in our study. Even if there is a renal vein pressure change that is not causing deterioration in the renal microstructure, may explain why ADC value is not affected. According to our results, it is possible to conclude that renal vein variations do not cause changes in the kidney microstructure as long as they are asymptomatic.

DWI measures the random motion of water molecules, which can be free or restricted by cellular membranes or other barriers (17). It provides microstructural information about tissue microstructure by using the movement of water to probe extracellular and intracellular extravascular spaces (24). However, the ADC value is affected by not only true water diffusion but also microperfusion and tubular flow in the renal tissue (25-27). In the literature, the use of novel DWI models, e.g. intravoxel incoherent motion (IVIM) and diffusion tensor imaging (DTI), in the assessment of diffuse renal pathologies has been investigated. IVIM could provide more accurate information on pseudo diffusion and true diffusion DTI, an advancement of DW MRI, can offer an insight into the structural properties of tissue by assessing the directionality of water diffusion, which is quantified as the percentage of spatially oriented diffusion. Diffusion anisotropy is related to structural organization, and therefore can be compromised in a pathological process (28). The evaluation of the effects of variations using DTI and IVIM can give more accurate information about the pure diffusion effect. In addition, directional information in DTI is an advantage for vascular structures.

Study Limitations

One of the limitations of our study is that all patients in the group with renal vein variations were asymptomatic. Hematuria and proteinuria were not present in either group. The absence of clinical symptoms in our patients may explain the similarity of the results between the renal vein variation and control groups. Clinically, nut-cracker syndrome is observed in a small proportion of patients with renal vein variations. Studies conducted with symptomatic group scan provide more accurate results. There is no consensus on the treatment method for symptomatic patients or the selection of appropriate cases for treatment. Further studies evaluating ADC parameters

in both symptomatic and asymptomatic groups based on the severity of findings can provide more information concerning the kidney microstructure. ADC values can be one of the parameters that can be considered in treatment selection by providing information about the renal microstructure. The other limitations of our study can be regarded as the relatively low number of patients with renal vein variations. However, this was inevitable considering the low incidence of such variations.

Conclusion

The patients with renal vein variations and the control group had similar ADC values for both the right and left kidneys. Thus, it can be stated that renal vein variations have no effect on kidney ADC values. However, right and left kidney ADC values being different in groups with and without the renal vein variation should be kept in mind when evaluating this parameter in other conditions.

Authorship Contributions

Concept: E.G., E.E., M.K. Design: E.G., M.O., M.K. Data Collection or Processing: E.E., M.O. Analysis or Interpretation: E.G., M.K. Literature Search: E.G., E.E., M.O. Writing: E,G.

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A Comparison of the Effectiveness of Subacromial Injection and Suprascapular Nerve Block in Chronic Shoulder Pain

Kronik Omuz Ağrısında Subakromiyal Enjeksiyon ve Supraskapular Sinir Bloğunun Etkinliğinin Karşılaştırılması

Gonca Sağlam, Fatma Başak Demir*, Berrin Hüner**, Ömer Kuru**

Erzurum Regional Training and Research Hospital, Clinic of Physical Therapy and Rehabilitation, Erzurum, Turkey

**Yalova Public Hospital, Clinic of Physical Therapy and Rehabilitation, Yalova, Turkey*

***Prof. Dr. Cemil Taşçıoğlu City Hospital, Clinic of Physical Therapy and Rehabilitation, İstanbul, Turkey*

Abstract

Aim: Despite the frequent use of local injections for shoulder pain, previous trials revealed conflicting results. In this research, we aimed to assess and compare the efficacy of suprascapular nerve block (SNB) and subacromial steroid injection (SSI) in improving pain, quality of life, functional status and sleep quality in patients with chronic shoulder pain.

Methods: Sixty patients with chronic shoulder pain were enrolled in this study. Thirty patients received SSI and 30 underwent SNB. Initial examinations before injection and in the first week and first and third months after injection were recorded. Pain intensity levels, shoulder functions, sleep quality and quality of life were assessed at each follow-up visit using a visual analogue scale, shoulder pain and disability index, Pittsburgh sleep quality index, and the health assessment questionnaire, respectively.

Results: A statistically significant improvement was observed in terms of pain and all clinical parameters from the first week after injection in both groups, but no significant difference was observed between the groups.

Conclusion: SNB or SSI combined with exercise significantly reduces pain and increase shoulder functions, sleep and quality of life in patients with chronic shoulder pain.

Keywords: Shoulder pain, subacromial injection, suprascapular nerve block, sleep quality

Öz

Amaç: Omuz ağrısında lokal enjeksiyonlar sık kullanılmalarına rağmen önceki çalışmaların çelişkili sonuçları olmuştur. Bu çalışmada, kronik omuz ağrısında supraskapular sinir bloğu (SSB) ve subakromiyal steroid enjeksiyonun (SSE) ağrı düzeyleri, yaşam kalitesi, fonksiyonel durum ve uyku kalitesi üzerine olan etkilerini değerlendirme ve karşılaştırmayı amaçladık.

Yöntemler: Çalışmaya kronik omuz ağrısı olan 60 hasta dahil edildi. Otuz hastaya SSE, 30 hastaya SSB uygulandı. Enjeksiyon öncesi, enjeksiyon sonrası birinci hafta, birinci ve üçüncü ay muayeneleri kayıt edildi. Her kontrolde görsel analog ölçeği ile ağrı şiddeti, omuz ağrı ve disabilite ölçeği ile omuz fonksiyonları, Pittsburgh uyku kalitesi ölçeği ile uyku kaliteleri ve sağlık değerlendirme anketi ile yaşam kalitesi değerlendirildi.

Bulgular: Ağrı ve tüm klinik parametreler açısından enjeksiyon sonrası ilk hafta itibariyle iki grupta da istatistiksel olarak önemli iyileşme gözlendi, ancak iki grup arası fark izlenmedi.

Sonuç: Kronik omuz ağrısında SSB veya SSE egzersizle kombine edildiğinde önemli oranda ağrıyı azaltır, omuz fonksiyonlarını, uyku ve yaşam kalitesini arttırır.

Anahtar Sözcükler: Omuz ağrısı, subakromiyal enjeksiyon, supraskapular sinir bloğu, uyku kalitesi

Address for Correspondence/Yazışma Adresi: Gonca Sağlam, Erzurum Regional Training and Research Hospital, Clinic of Physical Therapy and Rehabilitation, Erzurum, Turkey
E-mail: goncasaglam@hotmail.com ORCID: orcid.org/0000-0001-7713-4435

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Introduction

Shoulder pain is the third most prevalent type of musculoskeletal disorder for referral to clinics after waist and neck pain and may cause functional disability and decreased quality of life, particularly at more advanced ages (1). The most common source of shoulder pain is thought to involve the extra-articular structures such as muscles, tendons and bursae. An optimal approach to shoulder pain, including adequate analgesia, is important to gain functionality and encourage rehabilitation (2). The joint complex in the shoulder and surrounding structures is one of the most common areas to which local injection therapy is applied. These methods, applied as local anesthetic and steroid combinations, are effective in pain control and functional recovery (3). Subacromial steroid injection (SSI) is a widely used therapeutic method that can be employed in the treatment of shoulder pain. Anterior, posterior or posterolateral approaches can be selected (4).

The suprascapular nerve is a peripheral nerve formed by the involvement of C5 and C6 roots that innervates the back and upper part of the shoulder joint capsule, the acromioclavicular and glenohumeral joint, the coracoclavicular ligament and the subacromial bursa (5). Suprascapular nerve block (SNB) is an alternative analgesic injection for the pain management of many shoulder pathologies (6,7). It can be applied using various different techniques and the suprascapular notch is targeted where the suprascapular nerve passes below the superior transverse scapular ligament (8-10).

A small number of studies have compared these two injection techniques previously and sufficient data is not available to guide treatment for shoulder pain. In this study, we aimed to assess and compare the effects of SSI and SNB on pain, quality of life, functionality and sleep quality in patients with chronic shoulder pain.

Methods

This study was conducted with 60 patients (51 female and nine male) who required local injection therapy according to examination at the physical medicine and rehabilitation outpatient clinic. Patients with shoulder pain for three months and aged 18 or over were informed about the injection techniques. Following clinical and radiological evaluations, SSI or SNB was performed. The patients were randomized by one physician and another physician performed the injections. The exclusion criteria were as follows: having received physical therapy for the shoulder region within the past six months or local injection into the shoulder in the past three months, uncontrolled diabetes or hypertension, shoulder infection or a history of shoulder surgery, septic/tuberculous arthritis of the shoulder or anticoagulant use. Sociodemographic data including sex, age, height, body weight, chronic disease history, marital status, occupational status and education level, dominant hand, affected shoulder, duration of shoulder pain, presence of repetitive/compulsive shoulder activities and shoulder imaging results were recorded on a case report form. All patients were given a pre-injection exercise program including Codman's exercises, self-stretching exercises assisted with a stick, active range of motion (ROM) exercises, finger ladder exercises and ROM restraint.

The patients were assessed at baseline, post-injection week 1st, and month 1st and 3rd Pain levels during sleep, rest and activity were screened based on visual analog scale (VAS) scores. Functionality was evaluated using the shoulder pain and disability index (SPADI), sleep quality using the Pittsburgh sleep quality scale (PSQI) and quality of life using the health assessment questionnaire (HAQ). Patients' baseline, first, and third month scores were recorded assuming that PSQS indicated sleep quality in the previous month. The patients did not receive any medical prescription for their pain except paracetamol or sleep disturbances during follow-ups. Informed consent was obtained from all individual participants included in this study. We state that all methods were carried out in accordance with appropriate guidelines and we also confirm that our study was approved and initiated by the Clinical Research Ethics Committee of our hospital (Prof. Dr. Cemil Taşçıoğlu City Hospital, no: 499, date: 14/06/2016).

Injection Procedures

For subacromial injection, we adopted a posterior approach, which is easier to administer and involves less risk of harm to the neurovascular structure. In this method, the patient is in a sitting position with the forelimb in flexion and internal rotation, and the physician performing the procedure is behind the patient. Under sterile conditions, the posterior side of the acromion is palpated with the thumb, and the middle finger is placed on the choroid plexus. The injection is performed 1 cm inferior to the posterior corner of the acromion, and 2.5 cm from the medulla of the humerus, acromion and choroid. A mixture of 4 mL 2% lidocaine, 5 mL saline (0.9% NaCl) and 40 mg methylprednisolone acetate (1 mL) (total 10 mL), and a 21 Gx38 mm needle tip injector were used during injection in this study. The needle was advanced toward the anterior coracoid process and after negative aspiration, the drug mixture was administrated.

In this study, SNB was performed using the method described by Shanahan et al. (10). The block is performed with the patient sitting down and upper limbs pending beside the body. The intersection point is identified by drawing a line perpendicular to the scapula spiral from the

inferior edge of the scapula and the injection is applied 2 cm lateral (in the upper-outer quadrant of the scapula) to the intersection point. The block is performed at a depth of approximately 2.5 cm with a 21 Gx38 mm needle tip. The patients in this group also received 4 mL 2% lidocaine and 40 mg methylprednisolone acetate (1 mL).

Statistical Analysis

Sample size was determined by power analyses to determine the minimum number of patients to be included in our study population within 95% confidence. Statistical analyses were performed using the IBM SPSS Statistics 22 (IBM SPSS, Turkey) software. The normal distribution fitness of the parameters was determined using the Shapiro-Wilks test. Descriptive statistics (mean, standard deviation and frequency) were used for the analyses. Quantitative data of the two groups was compared with Student's t-test and the Mann-Whitney U test. ANOVA was used to determine repeated measures and the Bonferroni test to the time interval representing the source of differences. The Friedman test was used in evaluating parameters without normal distribution in the repeated measures, and the Wilcoxon Signed Ranks test was used to determine the time interval representing the source of differences. The chi-square test, Continuity (Yates) correction and Fisher's exact test were used in the analysis of qualitative data. A p value of <0.05 was considered statistically significant.

Results

The study involved 60 patients, 51 (85%) female and nine (15%) male. Demographic features are shown in Table 1. The mean age of patients was 50.80±10.09 years. The duration of shoulder pain ranged from three to 180 months, with a mean duration of 37.07±26.00 months. There was no significant between-group difference in socio-demographic and clinical characteristics (Table 2). The mean initial VAS, HAQ or PSQI values were also not statistically different. The mean activity VAS score was decreased from 7.79±2.19 before injection to 3.32±2.85 at three months after SSI, and from 7.80±1.95 before SNB to 3.23±1.94 at three months after nerve block without a statistically significant difference. In both groups, there was also a statistically significant improvement in terms of HAQ and PSQI values at first week, first month and third month post-injections (Table 3 and 4) (p=0.001). The SPADI scores in the SSI group were significantly higher at baseline and at the first week post-injection, indicating poorer functioning compared to the SNB group. However, there was a significant improvement in shoulder functions in both groups during follow-up. The initial and follow-up results are shown in Table 4.

Discussion

Chronic shoulder pain is a very common musculoskeletal condition with a high prevalence that can cause socioeconomic impairment (11). Therefore, research efforts need to be focused on obtaining more understanding about the best management of shoulder pain. SNB and SSI are injection techniques that can provide pain relief in patients who do not respond to exercise and medical treatment (12,13). The success rate of SSI can range from 29% to 83%, depending on factors such as injection schedule and the patient's diagnosis (14). However, the number of studies investigating the effect of SNB on rotator cuff (RC) diseases is limited. Most of these studies have involved patients with adhesive capsulitis, hemiplegic shoulder or inflammatory shoulder arthritis (15).

Overall, there are a few published studies comparing SSI with SNB in patients with chronic shoulder pain. Recently, a randomized, double-blind controlled trial in patients with RC tear demonstrated a superiority of SNB over SSI at 12 weeks (16). In this study, SSI group yielded a greater improvement in pain scores and functional status for up to 12 weeks in contrast to our findings. Similarly, Abdelshafi et al. (17) showed that SNB improves pain, disability, and ROM of the shoulders more compared to intra-articular corticosteroid injection of the shoulder and/or physiotherapy alone. However, a metaanalysis which explored the effectiveness of SNB in the treatment of chronic shoulder revealed that SNB had similar outcomes

Table 1. Demographic data

		Min-max*	Mean ± SD**
Age (years)		27-76	50.80±10.09
Sex (n, %)	**Female**	51	85.0
	Male	9	15.0
BMI# (kg/m²)		17.12-50.18	27.54±4.15
Education status (n, %)	**Not literate**	2	3.3
	Primary school graduate	41	68.4
	High school graduate	14	23.3
	University graduate	3	5.0
Profession (n, %)	**Public official**	3	5.0
	Manual	8	13.4
	Retired	5	8.3
	Self-employed	3	5.0
	Unemployed	2	3.3
	Housewife	39	65.0
Marital status (n, %)	**Married**	53	88.3
	Single	7	11.7

*Min-max: Minimum-maximum, **Mean-SD: Mean ± standard deviation, #BMI: Body mass index, n: Number

to intra-articular injection of the glenohumeral joints (18). Another study that compared the efficacy of SNB and local steroid injection on non-specific shoulder pain was conducted by Taskaynatan et al. (19). Patients were evaluated in terms of pain, ROM, satisfaction and disability before injection, and at one week and one month after injection. The authors concluded that both methods are effective and none is superior to each other according to follow-up parameters. Intra-articular steroid injection and SNB have also been compared in hemiplegic shoulder and adhesive capsulitis patients in various studies, with positive short-term results being obtained in terms of pain, function, disability and ROM (20-23).

Table 2. Clinical features and findings

		Min-max	Mean ± SD
Shoulder pain duration (months)		3-180	37.07±26.00
		n	%
Affected shoulder	Right	43	71.7
	Left	17	28.3
Dominant hand	Right	51	85.0
	Left	9	15.0
History of repetitive/ compulsive shoulder activity	(+)	21	35.0
	(-)	39	65.0
***Previous treatments for shoulder pathology**	Medical treatment	54	90.0
	Physical therapy	10	16.7
	Injection	11	18.3
***Comorbid diseases**	Comorbidity	33	55
	Diabetes	6	10
	Thyroid disease	5	8.3
	Pulmonary disease	4	6.7
	Hypertension	15	25
	Rheumatoid arthritis	4	6.7
	Ankylosing spondylitis	5	8.3
MRI findings	Impingement	20	33.3
	Glenohumeral degeneration	17	28.3
	Acromioclavicular degeneration	20	33.3
	Supraspinatus tendinosis	32	53.3
	Supraspinatus tear	20	33.3
	Infraspinatus tendinosis	1	1.7
	Bursitis	11	18.3
	Effusion	10	16.7
	Bicipital tendinitis	5	8.3

*More than one option may apply, SD: Standard deviation, MRI: Magnetic resonance imaging, n: Number

In our study, both SSI and SNB groups experienced a decrease in VAS values from the first week to the end of the third month, and both groups exhibited similar improvement. The mean SPADI and HAQ values in our study groups were similar at baseline and third month follow-up indicating the efficacy of both injection techniques. We also observed a significant decrease in PSQI scores one and three months after injection in both groups, and the increase in sleep quality was again in agreement with the previous literature. A few previous studies have evaluated sleep quality after local shoulder injections without a comparison of SNB and SSI groups, as in our study. Shin (24) reported an increase in sleep quality and a decrease in pain levels with indirect SNB and exercise programs in patients with partial RC rupture. Rached et al. (15) and Di Lorenzo et al. (25) showed similar improvements in sleep quality after SNB.

Before initiation of this study, we performed a power analysis to achieve the required number of patients throughout the study and to obtain significant results in correlation analyses between data that increased the power of our study. The injection groups were similar in terms of almost all sociodemographic characteristics and clinical parameters prior to treatment. In addition, patient assessments and injection procedures were performed by different clinicians under equivalent circumstances for each patient. This was another strength of our study that improved the reliability of our data. Injections and patient evaluations were performed by different physicians, and frequent evaluations were carried out one week, and one and three months after injection. Another factor increasing the power of our study is that we also assessed sleep quality, which has not been investigated in previous comparison of local steroid injections.

SNB and SSI are commonly used effective interventions for chronic shoulder pain, however, considering the detrimental effects of corticosteroids on articular cartilage, SNB can be regarded as an appropriate alternative for pain relief in patients with shoulder pain.

Study Limitations

This study has several limitations. The absence of a completely untreated control group due to ethical concerns made it difficult to determine the effectiveness of injections in isolation. We also think that the exercise program had positive effects on the clinical parameters investigated. The injections were not performed on a single disease group responsible for shoulder pain. RC diseases were present in the majority of patients. Other limitations include the fact that injection was applied to anatomical points, especially in the SNB group, without ultrasound imaging.

Table 3. Intra-group and inter-group evaluation of rest, activity and nocturnal VAS scores				
VAS		Subacromial injection group	Suprascapular nerve block group	[1]p
		Mean ± SD (median)	Mean ± SD (median)	
Rest	Baseline	3.22±3.17 (2)	3.37±3.15 (3.5)	**0.629**
	1st week	1.24±2.07 (0)	0.82±1.29 (0)	**0.599**
	1st month	0.84±1.66 (0)	0.77±1.65 (0)	**0.754**
	3rd month	0.90±1.71 (0)	0.60±1.45 (0)	**0.357**
	[2]p	**p<0.001**	**p<0.001**	
Activity	Baseline	7.79±2.19 (8)	7.80±1.95 (8)	**0.755**
	1st week	4.78±2.39 (5)	4.00±1.97 (3.5)	**0.124**
	1st month	3.56±2.16 (3)	3.54±2.21 (3)	**0.812**
	3rd month	3.32±2.85 (3)	3.23±1.94 (3)	**0.981**
	[2]p	**p<0.001**	**p<0.001**	
Nocturnal	Baseline	4.77±3.19 (5)	5.20±3.59 (5)	**0.823**
	1st week	2.40±3.49 (0)	1.60±2.44 (0)	**0.457**
	1st month	1.90±2.87 (0)	1.33±1.83 (0)	**0.771**
	3rd month	1.60±2.58 (0)	1.27±1.74 (0)	**0.890**
	[2]p	**p<0.001**	**p<0.001**	

[1]Mann-Whitney U Test, [2]Friedman Test, VAS: Visual anolog scale, SD: Standard deviation

Table 4. Intra-group and Inter-group evaluation of HAQ, SPADI and PSQI scores				
		Subacromial injection group	Suprascapular nerve block group	p
		Mean ± SD (median)	Mean ± SD (median)	
HAQ	Baseline	1.15±0.68	0.94±0.67	[1]**0.261**
	1st week	0.79±0.61	0.57±0.37	[1]**0.139**
	1st month	0.55±0.39	0.48±0.35	[1]**0.487**
	3rd month	0.50±0.47	0.45±0.37	[1]**0.566**
	[2]p	**p<0.001**	**p<0.001**	
SPADI	Baseline	65.88±21.46	58.13±16.77	[1]**0.042**
	1st week	40.55±24.92	30.25±13.53	[1]**0.051**
	1st month	29.03±20.71	25.11±19.84	[1]**0.426**
	3rd month	27.06±20.67	22.37±10.61	[1]**0.384**
	[2]p	**p<0.001**	**p<0.001**	
PSQI	Baseline	5.87±5.37 (4.5)	6.63±4.68 (5.5)	[3]**0.295**
	1st month	4.53±4.13 (4)	4.73±3.08 (4)	[3]**0.325**
	3rd month	4.20±3.61 (4)	4.53±2.64 (4)	[3]**0.250**
	[4]p	**p<0.001**	**p<0.001**	

[1]Student t-test, [2]ANOVA test, [3]Mann-Whitney U test, [4]Friedman test, HAQ: Health assessment questionnaire, SPADI: Shoulder pain and disability index, PSQI: Pittsburgh sleep quality scale, SD: Standard deviation

Conclusion

Cortisone is a powerful anti-inflammatory that can be injected into the shoulder area to help treat a variety of shoulder conditions. SNB and SSI are practical and economical methods, with a low risk of complications, and that elicit rapid responses from the first week in the treatment of chronic shoulder pain. Since a steroid should not be injected into the same joint more than once every 3 months, SNB may be an alternative treatment for this interval.

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Authorship Contributions

Surgical and Medical Practices: G.S. Concept: G.S. Design: B.H. Data Collection or Processing: G.S., F.B.D. Analysis or Interpretation: Ö.K. Literature Search: G.S. Writing: G.S.

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Papilödem: Leptomeninjiyal Metastazın Önemli Klinik İşareti Olabilir mi?

Papilledema: Could It Be an Important Clinical Sign of Leptomeningeal Metastasis?

Özge Arıcı Düz, Oktay Olmuşçelik*, Fadime Çadırcı**, Ömer Fatih Ölmez***

İstanbul Medipol Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, İstanbul, Türkiye
**İstanbul Medipol Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, İstanbul, Türkiye*
***İstanbul Medipol Üniversitesi Tıp Fakültesi, Nörobilim Anabilim Dalı, İstanbul, Türkiye*
****İstanbul Medipol Üniversitesi Tıp Fakültesi, Medikal Onkoloji Anabilim Dalı, İstanbul, Türkiye*

Öz

Amaç: Leptomeninjiyal metastaz (LM) tüm kanser tiplerinde izlenebilen nadir ancak kötü prognozlu bir klinik tablodur. Tanı, tedavi ve prognoz hastalığı yönetmekte önemli süreçlerdendir. Bu amaçla LM klinik ve laboratuvar özelliklerinin inceleyerek erken tanı için ipuçları ortaya koyabilmeyi amaçladık.

Yöntemler: Çalışmaya retrospektif olarak 2018-2020 yılları arasında Leptomeninjal tanısı almış 16 hasta dahil edildi. Hastaların beyin omurilik sıvısı (BOS) örnekleri ve kranial magnetik rezonans görüntüleme tetkikleri incelendi. Ayrıca hastalar papilödem varlığına göre iki gruba ayrıldı. İstatistiksel analiz uygulandı.

Bulgular: Hastaların yaş ortalaması 49 (19-73), %37,5'i kadındı. En sık izlenen histolojik tümör tipi adeno karsinom idi. En sık izlenen klinik bulgu multipl kranial nöropati idi. LM tanısına kadar geçen süre ortalama 20 ay (1-112 ay) idi. On altı hastanın 11'inde solid tümör, beşinde hematolojik malignite mevcuttu. Dokuz hastada papilödem mevcuttu. Baş ağrısı yakınması papilödem olan grupta istatistiksel olarak anlamlı şekilde daha yüksek iken (p=0,01) diğer klinik bulgularda anlamlı farklılık yoktu. LM sonrası ortalama yaşam süresi 8 aydı (1-48 ay). Dört hastanın BOS sitolojisinde malign hücreler tespit edildi (%30).

Sonuç: LM onkoloji hastalarında kötü prognozlu ve tüm tetkiklerin uygun koşullarda yapılmasına karşın tanısı zor konabilen bir durumdur. Papilödem varlığı LM hastalarında noninvaziv değerlendirme yöntemlerinden biri olarak tanıya katkı sağlayabileceği düşünülmüştür.

Anahtar Sözcükler: Leptomeninjial metastaz, papilödem, baş ağrısı

Abstract

Aim: Leptomeningeal metastasis (LM), which can be seen in all types of cancer, is a rare condition with poor prognosis. Diagnosis and treatment are important components of the management of the disease. We aimed to reveal clues for early diagnosis by examining the clinical and laboratory features of LM.

Methods: Sixteen patients who received the diagnosis of LM between 2018 and 2020 were included in the study retrospectively. The cerebrospinal fluid (CSF) samples and cranial magnetic resonance imaging of the patients were examined. In addition, the patients were divided into two groups according to the presence of papilledema.

Results: The mean age of the patients was 49 (19-73) and 37.5% were women. The most common histological tumor type was adenocarcinoma. The most common clinical finding was multiple cranial neuropathy. The mean time to the diagnosis of LM was 20 months. Eleven of the 16 patients had solid tumors, five had hematological malignancies. Nine patients had papilledema. Headache was significantly more common in the group with papilledema (p=0.01). The average lifespan after the diagnosis of LM was 8 months (1-48 months). Malignant cells were detected in the CSF cytology of four patients (30%).

Conclusion: LM is a condition with poor prognosis and difficult to diagnose in oncology patients, despite all tests being performed under appropriate conditions. Presence of papilledema is thought to contribute to the diagnosis since the evaluation of intracranial in LM patients is a non-invasive evaluation method.

Keywords: Leptomeningeal metastasis, papilledema, headache

Yazışma Adresi/Address for Correspondence: Özge Arıcı Düz, İstanbul Medipol Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, İstanbul, Türkiye
E-posta: drozge2004@hotmail.com ORCID: orcid.org/0000-0003-0334-811X
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Giriş

Leptomeninjial metastaz (LM), kanserin kötü prognozlu ve tanınması zor komplikasyonlarından biridir. Kanser hücreleri, subaraknoid alana ve meninkslere ulaşır, sinir sistemi tutulumlarına neden olur (1). Nodüler ve nodüler olmayan olmak üzere iki tipi tanımlanmıştır: nodüler olmayan formda subaraknoid mesafede serbest yüzen hücre ya da hücre kümeleri varken nodüler kontrast tutan lezyon yoktur (2). Özellikle lösemi, lenfoma, melanom, meme ve akciğer kanseri olmak üzere solid tümörlerde %5-30 arasında değişen oranlarda görülebilir (3,4). Görülme sıklığı kanser histolojisine ve tipine göre de değişmektedir: metastatik meme kanserinde %5-8, akciğer kanserinde %9-25, melanomda ise %6-18 oranında bildirilmektedir (5-7). Yeni gelişen kemoterapi tedavi protokollerine ve nörogörüntüleme yöntemlerindeki ilerlemeye rağmen LM önemini ve gizemini korumaktadır.

LM, nörolojik yakınması olan kanser hastalarında ayırıcı tanıda yer almalıdır. Erken tanınması yüksek mortalite ve morbiditesi nedeniyle önemlidir. Klinik olarak sinir paralizileri (%75) ve baş ağrısı (%66) sık izlenir. Sıklıkla bulgular artmış intrakranyal basınca bağlı olarak sinir paralizileri ve papilödem olarak ortaya çıkar (8). Erken tanı çok önemli olmasına karşın tanı için altın standart olan beyin omurilik sıvısı (BOS) incelemesi ve manyetik rezonans görüntüleme (MRG) bulguları sıklıkla normal sınırlarda tespit edilebilir (9,10). Solid tümörü ve nörolojik bulgusu olan hastaların otopsi çalışmalarında %20 oranında LM saptanırken, klinik olarak bu oran ancak %5-8'dir (11,12). LM şüphesi olan hastalara lomber ponksiyon yapılırken sitolojik incelemenin yanında BOS açılış basıncının ve BOS biyokimyası değerlendirmenin LM tanısına katkı sağlayacağı düşünülmektedir. LM tanısını düşündürecek indirek BOS bulguları; artmış BOS açılış basıncı, azalmış BOS glikoz seviyesi, artmış BOS protein seviyesi ve BOS'da hücre varlığı olarak sıralanabilir (13). LM olan hastalarda artmış kafa içi basıncı da beklenen bulgudur (14). Sitolojik incelemede atipik hücreyi tespit edebilmek güç olabilir bu nedenle 10 mL ve üzerindeki BOS volümlerinde sitoloji çalışılması uygun görülmüştür (15).

Bu çalışmada LM varlığında tanıyı erken belirleyebilmek amacıyla BOS bulgularını ve papilödem varlığını incelemeyi amaçladık.

Yöntemler

Hastalar

Çalışmaya retrospektif olarak 2018-2020 yılları arasında İstanbul Medipol Üniversitesi Hastanesi'nde LM tanısı almış 16 hasta dahil edildi. Hastaların nörolojik, dahili ve onkolojik muayeneleri yapılmıştı. Hastaların ilk nörolojik yakınmalarından sonra nörolojik muayeneleri değerlendirilmiş, özellikle göz dibi, kraniyal sinir ve mental muayeneleri değerlendirilmiş ve LM'ye ait olabilecek nörolojik bulgular kayıtlanmıştı. Nörolojik şikayet ve bulgular baş ağrısı, bilinç değişikliği, epileptik nöbet, çift görme, tinnitus, görme bulanıklığı ve multipl kraniyal nöropati olarak gruplandırıldı.

Hastaların lomber ponksiyon öncesi beyin MRG tetkiki değerlendirilmişti. MRG tetkiki, 3.0-T MRG tarayıcı (Philips Achieva 2012) kullanılarak kontrastlı çekim yapılmış ve aksiyel ve sagittal Fluid attenuated inversion recovery (FLAIR), aksiyel T2 ağırlıklı, difüzyon ağırlıklı ve pre ve post kontrastlı T1 ağırlıklı görüntüler alınmıştı. MRG pozitifliği radyolojik olarak epandimal tutulum, dural tutulum ve hidrosefali olarak sınıflandırıldı.

Lomber ponksiyon LM şüphesi olan dönemde, steril şartlarda L4-5 aralığından uygulanmıştı. BOS açılış ve kapanış basınçları, biyokimya, sitolojik ve patolojik incelemesi değerlendirildi. Patolojik BOS tanımlaması atipik hücre görülmesi ve/veya protein seviyesinin yüksekliği olarak tanımlandı.

LM tanısı; pozitif BOS sitolojisi ve MRG'de LM olası tutulumu ya da klinik değerlendirme ile konuldu. Tüm hastaların kanser öyküsü mevcuttu. Bilinen beyin parankim metastazı olan hastalar çalışmadan dışlandı. Çalışmada hastaların yaş, cinsiyet, kanser süresi, LM tanısına kadar geçen süre, kanser histolojisi ve lokalizasyonu, MRG ve BOS bulguları, nörolojik şikayet ve bulgular, mortalite durumu değerlendirildi. Ayrıca hastalar papilödem varlığına göre iki gruba ayrıldı. Çalışma etik kurul onayı İstanbul Medipol Üniversitesi Etik Kurulu'nun 11.01.2019 tarih ve 80 sayılı izni ile planlandı.

İstatistiksel Analiz

Sürekli değişkenleri (yaş, hastalık süresi vb.) tanımlamak için deskriptif istatistikler kullanılmıştır (ortalama, standart sapma, minimum, medyan, maksimum). Değişken grupları arasında analiz için Kruskal-Wallis ve Mann-Whitney U testleri kullanıldı. Kategorik değişkenler için ki-kare testi veya Fisher exact testi kullanıldı ve gözlem sayısı ve yüzdeleri olarak ifade edildi. İki taraflı p değeri 0,05'ten düşük olduğunda istatistiksel anlamlılık kabul edildi. İstatistiksel analiz, MedCalc Statistical Software sürüm 12.7.7 (MedCalc Software bvba, Ostend, Belçika; http://www.medcalc.org; 2013) kullanılarak yapıldı.

Bulgular

Demografik Özellikler

Çalışmaya yaşları ortalaması 49 (19-73) olan 16 LM tanılı hasta dahil edildi. Hastaların %37,5'i kadın ve en sık izlenen histolojik tümör tipi adeno karsinomdu. En sık izlenen klinik bulgu multipl kranial nöropati idi (Tablo 1). Ortalama kanser süresi 27 ay (0-120), LM tanısına kadar

geçen süre ortalama süre 20 ay (1-112 ay) idi. LM tanısı sonrası ortalama sağkalım 8,4 aydı (1-48 ay).

Kanser Özellikleri

On altı hastanın 11'inde solid tümör, beşinde hematolojik malignite mevcuttu. En sık izlenen solid tümör mide kanseriydi (%31,25), bunu beş hasta ile tüm hematolojik maligniteler, üç hasta meme, iki hasta kolon, bir hasta akciğer, bir hasta mesane kanseri ile izlemekteydi. En sık izlenen histolojik tip 10 adet ile adenokarsinomdu (Tablo 2).

Klinik Bulgular

En sık izlenen bulgular multipl kraniyal nöropati ve baş ağrısı idi (sırasıyla %81,3, %75). Bunu %62,5 ile çift görme, %50 ile tinnitus takip ediyordu. Solid tümörü olan 11 hastanın dokuzunda baş ağrısı varken, bu hastalarda en sık görülen kranial nöropati papilödem varlığı şeklinde ortaya çıkan optik sinir tutulumuydu. Bu hastalarda görme bulanıklığı kliniği sadece dört hastada varken yedi hastanın sadece papilödemi mevcuttu. Tüm hasta grubunda ise dokuz hastada papilödem mevcuttu. Hastalarımızda spinal sinir yada kök tutulumu bulguları izlenmedi. Dört hastada epileptik nöbet geçirme öyküsü mevcuttu.

Tablo 1. Hastaların klinik ve demografik özellikleri

	n	%
Yaş (ort)	49 (19-73)	
Cinsiyet (K)	6	37,5
Klinik semptom		
Baş ağrısı	12	75
Bilinç değişikliği	3	18,8
Nöbet	7	43,8
Çift görme	10	62,5
Tinnitus	8	50
Görme bulanıklığı	4	25
Multipl kraniyal nöropati	13	81,3

Ort: Ortalama, K: Kadın, n: Sayı

Tablo 2. Kanser özellikleri

	n	%
Histoloji		
Adenokanser	10	62,5
Anaplastik	1	6,25
Kötü diferansiyelli	1	6,25
Küçük hücreli	1	6,25
Nöroendokrin	1	6,25
T-hücreli	1	6,25
Taşlı yüzük hücreli	1	6,25
Kanser lokalizasyonu		
Mide	5	31,25
Kolon	2	12,5
Akciğer	1	6,25
Meme	3	18,75
Mesane	1	6,25
Hematolojik malignensi	5	31,25

n: Sayı

Papilödem Varlığına Göre Hastaların Özellikleri

Hastalar papilödem varlığına göre iki gruba ayrıldığında hastaların yaş, cinsiyet, sağkalım süresi ve MRG bulguları açısından anlamlı farklılık yoktu. Baş ağrısı yakınması papilödem olan grupta istatistiksel olarak anlamlı şekilde daha yüksekti (p=0,01), diğer klinik bulgular arasında anlamlı farklılık izlenmedi (Tablo 3). İstatistiksel anlamlılığa ulaşmamakla birlikte hidrosefali, papilödemi olan grupta daha sık izlendi (p=0,08). LM sonrası sağkalım açısından anlamlı farklılık yoktu (p>0,05).

BOS Bulguları

On altı hastanın 13'ünün BOS bulgularına ulaşılabildi. Dört hastanın BOS sitolojisinde atipik hücre tespit edildi (%30). BOS patolojisi pozitif olan iki hastada meme, bir hastada mide, bir hastada ise mesane kanseri mevcuttu. Ancak 11 hastanın BOS glikoz seviyesi düşük (%84) yedi hastanın protein seviyesi yüksek tespit edildi (%53,8). Altı hastanın BOS açılış basıncı 200 mmH_2O üzerindeydi (%46).

LM Tanısı

On hastaya MRG, 11 hastaya BOS, üç hastaya ise sadece klinik bulgular ile tanı konuldu. MRG bulguları bir

Tablo 3. Papilödem varlığına göre hastaların özellikleri

Papilödem	Var (+)	Yok (-)	p
Cinsiyet (K, n)	4	2	0,63
Yaş (ort)	49	50,86	0,6
Kanser süre (ay)	26,44	30	0,6
LM sonrası sağkalım (ay)	4,56	12,71	0,21
MRG bulgusu			
Ependimal tutulum	3/6	0/7	0,21
Dural tutulum	0/9	0/7	-
Hidrosefali	4/5	0/7	0,08
Klinik semptom			
Baş ağrısı	9/0	3/4	0,01
Bilinç değişikliği	2/7	1/6	1,00
Nöbet	4/5	3/4	1,00
Çift görme	5/4	5/2	0,63
Tinnitus	5/4	3/4	1,00
Görmede bulanıklık	3/6	1/6	0,58
Multipl kranial nöropati	8/1	5/2	0,55

K: Kadın, ort: Ortalama, MRG: Manyetik rezonans görüntüleme, LM: Leptomeninjial metastaz, n: Sayı

hastada ikinci MRG'de, bir hastada ise altıncı kez yapılan MRG'de izlenebildi. Spinal MRG tetkikinde hiçbir hastada anormallik saptanmadı.

LM Sonrası Sağkalım

On altı hastadan bir tanesi LM sonrası yaşıyordu, diğer 15 hastanın LM sonrası ortalama yaşam süresi 8 aydı (1-48 ay). MRG ve BOS pozitifliğine göre hastalar gruplandırdığında; grupların sağkalım süreleri arasında fark yoktu. Histolojik alt tipin ya da kanser lokalizasyonunun sağkalıma etkisi tespit edilmedi (p>0,05).

Tartışma

LM, tüm kanser türlerinde yaklaşık %5 oranında görülen önemli, kötü prognozlu bir klinik tablodur (16). Tedavi yöntemleri her ne kadar son dönemde çeşitlendirilebilse de mortalitesi halen yüksek olan LM'nin tanısı zordur ve beklenen yaşam süresi haftalar ile ifade edilmektedir (16,11). Bu nedenle LM'yi tanımak tedaviyi yönetmek kadar değerlidir.

Çalışmamızda hastaların %68,75'inde solid tümör mevcuttu, en sık izlenen solid tümör mide kanseriydi. Bunu sırasıyla; hematolojik kanserler, meme, kolon, akciğer ve mesane kanserleri takip ediyordu. Literatürde de benzer şekilde solid tümörlerde LM sıklığı daha fazla bildirilmiştir (11). Çalışmamızda en sık izlenen histolojik alt tip ise adeno kanserdi (%62,5).

Tanı için en değerli test BOS analizidir, ancak %10-15 olguda yalancı pozitiflik izlenebilir (17). Yapılan bir çalışmada LM tanısında tek başına MRG pozitifliği %21 oranında bildirilmiş (18). Farklı çalışmalarda farklı oranlar bildirilmiş, neden olarak da çalışmaya dahil edilen kanser türlerinin farklı olması belirtilmiş, özellikle solid tümörlerde MRG pozitiflik oranın daha yüksek olduğu gösterilmiş (19). Bu çalışmada bir hastaya sadece BOS, sekiz hastaya sadece MRG, beş hastaya hem BOS hem MRG ile tanı konulurken üç hastada tekrarlanan BOS örneklemesi, iki hastada ise tekrarlanan MRG değerlendirmesi sonucu LM tanısı konuldu. Bu nedenle klinik şüphe halinde atipik hücreyi gösterebilmek için tekrarlayan LP ve MRG'lerin gerekli olabileceği düşünüldü. Benzer şekilde uygun protokol ile yapılan MRG görüntülemelerinde yalancı pozitiflik oranı %30 olarak bildirilmektedir (20,21). LM tanılı hastalarla yapılan bir çalışmada hastaların %19'da normal BOS protein seviyeleri, %43'ünde ise normal BOS sitolojisi rapor edilmiş (22). MRG ve BOS sitolojinin LM tanısı koymaktaki sensitiviteleri sırasıyla; %76, %75 olarak bildirilmiştir (12). Bu çalışmada literatürle benzer şekilde BOS'de yalancı negatiflik oranı %31,25 MRG yalancı negatiflik oranı %37,4 olarak izlendi. Her ne kadar LM tanısı için MRG ve BOS kriterleri net tanımlanmamış olsa da LM tanısında hem BOS hem MRG hem de klinik tablo birlikte değerlendirilmeli, şüphe halinde tekrarlanan incelemelerle LM bulgusu aranmalıdır.

LM tanısı için önemli bir bulgu olarak artmış BOS basıncı bildirilmektedir (8). LM hastalarında yapılan radyoizotop çalışmalarında %30-60 oranında BOS akım patolojisi bildirilmektedir (23). Hem BOS emiliminin bozulması hem de BOS içeriğinin yoğunlaşması artmış intrakranyal basınç için neden olarak gözükmektedir (24). LM hastalarında yapılan ventrikülperitoeneal şant çalışmalarda ventriküler dilatasyon olmadan intrakranyal hipertansiyon varlığı bildirilmiştir (25). Bizim çalışmamızda intrakranyal hipertansiyonun göstergesi olan papilödem beş hastada izlendi. İstatistiksel anlamlılığa ulaşmasa da papilödemi olan beş hastanın üçünde hidrosefali vardı. Ancak papilödem olmayan grupla karşılaştırıldığında anlamlı fark izlenmedi. Bu nedenle hidrosefali bulguları olmadan ortaya çıkabilecek olan intrakranyal hipertansiyon tablosunun LM tanısı için önemli olabileceği düşünüldü.

Papilödem varlığına göre hastalar iki alt gruba ayrıldığında özellikle baş ağrısı açısından anlamlı farklılık vardı ve papilödem olan grupta baş ağrısı daha belirgindi. Diğer bulguların intrakranyal basınç artışını göstermesi açısından anlamlı farklılığı yoktu. Bu nedenle LM'nin önemli klinik bulgularından biri olan intrakranyal hipertansiyonu erken dönemde değerlendirmek için baş ağrısı sorgulamasının mutlaka ayrıntılı yapılmış olması gerektiğini ve görme kaybının daha kronik dönemde oluşması nedeniyle göz dibi muayenesinde izlenebilecek olan papilödem varlığının tanıya belirgin katkısı olabileceğini düşündük.

Çalışma grubumuzda ortalama sağkalım 8 aydı (1-48 ay). Bu süre daha önceki çalışmalarda tedavi edilmeyen grupta yaşam süresi haftalar ile ifade edilirken, tedavi alan grupta ortalama 4 ay olarak bildirilmektedir (26). Bizim çalışmamız literatürden farklı olarak daha uzun yaşam süresine sahipti; bunun nedeni olarak hastaların genç olması, ileri onkoloji merkezine sahip olmamız, LM tanısı sonrası uygulanan tedavi protokolleri ve tanı testlerinin uygun şekilde yapılarak uygun tedavilerin erken dönemde planlanıyor olması olabilir. Son dönemde hem LM'nin geliştirilen yöntem ve araçlarla daha sık tanınıyor olması hem de tedavi seçeneklerinin artması ile yaşam süresi bir miktar uzamıştır. Kranyal sinir tutulumu olması, LM için tedavi almamak, hidrosefali, akciğer kanseri ve melanom varlığı, ileri yaş ve yüksek BOS protein düzeyi) varlığı kötü prognostik faktörler olarak bildirilmiş (27-31). Çalışmamızda sağkalımı etkileyen anlamlı faktör bulunmadı, özellikle MRG pozitifliği ve histolojik alt tip değerlendirildiğinde, LM sonrası sağkalım açısından anlamlı farklılık izlenmedi. Tanısal anlamda önemli olduğunu düşündüğümüz papilödem varlığının LM sonrası sağkalım üzerine etkisi yoktu.

Çalışmanın Kısıtlılıkları

Çalışmamızın kısıtlılıkları arasında az sayıda hastanın değerlendirilmiş olmasıydı, ancak nadir izlenen bir klinik tablo olması nedeniyle uzun süreli takipler ile yapılacak geniş serilerdeki çalışmalarda bu çalışmada vurguladığımız papilödem değerlendirmesinin de ele alınabileceği algoritma çalışmalarına katkı sağlayabileceği düşünüldü.

Sonuç

LM onkoloji hastalarında kötü prognozlu ve tüm tetkiklerin uygun koşullarda yapılmasına karşın tanısı zor bir klinik tablodur. Klinik şüphe varlığında mutlaka tekrarlayan incelemelere ihtiyaç duyulabilir. Önemli klinik belirteçlerden biri intrakranyal hipertansiyonun göstergesi olan papilödemi varlığının değerlendirilmesi non-invazif bir değerlendirme yöntemi olması nedeniyle tanıya belirgin katkı sağlayacağı düşünülmüştür.

Yazarlık Katkıları

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The Effect of Autosomal Dominant Polycystic Kidney Disease on Spirometric Parameters

Spirometrik Parametrelere Otozomal Dominant Polisitik Böbrek Hastalığının Etkisi

Tuba Elif Özler, Faruk Karandere*, Egemen Cebeci, Meltem Gürsu**, Barış Döner, Abdullah Şumnu, Mustafa Sarı***, Gülfidan Çakmak ****, Zeynep Karaali*, Savaş Öztürk

University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital, Clinic of Nephrology, İstanbul, Turkey
**University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Turkey*
***Bezmialem Vakif University Faculty of Medicine, Department of Nephrology, İstanbul, Turkey*
****University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey*
*****University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital, Clinic of Chest Diseases, İstanbul, Turkey*

Abstract

Aim: There is no enough data on pulmonary involvement in autosomal dominant polycystic kidney disease (ADPKD). The aim of this study is to examine pulmonary function test in patients with ADPKD with varying stages of renal function and to compare them with those in healthy controls.

Methods: Forty-six patients with ADPKD and 43 healthy control subjects were included in the study. Pulmonary function test was performed for each patient after routine physical examination and biochemical analysis.

Results: Age, gender, weight, height and smoking rate were similar in both groups. Seven patients (15.2%) had restrictive pattern and one (2.1%) had obstructive pattern in ADPKD group while one patient (2.3%) had obstructive pattern and two (4.6%) had restrictive pattern in the control group. The frequency of restrictive pattern was not significantly higher (p=0.15), but forced vital capacity volume was significantly lower in the patient group (p=0.04).

Conclusion: Restrictive spirometric pattern was more prevalent in the patient group, but there was no statistically significant difference. It is thought that the difference may be statistically significant when the study is performed with kidney volume analysis and larger patient population.

Keywords: Autosomal dominant polycystic kidney disease, lung, pulmonary function test, spirometry

Öz

Amaç: Otozomal dominant polikistik böbrek hastalığında (ODPBH) akciğer tutulumu için literatürde yeterli veri yoktur. Bu çalışmanın amacı, ODPBH'nin ve farklı evrelerinini, solunum fonksiyon testleri üzerine etkisini incelemektir.

Yöntemler: Kırk altı ODPBH hastası ve 43 sağlıklı kontrol olgusu çalışmaya dahil edildi. Her olgu için rutin fizik muayene ve biyokimyasal analizden sonra solunum fonksiyon testleri yapıldı.

Bulgular: Yaş, cinsiyet, kilo, boy ve sigara içme oranı her iki grupta benzerdi. Otozomal dominant polikistik böbrek hastalığı grubunda yedi hastada (%15,2) restriktif patern, bir hastada (%2,1) obstrüktif patern, kontrol grubunda bir hastada (%2,3) obstrüktif patern, iki hastada (%4,6) restriktif patern tespit edildi. Restriktif patern, iki grupta benzer olmakla birlikte (p=0,15), zorlu vital kapasite hacmi hasta grubunda anlamlı olarak düşüktü (p=0,04).

Sonuç: Hasta grubunda restriktif spirometrik patern daha sık görüldü, ancak istatistiksel olarak anlamlı bir fark yoktu. Çalışma böbrek hacim analizi ve daha büyük hasta popülasyonu ile yapıldığında, farkın istatistiksel olarak anlamlı olabileceği düşünülmektedir.

Anahtar Sözcükler: Otozomal dominant polikistik böbrek hastalığı, akciğer, solunum fonksiyon testi, spirometri

Address for Correspondence/Yazışma Adresi: Tuba Elif Özler, University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital, Clinic of Nephrology, İstanbul, Turkey
E-mail: telifsenel@gmail.com ORCID: orcid.org/0000-0002-8637-3582
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Introduction

Autosomal dominant polycystic kidney disease (ADPKD), the most common hereditary kidney disorder, may causes pathologies in several systems such as cardiovascular, gastrointestinal, urogenital, and central nervous systems beside the kidneys (1,2). Although cystic and non-cystic extrarenal involvement of ADPKD in various organs are defined, pulmonary involvement has not been clarified yet (3-6). In a study by Moua et al. (6), patients with ADPKD were compared with those having chronic kidney disease (CKD), and bronchiectasis was observed more frequently in the ADPKD group, and it was frequently found to be localized in the lower lobes. One third of the patients, who were detected to have radiologic bronchiectasis, were symptomatic. Smoking was identified as an independent risk factor for the development of bronchiectasis in the ADPKD group (6). Mutations in polycystin genes show their direct effects on renal primary cilia. Polycystins are also expressed in the cilia of airway epithelial cells and airway smooth muscle cells (4,7). As a result, functional abnormalities in polycystins may decrease mucociliary clearance resulting in radiologic bronchiectasis (4).

The reason for most extrarenal involvement is the reflection of abnormalities in the collagen and extracellular matrix to all systems. Cardiovascular complications are more common in patients with ADPKD than in the general population and are the most important causes of death. These complications include early-onset hypertension, left ventricular hypertrophy, pericardial effusion, and heart valve diseases (3). Hypertension is the main risk factor for the development of early cardiovascular disease. Left ventricular hypertrophy is a major cause of mortality and morbidity (8-10).

We aimed to examine pulmonary function tests in patients with ADPKD and to compare the results with the healthy control group. We also investigated its relationship with kidney function test and respiratory function test.

Methods

This study was a single-center study, which enrolled patients over 18 years of age followed in our nephrology outpatient clinic. We compared the pulmonary function tests between patients with ADPKD and healthy controls. The study included forty-six patients and 43 healthy volunteers. Patients younger than 18 years of age, with acute respiratory system infection, history of any malignancy in remission, stage 3-4 heart failure, morbid obesity, connective tissue disorders, restrictive or obstructive lung disorder, neuromuscular disease, open lung surgery or abdominal surgery, decompensated liver disease, pleural and/or pericardial effusion, or nephrotic syndromes, those using immunosuppressive drugs and pregnant patients were excluded from the study.

The diagnosis of ADPKD was made using the Ravine criteria (11). Data on demographics, such as age, gender, height (m), weight (kg), and smoking status, and duration of ADPKD, and comorbid diseases were recorded. Body mass index was calculated as weight in kilograms divided by height in meters squared. Patients using antihypertensive drugs and/or having blood pressure 140/90 mmHg or higher at two different measurements were considered hypertensive. Patients using oral antidiabetic drugs and/or insulin and/or with fasting blood glucose level above 126 mg/dL and/or Hemoglobin A1c level 6.5% or higher were reported as diabetic. Patients with coronary heart disease confirmed by angiography or history of coronary revascularization were accepted as having ischemic heart disease. Serum glucose, urea, creatinine, albumin, alanine transaminase, aspartate transaminase, calcium and C-reactive protein levels were measured after 12 hours of fasting with routine laboratory methods using a Beckman Coulter AU 2700 auto-analyzer following the manufacturer's instruction. Complete blood count was done using ABX Penta DX120. Spot urine proteinuria was calculated by spot morning urine protein/urine creatinine ratio. Estimated glomerular filtration rate (eGFR) was calculated by the CKD epidemiology collaboration equation. The patient group was divided into two groups: eGFR below and above 60 mL/min/1.73 m^2.

Jaeger Master Scobe (version 4.5, Yorba Linda, CA, USA) was used in spirometric measurements. The patients rested 15 minutes before the test. Excepted parameters were calculated automatically by inserting the data of height, weight, and gender. The tests were performed with the patient sitting upright. First, the patient was asked to take normal breaths and then take a deep breath while still using the mouthpiece, followed by a further quick, full inspiration before a full expiration. The tests were repeated three times, and the best values were recorded as forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), peak expiratory flow, FEF25-75 and FEV1/FVC ratio were measured. The results were classified as obstructive, restrictive or normal according to the American Thoracic Society criteria.

There was not necessary to get ethics committee approval in that time the study conducted. Written informed consent was not obtained since the study did not require an invasive procedure.

Statistical Analysis

The analysis was performed using the SPSS 17 package program (SPSS for Windows 17.0 standard

version). Parametric values were expressed as mean ± standard deviation, whereas nonparametric variables were presented as median (interquartile range). For comparison of two groups, the independent samples t-test was used in parameters with normal distribution and the Mann-Whitney U test was used in parameters with abnormal distribution. The chi-square test and Fisher's exact test were used to evaluate categorical data. A p value of less than 0.05 was considered statistically significant.

Results

Forty-six patients and 43 healthy volunteers were included in the study. All patients had a family history of ADPKD. Demographic, clinical and biochemical data of the patient and control groups are given in Table 1. In the ADPKD group, 27 patients (58.7%) had hypertension, eight (17.4%) had ischemic heart disease and six patients (13%) had type 2 diabetes mellitus. Hypertension was significantly more common in the patient group (p<0.001).

The spirometry results of both groups are given in Table 2. The restrictive pattern was present in seven (15.2%) patients and obstructive pattern in one (2.1%); in the control group, restrictive pattern was present in two (4.6%) and obstructive in one (2.3%). There was no significant difference in the presence of restrictive pattern and obstructive pattern between the groups (p=0.15; p=1). In addition, there was no significant difference in the presence of obstructive and restrictive patterns between patients with eGFR below and above 60 mL/min/1.73 m^2 (Table 3).

Table 1. Comparison of demographic, clinical, and biochemical data of the patient and control group (values was given as mean ± SD)

	Patient group (n=46)	Control group (n=43)	p
Male gender, n (%)	20 (43.5)	23, (53)	0.34
Age (year)	47.6±14	41.9±13.9	0.059
Smoking rate, n (%)	16 (34.8)	20 (46.5)	0.26
Height (cm)	165±9	168±9	0.13
Weight (kg)	75.2±13.1	75.1±11.1	0.94
BMI (kg/m^2)	27.6±4.3	26.6±4	0.31
Glucose (mg/dL)	98±20	85±14	0.001
Urea (mg/dL)*	35 (25-58)	27 (21-32)	0.001
Creatinine (mg/dL)*	1.02 (0.63-1.67)	0.68 (0.56-0.83)	0.002
Albumin (g/dL)	4.3±0.2	4.4±0.2	0.12
Calcium (mg/dL)	9.4±0.4	9.7±0.3	0.002
Leukocyte (mm^3)	6710±1521	6860±1947	0.68
Hemoglobin (g/dL)	12.90±1.65	13.71±1.17	0.009
Hematocrit (%)	38.9±4.8	40.6±3.1	0.056
Thrombocyte (mm^3)	258.043±65.555	249.279±69.959	0.54
Proteinuria (mg/g)*	134 (86-483)	65 (50.5-78.5)	0.001
eGFR (mL/min/1.73 m^2)	77.1±43.1	113.5±18.3	<0.001

SD: Standard deviation, BMI: Body mass index, eGFR: Estimated glomerular filtration rate, n: Number *median (IQR 25-75)

Discussion

ADPKD disease is a multisystem disease characterized by expansion of kidney volume and multiple cysts in kidneys and other organs (12,13). While there are many studies on extrarenal manifestations of ADPKD, studies including pulmonary pathologies are limited (4,6,14-17). Airway dilatation seen in ADPKD could develop by abnormal expression of polycystin in smooth muscle likewise vascular aneurysms and colonic diverticulosis (2). Expansion of renal volume and increasing intra-abdominal pressure, over time, may decrease lung

Table 2. The results of spirometry in patient and control groups (values was given as mean ± SD)

	Patient group (n=46)	Control group (n=43)	p
FEV_1%	93.6±20.9	95.8±13.2	0.49
FVC%	93.8±19.5	96.9±12.7	0.04
FEV_1/FVC	83.8±7.3	82.6±6.2	0.50
PEF%	79.8±19.3	86.9±20.0	0.99
MEF_{25-75}%	81.0±24.9	86.0±24.7	0.64
Obstrictive pattern, n (%)	1 (2.1)	1 (2.3)	1
Restrictive pattern, n (%)	7 (15.2)	2 (4.6)	0.15

SD: Standard deviation, FVC: Forced vital capacity, FEV1: Forced expiratory volume in 1 second, PEF: Peak expiratory flow, MEF: Mean expiratory flow, n: Number

Table 3. The results of spirometry in patients with eGFR below and above 60 mL/min/1.73 m^2 (values was given as mean ± SD)

	eGFR ≥60 mL/min/1.73 m^2 (n=25)	eGFR < 60 mL/min/1.73 m^2 (n=21)	p
FEV_1%	90.6±19.2	96.8±22.9	0.60
FVC%	91.6±17.5	96.0±21.8	0.25
FEV_1/FVC	86.2±8.1	80.9±5.2	0.18
PEF%	81.7±19.5	77. 4±19. 4	0.96
MEF_{25-75}%	82.4±27.4	80.4±22.3	0.36
Obstrictive pattern, n (%)	2 (8)	0	1
Restrictive pattern, n (%)	5 (20)	4 (19)	0.12

SD: Standard deviation, eGFR: Estimated glomerular filtration rate, FVC: Forced vital capacity, FEV1: Forced expiratory volume in 1 second, PEF: Peak expiratory flow; MEF: Mean expiratory flow, n: Number

compliance and cause reduced FVC and also restrictive lung diseases. In addition, presence of respiratory function abnormalities is not surprising when common points in bronchiectasis pathogenesis and smooth muscle function defects found in other organs are taken into consideration. In this study, we aimed to demonstrate the effect of ADPKD on spirometry findings. In the literature, there is a limited number of studies on spirometry findings in ADPKD (6). Radiographically, presence of bronchiectasis was researched because of the idea that disruption of respiratory ciliary function may lead to bronchiectasis. Driscoll et al. (4) compared patients with ADPKD and non-ADPKD CKD patients whose etiology was different in terms of bronchiectasis detected by radiologic examination and found that the prevalence of bronchiectasis was higher in ADPKD patients. Although the disease was accompanied by bronchiectasis in patients with pulmonary involvement and pulmonary function findings of bronchiectasis with obstructive pattern, the frequency of restrictive pattern, and FVC were higher in ADPKD patients in our study (p=0.15 and p=0.04, respectively) (Table 2). While there was no significant difference in the incidence of restrictive patterns, the decrease in FVC, which is one of the most critical findings of restrictive lung diseases, supported the hypothesis of the effect of increased intraabdominal pressure on lung volume capacity. In a study conducted by Moua et al. (6), pulmonary function test was similar in patients with ADPKD and patients with CKD.

Patients with eGFR below and higher than 60 mL/min/1.73 m^2 were compared with each other, and we found no relationship between kidney function test and pulmonary function test (Table 3). The reason for not determining the relationship between them may be due to the number of participants or the lack of renal volume in the study. The mean eGFR was 35.4±14.3 in patients with an eGFR <60. Further studies on this subject are needed.

Study Limitations

It is obvious that if the study has been done with larger patient participation as well as kidney volume assessment, clearer data would be obtained.

Conclusion

Although the frequency of restrictive pattern was not significantly higher, FVC was significantly lower in ADPKD patients than in controls. This may reflect the indirect effects of enlarged kidneys. Further detailed studies, including renal volume, are needed.

Authorship Contribution

Concept: T.E.Ö, F.K. Design: E.C., M.G. Data Collection or Processing: T.E.Ö., F.K. Analysis or Interpretation: S.Ö., Z.K., E.C., B.D. and G.Ç. Literature Search: M.G., M.S., A.Ş. Writing: T.E.Ö., F.K.

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Microsatellite Instability in Ovarian Invasive and Borderline Epithelial Tumors and Comparison with Prognostic Parameters

Overin İnvazif ve Borderline Epitelyal Tümörlerinde Mikrosatellit İnstabilite ve Prognostik Parametreler ile Karşılaştırılması

Filiz İlhan Türkel, Aylin Ege Gül, Sibel Sensu*, Sevinç Hallaç Keser, Nagehan Özdemir Barışık

University of Health Sciences Turkey, Kartal Lütfü Kırdar Training and Research Hospital, Clinic of Pathology, İstanbul, Turkey
**İstinye University Faculty of Medicine, Department of Pathology, İstanbul, Turkey*

Abstract

Aim: Ovarian cancers, 20% of which are hereditary, are considered the most lethal gynecological malignancies. Defects on DNA *mismatch repair (MMR)* genes are responsible for hereditary ovarian tumors related with Lynch syndrome. In this study, we aimed to determine microsatellite instability status in invasive and borderline epithelial ovarian tumors diagnosed via immunohistochemistry in our clinic and compare the results with several prognostic parameters and survival.

Methods: In this retrospective study, 159 epithelial ovarian tumors were evaluated for age, tumor type, histological grade and Federation of Gynecology and Obstetrics (FIGO) stage as well as survival. MMR protein expression was immunohistochemically examined and absence of nuclear staining in tumor cells was considered MMR protein expression loss. All prognostic parameters were compared and analysed statistically.

Results: MMR protein expression loss showed no statistically significant relationship with FIGO stage, age, histological grade, and survival. The only correlation was detected between tumor type and MMR protein loss (p<0.001).

Conclusion: Although there are studies comparing microsatellite instability status of the tumors with several prognostic parameters, there is still no consensus on the issue. In this study on ovarian tumors, MMR protein expression loss was related with histological subtypes, but not with other prognostic parameters or survival. We believe that it is worth further investigating in larger studies with higher number of cases.

Keywords: Microsatellite instability, MMR expression, ovarian tumors, immunohistochemisty, prognosis, survival

Öz

Amaç: Yüzde 20'si herediter olan over kanseri en ölümcül jinekolojik malignitedir. DNA *mismatch onarım (MMR)* genlerindeki defektler, Lynch sendromu ile ilişkili herediter over tümörlerinden sorumludur. Bu çalışmada invazif ve borderline epitelyal over tümörlerinde mikrosatellit instabilite araştırılmakta olup sonuçlar çeşitli prognostik parametreler ile karşılaştırılmıştır.

Yöntemler: Bu retrospektif çalışmada 159 epitelyal over tümörü, yaş, tümör tipi, histolojik grade ve Uluslararası Kadın Doğum Dernekleri Federasyonu (FIGO) evreleme yanısıra sağkalım yönünden incelenmiştir. MMR ekspresyonu immünohistokimyasal olarak araştırılmış olup tümör hücrelerinde nükleer boyanma kaybı, MMR ekspresyon kaybı olarak kabul edilmiştir. Tüm prognostik parametreler karşılaştırılmış ve tüm veriler istatistiksel olarak incelenmiştir.

Bulgular: MMR protein ekspresyon kaybı ile FIGO evresi, yaş, histolojik grade ve sağkalım arasında istatistiksel olarak anlamlı ilişki saptanmamıştır. Sadece tümör tipi ile MMR kaybı arasında anlamlı bir korelasyon bulunmuştur (p<0,001).

Sonuç: Tümörün mikrosatellit instabilite durumu ile çeşitli prognostik parametreleri karşılaştıran çalışmalar mevcut olsa da sonuçlar çelişkilidir. Bu çalışmada over tümörlerinde, MMR ekspresyon kaybı histolojik alt tiplerle ilişkili bulunmuş olup diğer prognostik parametreler ve sağkalım ile ilişki saptanmamıştır. Bu konunun daha çok olgu içeren geniş çalışmalar eşliğinde irdelenmesi uygundur.

Anahtar Sözcükler: Mikrosatellit instabilite, MMR ekspresyonu, over tümörü, immünohistokimya, prognoz, sağkalım

Address for Correspondence/Yazışma Adresi: Sibel Sensu, İstinye University Faculty of Medicine, Department of Pathology, İstanbul, Turkey
E-mail: sibel.sensu@istinye.edu.tr ORCID: orcid.org/0000-0002-4607-780X
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Introduction

Ovarian cancer is one of the most frequent cancers (age standardized rate 6.4/100,000 person) and has the highest mortality rate among all gynecological malignancies (1,2). Well-accepted prognostic parameters for ovarian cancer are International Federation of Gynecology and Obstetrics (FIGO) stage, age, tumor type and histological grade (2). Approximately one fifth of ovarian tumors are hereditary and Lynch syndrome (LS) is responsible for 10-15% of these cancers (2,3). In LS, DNA *mismatch repair (MMR)* genes (mostly *MLH1*, *MSH2*, *MSH6*, and *PMS2*) have hereditary mutations which lead to the development of microsatellite instability (MSI). In addition, deletions in *EPCAM* gene responsible for *MSH2* gene promoter methylation might be found in LS. Microsatellites are short, repetitive DNA sequences unevenly distributed across the genome (3) on which insertion-deletion type mutations can emerge during DNA synthesis. These mutations, named MSI, are normally repaired by the MMR system. Due to mutations in repair genes, defects might not be repaired and subsequently, mutant copies might accumulate. Mutations developing on microsatellite foci that encode genes might lead to neoplastic alterations (2,4-7). MSI was first discovered in LS-related colon cancer, and subsequently, suggested to have a role in the pathogenesis of various genetic and sporadic cancers. MSI is also reported in approximately 10% of ovarian cancers (3,7,8).

MSI, which has a well-known prognostic and therapeutical significance in colon and endometrial cancers, might help clarify certain topics related with ovarian tumors, such as growth rate, precursor lesions, prognosis and response to therapy (3). MMR mutation and MSI are detected using methods such as immunohistochemisty (IHC) and polymerase chain reaction (PCR) (5,7,8). Although PCR and gene analysis give some idea on MSI status, these are troublesome, time-consuming and expensive methods (5,7,9,10). On the other hand, IHC analysis, which is routinely used in many pathology laboratories, is a simple, inexpensive, rapid and convenient method to investigate familial and sporadic MMR defects. In tumors with MMR pathway defects, it is possible to detect loss of one or more protein expressions.

In this study, we aimed to determine MSI status of invasive and borderline epithelial ovarian tumors using the IHC method and evaluate its correlation with several prognostic parameters and survival.

Methods

One hundred fifty-nine ovarian tumors diagnosed with morphological and immunohistochemical analysis in our pathology clinic between January 2012 and December 2016 were included in the study (ethic committee approval no: 2017/514/104/5, Kartal Dr. Lütfi Kirdar City Hospital). Slides, paraffin blocks and reports belonging to the cases were retrospectively analysed. Sections prepared from the paraffin blocks of selected slides were immunohistochemically stained, as explained below. The cases were reviewed by two pathologists using light microscopy. Demographic data were extracted from patient records. For staging, data from the archives of the medical oncology department were analysed according to the 2014 FIGO staging. For inclusion, the diagnosis of epithelial tumor should be made from surgical specimens, adequate tumor tissue should be present at blocks and slides of the case, positive internal control should be present, and besides, surgical specimen should be included if both biopsy and surgical specimens were available. Consultation cases, cases without paraffin blocks and cases with technically unsatisfactory IHC results were excluded. According to the Death Registration System, patients alive during the study period were recorded as "survived" cases.

For immunohistochemical examination, 4 µm thick sections prepared from formalin fixed-paraffin embedded tissues were used. Tissue sections were taken onto electrostatic loaded slides (isotherm) and placed into 70 °C incubator for at least 1 hour. All IHC procedures, including deparaffinization and antigen retrieval were performed in a full automated IHC stainer (Ventana BenchMark XT, Ventana Medical Systems, Tucson, AZ).

Instrument-ready, biotinylated, horseradish peroxidase multimer based, ready-to-use kit containing hydrogen peroxide substrate and 3.3'-diaminobenzidine tetrahydrochloride (DAB) chromogen (ultraView™ Universal DAB Detection Kit, Catalog number 760-500, Ventana Medical Systems, Tuscon, AZ) were used. Staining with *MLH1* (Clone: ES05, Dako North America, Ready to use), *MSH2* (Clone: FE11, Dako, North America, Ready to use), *MSH6* (Clone: EP49, Dako, North America, Ready to use), and *PMS2* (Clone: EP51, Dako, North America, Ready to use) antibodies, counterstaining with hematoxylin, dehydration and xylene clearing were performed and the slides were cover-slipped. Inflammatory and stromal cells on slides were considered positive internal control and nuclear staining for each antibody, positive staining. Absence of nuclear staining in tumor cells was interpreted as "loss of MMR proteins".

Statistical Analysis

Statistical analysis with SPSS version 15.0 software was used to investigate the appropriateness of the variables to normal distribution by using histogram graphs and the Kolmogorov-Smirnov test. Mean, standard deviation and median values were used for descriptive analyses. Two x two grids were compared with Pearson's chi-square and

Fisher's exact tests. ANOVA was used when variables with normal distribution (parametric) evaluated between more than two groups; the Mann-Whitney U test was used when variables showing non-normal distribution (nonparametric) were evaluated between binary groups; and the Kruskal-Wallis test, for more than two groups. The Spearman correlation coefficient was used to analyze the measurable data with each other. For overall comparison of survival function, log-rank test (Mantel-Cox) was used. A p value of less than 0.05 was considered statistically significant.

Results

Of the 159 study patients, 68% was under the age of 60 (18-79 year, mean age: 53.4). In 60% of the cases, tumor type was serous carcinoma and most of the cases (87%) were high grade. The most common borderline tumor was borderline mucinous carcinoma. Regarding stage, 43% of the patients had FIGO1 and 42% had FIGO3 disease (Table 1).

MMR loss was found in three of 159 cases of ovarian carcinoma (1 serious carcinoma, 1 clear cell carcinoma and 1 borderline endometrioid carcinoma). When the relationship between age, tumor type, FIGO stage, histological grade and MMR protein expression loss were analysed, a significant relationship was found only between tumor type and MMR loss (p<0.001). MMR protein expression loss was present in 1 of 2 (50%) borderline endometrioid tumors, one of nine (11%) clear cell carcinoma and 1 of 96 (1 %) serous carcinoma (p<0.001) (Table 2). In two patients, only MSH2 protein expression loss and in one patient, both MLH1 and PMS2 protein expression loss were detected (Table 3) (Figure 1 and 2).

Table 1. Clinicopathological characteristics of the cases

		n	%
Age (year)	<60	106	66.67
	≥60	53	33.33
Tumor type	Serous carcinoma	96	60.38
	Endometrioid carcinoma	10	6.29
	Mucinous carcinoma	3	1.89
	Clear cell carcinoma	9	5.66
	Transitional cell carcinoma	1	0.63
	Seromucinous carcinoma	1	0.63
	Borderline serous tumor	18	11.32
	Borderline endometrioid tumor	2	1.26
	Borderline mucinous tumor	16	10.06
	Borderline seromucinous tumor	3	1.89
Histological grade	Low grade	16	13.45
	High grade	103	86.55
FIGO stage	1	69	43.40
	2	18	11.32
	3	67	42.14
	4	5	3.14

FIGO: Federation of Gynecology and Obstetrics, n: Number

Totally, in 159 ovarian cancers, the rate of patients without MMR loss and who were still alive (70.5%) was below the rate of the all patients who were alive (71.1%) while the rate of patients who had MMR loss and survived was 67% (Table 4). The patient who had MMR loss and was paraplegic died in September 2018 due to a non-tumoral reason. A statistically significant relationship was not found between MMR protein expression loss and mortality [χ^2 (1)=0.044, p>0.005].

Discussion

Most frequent hereditary cancer syndromes related with ovaries are hereditary breast and ovarian cancer syndrome (HBOC) and LS. HBOC with BRCA1/2 mutations constitute 90% of cases and LS, the remaining 10% (11). LS previously was called hereditary nonpolyposis colorectal cancer, is an autosomal dominant familial syndrome seen at an early age, associated with a genetic predisposition to colorectal, endometrial, gastric or ovarian cancers and rarely found in patients having small intestine, pancreas, and brain tumors. In LS, hereditary mutations are observed in *MMR* genes. According to the literature, the most frequent histological subtypes in LS-related ovary tumors are clear cell and endometrioid type ovarian cancers (12,13). In a study by Song et al. (14), the mean cumulative risks of ovarian cancers by age 80 years were estimated to be 64%, 24% and 3.7% in the presence of *BRCA1*, *BRCA2* and *MMR* gene mutations.

In the study of Song et al. (14), the median age at diagnosis of hereditary ovarian cancer was 52 for BRCA1 mutation carriers, 57 for BRCA2 mutation carriers and 54 for *MMR* gene mutation carriers. Vierkoetter et al. (12) reported that patients with MMR protein expression loss were younger than patients without MMR loss (mean age, 47 and 58 years, respectively,) (p=0.014) In our study, three patients with MMR protein expression loss were 33, 48 and 60 years old, respectively (mean age: 48.6 year). Although the patients were younger in the group with MMR protein expression loss, we did not find any relationship between age and MMR loss. This may be due to small sample size.

Regarding tumor types, MSI was more frequently reported in several histological subtypes (10,13,15-17). In a study including 42 clear cell ovarian cancers, Cai et al. (18) reported that nine of the cases (21%) were related with MSI and high level of MSI was involved in the development of a subset of ovarian clear cell carcinomas.

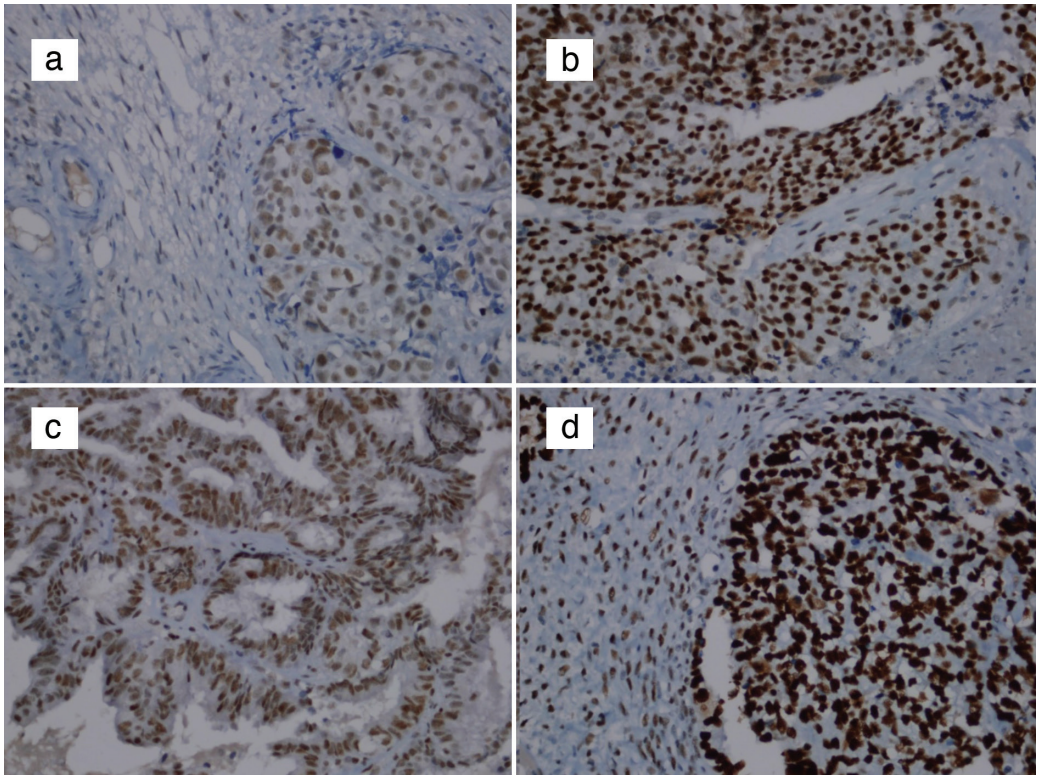

Figure 1. a-d. Immunohistochemical nuclear staining in cases with *MMR* gene expression (x400). MLH1 **(a)**. MSH2 **(b)**. PMS2 **(c)**. MSH6 **(d)**
MMR: Mismatch repair

Table 2. Relation between age, tumor type, FIGO stage, histological grade and MMR protein expression loss

		MMR protein expression				p
		Present		Absent		
		n	%	n	%	
Age (year)	<60	104	(98.11)	2	(1.89)	1.000
	≥60	52	(98.11)	1	(1.89)	
Tumor type	Serous carcinoma	95	(98.96)	1	(1.04)	<0.001
	Endometrioid carcinoma	10	(100.00)	0	(0.00)	
	Mucinous carcinoma	3	(100.00)	0	(0.00)	
	Clear cell carcinoma	8	(88.89)	1	(11.11)	
	Transitional cell carcinoma	1	(100.00)	0	(0.00)	
	Seromucinous carcinoma	1	(100.00)	0	(0.00)	
	Borderline mucinous tumor	16	(100.00)	0	(0.00)	
	Borderline seromucinous tumor	3	(100.00)	0	(0.00)	
	Borderline serous tumor	18	(100.00)	0	(0.00)	
	Borderline endometrioid tumor	1	(50.00)	1	(50.00)	
FIGO stage	1	68	(98.55)	1	(1.45)	0.675
	2	17	(94.44)	1	(5.56)	
	3	66	(98.51)	1	(1.49)	
	4	5	(100.00)	0	(0.00)	
Histological grade	Low grade	16	(100.00)	0	(0.00)	0.574
	High grade	101	(98.06)	2	(1.94)	

FIGO: Federation of Gynecology and Obstetrics, MMR: Mismatch repair, n: Number

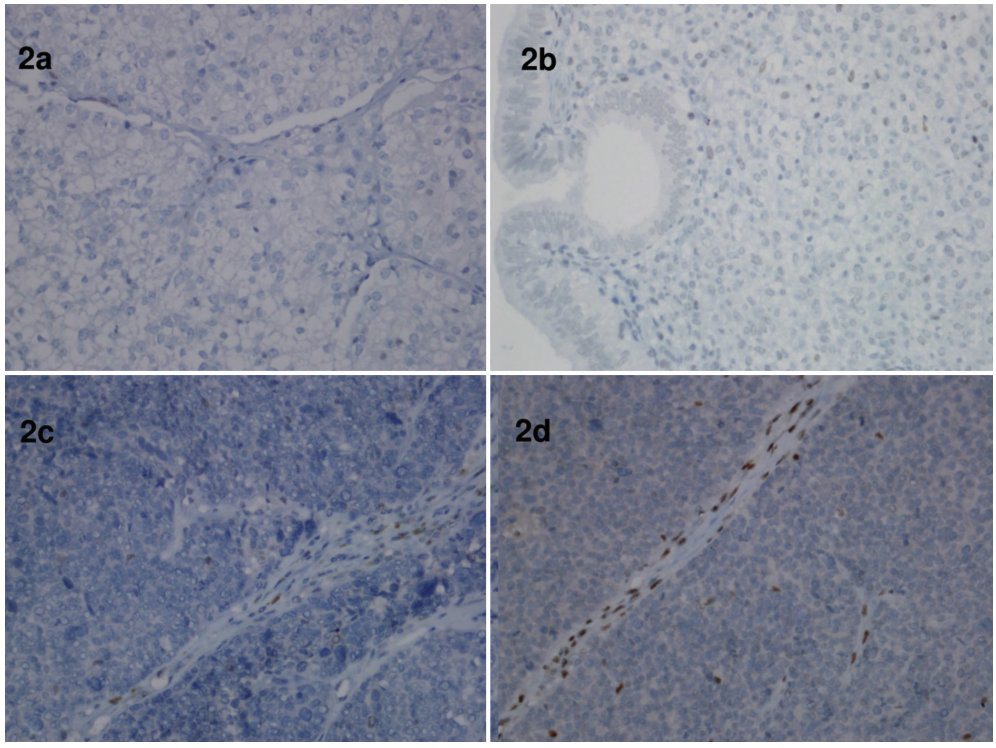

Figure 2. a-d. Absence of immunohistochemical nuclear staining in cases with *MMR* gene expression loss (x400). MSH2 - clear cell carcinoma **(a)**. MSH2 - borderline endometrioid tumor **(b)**. MLH1 -high grade mixed serous (undifferantiated) carcinoma **(c)**. PMS2 - high grade mixed serous (undifferantiated) carcinoma **(d)**
MMR: Mismatch repair

Table 3. MMR subtypes in cases that have MMR loss

	MLH1 loss	*MSH2* loss	*MSH6* loss	*PMS2* loss
Case 1	-	+	-	-
Case 2	-	+	-	-
Case 3	+	-	-	+

MMR: Mismatch repair

Table 4. Relation between MMR protein expression loss and mortality

MMR loss	**Total**	**Dead**	**Alive**	
	n	**n**	**n**	**%**
Absent	156	46	110	70.5%
Present	3	1	2	66.6%
Total	159	47	112	71.1%

MMR: Mismatch repair, n: Number

Gras et al. (13) found MSI in only endometrioid and clear cell ovarian cancers and its incidence was 12.5%. Lu et al. (16) found MSI more frequently, in poorly differentiated mucinous and clear cell ovarian cancers, however MSI level was not related with age, tumor differentiation or tumor type, but related with only stage (16). In a metaanalysis of 15 studies (n=159) that investigated the correlation between histological subtypes and *MMR* gene defect, Pal et al. (3) reported that, in ovarian tumors with *MMR* gene defect, non-serous histological subtypes were dominant and besides, mucinous and endometrioid type ovarian carcinomas were analogous to colon and endometrium cancers of LS (3). Ryan et al. (19), explained that, in LS-related cancers, dominant histological type was endometrioid carcinoma, however, *MMR* gene defect was also seen in high grade serous carcinomas. In our study, we found a relationship between tumor type and MMR protein expression loss (MMR loss was seen in a borderline endometrioid tumor, clear cell carcinoma and high grade mixed serous carcinoma). Even if we found a statistically significant relationship between MMR protein expression loss and tumor type, our patient group with MMR loss was small and this result should be supported with larger studies.

A retrospective study by the International LS Working Group on correlation between histological grade and MSI protein expression loss reported that LS-related ovarian cancers were mostly in early stage and low grade (20). Colle et al. (7) found that LS-related ovarian cancers were low-grade endometrioid and early stage tumors. Dellas et al. (21) reported that although MSI was more frequent in poorly differentiated cancers (p>0.05), a statistically

significant relationship existed only between early stage and MSI (p=0.03). In our study, one of the patients with MMR loss had borderline endometrioid carcinoma, one, high-grade clear cell carcinoma and the other had high-grade mixed serous carcinoma. Statistical analysis revealed that histological grade was not correlated with MMR loss in our series. Since the stages in our patients with MMR loss were Stage IA, Stage IIB and Stage IIIC, respectively, a statistically significant relationship was not established between MMR loss and FIGO stage. Small sample size might be the reason for not finding any relationship between histological grade, stage and MMR loss; therefore, we think that further analysis might be clarifying.

In a study by Ryan at al. (19) examining 1047 patients with *MMR* gene mutation, 53 patients had LS-related ovarian cancer; 85% of these patients presented at stage 1/2 and 5 years survival was 80%. Mallorca Group prospectively investigated 1942 patients without previous cancer, who were MMR mutation carriers, with colonoscopy and gynecological examination. In this study, 19 of 314 cancers developed during follow-up were ovarian cancers and cumulative ovarian cancer risk at age 70 was 11% for *MLH1* gene defect, 15% for *MSH2* gene defect and 0% for *MSH6* and *PMS2* gene defects. Most of the patients with ovarian cancer were younger than 50 and 10-year survival was 89% (22). The same study group, in a recent study including LS patients who did not have cancer previously, had early cancers and still alive, found that 5-year survival was 83% and 10-year survival was 74% in ovarian cancers (23). In our study, one of the three patients with MMR loss was paraplegic and died within 5 years of follow up. Statistical analysis revealed no relationship between patient survival and MMR loss. Nevertheless, we believe that survival should also be further investigated in larger series.

In the study by Mallorca group, MSH6 and PMS2 loss were not found in ovarian cancers. On the contrary, Norquist et al. (24) found *MMR* gene mutation in eight of 1,915 patients with ovarian cancer and 88% of these patients had *PMS2* or *MSH6* gene defect. In 2/3 patients with MSH6 mutation, there were endometrioid and early-stage cancers. The tumor type in four patients with PMS2 mutations was high grade serous carcinoma and was advanced stage. In the study by Song et al. (14), *MMR* gene mutation was seen in 17 patients and 10 of them had *MSH6*, four had *MSH2*, two had *MLH1* and one had *PMS2* gene mutation. In our study, immunohistochemical analysis with MLH1, MSH2, MSH6, and PMS2 markers revealed that two of three patients with MMR loss had only MSH2 protein expression loss and, one patient had both MLH1 and PMS2 loss. Normally, as a result of MSH2 protein expression loss, due to heterodimeric structure, MSH6 protein expression loss is also expected. But in two patients with MSH2 loss, no staining loss was seen in *MSH6*. This might be because of a variable immunohistochemical staining pattern of MSH6 (5). According to Terui et al. (25), 24% of mutations identified in LS are missense substitutions and this mostly occurs on *MSH6* gene. Mutant proteins that develop after missense mutations on genes, might be catalytically inactive but antigenically active (7). In our cases that show only MSH2 loss, MSH6 protein expression loss may not have been found because of missense mutation. In these patients, MSH2 loss might depend on *EPCAM* gene mutation, thus, we think that MSI status should be clarified with molecular analysis and, *EPCAM* gene analysis should be added.

Defect on DNA mismatch repair genes occur as a result of two mechanisms, one of which is germline mutations and the other is hypermethylation of CpG island on *MLH1* gene. In normal cells, these islands are not methylated. Since BRAF mutation is seen in 70% of cancers that occur after MLH1 methylation and is not seen in LS, MMR defect might be sporadic (26,27). When immunohistochemical MLH1 and PMS2 protein expression loss are found in a case, since the tumor may be hereditary as well as sporadic, the patient should be examined for BRAF mutation and MLH1 methylation. Our patient who had both MHL1 and PMS2 loss was old and the tumor type was high-grade serous mixed carcinoma. We assume that in such cases, besides genetic analysis for LS, BRAF mutation should also be analysed for identification of sporadic cases.

In a study by Park and Kim (11) investigating hereditary risk in borderline ovarian tumors immunohistochemically with MLH1, MSH2, BRCA1, and BRCA2 (n=32), 3% of the cases showed MSH2 protein expression loss. According to this study, although a relationship between borderline tumors and hereditary syndromes was not known, family history should be investigated and necessary tests should be done in suspicious cases (11). In our study, MMR protein expression loss was present in almost 2-3% of borderline tumors (1/39 borderline tumors). We found MMR protein expression loss in 1 of 2 borderline endometrioid tumors and in which MSH2 protein expression loss was present. In the borderline cases in our study, the incidence of MSH2 protein loss was similar to that in the study by Park and Kim (11) The patient with MMR protein loss had an endometriosis history as well as tumor in family history. Altogether, the results suggest a hereditary tumor in that patient.

In a study evaluating 834 ovarian cancers with IHC and molecular MSI test, Lee et al. (8) reported poor overall concordance (68%) between the two methods. They suggested that disconcordance might be due to different genetic features of ovarian tumors and also, due

to benign cases with MSI expression. Dellas et al. (21) found immunohistochemical MMR protein expression loss in 10/41 of patients and IHC could detect only a few (24%) MSI-positive cases. In our study, IHC detected MMR loss in three of 159 cases (1.8%). MSI is expected in 10-12% of ovarian cancers according to literature search, thus, IHC might have detected a small part of actual MSI cases (8).

Study Limitations

Our study has some limitations. Since some of ovarian cancers diagnosed between 2012 and 2016 were consultation cases, paraffin blocks were not available. Also, in some cases, due to technical problems, IHC did not reveal optimal results. Besides, detailed demographic and clinipathological data were not present in records of patients who received chemotherapy. These, altogether, negatively affected the included number of cases.

Conclusion

In our study, though MSI status of epithelial ovarian tumors was significantly related with histological subtypes, any relationship with other prognostic parameters and survival was not detected. We suggest that in patients with clear cell and endometrioid ovarian tumors under age 50 years, who have personal and/or family history of malignancy, or have concomitant secondary tumors; immunohistochemical MMR analysis might be helpful for monitoring the patients or patients' relatives. We think that since we had a limited number of cases, further studies with larger series will be clarifying.

Authorship Contributions

Concept: F.İ.T., A.E.G. Design: F.İ.T., A.E.G. Data Collection or Processing: F.İ.T., A.E.G., S.S., S.H.K., N.Ö.B. Analysis or Interpretation: F.İ.T., A.E.G., S.S., S.H.K., N.Ö.B. Literature Search: F.İ.T., S.S. Writing: S.S.

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Original Article / *Özgün Araştırma*

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Relationship of Gender and Serum Calcium and/or Phosphorus Levels on Admission with the Etiology and Early Prognosis of Hypercalcemia

Başvuru Anındaki Serum Kalsiyum ve/veya Fosfor Düzeyleri ve Cinsiyetin, Hiperkalseminin Etiyolojisi ve Erken Prognozu ile İlişkisi

Betül Erişmiş, Faruk Karandere, Deniz Yılmaz, Mehmet Hurşitoğlu, Abdulbaki Kumbasar

University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training of Research Hospital, Clinic of Internal Medicine, İstanbul, Turkey

Abstract

Aim: Hypercalcemia (HCM) is a common clinical problem characterized by a serum corrected calcium (cCa) level of >10.7 mg/dL. Primary hyperparathyroidism and malignancy are mostly (90%) involved in the etiology. In this study, we aimed to determine the relationship of cCa and phosphorus (P) levels, cCa/P ratio and gender with the etiology of HCM and one-week mortality.

Methods: Records of HCM patients older than 18 years of age who were hospitalized between January 1, 2017 and December 31, 2018 were retrospectively reviewed. Age, gender, cCa and P levels, HCM etiology and one-week survival status of the patients were recorded. Subsequently, the patients were divided into two groups according to whether the etiology of HCM was benign or malignant. Then, the groups were compared statistically in terms of gender, biochemical values and one-week survival.

Results: The median level of serum cCa was found to be significantly higher in males (p<0.00). The frequency of malignancy-associated HCM was higher in males than in females. When the groups were compared, serum cCa and P levels were found to be higher in malignancy-associated group (p<0.000 and p=0.005, respectively). The one-week mortality rate in all patients was 18.99%. However, surprisingly, the one-week mortality rate in malignancy-associated HCM was lower than in the other group.

Conclusion: Our study results show that serum cCa and P levels at the time of admission, and gender may help early evaluation of the etiology and/or prognosis of HCM.

Keywords: Hypercalcemia, mortality, calcium, phosphorus, prognosis

Öz

Amaç: Hiperkalsemi (HK), serum düzeltilmiş kalsiyum (dCa) seviyesinin 10,7 mg/dL'nin üzerinde olması ile karakterize yaygın bir klinik sorundur. Etiyolojide çoğunlukla (%90) primer hiperparatiroidizm ve malignite yer alır. Biz bu çalışmamızla tanı anındaki kalsiyum ve fosfor düzeyleri, dCa/P oranı ve cinsiyetin, hiperkalsemi etiyolojisi ve 1. hafta mortalitesi ile ilişkisini saptamayı amaçladık.

Yöntemler: 1 Ocak 2017 ve 31 Aralık 2018 tarihleri arasında hastanemizde yatarak tetkik ve tedavi edilen 18 yaşından büyük hiperkalsemili hastaların kayıtları retrospektif olarak incelendi. Hastaların yaş, cinsiyet, kalsiyum ve fosfor düzeyleri, HK etiyolojisi ve 1.hafta sağkalım durumları kaydedildi. Hastalar HK etiyolojisinin benign ya da malign nedenlere bağlı olmasına göre iki gruba ayrıldı. Gruplar, yaş, cinsiyet, belirtilen biyokimyasal değerler ve ilk hafta sağkalımı açısından istatistiksel olarak karşılaştırıldı.

Bulgular: Serum dCa'nın medyan seviyesi erkeklerde anlamlı olarak daha yüksek tespit edildi (p<0,00). Malignite ile ilişkili HK sıklığı erkeklerde kadınlardan daha fazlaydı. Malign ve benign etiyolojik gruplar karşılaştırıldığında, serum dCa ve P düzeyleri maligniteye bağlı hiperkalsemide daha yüksek saptandı (p<0,000 ve 0,005). Tüm hastaların ilk hafta mortalite oranı %18,99 idi. Ancak şaşırtıcı bir şekilde, malignite ilişkili HK'de 1. hafta ölüm oranı diğer gruptan daha düşüktü.

Sonuç: Çalışma sonuçlarımız, HK ile başvuran hastalarda başvuru anındaki serum dCa ve serum P düzeyleri ile cinsiyetin, hiperkalseminin etiyolojisi ve/veya prognozunun erken değerlendirilmesine yardımcı olabileceğini göstermektedir.

Anahtar Sözcükler: Hiperkalsemi, mortalite, kalsiyum, fosfor, prognoz

Address for Correspondence/Yazışma Adresi: Betül Erişmiş, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training of Research Hospital, Clinic of Internal Medicine, İstanbul, Turkey
E-mail: betul_erismis@yahoo.com ORCID: orcid.org/0000-0003-2970-2076
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Introduction

Hypercalcemia (HCM) is a common clinical problem characterized by a serum calcium level of >10.7 mg/dL (>2.6 mmol/L). HCM may be mild [serum calcium <12 mg/dL (3 mmol/L)], severe [serum calcium >14 mg/dL (3.5 mmol/L)], or moderate (in between the above levels). Primary hyperparathyroidism and malignancy account for about 90% of all cases of HCM (1,2).

Serum corrected calcium (cCa) level is used in evaluating HCM (2). In a study by Catalano et al. (3) from Italy, it was reported that hypocalcemia was more common in males while HCM did not show a gender difference. Also, unlike hypocalcemia, the incidence of HCM did not show a significant increase over time in the same study. In another study, although HCM was more common in females, malignancy-related HCM was found to be more frequent in males (4). As far as we know, there is no study about gender difference in the etiology of HCM and/or on the 1st week mortality of HCM in Turkey and the neighboring countries. To the best of our knowledge, there is also no study about the relationship of admission serum cCa and serum P levels (and cCa/P ratio) with the type of HCM (benign or malignancy-related) and/or with 1st week outcomes.

Methods

This retrospective study was approved by University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (decision no: 2019-19-02, date: 30.09.2019). This study was done in accordance with the RECORD Reporting Guidelines (5). Records of patients older than 18 years with HCM who were admitted to University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital between 1st January 2017 and 31st December 2018 were retrospectively reviewed. The patients were divided into two groups:

Group 1: consisted of patients with malignancy-associated HCM (n=113).

Group 2: non-malignancy (benign)-related HCM (due to primary, secondary or tertiary hyperparathyroidism, drug-induced vitamin D intoxication, granulomatous or other endocrinological causes) (n=98).

Inclusion criteria:

1. Age ≥18 years (both groups),
2. Availability of admission serum cCa, and serum P levels (both groups),
3. Availability of 1st week mortality and outcome records (both groups),

Exclusion criteria:

1. Temporary HCM
2. Uncertainty of the etiology of HCM (both groups)
3. Insufficient patient records (both groups)

Records of 230 patients were reviewed. Nineteen patients were excluded due to presence of at least one of the above-mentioned exclusion criteria. Thus, final analysis was done with a total of 211 hypercalcemic patients. The primary aim of this study was to compare age, sex, serum cCa and P levels, cCa/P ratio between the two groups. A secondary aim of the study was to investigate the relationship of these parameters with the 1st week outcomes of the patients.

Data Availability

Data are available for researchers (for research purposes only) on request by contacting the corresponding author.

Statistical Analysis

Statistical analyses were performed using the SPSS 22.0 statistical package for Windows. Description of data was expressed by mean, standard deviation, median and interquartile range, as appropriate. The distribution of variables was analyzed using the Kolmogorov-Smirnov test. For a comparison of variables of a normal distribution, the independent samples t-test was used and the Mann-Whitney U test was used for the comparison of variables with non-normal distribution. Pearson's correlation coefficient and its nonparametric equivalent Spearman's correlation coefficient were also used for evaluation of the correlation between quantitative variables. A p value of less than 0.05 was considered statistically significant.

Results

The mean age of the patients was 64.86±13.92 years. The female to male ratio was 114/97. The median serum cCa level in males was significantly higher than in females (p=<0.001). On the other hand, there was no significant difference in the median values of age, P and cCa/P ratio between the genders (p>0.05 for all) (Table 1). Comparing the patients according to malignant (group 1) or benign (group 2) etiology, serum cCa, and P levels were higher in malignancy-related HCM group (p=<0.0001 and p=0.005, respectively). However, age, and cCa/P ratio showed no significant difference between the groups (p<0.05) (Table 2). Comparison of males and females separately showed that serum cCa was higher in both females and males of group 1 (in comparison to group 2 females and males) (p≤0.0001 and p=0.017, respectively). Serum P level and cCa/P ratio were significantly higher in females (but not in males) in group 1 (p=0.002 and p=0.048, respectively). There was no significant difference in age between genders in both groups (p≤0.05) (Table 3). Of the total 113 patients with malignancy-related HCM, females [44 (39%)] were less than males [69 (61%)] (χ^2=5.53, p=0.019). Also, only

three of the 113 malignancy-related HCM patients died in the 1st week (χ^2=101.32, p≤0.0001).

Comparing these 211 hypercalcemic patients for 1st week mortality, nine (18.99%) died at the end of the 1st week follow-up. Comparison of the parameters of those who died with those who survived at the end of the 1st week is shown in Table 4. Serum P levels and cCa/P ratio were higher in patients who died than in survived patients (p=0.038 and p=0.046, respectively). Although the mean age and serum cCa level in the dead patients were higher than in those who survived, it did not reach a statistical significance (p>0.05). Eight of these nine patients were male (χ^2=5.44, p≤0.020). Further analysis of the survived 202 patients showed that 37 (18.32%) of them were admitted to an intensive care unit (ICU) during the 1st week of hospitalization. Comparison of data of survived patients who did and did not require ICU admission showed that only serum cCa levels were significantly higher in patients requiring ICU [14.5 (12.7-18.30) vs 13.10 (12.0-20.0) mg/dL, p<0.0001]. Also,

Table 1. Comparison of the patients by gender

Gender			Age	cCa	Ca/P ratio	Phosphorus
Female	N	Valid	114	114	96	96
		Missing	0	0	18	18
	Mean (SD)		65.01 (13.99)	13.42 (1.38)	5.42 (2.47)	2.94 (1.26)
	Median (min-max)		66.00 (18.00-91.00)	13.08 (12.00-19.30)	5.03 (2.16-13.7)	2.50 (1.00-6.00)
Male	N	Valid	97	97	70	70
		Missing	0	0	27	27
	Mean (SD)		64.68 (13.55)	14.49 (1.75)	5.38 (2.43)	3.20 (1.56)
	Median (min-max)		66.00 (20.00-97.00)	14.10 (12.10-20.40)	4.97 (1.94-13.10)	2.80 (1.00-7.60)
Total	N Mean (SD) Median (min-max)		211 64.86 (13.92) 66.00 (18.00-97.00)	211 13.91 (1.65) 13.50 (12.00-20.40)	166 5.40 (2.44) 4.98 (1.94-13.70)	166 3.05 (1.39) 2.74 (1.00-7.60)
P value			>0.05	**<0.00***	>0.05	>0.05

All data are non normally distributed.
NS: Not significant, SD: Standard deviation
cCa: corrected calcium, min: Minimum, max: Maximum, *Comparisons between females and males

Table 2. Comparison of the study parameters of group 1 with group 2

Etiology		Age	cCa	Ca/P ratio	Phosphorus
Group 1 (n=113)	Mean (SD)	65.13 (12.21)	14.53 (1.69)	5.35 (2.70)	3.30 (1.51)
	Median (min-max)	66.00 (20.00-93.00)	14.10 (12.20-20.40)	4.57 (2.13-13.70)	3.20 (1.00-7.60)
Group 2 (n=98)	Mean (SD)	64.55 (15.41)	13.20 (1.28)	5.46 (2.17)	2.79 (1.22)
	Median (min-max)	6.00 (18.00-97.00)	12.80 (12.00-16.80)	5.34 (1.94-13.10)	2.41 (1.00-6.50)
P value		NS	**<0.000**	NS	**0.005**

All data are non normally distributed.
NS: Not significant, SD: Standard deviation, n: Number, cCa: corrected calcium, min: Minimum, max: Maximum

Table 3. Comparing group 1 with 2 according to gender

Group	Gender		Age	cCa	cCa/P ratio	Phosphorus
Group 1 (Malignant etiology)	F (n=44)	Mean (SD)	64.04 (12.45)	14.22 (1.55)	5.25 (2.98)	3.37 (1.43)
		Median (min-max)	64.50 (38.00-86.00)	13.90 (12.20-19.30)	4.40 (2.16-13.70)	3.40 (1.00-6.80
	M (n=69)	Mean (SD)	65.82 (12.09)	14.73 (1,75)	5.43 (2.49)	3.25 (1.58)
		Median (min-max)	67.00 (20.00-93.00)	14.50 (12.30-20.40)	4.70 (2.13-11.73)	3.10 (1.10-7.60)
Group 2 (Benign etiology)	F (n=70)	Mean (SD)	65.62 (14.94)	12.92 (0.99)	5.52 (2.11)	2.67 (1.06)
		Median (min-max)	66.50 (18.00-91.00)	12.70 (12.00-16.80)	5.24 (2.22-12.20)	2.42 (1.00-5.80)
	M (n=82)	Mean (SD)	61.85 (16.51)	13.90 (1.63)	5.28 (2.33)	3.10 (1.55)
		Median (min-max)	62.50 (29.00-97.00)	13.25 (12.10-16.80)	5.40 (1.94-13.10)	2.30 (1.00-6.50)
P value			NS^F, NS^M	$<0.000^F$, 0.017^M	0.002^F NSM	0.048^F, NS^M

cCa: corrected calcium, F: Female, M: Male, SD: Standard deviation, min: Minimum, max: Maximum, n: Number

only 11 (29.73%) of these 37 ICU-requiring patients were female (χ^2=6.081, p≤0.014).

Spearman's correlation coefficient showed that serum cCa and serum P levels were positively correlated with malignancy-related HCM. However, there was a negative correlation between serum P levels and the 1st week outcomes (see Table 5).

Discussion

While primary hyperparathyroidism and malignancy account for 80-90% of all cases of HCM, the differential diagnosis has expanded to over 25 separate disease states. Among the outpatient population, primary hyperparathyroidism is the most common cause of HCM, but malignancy accounts for approximately 65% of hospitalized patients (6). Regardless of the etiology, the signs and symptoms of HCM are similar, but there are several clinical features that may help differentiate the etiology of HCM. Measurement of parathyroid hormone (PTH) and/or PTH-related protein (PTHrP) levels help identify the cause of HCM (7). However, these tests are not routine or early tests in the management of HCM. Also performing these tests needs somewhat more time than serum cCa and P tests. Additionally, PTHrP test is even not routine in most of the centers (at least in developing and/or in underdeveloped countries). HCM may be a life-threatening condition and may require urgent treatment and/or ICU admission. Thus, early evaluation (from etiology point of view) and planning further diagnostic studies and management are of paramount importance (8).

In our study, both serum cCa and serum P levels were higher in malignancy-related HCM (in comparison

Table 4. Comparison of the parameters of the patients according to 1st week outcomes

Groups	Gender		Age	cCa	Ca/P ratio	Phosphorus
Survived at 1st week	F (n=102)	Mean (SD)	65.27 (14.22)	13.30 (1.34)	5.27 (2.25)	2.97 (1.26)
		Median (min-max)	67.00 (18.00-91.00)	13.00 (12.00-19.30)	4.97 (2.16-12.20)	2.50 (1.00-6.80)
	M (n=63)	Mean (SD)	63.25 (12.63)	14.21 (1.74)	5.61 (2.34)	3.02 (1.50)
		Median (min-max)	64.00 (29.00-93.00)	13.70 (12.10-20.40)	5.23 (1.94-11.73)	2.70 (1.10-7.20)
	Total	Mean (SD)	64.86 (13.76)	13.91(1.65)	5.40 (2.44)	3.05 (1.39)
		Median (min-max)	66.00(18.00-97.00)	13.50 (12.00-20.40)	4.98 (1.94-13.70)	2.74 (1.00-7.60)
Non-survived at 1st week	F (n=1)	Mean (SD)	55.00	**15.70**	4.48	3.50
		Median (min-max)	55.00	**15.70**	4.48	3.50
	M (n=8)	Mean (SD)	72.50 (14.55)	14.48 (1.95)	3.77 (1.76)	4.25 (1.59)
		Median (min-max)	74.50 (51.00-97.00)	14.35 (12.10-16.80)	3.33 (2.51-7.22)	4.40 (1.80-6,50)
	Total	Mean (SD)	70.55 (14.80)	14.62 (1.87)	3.87 (1.63)	4.14 (1.48)
		Median (min-max)	73.00 (51.00-97.00)	15.70 (12.10-16.80)	3.66 (2.51-7.22)	4,30 (1,80-6.50)
P value			N^{ST}	N^{ST}	**0.046^{T}**	**0.038^{T}**

All data are non-normally distributed.
^{T}Comparing all survived with non-survived patients, SD: Standard deviation, F: Female, M: Male, cCa: corrected calcium, min: Minimum, max: Maximum, n: Number, NS: Not specified

Table 5. Spearman's correlation analysis results

			cCa	P	Etiology	cCa/Pratio	Mortalite (1st week)
Spearman's rho	cCA	Correlation coefficient	1.000	0.403**	0.471**	-0.186*	-0.074
		Sig. (2-tailed)	-	0.000	0.000	0.016	0.282
	P	Correlation coefficient	0.403**	1.000	0.218**	-0.966**	-0.161*
		Sig. (2-tailed)	0.000	-	0.005	0.000	0.038
	Etiology	Correlation coefficient	0.471**	0.218**	1.000	-0.122	0.086
		Sig. (2-tailed)	0.000	0.005	-	0.119	0.216
	cCa/P ratio	Correlation coefficient	-0.186*	-0.966**	-0.122	1.000	0.155*
		Sig. (2-tailed)	0.016	0.000	0.119	-	0.046
	Mortality (1st week)	Correlation coefficient	-0.074	-0.161*	0.086	0.155*	1.000
		Sig. (2-tailed)	0.282	0.038	0.216	0.046	.

Sig: Significance, *Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed), cCa: corrected calcium

to benign etiologies associated HCM) in all patients with no difference between males and females. Another important finding in our patient series is that the frequency of malignancy-related HCM was more common in males than females (Table 3). Correlation analysis also showed a significant positive correlation between these parameters and the presence of malignancy-related HCM (Table 5).

Previous studies showed that life expectancy was poor in cancer-associated HCM even in patients who were actively treated. Ralston et al. (9) showed that the availability of specific anticancer treatment was an important prognostic indicator; the median survival was 30 days who did not receive any specific anticancer treatment. In our study, the 1st week mortality rate in our inpatients with HCM was 18.99%. Surprisingly, the 1st week death rate in patients with malignancy-related HCM was lower than in the other group.

Also, the male/female ratio of death was higher in all patients in the 1st week. Although serum cCa levels showed no significant difference, serum P level and cCa/P ratio were higher in patients who died than in those who survived. In the survived ones, the number of patient who required intensive care after 1st week was higher in men than in women. Therefore, our study findings showed that serum cCa, and serum P could help predict the etiology of HCM. On the other hand, gender could be useful in predicting the etiology and 1st week mortality and need for ICU as well.

Study Limitations

One of the limitations of our study is its retrospective nature. PTHrP is not in routine use in our center. So, this parameter was not used in classifying HCM patients. Additionally, uncertain cases (from etiology point of view) were excluded from the final analysis (of 230 patients only 211 cases were included in the final analysis).

Conclusion

Our study results show that early admission data (gender, serum cCa level, and serum P level) may help early evaluation of the etiology and/or early prognosis of HCM. Further studies are needed in this field.

Authorship Contributions

Concept: B.E., F.K., D.Y., M.H., A.K. Design: B.E., M.H., A.K. Data Collection or Processing: B.E., F.K., D.Y. Analysis or Interpretation: B.E., F.K., M.H., A.K. Literature Search: B.E., F.K., D.Y., M.H. Writing: B.E., M.H.

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Evaluation of Maternal Serum PAPP-A and hCG Levels at 10-14 Weeks of Gestation in Hyperemesis Gravidarum

Hiperemezis Gravidarum Tanısı Alan 10-14 Haftalık Gebelerde Maternal Serum PAAP-A ve hCG Seviyelerinin Değerlendirilmesi

Anıl Turhan Çakır, Ahmet Birtan Boran*

Zonguldak Maternity and Child Health Hospital, Clinic of Gynecology and Obstetrics, Oncology Surgery, Zonguldak, Turkey
**İstanbul Training and Research Hospital, Clinic of Gynecology and Obstetrics, İstanbul, Turkey*

Abstract

Aim: The aim of this study is to determine the relationship between hyperemesis gravidarum and maternal serum pregnancy-associated plasma protein A (PAPP-A) and human chorionic gonadotropin (hCG) levels. This study was designed as a case-control study.

Methods: The study group consists of 54 pregnant women of 10-14 weeks who were diagnosed with hyperemesis gravidarum in the İstanbul Training and Research Hospital Hospital while the control group consists of 54 pregnant women of 10-14 weeks who did not have any complaints. Thyroid stimulating hormone, free T3, free T4, aspartate aminotransferase, alanine aminotransferase, PAPP-A, and hCG values and age were retrospectively scanned from files.

Results: We have observed that the hyperemesis gravidarum group has higher hCG levels as compared with the control group. The mean hCG level in control group and hyperemesis group was 1.10±0.569 and 1.55±1.140, respectively ($p<0.05$) The mean PAPP-A level in control group and hyperemesis group was 1.00±0.611, 1.36±0.887, respectively ($p<0.05$).

Conclusion: Elevated levels of PAPP-A and hCG are associated with hyperemesis gravidarum. More comprehensive studies are needed to explain the role of PAPP-A in the pathogenesis of hyperemesis gravidarum.

Keywords: PAPP-A, chorionic gonadotropin, hyperemesis gravidarum

Öz

Amaç: Araştırmamızdaki amacımız hiperemezis gravidarum ile ilk trimester maternal serum hamilelikle ilişkili plazma protein-A (PAPP-A) ve insan koryonik gonadotropin (hCG) seviyeleri arasındaki ilişkiyi saptamaktadır. Bu çalışma olgu-kontrol çalışması olarak planlandı.

Yöntemler: Çalışma grubu, İstanbul Eğitim ve Araştırma Hastanesi'nde hiperemezis gravidarum tanısı alan 10-14 haftalık 54 gebeden oluşmaktayken, kontrol grubu ise normal gebelik takibi için polikliniğe başvuran, herhangi bir şikayeti olmayan 10-14 haftalık 54 gebeden oluşmaktadır. Tiroit uyarıcı hormon, serbest T3, serbest T4, aspartat aminotransferaz, alanin aminotransferaz, PAPP-A, hCG değerleri ve yaşları retrospektif olarak dosyalardan taranıp karşılaştırıldı.

Bulgular: Çalışma grubundaki gebelerin kontrol grubu ile kıyaslandığında daha yüksek hCG değerlerine sahip olduğu gözlendi. Kontrol grubunda hCG ortalaması 1,10±0,569 iken çalışma grubunda 1,55±1,140 idi ($p<0.05$). Kontrol grubunda PAPP-A değerleri ortalaması 1,00±0,611 iken çalışma grubunda 1,36±0,887 idi ($p<0.05$).

Sonuç: Yüksek PAPP-A ve hCG seviyeleri hiperemezis gravidarum ile ilişkilidir. Hiperemezis gravidarum patogenezinde PAPP-A'nın rolünü açıklamak için daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: PAPP-A, koryonik gonadotropin, hiperemezis gravidarum

Address for Correspondence/Yazışma Adresi: Anıl Turhan Çakır, Zonguldak Maternity and Child Health Hospital, Clinic of Gynecology and Obstetrics, Oncology Surgery, Zonguldak, Turkey
E-mail: dranilturhan@hotmail.com ORCID: orcid.org/0000-0001-7976-4123
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Introduction

Nausea and vomiting of pregnancy is seen in approximately 50% to 80% of pregnant women in the first trimester of pregnancy and causes negative effects on women's social, professional and family life (1). Hyperemesis gravidarum (HG) can lead to excessive nausea, vomiting, weight loss (around 5% of body weight) and dehydration, ketosis, electrolyte and acid-base imbalance, sometimes hepatic and renal failure (2).

The etiology of HG has not been clarified. The presence of nausea and vomiting during periods of increased hCG in the blood, an increase in the incidence of HG in multiple pregnancies and gestational trophoblastic diseases shows that hCG may be effective in the etiology (3-5).

Pregnancy-associated plasma protein-A (PAPP-A) was isolated in 1974 as one of the four proteins, placenta-derived, found in high concentrations in the blood of pregnant women (6). Although its biological function was unknown for 25 years, it has been used for screening for Down's syndrome (7).

To date, few studies have investigated maternal serum PAPP-A levels in pregnant women with HG. In our study, we aimed to investigate the relationship between HG and PAPP-A and hCG.

Methods

This study was approved by the Scientific Research Ethics Committee of İstanbul Training and Research Hospital (approval number-202, date: 16.11.2012) and conducted in compliance with the ethical principles of the Declaration of Helsinki. The study was planned as a retrospective case-control study. Patient consent was not obtained because of the retrospective nature of the study. Study group consisted of 54 pregnant women at 10-14 weeks of gestation diagnosed with HG and the control group consisted of 54 pregnant women at 10-14 weeks of gestation who attended the outpatient clinic for normal pregnancy follow-up in İstanbul Training and Research Hospital.

Pregnant women with other diseases that may cause vomiting, such as gastritis, nephrolithiasis, cholelithiasis, gastroenteritis, hyperthyroidism and multiple pregnancies, were not included in the study.

Gestational age was determined based on the last menstrual period and ultrasonography measurements. Thyroid stimulating hormone (TSH), free T3 (FT3), free T4 (FT4), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) evalues were obtained from patient files. Pregnancy-associated plasma protein-A (PAPP-A) and human chorionic gonadotropin (hCG) values were achieved from the first trimester prenatal screening test by scanning the records. Plasma levels were expressed with gestational age-specific multiple of median (MoM).

In this study, a special statistical package program was used. Descriptive statistical methods (mean, standard deviation) were used to evaluate the data, as well as the independent samples t-test for comparison of binary groups, and chi-square test for comparison of qualitative data. Significance was evaluated at the level of $p<0.05$.

Results

The average age of the study and control groups was 27.62±5.037 years and 28.33±5.051 years, respectively. No statistically significant difference was found in average age between the groups (p=0.283) (Table 1).

The mean AST value in the study and control groups was 16.29±5.102 U/L and 15.35±6.697 U/L, respectively. The mean ALT value in the study and control groups was 13.99±7.682 U/L and 13.17±13.635 U/L, respectively. No statistically significant difference was found between the two groups (p=0.442 p=0.709) (Figure 1).

The mean FT3, FT4 and TSH values in the study group were 2.97±0.945 pg/mL, 1.133±0.328 ng/dL and 1.248±1.186 uIU/mL, respectively. The mean FT3, FT4 and TSH values in the control group were 2.99±0.346 pg/mL, 1.11±0.140 ng/dL and 1.68±1.336 uIU/mL, respectively. No statistically significant difference was found (p=0.916, p=0.803, p=0.087, respectively) (Figure 2).

It was observed that the pregnant women in the study group had higher hCG values compared to the control group. While the mean hCG value in the control group was 1.10±0.569, it was 1.55±1.140 in the study group (p=0.01). Similarly, PAPP-A values were found to be statistically significantly higher in pregnant women in the study group compared to the control group. The mean PAPP-A value in the control group was 1.00±0.611 while it was 1.36±0.887 in the study group (p=0.016) (Figure 3).

Comparison of laboratory values of patient and control groups is shown in Table 2.

Table 1. Average age of patient and control groups

	Min age	Max age	Mean ± SD
Patient	16	36	27.62±5.037
Control	20	38	28.33±5.051

p=0.283, SD: Standard deviaition, min: Minimum, max: Maximum

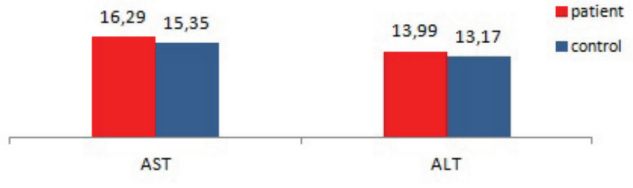

Figure 1. Average of AST and ALT values of patient and control groups
AST: Aspartate aminotransferase, ALT: Alanine aminotransferas

Discussion

The etiology of HG has not been clarified. However, hCG is the most likely endocrine factor associated with the development of HG. Presence of nausea and vomiting during periods when hCG peaked in the blood, an increase in the incidence of HG in multiple pregnancies and gestational trophoblastic diseases supports this theory (3-5).

Burmucic and Weiss (8) compared urine hCG levels in healthy pregnants at the first trimester and patients with HG in their study. As a result, urinary hCG excretion was found to be 86% higher in patients with HG.

Goodwin et al. (9) found significantly higher free β-hCG values in pregnant women with HG compared to controls.

In their study, Masson et al. (10) divided 116 patients into four group as asymptomatic group, nausea group, nausea + vomiting group and HG group. HCG values were higher in the group with nausea and in the group with nausea + vomiting compared to the asymptomatic group. In the fourth group, HG group, hCG was not higher than in the asymptomatic group.

In their study, Tan et al. (11) argued that hCG affects the severity of HG. They found a relationship between high hCG levels and long hospital stay.

In addition to these studies advocating the relationship between hCG and HG, there are also different studies. In their study, Panesar et al. (12) evaluated thyroid hormones and hCG in patients with HG and they found high hCG values in HG group. However, after logistic regression analysis, FT4 and TSH were found to be significantly independent variables, while hCG was not found.

Consistent with the majority of the literature, we found higher levels of hCG in the HG group compared to the control group. However, a causal relationship between HG and hCG has not been established in the literature yet.

Increased hCG production in HG can suppress TSH levels by performing a thyrotrophic effect (13,14). Therefore, FT4 and FT3 levels may increase and TSH level may decrease in the first trimester. This is particularly evident in patients with HG. In a systematic review published in 2014, it was found that two thirds of 34 studies reported a decreased TSH level or an increased FT4 level in pregnant women with HG compared to asymptomatic pregnant women. In this review, the authors point out that they were unable to investigate the diagnostic accuracy of thyroid function testing, however, because of the lack of reported cut-off values in the included studies and based on these findings, they recommend thyroid function testing be carried out only to rule out overt thyroid disease among patients with HG but not to diagnose or exclude HG (15).

In our study, no difference was found between the groups in terms of TSH, FT3 and FT4 levels. Although a decrease in TSH levels and an increase in FT4 levels were found in two-thirds of the studies, it was not found in one third. Not every pregnant woman with HG has to have hyperthyroidism. The reason for not finding a difference in the thyroid profile may be the fact that hCG was not high enough to stimulate the thyroid gland or the patients' thyroid glands were not very sensitive to hCG (16).

In 50% of patients with HG, one- or two-fold increase in aminotransferases can be detected (17). High transaminases can be induced by disorders in thyroid function (18). Hepatic damage occurs due to relative hypoxia in the perivenular area. Studies have shown that patients with HG having high

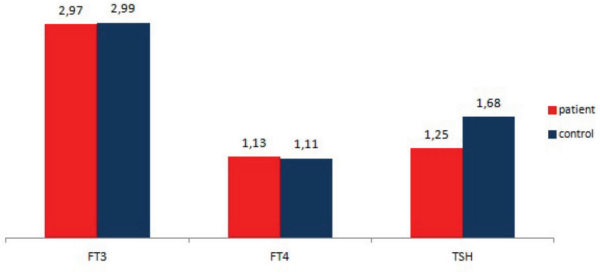

Figure 2. Average of FT3, FT4 and TSH values of patient and control groups
FT3: Free T3, FT4: Free T4, TSH: Thyroid stimulating hormone

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

	Patient (mean ± SD)	Control (mean ± SD)	p
PAPP-A	1.36±0.887	1.00±0.611	0.016
hCG	1.55±1.140	1.10±0.569	0.010
AST	16.29±5.102	15.35±6.697	0.442
ALT	13.99±7.682	13.17±13.635	0.709
FT3	2.97±0.945	2.99±0.346	0.916
FT4	1.133±0.328	1.11±0.140	0.803
TSH	1.248±1.186	1.68±1.336	0.087

PAPP-A: Pregnancy-associated plasma protein A, hCG: Human chorionic gonadotropin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, FT3: Free T3, FT4: Free T4, TSH: Thyroid stimulating hormone, SD: Standard deviation

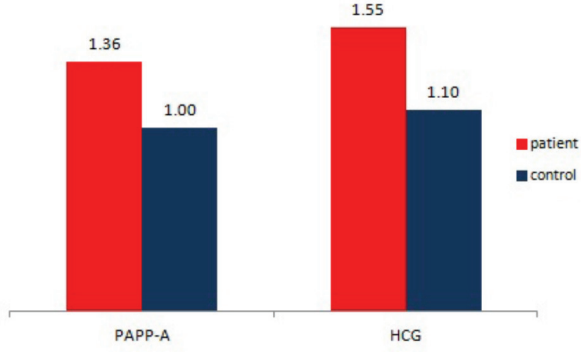

Figure 3. Average of PAPP-A and hCG values of patient and control groups
PAPP-A: Pregnancy-associated plasma protein A, hCG: Human chorionic gonadotropin

transaminases have low TSH levels and there was a positive relationship between ALT and FT4 (19). In addition, there are studies showing no difference between patients with HG and controls in terms of aminotransferase levels (20). In our study, low TSH levels were not detected in pregnant women with HG, therefore no significant difference was found between the groups in terms of AST and ALT levels.

It has been determined that PAPP-A has protease activity against insulin-like growth factor binding protein-4 (IGFBP-4) (21,22). It needs insulin-like growth factor 1 (IGF-1) or IGF-2 to divide IGFBP-4. PAPP-A can be synthesized by vascular smooth muscle cells, ovarian granulosa cells, trophoblasts and many other cells. It is not only a pregnancy-specific protein (23,24). There are studies suggesting that IGFBP protease plays an important role in adjusting local IGF concentration (25). IGFBP-4 has a high affinity for IGF and binds IGF. Thus, it prevents IGF-IGF-1 receptor interaction and inhibits cell growth. Tumor necrosis factor (TNF)-α and interleukin (IL)1-β are pro-inflammatory cytokines stimulating the production of PAPP-A in human fibroblasts (26). While PAPP-A production is stimulated by these cytokines, it can be reduced in human fibroblasts pretreated with antioxidant substances such as N-acetyl cysteine. Some of the effects produced by cytokines are associated with oxidative stress.

In a study by Derbent et al. (19), 115 pregnant women with HG and 110 pregnant women without any complaints who participated in the first trimester screening program were compared. Serum PAPP-A and free β-hCG values were found to be significantly higher in the HG group compared to the control group, and after multivariate analysis, PAPP-A and hCG were independently associated with HG after controlling for TSH, FT4, AST and ALT.

While free β-hCG, T3, AST, ALT and albumin values did not differ between the groups in a prospective case-control study conducted by Unlu et al. (20) including 169 patients hospitalized at least once in the antepartum period due to HG, in HG group, serum TSH values were lower and T4 values were significantly higher (p=0.001). PAPP-A values were significantly higher in the HG group than in the control group (p=0.002).

In addition, in a retrospective study conducted by Madendağ et al. (27), fetal nuchal translucency (NT), crown-rump-lenght (CRL), hCG and PAPP-A levels in pregnant women with HG and healthy pregnants were compared. While both groups were similar in terms of NT, CRL, free β-hCG values and hCG MoM values, PAPP-A levels were significantly lower in the HG group compared to the control group (p=0.044).

Consistent with most of the few studies examining the relationship between PAPP-A and HG, in our study, PAPP-A levels were found to be significantly higher in the HG group compared to the control group. Although the etiology of HG is not known exactly, it is thought that inflammation plays an important role in the pathogenesis. HG is seen as a result of an overactivated immune system. In recent studies, inflammatory markers were found to be higher in pregnant women with HG compared to healthy pregnant women (28). TNF-α and IL-1b, which are pro-inflammatory cytokines, are the most potent stimulators for PAPP-A and, TNF-α levels have been reported to be high in pregnant women with HG (20,29). The effects of these cytokines can be partially mediated by oxidative stress. Lipid peroxidation and oxidative stress increase due to an increase in free radical activity and deterioration in antioxidant defense system during pregnancy. Low antioxidant enzyme activity and increased oxidative stress have been reported in pregnant women with HG compared to normal pregnant women (30-32). An overactivated immune system and increased oxidative stress and decreased antioxidant activity in HG may cause increased PAPP-A expression (19).

Conclusion

This study showed that PAPP-A and hCG levels are elevated in the serum of pregnant women with HG in the first trimester. Although the relationship between hCG and HG has been shown in many studies previously, there are few studies examining the relationship between PAPP-A level and HG. The relationship between PAPP-A and HG has not been clearly elucidated. More comprehensive studies are needed to explain the role of PAPP-A in the pathogenesis of HG.

Authorship Contributions

Concept: A.T.Ç., A.B.B. Design: A.T.Ç., A.B.B. Data Collection or Processing: A.T.Ç. Analysis or Interpretation: A.T.Ç., A.B.B. Literature Search: A.T.Ç., A.B.B. Writing: A.T.Ç., A.B.B.

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

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Original Article / *Özgün Araştırma*

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Nasopharyngeal Carriage of Potential Pathogenic Bacteria in Healthy Children Living in İstanbul

İstanbul'da Yaşayan Sağlıklı Çocuklarda Potansiyel Patojen Bakterilerin Nazofarengeal Taşıyıcılığın Araştırılması

Nevriye Gönüllü*, Sevilay Yıldız*, Okan Aydoğan*,**, Zeynep Taner*,***, Sinem Özdemir*, Selcan Akyol*, Halit Tokman*, Fatma Köksal Çakırlar*

**İstanbul University Cerrahpaşa Faculty of Medicine, Department of Medical Microbiology İstanbul, Turkey*

***İstanbul Medipol University Faculty of Medicine, Department of Medical Microbiology, İstanbul, Turkey*

****İstanbul Altınbaş University Faculty of Medicine, Department of Medical Microbiology İstanbul, Turkey*

Abstract

Aim: The purpose of this study was to determine the prevalence of nasopharyngeal carriage of potentially pathogenic bacteria (especially *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*) in healthy 1-7 years old children and risk factors affecting it.

Methods: A total of four hundred forty-five healthy children (1-7 years old) from the European side of Istanbul (10 different units) were included in this cross-sectional study. Isolated microorganisms were identified by standard laboratory methods and the results were evaluated. Risk factors affecting the prevalence of nasopharyngeal carriage were also evaluated.

Results: In the study, 139 (31.2%) of the samples were positive. *S. pneumoniae* two (0.4%), *H. influenzae* 50 (11.2%); of them type b 10 (2.2%), *H. parainfluenzae* 10 (2.2%), *M. catarrhalis* 14 (3.1%), *S. aureus* 35 (7.9%), Group A β hemolytic streptococci (*Streptococcus pyogenes*) 13 (2.9%), Group B streptococci (*S. agalactiae*) 18 (4.0%), Non A Non B streptococci 16 (3.6%) were detected. The results obtained from different sites (places) were found to be variable in terms of pathogen density.

Conclusion: Nasopharyngeal carriage rates found in our study were generally lower than in some studies on this subject. However, when the samples taken from different places were evaluated one by one, it was seen that the colonization rate reached 45.9% in crowded and poor building properties (small, poorly ventilated, unhealthy buildings). The highest rate of *H. influenzae* carriage in the 2-3 age group was 33.3%. In this study, crowded and unhealthy school environments and low maternal education level have been determined as risk factors for increased nasopharyngeal carriage rate. Results of such studies vary depending on the region, sample frequency, individual and

Öz

Amaç: Bu çalışmada sağlıklı 1-7 yaş çocuklarda (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* başta olmak üzere) potansiyel patojen bakterilerin nazofaringeal taşıyıcılık prevalansının ve bunu etkileyen risk faktörlerinin belirlenmesi amaçlanmıştır.

Yöntemler: Bu kesitsel çalışmaya İstanbul Avrupa yakasından (10 farklı birimden) 1-7 yaş grubu toplam dört yüz kırk beş sağlıklı çocuk dahil edildi. İzole edilen mikroorganizmalar standart laboratuvar yöntemleri ile tanımlanarak elde edilen sonuçlar değerlendirildi. Ayrıca, nazofaringeal taşıyıcılık prevalansını etkileyen risk faktörleri değerlendirildi.

Bulgular: Çalışılan örneklerin 139'u (%31,2) pozitifti. *S. pneumoniae* iki (%0,4), *H. influenzae* 50 (%11,2); bunlardan tip b 10 (%2,2), Haemophilus parainfluenzae 10 (%2,2), *M. catarrhalis* 14 (%3,1), *S. aureus* 35 (%7,9), A grubu β hemolitik streptokok (*Streptococcus pyogenes*) 13 (%2,9), B Grubu streptokok (*S. agalactiae*) 18 (%4,0), Non A Non B streptokok 16 (%3,6) oranlarında tespit edildi. Farklı yerlerden elde edilen sonuçlarda, patojen yoğunluğunun ve çeşitliliğinin değişken olduğu görüldü.

Sonuç: Çalışmamızda tespit edilen nazofaringeal taşıyıcılık oranları bu konuda yapılmış bazı çalışmalara göre düşük bulundu. Ancak örnek alınan farklı kurumlar tek tek değerlendirildiğinde, mevcudu fazla ve bina özellikleri kötü olan yerlerde (kalabalık, küçük, havalandırılması iyi yapılamayan, sağlıksız binalar) oranın %45,9'a kadar ulaştığı görüldü. *H. influenzae* taşıyıcılığında ise 2-3 yaş grubunda en yüksek oranı %33,3 olarak tespit edildi. Bu tür çalışmaların sonuçları bölgeye, örnekleme sıklığına, bireysel ve sosyal faktörlere göre değişiklik göstermektedir. Daha sağlıklı sonuçlara ulaşmak için daha fazla çalışmaya ihtiyaç vardır.

Address for Correspondence/Yazışma Adresi: Okan Aydoğan, İstanbul University Cerrahpaşa Faculty of Medicine, Department of Medical Microbiology İstanbul, Turkey, İstanbul Medipol University Faculty of Medicine, Department of Medical Microbiology İstanbul, Turkey
E-mail: okanaydogan4@gmail.com ORCID: orcid.org/0000-0001-7275-8724

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Abstract

social factors. Further studies are needed in order to achieve healthier results.

Keywords: Nasopharyngeal carriage, potential pathogenic bacteria, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, vaccinated healthy children, risk factors

Öz

Anahtar Sözcükler: Nazofaringeal taşıyıcılık, potansiyel patojen bakteriler, *S. pneumoniae, H. influenzae, M. catarrhalis*, aşılanmış sağlıklı çocuklar, risk faktörleri

Introduction

Nasopharynx is heavily colonized by commensal bacteria as well as by a variety of microorganisms, including potential pathogens such as *Streptococcus pneumoniae, Haemophilus influenzae* (essentially non-typeable strains) and Moraxella catarrhalis. Nasopharyngeal microbiota occurs in the first year after birth, and changes throughout life due to different factors. Carriage rates generally decrease with age. However, these rates are also high in adults with chronic respiratory diseases. Reported nasopharyngeal carriage rates of potentially pathoge,nic bacteria vary widely between different studies and geographic regions. There are a lot of parameters including genetic factors and socio-economic conditions, access to health services, poor hygiene, number of family members, household crowding, access to health services, number of siblings, vaccination, age, type of child care, acute respiratory disease, and sleeping position (1). In Turkey, pneumococcal conjugate vaccine pneumococcal vaccine (PCV) 7 was introduced into the national immunization program in 2008, with a switch to PCV13 in 2011; the vaccination rate is estimated to be higher than 95% for children <2 years of age and it begins at 2 months of age with the other doses at 4 and a booster dose at 12 months. *H. influenzae* type b (Hib) vaccination is performed also at 2, 4 and 6 months of age with a booster at 18 months. Different results have been reported from different countries, and the different regions of Turkey about the rate of nasopharyngeal carriage of potentially pathogenic bacteria (1-3). In this study, we aimed to determine the rates of nasopharyngeal colonization of potential respiratory pathogens isolated from healthy school children vaccinated in Istanbul and some risk factors for nasopharyngeal carriage.

Methods

This cross-sectional study was conducted between 2014 and 2017 (sample collection, February-April 2016). The study involved four hundred forty-five children aged 1-7 years, asymptomatic, who had not taken antibiotics in the past 15 days, and were vaccinated in ten different institutions in the European side of İstanbul. Sociodemographic characteristics of the children (age, gender, number of household members, average income, etc.) and situations that may be risk factors for carriage (antibiotic use in the past month, number of people sharing the same room in the family, presence of siblings under the age of 5, exposure to smoke at home, etc.) were questioned.

Nasopharyngeal samples were collected using cotton tipped swabs and immediately transferred into transport medium and delivered to the laboratory. On the same day, 5% sheep blood agar and chocolate agar (Becton Dickinson, USA) were cultured by single colony method. After 24 hours of incubation at 37 °C, Gram staining was performed from suspicious colonies that grew. Standard tests were applied for identification. For the detection of Streptococcus, bacteria displaying beta hemolysis (β-hemolysis) were first identified by classical methods. Group identifications were performed using bacitracin (0.04 units), trimethoprim (1.25 µg) -sulfamethoxazole (23.75 µg) discs and commercial latex agglutination kits (Dryspot Streptococcal Grouping Kit-Oxoid, England). Bacitracin-sensitive and trimethoprim-sulfamethoxazole-resistant ones were accepted as Group A beta-hemolytic streptococci (GABHS). Catalase test was applied for differentiation between streptococcus and staphylococcal microorganisms with similar hemolysis properties. *In vitro* coagulase test to determine the pathogenicity of growing staphylococci, optochin susceptibility test and bile dissolution tests to distinguish pneumococci were performed. *H. influenzae* needs both X and V factors simultaneously. With this feature, diagnosis was made. Typing was done by slide agglutination using antiserum specific for Hib (Denka Seiken™, Japan). Biochemical properties of the growing Gram-negative bacilli were also examined and detected. Identification of *S. aureus* isolates was performed according to standard microbiological procedures (morphology, Gram stain, catalase test, coagulase test, mannitol salt agar fermentation).

This research study was approved by the İstanbul University-Cerrahpaşa Faculty of Medicine Ethics Committee of Clinical Research (approval no: A-12/07 Jan 2014). Written informed consent was obtained from all of the parents of children who participated in the study.

Necessary permissions were obtained from the İstanbul Governorship, the Provincial Health Directorate and the Provincial Directorate of National Education for the study.

Results

Four hundred forty-five healthy children, including two hundred three girls (45.6%) and two hundred forty-two boys (54.4%), aged 1-7 years were included in the study. The number of positive specimens was a hundred thirty-nine (31.2%), and the carriage rate was 48% in girls and 52% in boys. Eleven bacteria species were isolated in the study. Potential pathogenic bacteria isolated from nasopharyngeal specimens are given below (Table 1, 2).

In this study, samples from 10 different educational institutions (10 different groups) were collected. The results obtained for five types of bacteria from each of these are given in Figure 1. It was observed that the obtained positivity rates and microorganism distributions differ between institutions. The results show that the carriage rates have increased significantly in crowded places. The positivity rate reached 45.8% in a crowded school. The carriage rates were between 12.5% and 45.8% in different institutions. *H. influenzae* was the most commonly detected microorganism with 33.3% in children aged 2-3 years in a nursery. Gender, exposure to the negative effects of cigarette smoke (passive smoking), crowded household and recent respiratory infections do not constitute important risk factors for carriage; however, low maternal education level, and crowded and unsuitable school environments were found to be risk factors that increase carriage. There was no significant difference between the socio-economic levels of the groups. The characteristic features of the study group are given in Table 3.

Table 1. Distribution of microorganisms isolated from nasopharyngeal specimens

Distribution types	Microorganisms	n (%)
1	*H. influenzae*	36 (8.9)
2	*H. influenzae* + *S. aureus*	3 (0.7)
3	*H. influenzae* + *S. pyogenes*	4 (0.9)
4	*H. influenzae* + non-A non-B *Streptococci*	4 (0.9)
5	*H. influenzae* + group B *Streptococci*	1 (0.2)
6	*H. influenzae* + non-A non-B *Streptococci* + *S. aureus*	2 (0.4)
7	*H. parainfluenzae*	8 (1.8)
8	*H. parainfluenzae* + *S. aureus*	2 (0.4)
9	*S. aureus*	25 (5.6)
10	*S. aureus* + *Pseudomonas*	1 (0.2)
11	*M. catarrhalis*	12 (2.7)
12	*M. catarrhalis* + *S. aureus*	2 (0.4)
13	*S. pyogenes*	9 (2.0)
14	non-A non-B *Streptococci*	10 (2.2)
15	Group B *Streptococci*	16 (3.6)
16	Group B *Streptococci* + *S. aureus*	1 (0.2)
17	*S. pneumoniae*	2 (0.4)
18	*Acinetobacter*	1 (0.2)
19	*E. coli*	1 (0.2)

n: Number

Table 2. Microorganisms isolated from nasopharyngeal samples

Bacteria types	Microorganisms	n (%)
1	*H. influenzae*	50 (11.2)
2	*H. parainfluenzae*	10 (2.2)
3	*M. catarrhalis*	14 (3.1)
4	*S. pneumoniae*	2 (0.4)
5	*S. aureus*	35 (7.9)
6	*S. pyogenes*	13 (2.9)
7	*Group B Streptococci*	18 (4.0)
8	*Non-A Non-B Streptococci*	16 (3.6)
9	*Acinetobacter*	1 (0.2)
10	*Pseudomonas*	1 (0.2)
11	*E. coli*	1 (0.2)

n: Number

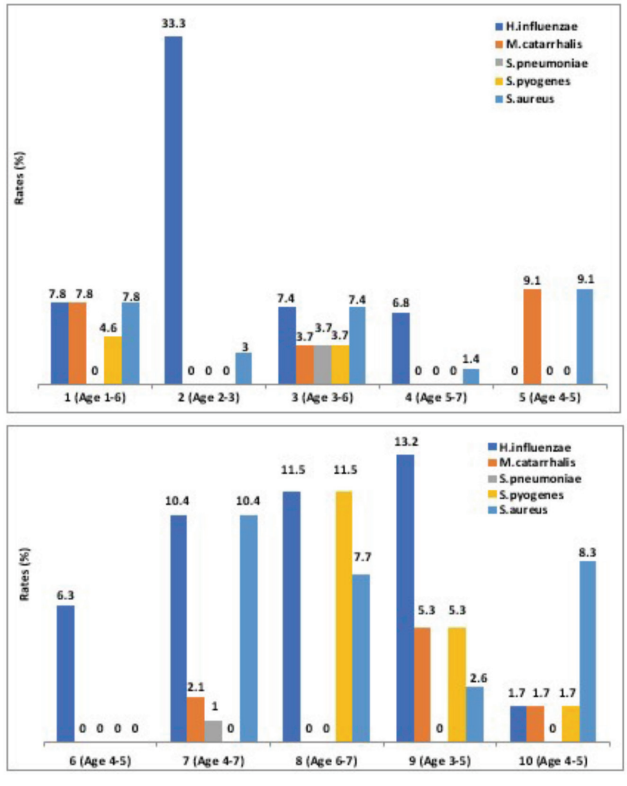

Figure 1. Carriage percentages of five bacteria in ten different educational institutions

Discussion

For hundred and forty-five healthy children aged 1-7 years from 10 different places (nursery, kindergarten and primary school 1st grade) were included in the study. According to the results we have achieved; the total nasopharyngeal carriage rate for 11 types of potential respiratory pathogens was 31.23%: *S. pneumoniae* 0.44%, *H. influenzae* 11.23%; type b 2.24%, *H. parainfluenzae* 2.24%, *M. catarrhalis* 3.14%, *S. aureus* 7.86%, *S. pyogenes* 2.92%. It is seen that the results about multiple bacteria colonization were obtained only in a small number of publications and they are different from each other (2,4-6). This situation can be attributed to the effect of many factors on nasopharyngeal carriage (1).

The distribution of the pathogens are shown in Table 4 and compared with other studies' findings.

Torun et al. (2) conducted a study with 330 healthy children in the 6-10 age group in İstanbul and they found *H. influenzae* in 48.7%, type b 7.2%, *S. pneumoniae* in 29.1%, and *M. catarrhalis* in 23.9%. This study is most suitable for comparing our results with the situation in previous years. However, given the possible differences in risk factors, healthy comparisons cannot be made.

Principi et al. (4) conducted a study with a thousand seven hundred twentythree children aged 1-7 years from eighteen schools and day care centers in eighteen Italian cities. They found that the rate of carriage respiratory pathogens was 17.9% (*S. pneumoniae* 3.5%, *H. influenzae* 11.9%, *M. catarrhalis* 4.1%). Especially in children aged 1-5, siblings under 3 years of age, living in rural areas and staying in a full-day care home significantly affect carrier rates; however, they found that breast-feeding, gender, passive smoking, and recent respiratory infections were not significant variables. In this study, it was reported that antibiotic treatment in the previous three months did not affect nasopharyngeal carriage and *S. pneumoniae* carriage was associated with recurrent macrolide treatment.

In Belgium, a study with three hundred thirthy three healthy children of different socio-economic levels aged 3-6 point out that 50% of children were colonized at least once with *S. aureus*, 69% with *S. pneumoniae*, 67% with *M. catarrhalis* and it was found that 83% of them were colonized with *H. influenzae* (5).

Table 3. Characteristics of 445 children

Characteristics (n=445)	Number (%)
Sex	
Male	242 (54.4)
Female	203 (45.6)
Age	
1-7	445 (100)
Education of mother	
High	98 (22)
Low	347 (78)
Number of people at home	
≤3	136 (30.6)
≥3	309 (69.4)
Exposure to smoke at home	
Yes	254 (57.1)
No	191 (42.9)
Family economic status	
Low	-
Medium	445 (100)
High	-

n: Number

Table 4. Distribution of pathogens in our study and compared with other studies from different countries.

Study (Reference)	Country	n	*S. pneumoniae* (%)	*H. influenza* (%)	*H. influenza* type B (%)	*H. parainfluenza* (%)	*M. catarrhalis* (%)	*S. aureus* (%)	*S. pyogenes* (%)
Our Study	Turkey	445	0.44	11.23	2.24	2.24	3.14	7.86	2.92
Torun et al. (2)	Turkey	330	29.1	48.7	7.2	–	23.9	–	–
Principi et al. (4)	Italy	1723	3.5	11.9	–	–	4.1	–	–
Jourdain et al. (5)	Belgium	333	67	–	–	–	83	69	–
Dunne et al. (6)	Indonesia	302	49.5	27.5	–	–	42.7	7.3	–
Abaye et al. (8)	Ethiopia	–	18.4	–	–	–	–	–	–
Wada et al. (9)	Ethiopia	–	43.8	–	–	–	–	–	–
Claire et al. (11)	Kenya	323	19.4-20.0	–	–	–	–	–	–
Birindwa et al. (12)	Congo	794	21	–	–	–	–	–	–
Koliou et al. (13)	Cyprus	402	35.3	–	–	–	–	–	–
Yang et al. (16)	China	17338	–	17.1	–	–	–	–	–
Ortiz-Romero et al (17)	Spain	404	–	–	–	–	–	–	–
Toprak et al. (21)	Turkey	1129	–	–	–	–	–	–	6.5

In a study conducted by Dunne et al. (6) with three hundred two healthy children aged 12-24 months, the carriage prevalence was 49.5% for *S. pneumoniae*, 27.5% for *H. influenzae*, 42.7% for *M. catarrhalis* and 7.3% for *S. aureus*.

In our country, studies conducted in Istanbul in recent years showed that the rate of *S. pneumoniae* carriage varies depending on age and the rates decreased after vaccination (3,7).

Arvas et al. (3) found 14% *S. pneumoniae* carriage in their study with a hundred fifty vaccinated healthy children (in 2014) aged 0-6 in İstanbul. However, the rate of *S. pneumoniae* carriage in young children of 24 months has been reported to be 76.2%. The low, 0.44%, *S. pneumoniae* rate detected in our study suggests that other factors may also be effective. In our study, this can be attributed to the fact that the number of children under 2 was quite low.

In a study by Soysal et al. (7), the low prevalence of pneumococcal carriage was remarkable. Soysal et al. (7) determined the prevalence of pneumococcal carriage as 6.4% 5 years after PCV-7 vaccination and 2 years after PCV-13 childhood vaccination in 2,165 healthy children in the 0-18 age group in Istanbul between 2011 and 2013.

In recent years, there are important findings related to pneumococcal carriage risk factors in studies conducted abroad: the number of siblings under certain ages, sleeping in the same room, crowded family environment, young age, mothers with low education level and low socioeconomic status were found to be related to carriage (8-10).

In their study including children aged ≤6 years, Abaye et al. (8) found a general pneumococcal carriage rate of 18.4%. It was determined that there was no significant variation in colonization according to gender and age of children. Children living with younger siblings (1-2<6 years) and number of persons >5 in the household were associated with higher rates of *S. pneumoniae* carriage.

Wada et al. (9) found a *S. pneumoniae* carriage rate of 43.8% in seven hundred fourteen children aged 3-13 years. The rate was determined as 62.5% in 3-5 years old children and 38.6% in 6-13 years old children. Sleeping with siblings and age below five years were significantly associated with *S. pneumoniae* carriage. Findings of Fadlyana et al. (10) emphasized the association of the level of maternal education and socio-economic factors with nasopharyngeal carriage. Having more than one small child in the household has been identified as a risk factor for transport of potential pathogenic bacteria. There was no difference in the frequency of carriage of *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. aureus* among urban and semi-rural children. Low maternal education level is also valid for our study group as a risk factor that increases carriage.

Some publications suggest that vaccination affects the overall prevalence of pneumococcal carriage, and among other known risk factors, the prevalence of serotypes included in the vaccine (vaccine strains) is lower in vaccinated children and the prevalence is higher in children without vaccination and in poor living conditions (11-13). It has been reported that pneumococcal conjugate vaccines could have a protective effect against colonization by drug-resistant pneumococcal strains (11-13).

Claire et al. (11) determined in a study with nasopharyngeal swab samples from 323 children aged 4-7 years from coastal Kenya before and after vaccination with 10-valent pneumococcal vaccine, it was found that vaccination did not decrease the overall prevalence of pneumococcal carriage; the number of colonized children before vaccination was 65 (20%) and the number of colonized children after vaccination was 63 (19.4%). However, they determined that the prevalence of serotypes (vaccine strains) included in the vaccine decreased from 43% to 19%.

In 2014 and 2015 Birindwa et al. (12) investigated, pneumococcal carriage in seven hundred ninety fdur healthy children aged 1 to 60 months who attended health centers in the east part of Congo and who were vaccinated with a 13-valent conjugated PCV13 in 2013. According to their results, the rate of pneumococcal carriage was 21%. They found that the rate of carriage was higher in children who had not received PCV13 vaccination, lived in rural areas, in a house without an enclosed kitchen, malnourished and had high fever. It is stated that the results show that in addition to PCV13 vaccination, better living conditions are needed to reduce pneumococcal burden. In the study, worryingly decreased susceptibility to commonly used antibiotics for pneumococci infections and need for more appropriate use of antibiotics in the region were highlighted.

Koliou et al. (13) found that 35.3% of the children were colonized with *S. pneumoniae* in a study they conducted with four hunred two healthy children aged 6 months-5 years in Cyprus. Attending a day-care center has been identified as a risk factor that increases colonization approximately by 3 times. They stated that factors such as age, gender, breastfeeding history and passive exposure to cigarette smoke were not statistically significantly related to the risk of *S. pneumoniae* colonization. On the other hand, complete vaccination with PCV7 has been shown to have a protective effect against colonization compared to unvaccinated children (the risk decreased two times).

Conclusion

It has been stated that the careful use of antibiotics for upper respiratory tract infections, especially in children, and increasing the coverage of pneumococcal conjugate vaccines can be effective in reducing levels of colonization by drug-resistant pneumococcal strains.

In our study, the *H. influenzae* carriage rate was 11.23%, while in Italy, it was 14.1% (14) in a study involving seven hundred seventeen healthy children <6 years of age, 15 years after vaccination of Hib. On the other hand, in a study conducted in Spain, it was found that 42% of 960 healthy <5 years old children were colonized with *H. influenzae* and the rate varied between centers (12-83%) (15). In our study, it was determined that there was variability among institutions (0-33.3%).

H. influenzae carriage rate was determined to be 17% in children in a study in which a total of 42 studies with 17,388 participants were included in China. It was reported that the rate was relatively low in healthy population, but showed great differences between provinces (16). This study also explains the differences in carriage rates.

Ortiz-Romero et al. (17) performed a study with four hundred four healthy children <5 years of age in Spain and determined the rate of *H. influenzae* carriage as 73.2% in winter and 26.8% in summer.

As a result, according to our findings, *Haemophilus influenzae* carriage rates vary depending on factors such as study region, centers, seasons (15-17).

Staphylococcus aureus carriage rates are known to vary by country, demographic group and occupation (5,18).

Streptococcus agalactiae, known as group B *Streptococcus* GBS, is an important cause of neonatal sepsis and meningitis (19). In our study, 4.04% of carriers were detected to have this bacterium. The natural reservoir for GABHS is humans. They are the most common cause of streptococcal pharyngitis. It is generally seen in school age children at the ages of 5-15 (20). Toprak et al. (21) detected 6.5% *S. pyogenes* carriage in 6.5% of 1,129 primary school children in the 7-15 age group in the city center of Afyonkarahisar. Tonsillopharyngitis developed in 5.5% of the children within a year. In our study, *S. pyogenes* carriage rate was found to be 2.9%. However, in one group (6-7 years) the rate was 11.5%.

When looking at the results obtained from different places in different studies, the differences between them (carriage rates and microorganism diversity, etc.) are thought-provoking. In order to minimize the health problems associated with carriage, there is a need for new studies in which the determination of carriage rates will be handled together with risk factors.

It is an advantage of our study that this study was not performed in a single center. We observed that the carriage prevalence varies considerably between institutions. At the same time, the change in the diversity of microorganisms has emerged strikingly. Low maternal education level and crowded classroom environments were found to increase the prevalence of nasopharyngeal carriage. Especially *S. pneumoniae* carriage rate was very low. Among the possible reasons for this result; the age of the children in our study (scarcely any number of children under the age of 2) and their vaccination are important. Besides, the leading factors affecting the results are: there was no significant difference in the socio-economic status which was at a good level, between the families, and the children could benefit from health services adequately and correctly.

Authorship Contributions

Concept: N.G., S.Y., O.A., Z.T., S.Ö., S.A., H.T., F.K.Ç. Design: N.G., S.Y., O.A., Z.T., S.Ö., S.A., H.T., F.K.Ç. Data Collection or Processing: N.G., S.Y., O.A., Z.T., S.Ö., S.A., H.T., F.K.Ç. Analysis or Interpretation: N.G., S.Y., O.A., Z.T., S.Ö., S.A., H.T., F.K.Ç. Literature Search: N.G., S.Y., O.A., Z.T., S.Ö., S.A., H.T., F.K.Ç. Writing: N.G., S.Y., O.A., Z.T., S.Ö., S.A., H.T., F.K.Ç

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Gastrointestinal Sistem Kanaması Bulguları ile Başvuran Böbrek Nakilli Bir Hastada Sitomegalovirüs Duodeniti: Olgu Sunumu

Cytomegalovirus Duodenitis in a Renal Transplant Patient Presenting with Signs of Gastrointestinal Bleeding: A Case Report

Atilla Bulur, Uğuray Payam Hacısalihoğlu*, Özgür Merhametsiz**, Mehmet Emin Demir**

İstanbul Yeni Yüzyıl Üniversitesi Tıp Fakültesi, Gaziosmanpaşa Hastanesi, Gastroenteroloji Kliniği, İstanbul, Türkiye
***İstanbul Yeni Yüzyıl Üniversitesi Tıp Fakültesi, Gaziosmanpaşa Hastanesi, Patoloji Kliniği, İstanbul, Türkiye*
****İstanbul Yeni Yüzyıl Üniversitesi Tıp Fakültesi, Gaziosmanpaşa Hastanesi, Nefroloji Kliniği, İstanbul, Türkiye*

Öz

Sitomegalovirüs (CMV) bağışıklığı baskılanmış hastalarda birçok organ sisteminde fırsatçı enfeksiyonlara yol açan yaygın görülen bir virüstür. Böbrek nakilli hastalarda da CMV enfeksiyonları önemli bir sorundur. CMV enfeksiyonu gastrointestinal sistemde (GİS) sıklıkla komplikasyonlara neden olur. CMV duodenit tablosu ise GİS içerisinde çok nadir görülen bir tutulumdur. CMV enfeksiyonu bulbus ve duodenumda erozyon, ülser, yapışıklık, perforasyon ve kanama gibi komplikasyonlara yol açabilmektedir. Bizim olgumuz böbrek naklinden 10 ay sonra üst GİS kanama bulguları ile başvurmuş ve yapılan endoskopik incelemede antrum ve bulbusta ülserler görülen, alınan duodenal biyopsilerde CMV için tipik inklizyon cisimcikleri ve intranükleer CMV immünreaktivitesi tespit edilen ve antiviral tedavi ile yakınmaları gerileyen bir olgudur.

Anahtar Sözcükler: CMV, gastrointestinal kanama, böbrek nakli

Abstract

Cytomegalovirus (CMV) is a common virus that causes opportunistic infections in many organ systems in immunocompromised patients. CMV infections are also an important problem in renal transplant patients. CMV infection often causes complications in gastrointestinal system (GIS). CMV duodenitis is a very rare involvement in the GIS. CMV infection can lead to complications, such as erosion, ulcer, adhesion, perforation and bleeding in the bulbus and duodenum. Our case was admitted with the signs of upper GIS bleeding 10 months after renal transplantation. Ulcers in the antrum and bulbus were observed in the endoscopic examination, typical incision bodies for CMV and intranuclear CMV immunoreactivity were detected in duodenal biopsies, and complaints regressed with antiviral treatment.

Keywords: CMV, gastrointestinal bleeding, renal transplantation

Giriş

Sitomegalovirüs (CMV) primer enfeksiyon sonrası latent hale gelen, özellikle bağışıklığı baskılanmış konaklarda reaktivasyon ile yeniden enfeksiyona neden olabilen dünyada yaygın görülen bir virüstür. Böbrek nakli gibi solid organ nakli uygulanan hastalarda CMV enfeksiyonu sıkça görülebilir. CMV gastrointestinal sistemi (GİS) sıklıkla tutar, en sık kolon tutulumu görülmekte olup, mide ve özofagusta da tutulum görülebilmektedir. Duodenal tutulum ise alışılagelmiş bir lokalizasyon değildir (1-3). Virüs ile enfekte olan GİS tutulumlu hastalar genellikle asemptomatik olmakla birlikte karın ağrısı, şişkinlik, ülser, reflü, bulantı, ishal, rektal kanama, kilo kaybı gibi uzun süreli semptomlarla başvurabilirler. CMV duodenit tablosunda oluşabilecek ülserler GİS kanamaya yol açabilir (4-6). CMV enfeksiyonunun tanısında serum ve plazma örneklerinden bakılabilen viral yükü gösteren kalitatif ve kantitatif polimeraz zincir reaksiyon (PCR) testlerinin faydası

Yazışma Adresi/Address for Correspondence: Atilla Bulur, İstanbul Yeni Yüzyıl Üniversitesi Tıp Fakültesi, Gaziosmanpaşa Hastanesi, Gastroenteroloji Kliniği, İstanbul, Türkiye
E-posta: atillabulur@hotmail.com ORCID: orcid.org/0000-0001-8089-7740
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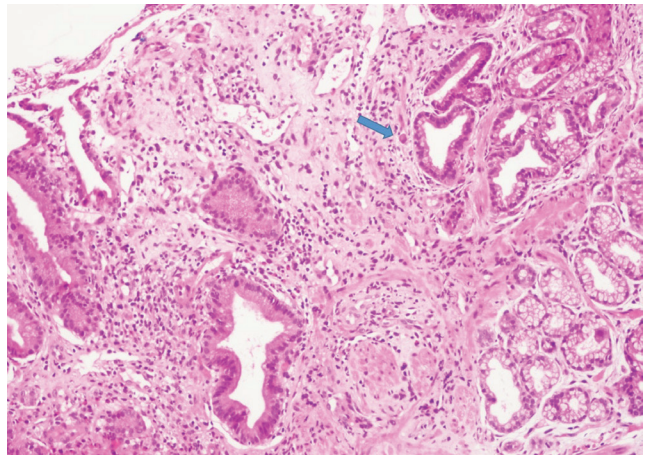
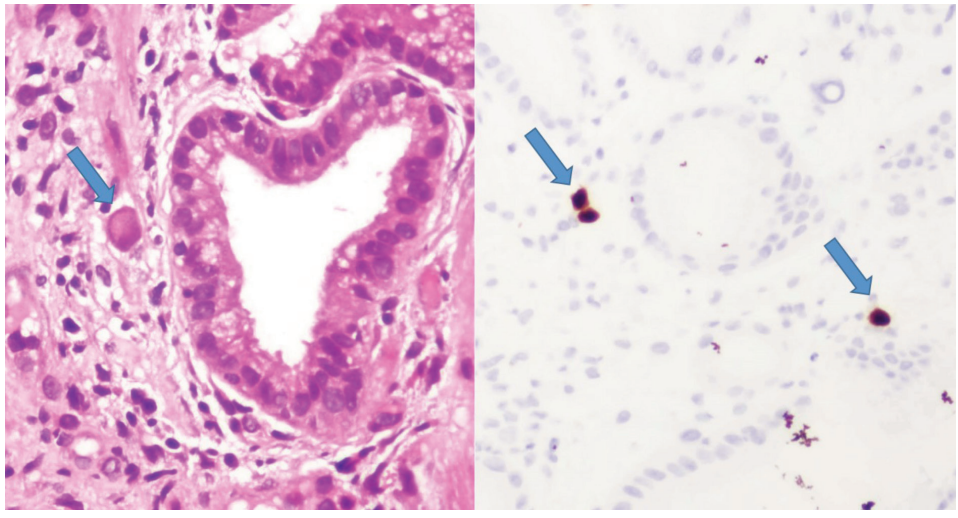
pek çok çalışmada gösterilmiştir, ancak bazen bu testler negatif sonuçlanabilmektedir. Tanıda altın standart CMV enfeksiyonuna özgü inklizyonların veya immünohistokimya boyamasının doku örneklerinde gösterilmesidir (7,8).

Olgu

Altmış yaşında, bilinen diabetes mellitus, kronik iskemik kalp hastalığı ve 10 ay önce diyabetik nefropatiye sekonder kronik böbrek yetmezliği tanısı ile hastanemizde canlı vericiden böbrek nakli yapılmış olan erkek hasta; bir haftadır siyah renkli dışkılama, halsizlik, gaz, şişkinlik yakınmaları ile gastroenteroloji polikliniğimize başvurdu. Takrolimus, mikofenolat mofetil, prednizolon, asetil salisilik asit (ASA), klopidogrel, uzun ve kısa etkili insülin ve pantoprazol tedavileri almakta idi. Anamnezi derinleştirildiğinde bir haftadır dışkısının katran gibi siyah renkte, yumuşak kıvamda ve kötü kokulu olduğunu, mide kanaması geçirdiğini düşünerek ASA ve klopidogrel tedavilerini kestiği öğrenildi. Ayrıca birkaç aydır halsizlik, iştahsızlık, gaz, şişkinlik, karın ağrısı, kilo alamama ve ara ara ishal yakınmalarının olduğu öğrenildi. Hastanın fizik muayenesinde soluk ve halsiz görünümdeydi, vital bulguları stabil, batında hassasiyet yoktu, rektal tuşede siyah, sıvı kıvamda dışkı (melena) olduğu görüldü. Hasta servisimize yatırılarak, yakın vital bulgu takibine alındı, oral alımı sonlandırılıp parenteral pantoprazol infüzyon tedavisi başlandı. Laboratuvar incelemelerinde hemoglobin (Hb): 11,2 gr/dL (normal aralık: 12-16 gr/dL, 2 ay önceki kontrolde Hb: 12,1 gr/dL), hematokrit (Hct): %31, transferrin satürasyonu: %22 olarak tespit edildi, böbrek ve karaciğer fonksiyon testleri normal sınırlarda idi. Hastaya aynı gün özofagogastroduodenoskopi (ÖGD) işlemi yapıldı, incelemede antrumda benign görünümde ülserler (Forrest sınıflamasına göre III), bulbusta ülserler (Forrest sınıflamasına göre III) ve duodenumda eritemli görünüm izlendi, kanama bulgusu izlenmedi, antrum, korpus, incisura ve duodenumdan çoklu biyopsiler alındı. Hastadan alınan biyopsilerin histopatolojik incelemesinde *Helicobacter pylori (H. pylori)* negatif gastrit, malignite bulgusu içermeyen antrum ülser çevresi doku örnekleri, fokal aktif duodenit rapor edildi. Ayrıca duodenumda hematoksilen ve eozin boyası ile lamina propriada lenfoplazmositer hücrelerin yanısıra CMV ile enfekte stromal hücrede tipik eozinofilik inklüzyonlar (Resim 1) ve büyük büyütmede CMV inklizyonu ve intranükleer CMV immünreaktivitesi tespit edildi (Resim 2). Bunun üzerine periferik kandan PCR yöntemi ile CMV DNA tetkiki istendi, negatif olarak rapor edildi. Ardından halsizlik, kilo alamama, dispeptik



Resim 1. Duodenumda, CMV ile enfekte (mavi ok) stromal hücrelerde eozinofilik inklizyonlar
CMV: Sitomegalovirüs



Resim 2. Duodenumda büyük büyütmede CMV inklizyonu (soldaki resim ve mavi ok) ve immünohistokimyasal olarak enfekte hücrelerde intranükleer CMV immünreaktivitesi (sağdaki resim ve mavi ok). Hematoksilen & Eozin x400; CMV immünohistokimya x400
CMV: Sitomegalovirüs

yakınmalar, geçirilmiş üst GİS kanama bulguları ile birlikte histopatolojik olarak kanıtlanmış invazif CMV duodenit tanısı ile immünsupresif tedavisi azaltıldı ve mikofenolat mofetil tedavisi kesilip, günde iki doz halinde intravenöz 5 mg/kg gansiklovir tedavisi başlanma kararı alındı, almakta olduğu diğer immünsupresif olan oral prednizolon 5 mg tedavisine ise devam edildi. Hastanın izlemlerinde yakınmalarının azaldığı, kanama semptomunun olmadığı, Hb/Hct takiplerinde düşme olmadığı görülmüş ve valgansiklovir 900 mg/gün oral tedavisi ile tedavi 21 güne tamamlanıp kesilmiştir. Tedavi sonrası kontrol CMV DNA, ÖGD ve kolonoskopi yapılmış, PCR testi sonucunda CMV DNA saptanmamış, antrum ve bulbustaki ülserlerde regresyon görülmüş, duodenal mukozadan biyopsi alınmış ve histopatolojik incelemelerde CMV enfeksiyonu lehine bulgu izlenmemiş, ileokolonoskopisi normal saptanmıştır.

Tartışma

CMV tüm dünyada, yaş, cinsiyet veya ırk ayırt etmeksizin yaygın olarak enfeksiyona neden olan Herpes virüs ailesinden bir virüstür (5). CMV'ye bağlı hastalık spektrumu geniştir ateşli sendromlar, pnömoni, hepatit, ensefalit, retinit, özofajit ve kolit en sık görülen tablolardır. CMV enfeksiyonları böbrek nakilli hastalar gibi bağışıklığı baskılanmış hastalarda önemli bir fırsatçı patojendir, hatta bu hastalarda greft rejeksiyonunu tetikleyebilir. Literatür incelendiğinde CMV enfeksiyonları böbrek nakilli hastalarda nakil sonrası ilk bir yılda daha fazla görülmektedir, bizim vakamızda da nakil sonrası onuncu ayda CMV duodenit tanısı koyulmuştur (4). Hastalar genellikle asemptomatik olmakla birlikte karın ağrısı, şişkinlik, ülser, reflü, bulantı, ishal, rektal kanama, kilo kaybı gibi uzun süreli GİS semptomlarının ve bulgularının varlığında CMV'nin GİS tutulumu akla gelmelidir (5,6). Olgumuzda olduğu gibi Bernard ve ark.'nın (4) sunduğu pediyatrik böbrek nakilli bir hastada CMV dudenit olgusu ve üst GİS kanaması bildirilmiştir. Bonetti ve ark.'nın (9) yaptığı 30 hastalık çalışmada üst GİS'de en sık mide (özellikle antrum), ardından özofagus tutulumu bildirilmiştir, CMV duodenit ise bir olguda tespit edilmiştir. Bizim olgumuzda olduğu gibi CMV duodenit olguları çok nadir görülmektedir. Ancak son zamanlarda yapılan çalışmalarda CMV'nin alt GİS'ye göre üst GİS'de daha kolay hastalık oluşturabildiği belirtilmektedir (1-3). Bizim olgumuzda *H. pylori* negatif saptanmıştı ve çok muhtemel bu ülserler CMV enfeksiyonuna ve/veya nonsteroid antienflamatuvar ilaç kullanımlarına sekonder gelişmişti. Bu ülserlere sekonder olarak da üst GİS kanama gelişmişti, çünkü ASA ve/veya klopidogrel tedavileri alan hastalarda ülser kanamaları daha sık gelişebilmektedir. Bağışıklığı baskılanmış bir hastada CMV hastalığının tanısı seroloji, kalitatif ve kantitatif PCR testleri, pp65 antijenemisi, kültür ve histopatoloji ile konulabilir (7,8). İnvazif GİS tutulumunda plazma veya serumda CMV DNA testleri bazen negatif saptanabilir, bu durumlarda tanı kültür ve histopatoloji ile konabilir. CMV enfeksiyonunun tanısında ve tedavinin takibinde plazma ve serumdan bakılabilen viral yükü gösteren kantitatif PCR testlerinin faydası pek çok çalışmada gösterilmiştir, ancak invazif CMV enfeksiyonunda CMV inklizyonlarının veya CMV'ye özgü immünhistokimya boyamasının doku örneklerinde gösterilmesi tanıda altın standarttır (7,8). Duran ve ark.'nın (10) yaptığı seksen bir solid organ nakli yapılmış (çoğunlukla böbrek ve karaciğer) hastanın incelendiği retrospektif bir çalışmada biyopsi ile kanıtlanmış 20 GİS tutulumlu CMV olgusu bildirilmiş olup, bu hastaların üçünde CMV DNA negatif olarak tespit edilmiştir, GİS tutulumlu CMV enfeksiyonu tanısında PCR yöntemi ile tanı duyarlılığı %85, özgüllüğü ise %95 olarak bildirilmiştir (11). Bizim olgumuzda da serumda PCR yöntemi ile bakılan CMV DNA testi negatif saptanmış, duodenal biyopsilerde inklizyon cisimcikleri ve CMV'ye özgü immünhistokimya boyaması net olarak gösterilmiştir. CMV'nin GİS tutulumu olan hastalarda azatiyopurin ve mikofenolat mofetil tedavilerinin kesilmesi önerilmektedir, biz de nefroloji ve enfeksiyon hastalıkları görüşü de alarak mikofenolat mofetil tedavisini kesip, prednizolon tedavisine devam ederek, günde iki doz halinde 5 mg/kg gansiklovir tedavisi başladık (12). Hastanın izlemlerinde yakınmalarının azaldığı, kanama semptomunun olmadığı, Hb/Hct ölçümlerinde düşme olmadığı görülmüş ve valgansiklovir 900 mg/gün oral tedavisi ile tedavi yirmi bir güne tamamlanıp kesilmiştir. Tedavi sonrası yapılan ÖGD'de CMV lehine histopatolojik bulgu izlenmemiş, ileokolonoskopik incelemesi normal saptanmış, CMV DNA negatif olarak rapor edilmiştir.

Olgumuzda bağışıklığı baskılanmış böbrek nakilli hastamız GİS kanama bulguları ile tarafımıza başvurmuş ve ÖGD'de antrum ve bulbusta ülserler görülmüş, alınan duodenal biyopsilarin histopatolojik incelemelerinde CMV duodenit tespit edilmiştir. Bu olgumuz ile GİS kanama bulguları ile başvuran bağışıklığı baskılanmış hastalarda çok nadir görülse de ayrıcı tanıda CMV duodenit tanısının düşünülmesi gerekliliği ortaya çıkmıştır.

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