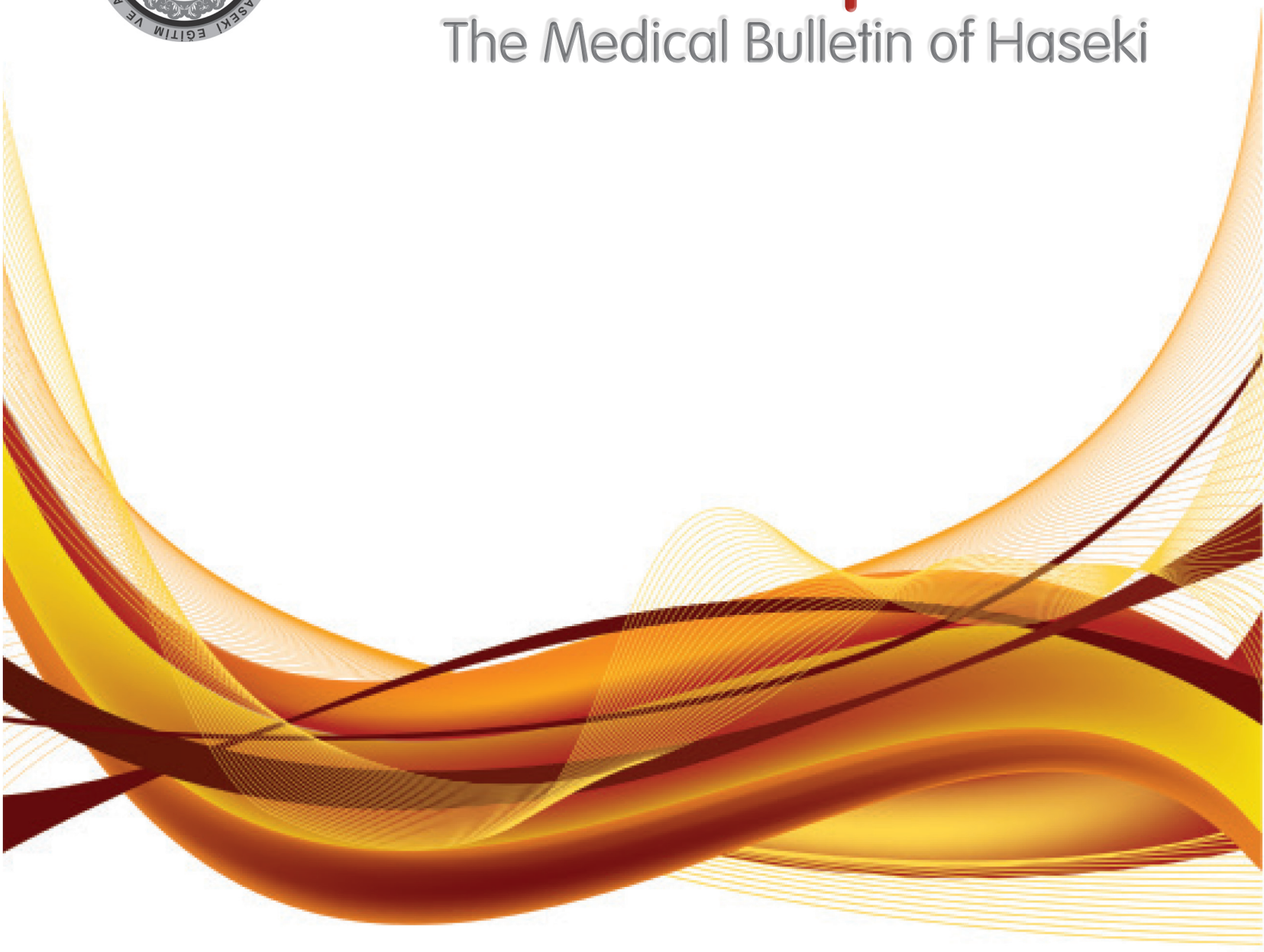
ISSN 1302-0072

Haseki Tıp Bülteni

The Medical Bulletin of Haseki



2017
Cilt/Volume 55
Sayı/Issue 1
Mart/March

www.hasekidergisi.com

Haseki Tıp Bülteni / The Medical Bulletin of Haseki
Cilt / Vol: 55 Sayı / Issue: 1 Mart / March 2017 Sayfa / Page: 1-84

Haseki Tıp Bülteni

The Medical Bulletin of Haseki

Yayın Kurulu / Editorial Board

Bu dergide kullanılan kağıt ISO 9706: 1994 standardına uygundur. (Requirements for Permanence) National Library of Medicine biyomedikal yayınlarda asitsiz kağıt (acid-free paper/ alkalin kağıt) kullanılmasını önermektedir.

The paper used to print this journal conforms to ISO 9706: 1994 standard (Requirements for Permanence). The National Library of Medicine suggests that biomedical publications be printed on acid-free paper (alkaline paper).

Dergide yayınlanan makalelerin, dergi standartlarına uygunluğunun kontrolü, dizimi, ingilizce makale ve özetlerin, kaynakların kontrolü, düzeltilmesi ve kaynaklara link verilmesi derginin yayına hazır hale getirilmesi ve baskısı GALENOS Yayınevi Tic. Ltd. Şti. tarafından gerçekleştirilmiştir.

Reviewing the articles' conformity to the publishing standards of the Journal, typesetting, reviewing and editing the manuscripts and abstracts in English, creating links to source data, and publishing process are realized by Galenos.

Yayıncı/Publisher
Erkan Mor

Yayın Yönetmeni/Publication Director
Nesrin Çolak

Yayın Koordinatörü/Publication Coordinator
Burak Sever

Web Koordinatörleri/Web Coordinators
Eren Arsel
Soner Yıldırım
Turgay Akpınar

Araştırma&Geliştirme/Research&Development
Büşrah Toparslan

Proje Koordinatörleri/Project Coordinators
Ebru Boz
Eda Kolukısa
Hatice Balta
Melis Kuru
Zeynep Altındağ

Grafik Departmanı/Graphics Department
Ayda Alaca
Çiğdem Birinci

Mali İşler Koordinatörü/Finance Coordinator
Sevinç Çakmak

Yayınevi İletişim/Publisher Contact
Adres/Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Türkiye
Telefon/Phone: +90 (212) 621 99 25 **Faks/Fax:** +90 (212) 621 99 27
E-posta/E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Basım Yeri/Printing at: Özgün Ofset Ticaret Ltd. Şti.
Yeşilce Mah. Aytekin Sk. No: 21 34418 4. Levent, İstanbul, Türkiye
Telefon/Phone: +90 (212) 280 00 09
Basım Tarihi/Printing Date: Mart 2017/March 2017
ISSN: 1302-0072

Üç ayda bir yayımlanan süreli yayındır.
International scientific journal published quarterly.

Haseki Tıp Bülteni

The Medical Bulletin of Haseki

Bilimsel Danışma Kurulu / Scientific Advisory Board

Haseki Tıp Bülteni

The Medical Bulletin of Haseki

Bilimsel Danışma Kurulu / Scientific Advisory Board

Haseki Tıp Bülteni

The Medical Bulletin of Haseki

Amaç ve Kapsam

Haseki Tıp Bülteni, S.B. 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, **Gale/Cengage Learning, Index Copernicus, EBSCO Database, Turkish Medline-National Citation Index, Excerpta Medica/ EMBASE, SCOPUS, Reaxys, Engineering Village, Emerging Sources Citation Index (ESCI), TÜBİTAK/ULAKBİM Türk Tıp Dizini, CINAHL, DOAJ ve Türkiye Atıf Dizini** tarafından indekslenmektedir.

Açık Erişim Politikası

Dergide açık erişim politikası uygulanmaktadır. Açık erişim politikası Budapest Open Access Initiative(BOAI) http://www.budapestopenaccessinitiative.org/ kuralları esas alınarak uygulanmaktadır.

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.

Abone İşlemleri

Haseki Tıp Bülteni, S.B. Haseki Eğitim ve Araştırma Hastanesi'ndeki üyelerine ücretsiz gönderilir. Adres değişiklikleri bağlı olduğu şube ve yazı işleri sorumlusuna derhal bildirilmelidir. Ait olduğu dönemler içinde dergi eline ulaşmamış aboneler, yazı işleri sorumlusuna müracaat etmelidirler. Derginin tüm sayılarına ücretsiz olarak www.hasekidergisi.com adresinden tam metin ulaşılabilir. Dergiye abone olmak isteyen kişiler S.B. Haseki Eğitim ve Araştırma Hastanesi Haseki Tıp Bülteni Sekreterliği'ne başvurmalıdır.

Yazışma Adresi

S.B. Haseki Eğitim ve Araştırma Hastanesi Haseki Tıp Bülteni Sekreterliği
Adnan Adıvar Caddesi 34906 Haseki-Aksaray-İstanbul-Türkiye
Tel.: +90 212 529 44 00/1133
Faks: +90 212 530 84 23
İnternet sayfası: www.hasekidergisi.com
E-posta: hasekidergisi@gmail.com

Dergimizde "acid-free" kağıt kullanılmaktadır.

Baskı İzinleri

Baskı izinleri için başvurular dergi ofisine yapılmalıdır.
Editör: Doç. Dr. Savaş Öztürk
Haseki Eğitim ve Araştırma Hastanesi, Nefroloji Kliniği, İstanbul, Türkiye
Adnan Adıvar Caddesi 34906 Haseki-Aksaray-İstanbul-Türkiye
Tel.: +90 212 529 44 00/1133
Faks: +90 212 530 84 23
İnternet Sayfası: www.hasekidergisi.com
E-posta: hasekidergisi@gmail.com

Reklam

Reklam ile ilgili başvurular dergi editor yardımcısına yapılmalıdır
S.B. Haseki Eğitim ve Araştırma Hastanesi Haseki Tıp Bülteni Sekreterliği
Adnan Adıvar Caddesi 34906 Haseki-Aksaray-İstanbul-Türkiye
Tel.: +90 212 529 44 00/1133
Faks: +90 212 530 84 23
İnternet Sayfası: www.hasekidergisi.com
E-posta: hasekidergisi@gmail.com

Yayınevi Yazışma Adresi

Galenos Yayınevi Tic. Ltd. Şti.
Adres: Molla Gürani Mahallesi Kaçamak Sokak No: 21 34093 Fındıkzade - İstanbul - Türkiye
Tel.: +90 212 621 99 25
Faks: +90 212 621 99 27
E-posta: info@galenos.com.tr

Yazarlara Bilgi

Yazarlara Bilgi, dergi sayfalarında ve www.hasekidergisi.com web sayfasında yayınlanmaktadır.

Materyal Sorumluluk Reddi

Haseki Tıp Bülteni'nde yayınlanan tüm yazılarda görüş ve raporlar yazar(lar)ın görüşüdür ve Editör, Editörler Kurulu ya da yayıncının görüşü değildir; Editör, Editörler Kurulu ve yayıncı bu yazılar için herhangi bir sorumluluk kabul etmemektedir.

Haseki Tıp Bülteni

The Medical Bulletin of Haseki

Aims and Scope

The Medical Bulletin of Haseki is the official scientific journal of the 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 Gale/Cengage Learning, Turkish Medline-National Citation Index, Excerpta Medica/EMBASE, SCOPUS, Reaxys, Engineering Village, Emerging Sources Citation Index (ESCI), TUBITAK/ULAKBIM, CINAHL, DOAJ, and Turkiye Citation Index** databases.

Open Access Policy

This journal provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

Open Access Policy is based on rules of Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/

http://www.budapestopenaccessinitiative.org/ By "open access" to [peer-reviewed research literature], we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, should be to give authors control over the integrity of their work and the right to be properly acknowledged and cited.

Subscription Information

The Medical Bulletin of Haseki is distributed free of charge to the subscribers in Haseki Training and Research Hospital. All notice of change of address should be sent to the editorial officer as immediate as possible. Subscribers, who did not receive an issue within the related period, should inform the editorial officer accordingly. All published volumes in full text can be obtained free of charge at www.hasekidergisi.com. Nonmembers who wish to subscribe to the journal should apply to the secretariat of The Medical Bulletin of Haseki, Haseki Training and Research Hospital.

Address
Haseki Training and Research Hospital
Secretariat of The Medical Bulletin of Haseki
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
E-mail: hasekidergisi@gmail.com

Our Journal is printed on "acid-free" paper.

Permissions
Request for permission for reproduction of the published materials should be made to the editorial office.
Associate Editor: Assoc. Prof. Savaş Öztürk
Haseki Training and Research Hospital, Clinic of Nephrology
Tel.: +90 212 529 44 00/1133
Faks: +90 212 530 84 23
Web Page: www.hasekidergisi.com
E-mail: hasekidergisi@gmail.com

Advertisement
Applications concerning advertisement should be addressed to the Associate Editor.
Haseki Training and Research Hospital
Secretariat of The Medical Bulletin of Haseki
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
E-mail: hasekidergisi@gmail.com

Publisher Corresponding Address
Galenos Yayınevi Tic. Ltd. Şti.
Molla Gürani Mahallesi Kaçamak Sokak No: 21 34093
Fındıkzade - İstanbul - Türkiye
Phone: +90 212 621 99 25
Fax: +90 212 621 99 27
E-mail: info@galenos.com.tr

Instructions for Authors
Instructions for authors are published in the journal and may be obtained from www.hasekidergisi.com

Material Disclaimer
The opinions and reports published in The Medical Bulletin of Haseki are those of the author(s), and not of the Editor, Editorial Publishing Directors or the Publisher. The author(s) is (are) responsible from the articles published in the Haseki Medical Bulletin. The Editor, Editorial Board and the Publisher do not accept any responsibility.

Haseki Tıp Bülteni

The Medical Bulletin of Haseki

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.

Genel Kurallar

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.

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..).

Kaynaklar listesi makale metninin sonunda ayrı bir sayfaya yazılmalıdır. Altıdan fazla yazarın yer aldığı kaynaklarda 3. isimden sonraki yazarlar için "et al" ("ve ark") kısaltması kullanılmalıdır. Dergi isimlerinin kısaltmaları Index Medicus'taki stile uygun olarak yapılır. Tüm referanslar Vancouver sistemine göre aşağıdaki şekilde yazılmalıdır.

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.

5) Tablolar-Grafikler-Şekiller-Resimler: Tüm tablolar, grafikler veya şekiller ayrı bir kağıda basılmalıdır. Her birine metinde geçiş sırasına göre numara verilmeli ve kısa birer başlık yazılmalıdır. Kullanılan kısaltmalar alt kısımda mutlaka açıklanmalıdır. Özellikle tablolar metni açıklayıcı ve kolay anlaşılır hale getirme amacı ile hazırlanmalı ve metnin tekrarı olmamalıdır. Başka bir yayından alıntı yapılıyorsa yazılı baskı izni birlikte yollanmalıdır. Fotoğraflar parlak kağıda basılmalıdır. Çizimler profesyonellerce yapılmalı ve gri renkler kullanılmamalıdır.

Özel Bölümler

1) Derlemeler: Derginin ilgi alanına giren tüm derlemeler editörlerce değerlendirilir; editörler ayrıca konusunda uzman ve deneyimli otoritelerden dergi için derleme talebinde bulunabilir.

2) Olgu Sunumları: Nadir görülen ve önemli klinik deneyimler sunulmalıdır. Giriş, olgu ve tartışma bölümlerini içerir.

3) Editöre Mektuplar: Bu dergide yayınlanmış makaleler hakkında yapılan değerlendirme yazılarıdır. Editör gönderilmiş mektuplara yanıt isteyebilir. Metnin bölümleri yoktur.

Yazışma

Tüm yazışmalar dergi editörlüğünün aşağıda bulunan posta veya e-posta adresine yapılabilir.

Haseki Tıp Bülteni Editörlüğü
S.B. Haseki Eğitim ve Araştırma Hastanesi Nefroloji Kliniği
Adnan Adıvar Caddesi 34906 Haseki-Aksaray-İstanbul-Türkiye
Tel.: +90 212 529 44 00/1133
Faks: +90 212 530 84 23
İnternet Sayfası: www.hasekidergisi.com
E-posta: hasekidergisi@gmail.com

Haseki Tıp Bülteni

The Medical Bulletin of Haseki

Instruction to Authors

The Medical Bulletin of Haseki publishes papers on all aspects of general medicine. In addition to original articles, review articles, original case reports, letters to the editor and announcements of congress and meetings are also published. The scientific board guiding the selection of the papers to be published in the journal consists of elected experts of the journal and if necessary, is selected from national and international authorities.

Turkish language Institution dictionary and orthography guide should be taken as a basis for the literary language. Papers written in English language are particularly supported and encouraged.

Ethical committee approval may be requested by the Editor or Associate Editors for clinical research studies.

Authors are responsible for the contents of the manuscripts and for the accuracy of the references.

The authors should guarantee that the manuscripts have not been previously published and/or are under consideration for publication elsewhere. Only those data presented at scientific meetings in form of abstract which do not exceed 200 words may be accepted for consideration, however, the date, name and place of the meeting in which the paper was presented should be stated. The signed statement of scientific contributions and responsibilities of all authors, and statement on the absence of conflict of interests are required. All manuscripts are reviewed by the editor, related associate editor and at least three experts/referees. The authors of the accepted for publication manuscripts should agree that the editor and the associate editors can make corrections on condition that there are no changes in the main text of the paper. Manuscript format should be in accordance with Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (available at http://www.icmje.org/)

The Medical Bulletin of Haseki does not charge any article submission or processing charges.

The journal should be abbreviated as Med Bull Haseki when referenced.

General Guidelines

Manuscripts are accepted only online and can be submitted electronically through web site (http://hasekitip.dergisi.org) after creating an account. This system allows online submission and review.

The manuscripts gathered with this system are archived according to ICMJE-www.icmje.org, Index Medicus (Medline/PubMed) and Ulakbim-Turkish Medicine Index Rules. Rejected manuscripts, except artworks are not returned.

Articles sent to the editor for publication should be written single-sided on A4 pages, double-spaced in 12-point, arial/times, new roman font and with 2.5 cm margins. Abbreviations must be explained clearly in parentheses in their first instance within the text and custom abbreviations should not be used. Numbers 1 to 10 should be given as text (In the two treatment groups the second day) and numbers 11 or bigger given as numbers. However, numbers 1-10 with a descriptive suffix should be given with numbers (1 year) while numbers that start sentences (Fifteen-year-old female patient) should be given as text.

The manuscript should not exceed 5000 words in total. All pages of the manuscript should be numbered at the top right-hand corner, except for the title page. Papers should include the necessary number of tables and figures in order to provide better understanding.

The rules for the title page, references, figures and tables are valid for all types of articles published in this journal.

Patients have a right to privacy. When not essential, identifying information, patient names and photographs should not be published, unless the written informed consent of the patient (parent or guardian) has been given.

The patient should, therefore, be given a draft of the paper in order to obtain written informed consent. When not necessary, any identifying details of the patient should not be published. Complete anonymity is difficult to attain, however, informed consent should be obtained if any doubt exists. For example, masking the eye region of a patient's photograph provides incomplete anonymity.

For the experimental, clinical and drug studies having the obligation of being approved by ethical committee and being sent in order to be published in The Medical Bulletin of Haseki, ethical committee approval report being in accordance with the international agreements with Helsinki Declaration revised 2013 is required (http://www.wma.net/en/30publications/10policies/b3/). In experimental animal studies, the authors should indicate that the procedures followed were in accordance with animal rights (Guide for the care and use of laboratory animals. (https://oacu.oir.nih.gov/regulations-standards) and they should obtain animal ethics committee approval. The approval of the ethical committee including approval number and the fact that the "informed consent" is given by the patients should be indicated in the "Methods" section. Authors should declare the conflict of interest concerning their articles and the financial supports.

Original Articles

1) Title Page (Page 1): This page should include the titles of the manuscripts, information about the author(s), key words and running titles.

For papers n Turkish language, a title in English should be included. Similarly, articles in English should include a title in Turkish. Key words in English and Turkish, and running titles should also be included in the title page.

The names, affiliated institutions and full addresses of the authors should be given. The author to whom correspondence is to be addressed should be indicated separately. As e-mail addresses will be used preferentially for communication, the e-mail address of the corresponding author should be stated. In addition, telephone and fax numbers must be notified.

If the content of the paper has been presented before, and if the summary has been published, the time and place of the conference should be denoted on this page.

If any grants or other financial support has been given by any institutions or firms for the study, information must be provided by the authors.

2) Summary (Page 2): In the second page, summaries of the manuscripts (maximum 200 words for each) and the key words in Turkish and English language should be given.

The Summary Should Consist of the Following Sub Sections: Aim, Methods, Results, Conclusion. Separate sections are not used in the summaries of the review articles, case reports and educational articles. For these articles, the summaries should not exceed 200 words and include the scope and aims of the study, the salient findings and conclusions.

The references should not be cited in the summary section. As far as possible, use of abbreviations are to be avoided. Any abbreviations used must be taken into consideration independently of the abbreviations used in the text.

3) Text (From the Page 3 or 4, according to the length of the summaries)

Please follow the instructions in "general guidelines."

The Main Headings of the Text Should be as Follows: Introduction, Methods, Results, Discussion. Study Limitations and Conclusion

The introduction should include the rationale for investigation and the background of the present study. Results of the study should not be discussed in this part.

"Materials and methods" section should be presented in sufficient details to permit the repetition of the work. The statistical methods used should be clearly indicated.

Results should also be given in detail to allow the reproduction of the study.

The Discussion section should provide a correct and thorough interpretation of the results. The references should be directly related to the findings of the authors.

Study Limitation should be detailed in the section.

Conclusion section should provide highlighted and interpreted with the study's new and important findings.

Acknowledgements should be as brief as possible. Any support should be acknowledged in this section. (Acknowledgements should be only send with the "Cover Page".)

The excessive use of abbreviations is to be avoided. All abbreviations should be defined when first used by placing them in brackets after the full term. Abbreviations made in the abstract and in the text are taken into consideration separately. Abbreviations of the full terms stated in the abstract must be re-abbreviated after the same full term in the text.

4) References: Accuracy of reference data is the author's responsibility.

References should be numbered according to the consecutive citation in the text. References should be indicated in brackets in the text.

Personal communications, unpublished data and submitted manuscripts must be cited, not in this section, but in the text as "(name(s), unpublished data, 19)."

The reference list should be typed on a separate page at the end of the manuscript. If there are more than 6 authors, abbreviation of "et al." should be used for the authors out of the first three. Journal titles should be abbreviated according to the style used in the Index Medicus. All the references should be written according to the Vancouver system as follows:

a) Standard Journal Article: 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) Book: Getzen TE. Health economics: fundamentals of funds. New York: John Wiley & Sons; 1997.

c) Chapter of a Book: 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.

If more than one editor: editors.

d) Conference Papers: 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) Journal on the Internet: 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) Thesis: Kaplan SI. Post-hospital home health care: the elderly access and utilization (thesis). St. Louis (MO): Washington Univ; 1995.

5) Tables, Graphics, Figures and Pictures: All tables, graphics or figures should be presented on a separate sheet. All should be numbered consecutively according to their place in the text and a brief descriptive caption should be given. Abbreviations used should be explained further in the figure's legend. The text of tables especially should be easily understandable and should not repeat the data of the main text. Illustrations already published are acceptable if supplied by permission of the authors for publication. Photographs should be printed on glossy paper. Figures should be done professionally and no grey colors should be used.

Special Sections

1) Reviews: All reviews within the scope of the journal will be taken into consideration by the editors; also the editors may solicit a review related to the scope of the journal from any specialist and experienced authority in the field.

2) Case Reports: Case reports should present important and rare clinical experiences. They should consist of the following parts: introduction, case, discussion.

3) Letters to the Editor: These are views about articles published in this journal. The editor may request responses to the letters. There are no separate sections in the text.

Correspondence

For all correspondence with the editorial board, mail or e-mail addresses given below may be used.

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
E-mail: hasekidergisi@gmail.com

Haseki Tıp Bülteni

The Medical Bulletin of Haseki

İçindekiler

Haseki Tıp Bülteni

The Medical Bulletin of Haseki

İçindekiler

Haseki Tıp Bülteni

The Medical Bulletin of Haseki

Contents

Haseki Tıp Bülteni

The Medical Bulletin of Haseki

Contents

Review / Derleme

DOI: 10.4274/haseki.3527
Med Bull Haseki 2017;55:1-6

Acute Kidney Injury and Chronic Kidney Disease: A Bidirectional Road

Akut Böbrek Hasarı ve Kronik Böbrek Hastalığı: İki Yönlü Yol

Meltem Gürsu, Sami Uzun*, Rümeyza Kazancıoğlu, Savaş Öztürk*

Bezmialem Vakıf University Faculty of Medicine, Department of Nephrology, İstanbul, Turkey
**Haseki Training and Research Hospital, Clinic of Nephrology, İstanbul, Turkey*

Abstract

Acute kidney injury (AKI) and chronic kidney disease (CKD) have many common points regarding risk factors, etiology, clinical and laboratory factors. We aimed in this review to discuss the outcome, the risk of CKD, cardiovascular and overall mortality risk after AKI, and the mechanisms underlying the relationship between AKI and CKD.

Keywords: Acute kidney injury, chronic kidney disease, mortality, outcome

Öz

Akut böbrek hasarı (ABH) ve kronik böbrek hastalığının (KBH) risk faktörleri, etiyoloji, klinik ve laboratuvar bulgular açısından pek çok ortak noktası bulunmaktadır. Bu derlemede ABH sonrası sonlanımı, KBH riskini, kardiyovasküler ve tüm nedenlere bağlı mortaliteyi ve ABH ve KBH arasındaki ilişkinin altında yatan mekanizmaları tartışmayı amaçladık.

Anahtar Sözcükler: Akut böbrek hasarı, kronik böbrek hastalığı, mortalite, sonlanım

Introduction

Acute kidney injury (AKI) and chronic kidney disease (CKD) have many common features regarding risk factors, etiology, clinical and laboratory findings. However, the most important common similarity is their outcome. Moreover, both clinical entities are related with progressive loss of kidney function, decreased life quality, increased cardiovascular risk and mortality.

Is Acute Kidney Injury a Risk Factor for Chronic Kidney Disease?

The previous data was consistent with a good long-term outcome after AKI. Liano et al. (1) followed up 187 consecutive patients without known nephropathy and hospitalized after 1992 due to acute tubular necrosis (ATN) for a median of 7.2 years (7-22 years) after their discharge. Ten patients were lost-to-follow-up during this period and 95 patients died. The clinical evaluation of 58 of 82 patients who survived in years 2000-2001 revealed that 81% of them had normal renal functions. One-, 5-, 10- and 15-year survival rates were detected to be 89%, 67%, 50% and 40%, respectively. Survival was better in young patients, those who had ATN after trauma, patients without a comorbidity and those who were followed up in intensive care units. The authors commented that renal functions remained well in most of the patients although long-term mortality was high.

On the other hand, there is data in the literature showing that the long-term results are not so good after AKI. Ishani et al. (2) evaluated patients older than 67 years who were discharged after hospitalization in 2000 using Medicare and United States Renal Data System (USRDS) data. Patients with a history of AKI within the last two years and those who were diagnosed to have end-stage renal disease (ESRD) during hospitalization were excluded. Among the 233.803 patients involved, AKI was diagnosed in 3.1% of patients of whom 34.3% had history of CKD. The rate of ESRD was 0.5% in the overall group, and 25.2% of them were discharged with the diagnosis of AKI. The percentage of patients diagnosed with ESRD was

Yazışma Adresi/Address for Correspondence: Meltem Gürsu
Bezmialem Vakıf University Faculty of Medicine, Department of Nephrology, İstanbul, Turkey
Phone: +90 505 295 33 71 E-mail: meltem1401@yahoo.com
Received/Geliş Tarihi: 28 November 2016 **Accepted/Kabul Tarihi:** 23 December 2016

similar to that of patients without a history of either AKI or CKD (0.208%) and those with CKD (1.988%), while this rate was 2.45% in patients with AKI and 7.94% in those with AKI on CKD (2). The risk of ESRD was 54% higher in patients with AKI compared to those with CKD. The presence of AKI and CKD together increased the risk of ESRD markedly in comparison with patients with neither of them (hr: 41.19).

In their meta-analysis, Coca et al. (3) studied the observational and randomized controlled studies published about the subject between 1990 and 2007. The overall analysis of more than 3000 patients involved in the 13 studies revealed that the risk of ESRD increases after AKI (hr: 3.10) (3).

Therefore, studies state that AKI increases the risk of CKD, the progression of CKD, and ESRD (2-6).

Is Acute Kidney Injury Related with Mortality?

Ishani et al. (2) analyzed the mortality rates in their previously mentioned study. Patients with AKI had 2.38 times higher mortality rate compared to patients without AKI. When compared to patients with normal renal functions, mortality rate was 1.45 times higher in patients with CKD, 2.48 times in those with AKI and 3.24 times in patients with both AKI and CKD (2).

Chertow et al. (4) analyzed the mortality rate in 19.982 patients with one or two creatinine level measured during their hospitalization and in 9.205 patients with two or more measurements of creatinine. The mortality rate increased parallel to serum creatinine levels when patients were grouped as those with a serum creatinine level of 0.3-0.4 mg/dL [odds ratio (OR): 4.1], 0.5-0.9 mg/dL (OR: 6.5), 1.0-1.9 mg/dL (OR: 9.7) and ≥2 mg/dL (OR: 16.4) (4).

Coca et al. (5) studied the risk of 30-day mortality in patients with small acute changes in serum creatinine levels in their meta-analysis. The relative risk of mortality was 1.8, 3.0 and 6.9 times higher in patients showing 10-24%, 25-49% and >50% increase in serum creatinine levels, respectively compared to the control group. It was concluded that even small changes in serum creatinine level was related with worse short- and long-term outcomes whether or not there was CKD.

Lo et al. (6) reported in their study that 322 patients had CKD during 10.344 patient-years of follow-up, and ESRD developed in 41 of them. The rate of CKD was 47.9/100 patient years and 1.7/100 patient years in patients with or without a history of AKI, respectively. Moreover, all the 41 patients who had ESRD were in the AKI group. There were 703 patients who suffered dialysis-requiring. ARF of these patients, 295 died in hospital and ESRD developed in 65 of them. Mortality and ESRD was recorded in 6416 and 22 patients respectively among 562.076 AKI cases without need for dialysis. Dialysis requiring AKI was shown to increase CKD risk by 28 times and death risk by 2.3 times when other intervening factors were excluded.

Patients with AKI requiring in-hospital dialysis were compared with those who did not require dialysis for at least 30 days following discharge in a Canadian study (7). It was reported that the previous group had three times higher risk of ESRD while mortality rate did not increase.

Amdur et al. (8) studied patients who were hospitalized due to either AKI or ATN between years 1999 and 2005, and compared them with a control group including patients with pneumonia or myocardial infarction (MI). Patients were divided into four groups: ATN (+), pneumonia or MI (-) (345 patients); AKI (+), ATN (-), pneumonia or MI (-) (5021 patients); pneumonia or MI (+), AKI (-), ATN (-) (62.850 patients), stage 3-5 CKD (+) and ATN or pneumonia or MI (+) (44.076 patients). The mortality was increased 1.12 times in patients with AKI and 1.2 times in those with CKD compared to the control group.

The 2007 Annual Data of the USRDS reported that AKI increased the risk of rehospitalization, ESRD and death in patients with CKD (9).

Hence, we can conclude that the long-term outcome of AKI is not good; and is related with the increased risk of CKD, ESRD and death.

Which Patients Have Higher Risk for Chronic Kidney Disease and Mortality After an Attack of Acute Kidney Injury?

Previous studies reported increased mortality in patients with AKI (10). Chawla et al. (11) studied 5.351 patients hospitalized due to AKI or ATN between 1999 and 2005 and compared them with 15.917 control subjects. The number of patients who developed stage-4 CKD was 728 in the patient group (13.6%) and 1.348 in the control group (8.5%). Advanced age (OR: 1.01, p=0.019), longer period under the risk (OR: 1.12, p=0.0004), need for renal replacement therapy (OR: 2.4; p=0.0063), higher risk, injury, failure, loss of kidney function, and End-stage kidney disease score (OR: 1.88, p<0.0001) and lower serum albumin (OR: 0.33, p<0.0001) were reported to be the risk factors for CKD.

Thakar et al. (12) evaluated 4.082 diabetics who had received health care between 1999 and 2004 and followed them until the end of 2008. Primary and secondary end points were the development of stage-4 CKD and all-cause mortality, respectively. Eight hundred and five attacks of AKI were recorded in 530 patients during the follow up. The number of AKI attacks was 1 in 70% and 2 or more in 30% of patients. The risk factors for development of stage-4 CKD were found to be occurrence of AKI in

hospital, higher basal serum creatinine level, presence of proteinuria, hypertension, and female gender. CKD risk was highest in patients who had three attacks of AKI with the risk decreasing progressively in patients with two, one or no attacks of AKI (12).

Another study by Ozturk et al. (13) determined advanced age, lower initial creatinine and albumin levels at the first session as major factors affecting mortality in patients with AKI requiring dialysis. The mean number of hemodialysis sessions was higher in patients who survived after AKI attacks (13).

Therefore, need for renal replacement therapy and/or repeated AKI attacks increases the risk of CKD. The roles of gender, age, the place where it developed (home, hospital-clinic, and intensive care unit), etiology, comorbidities and specific renal disease are controversial.

Does Acute Kidney Injury Increase the Cardiovascular Risk?

James et al. (14) retrospectively evaluated 14.782 patients who had coronary angiography between 2004 and 2006 for the rate of AKI and long-term outcome including mortality, ESRD, cardiovascular events and hospitalization. AKI was more frequent in patients who had high serum creatinine levels before angiography and those with proteinuria with the stage of AKI increasing as estimated glomerular filtration rate (eGFR) decreased. Moreover, AKI risk was higher in patients with diabetes mellitus, heart failure, cerebrovascular disease, peripheral artery disease, and chronic pulmonary or liver disease. The risk of death and ESRD was lower in patients without AKI; higher in patients with stage 1 AKI; and highest in those with stage 2-3 AKI. Hospital stay was also longer in patients with AKI. The authors stated that AKI increased the risk of not only mortality and ESRD, but also hospitalization due to MI and heart failure.

Stroke patients were studied in another study in which patients with renal dysfunction were found to have higher risk for mortality and new cardiovascular events (15).

Patients who had AKI or MI between 1999 and 2005 according to the records of veterans affairs database were studied more recently (16). They were divided into three groups as AKI group, MI group and AKI+MI group after exclusion of patients with eGFR<45 mL/min/1.73 m^2. Primary end points were death and new renocardiac event in this study that included 36.980 patients. Death rate was highest in AKI+MI group (57.5%) and lowest in MI group (32.3%). Major renocardiac events were more frequent in AKI+MI group compared to MI group. Moreover, death, hospitalization due to stroke, heart failure, and recurrent MI were more common in patients who had AKI.

Consequently, it can be concluded that the risk of major cardiovascular event increases in patients with AKI independent from the presence of a previous cardiovascular disease.

How Does Acute Kidney Injury Increase the Risk of Cardiovascular Mortality?

Although AKI is a localized tissue damage, it triggers systemic inflammatory response, irrespective of the initial cause (17). The chemoattractants released from activated endothelial cells and damaged epithelial cells cause migration of neutrophils, monocyte/macrophages and lymphocytes. Cytokines, chemokines, reactive oxygen products and nitrogenous products released from these cells cause acute aseptic inflammation.

This fact leads to the question whether renoprotection is possible with inhibition of inflammatory infiltration or not. Several studies have been carried out with ATN models. Ischemic injury stimulates toll-like receptors (TLR) leading to exocytosis of Weibel-Palade bodies from endothelial cells. This leads to release of von Willebrand factor, interleukin (IL)-8, angiopoietin-2, eotaxin, endothelin-1, and other biologically active substances that cause stem cell mobilization, inflammation, coagulation and increased vascular permeability. It is thought that substances released from Weibel-Palade bodies have pro-inflammatory effects in the early period while they may have pro-regenerative roles in the later stages. Therefore, selective inhibition of pro-inflammatory mediators may be a realistic approach in the future.

Concomitant with this pathway, purine metabolism is accelerated due to ischemic damage leading to increased production of uric acid which is known to be the prototype alarm signal. Uric acid together with high mobility group box-1 protein provides engagement of endothelial progenitor cells to the ischemic tissue and release of pro-inflammatory cytokines.

Systemic inflammatory response may affect other organs, such as heart, lung and liver, increasing the mortality risk further. Thus, patients die 'with AKI' but not 'due to AKI'.

The Mechanisms Underlying the Pathophysiology of Chronic Kidney Disease after Acute Kidney Injury

There are many studies showing increased frequency of CKD after AKI (2,3,6,18-20). However, it is stated in all of these articles that the pathophysiology is not clear.

Loss of tubular brush border, loss of tubular cells, proximal tubular dilation, cylinders within the distal tubules, and areas of cellular regeneration are among the findings seen following ATN (20). Although there are many

genes reported to be related to these events, there is no specific one. Endothelial damage in ATN decreases renal blood flow. Increased endothelin level and decreased nitric oxide level aggravates ischemia. Meanwhile, an increase in the expression of both intracellular adhesion molecules (endothelium mediated damage), and TLRs (epithelial damage caused by ischemia related cytokines), and a decrease in peroxisome proliferator-activated receptors activation take place.

Moreover, neutrophils, natural killer cells and macrophages become activated by stimulation of the immune system. Complement system and various adhesion molecules are activated and release of tumor necrosis factor (TNF)-alpha, IL-6 and IL-8 are increased (21).

Basile et al. (22) analyzed renal biopsy samples from male rats obtained four, eight and 40 weeks after ischemia reperfusion injury or sham operation. The authors found that some of the tubules were not repaired and there was interstitial hypercellularity four weeks after acute renal failure. Tubular structure was normal at the 8th week except hypercellularity while glomerular atrophy in some regions and glomerular hypertrophy in others, cellular infiltration and tubulointerstitial scarring were observed at 40th week.

Zager et al. (23) compared the weight of ischemic and the contralateral kidneys of rats one day, one week and three weeks after unilateral ischemia-reperfusion injury. The weight of the ischemic kidney increased on the first day of ischemia, but started to decrease progressively thereafter, while the weight of the contralateral kidney increased progressively. TNF-alpha mRNA and membrane cofactor protein-1 mRNA levels in the ischemic kidney were higher compared to the contralateral kidney in the first day, reaching maximum levels in the first week, and decreasing thereafter. Transforming growth factor (TGF)-β1 mRNA levels were reported to increase with time progressively (23).

Renal cortical endothelin-1 mRNA level was studied in another study 24 hours and two weeks after unilateral ischemia reperfusion (19). Endothelin level was higher in the ischemic kidney at both time periods being more prominent at the 2nd week (19). The lack of increase in the plasma and contralateral kidney led to the idea that endothelin synthesis was local. Another interesting finding was that the increase was mainly in endothelin A receptor mRNA (19). The authors reported that atrosentan given before and after ischemia did not prevent the decrease in kidney weight (19).

Similarly, Zager et al. (23) revealed a prominent decrease three weeks after ischemia reperfusion injury and TGF-beta RNA level and increased ratio of TGF-beta acetylation.

Endothelin has prime role in ischemic renal damage. It decreases blood flow by vasoconstriction and causes inflammation and oxidative stress (18). Endothelin-A receptor antagonists may be effective by blocking these steps (18).

Systemic and intrarenal hypertension, glomerular hyperfiltration, tubular hypertrophy and atrophy,

Table. Summary of acute kidney injury related main risks regarding chronic kidney disease, end-stage renal disease, mortality and inflammation
Increased risk of CKD:
AKI increases the risk of CKD and the progression of CKD (2-6)
Repeated AKI attacks increases the risk of CKD markedly (12,13)
Increased risk of ESRD:
AKI increases risk of ESRD (3)
AKI and CKD together increase the risk of ESRD markedly (2)
AKI on CKD increases the progression of CKD to ESRD (6)
Increased mortalitiy:
AKI increases patients' mortality rates (2,10)
Mortality increases parallel with the severity of the AKI (4-5,14)
Dialysis requiring AKI increases death risk (6)
Risk of major cardiovascular events increases in patients with AKI independent from the presence of a previous cardiovascular disease (16)
Young patients, those who had ATN after trauma, patients without a comorbidity and those who were followed in intensive care units have better survival rate (1)
Increased systemic inflammation:
AKI triggers systemic inflammatory response (17)
This maybe irrespective of the initial reason
Systemic inflammatory response may affect other organs like heart, kidneys, lung and liver increasing morbiditiy and mortality risk further
Legends for illustration: Mechanisms responsible for the progression AKI to CKD CKD: Chronic kidney disease AKI: Acute kidney injury related, ATN: Acute tubular necrosis, ESRD: End-stage renal disease

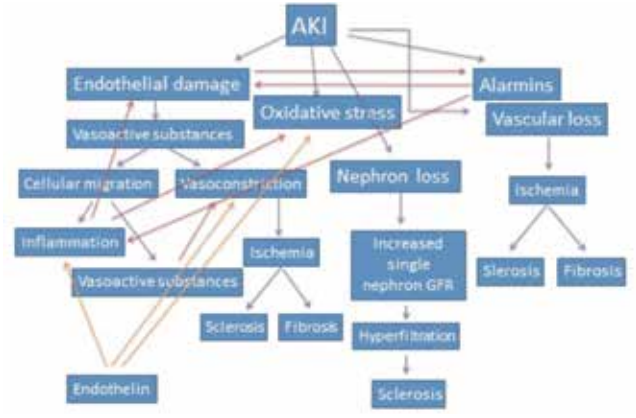


Figure. The Mechanisms Underlying the Pathophysiology of chorinic kidney disease after acute kidney injury
AKI: Acute kidney injury related, GFR: Glomerular filtration rate

tubulointerstitial fibrosis, progressive glomerular sclerosis, arteriosclerosis, genetic propensity, defects in humoral response, uncontrolled apoptosis, abnormal responses of epithelial cells, pericytes, myofibroblasts and bone marrow cells, defects in differentiation, proinflammatory signals, and progressive capillary loss are all active in the process leading AKI to CKD (24-26).

These mechanisms are summarized in the Figure.

Is Chronic Kidney Disease a Risk Factor for Acute Kidney Injury?

The principle risk factors described are advanced age, black race, genetic factors, hypertension, diabetes mellitus, and metabolic syndrome (2,4,27). Above all of them, CKD increases the risk of AKI more than 10 times (2,9,27).

Hsu et al. (28) compared patients who had AKI during hospitalization with those who did not have. The mean eGFR level before hospitalization was lower in the AKI group. Hypertension, diabetes mellitus and proteinuria were reported to be the other risk factors for AKI (28).

Patients with CKD are at risk of having temporary decreases in renal functions. Distorted autoregulation, abnormal vasodilation, increased sensitivity to diuretics and nephrotoxic agents, and age-related changes in renal physiology may be the underlying factors.

Another facilitative factor may be heart failure that is common in patients with CKD (25,29). CKD has also been shown in animal models to increase sepsis-related AKI by intervening vascular endothelial growth factor and high-mobility group box 1 protein (30). Roles of specific gene expressions and transplantation, epigenetic changes and uremic milieu are still subject of debate.

AKI related main risks about the topic were summarized in the Table.

Conclusion

In conclusion, AKI is not innocent even after recovery of renal functions. It is associated with increased risk of CKD. Need for renal replacement therapy and/or repeated AKI attacks increases the risk of CKD. AKI also increases cardiovascular mortality. Physicians should be alert dealing with AKI about cardiovascular events, and should follow these patients after full or partial recovery of renal functions.

Ethichs

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Meltem Gürsu. Concept: Meltem Gürsu, Rümeyza Kazancıoğlu. Design: Sami Uzun, Savaş Öztürk. Data Collection or Processing: Meltem Gürsu, Sami Uzun. Analysis or Interpretation: Rümeyza Kazancıoğlu, Savaş Öztürk. Literature Search: Meltem Gürsu, Sami Uzun. Writing: Meltem Gürsu.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Liano F, Felipe C, Tenoiro MT, et al. Long-term outcome of acute tubular necrosis: a contribution to its natural history. Kidney Int 2007;71:679-86.
2. Ishani A, Xue JL, Himmelfarb J, et al. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol 2009;20:223-8.
3. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int 2012;81:442-8.
4. Chertow MG, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005;16:3365-70.
5. Coca SG, Peixoto AJ, Garg AX, Krumholz HM, Parikh CR. The prognostic importance of a small acute decrement in kidney function in hospitalized patients: a systematic review and meta-analysis. Am J Kidney Dis 2007;50:712-20.
6. Lo LJ, Go AS, Chertow GM, et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. Kidney Int 2009;76:893-9.
7. Wald R, Quinn RR, Luo J, et al. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA 2009;302:1179-85.
8. Amdur RL, Chawla LS, Amodeo S, Kimmel PL, Palant CE. Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. Kidney Int 2009;76:1089-97.
9. USRDS 2007 Annual Data Report. http://www.usrds.org/atlas07.aspx.
10. Star RA. Treatment of acute renal failure. Kidney Int 1998;54:1817-31.
11. Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney Int 2011;79:1361-9.
12. Thakar CV, Christianson A, Himmelfarb J, Leonard AC. Acute kidney injury episodes and chronic kidney disease risk in diabetes mellitus. Clin J Am Soc Nephrol 2011;6:2567-72.
13. Ozturk S, Arpaci D, Yazici H, et al. Outcomes of acute renal failure patients requiring intermittant hemodialysis. Ren Fail 2007;29:991-6.
14. James MT, Ghali WA, Knudtson ML, et al. Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography. Circulation 2011;123:409-16.
15. Tsagalis G, Akrivos T, Alevizaki M, et al. Renal dysfunction in acute stroke: an independent predictor of long-term all combined vascular events and overall mortality. Nephrol Dial Transplant 2009;24:194-200.

16. Chawla LS, Amdur RL, Shaw AD, Faselis C, Palant CE, Kimmel PL. Association between AKI and long-term renal and cardiovascular outcomes in United States veterans. Clin J Am Soc Nephrol 2014;9:448-56.
17. Ratliff BB, Rabadi MM, Vasko R, Yasuda K, Goligorsky MS. Messengers without borders: mediators of systemic inflammatory response in AKI. J Am Soc Nephrol 2013;24:529-36.
18. Dhaun N, Webb DJ. The road from AKI to CKD: the role of endothelin. Kidney Int 2013;84:637-8.
19. Zager RA, Johnson AC, Andress D, Becker K. Progressive endothelin-1 gene activation initiates chronic/end stage renal disease following experimental ischemic-reperfusion injury. Kidney Int 2013;84:703-12.
20. Reichel RR. Acute kidney injury: quoi de neuf? Ochsner J 2014;14:359-68.
21. Leemans JC, Stokman G, Claessen N, et al. Renal-associated TLR2 mediates ischemia/reperfusion injury in the kidney. J Clin Invest 2005;115:2894-903.
22. Basile DP, Donohoe D, Roethe K, Osborn JL. Renal ischemic injury results in permanent damage to peritubular capillaries and influences long-term function. Am J Physiol Renal Physiol 2001;281:887-99.
23. Zager RA, Johnson AC, Becker K. Acute unilateral ischemic renal injury induces progressive renal inflammation, lipid accumulation, histone modification, and "end-stage" kidney disease. Am J Physiol Renal Physiol 2011;301:1334-45.
24. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. Kidney Int 2012;82:516-24.
25. Venkatachalam MA, Griffin KA, Lan R, Geng H, Saikumar P, Bidani AK. Acute kidney injury: a springboard for progression in chronic kidney disease. Am J Physiol Renal Physiol 2010;298:1078-94.
26. Hostetter TH. Progression of renal disease and renal hypertrophy. Annu Rev Physiol 1995;57:263-78.
27. Xue JL, Daniels F, Star RA, et al. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. J Am Soc Nephrol 2006;17:1135-42.
28. Hsu CY, Ordonez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int 2008;74:101-7.
29. Berk BC, Fujiwara K, Lehoux S. ECM remodeling in hypertensive heart disease. J Clin Invest 2007;117:568-75.
30. Leelahavanichkul A, Huang Y, Hu X, et al. Chronic kidney disease worsens sepsis and sepsis-induced acute kidney injury by releasing High Mobility Group Box Protein-1. Kidney Int 2011;80:1198-211.

Original Article / *Özgün Araştırma*

DOI: 10.4274/haseki.3231
Med Bull Haseki 2017;55:7-14

A Retrospective Evaluation of Patients with Recurrent Aphthous Stomatitis

Rekürren Aftöz Stomatitli Hastaların Retrospektif Olarak Değerlendirilmesi

Filiz Topaloğlu Demir, Mustafa Demir*, Zafer Türkoğlu, Nazlı Dizen Namdar**

Haseki Training and Research Hospital, Clinic of Dermatology, İstanbul, Turkey
**Bartın State Hospital, Clinic of Ophthalmology, Bartın, Turkey*
***Dumlupınar University Faculty of Medicine, Department of Dermatology, Kütahya, Turkey*

Abstract

Aim: To determine the factors in the etiology of recurrent aphthous stomatitis (RAS) and to evaluate patients in the terms of RAS associated systemic disorders especially Behçet's disease.

Methods: Patients with RAS, who were followed up in Bartın State Hospital Dermatology Clinic between July 2013 and April 2015, were retrospectively evaluated.

Results: A total of 123 patients (86 female, 37 male) were included in this study. Thirteen (106%) patients were children. The mean age of patients was 34.5±14.7 years (range: 8-69 years). Minor aphthous somatitis was the most frequent clinical type (68.3%). Family history was positive in 52.8% of patients. The triggering factors in the etiology of RAS were stress (54.5%), trauma (40.2%), gingivitis (29.3%), food (9.8%), medicines (5.7%), menstruation in female patients (3.3%), and throat infections (2.4%). Nutritional deficiencies were found in 39% of patients. There was a statistically significant difference in attack frequency (p=0.017) and throat infection history (p=0.029) between adults and pediatric patients. Fourteen (11.4%) patients were diagnosed with Behçet's disease. When we compared the RAS patients diagnosed with Behçet's disease and the other RAS patients, a significant difference was found in pathergy test (p<0.001) and ferritin levels (p=0.020).

Conclusion: Patients with RAS should be followed up for a long time for systemic disorders, especially for Behçet's disease, accompanying RAS.

Keywords: Aphthous stomatitis, oral ulcer, Behçet's disease

Öz

Amaç: Rekürren aftöz stomatit (RAS) tanısı ile takibe alınan hastalarda etiyolojide yer alan faktörleri belirlemek ve başta Behçet hastalığı olmak üzere RAS'la ilişkilendirilmiş sistemik hastalıklar açısından hastaları değerlendirmektir.

Yöntemler: Temmuz 2013 ve Nisan 2015 tarihleri arasında Bartın Devlet Hastanesi Dermatoloji Polikliniği'ne başvuran, RAS tanısı alan hastalar retrospektif olarak değerlendirildi.

Bulgular: Toplam 123 hasta (86'sı kadın, 37'si erkek, yaş aralığı 8-69) çalışmaya dahil edildi. Yaş ortalaması 34,5±14,7 idi. En sık minör aft (%68,3) saptandı. Aile öyküsü hastaların %52,8'inde pozitifti. RAS'li hastalarda etiyolojide yer alan tetikleyici faktörler; stres (%54,5), travma (%40,2), gingivit (%29,3), yiyecekler (%9,8), ilaçlar (%5,7), kadın hastalarda menstruasyon (%3,3) ve boğaz enfeksiyonu (%2,4) olarak saptandı. Hastaların %39'unda nütrisyonel eksiklik mevcuttu. RAS'li çocuk hastalar ile erişkin hastaları karşılaştırdığımızda atak sıklığı ve boğaz enfeksiyonu (p=0,029) dışında istatistiksel açıdan anlamlı bir fark gözlenmedi. On dört hastaya (%11,4) Behçet hastalığı tanısı konuldu. Behçet hastalığı tanısı alan hastalar ile diğer RAS'li hastaları kıyasladığımızda, paterji pozitifliği (p<0,001) ve ferritin düzeyleri (p=0,020) arasındaki fark istatiksel açıdan anlamlıydı.

Sonuç: RAS hastalarını sadece etiyolojik faktörler ve hematinik eksikler açısından değerlendirmek yeterli değildir. Bu hastalar başta Behçet hastalığı başta olmak üzere RAS'nin eşlik ettiği diğer sistemik hastalıklar açısından uzun süre takibe alınmalıdır.

Anahtar Sözcükler: Aftöz stomatit, oral ülser, Behçet hastalığı

Introduction

Recurrent aphthous stomatitis (RAS) is the most common oral mucosal disease, characterized by chronic, painful, repetitive in character, round or oval, smooth-edged, and necrotizing ulcerations (1). Many factors, such as local, microbial, systemic, nutritional, genetic immunological and allergic, are blamed in the etiology but it is not yet fully understood (2). Behçet's disease, mouth and

Address for Correspondence/Yazışma Adresi: Filiz Topaloğlu Demir
Haseki Training and Research Hospital, Clinic of Dermatology, İstanbul, Turkey
E-mail: filizsvet@yahoo.com
Received/Geliş Tarihi: 06 April 2016 **Accepted/Kabul Tarihi:** 20 April 2016

genital ulcers with inflamed cartilage (MAGIC) syndrome, gastrointestinal disorders (Crohn's disease, ulcerative colitis and celiac disease), human immunodeficiency virus (HIV) infection, Sweet's syndrome, periodic fevers with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome, and cyclic neutropenia are major systemic diseases which may be associated with RAS (3).

As therapeutic approach varies according to triggering factors, frequency of recurrence and concomitant systemic disease, RAS patients in our study were evaluated in terms of all these factors. Behçet's disease, if present, was noted as a concomitant condition.

Methods

A hundred twenty three patients, who were admitted to the dermatology clinic at Bartın State Hospital between July 2013 and April 2015 and diagnosed with RAS by history and clinical findings, were included in the study. Patients who had previously been diagnosed with Behçet's disease, oral colchicine users and those without aphthous stomatitis on clinical examination were excluded. Records of patients with the diagnosis of RAS were retrospectively analyzed. Data on age, gender, history of systemic disease, smoking and drug use, duration of the disease (in months), clinical type of the aphthous lesion, family history, and frequency of recurrence were noted. The patients were divided into 3 groups according to the frequency of attacks in a year (≤5, 6-9, ≥10). The classification of aphthous lesions were based on lesion diameter (minor: ≤1 cm, major: >1 cm) and clinical features. The patients were also evaluated for other triggering factors, such as trauma, food, beverages, stress, frequency of throat infection, gum and tooth disease, besides, menstruation, oral contraceptive use and pregnancy for the female patients. Hematological laboratory tests, such as hemogram, iron, iron binding, ferritin, vitamin B12, and folate were recorded. Laboratory values of 12-16 g/dL (female) and 14-18 g/dL (male) for hemoglobin, 11-306.8 ng/mL (female) and 23.9-336.2 ng/mL (male) for serum ferritin, 2.33-17.24 ng/mL for folate and 126.5-505 pg/mL for vitamin B12 were considered normal. All patients were evaluated for RAS-associated systemic disorders, such as Behçet's disease, Reiter's syndrome, gastrointestinal systemic diseases (inflammatory bowel disease, celiac disease), immune disorders, MAGIC syndrome, periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome, Sweet's syndrome, and cyclic neutropenia. Pathergy test was performed in all patients to evaluate Behçet's disease. History of genital ulcer, erythema nodosum, thrombophlebitis, papulopustular lesions and arthritis, clinical findings and biopsy results from suspicious lesions were recorded for all patients. Ophthalmologic examination was performed in all patients. The relevant clinics were consulted for patients having headache, stomachache, diarrhea, and joint pain.

Statistical Analysis

SPSS 15.0 for Windows was used for statistical analysis. Descriptive statistics; numbers and percentages for categorical variables, average, standard deviation, minimum and maximum were given for numeric variables. Categorical variable rates between groups were analyzed by chi-square test. When the condition could not be achieved in the case, the Bonferroni correction or Monte Carlo simulation were applied. Mann-Whitney U test was used to compare the numerical variable of independent two-groups when the normal distribution condition was not provided. A p value of less than 0.05 was considered statistically significant.

Results

A total of 123 patients (86 female, 37 male) were included in this study. Thirteen (106%) patients were children. Female/male ratio was 2.32 and the mean age of the patients was 34.5±14.7 years (range: 8-69 years). The mean duration of disease was 83.9±78.9 months (range 4-360). Minor aphthous somatitis was the most frequent clinical type in RAS patients. Minor aphthous somatitis was seen in 84 patients (68.3%), major somatitis in 24 (19.5%), and both minor and major types were seen in 14 patients (11.4%). Herpetiform type was seen in only one (0.8%) patient (Figure 1, 2).

Family history was positive in 65 patients (52.8%). Fifty-four patients (43.9%) had positive family history in their first-degree relatives, seven (5.7%) patients had this condition in their second-degree relatives and four (3.3%) patients had positive history in both first-and second-degree relatives. In our study, the mean duration of the disease was 102.2±86.2 months in family history-positive patients and 63.5±64.6 months in family history-negative patients. The relationship between family history and disease duration was statistically significant (p=0.003).

When the adults patients were evaluated in terms of smoking, it was found that only nine (8.2%) were smokers and 12 (10.9%) have had stopped smoking. In two patients (1.8%), RAS occurred after stopping smoking and in five patients (4.5%), there was an increase in the frequency of oral aphthae after stopping smoking. Eighty-nine patients (80.9%) were non-smokers. There was no significant difference in the number of attacks and clinical type of RAS between smokers, non-smokers and patients who stopped smoking.

When the relationship between RAS and traumatic events (such as bite, brushing teeth, chewing gum) was examined, trauma was detected to be the triggering factor in 49 patients (40.2%). RAS was associated with

stress in 67 patients (54.5%). In seven patients (5.7%), RAS was associated with non-steroidal anti-inflammatory drug (NSAID) use. There was a history of triggering with food in 12 patients (9.8%). Spicy foods, citrus fruits and nuts were most commonly cited group for causing RAS. When we questioned the relationship between RAS and hormonal factors in adult female patients, we found that only four patients (3.6%) reported the association between menstruation and RAS. Gingivitis was detected in 36 patients (29.3%). While only three patients (2.4%) reported frequent throat infection, one patient had hepatitis B and one patient had hepatitis C. HIV infection; cyclic neutropenia or any other diseases which can cause immunosuppression were not detected in our patients.

The mean hemoglobin (Hb) level was 13.4±1.8 g/dL. Anemia was detected in 33 patients (26.8%). The lowest Hb level was 9 g/dL. The mean serum iron level was 70.9±33.2 µg/dL. Twelve patients (9.8%) had low serum iron level. The mean ferritin level was found to be 50.6±77.9 ng/mL. Ferritin level was low in 31 patients (25.2%). The mean folate level was 12.0±20.3 ng/mL. Folate levels were normal in all patients. The mean vitamin B12 level was 273.7±168.4 pg/mL. Seventeen patients (13.8%) had low vitamin B 12 level. Both ferritin and vitamin B 12 deficiency were detected in four patients (3.3%) and only three (2.4%) patients had iron-deficiency anemia. There was no statistically significant difference between genders in terms of laboratory values. While 48% of patients had at least one pathology in the studied parameters, nutrition deficiency was found in 39% of patients. When we compared pediatric and adult patients with RAS, we found no significant difference except for frequency of attacks (p=0.017) and history of throat infection (p=0.029) (Table 1).

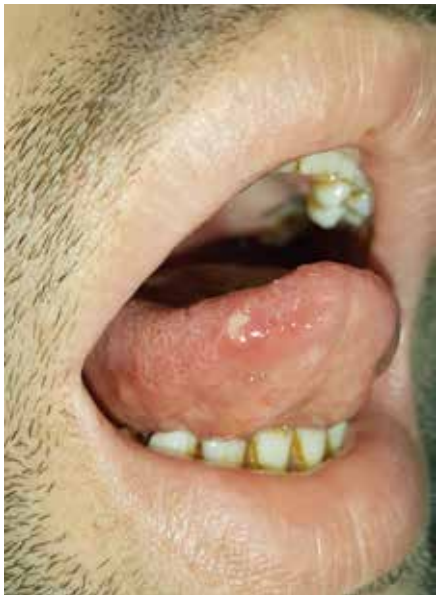


Figure 1. Minor aphthae

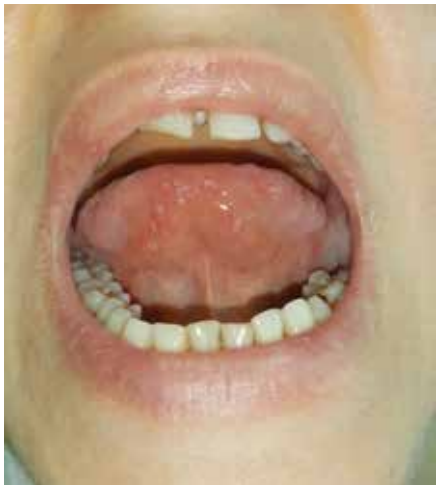


Figure 2. Herpetiform aphthae

While pathergy test was positive in 21 patients (17.1%), genital ulcer was detected in seven (5.7%) and genital scar was detected in two patients (1.6%). Eritema nodosum was detected in four patients (3.3%) and, two patients (1.6%) had a history of eritema nodosum. Previous thrombophlebitis and deep vein thrombosis history was present in only one patient (0.8%). Ten patients (8.1%) had papulopustular lesions histologically consistent with Behçet's disease and 13 patients (10.6%) had a history of papulopustular lesions which could be seen in Behçet's disease. There was no statistically significant relationship between pathergy test, trauma and papulopustular lesions. Arthralgia history was seen in 24 patients (19.6%), however, there was only one patient (0.8%) with arthritis detected on physical examination. Previous uveitis findings were present in two patients (1.6%) (one anterior and one posterior uveitis). Headache history was found in 52 patients (42.3%) but only one patient was diagnosed as having neuro-Behçet disease. Headache complaints in other patients were associated with migraine, tension headache and sinusitis. Abdominal pain and diarrhea were detected in 29 patients (23.6%) but entero-Behçet's disease and any other gastrointestinal system disease were not observed in any patients. Fourteen patients (11.4%) were diagnosed with Behçet's disease with these findings. When we compared RAS patients diagnosed with Behçet's disease and other RAS patients, we found that there was a significant difference in pathergy test (p<0,001) and ferritin levels (p=0.020) (Table 2).

Discussion

RAS is an inflammatory disease of oral mucosa with unknown etiology which is characterized by painful, recurrent, single or multiple ulcerations (4). Although

Table 1. Comparison of pediatric and adult patients with recurrent aphthous stomatitis

		RAS				
		Pediatrics		Adults		
		n	%	n	%	p
Gender	Female	10	76.9	76	69.1	0.753
	Male	3	23.1	34	30.9	
Type of RAS	Minor type	10	76.9	74	67.3	0.580
	Major type	1	7.7	23	20.9	-
	Herpetiform type	0	0.0	1	0.9	-
	Both minor and major type	2	15.4	12	10.9	-
Attack frequency	≤5	2	15.4	12	10.9	**0.017**
	6-9	5	38.5	13	11.8	-
	≥10	6	46.2	85	77.3	-
Genital ulcer	None	13	100.0	101	91.8	1.000
	Genital ulcer (+) at visit	0	0.0	7	6.4	-
	Scar form	0	0.0	2	1.8	-
Eritema nodosum	None	13	100.0	103	94.5	1.000
	Positive at first visit	0	0.0	4	3.7	-
	Previous EN history	0	0.0	2	1.8	-
Pseudofolliculitis	None	11	84.6	89	80.9	1.000
	Positive at first visit	1	7.7	9	8.2	-
	Previous PF history	1	7.7	12	10.9	-
Tromboflebitis	None	13	100.0	109	99.1	1.000
	Previous tromboflebitis	0	0.0	1	0.9	-
Pathergy	Negative	12	92.3	90	81.8	0.695
	Positive	1	7.7	20	18.2	-
Ocular involvement	None	13	100.0	108	98.2	1.000
	Anterior uveitis	0	0.0	1	0.9	-
	Posterior uveitis	0	0.0	1	0.9	-
Neuro Behçet's	-	0	0.0	1	0.9	-
Joint symptoms	None	12	92.3	86	78.2	0.827
	Artritis	0	0.0	1	0.9	-
	Artralgia	1	7.7	19	17.3	-
	Artritis ve artralgia history	0	0.0	4	3.6	-
Family history	-	6	46.2	59	53.6	0.609
Family history	None	7	53.8	51	46.4	1.000
	1st degree relatives	6	46.2	48	43.6	-
	2nd degree relatives positive	0	0.0	7	6.4	-
	1st and 2nd degree relatives RAS history	0	0.0	4	3.6	-
Gingivitis	-	1	7.7	35	31.8	0.106
Stress	-	4	30.8	63	57.3	0.070
Trauma	-	4	30.8	45	41.3	0.465
Throat infection	-	2	15.4	1	0.9	**0.029**
Food allergy	-	1	7.7	11	10.0	1.000
Drugs	-	0	0.0	7	6.4	1.000
Menstruation	-	0	0.0	4	3.6	1.000

Table 1. Comparison of pediatric and adult patients with recurrent aphthous stomatitis (Continued)

		RAS				
		Pediatrics		Adults		
		n	%	n	%	P
Behçet's disease		0	0.0	14	12.7	-
Hemoglobin	Normal	10	76.9	80	72.7	1.000
	Low	3	23.1	30	27.3	-
Iron	Normal	12	92.3	99	90.0	1.000
	Low	1	7.7	11	10.0	-
Ferritin	Normal	11	84.6	81	73.6	0.514
	Low	2	15.4	29	26.4	-
Vitamin B12	Normal	10	76.9	96	87.3	0.388
	Low	3	23.1	14	12.7	-

RAS: Recurrent aphthous stomatitis, PF: Pharyngitis

seen in both genders, RAS is detected more frequently in female gender (5). The majority of RAS patients were female in our study similar to that in other studies (6,7). Minor aphthae is the most frequent clinical form which seen in 75-85% of RAS patients. Minor aphthae form is followed by major aphthae form (10-15) and herpetiform aphthae (5-10%) (8). Generally, patients have only one clinical type of the disease. Nevertheless, it has been reported that two separate clinical types can be found at the same time (9). In their including 100 patients with RAS, Bahalı et al. (6) reported that 88 patients (88%) had minor aphthae, 10 patients (10%) had minor and major aphthae and two patients (2%) had minor and herpetiform aphthae. Although minor aphthae rate was lower in our study than in the literature, it was still the most frequent RAS type. While major aphthae rate was higher than in the literature, herpetiform aphthae rate was lower. In addition,

Table 2. Comparison of recurrent aphthous stomatitis patients diagnosed with Behçet's disease and the other recurrent aphthous stomatitis patients

		Diagnosis of Behçet's disease				
		No		Yes		p
Age		34.4±14.8		34.7±14.7		0.994
		n	%	n	%	
Gender	Female	77	70.6	9	64.3	0.758
	Male	32	29.4	5	35.7	-
Type of RAS	Minor type	73	67.0	11	78.6	0.917
	Major type	22	20.2	2	14.3	-
	Herpetiform type	1	0.9	0	0.0	-
	Both minor and major type	13	11.9	1	7.1	-
Pathergy	Negative	100	91.7	2	14.3	**<0.001**
	Positive	9	8.3	12	85.7	-
Vitamin B12	Normal	95	87.2	11	78.6	0.409
	Low	14	12.8	3	21.4	-
Hemoglobin	Normal	79	72.5	11	78.6	0.757
	Low	30	27.5	3	21.4	-
Iron	Normal	99	90.8	12	85.7	0.627
	Low	10	9.2	2	14.3	-
Ferritin	Normal	78	71.6	14	100	**0.020**
	Low	31	28.4	0	0.0	-

RAS: Recurrent aphthous stomatitis

minor and major aphthae were observed at the same time in 11.4% of patients.

The presence of family history has been identified as a risk factor affecting the disease progression and the clinical course in RAS patients. In the literature, positive family history was determined in 42 to 67.3% of patients (10-12). In our study, consistent with the literature, positive family history was determined in 52.8% of patients. Disease duration was longer in patients with positive family history, but there was no relationship of positive family history, with clinical form and attack frequency. These findings were different from the literature showing the association between family history and disease severity (13,14).

It has been reported that RAS is rare in smokers. This preventive effect of smoking is associated with oral mucosal keratinization, which is seen in smokers, and anti-inflammatory effect of nicotine (15,16). Only 8.2% of the patients in our study were smoker. RAS occurred after stopping smoking in two patients and frequency of RAS increased after stopping smoking in five patients. These results indirectly support the protective activity of smoking on RAS.

Some triggering factors are blamed in the development of RAS. Filiz et al. (17) reported in their study including 39 patients with RAS and 36 healthy controls, that oral aphthae were associated with trauma in 12.8 of subjects, with foods in 15.3%, with stress in 66.6% and with menstruation in 8.6% of subjects. Bahalı et al. (6) reported that RAS was associated with bite (12%), brushing teeth (18%), the presence of dental disease (82%), food (39%), menstruation (10.3%) and stress (76%). Also in their study on 30 RAS patients and 49 patients with Behçet's disease, Gungor et al. (7) reported that oral aphtae were associated with trauma in 30% of subjects, with stress in 60% and with menstruation in 10% of female patients. In our study, we found that RAS was associated with trauma in 40.2%, with food in 9.8%, with stress in 54.5% of patients and with menstruation in 3.6% of female patients. The main drugs that can cause aphthous-like lesions are NSAIDs, β-blockers, captopril, gold salts, nicorandil, niflumic acid, phenindione, phenobarbital, piroxicam, and sodium hypochlorite (18). In our study, RAS was associated with drugs (NASIDs) in 5.7% of patients. The patients confirmed that they often used NSAIDs for various reasons and after usage, oral aphthae occurred. Some authors reported that microbiological mechanisms can cause RAS (8). In this respect, it has been suggested that oral streptococci could play a role in the pathogenesis of RAS (19). In our study, only three patients (2.4%) had a history of frequent throat infections and only one of them was group A beta-hemolytic streptococci-positive in throat culture.

Nutritional deficiencies may play a role in the etiology of RAS. In a study by Solak et al. (20), hematological changes were detected in 61.8% of RAS patients. In that study 30% of patients had anemia, 26.3% had vitamin B12 deficiency and 25.4% of patients had ferritin deficiency. Bahalı et al. (6) in their study examining the relationship between RAS and hematinic deficiencies, reported that 16 patients (16.7%) had only iron deficiency, 22 patients (22.4%) had only vitamin B12 deficiency and four patients (4.3%) had both iron and vitamin B12 deficiency; ferritin levels were low in 18 patients (18%) and folat levels were normal in all patients. Compilato et al. (21) reported that 56% of RAS patients had pathological values with hematologic tests, therefore, they suggested that in all RAS patients hematological tests must be done and deficiencies must be treated. This rate was determined as 26% in a study by Barnadas et al. (22). In our study, we detected anemia in 26.8% of patients, vitamin B12 deficiency in 13.8%, low ferritin levels in 25.2%, and low serum iron levels in 9.8% of patients. Folat deficiency was not observed. While 3.3% of patients had both ferritin and vitamin B12 deficiency, only 2.4% of patients had iron-deficiency anemia. Pathology was detected in at least one of the studied parameters in 48% of patients, and also nutritional deficiency was detected in 39% of patients. Although the relationship between RAS and hematinic deficiency is still uncertain, especially vitamin B12, ferritin and iron deficiency should be investigated and treated.

In our study, 10.6% of patients were children. This finding made us to think that child patients may be admitted to pediatric clinics for RAS instead of dermatology clinics. When we compare these patients with adult patients, we found no significant difference between them except for attack frequency and throat infection history.

It is known that RAS can be related with many systemic diseases such as Behçet's disease, MAGIC syndrome, Crohn's disease, ulcerative colitis, celiac disease and cyclic neutropenia (3). In our study, we did not find any systemic disease in RAS patients except for Behçet disease. Oral ulcerations which are major criteria for Behçet's and ulcerations that seen in RAS patients cannot be differentiated clinically and the number of relevant studies in the literature is limited (23,24). Gungor et al. (7) reported that Behçet's disease began at an earlier age than RAS and, duration of the disease was longer in Behçet's disease. They found no statistically significant difference in family history between patients with Behçet's disease and RAS. The authors attributed this result to genetic factors that could play a role in the immunopathogenesis of both diseases. In a study by Main and Chamberlain (25), a statistically significant difference

was not detected between patients with Behçet's oral ulceration and conventional oral ulceration with respect to onset of illness, age, family history, frequency and duration of oral ulcers. In our study, Behçet's disease was detected in 11.4% of patients who were admitted with RAS. There was no statistically significant difference between patients with Behçet's disease and those with RAS in terms of age, gender, duration of the disease, attack frequency and family history. Positive pathergy test was observed in 85.7% of Behçet's disease patients; this rate was 8.3% in RAS patients. Ferritin levels were normal in Behçet's patients but 28.4% of RAS patients had low ferritin levels. The difference in pathergy test positivity and ferritin levels was statistically significant. Aphthous lesions are the most common symptom of Behçet's disease and may continue 6-8 years in some patients before the diagnosis is established (23,24). In the study of Bang and colleagues which followed up 67 patients presenting with recurrent oral ulcers, 52.2% of patients were diagnosed with Behçet's disease for an average of 7.7 years (24). In our study, the proportion of patients diagnosed with Behçet's disease was low compared to the literature because of the short follow-up period.

Conclusion

In conclusion, genetic features and predisposing factors such as trauma, stress, microbial factors, food, drug reactions, immune disorders, hormonal imbalances, and hematinic deficiencies may play a role in the etiology of RAS. RAS is also associated with many of the systemic disorders, mainly Behçet's disease. As a result, family history, clinical findings and laboratory results are not enough to classify ulcers according to systemic disorders. Patients with ongoing aphthae should be followed for a long time in terms of systemic disorders, especially Behçet's disease.

Ethics

Ethics Committee Approval: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Filiz Topaloğlu Demir. Concept: Filiz Topaloğlu Demir. Design: Filiz Topaloğlu Demir. Data Collection or Processing: Filiz Topaloğlu Demir. Mustafa Demir. Analysis or Interpretation: Filiz Topaloğlu Demir, Mustafa Demir, Nazlı Dizen Namdar. Literature Search: Filiz Topaloğlu Demir, Zafer Türkoğlu. Writing: Filiz Topaloğlu Demir.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Odom RB, James WD, Berger TG. Recurrent aphthous stomatitis. Andrews' disease of the skin. 9th ed. Philedephia: WB Saunders Company; 2000.p.1006-8.
2. Ship JA. Recurrent aphthous stomatitis: An update. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;81:141-7
3. Scully C, Porter S. Oral mucosal disease: recurrent aphthous stomatitis. Br J Oral Maxillofac Surg 2008;46:198-206.
4. Graykowski EA, Barile MF, Lee WB, Stanley HR Jr. Recurrent aphthous stomatitis. Clinical, therapeutic, histopathologic, and hypersensitivity aspects. JAMA 1966;196:637-44.
5. Hutton KP, Rogers RS 3rd. Recurrent aphthous stomatitis. Dermatol Clin 1987;5:761-8.
6. Bahalı AG, Kokturk A, Guvenc U. Sociodemographic and clinical characteristics of patients with recurrent aphthous stomatitis. Turkderm 2014;48:242-8.
7. Gungor S, Akbay G, Eksioglu M. Clinical Comparison of Aphthae in Recurrent Aphthous Stomatitis and Behçet's Disease. Turkderm 2010;44:150-2.
8. Scully C, Porter S. Recurrent aphthous stomatitis: current concepts of etiology, pathogenesis and management. J Oral Pathol Med 1989;18:21-7.
9. Vanhale HM, Rogers RS, Doyle JA, Schroeter Al. Immunofluorescence microscopic studies of recurrent aphthous stomatitis. Arch Dermatol 1981;117:779-81.
10. McCullough MJ, Abdel-Hafeth S, Scully C. Recurrent aphthous stomatitis revisited; clinical features, associations, and new association with infant feding practices? J Oral Pathol Med 2007;36:615-20.
11. Safadi RA. Prevalence of recurrent aphthous ulceration in Jordanian dental patients. BMC Oral Health 2009;9:3.
12. Shohat-Zabarski R, Kalderon S, Klein T, Weinberger A. Close association of HLA-B51 in persons with recurrent aphthous stomatitis. Oral Surg Oral Med Oral Pathol 1992;74:455-8.
13. Miller MF, Garfunkel AA, Ram CA, Ship II. The inheritance of recurrent aphthous stomatitis. Observations on susceptibility. Oral Surg Oral Med Oral Pathol 1980;49:409-12.
14. Ship II. Inheritance of aphthous ulcers of the mouth. J Dent Res 1965;44:837-44.
15. Tüzün B, Wolf R, Tüzün Y, Serdaroğlu S. Recurrent aphthous stomatitis and smoking. Int J Dermatol 2000;39:358-60.
16. Scully C, Gorsky M, Nur FL. Aphthous ulcerations. Dermatologic Therapy 2002;15:185-205.
17. Filiz EE, Öztürkcan S, Yüceyar H, Kandiloğlu AR, Şendil AZ. Rekürren aftöz stomatit etiyolojisinde Helikobakter pilorinin rolü. Turkiye Klinikleri J Dermatol 2002;12:61-5.
18. Natah SS, Konttinen YT, Enattah NS, Ashammakhi N, Sharkey KA, Häyrinnen- Immonen R. Recurrent aphthous ulcers today: a review of the growing knowledge. Int J Oral Maxillofac Surg 2004;33:221-34.
19. Francis TC, Oppenheim JJ. Impaired lymphocyte stimulation by some streptococcal antigens in patients with recurrent aphthous stomatitis and rheumatic heart disease. Clin Exp Immunol 1970;6:573-86.

20. Solak TN, Aydemir S, Sezer T, Duysak S, Altınyazar HC. Rekürren aftöz stomatitli hastalarda hematolojik değişiklikler. Turkiye Klinikleri J Dermatol 2007;17:150-4.
21. Compilato D, Carroccio A, Calvino F, Di Fede G, Campisi G. Haematological deficiencies in patients with recurrent aphthosis. J Eur Acad Dermatol Venereol 2010;24:667-73.
22. Barnadas MA, Remacha A, Condomines J, de Moragas JM. Hematologic deficiencies in patients with recurrent oral aphthae. Med Clin (Barc) 1997;109:85-7.
23. Verpilleux MP, Bastuji-Garin S, Revuz J. Comparative analysis of severe aphthosis and Behçet's disease: 104 cases. Dermatology 1999;198:247-51.
24. Bang D, Hur W, Lee ES, Lee S. Prognosis and clinical relevance of recurrent oral ulceration in Behçet's disease. J Dermatol 1995;22:926-9.
25. Main DM, Chamberlain MA. Clinical differentiation of oral ulceration in Behçet's disease. Br J Rheumatol 1992;31:767-70.

Original Article / *Özgün Araştırma*

DOI: 10.4274/haseki.3179
Med Bull Haseki 2017;55:15-20

Association Between Maternal Vitamin D Status and Risk of Gestational Diabetes Mellitus in Pregnant Women

Gebelerde Ölçülen D Vitamini Seviyeleri ile Gestasyonel Diabetes Mellitus Riski Arasındaki İlişki

Seda Ateş, Serdar Aydın, Ayşe Filiz Gökmen Karasu, Banu Dane

Bezmialem Vakıf University Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul, Turkey

Abstract

Aim: To investigate whether maternal serum levels of 25-hydroxyvitamin D [25(OH)D] in the first trimester is associated with an increased risk of gestational diabetes mellitus (GDM).

Methods: We conducted a cross-sectional study of a cohort of pregnant women who had undergone routine genetic multiple marker screening and subsequent glucose tolerance testing. Twenty-five women with GDM and 208 controls without GDM were included in this study. Plasma 25(OH)D concentrations were measured using liquid chromatography-tandem mass spectrometry.

Results: Mean 25(OH)D concentrations at 11-14 weeks of gestation were not significantly different in women who subsequently developed GDM compared with those who did not (mean ± standard deviation: 13.96 9.05 versus 13.43±9.72; p=0.8). The prevalence of first-trimester severe 25(OH)D deficiency (<10 ng/mL) was similar between women with GDM and healthy controls (44% vs. 44.7%, respectively; p=0.9). The mean concentration of 25(OH)D slightly increased over the two gestational age windows both in women with GDM [mean Δ25(OH)D: 0.25±5.8 ng/mL] and controls [mean Δ25(OH)D: 0.84±12.84 ng/mL], but the difference was not statistically significant (p=0.8).

Conclusion: Vitamin D deficiency in early pregnancy is not significantly associated with elevated risk of GDM.

Keywords: Severe vitamin D deficiency, gestational diabetes mellitus, pregnancy

Öz

Amaç: Birinci trimesterde ölçülen maternal 25-hidroksi D [25(OH)D] vitamini serum düzeylerinin gestasyonel diabetes mellitus (GDM) ile ilişkisinin araştırılması.

Yöntemler: Bu kesitsel kohort çalışmayı birinci trimesterde rutin genetik tarama testi yapılan ve sonrasında glukoz tolerans testi uygulanan gebeler üzerinde yaptık. Gestasyonel diyabet tanısı alan 25 gebe ve gestasyonel diyabet tanısı almayan 208 gebe çalışmaya dahil edildi. Plazma 25(OH)D konsantrasyonları, sıvı kromatografisi-tandem kütle spektrometresi yöntemiyle ölçüldü.

Bulgular: GDM gelişen gebelerin ve kontrol grubunun 11-14.gebelik haftalarında ölçülen ortalama 25(OH)D vitamini konsantrasyonları arasında anlamlı fark yoktu (sırasıyla ortalama ± standart deviasyon: 13,96±9,05 vs 13,43±9,72, p=0,8). Ortalama 25(OH)D konsantrasyonları, hem gestasyonel diyabetli gebelerde hem de kontrol grubunda iki ayrı gebelik haftası aralığında (11-14 gebelik haftası ve 24-28 gebelik haftası) hafifçe artmıştı [ortalama Δ25(OH)D: 0,25±5,8 ng/mL ve ortalama Δ25(OH)D: 0,84±12,84 ng/mL]; ancak bu fark istatistiksel olarak anlamlı değildi (p=0,8).

Sonuç: Erken gebelik haftasında saptanan 25(OH)D vitamin eksikliği, GDM riski ile ilişkili değildir.

Anahtar Sözcükler: Ciddi D vitamin eksikliği, gestasyonel diabetes mellitus, gebelik

Introduction

High prevalence of vitamin D deficiency has been established among pregnant women in several countries (1). The estimated prevalence ranges from 3% to 24% depending on the country of residence, clothing style, dietary intake, skin pigmentation, sunshine exposure, usage of prenatal vitamins, and definition of vitamin D deficiency (2). Vitamin D is mainly derived from skin photosynthesis and minor proportion is obtained from digestive absorption. Vitamin D is transformed and metabolized to 25-hydroxyvitamin D [25(OH)D] which is the best determinant of patient's vitamin D status in

Address for Correspondence/Yazışma Adresi: Seda Ateş
Bezmialem Vakıf University Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul, Turkey
Phone: +90 505 392 92 74 E-mail: drsedaates@yahoo.com
Received/Geliş Tarihi: 07 March 2016 **Accepted/Kabul Tarihi:** 21 April 2016

the liver, then, 25(OH)D is metabolized to its active form, [1.25(OH)D_2] in the kidneys (3).

Vitamin D is proposed to play an important role in release and maintenance of glucose tolerance, and in insulin synthesis (4). It is well established that pancreatic b-cells express vitamin D receptor (5). Several studies also support that vitamin D deficiency reduces insulin secretion and 1.25(OH)D_2 administration improves b-cell function and glucose tolerance (6,7). Vitamin D deficiency predisposes to the development of both type 1 and 2 diabetes (8,9). However, the association of vitamin D deficiency with gestational diabetes mellitus (GDM) is not well established and remains controversial. There is an increasing interest in the relationship between vitamin D status and GDM. Some studies suggested an association between GDM and lower levels of 25(OH)D in pregnant women (10,11), but others reported no significant difference from normoglycaemic controls (12,13).

The present study aimed to examine whether there is an association between maternal vitamin D status in early trimester and the risk of developing GDM. We conducted a secondary analysis to compare the 25(OH)D levels in the first and second trimesters.

Methods

We conducted a cross-sectional study of a cohort of pregnant women who attended Bezmialem Vakıf University Faculty of Medicine in İstanbul for routine genetic multiple marker screening between 11 and 14 weeks' gestation between December 2012 and July 2014. All the subjects subsequently had a screening test for gestational diabetes at our hospital during the same pregnancy.

We measured maternal serum levels of 25(OH)D in 233 consecutive pregnant women in the first trimester after informing about the research. In this visit, we recorded maternal characteristics, medical history and information about the factors associated with vitamin D status. Serum 25(OH)D was also measured in follow-up samples collected at 24-28 weeks of gestation in a subset of 152 participants. All participants gave informed consent for participation in the study, which was approved by the Ethics Committee of Bezmialem Vakıf University, (71306642/050-01-04/553).

Data on maternal characteristics included age, parity, blood pressure, pre-pregnancy weight, height, date of the last menstrual period, education level, gestational age at blood sampling, type of clothing, use of multivitamin supplements, and season of blood collection. Gestational age was calculated according to the last menstrual period and ultrasound estimates of gestational age were used in cases of uncertain menstrual dates. Covered dressing style was defined as wearing dresses which cover body completely excluding hands and face whereas uncovered dressing style was wearing dresses exposing body to more sun light in a permissive manner. The season for blood collection was dichotomized into winter months (November-April) and summer months (May-October). Maternal body mass index (BMI) was calculated from the patient's self-reported height and pre-pregnancy weight. Education was categorized as low (≤5 years of education), mid (6-10 years), and high (≥9 years).

Women with known or clinically suspected pregestational diabetes, pregestational hypertension, history of thyroid, parathyroid or adrenal disease, hepatic or renal failure, metabolic bone disease and those taking medications that might affect vitamin D metabolism were excluded from the study. Multiple pregnancies were also excluded. None of the women in this study had previously received vitamin D or calcium supplementation.

In this study, the cases were defined as women who met the diagnostic criteria for GDM. The diagnosis of GDM was based on using a two-step approach. Initial screening for GDM was performed between 24 and 28 weeks of gestation using a 1-hour 50-gram glucose challenge test. Patients with a blood glucose level of >185 mg/dL at the first hour were considered to have GDM and, if the concentration was more than 140 mg/dL, an oral glucose tolerance test (OGTT) using a 100-g oral glucose load was carried out within the subsequent 2 weeks. GDM was diagnosed if at least two plasma glucose levels were above the following cut-offs, including fasting plasma glucose ≥95 mg/dL, plasma glucose one hour after OGTT ≥180 mg/dL, plasma glucose two hours after OGTT ≥155 mg/dL and plasma glucose three hours after OGTT ≥140 mg/dL (14). Women with a diagnostically negative 50-g glucose challenge test were eligible to serve as controls.

Measurement of 25(OH)D_3 and 25(OH)D_2 in human serum was made by using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with an Agilent 1200 Infinity LC (Agilent Technologies) coupled to an Agilent Technologies 6460 LC-MS/MS. The summation of serum 25(OH)D_2 and 25(OH)D_3 was used to reflect total serum 25(OH)D concentrations. The inter-assay and intra-assay coefficients of variation of total serum 25(OH)D level were 6.84% and 2.21%, respectively. The lower and upper limits of detection were 4.0 and 200 ng/mL, respectively. Values that were outside the limits of detection were excluded from the analysis. We used the cutoff point of 10 ng/mL which has been suggested by some experts to define severe vitamin D deficiency (15). Depending on their 25(OH)D levels, the women were categorized into two groups. Values of 25(OH)D <10 ng/mL were included in group 1 and the values ≥10 ng/mL were included in group 2.

Statistical Analysis

Data were expressed as mean ± standard deviation or number and percentage as appropriate and a p value of less than 0.05 was considered statistically significant. Statistical analysis was performed after normality testing (histogram analysis and/or Kolmogorov-Smirnov) using IBM SPSS version 21. Student's t-test was used for comparisons of normally distributed variables, the Mann-Whitney U test for non-normally distributed variables. Chi-square and Fisher's exact tests were used to compare the proportion of categorical variables.

Results

A total of 286 women (11-14 weeks of pregnancy) were recruited during the study period. 53 of them were excluded from the analysis. Reasons for exclusion were deciding to be followed-up elsewhere (n=15), being lost-to-follow up (n=27), insufficient serum available for analysis (n=8), miscarriage (n=2) and termination of pregnancy because of Down syndrome (n=1). After exclusion of the women mentioned above, 233 women were available to be included in the analysis. Of the 233 participants, we consecutively enrolled 25 pregnant women with GDM as the study group and 208 women without GDM as the control group.

The demographic and clinical characteristics of pregnant women with GDM and controls are given in Table 1. The mean maternal age was 30.7±4.5 years in women with GDM and 29.1±5 in nondiabetic controls. The mean BMI in women with GDM and controls was 27.33±6.05 and 25.29±5.47 kg/m^2, respectively (p=0.09). There were no differences between the two groups concerning age, BMI, parity, education level, dressing style, use of multivitamin supplements or the season when blood sample was drawn. The median serum 25(OH)D concentration was 13.96±9.05 ng/mL in women with GDM and 13.43±9.72 ng/mL in controls at 11-14 weeks of gestation. Maternal 25(OH)D concentrations in women who developed GDM were similar to those in controls at the first trimester. Women who subsequently developed GDM had a higher diastolic blood pressure at the 11-14 weeks of gestation compared to controls (p=0.03), however, the systolic blood pressures in the GDM group were not significantly different from controls.

The prevalence of severe first-trimester maternal 25(OH)D deficiency (<10 ng/mL) was similar between women with GDM and healthy controls (44% vs. 44.7%, respectively; p=0.9). In a subset of 152 women, the 25(OH) D levels were also determined during the second trimester. The prevalence of severe 25(OH)D deficiency (<10 ng/mL) at 24-28 weeks of gestation was 33.3% in women with GDM and 46.7% in nondiabetic controls (p=0.3). The mean 25(OH)D concentration slightly increased over the two gestational age windows both in women with GDM

Table 1. The demographic and clinical characteristics of pregnant women with gestational diabetes and controls

	Women with gestational diabetes (n=25)	Control subjects (n=208)	p
Maternal age (years)	30.7±4.5	29.1±5	0.1
BMI (kg/m^2)	27.33±6.05	25.29±5.47	0.09
Parity	1.83±0.5	1.65±0.5	0.1
Education, n (%) 0-5 years 6-8 years ≥9 years	 11 (44) 5 (20) 9 (36)	 69 (33.2) 42 (20.2) 97 (66.6)	0.5
Mean systolic BP at trial entry (mmHg)	105.4±9.3	103.3±11	0.3
Mean diastolic BP at trial entry (mmHg)	70.4±8.1	66.5±8.5	0.03
Use of multivitamin, n (%)	9 (36)	87 (41.8)	0.1
Dressing style, n (%) Covered Uncovered	 12 (48) 13 (52)	 109 (52.4) 99 (47.6)	0.7
25(OH)D concentration (ng/mL) measured at 11-14 weeks of gestation (visit 1)	13.96±9.05	13.43±9.72	0.8
25(OH)D concentration (ng/mL) measured at 24-28 weeks of gestation (visit 2)	14.99±10.2 (n=15)	14.43±10.96 (n=137)	0.8
Season of blood draw (visit 1), n (%) Winter (November-April) Summer (May-October)	 12 (48) 13 (52)	 99 (47.6) 109 (52.4)	0.9
Season of blood draw (visit 2), n (%) Winter (November-April) Summer (May-October)	 8 (56.3) 7 (43.7)	 77 (56.2) 60 (43.8)	0.6

Data are shown as mean ± standard deviation, median (minimum-maximum) or n (%), BP: Blood pressure, 25(OH)D: 25-hydroxyvitamin D, BMI: Body mass index

(mean Δ25(OH)D=0.25±5.8 ng/mL) and normal pregnant women (mean Δ25(OH)D=0.84±12.84 ng/mL), whereas the difference was not statistically significant (p=0.8) (Table 2).

The serum concentrations of 25(OH)D in women with GDM and controls are presented in Table 3. The first-trimester 25(OH)D concentrations in women whose blood samples were drawn during the winter (November-April) were significantly lower than those in women whose first trimester occurred during the summer (May-October) (p<0.0001) while, no significant difference was observed in mean serum 25(OH)D concentration in the second trimester both in summer and winter season (p=0.3).

Discussion

The main finding of our study is the lack of significant difference in maternal vitamin D levels between pregnant women who develop GDM and normoglycemic controls. The association between GDM and vitamin D deficiency is controversial. Savvidou et al. (16) investigated maternal serum 25(OH)D levels at 11^{+0}-13^{+6} weeks of gestation in three groups of complicated pregnancies including women who had type 2 diabetes, women who subsequently developed GDM and nondiabetic women who delivered macrosomic neonates, and they failed to find a significant difference in vitamin D levels compared to those in nondiabetic controls. Similarly, Makgoba et al. (17) examined first-trimester maternal serum 25(OH) D levels and GDM in a case-control study of 90 pregnant women and did not find an evidence of an association in women with GDM compared to 158 controls. In another study, Farrant et al. (13) measured maternal serum 25(OH) D concentrations at 30 weeks of gestation in 559 women and did not find an association between maternal 25(OH)D deficiency and the risk of GDM. Another case-control study found no association between maternal serum 25(OH)D levels (measured between 11 and 14 weeks of pregnancy) and the development of GDM among pregnant women, which is consistent with our results (18).

On the other hand, there are several studies which reported a significant association between vitamin D deficiency and GDM. Recently, Zuhur et al. (19) studied 234 cases of GDM and 168 controls in Turkey and reported that only severely deficient maternal serum 25(OH)D levels (<5.2 ng/mL) were significantly associated with an elevated relative risk of GDM. Likewise, Maghbooli et al. (11) studied maternal vitamin D deficiency and GDM in a cross-sectional study of 741 pregnant women at 24-28-weeks gestation and found significantly lower levels of 25(OH)D in women with GDM compared to normoglycaemic controls. They reported higher rate of severe vitamin D deficiency (<10 ng/mL) (70.6%) compared to that in our study (44.6%) and suggested that severe vitamin D deficiency might contribute to insulin resistance. In a large cohort study, Zhang et al. (20) studied vitamin D deficiency in early pregnancy (mean gestational age: 16 weeks) and found a 2.66-fold increased risk of GDM in women with vitamin D deficiency. The prevalence of vitamin D deficiency (<20 ng/mL) was found to be high in 20% of women in this cohort. Previous studies have reported conflicting results about the association between vitamin D deficiency and GDM which may be explained by the methodological issues, such as sample size, study design, gestational age at sampling (early or late gestation), and the method used to measure vitamin D. Additionally, some other factors, such as criteria of GDM, definition of vitamin D deficiency, ethnic and genetic characteristics of the participants might contribute to inconsistent findings between the studies.

There are several studies reporting high prevalence of vitamin D deficiency among pregnant women and

Table 2. Maternal severe vitamin D deficiency at 11-14 and 24-28 weeks of gestation

	Women with gestational diabetes	Control subjects	p
Severe vitamin D deficiency [25(OH)D level <10 ng/mL] measured at 11-14 weeks of gestation (visit 1), n (%)	11 (44%)	93 (44.7%)	0.9
Severe vitamin D deficiency (25(OH)D level <10 ng/mL) measured at 24-28 weeks of gestation (visit 2), n (%)	5 (33.3%)	63 (46.7)	0.3
Δ25(OH)D (V2-V1)	0.25±5.8	0.84±12.84	0.8

Data are shown as mean ± standard deviation, median (minimum-maximum) or n (%), 25(OH)D: 25-hydroxyvitamin D

Table 3. Seasonal variations of serum 25-hydroxyvitamin D concentrations

	Summer season (May-October)	Winter season (November-April)	p
25(OH)D concentration (ng/mL) measured at 11-14 weeks of gestation (visit 1)	16.48±11.02	10.2±6.43	<0.0001
25(OH)D concentration (ng/mL) measured at 24-28 weeks of gestation (visit 2)	15.5±9.61	13.74±11.79	0.3

Data are shown as mean ± standard deviation, 25(OH)D: 25-hydroxyvitamin D

advocating the need for pharmacological intervention as low maternal vitamin D status was thought to be related to the increased risk of adverse pregnancy outcomes (21,22).

The 25(OH)D levels showed a moderate, but statistically non-significant increase towards the first to the second trimester in the present study. This is in contrast with the findings of the study by Fernández-Alonso et al. (23) who reported a decline in serum 25(OH)D concentration with progression of pregnancy. In agreement with our findings, Marwaha et al. (24) have shown no change in 25(OH) D concentrations with progression of pregnancy which could partly be explained by the food products that are not fortified with vitamin D and the absence of current guidelines on recommending mandatory vitamin D supplementation during pregnancy. In a study by Zhao et al. (25), the mean level of 25(OH)D in the second trimester was significantly higher than the one in the first trimester and equivalent to the one in the third trimester. Our results are compatible with the recent study which reported high prevalence of severe vitamin D deficiency [25(OH) D<10 ng/mL] (45.6%) among pregnant women in Turkey (26). These findings indicate that vitamin D deficiency is a major health problem in our population as well. A previous study demonstrated that ethnic differences in serum 25(OH)D levels were the primary determinant of increased risk of diabetes (27). Decreasing the risk of GDM in pregnancy may have a beneficial effect in reducing the number of adverse perinatal complications, including fetal macrosomia, prematurity, hypoglycaemia, birth trauma, hyperbilirubinemia and Caesarean section that have been linked to GDM (28).

Strengths of the current study include its prospective design and the use of the gold standard method for measuring 25(OH)D levels. One of the limitations of our study was its relatively small sample size and the small number of women with GDM compared with other studies. Secondly, we only measured 25(OH)D levels at two time points in pregnancy with the second time point including a significantly smaller number of participants.

Conclusion

In conclusion, our study demonstrated that vitamin D deficiency in early pregnancy is not significantly associated with elevated risk for GDM. Further well-designed, large and prospective cohort studies are required to explore the effects of vitamin D deficiency on GDM and the dose of vitamin D supplementation that ensures adequate vitamin D status in pregnancy.

Ethics

Ethics Committee Approval: Bezmialem Vakif University, 71306642/050-01-04/553. Informed Consent: All participants gave informed consent for participation in the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Seda Ateş, Serdar Aydın. Concept: Seda Ateş, Banu Dane. Design: Seda Ateş, Serdar Aydın. Data Collection or Processing: Seda Ateş, Serdar Aydın. Analysis or Interpretation: Serdar Aydın. Literature Search: Seda Ateş, Ayşe Filiz Gökmen Karasu. Writing: Seda Ateş.

Conflict of Interest: The authors report no declarations of interest.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Kimball S, Fuleihan Gel-H, Vieth R. Vitamin D: a growing perspective. Crit Rev Clin Lab Sci 2008;45:339-414.
2. Mulligan ML, Felton SK, Riek AE, Bernal-Mizrachi C. Implications of vitamin D deficiency in pregnancy and lactation. Am J Obstet Gynecol 2010;202:429.
3. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
4. Teegarden D, Donkin SS. Vitamin D: emerging new roles in insulin sensitivity. Nutr Res Rev 2009;22:82-92.
5. Lee S, Clark SA, Gill RK, Christakos S. 1,25-Dihydroxyvitamin D3 and pancreatic beta-cell function: vitamin D receptors, gene expression, and insulin secretion. Endocrinology 1994;134:1602-10.
6. Ye WZ, Reis AF, Dubois-Laforgue D, et al. Vitamin D receptor gene polymorphisms are associated with obesity in type 2 diabetic subjects with early age of onset. Eur J Endocrinol 2001;145:181-6.
7. Norman AW, Frankel JB, Heldt AM, Grodsky GM. Vitamin D deficiency inhibits pancreatic secretion of insulin. Science 1980;209:823-5.
8. Mathieu C, Badenhoop K. Vitamin D and type 1 diabetes mellitus: state of the art. Trends Endocrinol Metab 2005;16:261-6.
9. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab 2007;92:2017-29.
10. Soheilykhah S, Mojibian M, Rashidi M, Rahimi-Saghand S, Jafari F. Maternal vitamin D status in gestational diabetes mellitus. Nutr Clin Pract 2010;25:524-7.
11. Maghbooli Z, Hossein-Nezhad A, Karimi F, Shafaei AR, Larijani B. Correlation between vitamin D3 deficiency and insulin resistance in pregnancy. Diabetes Metab Res Rev 2008;24:27-32.
12. Clifton-Bligh RJ, McElduff P, McElduff A. Maternal vitamin D deficiency, ethnicity and gestational diabetes. Diabet Med 2008;25:678-84.
13. Farrant HJ, Krishnaveni GV, Hill JC, et al. Vitamin D insufficiency is common in Indian mothers but is not associated with

gestational diabetes or variation in newborn size. Eur J Clin Nutr 2009;63:646-52.

14. No authors listed. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. Diabetes 1979;28:1039-57.
15. Holick MF, Siris ES, Binkley N, et al. Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinol Metab 2005;90:3215-24.
16. Savvidou MD, Akolekar R, Samaha RB, Masconi AP, Nicolaides KH. Maternal serum 25-hydroxyvitamin D levels at 11(+0) -13(+6) weeks in pregnant women with diabetes mellitus and in those with macrosomic neonates. BJOG 2011;118:951-5.
17. Makgoba M, Nelson SM, Savvidou M, Messow CM, Nicolaides K, Sattar N. First-trimester circulating 25-hydroxyvitamin D levels and development of gestational diabetes mellitus. Diabetes Care 2011;34:1091-3.
18. Baker AM, Haeri S, Camargo CA Jr, Stuebe AM, Boggess KA. First-trimester maternal vitamin D status and risk for gestational diabetes (GDM) a nested case-control study. Diabetes Metab Res Rev 2012;28:164-8.
19. Zuhur SS, Erol RS, Kuzu I, Altuntas Y. The relationship between low maternal serum 25-hydroxyvitamin D levels and gestational diabetes mellitus according to the severity of 25-hydroxyvitamin D deficiency. Clinics (Sao Paulo) 2013;68:658-64.
20. Zhang C, Qiu C, Hu FB, et al. Maternal plasma 25-hydroxyvitamin D concentrations and the risk for gestational diabetes mellitus. PLoS One 2008;3:3753.
21. Johnson DD, Wagner CL, Hulsey TC, McNeil RB, Ebeling M, Hollis BW. Vitamin D deficiency and insufficiency is common during pregnancy. Am J Perinatol 2011;28:7-12.
22. Barrett H, McElduff A. Vitamin D and pregnancy: An old problem revisited. Best Pract Res Clin Endocrinol Metab 2010;24:527-39.
23. Fernández-Alonso AM, Dionis-Sánchez EC, Chedraui P, González-Salmerón MD, Pérez-López FR; Spanish Vitamin D and Women's Health Research Group. First-trimester maternal serum 25-hydroxyvitamin D_3 status and pregnancy outcome. Int J Gynaecol Obstet 2012;116:6-9.
24. Marwaha RK, Tandon N, Chopra S, et al. Vitamin D status in pregnant Indian women across trimesters and different seasons and its correlation with neonatal serum 25-hydroxyvitamin D levels. Br J Nutr 2011;106:1383-9.
25. Zhao Y, Miao W, Li C, et al. Dynamic changes in serum 25-hydroxyvitamin D during pregnancy and lack of effect on thyroid parameters. PLoS One 2014;9:90161.
26. Ustuner I, Keskin HL, Tas EE, Neselioglu S, Sengul O, Avsar AF. Maternal serum 25(OH)D levels in the third trimester of pregnancy during the winter season. J Matern Fetal Neonatal Med 2011;24:1421-6.
27. Scragg R, Sowers M, Bell C; Third National Health and Nutrition Examination Survey. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. Diabetes Care 2004;27:2813-8.
28. Mitanchez D. Foetal and neonatal complications in gestational diabetes: perinatal mortality, congenital malformations, macrosomia, shoulder dystocia, birth injuries, neonatal complications. Diabetes Metab 2010;36:617-27.

Original Article / *Özgün Araştırma*

DOI: 10.4274/haseki.3265
Med Bull Haseki 2017;55:21-6

The Relationship Between Myocardial Bridge and Electrocardiographic Tp-e Interval, Tp-e/QT and Tp-e/QTc Ratio

Elektrokardiyografik Tp-e İntervali, Tp-e/QT ve Tp-e/QTc Oranı ile Miyokardiyal Bridge Arasındaki İlişki

Erkan Yıldırım, Emrah İpek, Kamuran Kalkan, Mustafa Öztürk, Mahir Cengiz*, Hikmet Hamur**

Erzurum Region Training and Research Hospital, Clinic of Cardiology, Erzurum, Turkey
**İstanbul University Cerrahpaşa Faculty of Medicine, Department of Internal Diseases, İstanbul, Turkey*
***Erzincan University Faculty of Medicine, Department of Cardiology, Erzincan, Turkey*

Abstract

Aim: Myocardial bridge (MB) is generally known as an asymptomatic and benign anomaly, however, it can cause serious clinical conditions such as exercise-induced ventricular tachycardia and sudden death. Tp-e interval is the distance between the peak and the end of the T wave in electrocardiography. Tp-e/QT and Tp-e/QTc ratios are used as electrocardiographic indicators of ventricular arrhythmias. We have studied the effect of coronary angiographic features (the degree of stenosis and length of MB) of MB on myocardial repolarization parameters.

Methods: The study group consisted of 53 patients with isolated MB and 58 patients with normal coronary arteries.

Results: The QT interval and QTc were similar between the groups, however, Tp-e interval (92.72±14.72 and 79.59±12.12, respectively; p<0.001) and Tp-e/QT (0.24±0.041 and 0.21±0.025, respectively; p<0.001) and Tp-e/QTc (0.22±0.037 and 0.19±0.025, respectively; p<0.001) ratios were found to be significantly increased in MB group compared to the control group. In the comparison of the MB patients with critical and those with noncritical stenosis, Tp-e interval (100.69±10.79, 80.57±11.25, respectively; p<0.001) and Tp-e/QT (0.266±0.033, 0.219±0.037, respectively; p<0.001) and Tp-e/QTc (0.244±0.029, 0.196±0.027, respectively; p<0.001) ratios were higher in the MB with critical stenosis group.

Conclusion: Our results indicate that these parameters can be practical ECG markers of ventricular arrhythmias in patients with MB.

Keywords: Myocardial bridge, critical stenosis, Tp-e interval

Öz

Giriş: Miyokardial bridge (MB) genellikle asemptomatiktir ve iyi huylu olarak bilinir ancak egzersizin indüklediği ventriküler taşikardi, ani ölüm gibi ciddi klinik durumlara neden olabilir. Tp-e intervali elektrokardiyografide T dalgasının tepesi ile sonu arasındaki mesafedir. Tp-e/QT ve Tp-e/QTc oranları ventriküler aritmilerin elektrokardiyografik göstergesi olarak kullanılır. Biz MB'nin koroner anjiyografik özelliklerinin (MB'nin darlık derecesi ve uzunluğu) miyokardiyal repolarizasyon parametreleri üzerindeki etkisini araştırdık.

Yöntemler: Bu çalışma izole MB'li 53 ve normal koroner artere sahip 58 hastadan oluşmaktadır.

Bulgular: QT intervali ve QTc gruplar arasında benzerdi, Tp-e intervali (92,72±14,72 ve 79,59±12;12, p<0,001), Tp-e/QT (0,24±0,041 ve 0,21±0,025; p<0,001) ve Tp-e/QTc (0,22±0,037 ve 0,19±0,025; p<0,001) kontrol grubu ile karşılaştırıldığında MB grubunda belirgin olarak artmış bulundu. Kritik ve kritik olmayan darlığı bulunan MB hastaları karşılaştırıldığında, Tp-e intervali (100,69±10,79; 80,57±11,25; p<0,001), Tp-e/QT (0,266±0,033; 0.219±0,037; p<0,001) ve Tp-e/QTc (0,244±0,029; 0,196±0,027; p<0,001) kritik darlığı olan MB hastalarında daha yüksekti.

Sonuç: Sonuçlarımız MB hastalarında bu parametrelerin ventriküler aritmilerin pratik elektrokardiyografi belirteçleri olabileceğini göstermiştir.

Anahtar Sözcükler: Miyokardiyal bridge, kritik darlık, Tp-e interval

Address for Correspondence/Yazışma Adresi: Erkan Yıldırım
Erzurum Region Training and Research Hospital, Clinic of Cardiology, Erzurum, Turkey
Phone: +90 442 232 55 55 E-mail: drerkan23@yahoo.com
Received/Geliş Tarihi: 06 May 2016 **Accepted/Kabul Tarihi:** 12 June 2016

Introduction

Myocardial bridge (MB) is an inborn coronary anomaly which is defined as an abnormal intramyocardial course of a segment of a major coronary artery (1). Although MB can be seen in any of the epicardial coronary arteries, it is mostly observed in the left anterior descending artery with an incidence of 67-98% (2,3). In autopsy series, angiographically detected MB was reported to have a prevalence between 0.5% and 16% The rate of angiographic bridging is <5%, attributable to thin bridges causing little compression. In subjects with angiographically normal coronary arteries, the use of provocation tests may enhance systolic myocardial compression and thereby reveal MBs in ≤40% of cases and the length was found to be between 4 to 80 mm (4). MB is generally known to be an asymptomatic and benign anomaly, however, it can cause serious clinical conditions, such as severe myocardial ischemia, acute myocardial infarction, syncope, exercise-induced ventricular tachycardia and atrioventricular block, acute left ventricular failure, and sudden death (5,6).

Myocardial repolarization is evaluated by QT interval (QT), corrected QT interval (QTc), QT dispersion (QTd) and transmular dispersion of repolarization (TDR). Tp-e interval is the distance between the peak and the end of the T wave in electrocardiography (ECG) and it is assumed as an index for TDR (7). Tp-e/QT and Tp-e/QTc ratios are used as electrocardiographic indicators of ventricular arrhythmias (8). We studied the effect of coronary angiographic features (the degree of stenosis and length of MB) of MB on myocardial repolarization parameters.

Methods

Study Population

A total of 165 consecutive patients, who were referred to our clinic for diagnostic coronary angiography (CAG) between January and November 2015, were prospectively enrolled in the study. The study group consisted of 53 patients with isolated MB and 58 patients with normal coronary arteries. Patients with coronary artery disease (CAD), left ventricular systolic dysfunction, pulmonary hypertension, chronic obstructive pulmonary disease, diabetes, valvular disease, cardiomyopathy, abnormal thyroid function test, electrolyte imbalance, renal failure, and abnormal ECG, as well as those who had a pacemaker and on antiarrhythmic drug therapy were excluded. Patients whose ECGs could not be analyzed clearly were also excluded.

Coronary Angiography

The femoral route was used in all patients. The images were recorded in digital angiography system (ACOM.PC; Siemens, Germany and Digital Radiography System, Toshiba DSR, Japan) with a speed of 15 frame per second. The contrast agent lopromide (Ultravist 370, Bayer Pharma AG, Berlin, Germany) was used. The conventional CAG images were evaluated by three independent cardiologists. MB was defined as an abnormal intramyocardial course of a segment of a major coronary artery. The length and degree of stenosis (%) of the bridged segment were calculated angiographically by quantitative coronary analysis. The patients were allocated into two groups according to the degree of stenosis including MB with critical (70% or greater stenosis) and noncritical stenosis (stenosis less than 70%) groups.

Electrocardiography

Twelve-lead ECG was performed in each patient in the supine position by a conventional ECG device (Nihon Kohden, Tokyo, Japan) with a speed and amplitude of 25 mm/s and 10 mm/mV, respectively. The ECG measurements were evaluated by two independent cardiologists who were blinded to the clinical data of the patients. In order to minimize the measurement errors, an electronic caliper was utilized. The mean value of the measurements was taken in order to increase accuracy. Heart rate and rhythm were determined and Tp-e interval and Tp-e/QT and Tp-e/QTc ratios were measured. QT interval was defined as the distance between the onset of QRS and the end of T wave where it intersects the isoelectric line. QTc was calculated by Bazett's formula (9). The Tp-e interval was defined as the distance between the peak and the end of the T wave (Figure 1) (10). The measurement of Tp-e interval was performed using precordial leads as previously defined (11). The intraobserver and interobserver coefficients of variation [the standard deviation (SD) of differences between two observations divided by the mean value and expressed as a percentage] were found to be <5%.

Echocardiography

Transthorasic echocardiography was performed in all patients in the left lateral decubitus position by a

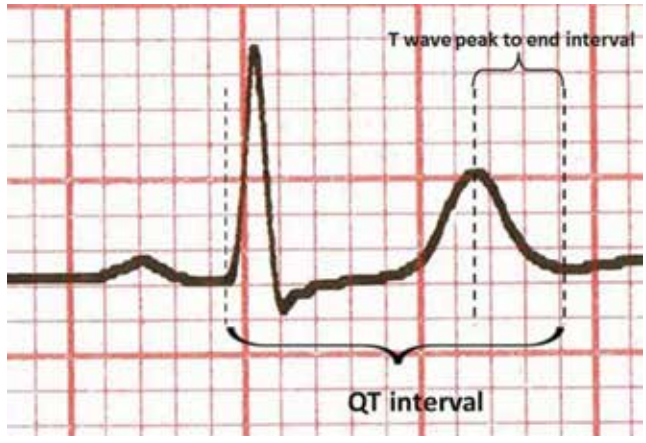


Figure 1. Demonstration of Tp-e and QT intervals

Vivid 3 echocardiography device (GE Medical Systems, USA). The parasternal long and short axis, apical four- and two-chamber images were taken and evaluated according to the criteria of the American Society of Echocardiography (12).

Statistics Analysis

The normal distribution of data was tested by the 1-sample Kolmogorov-Smirnov test. Continuous variables are presented as mean ± SD. Categorical variables are presented as counts. All statistical comparisons were performed using the two-sided Student's t-test. Categorical variables were compared using the chi-square test or Fisher's exact test for small samples. Pearson's correlation was used for numerical data. Spearman's correlation was used for nominal data. A p value of less than 0.05 was considered statistically significant. Multivariate logistic regression model was performed to determine the effect of independent risk factors for prolonged Tp-e interval. Statistical analyses were performed using SPSS 22.0 software for Windows (SPSS Inc, Chicago, IL).

Results

A total of 165 patients were evaluated initially and after exclusion of 54 patients, 111 patients were included in the study. The number of patients with MB and controls was 53 and 58, respectively. The general characteristics of the study groups are shown in Table 1. 49 of the participants were female (44%) while 62 were male (56%) and the average age of the participants was 54.66±9.53 years in MB group and 60±9.15 years in the control group. Age and gender distribution did not differ between the groups. There were no significant differences between the groups in terms of baseline laboratory and clinical characteristics. The length of MB was found to be 15.1±3.7 mm in the MB patient group and the degree of diameter reduction in the bridged segments was found to be 69±15.4%. In MB group, the number of patients with critical (70% or greater stenosis) and non-critical stenosis (stenosis less than 70%) was found to be 32 (60.7%) and 21 (39.6%), respectively. No significant differences were observed in terms of conventional echocardiographic measurements between the groups ($p>0.05$) (Table 1). The QT interval and QTc were similar between the groups, however, Tp-e interval (92.72±14.72 and 79.59±12.12, respectively; $p<0.001$), Tp-e/QT (0.24±0.041 and 0.21±0.025,respectively; $p<0.001$) and Tp-e/QTc (0.22±0.037 and 0.19±0.025, respectively; $p<0.001$) ratio were found to be significantly increased in MB group compared to the control group (Table 1). In the comparison of the MB patients with critical and noncritical stenosis, Tp-e interval (100.69±10.79, 80.57±11.25, respectively; $p<0.001$) and Tp-e/QT (0.266±0.033, 0.219±0.037, respectively; $p<0.001$) and Tp-e/QTc (0.244±0.029, 0.196±0.027, respectively; $p<0.001$) ratios were higher in the MB with critical stenosis group compared to the ones with noncritical stenosis (Table 2). There was not any statistically significant difference between control and MB with noncritical stenosis groups in terms of ECG parameters. Multivariate analysis demonstrated that the degree of diameter reduction (standardized b coefficient=0.681; $p<0.001$) is an independent predictor of a prolonged Tp-e interval in the multivariate stepwise logistic regression model (Table 3).

Discussion

Our study is important as it showed significantly increased Tp-e interval and Tp-e/QT and Tp-e/QTc ratios in MB patients with angiographically detected critical stenosis, although there was not any significant relationship between these parameters and bridge length. These findings can be an evidence of relationship between ventricular repolarization change and MB. These results can also contribute to the explanation of pathophysiologic mechanisms of ventricular arrhythmias and the increase in the prevalence of sudden cardiac death among patients with MB.

In some studies, it was shown that increased repolarization dispersion alone can lead to ventricular arrhythmias (13,14). In a study by İlgenli et al. (15) the ventricular arrhythmias were reported to have a significant correlation with longer Tp-e intervals.

The duration of action potential (AP) is longer in midmyocardial M cells than in the other myocardial cells (16). The repolarization is completed first in epicardial cells. The end of epicardial AP indicates the peak of the T wave and the end of the midmyocardial AP indicates the end of the T wave. As a result, the Tp-e interval shows the transmural dispersion of repolarization (16). In previous studies, the relationship of increased Tp-e interval with Brugada syndrome, myocardial infarction treated by primary percutaneous coronary intervention (PCI), long QT syndrome, hypertrophic cardiomyopathy (HCM) (11-14), obstructive sleep apnea syndrome (17), mitral valve prolapsus (10), heavy smoking (15), and exercise in MB patients (18), was studied.

The characteristic angiographic finding of MB is systolic stenosis (milking effect). On the other hand, the intracoronary ultrasound and Doppler studies have shown that coronary obstruction also involves the diastolic period. Additionally, these studies indicated that a decrease in systolic minimal lumen diameter (MLD) greater than 70% and a decrease in mid to late diastolic MLD more than 35% indicate a significant obstruction in the bridged segment (19,20). Exercise and emotional stress increase

heart rate and contractility leading to increased oxygen demand. These conditions can trigger ischemia in patients with MB.

The data about the relationship between MB and atherosclerosis is scant. In contrast to the location of the MB, the proximal part of the bridged segment has been reported to be more prone to the atherosclerotic process (21). Two main reasons for atherosclerosis in the proximal part have been shown to be increased shear stress on the vessel wall and distribution of blood flow (22). Additionally, the vasoactive agents (endothelin-1, endothelial nitric oxide synthase, angiotensin-converting

Table 1. Demographic, clinical and laboratory characteristics of the myocardial bridge and control groups

Variables	Control group (n=58)	MB group (n=53)	p
Age, years	60±9.15	54.66±9.53	0.131
Gender, male %	56	54.7	0.825
White blood cell count, $10^3/mm^3$	9.1±1.25	9.1±1.3	0.690
Hemoglobin, gr/L	13.33±0.83	13.36±0.82	0.887
Hemotocrit	38.9±2.35	38.93±2.33	0.993
Platelet count, $/mm^3$	220±84	228±84.26	0.553
Creatinine, mg/dL	0.69±0.17	0.69±0.17	0.848
Triglyceride, mg/dL	156.88±22.75	157.28±22.17	0.948
Total cholesterol, mg/dL	188.67±15.95	188.62±15.75	0.988
HDL, mg/dL	40.52±2.77	40.74±2.71	0.558
LDL, mg/dL	111.33±11.83	111.92±13.06	0.896
Glucose, mg/dL	86.86±7.29	87.25±7.17	0.687
Na, mmol/L	139.34±3.27	139.91±3.2	0.410
K, mmol/L	4.5±0.35	4.62±0.38	0.564
Ca, mg/dL	9.27±0.45	9.19±0.44	0.328
Systolic BP, mmHg	121.12±10.84	124.62±14.23	0.248
Diastolic BP, mmHg	78.19±4.83	79.43±5.34	0.282
Heart rate, beat/min	78.98±12.55	79.23±12.43	0.903
LVEDD, mm	48.21±2.19	48.23±2.22	0.905
LVESD, mm	31.88±4.11	31.92±4.12	0.961
LVEF, %	61.02±2.98	60.96±3.006	0.905
LA, mm	33.78±1.82	34.06±1.86	0.455
IVS thickness, mm	9.98±0.63	9.96±0.64	0.864
PW thickness, mm	9.98±0.63	9.96±0.64	0.864
Tp-e, msec	79.59±12.12	92.72±14.72	<0.001
QT, msec	368.62±21.39	375.85±25.90	0.193
QTc, msec	409.45±21.06	411.77±13.58	0.095
Tp-e/QT ratio	0.21±0.025	0.24±0.041	<0.001
Tp-e/QTc ratio	0.19±0.025	0.22±0.037	<0.001
Site of MB LAD, n (%) LCX, n (%) RCA, n (%)		 49 (92.5) 2 (3.8) 2 (3.8)	
Degree of stenosis, <70, n (%) ≥70, n (%)		 21 (39.6) 32 (60.7)	
Length of MB (mm) degree of diameter reduction (%)		15.1±3.7 69±15.4	

HDL: High-density lipoprotein, IVS: Ventricular septal, LA: Left atrium, LAD: Left anterior descending artery, LCX: Left circumflex coronary artery, LDL: Low-density lipoprotein, LVEDD: Left ventricular end-diastolic dimension, LVEF: Left ventricular ejection fraction, LVESD: Left ventricular end-systolic dimension, msec: millisecond, MB: Myocardial bridge, PW: Posterior wall, RCA: Right coronary artery, QT: QT interval, QTc: Corrected QT, Tp-e: T wave peak to end interval

enzyme) were detected to be in higher concentrations in the proximal part than in the bridged segment (23).

Another probable mechanism of ischemia in patients with MB is coronary vasospasm (24). The coronary vasospasm has been shown to be present in the proximal part of the bridged segment (25). This may be due to vasoactive agents released from this part. The recent histopathologic studies indicated that myocardial fibrosis and interstitial edema can occur in the area of MB (26). Similarly, in a report by Hostiuc et al. (27), significant myocardial fibrosis and interstitial edema were demonstrated in the bridged segment in patients who had sudden cardiac death. Death in these patients was emphasized to be related to increased electrical instability due to myocardial fibrosis.

The relationship of Tp-e interval and Tp-e/QT and Tp-e/QTc ratios with myocardial ischemia was studied previously by some researchers. Xiao et al. (28) reported a significant decrease in Tp-e and QTc intervals, and Tp-e/QT ratio in patients with ST segment elevation myocardial infarction (STEMI) after successful thrombolytic therapy. In a study by Tatlisu et al. (29), Tp-e interval was shown to be a predictor of target vessel revascularization and death in patients with STEMI.

The shortening of Tp-e interval was demonstrated in STEMI patients with successful reperfusion who were treated by primary PCI (30). Aksan et al. (18) showed a significant increase in Tp-e interval and Tp-e/QT ratio after exercise in patients with MB. The findings of these two studies indicated that the percentage of MB stenosis and length of the bridged segment are the predictors of lengthening of Tp-e interval. In contrast, in our study, we did not see any significant relationship between the length of the bridged segment and the repolarization parameters. Here, we can speculate that the length of the bridged segment may not have a more important role in producing ischemia than the degree of stenosis.

Study Limitations

The number of study population is small. More accurate results can be achieved in a larger study group. Additionally, the relationship of Tp-e interval with ventricular arrhythmia incidence could not be evaluated. As a result, the prognostic role of increase in Tp-e interval and Tp-e/QT and Tp-e/QTc ratios in this patient group remained unclear.

Conclusion

In our study, we tried to figure out the relationship between angiographically detected MB and echocardiographic repolarization parameters. The Tp-e interval and Tp-e/QT and Tp-e/QTc ratios were found to be significantly increased in MB patients with 70% or greater stenosis. As a result, the presence of critical stenosis in the bridged segment should alert the physician about the deadly complications such as ventricular arrhythmias and sudden cardiac death.

Additionally, our results may indicate that these parameters can possibly be practical ECG markers of morbidity and mortality in patients with MB.

Ethics

Ethics Committee Approval: The study has been approved by Erzurum Region Training and Research Hospital Ethics Committee. Informed Consent: written informed consent was obtained from each participant.

Peer-review: Externally peer-reviwed.

Authorship Contributions

Surgical and Medical Practices: Erkan Yıldırım, Kamuran Kalkan. Concept: Erkan Yıldırım, Emrah İpek. Design: Erkan Yıldırım, Emrah İpek. Data Collection or Processing:

Table 2. Electrocardiographic repolarization parameters in non-critical and critical stenosis groups

Variables	Non-critical stonosis (n=21)	Critical stenosis (n=32)	p
Tp-e, msec	80.57±11.25	100.69±10.79	**<0.001**
QT, msec	370.48±25.78	379.38±25.77	0.225
QTc, msec	410.19±10.46	412.81±15.37	0.497
Tp-e /QT ratio	0.219±0.037	0.266±0.033	**<0.001**
Tp-e /QTcratio	0.196±0.027	0.244±0.029	**<0.001**

msec: millisecond, QT: QT interval, QTc: Corrected QT, Tp-e: T wave peak to end interval

Table 3. Multivariate logistic regression analysis to demonstrate independent predictors of prolonged Tp-e interval

Variables	Coefficient	SE	OR (95% CI)	p
Age, years	-0.071	0.172	-0.110 (-0.457-0.236)	0.526
Degree of narrowing	0.681	0.122	0.648 (0.403-0.894)	**<0.001**
Bridging segment characteristics, length of MB (mm)	-0.139	0.503	-0.541 (-1.551-0.469)	0.287

MB: Myocardial bridge, OR: Odds ratio, SE: Standart error, CI: Confident interval

Erkan Yıldırım, Emrah İpek, Kamuran Kalkan. Analysis or Interpretation: Erkan Yıldırım, Mustafa Öztürk, Hikmet Hamur. Literature Search: Mahir Cengiz, Erkan Yıldırım. Writing: Erkan Yıldırım, Emrah İpek.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Angelini P, Trivellato M, Donis J, Leachman RD. Myocardial bridges: a review. Prog Cardiovasc Dis 1983;26:75-88.
2. Loukas M, Curry B, Bowers M, et al. The relationship of myocardial bridges to coronary artery dominance in the adult human heart. J Anat 2006;209:43-50.
3. Qian JY, Zhang F, Dong M, et al. Prevalence and characteristics of myocardial bridging in coronary angiogram-data from consecutive 5525 patients. Chin Med J(Engl) 2009;122:632-5.
4. Möhlenkamp S, Hort W, Ge J, Erbel R. Update on myocardial bridging. Circulation 2002;106:2616-22.
5. Morales AR, Romanelli R, Boucek RJ. The mural left anterior descending coronary artery, strenuous exercise and sudden death. Circulation 1980;62:230-7.
6. Bestetti RB, Costa RS, Zucolotto S, Oliveira JS. Fatal outcome associated with autopsy proven myocardial bridging of the left anterior descending coronary artery. Eur Heart J 1989;10:573-6.
7. Kors JA, Ritsema van Eck HJ, van Herpen G. The meaning of the Tp-Te interval and its diagnostic value. J Electrocardiol 2008;41:575-80.
8. Gupta P, Patel C, Patel H, et al. T(p-e)/QT ratio as an index of arrhythmogenesis. J Electrocardiol 2008;41:567-74.
9. Day CP, McComb JM, Campbell RW. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. Br Heart J 1990;63:342-4.
10. Yontar OC, Karaagac K, Tenekecioglu E, Tutuncu A, Demir M, Melek M. Assessment of ventricular repolarization inhomogeneity in patients with mitral valve prolapse: value of T wave peak to end interval. Int J Clin Exp Med 2014;7:2173-8.
11. Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol 2006;47:1828-34.
12. Zhao X, Xie Z, Chu Y, et al. Association between Tp-e/QT ratio and prognosis in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Clin Cardiol 2012;35:559-64.
13. Topilski I, Rogowski O, Rosso R, et al. The morphology of the QT interval predicts torsade de pointes during acquired bradyarrhythmias. J Am Coll Cardiol 2007;49:320-8.
14. Shimizu M, Ino H, Okeie K, et al. T-peak to T-end interval may be beter predictor of high-risk patients with hypertrophic cardiomyopathy associated with a cardiac troponin I mutation than QT dispersion. Clin cardiol 2002;25:335-9.
15. İlgenli TF, Tokatlı A, Akpınar O, Kılıçaslan F. The effects of cigarette smoking on the Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio. Adv Cli Exp Med 2015;24:973-8.
16. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. Circulation 1998;98:1928-36.
17. Kilicaslan F, Tokatli A, Ozdag F, et al. Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio are prolonged in patients with moderate and severe obstructive sleep apnea. Pacing Clin Electrophysiol 2012;35:966-72.
18. Aksan G, Nar G, İnci S, et al. Exercise-induced repolarization changes in patients with isolated myocardial bridging. Med Sci Monit 2015;21:2116-24.
19. Schwarz ER, Klues HG, vom Dahl J, Klein I, Krebs W, Hanrath P. Functional characteristics of myocardial bridging. A combined angiographic and intracoronary doppler flow study. Eur Heart J 1997;18:434-42.
20. Bourassa MG, Butnaru A, Lesperance J, Tardif JC. Symptomatic myocardial bridges: overview of ischemic mechanisms and current diagnostic and treatment strategies. J Am Coll Cardiol 2003;41:351-9.
21. Ishii T, Asuwa N, Masuda S, Ishikawa Y. The effects of a myocardial bridge on coronary atherosclerosis and ischemia. J Pathol 1998;185:4-9.
22. Ge J, Eebel R, Görge G, Haude M, Meyer J. High wall shear stres proximal to myocardial bridging and atherosclerosis. İntracoronary ultrasound and pressure measurements. Br Heart 1995;73:462-5.
23. Masuda T, Ishikawa Y, Akasaka Y, Itoh K, Kiguchi H, Ishii T. The effect of myocardial bridging of the coronary artery on vasoactive agents and atherosclerosis localization. J Pathol 2001;193:408-14.
24. Maseri A, Beltrame JF, Shimokawa H. Role of coronary vasoconstriction in ischemic heart disease an search for novel therapeutic targets. Circ J 2009;73:394-403.
25. Ciampricotti R, el Gamal M. Vasospastic coronary occlusion associated with a myocardial bridge. Catheter Cardiovasc Diagn 1988;14:118-20.
26. Brodsky SV, Roh L, Ashar K, Braun A, Ramaswamy G. Myocardial bridging of coronary arteries: a risk factor for myocardial fibrosis? Int J Cardiol 2008;124:391-2.
27. Hostiuc S, Curca GC, Dermangiu D, Dermengiu S, Hostiuc M, Rusu MC. Morphological changes associated with hemodynamically significant myocardial bridges in sudden cardiac death. Thorac Cardiovasc Surg 2011;59:393-8.
28. Xiao WT, Wang XP, Gao CY, et al. Predictive value of corrected QT interval, corrected Tp-e interval and Tp-e/QT ratio on malignant arrhythmia events in acute ST-segment elevation myocardial infarction patients undergoing thrombolysis. Zhonghua Xin Xue Guan Bing Za Zhi 2012;40:473-6.
29. Tatlisu MA, Özcan KS, Güngör B, et al. Can the T-peak to T-end interval be a predictor of mortality in patients with ST-elevation myocardial infarction? Coron Artery Dis 2014;25:399-404.
30. Eslami V, Safi M, Taherkhani M, Adibi A, Movahed MR. Evaluation of QT, QT dispersion, and T-wave peak to end time changes after primary percutaneous coronary intervention in patients presenting with acute ST-elevation myocardial infarction. J Invasive Cardiol 2013;25:232-4.

Original Article / *Özgün Araştırma*

DOI: 10.4274/haseki.3194
Med Bull Haseki 2017;55:27-31

How Much Extent can We Rely on Partial Sampling of Radical Prostatectomy Specimens?

Radikal Prostatektomi Materyallerinde Parsiyel Örnekleme Yöntemi Ne Kadar Güvenilir?

Tuba Dilay Kökenek Ünal, Ayşe Selcen Oğuz Erdoğan*, Nesrin Gürçay**, Murat Alper**

Kayseri Training and Research Hospital, Clinic of Pathology, Kayseri, Turkey
**Ankara Children's Hematology and Oncology Hospital, Clinic of Pathology, Ankara, Turkey*
***Dışkapı Yıldırım Beyazıt Training and Research Hospital, Clinic of Pathology, Ankara, Turkey*

Abstract

Aim: Prostatic adenocarcinoma is the most common cancer among men in the world and prostatectomy specimens are one of the most commonly encountered materials in pathology laboratories. Histopathological evaluation of radical prostatectomy specimens provides very important prognostic parameters to predict patient's prognosis and to choose an appropriate treatment. There is no globally accepted standard grossing method for radical prostatectomy materials. Different grossing protocols are preferred in different centers considering financial condition, storage spaces, number of technicians and pathological workload.

Methods: In this study, we evaluated 50 radical prostatectomy specimens using total and partial sampling methods and compared the results.

Results: As a result of the partial sampling method the number of blocks per case was reduced prominently, and depending on this workload and financial burden also reduced. The correlation between total and partial sampling methods was statistically significant.

Conclusion: Partial sampling method can be a choice of grossing of radical prostatectomy specimens with the help of macroscopic, clinical and radiological findings.

Keywords: Prostate, radical prostatectomy, sampling methods

Öz

Amaç: Prostatik adenokarsinomlar dünyada erkeklerde görülen kanserler arasında en yaygın olarak görülen kanser olup radikal prostatektomi materyalleri patoloji laboratuvarlarında en çok takibe alınan materyallerin başında gelmektedir. Prostatektomi materyallerinin histopatolojik incelemesi sonucunda elde edilen prognostik parametreler hastalığın seyri ve uygulanacak tedavi yöntemi konusunda klinisyene yol göstermektedir. Radikal prostatektomi materyalleri için dünya çapında kabul görmüş tek bir örnekleme yöntemi bulunmamaktadır. Farklı merkezlerde farklı yöntemler tercih edilmektedir. Bu tercihte mali sorunlar, arşivleme kapasitesi, personel sayısı gibi faktörler rol oynamaktadır.

Metod: Bu çalışmada kliniğimize kabul edilen 50 radikal prostatektomi materyali total ve parsiyel örnekleme yöntemi ile değerlendirilerek sonuçlar karşılaştırılmıştır.

Bulgular: Parsiyel örnekleme yöntemi sonucunda elde edilen blok sayısında belirgin ve dolayısıyla iş yükünde ve mali yükte bir azalma görülürken sonuçların istatistiksel olarak korelasyon gösterdiği sonucuna varıldı.

Sonuç: Çalışmamız göstermiştir ki, parsiyel örnekleme yöntemi ile klinik için önemli olan parametrelere ulaşılabilmektedir ve klinik ve radyolojik bulgulardan da destek alınarak radikal örnekleme yerine tercih edilebilecek bir yöntemdir.

Anahtar Sözcükler: Prostat, radikal prostatektomi, örnekleme yöntemler

Address for Correspondence/Yazışma Adresi: Tuba Dilay Kökenek Ünal
Kayseri Training and Research Hospital, Clinic of Pathology, Kayseri, Turkey
E-mail: tubadilay@gmail.com
Received/Geliş Tarihi: 21 March 2016 **Accepted/Kabul Tarihi:** 23 May 2016

This study was presented in part as poster presentation at 24th European Congress of Pathology, which was held on 8-12 September 2012, in Prague and published in part in Virchows Archiv. 2012;(Suppl 1): S291.

Introduction

Prostatic adenocarcinoma is the most common cancer and second leading cause of cancer death among men in the world (1). The incidence of prostate cancer in early stage had been sharply increased at the end of twentieth century as a result of efficiency of modern cancer scanning programs detecting asymptomatic diseases and developing awareness of the disease (1). Radical prostatectomy is an initial and the most important step in the treatment of prostatic adenocarcinoma because only accurate pathological examination of specimens provides important diagnostic, prognostic, and therapeutic clues. Therefore, there is a considerable increase in the number of radical prostatectomy specimens in pathology laboratories of university and research hospitals. Several different sampling methods are recommended by surgical pathology text books, grossing manuals, and published working group reports. Histopathological evaluation of prostatectomy materials provides important pathologic information such as Gleason score, margin status, and pathologic stage which are crucial for selecting adjuvant therapy and for determining the prognosis (2). Preferred sampling method should provide all these necessary parameters. The 2009 International Society of Urological Pathology (ISUP) Consensus Conference put emphasis on cost restraints and time consuming procedures of total embedding and left to the pathologist's decision and recommended some strict protocols to be followed if partial embedding will be used (3). A survey conducted by the American Society of Clinical Pathologists concluded that only 12% of pathologists used entire sampling method (4). Another survey performed in our country, Turkey, revealed that 57% of our pathologists embeded entire gland (5). Total embedding is a costly and time-consuming procedure and causes increased workload in all sampling, blocking, staining, scanning and archiving stages. The aim of this study was to compare the results of total and alternative sampling methods in radical prostatectomy specimens and to investigate the reliability of alternative sectioning methods in terms of key pathologic prognostic parameters.

Methods

With the approval of institutional review board of Dışkapı Yıldırım Beyazıt Training and Research Hospital (approval ID: 230515.21/17), 50 patients, who underwent radical prostatectomy with the diagnosis of acinar prostatic adenocarcinoma between 2009 and 2011, were randomly included in this study. Originally all samples were assessed according to total embedding protocol as summarized below. Formalin-fixed surgical specimens were weighed, measured and inked carefully. The apical and basal margins were sectioned parallel to the urethra in 5 mm thickness and serially resected perpendicular to the inked margin. Seminal vesicles and ducts were totally embedded. After that, serial transverse sections of 3-5 mm thickness were made. The sections were evaluated carefully for macroscopically identifiable tumor and dissected into four quadrants as right posterior, left posterior, right anterior and left anterior segments. Each segment was blocked separately and named precisely. Average block number was 38 per case.

All tumor samples were evaluated for key pathologic parameters, such as Gleason score, presence of perineural invasion, extraprostatic extension and pathologic stage.

Then, all cases were reevaluated with selected slides in accordance with partial sampling method by two other pathologists. The limited sampling method was built to include haematoxylin and eosin stained slides representing the whole slice which were selected by skipping every other slice beginning from apical portion as forming an alternate slicing. Slides representing apical margins, bladder neck margins and seminal vesicles were retained. Selection of blocks according to alternate slice method resulted in an average of 22 blocks per case.

Results

The sampled surgical specimens weighed 45.54 g on average (range: 21-75 g). The specimens were sectioned into 7-12 slices (mean: 7.32). The macroscopic features of the surgical specimens are summarized in Table 1. 37% reduction was achieved in the number of blocks (Table 2). The sensitivity of partial sampling method for Gleason score 7 was 87.5%, but the sensitivity of partial sampling method for Gleason score ≥7 was 8% 4. However, the specificity of alternative method for Gleason score ≤7 was 44% (Table 3). For extraprostatic extension, the sensitivity and specificity rates were 61.5% and 100%, respectively. The correlation rates between two sampling methods were 70.3%, and 60%, respectively for extraprostatic extension and pathologic stages. There was complete correlation in surgical margin and perineural invasion evaluation between the two sampling methods. Alternative slicing and total sampling methods provided identical pathologic stage in 76% of cases (Table 4). All correlation rates were statistically significant ($p<0.001$).

Statistical Analysis

Statistical analysis was performed by using SPSS for Windows Version 15.0 Software Package and Cohen's Kappa statistics was used to measure the agreement of two sampling methods.

Discussion

Radical prostatectomy specimens are one of the most common materials which pathologists encounter in routine

practice. For grossing radical prostatectomy specimens, many protocols and recommendations have been proposed, but general consensus has not been achieved yet (3,6-11). Although recent conference of the ISUP concluded that partial methods were also acceptable (3), there are still controversies on partial sampling of radical prostatectomy materials. In macroscopic examination, recognizing tumoral areas is often difficult, especially in early stages (12-14). Therefore, some pathologists prefer total embedding as the safest method (5,13). On the other hand, many studies revealed that limited sample methods also provided key histopathologic parameters (14-17). In terms of partial sampling of radical prostatectomy materials, there are many different approaches (14,18). In the presence of grossly visible tumor, it is recommended to embed proximal and distal margins, seminal vesicles, visible tumors with relevant margins and susceptible other tumor foci (19). Some guidelines also recommend embedding of the posterior aspects of every transverse slice and single mid anterior slice form each side in addition to proximal and distal margins and seminal vesicles in the absence of grossly visible tumor (19). In this study, we preferred to perform alternate slicing method as one of the partial sampling methods. It is a simple, easy-to-use method and allows the pathologist or inexperienced residents good orientation of unsampled tissue in case of necessity. In the case of macroscopically identifiable tumor, it can be appropriate to include extra blocks representing all tumoral or suspected areas. In some centers, digital images of gross specimens are taken and saved (20). It is also a useful method to reevaluate macroscopic appearance of slices in some circumstances.

Table 1. Macroscopic features of surgical specimens

	Mean	Median	Standard deviation	Minimum	Maximum
Weight	45.54 gr	42.50 gr	13.964 gr	21 gr	75 gr
Number of slices	7.32	7.00	1.285	5	12
The largest diameter	5.06 cm	5.00 cm	1.018 cm	3 cm	9 cm

gr: Gram, cm: Centimeter

Table 2. The number of blocks per specimen

	Mean (n)	Median (n)	Standard deviation (n)	Number of blocks per specimen	
				Minimum	Maximum
Total sampling	37.98	35.50	7.795	27	61
Partial sampling	22.56	22.00	4.643	10	33

n: number

Table 3. Gleason scores achieved by total and partial sampling method

		Gleason score (total sampling) (p)			
		2-6	7	8-10	Total (n)
Gleason score (partial sampling) (p)	2-6	10	3	0	12
	7	8	21	6	35
	8-10	0	0	2	2
Total (n)		18	24	8	50

n: number of cases, p: points

Table 4. Pathologic grades achieved by total and partial sampling method

		Pathologic stage (total sampling) (n)				
		T2a	T2c	T3a	T3b	Total (n)
Pathologic stage (partial sampling) (n)	T2a	7	3	1	0	11
	T2c	1	24	2	3	30
	T3a	0	0	2	2	4
	T3b	0	0	0	5	5
Total (n)		8	27	5	10	50

n: Number of cases

In addition, in the presence of preoperative needle biopsy reports, additional samples from positive quadrants can be taken. In comparison with total embedding method, the alternate slicing method successfully estimated all histopathologic predictive parameters and had a statistically significant correlation with total sampling in our study. We obtained identical Gleason score in 34 of the cases (68%). When we consider interobserver variability and reproducibility levels for Gleason scoring, this partial sampling method provided good correlation (21). We obtained complete correlation in perineural invasion and surgical margin evaluation between the two methods. Partial sampling method was failed to detect extraprostatic extension only in five of the cases (10%). However, we assume that it is a reasonable result, because there was no complete concordance in interpretation of extraprostatic extension among even expert pathologists (22). In addition to that, partial sampling method is a very practical and time-saving method providing an important reduction in block numbers and reducing financial costs in pathology laboratories.

Conclusion

In conclusion, although the limited sampling protocol provides statistically significant results, because of the critical role of pathological assessment in the treatment of prostatic adenocarcinoma, it can be found unsatisfactory by some pathologists. However, we think that with the help of advanced radiologic modalities, and macroscopic and clinical findings, an alternate slicing method can be preferred and it can provide key prognostic parameters.

Ethics

Ethics Committee Approval: This study was approved by Ethics Committee of Board of Dışkapı Yıldırım Beyazıt Training and Research Hospital with approval ID: 230515.21/17. Informed Consent: It was taken.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Tuba Dilay Kökenek Ünal, Ayşe Selcen Oğuz Erdoğan, Nesrin Gürçay. Concept: Tuba Dilay Kökenek Ünal, Ayşe Selcen Oğuz Erdoğan, Murat Alper. Design: Tuba Dilay Kökenek Ünal, Ayşe Selcen Oğuz Erdoğan, Murat Alper. Data Collection or Processing: Tuba Dilay Kökenek Ünal. Analysis or Interpretation: Tuba Dilay Kökenek Ünal, Ayşe Selcen Oğuz Erdoğan. Literature Search: Tuba Dilay Kökenek Ünal, Nesrin Gürçay. Writing: Tuba Dilay Kökenek Ünal.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29.
2. Kench JG, Clouston DR, Delprado W, et al. Prognostic factors in prostate cancer. Key elements in structured histopathology reporting of radical prostatectomy specimens. Pathology 2011;43:410-9.
3. Samaratunga H, Montironi R, True L, et al. International society of urological pathology (ISUP) consensus conference on handling and staging of radical prostatectomy specimens. working group 1: specimen handling. Mod Pathol 2011;24:6-15.
4. True LD. Surgical pathology examination of the prostate gland. Practice survey by American society of clinical pathologists. Am J Clin Pathol 1994;102:572-9.
5. Doganavsargil B, Nalbantoglu I, Hekimgil M. Handling and reporting of radical prostatectomy specimens: A practice survey among pathologists. Turkish Journal of Pathology 2007;23:74-81.
6. Egevad L. Handling of radical prostatectomy specimens. Histopathology 2012;60:118-24.
7. Gill PS, Roberts IS, Browning L, et al. The handling and sampling of radical prostatectomy specimens for reporting and research: the Oxford approach. J Clin Pathol 2012;65:1057-61.
8. Ohori M, Kattan M, Scardino PT, Wheeler TM. Radical prostatectomy for carcinoma of the prostate. Mod Pathol 2004;17:349-59.
9. Sung MT, Davidson DD, Montironi R, Beltran AL, Cheng L. Radical prostatectomy specimen processing: A critical appraisal of sampling methods. Diagn Histopatol 2007;13:490-8.
10. Sringley JR. Key issues in handling and reporting radical prostatectomy specimens. Arch Pathol Lab Med 2006;130:303-17.
11. Montironi R, Van der Kwast T, Boccon-Gibod L, Bono AV, Boccon-Gibod L. Handling and pathology reporting of radical prostatectomy specimens. Eur Urol 2003;44:626-36.
12. Renshaw AA. Correlation of gross morphologic features with histologic features in radical prostatectomy specimens. Am J Clin Pathol 1998;110:38-42.
13. Bell KB, Kida M, Cooper K. Histopathology sampling of radical prostatectomy specimens: representative or entire submission? Histopathology 2011;59:1013-4.
14. Sehdev AE, Pan CC, Epstein JI. Comparative analysis of sampling methods for grossing radical prostatectomy specimens performed for nonpalpable (stage T1c) prostatic adenocarcinoma. Hum Pathol 2001;32:494-9.
15. Kim K, Pak PJ, Ro JY, Shin D, Huh SJ, Cho YM. Limited sampling of radical prostatectomy specimens with excellent preservation of prognostic parameters of prostate cancer. Arch Pathol Lab Med 2009;133:1278-84.
16. Llanos CA, Blieden C, Vernon SE. Processing radical prostatectomies: an alternate-slice method is comparable with total embedding. Ann Diagn Pathol 2012;16:284-7.

17. Vainer B, Toft BG, Olsen KE, Jacobsen GK, Marcussen N. Handling of radical prostatectomy specimens: total or partial embedding? Histopathology 2011;58:211-6.
18. Doganavsargil B, Hekimgil M, Simsir A, Cal C, Soydan S. A study on histological prognostic factors and partial sampling methods in radical prostatectomy. Ege J Med 2002;41:133-41.
19. Association of Clinical Pathologists. Guidelines for the macroscopic processing of radical prostatectomy and pelvic lymphadenectomy specimens. J Clin Path 2008;61:713-21.
20. Trpkov K, Warman L. Use of digital maps and sampling of radical prostatectomy specimens. Arc Pathol Lab Med 2006;130:1751-2.
21. Kuroiwa K, Shiraishi T, Ogawa O, et al. Discrepancy between local and central pathological review of radical prostatectomy specimens. J Urol 2010;183:952-7.
22. Evans AJ, Henry PC, Van der Kwast TH, et al. Interobserver variability between expert urologic pathologists for extraprostatic extension and surgical margin status in radical prostatectomy specimens. Am J Surg Path 2008;32:1503-12.

Original Article / *Özgün Araştırma*

DOI: 10.4274/haseki.3278
Med Bull Haseki 2017;55:32-6

Which Criteria are More Valuable in Defining Hemodynamic Significance of Patent Ductus Arteriosus in Premature Infants? Respiratory or Echocardiographic?

Prematüre Bebeklerde Hemodinamik Anlamlı Patent Duktus Arteriyozusun Tanımlanmasında Hangi Kriterler Daha İyidir? Solunumsal mı Ekokardiyografik mi?

İrfan Oğuz Şahin, Canan Yolcu, Ayşegül Elbir Şahin*, Mustafa Kara**, Yaşar Demirelli**, Haşim Olgun, Naci Ceviz

Atatürk University Faculty of Medicine, Department of Pediatric Cardiology, Erzurum, Turkey
**Palandöken State Hospital, Clinic of Anesthesiology and Reanimation, Erzurum, Turkey*
***Atatürk University Faculty of Medicine, Department of Neonatology, Erzurum, Turkey*

Abstract

Aim: Patent ductus arteriosus (PDA) is a frequent health problem in premature infants. Pharmacologic closure is recommended only for hemodynamically significant PDA (hsPDA) that is defined according to the clinical and echocardiographic criteria. The aim of this study was to explore the value of commonly used criteria in defining hsPDA and predicting the required number of courses of ibuprofen treatment to close PDA in premature infants.

Methods: Sixty premature infants with a gestational age of ≤33 weeks were evaluated prospectively. Clinical and echocardiographic criteria [O_2 requirement, ductus diameter (DD) and left atrial-to-aortic root diameter ratio (LA:Ao)] were used to define hsPDA. Clinical improvement after pharmacologic closure of PDA and association between the criteria and required number of ibuprofen courses were investigated.

Results: O_2 requirement decreased by PDA closure but was not different between patients with hsPDA and the others with PDA. Also, O_2 requirement was not found to be associated with required number of ibuprofen courses. DD and LA:Ao were greater in patients with hsPDA. DD was found to be associated with required number of courses of ibuprofen treatment.

Conclusion: Although there was an improvement in O_2 requirement with PDA closure, echocardiographic criteria were found to be more valuable in defining hsPDA. DD should also be used to estimate the duration of treatment.

Keywords: Criteria, patent ductus arteriosus, prematurity

Öz

Giriş: Patent duktus arteriyozus (PDA) prematüre bebeklerde sık karşılaşılan bir problemdir. Farmakolojik kapama sadece klinik ve ekokardiyografik kriterlerle tanımlanan hemodinamik anlamlı PDA (haPDA) için önerilmektedir. Bu çalışmanın amacı yaygın olarak kullanılan kriterlerin haPDA tanımlanmasındaki ve PDA kapatılması için gereken ibuprofen kür sayısını tahmin etmedeki değerini incelemektir.

Yöntemler: Gestasyonel yaşı ≤33 hafta olan 60 prematüre bebek prospektif olarak incelenmiştir. Klinik ve ekokardiyografik kriterler [O_2 ihtiyacı, duktus çapı (DÇ) ve sol atriyumun aort köküne oranı (SA:Ao)] haPDA tanımlanmasında kullanıldı. PDA'nın farmakolojik kapatılmasından sonra klinik düzelme olması ve kriterler ile gereken ibuprofen kür sayıları arasındaki ilişki incelendi.

Bulgular: O_2 ihtiyacı PDA kapanması ile azalmakla birlikte bu azalma haPDA olan bebeklerde diğer PDA olan bebeklerden farklı değildi. Ayrıca O_2 ihtiyacı ile gereken ibuprofen kür sayısı arasında ilişki bulunmadı. DÇ ve SA:Ao haPDA olan bebeklerde daha büyüktü. DÇ gereken ibuprofen kür sayısı ile ilişkili bulundu.

Sonuç: PDA kapanması ile O_2 ihtiyacında düzelme görülmekle birlikte ekokardiyografik kriterler haPDA tanımlanmasında daha değerli bulunmuştur. DÇ ayrıca tedavi süresini tahmin etmede kullanılabilir.

Anahtar Sözcükler: Kriterler, patent duktus arteriyozus, prematürite

Address for Correspondence/Yazışma Adresi: İrfan Oğuz Şahin
Atatürk University Faculty of Medicine, Department of Pediatric Cardiology, Erzurum, Turkey
Phone: +90 362 311 40 40 E-mail: rfnshn@yahoo.com
Received/Geliş Tarihi: 18 May 2016 **Accepted/Kabul Tarihi:** 22 June 2016

Introduction

Ductus arteriosus (DA) is the arterial structure between the pulmonary artery and aorta and normally closes spontaneously after birth (1). Patent ductus arteriosus (PDA) is a congenital abnormality in which DA remains open and it is a frequent problem in neonatology units, especially among preterm infants (2). The incidence of PDA is inversely proportional to gestational age (GA) (3). PDA occurs in about one-third of preterm infants, two-thirds of extremely low-birth-weight infants and 75% of those born before 28 weeks of gestation (4-6).

Hemodynamically significant PDA (hsPDA) can result in congestive heart failure, pulmonary edema-bleeding, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, feeding intolerance, and retinopathy in premature infants (7).

The safety and efficacy of closing PDA by pharmacologic agents and surgery are well defined. However, there is not a complete consensus on patient selection and optimal method and timing for closing PDA in premature infants. Also, long-term benefits of closing PDA are still controversial (8). Therefore, PDA treatment strategies differ between centers. The decision whether, when, or how to administer therapies to close PDA in premature infants remains challenging (9). Treatment is commonly prescribed for hsPDA (10).

Most centers use clinical criteria [(a) respiratory signs, including increased respiratory support, failure to wean from respiratory support or O_2 need; (b) physical signs, including murmurs, hyperdynamic precordium or bounding pulses; (c) blood pressure problems, including decreased mean or diastolic pressure or increased pulse pressure; (d) signs of congestive heart failure, including cardiomegaly, hepatomegaly or pulmonary congestion] and echocardiographic criteria [(a) a left atrial-to-aortic root diameter ratio of >1.30 (LA:Ao); (b) a ductus diameter (DD) of >1.5-2 mm] to define hsPDA but there is a wide variety of strategies used in different clinics (10).

In this study, we aimed to investigate the value of commonly used clinic (O_2 requirement) and echocardiographic (DD, LA:Ao) criteria in defining hsPDA and in predicting the required number of courses of ibuprofen treatment to close PDA in premature infants.

Methods

This prospective study was performed in the neonatology department at Atatürk University Faculty of Medicine between October 2011 and April 2013. The study was approved by the local ethics committee. Premature infants with a GA of ≤33 weeks who had hsPDA or insignificant PDA (hiPDA) were included in the study.

Clinical and echocardiographic evaluations were performed to define hsPDA in cooperation with neonatology and pediatric cardiology physicians. We used respiratory problems (respiratory distress, increased O_2 or ventilation requirements, tachypnea, hypoxia, and apnea without an evident reason) as clinical criteria and large ductal size (>1.5 mm) and increased LA:Ao (>1.4) as echocardiographic criteria. M-mode images of the left atrium and aortic root were obtained from a parasternal long-axis view. Ductal sizes were obtained by both B-mode and color Doppler from the high left parasternal view but predominantly the narrowest diameter of color Doppler flow in parasternal short axis view was used to determine the ductal diameter because it is hard to achieve reliable anatomic measurements with B-mode.

Premature infants with hiPDA were followed up only with conservative approaches. In the absence of contraindications, enteral ibuprofen was used to close hsPDA in 60 premature infants.

Enteral ibuprofen was administered via nasogastric tube as courses. Three doses (10, 5 and 5 mg/kg) were accepted as one course and the treatment protocol consisted of up to 3 courses (9 doses). Echocardiographic evaluations were performed after courses. In case of hsPDA continuation after 3 courses, patients were referred for surgical closure.

GA, mechanical ventilation parameters, DD, and LA:Ao were recorded during treatment. Echocardiographic investigations were performed by the same physician with a Vivid 7 echocardiography device (General Electric, USA®) and 10S probe.

Statistical Analysis

Descriptive methods (frequency, percentage, mean, standard deviation) were used to analyze data and the Kolmogorov-Smirnov test to analyze normality of distribution. Pearson's chi-square test and Fisher's exact tests were used for comparison of qualitative data. The independent samples t-test was used for quantitative comparison of data between two groups. One-way ANOVA was used for comparison of data between groups more than two. The results were analyzed at a 95% confidence interval and a p value of less than 0.05 was considered statistically significant.

Results

53.3% (32/60) and 48.4% (30/62) of subjects were female and 46.7% (28/60) and 51.4% (32/62) were male in hsPDA and hiPDA groups, respectively (p=0.076). The mean GA was 29.18 and 29.76 weeks in hsPDA and hiPDA groups, respectively (p=0.125). In two patients, ibuprofen was contraindicated due to necrotizing enterocolitis (one had trombocytopenia also). In these

patients, successful pharmacologic closure was achieved with paracetamol. Oxygen need was not significantly different between premature infants with hiPDA and hsPDA before PDA closure (Table 1). However, there was a significant difference in O_2 requirement of patients after PDA was closed pharmacologically (Table 2). Two patients underwent surgical closure after 3 courses of ibuprofen failed and these patients were not evaluated in terms of oxygen need. DD and LA:Ao were found to be significantly greater in patients with hsPDA and hiPDA (Table 3). There was no significant relationship between the required number of ibuprofen courses to close PDA and O2 requirement or LA:Ao in patients but DD was found to be significantly higher in patients who required 2 and 3 courses than in those required 1 (Table 4).

Discussion

The relationship of PDA and associated morbidities with utility of closing PDA pharmacologically is subject of discussion and closing PDA pharmacologically is not a standard recommendation for premature infants. Clinicians should weigh the risks associated with medications to close PDA versus PDA. The decision of pharmacologic treatment should be based on hemodynamic significance of PDA but this is not always easy to identify (3,11). Many criteria have been used to define hsPDA in premature infants.

In recent publications, it has been shown that electrocardiographic and radiological criteria were nonspecific. Clinical (respiratory signs, physical signs, blood pressure problems, congestive heart failure signs) and echocardiographic (LA:Ao>1.30 and DD>1.5-2 mm) criteria were commonly used to define hsPDAs (10). Unfortunately, the optimal criteria for defining hsPDA are lacking and there is a wide variety of strategies used in different clinics (12). Therefore, the optimal timing of pharmacological treatment for PDA in preterm infants is still controversial (13).

In a study, 29.5%, 16.7% and 53.8% of patients with hsPDA were found to be on O_2 supplement, continuous positive airway pressure and synchronized intermittent mandatory ventilation (1). In our study, O_2 requirements were not found to be different between patients with hiPDA and hsPDA (Table 1). This suggests that O_2 need was not a good criterion for defining hsPDA.

Some studies reported positive changes in lung compliance in premature infants (14,15) but some

Table 1. O_2 requirements in patients with hemodynamically insignificant patent ductus arteriosus and hemodynamically significant patent ductus arteriosus before patent ductus arteriosus closure

	hiPDA		hsPDA	
	n	%	n	%
O_2 into incubator	8	12.9	7	11.6
O_2 into hood	5	8.0	3	5.0
CPAP	38	61.3	40	66.7
SIMV	11	17.8	10	16.7
Total	62	100	60	100

hiPDA: Hemodynamically insignificant patent ductus arteriosus, hsPDA: Hemodynamically significant patent ductus arteriosus, CPAP: Continuous positive airway pressure, SIMV: Synchronized intermittent mandatory ventilation

Table 2. Difference in O_2 need of patients with hemodynamically significant patent ductus arteriosus before and after pharmacologic patent ductus arteriosus closure

	Before PDA closed		After PDA closed		p
	n	(%)	n	(%)	
O_2 into incubator	7	11.7	9	15.5	0.033
O_2 into hood	3	5	8	13.8	
CPAP	40	66.6	33	56.9	
SIMV	10	16.7	8	13.8	
Total	60	100	58[§]	100	

PDA: Patent ductus arteriosus, CPAP: Continuous positive airway pressure, SIMV: Synchronized intermittent mandatory ventilation, Two patients were not included because of surgical closure

Table 3. Ratio of left atrium to aortic root and ductal diameters of patients

	hiPDA	hsPDA	p
LA:Ao	1.11±0.48	1.36±0.27	<0.0001
Ductal diameter (mm)	1.65±0.32	2.25±0.44	<0.0001

hiPDA: Hemodynamically insignificant patent ductus arteriosus, hsPDA: Hemodynamically significant patent ductus arteriosus, LA:Ao: Ratio of left atrium to aortic root

Table 4. Relationship between O_2 requirement, ratio of left atrium to aortic root, ductal diameter and required course number of ibuprofen to close patent ductus arteriosus in patients

	1 course		2 courses		3 courses		p
	n	%	n	%	n	%	
O_2 into incubator	7	11.5	3	5.0	-	-	0.508 (χ^2=2.321)
O_2 into hood	3	5.0	1	1.7	-	-	
CPAP	32	53.3	2	3.5	1	1.7	
SIMV	7	11.5	3	5.0	1	1.7	
	1 course		2 courses		3 courses		p
LA:Ao	1.35±0.28		1.43±0.21		1.46±0.19		0.381
Ductal diameter (mm)	2.18±0.36		2.62±0.65		2.76±0.55		

CPAP: Continuous positive airway pressure, SIMV: Synchronized intermittent mandatory ventilation, LA:Ao: Ratio of left atrium to aortic root

reported no difference in respiratory parameters (16,17) after pharmacologic closure of PDA. It is hard to show the isolated effect of PDA closure on respiratory system due to co-affecting factors especially like worsening or ameliorating respiratory distress syndrome, but our study supports that a significant difference in O_2 requirement of premature infants could be provided with pharmacological PDA closure (Table 2).

Echocardiographic criteria, such as left ventricular outflow/superior vena cava flow ratio, diastolic and mean flow velocities of the left pulmonary artery, but especially DD and LA:Ao, were found to be adequate and reliable markers of hsPDA (18,19). In our study, DD and LA:Ao were found to be significantly higher in premature infants who needed treatment than in those PDA closed spontaneously (Table 3). This suggests that DD and LA:Ao reflect hemodynamic significance of PDA and could be used in estimating the necessity of pharmacologic treatment of PDA.

Response to pharmacologic agents that were administered to close PDA is related with GA and/or birth weight but do not depend only on those. Despite spontaneous ductus closure in some extremely immature premature infants, some premature large-for-gestational-age infants do not respond to one course of ibuprofen and require additional courses or surgical intervention (20,21). There are multiple factors affecting ductus closure. In our study, the number of ibuprofen courses required to close PDA was not found to be associated with O_2 requirement but with DD (Table 4). This suggests that anatomic size of PDA is the most reliable criterion in defining hsPDA and could be used to estimate the duration of treatment to close PDA.

Although high rates of pharmacologic closure are achieved with ibuprofen, it is not completely safe. Paracetamol may be a medical alternative in the management of PDA (22). Paracetamol was used successfully for PDA closure in our two patients who had contraindications for ibuprofen.

Conclusion

In conclusion, there is a need for an international consensus on criteria for defining hsPDA. Oxygen requirement of premature infants is not different between patients with hsPDA and hiPDA but decreases by PDA closure. Echocardiographic criteria seem more reliable than respiratory criteria in predicting hsPDA and, ductus diameter should also be used to estimate the duration of treatment. Further studies are needed to evaluate the value of each criterion in defining hsPDA.

Ethics

Ethics Committee Approval: Atatürk University, Ethics Committee of Medicine Faculty, 18.08.2011, meeting number 7, Decision number 19.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İrfan Oğuz Şahin, Canan Yolcu. Concept: İrfan Oğuz Şahin, Haşim Olgun, Naci Ceviz. Design: İrfan Oğuz Şahin, Canan Yolcu. Data Collection or Processing: İrfan Oğuz Şahin, Mustafa Kara, Yaşar Demirelli. Analysis or Interpretation:İrfan Oğuz Şahin, Ayşegül Elbir Şahin. Literature Search: İrfan Oğuz Şahin, Ayşegül Elbir Şahin. Writing: İrfan Oğuz Şahin, Haşim Olgun, Naci Ceviz.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Terek D, Yalaz M, Ulger Z, Koroglu OA, Kultursaray N. Medical closure of patent ductus arteriosus does not reduce mortality and development of bronchopulmonary dysplasia in preterm infants. J Res Med Sci 2014;19:1074-9.
2. Schneider DJ, Moore JW. Patent ductus arteriosus. Circulation 2006;114:1873-82.
3. Rolland A, Shankar-Aguilera S, Diomandé D, Zupan-Simunek V, Boileau P. Natural evolution of patent ductus arteriosus in the extremely preterm infant. Arch Dis Child Fetal Neonatal Ed 2015;100:55-8.
4. Hamrick SE, Hansmann G. Patent ductus arteriosus of the preterm infant. Pediatrics 2010;125:1020-30.
5. Koch J, Hensley G, Roy L, Brown S, Ramaciotti C, Rosenfeld CR. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. Pediatrics 2006;117:1113-21.
6. Narayanan M, Cooper B, Weiss H, Clyman RI. Prophylactic indomethacin: factors determining permanent ductus arteriosus closure. J Pediatr 2000;136:330-7.
7. Cambonie G, Dupuy AM, Combes C, Vincenti M, Mesnage R, Cristol JP. Can a clinical decision rule help ductus arteriosus management in preterm neonates? Acta Paediatr 2012;101:213-8.
8. Perez KM, Laughon MM. What is new for patent ductus arteriosus management in premature infants in 2015? Curr Opin Pediatr 2015;27:158-64.
9. Mitra S, Ronnestad A, Holmstrom H. Management of patent ductus arteriosus in preterm infants: where do we stand? Congenit Heart Dis 2013;8:500-12.
10. Zonnenberg I, de Waal K. The definition of a haemodynamic significant duct in randomized controlled trials: a systematic literature review. Acta Paediatr 2012;101:247-51.
11. Abdel-Hady H, Nasef N, Shabaan AE, Nour I. Patent ductus arteriosus in preterm infants: do we have the right answers? Biomed Res Int 2013;2013:676192.
12. Perez KM, Laughon MM. What is new for patent ductus arteriosus management in premature infants in 2015? Curr Opin Pediatr 2015;27:158-64.
13. Gudmundsdottir A, Johansson S, Håkansson S, Norman M, Källen K, Bonamy AK. Timing of pharmacological treatment

for patent ductus arteriosus and risk of secondary surgery, death or bronchopulmonary dysplasia: a population-based cohort study of extremely preterm infants. Neonatology 2015;107:87-92.

14. Stefano JL, Abbasi S, Pearlman SA, Spear ML, Esterly KL, Bhutani VK. Closure of the ductus arteriosus with indomethacin in ventilated neonates with respiratory distress syndrome. Effects of pulmonary compliance and ventilation. Am Rev Respir Dis 1991;143:236-69.
15. Gerhardt T, Bancalari E. Lung compliance in newborns with patent ductus arteriosus before and after surgical ligation. Biol Neonate 1980;38:96-105.
16. Krauss AN, Fatica N, Lewis BS, et al. Pulmonary function in preterm infants following treatment with intravenous indomethacin. Am J Dis Child 1989;143:78-81.
17. Morrow WR, Taylor AF, Kinsella JP, Lally KP, Gerstmann DR, deLemos RA. Effect of ductal patency on organ blood flow and pulmonary function in the preterm baboon with hyaline membrane disease. Crit Care Med 1995;23:179-86.
18. El Hajjar M, Vaksmann G, Rakza T, Kongolo G, Storme L. Severity of the ductal shunt: a comparison of different markers. Arch Dis Child Fetal Neonatal Ed 2005;90:419-22.
19. Kluckow M, Evans N. Early echocardiographic prediction of symptomatic patent ductus arteriosus in preterm infants undergoing mechanical ventilation. J Pediatr 1995;127:774-9.
20. Peckham GJ, Miettinen OS, Ellison RC, et al. Clinical course to 1 year of age in premature infants with patent ductus arteriosus: results of a multicenter randomized trial of indomethacin. J Pediatr 1984;105:285-91.
21. Tekşam Ö, Yiğit Ş, Karagöz T, et al. Oral ibuprofen and intravenous indomethacin for treatment of patent ductus arteriosus in newborn infants: retrospective study. Turk J Ped 2004;47:96-102.
22. Oncel MY, Yurttutan S, Erdeve O, et al. Oral paracetamol versus oral ibuprofen in the management of patent ductus arteriosus in preterm infants: a randomized controlled trial. J Pediatr 2014;164:510-4.

Original Article / *Özgün Araştırma*

DOI: 10.4274/haseki.3168
Med Bull Haseki 2017;55:37-41

Effect of Nitrous Oxide Anaesthesıa on Endotracheal Cuff Pressure

Anestezide Azotprotoksit Kullanımının Endotrakeal Kaf Basıncına Etkisi

Özlem Koşar, Öznur Şen*, Mehmet Toptaş*, Gamze Mısırlıoğlu**, Nurdan Aydın*, Emel Koçer Gür*, Tarık Umutoğlu***

Sivas Suşehri State Hospital, Clinic of Anesthesiology and Reanimation Sivas, Turkey
**Haseki Training and Research Hospital, Clinic of Anesthesiology, İstanbul, Turkey*
***Gebze Fatih State Hospital, Clinic of Anesthesiology, İstanbul, Turkey*
****Bezmialem Vakıf University Faculty of Medicine, Department of Anesthesiology, İstanbul, Turkey*

Abstract

Aim: When N_2O is used for general anaesthesia, it diffuses into the air-filled endotracheal cuff causing the cuff pressure to rise by over inflating the cuff, which results in tracheal damage. This study aimed to estimate changes in the endotracheal-cuff pressure with time during oxygen-air- and oxygen-N_2O-induced anaesthesia and to determine its sore throat and hoarseness incidence.

Methods: Fifty patients with American Society of Anesthesiologists physical status 1-2, aged 18-60 years were icluded to our study. Orotracheal intubation was performed using polyvinyl chloride high volume-low pressure endotracheal tubes. The AIR group 40% O_2/60% air and N_2O group 40% O_2/60% N_2O was used. The endotracheal cuff pressure at 5, 10, 15, 20 minutes immediately after intubation and at 10-minute intervals were recorded. When the cuff pressure reached 45 cm H_2O, was attenuated to 25-30-cm H_2O. At the post operative first and the 24th hour, the patients were queried for sore throat and hoarseness.

Results: The N_2O-group cuff pressure rose from the fifth minute onwards. Also, the N_2O group had a higher incidence of sore throat and hoarseness.

Conclusion: N_2O results in elevated cuff pressure and tracheal morbidities. Cuff-pressure should be routinely monitored during anaesthesia using N_2O.

Keywords: General anaesthesia, nitrous oxide, tracheal intubation, cuff pressure, tracheal morbidities

Öz

Amaç: Genel anestezide N_2O kullanıldığında, hava dolu endotrakeal kaf içine diffüze olup, kanın basıncını arttırarak trakeal hasara neden olabilir. Çalışmamızda; oksijen-azotprotoksit ile oksijen-hava kullanımının, endotrakeal kaf basıncı, postoperatif boğaz ağrısı ve ses kısıklığına etkilerinin araştırılması amaçlandı.

Yöntemler: Alt batın operasyonu geçirecek Amerikan Anestezi Derneği 1-2 grubu, 18-60 yaş arası 50 olgu çalışmaya dahil edildi. Anestezi indüksiyonundan sonra oratrakeal entübasyon polivinilklorürden yapılmış, yüksek-volüm, düşük-basınçlı, endotrakeal tüpler ile gerçekleştirildi. Azotprotoksit grubu (grup N_2O) %40 O2/%60 N_2O, hava grubuna (grup AİR) %40 O_2/%60 hava olacak şekilde anestezi idamesi sağlandı. Endotrakeal kaf basıncı entübasyondan hemen sonraki 5, 10, 15, ve 20. dakikada ve daha sonra 10 dakikalık aralarla kaydedildi. Kaf basıncı 45 cm H_2O ve üzeri olduğunda, basınç 25-30 cm H_2O ve üzeri olduğunda, basınç 2. saat ve 24 saatte boğaz ağrısının olup olmadığı sorgulandı.

Bulgular: Kaf basınçları karşılaştırıldığında, azotprotoksit grubunda beşinci dakikadan itibaren kaf basınçları giderek yüksek bulunmasına rağmen, hava grubunda basınçlarda anlamlı bir değişiklik görülmedi. Ayrıca azotprotoksit grubunda boğaz ağrısı ve ses kısıklığı daha fazla görüldü.

Sonuç: Genel anestezi sırasında uygulanan azotprotoksit, yüksek kaf basınçlarına ve buna bağlı komplikasyonlara neden olabilmektedir. Bu nedenle azotprotoksit anestezi sırasında kaf basıncı rutin olarak monitörize edilmelidir.

Anahtar Sözcükler: Genel anestezi, nitröz oksit, endotrakeal tüp kaf basıncı, boğaz ağrısı, ses kısıklığı

Address for Correspondence/Yazışma Adresi: Öznur Şen
Haseki Training and Research Hospital, Clinic of Anesthesiology, İstanbul, Turkey
Phone: +90 212 529 44 00 E-mail: senoznur@gmail.com
Received/Geliş Tarihi: 06 March 2016 **Accepted/Kabul Tarihi:** 28 June 2016

Introduction

Intubation process during anaesthesia is essential for maintaining the patent airway, control of the airway and respiration, airway control during the resuscitation procedure, reduction of the respiratory effort, dead spaces and aspiration risk, and removal of the the equipment from proximity of the surgical team facilitating their activity. Tracheal intubation is the fundamental step in controlling the airways during general anaesthesia (1).

To prevent air escape, cuffed endotracheal tubes are widely preferred in adult patients.

Endotracheal tube (ETT) cuff ensures formation of positive pressure in the airway by preventing air escape during ventilation and prevents aspiration of the pharyngeal contents (1). ETT cuffs are made of polyvinyl chloride (PVC). During general anaesthesia, N_2O penetrates the inflated cuff. Cuffs made of materials including rubber are more permeable to N_2O compared to those made of PVC (2,3). When the cuff pressure exceeds 40 cm H_2O, capillary blood flow is impeded which can cause damage to tracheal structures. If, on the other hand, cuff pressure falls below 25 cm H_2O, aspiration risk arises (4).

Reported incidence of sore throat after general anaesthesia with endotracheal intubation varies between 14.4% and 50%, making up the most frequent complication of the intubation process (5). This complaint has been ascribed to the mechanical pressure of the tube, high cuff pressure and ventilation with dry air (4). Other frequently observed complications include hoarseness and dysphagia; and when intubation time is prolonged, tracheal stenosis and tracheomalacia may also occur (5,6). In order to avoid these complications, proper ETT cuff inflation should be obtained for suitable pressure which can be easily and accurately measured with aneroid manometers; but, these gauges are not widely used in Turkey (7).

Our study aimed to monitor and compare the recorded variations of cuff pressure during anaesthesia with oxygen and N_2O mixture and with oxygen and air mixture using high volume-low pressure ETT cuffs; and to evaluate the effects of these variations on the haemodynamic parameters of blood pressure (BP), mean arterial pressure (MAP), SPO_2, peak heart rate (PHR) and post-operative damage to tracheal structures by checking hoarseness and sore throat.

Methods

This study was carried out after obtaining the approval of the ethics committee of Haseki Training and Research Hospital (İstanbul) as well as the informed consent of patients included in the study. Our patients, known to have American Society of Anesthesiologists (ASA) physical status 1-2, aged between 18 and 65 years, were scheduled for elective lower abdominal surgery. After entry into the operation room, the patients were given premedication consisting of 0.03 mg/kg midazolam. HR, systolic BP, mean BP (MBP), diastolic BP, and peripheral oxygen SpO_2 were monitored. Anaesthesia was induced by a combination of 7 mg/kg pentothal sodium, 1-2 µg/kg fentanyl citrate and 0.6 mg/kg rocuronium bromide. After achieving muscular relaxation, intubation was carried out using high-volume low-pressure siliconized PVC ETTs. Patients who could not be intubated at the first attempt were excluded from the study. ETT cuff was inflated with air with adjustments by palpating the pilot balloon, and then, the pilot balloon and the pressure manometer (Rüsch EndoTest) were connected, and the pressure measurements were recorded. The initial cuff pressure exceeding 35 cm H_20 was reduced by means of the manometer to 25-30 cm H_20 without air escape.

The patients were randomly (by drawing closed envelopes) divided into two groups.

One group designated as the N_2O group who were anaesthetized with 40/60 O_2/N_2O and the other group designated as the AIR group who were anaesthetized with 40/60 and O_2/air while desfluran (Suprane, Baxter, Puerto Rico, USA) with minimum alveolar concentration of 1% was included. Anaesthesia was maintained by 2 L/minute flow; respiration frequency of 12/minute; tidal volume 8 m/kg; inspiration/expiration (I/E) ratio of 1:2 and end expiratory pressure: 5 mmHg in all patients

HR, MBP, and SpO_2 were recorded 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90 minutes before and after intubation and 5 minutes before and after extubation. ETT cuff pressure in both groups were measured and recorded at 5, 10, 15, 20, 30, 40, 60, 70, 80 and 90 minutes during intubation and immediately before extubation. In order to avoid tracheal damage, ETT cuff pressure at each measurement time was reduced to the initial level if exceeded 45 cm H_2O and air escape sound was controlled over the sternal notch.

At the end of the surgery, both groups were ventilated with 100% O_2 and the inhalation agent was closed. When spontaneous respiration commenced, extubation was implemented after decurarisation. All patients were given 15 mg/kg paracetamol intravenous for analgesia. In the recovery room, the patients were given nasal O_2 (2 L/min). One hour and 24 hours post-operation, the patients were evaluated for sore throat and hoarseness.

Statistical Analyses

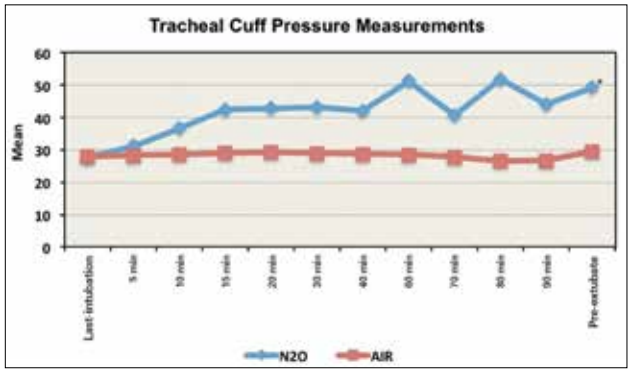
Statistical analyses were made using the Number Cruncher Statistical System 2007 and Power Analysis and Sample Size 2008 Statistical Software (Utah, USA) program. Data were evaluated by definitive criteria of the mean, standard deviation, median, frequency, ratio, minimum,

and maximum. Also for the comparison of the quantitative data on normally distributed variables for two groups, the student's t-test, and for two groups of parameters without normal distribution, the Mann-Whitney U test was used. Qualitative data were compared using Fisher's exact test and the Yates' continuity correction (Yates' correction on the chi-square approximation). Intragroup comparison of parameters with normal distribution was carried out using the paired-samples t-test. Correlation between parameters was estimated by means of the Spearman's correlation analysis. A p value of less than 0.01 and 0.05 was considered statistically significant.

Table. Demographic values

Median ± SD		N_2O (n=24)	AIR (n=26)	p
		Median ± SD		
Age		51.38±13.33	48.27±16.89	[a]0.477
Height (cm)		166.67±6.08	167.62±7.12	[a]0.616
Weight (kg)		69.17±10.03	70.58±9.79	[a]0.617
BMI (kg/m^2)		24.88±3.17	25.11±3.01	[a]0.791
Operation time (min); (median)		112.29±62.42 (107.0)	96.88±52.55 (82.5)	[b]*0.386*
		n (%)	n (%)	p
Gender	Women	13 (54.2%)	14 (53.8%)	[c]*1.000*
	Men	11 (45.8%)	12 (46.2%)	
ASA score	1	14 (58.3%)	15 (57.7%)	[c]*1.000*
	2	10 (41.7%)	11 (42.3%)	
Mallampati score	1	7 (29.2%)	6 (23.1%)	[c]*0.867*
	2	17 (70.8%)	20 (76.9%)	
Tube number	7.0	6 (25.0%)	6 (23.1%)	[c]*1.000*
	7.5	9 (37.5%)	10 (38.5%)	[c]*1.000*
	8.0	7 (29.2%)	9 (34.6%)	[c]*0.913*
	8.5	2 (8.3%)	1 (3.8%)	[d]*0.602*

[a] Student t test, [b] Mann Whitney U test, [c] Yates Continuity Correction test, [d] Fisher's exact test, SD: Standard deviation, ASA: American Society of Anesthesiology



Graphic 1. Tracheal cuff pressure values

Results

There was no statistically significant difference (p>0.05) in the demographic characteristics, ASA classification, Mallampati scores and the intubation tube numbers between the groups (Table).

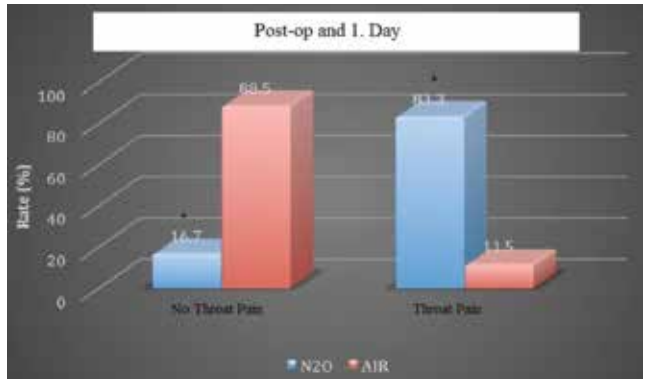
Haemodynamic parameters of BP and HR did not differ significantly between the two patient groups.

Cuff pressure values were significantly higher (p<0.001) in the N_20 group throughout the anaesthesia duration as compared to the AIR group (Graphic 1). Also, a slight but positive correlation (r=0.281; p<0.05) was determined between the tube numbers and the cuff pressure after intubation.

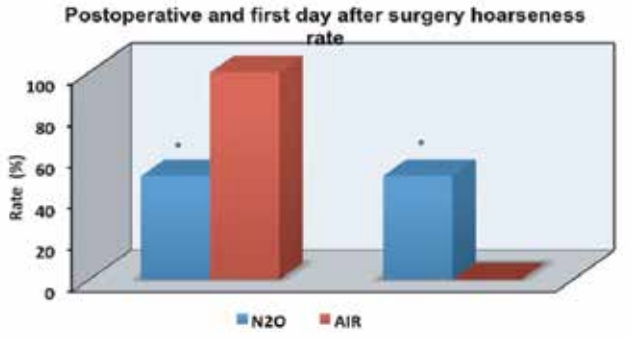
When comparing the data on the incidences of sore throat and hoarseness between the two groups, the value for the N_2O group was found to be significantly higher (p<0.001) than that for group AIR (Graphic 2,3).

Discussion

Since N_2O is 35-fold more soluble in blood than N_2 gas, during general anaesthesia, it diffuses rapidly into air filled spaces like ETT cuff. The chemical make-up of the material used for ETT also contributes to the degree of N_2O permeation (2). The high-volume low-pressure ETT



Graphic 2. Postop sore throat incidence,



Graphic 3. Postoperative hoarseness rate

used currently are made of PVC and N_2O permeability of this material is high (3), although cuffs made of materials containing rubber have even higher permeability (2,3).

During general anaesthesia N_2O diffusion into the ETT cuff increases the cuff pressure. Studies have estimated that cuff pressure reaches in 1 hour to levels that impair microcirculation. Use of special tubes could extend this time to 210 hours (5,8). At 35 cm H_20, cuff pressure partially reduces the mucosal blood flow and total obstruction and ischaemia results at 45 cm H_20 within 15-30 minutes (2,9). ETT cuff pressure adequacy is judged by the non-quantitative method of palpation, and results in high incidence of errors (2).

After using the cuff balloon palpation method for adjusting EET cuff pressure in the operation rooms of our hospital for long years, use of pressure measuring manometers have been started during the last year for cuff pressure measurement and control during anaesthesia.

In this study, the time-dependent changes that take place during general anaesthesia induced by using O_2/N_2O gas mixture in the high volume low-pressure ETT cuff and post-operative sore throat and hoarseness were investigated and compared to the corresponding results of general anaesthesia with O_2/air mixture. A previous controlled study on the time-dependent effect of N_2O on cuff pressure showed no change in cuff pressure in the first 15 minutes of intubation, but significantly higher ($p<0.05$) values were recorded at 30 minutes in the group anaesthetized with N_2O. Intragroup comparisons on the cuff pressure in the N_2O anaesthetized group showed a statistically significant increase in the cuff pressure starting at 10 minutes after intubation and reaching significantly high levels exceeding 45 cm H_20 at the 45th minute. In this particular study, high-volume low-pressure ETT made from siliconized PVC with a cuff thickness of 0.12 mm was used (10). Results of a study on N_2O effect on the pressure in cuffs inflated with air or physiological serum showed continual increase in the air filled cuff pressure reaching levels above 40 cm H_2O by 90 minutes (3). Our results have confirmed these reports in that in the N_2O group, in comparison to the AIR group, the cuff pressure had risen significantly and had reached above 45 cm H_2O at the 45th minute after intubation.

The intragroup variation in the rate of increase in cuff pressure can be ascribed to the use of tracheal tubes with differing N_2O permeability. For example, it has been shown that cuff thickness varied inversely with the cuff N_2O permeability (3,9). PVC made ETT with a thickness of 0.06 mm had low N_2O permeability and high compliance (11). In our study, thickness of the high-volume low-pressure cuffs made of PVC was 0.08 mm.

Checking cuff pressure by palpating the cuff balloon is a non-quantitative method with a high potential of erroneous results (2). Studies have stressed that this is not corrigible by means of training or taking the time for expertise, and that standard manometers should be used instead (12,13). Indeed, it has been shown that manometrically estimated cuff pressures were lower than the estimations made by the expertly palpation of the cuff balloon, which were higher than the expected values (14).

In our study, there was no statistically significant difference in ETT cuff pressure after intubation between the groups. After intubation, the first values of the pressures in the cuffs inflated by the palpation method in the N_2O group and AIR group were found to be 27.67±0.76 cm H_2O and 27.81±0.94 cm H_2O, respectively; these readings are at the upper limit of the ideal cuff pressure range. The lowest and the highest estimated limits were 17 cm H_2O and 52 cm H_2O, respectively. In addition, there was a slight positive correlation between these pressure levels and the ETT numbers ($r=0.281$; $p<0.05$), which however, was not observed in the following estimations on the increasing cuff pressure with time after intubation.

There are a number of reasons for sore throat experienced after ETT intubation, including not using lubricants during intubation, drying of the mucosal lining of the mouth and the glottis, pressure on the arytenoid cartilages and elevated cuff pressure (1). There are studies reporting the existence and the absence of a correlation between sore throat and ETT cuff pressure (1,15,16). Tracheal tube dimensions and design are also important causal factors. Routine endotracheal intubation for elective surgery can result in pathological changes, traumas and nerve damage (17). Observation of no differences of sore throat incidence in groups anaesthetized with or without N_2O use was attributed to the normalization of cuff pressure when it reached 45 cm H_2O during the anaesthesia in a study (10). The authors attributed this situation to the fact that they fixed blood pressure at 45 cm H_2O and used nasogastric tube in whole abdominal cases.

A study on 167 patients intubated for short periods of time, 54 (32%) complained of hoarseness post surgery, and the symptoms completely disappeared within 5 days (18). In two patients with persistent hoarseness for 54 and 99 days, vocal cord granulomas were detected. In our study, analysis of the incidence of hoarseness and sore throat 1 and 24 hours after extubation showed that 50% of patients had hoarseness in the N_2O group while no patient had hoarseness in the AIR group; 70.83% of patients (17 of 24) in the N_2O group and 11.5% of patients (3 of 26) in the AIR group had sore throat.

Conclusion

When high-volume low-pressure ETTS made of PVC with a cuff thickness of 0.08 mm were used in anaesthesia with N_2O inclusion, we observed, that the cuff pressures were high enough to impair the tracheal mucosa within 40 minutes of intubation. Hence, it is obvious that N_2O diffusion into the ETT cuff will increase the cuff pressure to levels that will cause tracheal morbidity. It has also been shown in this study that palpation method of adjusting cuff pressure results in wrong pressures, higher than expected. Additionally, as the tube dimensions increase, there is a slight but definite possibility of increased risk of inflating the cuff with wrong high pressure. We believe that the best approach in anaesthesia practice to prevent or minimize complications arising from tracheal mucosal damage caused by elevated ETT cuff pressure is to monitor the cuff pressure regularly during anaesthesia and make readjustments to normal levels if necessary.

Ethics

Ethics Committee Aprovel: Haseki Training and Research Hospital aprovel ID: 43, 11.10.2013. Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contribution

Surgical and Medical Practices: Özlem Koşar, Öznur Şen, Gamze Mısırlıoğlu. Consept: Özlem Koşar, Öznur Şen. Design: Öznur Şen, Özlem Koşar, Mehmet Toptaş, Nurdan Aydın. Data Collection or Practices: Özlem Koşar, Öznur Şen, Gamze Mısırlıoğlu, Nurdan Aydın, Emel Koçer Gür, Tarık Umutoğlu. Analysis or Interpretation: Özlem Koşar, Öznur Şen, Tarık Umutoğlu. Literature Search: Özlem Koşar, Öznur Şen, Nurdan Aydın. Writing: Özlem Koşar, Öznur Şen.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Kayhan Zeynep. Klinik Anestezi. Endotrakeal Entübasyon. 3. Baskı. Logos Yayıncılık, İstanbul; 2004.
2. Somri M, Fradis M, Malatskey S, Vaida S, Gaitini L. Simple on-line endotracheal cuff pressure relief valve. Ann Otol Rhinol Laryngol 2002;111:190-4.
3. Combes X, Schauvliege F, Peyrouset O, et al. Intracuff pressure and tracheal morbidity: influence of filling with saline during nitrous oxide anesthesia. Anesthesiology 2001;95:1120-4.
4. Stewart SL, Secrest JA, Norwood BR, Zachary R. A comparasion of endotracheal tube cuff pressures using estimation techniques and direct intracuff measurement. AANA J 2003;71:443-7.
5. Benneth MH, Isert PR, Cumming RG. Postoperative sore throat and hoarseness following tracheal entubation using air or saline to inflate the cuff-a randomized controlled trial. Anaesth Intensive Care 2000;28:408-13.
6. Beebe DS. Complications of tracheal entubation. Semin Anesth Perioperat Med Pain 2001;20:166-72.
7. Seegobin RD, Hasselt GL. Endotracheal cuff pressure and tracheal mucosal blood flow: Endoscopic study of effects of four large volume cuffs. Br Med J (Clin Res Ed) 1984;288:965-8.
8. Karasawa F, Mori T, Okuda T, Satoh T. Profile soft-seal cuff, a new endotracheal tube, effectively inhibits an increase in the cuff pressure through high compliance rather than low diffusion of nitrous oxide. Anesth Analg 2001;92:140-4.
9. al-Shaikh B, Jones M, Baldwin F. Evaluation of pressure changes in a new design tracheal tube cuff, the Portex Soft Seal, during nitrous oxide anaesthesia. Br J Anaesth 1999;83:805-8.
10. Altunkaya H, Çıtır S, Özkoçak I, et al. Azotprotoksitin Zamana Göre Endotrakeal Kaf Basıncına Etkisi. Türk Anest Rean Der Dergisi 2004;32:362-6.
11. AlShaikh B. New cuff design prevents N2O diffusion. Anesth Analg 2000;91:10-2.
12. Ayoğlu H, Yurtlu BS, Hancı V, et al. Anestezi çalışanlarınca pilot bolanun palpasyonu ile ayarlanan endotrakeal tüp kaf basınçlarının değerlendirilmesi. Türkiye Klinikleri J Anest Reanm 2009;7:88-92.
13. Al-Metwalli RR, Al-Ghamdi AA, Mowafi HA, Sadek S, Abdulshafi M, Mousa WF. Is sealing cuff pressure easy, reliable and safe tecnigue for endotracheal tube cuff inflation?: A comparative study. Saudi J Anaesth 2011;5:185-9.
14. Liu J, Zhang X, Gong W, et al. Correlations between controlled endotracheal tube cuff pressure and postprocedural complications: a multicenter study. Anesth Analg 2010;111:1133-7.
15. Atkinson RS, Rusman GB, Davies NJH. Lee's Synopsis of Anesthesia. 11th ed. Oxford: Butterworth- Heinemann; 1993. p. 217-38.
16. Kayhan Z. Anesteziyolojinin Tarihsel Gelişimi ve Geleceği. Klinik Anestezi. 3.baskı. İstanbul: Logos yayıncılık; 2004.
17. McHardy FE, Chung F. Postoperative sore throat: cause, prevention and treatment. Anaesthesia 1999;54:444-53.
18. Jones MW, Catling S, Evans E, Green DH, Green JR. Hoarseness after tracheal intubation. Anaesthesia 1992;47:213-6.

Original Article / *Özgün Araştırma*

DOI: 10.4274/haseki.3158
Med Bull Haseki 2017;55:42-6

Accidental Carbon Monoxide Poisonings in Adana, Turkey: A 14-year Study

Adana'da Taksirle Meydana Gelen Karbon Monoksit Zehirlenmeleri: 14 Yıl Çalışması

Murat Darçın

Ministry of Interior Affairs, Gendarmerie and Coast Guard Academy, Ankara, Turkey

Abstract

Aim: Carbon monoxide (CO) is often referred to as the "silent killer" because its victims cannot see it, smell it or taste it. CO is responsible for a large percentage of the accidental poisonings and deaths reported throughout the world. CO poisoning therefore is considered a serious global health threat. The aim of the present study was to describe the cases of CO poisoning in a rural areas of Adana, Turkey between 2002 and 2015 based on data collected from incident reports.

Methods: The cases of accidental CO poisoning were statistically analyzed. During that period, 74 incidents occurred and 154 people were poisoned by accidental CO poisoning.

Results: The results of this analysis indicate that men and adults aged ≥65 years were more likely to die from CO poisoning than others. The number of CO poisoning cases was highest during the heating season. The majority (72%) of poisoning resulting in hospitalization with a life-threatening condition or death occurred within the home.

Conclusion: CO poisoning is a serious danger. People must be informed about this hazard. By educating risk groups about the dangers of CO poisoning, it is possible to save many lives as well as reduce the health risks.

Keywords: Accident, carbon monoxide poisoning, health and safety, public health

Öz

Amaç: Karbon monoksit (CO), kurbanları onu göremediği, koklayamadığı ve tadamadığı için genellikle sessiz katil olarak anılır. CO zehirlenmeleri dünya çapında rapor edilen taksirle zehirlenme sonucu ölümlerin önemli bir yüzdesinden sorumludur. Bu yüzden CO zehirlenmesi küresel ölçekte ciddi bir sağlık tehdidini karakterize eder. Bu çalışmanın amacı, 2002-2015 arasındaki dönemde meydana gelen CO zehirlenmelerini, Adana ili şehir merkezi dışı alanlarda vuku bulan CO zehirlenmesi olgularına ilişkin olay raporlarından toplanan verilere dayanarak ortaya koymaktır.

Yöntemler: Çalışmada, taksirle CO zehirlenmeleri istatistiksel olarak incelenmiştir. Dönem boyunca gerçekleşen 74 olayda 154 kişi kazayla CO maruziyeti sonucu zehirlenmiştir.

Bulgular: Bu analizin sonuçları, erkeklerin ve 65 yaş üstü yetişkinlerin diğerlerine oranla CO zehirlenmesi sonucu ölme olasılığının daha yüksek olduğunu ortaya koymuştur. CO zehirlenme olgularının sayısı ısıtma sezonunda en yüksek seviyededir. Ölüm veya hayati tehlike kaydı ile hastaneye yatışla sonuçlanan zehirlenme olgularının büyük bir kısmı (%72) evde gerçekleşmiştir.

Sonuç: CO zehirlenmesi ciddi bir tehlikedir. İnsanlar bu tehlike hakkında bilgilendirilmek zorundadır. Risk gruplarını CO zehirlenmesinin tehlikeleri konusunda eğiterek, sağlık risklerini azaltmakla birlikte birçok hayat kurtarmak da mümkündür.

Anahtar Sözcükler: Kaza, karbon monoksit zehirlenmesi, sağlık ve güvenlik, halk sağlığı

Introduction

Carbon monoxide (CO) is a colorless, odorless, tasteless, nonirritating, invisible and poisonous gas, which is predominantly produced as a result of incomplete combustion of carbon-containing materials, such as gas, coal, coke, wood, etc. CO is often referred to as the "silent killer" because its victims cannot see it, smell it or taste it. Exposure to higher concentrations of CO can result in death (1).

The exact number of individuals who have suffered from CO intoxication is not known because of unreported incidents. As one of the most common cause of poisoning in the developed and developing countries alike (2,3), CO poisoning is responsible for a large percentage of

Address for Correspondence/Yazışma Adresi: Murat Darçın
Ministry of Interior Affairs, Gendarmerie and Coast Guard Academy, Ankara, Turkey
Phone: +90 505 751 15 16 E-mail: mrtdrc@yahoo.com
Received/Geliş Tarihi: 01 March 2016 **Accepted/Kabul Tarihi:** 03 July 2016

the accidental poisoning deaths reported throughout the world. CO poisoning, which may be the cause of more than 50% of the fatal poisonings reported in many countries (4,5), has also been determined to be the leading cause of death of accidental poisoning in Europe (6). CO poisoning therefore is a serious health threat on a global level. Most of poisoning deaths caused by accidental CO poisoning can be prevented with simple prevention measures (7).

CO poisoning from coal and gas heaters is one of the major public health problems in Turkey, and the number of studies on CO poisoning is limited. The aim of the present study was to describe CO poisonings between 2002 and 2015 based on data collected from incident reports of CO poisoning cases occurring in rural areas of Adana, Turkey.

Methods

Accidental CO poisonings in the rural areas of Adana were investigated on the incident reports during the period 2002-2015. Data were analyzed with respect to type, cause, result and time of incident, age and gender of victims, and other factors. Initially, 74 accidental CO poisoning incidents were identified. Data used this study was taken from Gendarmerie accident and incident reports.

The statistics program XLSTAT was used for the descriptive and analytical evaluation of the parameters of the CO poisoning incidents. Association rules were used as the statistical method to find the relationship between data items in a transactional database. As an important branch of data mining techniques, association rules mining aims to find the associations between features in large dataset. A rule describes the association between two sets (X and Y) that have no collective elements. $X \Rightarrow Y$ means, if we have X in a process; in this case, we can have Y in the same process. Support of a rule is the possibility of finding sets X and Y in a process. How frequently the items in a rule occur together is indicated as the support of a rule. This value ranges from 0 to 1. In association rule analysis, the confidence of a rule is defined as follows: Confidence ($X \Rightarrow Y$) = support ($X \cup Y$) / support (X). The confidence is how often a rule has been encountered in the data, The lift of a rule is the ratio of the observed support to that expected if X and Y were independent. A lift value greater than 1 indicates a positive relationship between the itemsets; lift value less than 1 indicates a negative link; and where the value of lift equals 1, the correlation is independent and there is no association between the itemsets (8).

Results

During the 14-year period, 1844 people were poisoned in 1292 poisoning cases. Victims were poisoned because of products used for human health (27.8%; n=512), foods (22.6%; n=416), agricultural pesticides and animal health products (21%; n=388), CO (8.4%; n=154), plants and wild mushrooms (7.2%; n=33), household chemicals (4.4%; n=82), industrial chemicals (1.8%; n=34), animals (1%; n=18), and other reasons (5.8%; n=107) (Figure 1).

During the period, 74 incidents were occurred and 154 people were intoxicated due to accidental CO poisoning. 13 CO-poisoned victims died, 16 people were hospitalized with a life-threatening condition, and 125 people were hospitalized without a life-threatening condition.

79% of poisoned people who were hospitalized with a life-threatening condition or dead were male. The rate of severe poisoning resulting in hospitalization with a life-threatening condition or death was highest among elderly. More than 50% died victims were over 65 years of age (Figure 2). The results of this analysis indicate that men and adults aged ≥65 years were more likely to die from CO poisoning than other persons. 15% of fatal CO poisoning and more than one-third of total CO poisoning occurred among those younger than 18 years of age (Figure 2,3).

The number of CO poisoning cases was highest during the heating season. CO poisoning was most common in winter. The period November through February represent the leading months for CO poisoning resulting in hospitalization with a life-threatening condition or death in rural areas of Adana, with a peak in December (Figure 4). A large number of fatal CO poisoning (85%) also occurred during the winter months.

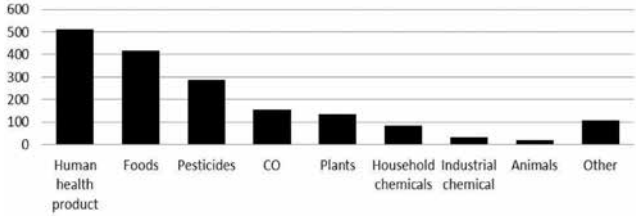


Figure 1. Poisoned victims during the fourteen-year period

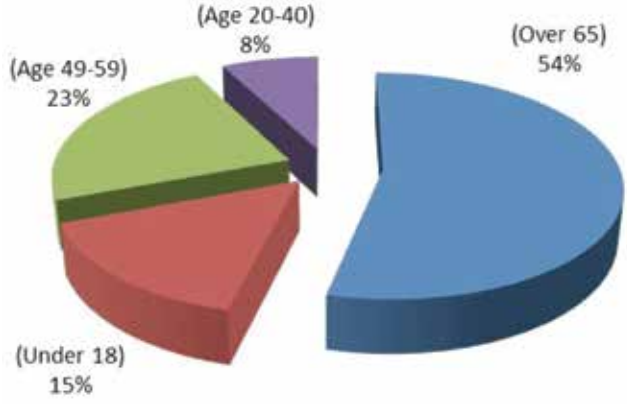


Figure 2. Died victims due to carbon monoxide poisoning

The majority (72%) of poisonings resulting in hospitalization with a life-threatening condition or death occurred within the home (Figure 5). Another finding of this study is that 21% of poisonings resulting in hospitalization with a life-threatening condition or death occurred within a tent which is used by agriculture workers (Figure 5). Nearly one-third (31%) of all CO deaths occurred inside tents.

During the period, any criminal investigation about CO-related suicide was not conducted and no case was recorded as suicide in this study. Another important result of the study is that 69% of fatal CO poisoning victims were alone while poisoning has occurred.

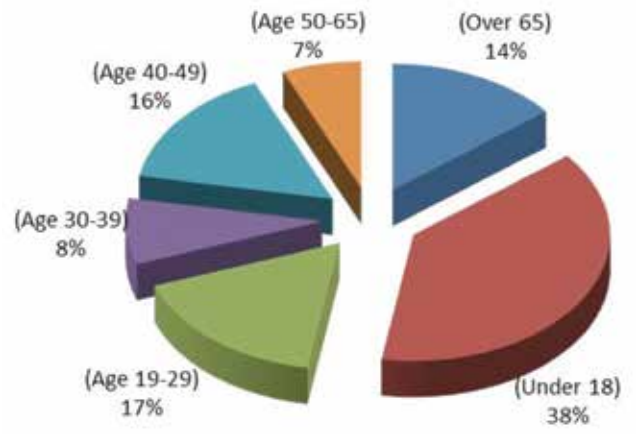


Figure 3. Fatal and nonfatal carbon monoxide poisoning due to age

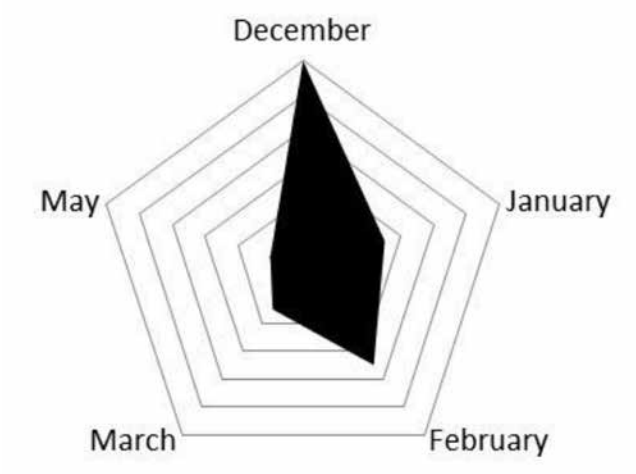


Figure 4. Fatal carbon monoxide poisoning due to months

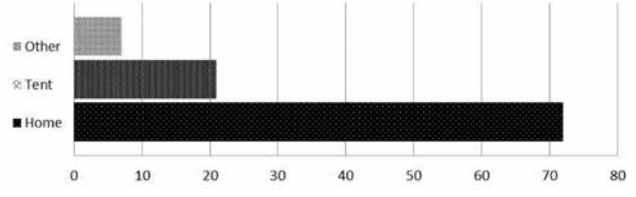


Figure 5. Place of carbon monoxide poisoning resulting in hospitalization with a life-threatening condition or death

The summary of association rules analysis is shown in Table 1 (minimum support: 0.06; minimum confidence: 0.95; minimum number antecedent: 4; items: 28; rules: 13).

One of the rules with the highest confidence says that if a female under the age 18 is exposed to non-fatal CO poisoning at home, then there is 100% chance that she is also not alone in the home. This rule is found in 12.2% of the transactions. The lift is 1.103 which means that having (<18 - female - Home - non-fatal poisoning) or respectively (Not-Alone) increases the chance of having (Not-Alone) or respectively (<18 - female - Home - non-fatal poisoning) by a factor of 1.103. The same rule also applies to men.

Another rule says that if a male age 30-39 is not alone at a workplace, then there is 100% chance that he is also exposed to non-fatal CO poisoning. This rule is found in 6.4% of the transactions. The lift is 1.255 which means that having (30-39 - male - Not-Alone - Workplace) or respectively (Non-Fatal poisoning) increases the chance of having (Non-Fatal poisoning) or respectively (30-39 - Male - Not-Alone - Workplace) by a factor of 1.255. Some of the other rules are displayed in Table 2 (minimum support: 0.05; minimum confidence: 0.95; minimum number antecedent: 2; items: 28; rules: 148).

Rules say that:

-If a person who died from poisoning is alone at the time of poisoning, then there is 100% chance that the person is a man. This rule is found in 5.2% of the transactions.

-If a person over age 65 is not alone, then there is 100% chance that the person is at home. This rule is found in 5.2% of the transactions.

-If a person is exposed to non-fatal CO poisoning in a tent, then there is 100% chance that he/she is also not alone in the tent. This rule is found in 12.8% of the transactions.

-If a female is in a tent, then there is 100% chance that she is also not alone. This rule is found in 9.3% of the transactions.

-If a female is exposed to non-fatal CO poisoning in a tent, then there is 100% chance that she is also not alone in the tent. This rule is found in 8.7% of the transactions.

Discussion

Characteristics of the at-risk population for severe and fatal CO poisoning in this study is largely consistent with previous studies that both male and elderly population subgroups have the highest rates of CO-related hospitalization and death (4,9-12). Although all people need to be aware of the CO poisoning threats, vulnerable

populations such as unborn babies, infants, elderly, and those who suffer from anemia, heart disease or respiratory problems are generally more at risk than others (13).

Most CO exposures and poisonings occur when people are in the home (7,12,14). Especially in the winter months, leaks from coal heaters are the major instruments of deaths (15,16). Data from Bursa, Turkey for the period between 1996 and 2006 showed that coal heater emissions were the source in 86% of CO poisoning cases (7). The present study found that 92% of fatal CO poisonings were

Table 1. Summary of association rules (minimum number antecedent: 4)

Antecedent	Consequence	Confidence	Support	Lift
<18 - Female - Home - Non-Fatal poisoning	Not-Alone	1.000	0.122	1.103
<18 - Female - Home - Not-Alone	Non-Fatal poisoning	0.955	0.122	1.198
<18 - Home - Male - Non-Fatal poisoning	Not-Alone	1.000	0.122	1.103
Female - Home - Jan - Non-Fatal poisoning	Not-Alone	1.000	0.093	1.103
<18 - Home - Jan - Non-Fatal poisoning	Not-Alone	1.000	0.076	1.103
<18 - Home - Jan - Not-Alone	Non-Fatal poisoning	1.000	0.076	1.255
Dec - Male - Not-Alone - Non-Fatal poisoning	Home	1.000	0. 076	1.445
Dec - Home - Male - Non-Fatal poisoning	Not-Alone	1.000	0.076	1.103
<18 - Female - Jan - Non-Fatal poisoning	Not-Alone	1.000	0.070	1.103
<18 - Female - Jan - Not-Alone	Non-Fatal poisoning	1.000	0.070	1.255
30-39 - Not-Alone - Non-Fatal poisoning - Workplace	Male	1.000	0.064	1.849
30-39 - Male - Non-Fatal poisoning - Workplace	Not-Alone	1.000	0,064	1.103
30-39 - Male - Not-Alone - Workplace	Non-Fatal poisoning	1.000	0.064	1.255

Dec: December, Jan: January

Table 2. Some of the other association rules (minimum number antecedent: 2)

Antecedent	Consequence	Confidence	Support	Lift
Not-Alone - Workplace	Male - Non-Fatal poisoning	1.000	0.110	2.646
30-39 - Workplace	Male - Non-Fatal poisoning	1.000	0.064	2.646
30-39 - Not-Alone - Workplace	Male - Non-Fatal poisoning	1.000	0.064	2.646
30-39 - Workplace	Male - Not-Alone - Non-Fatal poisoning	1.000	0.064	2.646
Non-Fatal poisoning - Workplace	Male - Not-Alone	1.000	0.110	2.098
30-39 - Workplace	Male - Not-Alone	1.000	0.064	2.098
30-39 - Non-Fatal poisoning - Workplace	Male - Not-Alone	1.000	0.064	2.098
Not-Alone - Workplace	Male	1.000	0.110	1.849
Not-Alone - Non-Fatal poisoning - Workplace	Male	1.000	0.110	1.849
Alone - Fatal poisoning	Male	1.000	0.052	1.849
>65 - Not-Alone	Home	1.000	0.099	1.445
DEC - Male - Not-Alone - Non-Fatal poisoning	Home	1.000	0.076	1.445
>65 - Female	Home	1.000	0.052	1.445
>65 - Non-Fatal poisoning	Home	1.000	0.052	1.445
>65 - Male - Not-Alone	Home	1.000	0.052	1.445
30-39 - Male - Workplace	Not-Alone - Non-Fatal poisoning	1.000	0.064	1.293
<18 - Female - Home	Not-Alone - Non-Fatal poisoning	0.955	0.122	1.234
Non-Fatal poisoning - Tent	Not-Alone	1.000	0.128	1,103
Female - Tent	Not-Alone	1.000	0.093	1.103
Female - Non-Fatal poisoning - Tent	Not-Alone	1.000	0.087	1.103

Dec: December

caused by wood or coal heaters. This result also supports previous research. A study from the USA found that the most common sources of CO poisoning in homes were the use of gasoline-powered engines, such as electric generators, and malfunctioning heating and cooking appliances (17). Incorrectly installed, poorly maintained or poorly ventilated cooking and heating devices are often the foremost causes of CO poisoning.

CO alarms are an important part of a whole strategy for the prevention of CO poisoning and deaths. Of all the CO incidents recorded in this study, none of those involving an alarm resulted in a fatality or serious injury. Similar to this study, it has been found that households do not have a working CO alarm (12). Different from other countries, CO is rarely used as a suicide method in Turkey.

Conclusion

CO poisoning is common, severe and ignored incident throughout the world, with a relatively high risk of immediate death, complications or late health problems. CO poisoning is a mostly avoidable and preventable public health problem that usually occur by accidents. Public awareness and education is vital for protection from poisoning. It is important to avoid dangerous CO concentrations exposures in homes and other indoor environments. CO poisoning can be reduced through measures such as regular checks and maintenance of heating systems, use of monitoring devices/CO alarm detectors for the early detection of excess CO, development of alternative heating systems, adequate ventilation, not using unventilated combustion sources indoors, and improving protective properties against CO leaks in the existing heating system.

CO poisoning is a serious danger. People must be informed about it. By educating risk groups about the dangers of CO poisoning, it is possible to reduce the health risk as well as save many lives.

Ethics

Peer-review: Externally peer-reviewed.

References

1. Ait EL Cadi M, Khabbal Y, Idrissi L. Carbon monoxide poisoning in Morocco during 1999-2007. J Forensic Leg Med 2009;16:385-7.
2. Iheagwara KN, Thom SR, Deutschman CS, Levy RJ. Myocardial cytochrome oxidase activity is decreased following carbon monoxide exposure. Biochim Biophys Acta 2007;1772:1112-6.
3. Gorman D, Drewry A, Huang YL, Sames C. The clinical toxicology of carbon monoxide. Toxicology 2003;187:25-38.
4. Cobb N, Etzel R. Unintentional carbon monoxiderelated deaths in the United States, 1979 through 1988. JAMA 1991;266:659-63.
5. Varon J, Marik PE, Fromm RE Jr, Gueler A. Carbon monoxide poisoning: a review for clinicians. J Emerg Med 1999;17:87-93.
6. Burette P, Vanmeerbeek M, Boüüaert C, Giet D. Family practitioner and carbon monoxide poisoning. Rev Med Liege 2006;61:285-90.
7. Akköse S, Türkmen N, Bulut M, Akgöz S, Iscimen R, Eren B. An analysis of carbon monoxide poisoning cases in Bursa, Turkey. East Mediterr Health J 2010;16:101-6.
8. XLSTAT, 2014. https://www.xlstat.com/en/
9. Centers for Disease Control and Prevention (CDC). Unintentional non-fire-related carbon monoxide exposures–United States, 2001-2003. MMWR Morb Mortal Wkly Rep 2005;54:36-9.
10. Centers for Disease Control and Prevention (CDC). Carbon monoxide–related deaths–United States, 1999-2004. MMWR Morb Mortal Wkly Rep 2007;56:1309-12.
11. Iqbal S, Law HZ, Clower JH, Yip FY, Elixhauser A. Hospital burden of unintentional carbon monoxide poisoning in the United States, 2007. Am J Emerg Med 2012;30:657-64.
12. Sircar K, Clower J, Shin MK, Bailey C, King M, Yip F. Carbon monoxide poisoning deaths in the United States, 1999 to 2012. Am J Emerg Med 2015;33:1140-5.
13. Centers for Disease Control and Prevention. 2012. What is Carbon Monoxide? Available from: http://www.cdc.gov/co/pdfs/faqs.pdf. Accessed December 20, 2015.
14. Iqbal S, Clower JH, Hernandez SA, Damon SA, Yip FY. A review of disaster-related carbon monoxide poisoning: surveillance, epidemiology, and opportunities for prevention. Am J Public Health 2012;102:1957-63.
15. Aksoy E, Polat O, İnanıcı MA. Retrospective analysis of 293 carbon monoxide poisoning cases. Clinical development 1995;8:3545-9.
16. Turkmen N, Akgoz S. Carbon monoxide intoxication related deaths autopsies in Bursa. J Forensic Med 2005;19:20-5.
17. United States Environmental Protection Agency. An Introduction to Indoor Air Quality (IAQ). Carbon Monoxide (CO). Available from: URL:http://www.epa.gov/iaq/co.html. Accessed December 20, 2015.

Özgün Araştırma / *Original Article*

DOI: 10.4274/haseki.3290
Med Bull Haseki 2017;55:47-51

Parsiyel Vermilion Defektlerinin Mukozal Transpozisyon Flebi ile Onarımı

Reconstruction of Partial Vermilion Defects with Mucosal Transposition Flap

Süleyman Taş

Kemerburgaz Üniversitesi Tıp Fakültesi, Plastik, Rekonstrüktif ve Estetik Cerrahi Anabilim Dalı, İstanbul, Türkiye

Öz

Giriş: Dudak hem estetik hem fonksiyonel açıdan yüzün 1/3 alt kısmında bulunan çok önemli bir anatomik yapıdır. Vermilion ise dudağın estetik ve duyusal fonksiyonu açısından çok önemli subünitidir. Travma ya da kanser cerrahileri sonrası, vermilion onarımı da bu önemli özellikler nedeniyle zor ve tecrübe gerektiren bir cerrahiyi gerektirmektedir. Bu makalede, alt dudağın prekanseröz lezyonlarının eksizyonu sonrası oluşan parsiyel vermilion defektlerinin onarımı için kullanılan mukozal transpozisyon flebi ile ilgili deneyimin, operasyon tekniği, hasta sonuçları ve detaylı literatür tartışması ile birlikte aktarılması amaçlamaktadır.

Yöntemler: Şubat 2014 - Mayıs 2015 tarihleri arasında, punch biyopsi ile prekanseröz lezyon tanısı alan, yaşları ortalaması 45 olan (34-52 yaş), dokuz hasta (sekiz erkek, bir kadın), lokal anestezi altında tümör eksizyonu ve tariflenen teknik ile vermilion rekonstrüksiyonu operasyonu geçirdi. Hastalar 1 yıl süre ile belirli intervallerde takip edildi (postoperatif 7. gün ve 1, 3, 6, 12. ay). Histopatolojik tanıları kayıt edilerek, fonksiyonel ve estetik sonuçları değerlendirildi.

Bulgular: Tüm hastalarda fonksiyonel ve estetik açıdan mükemmel sonuçlar elde edilirken, takip süresi boyunca herhangi bir komplikasyon ya da nüks gözlenmedi.

Sonuç: Fonksiyonel ve estetik açıdan başarısı ve donör morbiditesi bırakmaması ile parsiyel vermilion defektlerinin onarımında oral mukozal transpozisyon fleplerinin ilk tercih olabilecekleri düşünülmektedir.

Anahtar Sözcükler: Dudak, vermilion, onarım, mukoza, transposizyon, flep

Abstract

Aim: Lip, located in lower 1/3 of the face, is very important unit from aesthetic and functional aspect. Vermilion is a subunit of the lip and also has aesthetic and sensorial functions. Following the trauma and cancer surgeries, vermilion reconstruction is needed and it needs experienced and meticulous procedures. Here, it is aimed to describe the experience of mucosal transposition flap in reconstruction of partial vermilion defects with a detailed operation technique, the results of the patients and review of the literature.

Methods: Between February 2014 and May 2015, nine patients (eight male, one female; mean age 45, range 34 to 52) were diagnosed precancerous lesion with punch biopsy and were underwent a surgical excision and vermilion reconstruction under local anesthesia. The patients were followed up 1 year with a interval of postoperative 7. 7. day and 1, 3, 6 and 12. month. The histopatologic, functional and aesthetic records were evaluated.

Results: Functional and excellent aesthetic results were achieved in all patients. No complication nor recurrence was observed during follow-up period.

Conclusion: Oral mucosal transposition flap was considered as first choice in reconstruction of the partial vermilion defects since its functional and aesthetic success and no donor tissue morbidity.

Keywords: Lip, vermilion, reconstruction, mucosa, transposition, flap

Giriş

Dudağın prekanseröz lezyonları; eritroplaki, lökoplaki, aktinik keilitis (aktinik keratoz), displazi vermilionektomi prosedürü ile cerrahi eksizyonu gerektirir (1). Vermilion ise dudağın estetik ve duyusal fonksiyonu açısından çok önemli subünitidir. Fonksiyonel ve estetik sonuçları optimize edebilmek için, vermilion rekonstrüksiyonu, defekt boyutunda, şeklinde, aynı özelliği ve rengi taşıyan bir doku ile yapılmalıdır (2).

Total vermilion rekonstrüksiyonunda genel olarak "lip shaving" prosedürü alarak adlandırılan, vermilionun eksize edilmesinden sonra dudak iç mukozasının dekole edilmesinden sonra ilerletilerek defekti kapatacak şekilde

Yazışma Adresi/Address for Correspondence: Süleyman Taş
Kemerburgaz Üniversitesi Tıp Fakültesi, Plastik, Rekonstrüktif ve Estetik Cerrahi Anabilim Dalı, İstanbul, Türkiye
Tel.: +90 212 604 01 00 E-posta: drsuleymantas@live.com
Geliş Tarihi/Received: 23 Mayıs 2016 **Kabul Tarihi/Accepted:** 27 Haziran 2016

sütüre edilmesi ile yapılmaktadır. Ancak bu teknikte, alt dudak vermilion ünitesinin ince kalması, bukkal mukozanın sığlaşması, dudakta kuruluk oluşması gibi dezavantajlar bulunmaktadır. Parsiyel vermilion rekonstrüksiyonunda ise genel olarak, dudak iç mukozasından planlanan V-Y ilerletme flebi kullanılmaktadır. Ancak bu teknikte de, mukozanın yeteri kadar ilerlememesinden kaynaklanan, vermilion kontur problemleri, vermilionun onarılan kısmında ince kalması gibi estetik problemlere neden olabilmektedir (1-4).

Bu makalede, parsiyel vermilion defektlerinin onarımı için kullanılan mukozal transpozisyon flebi ile elde edilen sonuçlar, operasyon tekniği ve literatürün gözden geçirilmesi ile birlikte sunulması amaçlanmıştır.

Yöntemler

Şubat 2014 - Mayıs 2015 tarihleri arasında, punch biyopsi ile prekanseröz lezyon tanısı alan, tümör eksizyonu ve mukozal transpozisyon flebi ile rekonstrüksiyon yapılan tüm hastalar retrospektif olarak incelendi. Yaş ortalaması 45 olan (34-52 yaş), toplam dokuz hastanın (sekiz erkek, bir kadın), lokal anestezi altında tümör eksizyonu ve mukozal transpozisyon flebi ile vermilion rekonstrüksiyonu operasyonu geçirdiği tespit edildi. Hastalara ait bilgiler Tablo 1'de özetlenmiştir. Tüm hastaların defekti alt dudakta idi. Hastalara preoperatif punch biyopsi yapılarak, histopatolojik tanı konuldu. Hastaların etiyopatogenezinde; beş hastada aktinik keilitis, üç hastada displazi, bir hastada lökoplaki vardı. İki mm güvenlik marjı bırakılarak yapılan eksizyonlar sonrası, vermilion hattına sınırlı, 2x1 cm'den 4x2 cm'ye değişkenlik gösteren defektler, mukozal transpozisyon flebi ile onarıldı. Çıkarılan piesmenler, incelenmek üzere patoloji laboratuvarına gönderildi. Tüm hastalar, yapılacak işlem ile ilgili detaylı olarak bilgilendirildi. Hastalar, ameliyat sonrası 7. gün, 1., 3., 6. ve 12. aylarda kontrole çağrılarak takip edildi. Aydınlatılmış yazılı hasta onamı bu çalışmaya katılan tüm hastalardan alınmıştır.

Cerrahi Teknik

Mutad ameliyat hazırlığının ardından, mevcut lezyonun 2 mm'lik cerrahi güvenlik marjı bırakılacak şekilde eksizyon sınırları marker kalem ile işaretlenir. Cetvel yardımı ile oluşacak olan defekt ölçülerek, ağız içi mukozasından defektten fornikse doğru, oluşacak olan defekt büyüklüğünde, pivot noktası defektin sağ ya da sol köşesi olacak şekilde, defekte 60 derece açı ile mukozal transpozisyon flebi işaretlenir. 1/200,000'lik adrenalinli lidokain solüsyonu enjeksiyonu ile lokal anestezi sağlandıktan sonra operasyona başlanır. Lezyon eksizyonunun ardından, mukozal transpozisyon flebi, orbikülaris oris kası üzerindeki plandan eleve edilir ve bipolar koter ile yapılan kanama kontrolünün ardından, defekte 4/0 sütür ile adapte edilir (olgu 1; Şekil 1, 2, 3, olgu 2; Şekil 4, 5). Donör alan 4/0 sütür ile primer onarılır. Lokal pansumanın ardından operasyona son verilir.

Bulgular

Mukozal transpozisyon flebi, tüm olgularda sorunsuz bir şekilde yaşadı. Yara iyileşme problemi, parsiyel ya da total nekroz, sütür reaksiyonu, yara dehisansı, kanama gibi herhangi bir komplikasyon görülmedi. Histopatolojik inceleme sonucu, beş hastada aktinik keilitis, üç hastada displazi ve bir hastada lökoplaki olarak geldi. Cerrahi sınırlar tüm hastalarda temiz ve cerrahi güvenlik marjı (2 mm) içerisinde idi. Hasta takip süresi 12 ay idi. Onarılan dudak bölgesindeki dokunun renk ve uyumu, normal vermiliona çok yakındı ve fark edilebilir bir skar yok idi (Şekil 3, 5). Donör alanda herhangi bir skar ya da skar kontraksiyonu takip süresi boyunca gözlenmedi (Şekil

Tablo 1. Hastalara ait veriler

Hasta no	Yaş (Yıl)	Cinsiyet	Lezyon lokalizasyonu	Tanı	İntraoperatif defekt boyutu
1	44	E	Alt dudak orta hat	Aktinik keilitis	2x2 cm
2	47	E	Alt dudak paramediyan	Displazi	4x2 cm
3	41	E	Alt dudak orta hat	Aktinik keilitis	2x1 cm
4	52	E	Alt dudak köşe	Displazi	3x1 cm
5	51	E	Alt dudak orta hat	Aktinik keilitis	4x2 cm
6	48	E	Alt dudak orta hat	Lökoplaki	3x2 cm
7	46	E	Alt dudak paramediyan	Aktinik keilitis	4x2 cm
8	42	K	Alt dudak paramediyan	Aktinik keilitis	3x1 cm
9	34	E	Alt dudak orta hat	Displazi	2x1 cm

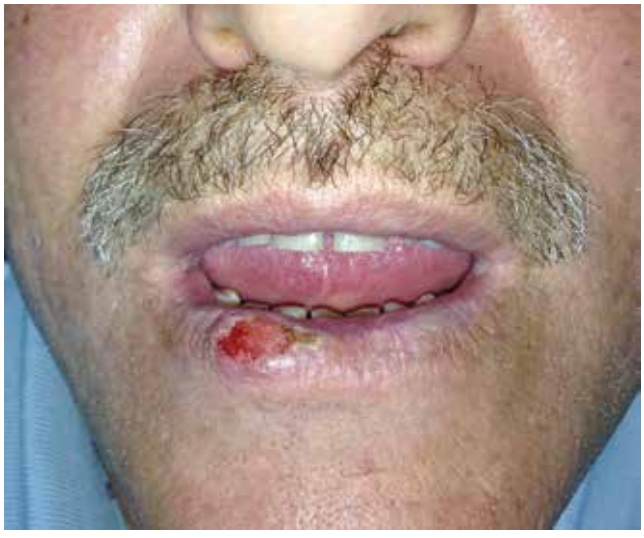
E: Erkek, K: Kadın
Yaş ortalaması: 45

5b). Tüm hastalarda, dudak fonksiyonları ve duyu özelliği normal idi. Tüm hastalar fonksiyonel ve kozmetik sonuçtan memnun idi.

Olgu Sunumları

Olgu 1

Kırk altı yaşında erkek hastaya, alt dudak paramediyan hatta, aktinik keilitis tanısıyla lokal anestezi altında operasyon planlandı (Şekil 1). Mevcut lezyon, 2 mm'lik güvenlik marjı ile orbikülaris oris kası korunarak eksize edildi ve 4x2 cm defekt oluştuğu izlendi (Şekil 2a). Oluşan defekt aynı ebatta planlanan mukozal transpozisyon flebi ile onarıldı (Şekil 2b, 2c). Hastanın postoperatif birinci yılındaki görüntüsü hem cerrah hem de hasta için sorunsuzdu (Şekil 3).



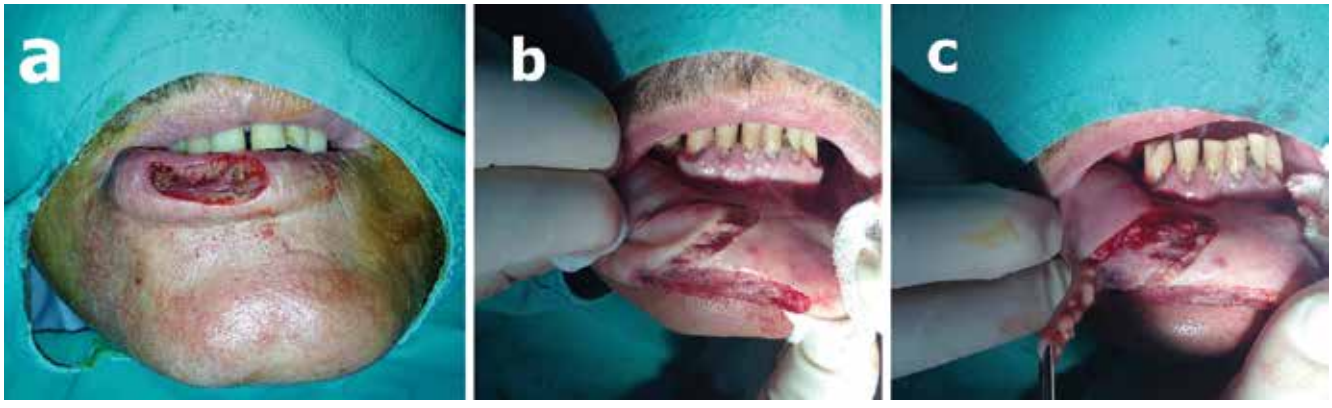
Şekil 1. Kırk altı yaşında erkek hasta, alt dudak paramediyan hatta, aktinik keilitis tanısıyla opere edildi, preoperatif görüntüsü

Olgu 2

Kırk yedi yaşındaki erkek hastaya, alt dudak paramediyan hatta, mukozal displazi tanısıyla operasyon planlandı (Şekil 4a). Cerrahi güvenlik marjı (2 mm) bırakıldıktan sonra orbikülaris oris kası üzerindeki plandan tümöral lezyon eksize edildi (Şekil 4b, 4c). 4x2 cm ebadındaki defekt aynı boyuttaki mukozal transpozisyon flebi ile onarıldı. Operasyondan bir yıl sonraki görüntü hem fonksiyonel hem de estetik açıdan sorunsuzdu. (Şekil 5a, 5b).

Tartışma

Vermilion, her iki dudağın birbirine değdiği mukoza hattından deri bileşkesine kadar uzanan kırmızı renkli anatomik üniteye verilen isimdir. Vermilion, her iki dudağın birbirine değdiği bölgede ıslak ve dışa bakan kısmında kuru olmak üzere iki farklı alan daha içermektedir. Vermilionun prekanseröz lezyonları, vermilionektomi adı verilen, eksizyon içeren bir cerrahi işlemi gerektirmektedir. Sadece yüzeyel lezyonların tedavisinde uygulanmaktadır. Özellikle, aktinik keilitis gibi displazik lezyonların tedavisinde efektif bir tedavi yöntemidir. Bu durumda oluşan defektin rekonstrüksiyonu klasik olarak, dudak ya da yanak mukozasından planlanan bir ilerletme flebi ile yapılabilir. Undermine edilen flep, defekti kapatacak şekilde ilerletilerek sütüre edilir. Bu prosedür "lip shave" olarak adlandırılmaktadır (5). Vermilion onarımında etkili tedavidir. Ancak, bazen hastalar, dudak kuruluğundan şikayetçi olabilirler. Bu durum hasta konforu ve memnuniyetini azaltmasına rağmen, nemlendirici kremler ile bu şikayet azaltılabilir. Ancak, hastalar vermilion bölgesindeki duyu azalması ve vermilion hattının incelmesi açısından uyarılmalıdırlar. İlerletme flebinin uygun bir şekilde undermine edilmesi ve ilerletilmesi hem dudağın incelmesini önlemek hem de dudak ekstropion riskini önlemek açısından önemlidir. Yine de, alt dudağın incelmesi ve gingivobukkal sulkusun sığlaşması bu teknik ile



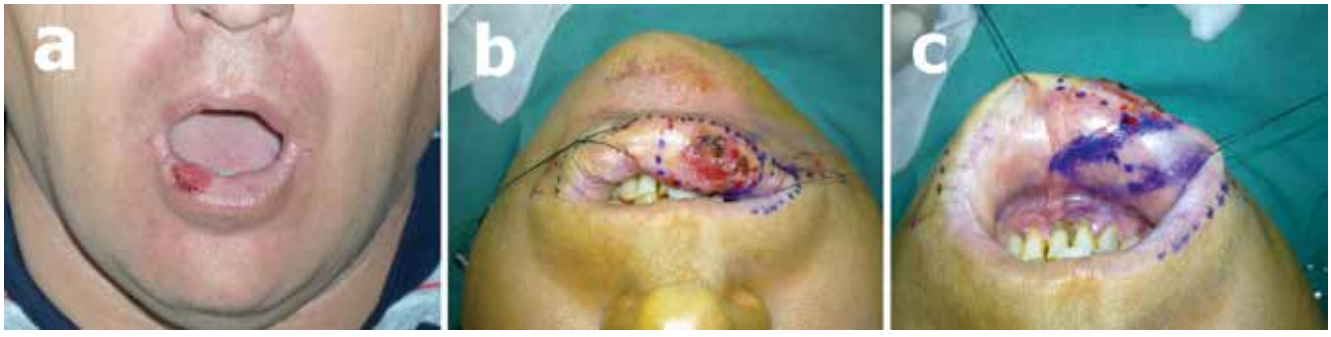
Şekil 2. a) Mevcut lezyon, 2 mm'lik güvenlik marjı ile orbikülaris oris kası korunarak eksize edildi ve 4x2 cm defekt oluştuğu izlendi, intraoperatif görüntüsü, b) Mevcut defekti onarmak için ağız içi mukozasından planlanan flep insize edildi, c) Planlanan flep, orbikülaris oris kası üzerindeki plandan eleve edildi

görülen komplikasyonlardır (1-5). Gingivobukkal sulkusun sığlaşması, yeme esnasında yiyeceklerin dökülmesine neden olabilmektedir. Aynı zamanda, dudak kenarı da içeri çekileceği için özellikle erkeklerde alt dudağın sakallı bölgesi üst dudakta erozyona sebep olabilmektedir (6). Wilson ve Walker (7), bu problemlerin üstesinden gelebilmek için, bu ilerletme flebine, gingivobukkal sulkusta bir serbestleme insizyonu eklemişlerdir. Böylece mukoza flebi bipediküllü flep olarak kullanılmıştır.

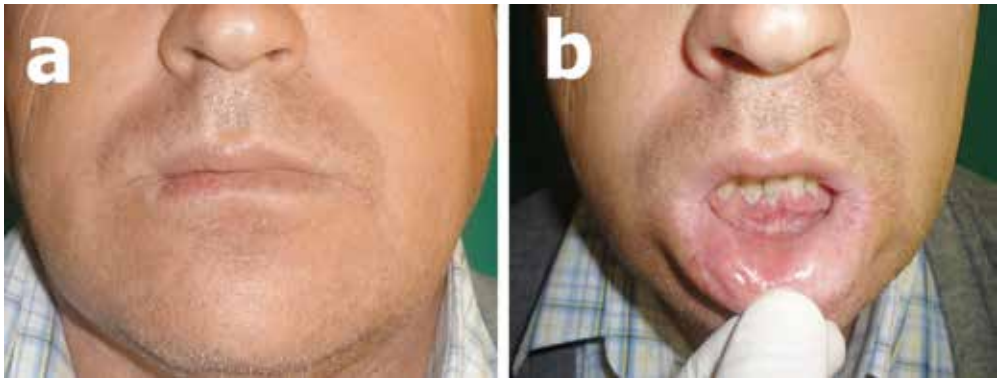
Şekil 3. Hastanın postoperatif 12. ay görüntüsü

Vermilion rekonstrüksiyonundaki diğer yöntemler başında; mukozal V-Y ilerletme flebi gelmektedir (6-8). Daha sıklıkla parsiyel vermilion rekonstrüksiyonunda kullanılan bu flep tekniğinde, oral mukozadan planlanan V şeklindeki mukozal flep, dekole edildikten sonra ilerletilerek defekte adapte edilir ve Y şeklinde bir sütürasyon hattı elde edilir. Teknik olarak basit olması, vermilionun kalan kısmı ile renk ve doku uyumu sağlaması gibi nedenlerden dolayı sık tercih edilmesine rağmen bu teknik ile kısıtlı ilerleme kayıt edilmesi, vermilion kontur problemleri, vermilionun onarılan kısmında ince kalması gibi estetik problemlere neden olabilmektedir (1-4).

Bahsedilen problemlerden dolayı, ideal flep arayışları hep devam etti. Literatüre bakıldığında alt dudak vermilion onarımı ile ilgili ilk makalede 1894 yılında Schulten (9) tarafından üst dudaktan bipediküllü flep ile yapıldığı görülmektedir. Schulten'dan (9) sonra çeşitli vermilion flepleri tarif edildi. Komşu vermiliondan ilerletme flebi küçük defektlerin onarımında ilk seçenek olarak önerilmektedir (10-12). Karşı dudaktan planlanan vermilion flepleri ise diğer bir alternatiftir. Bu teknikler ile iyi sonuçlar rapor edilmesine rağmen genel olarak 2 majör



Şekil 4. a) Kırk yedi yaşındaki erkek hasta, alt dudak paramediyan hatta, mukozal displazi tanısıyla opere edildi, preoperatif görüntüsü b) lezyonun eksizyon sınırları 2 mm'lik güvenlik marjı bırakılarak belirlendi, intraoperatif görüntüsü c) ağız içinden defekt ile 60 derece açı yapacak şekilde 4x2 cm ebadındaki mukozal transpozisyon flebi planlandı



Şekil 5. a) Hastanın, postoperatif 12. ay görüntüsü, b) hastanın takip süresi boyunca, ağız içinde, flebin kaldırıldığı donör sahada herhangi bir skar kontraksiyonu ya da fornikste sığlaşma gibi bir, komplikasyon ile karşılaşılmadı, operasyona bağlı skar fark edilecek ölçüde değildi

dezavantajdan bahsetmek gerekir; operasyon iki aşamalıdır, karşı vermilionda da deformiteye neden (13,14). Dil flebi, vermilion onarımında kullanılan başka bir seçenektir. Dil flebinin zengin vaskülarizasyonu bu flebi olanaklı hale getirmiştir. Ancak yine 2 aşamalı bir prosedür olması ve flep ayrılana kadar hasta konforunu göz ardı eden bir teknik olması ama en önemlisi her zaman sonucun estetik açıdan başarılı olamaması bu tekniğin dezavantajlarıdır (15).

Pelly ve Tan (16) alt vermilion rekonstrüksiyonu için üst dudak bukkal kısmından kommissür bazlı, muskulomukozal bir flep kullanmışlardır. Ancak, üst dudaktaki limitli doku nedeniyle, geniş defektlerin onarımında bu teknik ile kısıtlılık yaşanabilmektedir.

İlk mukozal ada flebi Carstens ve ark. (17) tarafından tarif edilmiştir. Yaptıkları çalışmada fasiyel arter bazlı 7x5 cm ebadında, bu flebin kaldırılabildiğini göstermişlerdir. Bu teknik, loop ile dikkatli bir diseksiyon ve eksternal nazolabial bir insizyon gerektirmektedir. Daha sonra, Pribaz ve ark. (18) fasiyel arter bazlı başka bir tip muskulomukozal flep tarif etmiştir. Bu flep, Doppler ultrason ile tespit edilen fasiyel arter trasesi boyunca planlanır ve mukoza, submukoza ve bir miktar bussinator kas içeren fasiyel arter bazlı aksiyel bir fleptir. Flebin pivot noktası, retromolar trigondur ve üst gingivobukkal sulkusa kadar uzanmaktadır. Ameliyat boyunca diseksiyon dikkatli ve özenli yapılmalıdır. İyi ve yüz güldüren sonuçlar bildirilmesine rağmen, cerrahi olarak zor bir tekniktir (19). Tezel ve ark. (20) komissür bazlı random paternli bir bukkal mukozal flep tariflemişlerdir. Bu flep parotid dukta kadar uzanmaktadır ve mukoza submukoza ve sadece ilk 1,5-2 cm'lik mesafesinde kas içermektedir. Flebin 3x6 cm ebadında kaldırılabileceği rapor edilmiştir.

Sonuç

Sunulan çalışmada, defektin hemen yanını pivot nokta olarak alan, random paternli mukoza ve submukozayı içeren alt dudak iç mukozasından eleve edilen bir transpozisyon flebi, ölçüleri 2x1 cm den 4x2 cm arasında değişkenlik gösteren vermilion defektlerinin onarımında kullanılmış, estetik ve fonksiyonel sonuçları, literatür gözden geçirilerek sunulmuştur. Oral mukozal transpozisyon flepleri, parsiyel vermilion defektlerinin onarımında hem estetik hem de fonksiyonel açıdan başarılı bulunmuş ve vermilion rekonstrüksiyonunda cerrahların ilk tercih seçenek olarak kullanabilecekleri bir teknik olduğu düşülmektedir.

Etik

Etik Kurul Onayı: Retrospektif çalışma.

Hakem Değerlendirmesi: Editörler kurulu tarafınca değerlendirilmiştir.

Kaynaklar

1. Sand M, Altmeyer P, Bechara FG. Mucosal advancement flap versus primary closure after vermilionectomy of the lower lip. Dermatol Surg 2010;36:1987-92.
2. Neligan PC. Strategies in lip reconstruction. Clin Plast Surg 2009;36:477-85.
3. Jin X, Teng L, Zhang C, et al. Reconstruction of partial-thickness vermilion defects with a mucosal V-Y advancement flap based on the orbicularis oris muscle. J Plast Reconstr Aesthet Surg 2011;64:472-6.
4. Tezel E. Buccal mucosal flaps: a review. Plast Reconstr Surg 2002;109:735-41.
5. Neligan P, Gullane P, Werning J. Lip reconstruction. In: Werning J, editor. Oral cancer. New York: Thieme Medical Publishing Inc; 2006. p. 180-93.
6. Kolhe PS, Leonard AG. Reconstruction of the vermilion after lip-shave. Br J Plast Surg 1988;41:68-73.
7. Wilson JS, Walker EP. Reconstruction of the lower lip. Head Neck Surg 1981;4:29-44.
8. Carvalho LM, Ramos RR, Santos ID, Brunstein F, Lima AH, Ferreira LM. V-Y advancement flap for the reconstruction of partial and full thickness defects of the upper lip. Scand J Plast Reconstr Surg Hand Surg 2002;36:28-33.
9. Schulten MW. En method att erstta en defekt af ena lappen medelst en bryggformad lamba fran den andra. Finska Lök-Sallsk-Hande 1894:35:859.
10. Goldstein MH. A tissue-expanding vermilion myocutaneous flap for lip repair. Plast Reconstr Surg 1984;73:768-70.
11. Ohtsuka H, Nakaoka H. Bilateral vermilion flaps for lower lip repair. Plast Reconstr Surg 1990;85:453-6.
12. Sakai S, Soeda S, Terayama I. Bilateral island vermilion flaps for vermilion border reconstruction. Ann Plast Surg 1988;20:459-61.
13. Standoli L. Cross lip flap in vermilion reconstruction. Ann Plast Surg 1994;32:214-7.
14. Wagner JD, Newman MH. Bipedicled axial cross-lip flap for correction of major vermilion deficiency after cleft lip repair. Cleft Palate Craniofac J 1994;31:148-51.
15. Baumann D, Robb G. Lip reconstruction. Semin Plast Surg 2008;22:269-80.
16. Pelly AD, Tan EP. Lower lip reconstruction. Br J Plast Surg 1981;34:83-6.
17. Carstens MH, Stofman GM, Hurwitz DJ, Futrell JW, Patterson GT, Sotereanos GC. The buccinator myomucosal island pedicle flap: anatomic study and case report. Plast Reconstr Surg 1991;88:39-50.
18. Pribaz J, Stephens W, Crespo L, Gifford G. A new intraoral flap: facial artery musculomucosal (FAMM) flap. Plast Reconstr Surg 1992;90:421-9.
19. Pribaz JJ, Meara JG, Wright S, Smith JD, Stephens W, Breuing KH. Lip and vermilion reconstruction with the facial artery musculomucosal flap. Plast Reconstr Surg 2000;105:864-72.
20. Tezel E, Numanoğlu A, Celebiler O, Bayramiçli M. Commissure-based buccal mucosal flap. Plast Reconstr Surg 1998;101:1223-7.

Özgün Araştırma / *Original Article*

DOI: 10.4274/haseki.3190
Med Bull Haseki 2017;55:52-5

Yoğun Bakım Ünitelerinde Yatan Hastalardan Elde Edilen Metisilin Dirençli Stafilokok Suşlarında Tigesiklin Etkinliğinin Araştırılması

Investigation of Antimicrobial Activity of Tigecycline in Methicillin Resistant Staphylococci Isolated from Hospitalized Patients in Intensive Care Units

Emine Küçükateş, Nazmi Gültekin*

İstanbul Üniversitesi Kardiyoloji Enstitüsü, Mikrobiyoloji ve Klinik Mikrobiyoloji Laboratuvarı, İstanbul, Türkiye
**İstanbul Üniversitesi Kardiyoloji Enstitüsü, Kardiyoloji Anabilim Dalı, Haseki, İstanbul, Türkiye*

Öz

Amaç: Çalışmamızda yoğun bakım ünitelerinde yatan hastalardan izole edilen metisilin dirençli stafilokok suşlarında tigesiklinin *in vitro* aktivitesinin değerlendirilmesi amaçlandı.

Yöntemler: Haziran 2014-Aralık 2015 tarihleri arasında İstanbul Üniversitesi Kardiyoloji Enstitüsü Koroner ve Cerrahi Yoğun Bakım Üniteleri'nde yatan hastaların kan, yara, idrar, kateter ucu, endotrakeal aspirasyon (ETA) ve balgam kültürlerinden izole edilen metisilin dirençli stafilokoklar incelendi. Stafilokokların identifikasyonu için konvansiyonel metodlar kullanıldı ve antibiyotik duyarlılık testleri Mueller Hinton Agar'ın Kirby-Bauer disk difüzyon yöntemi ile yapıldı.

Bulgular: Altmış yedi metisilin dirençli stafilokok suşunun 37'si (%55,2) *Staphylococcus aureus* (MRSA) ve 30'u (%44,8) koagülaz negatif stafilokok (MRKNS) olarak tanımlandı. MRSA'ların 20'si kan, 10'u yara, üçü ETA, ikisi idrar, biri kateter ucu ve biri de balgamdan izole edildi. MRKNS'lerin 20'si kan ve 10'u yaradan izole edildi ve tigesikline direnç saptanmadı.

Sonuç: Çalışmamızda metisilin dirençli stafilokok suşlarının tamamı tigesikline duyarlı bulundu. Tigesiklin, metisilin dirençli stafilokoklarla oluşan enfeksiyonlara karşı alternatif ilaç olarak kullanılabilir.

Anahtar Sözcükler: Yoğun bakım ünitesi, metisilin dirençli stafilokok, tigesiklin

Abstract

Aim: The aim of this study was to evaluate the *in vitro* antimicrobial efficacy of tigecycline in methicillin-resistant staphylococci isolated from patients hospitalized in intensive care units.

Methods: We investigated methicillin-resistant staphylococci isolated from blood, wound, urine, catheter tips, endotracheal aspiration fluids (ETA), and sputum specimens of patients hospitalized in the coronary and surgical intensive care units at İstanbul University Cardiology Institute, between June 2014 and December 2015. All staphylococci were identified by the conventional methods and susceptibility testing was performed using Mueller-Hinton Agar by the Kirby-Bauer disc diffusion method.

Results: Of 67 methicillin-resistant staphylococci, 37 (55.2%) were *Staphylococcus aureus* (MRSA) and 30 (44.8%) were coagulase negative staphylococci (MRCNS). MRSA were isolated from blood (20), wound (10), ETA (3), urine (2), catheter tips (1) and sputum (1). MRCNS were also identified in blood (20) and wound (10). All staphylococci were susceptible to tigecycline.

Conclusion: In our study, tigecycline was effective against all methicillin resistant staphylococci. Tigecycline can be an alternative to other drugs against infections caused by methicillin-resistant staphylococci.

Keywords: Intensive care unit, methicillin resistant *staphylococci*, tigecycline

Giriş

Stafilokoklar insan bakteri florasının bir üyesidirler ve insanda zararsız bir şekilde kolonize olabilirler. *Staphylococcus aureus* bütün dünyada toplum ve hastane kaynaklı enfeksiyonların en önemli nedenidir. Hastane enfeksiyonları günümüzde çok önemli bir morbidite ve mortalite nedenidir. Günümüzde koagülaz negatif stafilokoklar da hastane enfeksiyonları etkenleri arasında

Yazışma Adresi/Address for Correspondence: Emine Küçükateş
İstanbul Üniversitesi Kardiyoloji Enstitüsü, Mikrobiyoloji ve Klinik Mikrobiyoloji Laboratuvarı, İstanbul, Türkiye
Tel.: +90 212 459 20 24 E-posta: eates2002@yahoo.com
Geliş Tarihi/Received: 21 Mart 2016 **Kabul Tarihi/Accepted:** 12 Mayıs 2016

önemli bir yer yere sahiptir. Hastane enfeksiyonlarının üçte biri yoğun bakım ünitelerinde (YBÜ) oluşur. Bu enfeksiyonların gelişmesi; YBÜ'lerine yatan hastaların antibiyotik kullanımı ve dirençli mikroorganizmalarla kolonizasyon, invaziv cihazların ve işlemlerinin süresi, tipi ve sayısı, YBÜ'de kalış süresi, bozulmuş konak savunması ve altta yatan hastalığın mevcudiyeti gibi predispozan faktörlerin yüksek insidansına bağlıdır (1-6). *Staphylococcus aureus*'a metisilin direnci ilk olarak 1961 yılında bildirilmiştir. Metisilin dirençli *Staphylococcus aureus* (MRSA) suşları bütün beta laktam antibiyotiklere dirençlidirler. Bu nedenle glikopeptid antibiyotikler MRSA tedavisinde ilk seçenek olmuştur. Son yıllarda vankomisin intermediate ve hetero-rezistan MRSA suşların bildirilmesiyle birlikte alternatif antibiyotiklere gereksinim oluşmuştur (1-3,7).

Tigesiklin, klasik tetrasiklinlerin semi-sentetik analoğu olan glisilsiklin denen antibiyotik grubunun ilk üyesidir. Tigesiklin pasif difüzyonla porinler yoluyla bakterilerin dış membranından geçerek enerji bağımlı mekanizma tarafından sitoplazmaya ulaşarak ribozomlardaki protein sentezini inhibe eder. Bu etki, ilacın bakterilerin 30S ribozomal alt ünitesine bağlanarak aminoacyl tRNA'nın hedefine girişini engelleyerek oluşur ve etki bakteriyostatiktir. Tigesiklinin en önemli özelliği, ribozomal korunma ve efluks mekanizmaları gibi iki büyük tetrasiklin direnç mekanizmasına karşı etkili olmasıdır. Tigesiklin ve diğer antibiyotikler arasında çapraz direnç gözlenmemiştir. Tigesiklin aerob, Gram pozitif, Gram negatif, anaerop ve atipik bakteriyel patojenlere karşı geniş spektrumlu *in vivo* ve *in vitro* etkiye sahiptir. MRSA, penisiline dirençli *Streptococcus pneumoniae*, vankomisine dirençli enterokoklar, genişlemiş spektrumlu beta-laktamaz üreten *Enterobacteriaceae* ve karbapenem dirençli *Acinetobacter* cinsi çoğul dirençli bakterilere de etkilidir. *Bacteroides* cinsi *Clostridium perfringens* ve *Peptostreptococcus* cinsi anaerobik bakterilere, intrasellüler mikroorganizmalara ve non-tüberküloz mikobakterilere karşı da etkilidir. Bununla birlikte, *Pseudomonas aeruginosa*'ya karşı aktivitesi düşüktür ve *Proteus mirabilis*'e karşı ise orta derecede etkiye sahiptir (8-13).

Çalışmamızda, Haziran 2014-Aralık 2015 tarihleri arasında İstanbul Üniversitesi Kardiyoloji Enstitüsü koroner ve cerrahi ünitelerinde yatan hastalardan izole edilen metisilin dirençli stafilokokların tigesikline karşı *in vitro* etkinliğinin belirlenmesi amaçlanmıştır.

Yöntemler

Haziran 2014-Aralık 2015 tarihleri arasında İstanbul Üniversitesi Kardiyoloji Enstitüsü Koroner ve Cerrahi YBÜ'lerinde yatan hastaların mikrobiyoloji laboratuvarına gönderilen çeşitli klinik örneklerinden (kan, yara, idrar, kateter ucu, endotrakeal aspirasyon ve balgam) izole edilen 67 metisilin dirençli stafilokok çalışmaya alındı (Tablo). Her hastaya ait aynı örnekten bir suş çalışılmıştır. Kan kültürleri BACTEC/9050 (Becton Dickinson, Maryland, USA) otomatize kan kültür sisteminde inkübe edildi. Örneklerin %5 koyun kanlı agar ve endo besiyerlerine ekimleri yapıldı ve 37°C'de 24 saat inkübe edildi. Üreyen mikroorganizmaların makroskopik görünümleri, koloni morfolojileri ve Gram boyama özellikleri incelendi. Bütün mikroorganizmaların identifikasyonu konvansiyonel metodlarla yapıldı. Antibiyotik duyarlılık testleri Kirby-Bauer disk difüzyon yöntemi ile Klinik ve Laboratuvar Standartları Enstitüsü (CLSI) kriterlerine göre yapıldı ve değerlendirildi (14). Kontrol suşu olarak *Staphylococcus aureus* ATCC 29213 kullanıldı. Stafilokokların metisilin duyarlılığı disk difüzyon yöntemi ile yapıldı ve CLSI standartları doğrultusunda değerlendirildi. Bu amaçla Mueller Hinton Agar (MHA) (Oxoid, UK) besiyerine 0,5 McFarland bulanıklığındaki bakteri süspansiyonu yayıldı ve üzerine 30 µg sefoksitin (Oxoid, UK) diski yerleştirildi. 37°C'de 24 saat inkübe edildi ve zon çapları değerlendirildi.

Tigesiklin duyarlılığı için metisilin dirençli stafilokokların saf ve taze bakteri kültüründen 0,5 McFarland bulanıklığında süspansiyon hazırlandı ve MHA plakları yüzeyine yayıldı. Besiyerlerinin yüzeyine tigesiklin (15 µg) diski yerleştirildi. Plaklar 37°C'de 24 saat inkübe edildi ve zon çapları değerlendirildi. Tigesiklin sonuçları Amerikan Gıda ve İlaç Dairesi (FDA) önerileri doğrultusunda değerlendirilmiştir. Tigesiklin zon çapı 19≥ mm duyarlı olarak değerlendirildi.

Bulgular

Çalışmamıza 67 metisilin dirençli stafilokok suşu dahil edilmiştir. Altmış yedi suşun 37'si (%55,2) *Staphylococcus aureus* ve 30'u (%44,8) ise koagülaz negatif stafilokok idi. Metisilin dirençli *Staphylococcus aureus* ve koagülaz negatif stafilokok suşlarında tigesikline direnç saptanmadı.

Tartışma

YBÜ'ler hastane enfeksiyonları yönünden yüksek riskli alanlardır ve bütün hastane yataklarının %5-10'unu oluştururlar. YBÜ'lerdeki enfeksiyonlar diğer

Tablo. İzole edilen metisilin dirençli stafilokokların dağılımı

Örnek	MRSA	MRKNS
Kan	20	20
Yara	10	10
ETA	3	-
İdrar	2	-
Kateter ucu	1	-
Balgam	1	-
Toplam	37	30

ETA: Endotrakeal aspirasyon, MRSA: Metisilin dirençli *Staphylococcus aureus*, MRKNS: Metisilin dirençli koagülaz negatif stafilokok

birimlere göre beş ile yedi kat daha fazladır. YBÜ'lerde el hijyenine önem verilmelidir. Alkol bazlı sabun kullanımının bakteriyel enfeksiyon riskini azalttığı bildirilmektedir. Dirençli mikroorganizmaların sağlık personeli ile taşınması önlenmeli, dirençli enfeksiyonlarda mutlaka eldiven kullanılmalı ve standart prosedürlere uyulmalıdır. Metisilin direnci bütün dünyada YBÜ'lerde ortaya çıkan bir problemdir. Hastanelerde özellikle de YBÜ'lerde MRSA enfeksiyonlarının yayılımını önlemek için gerekli enfeksiyon kontrol önlemlerinin alınması ve uygulanması çok önemlidir (1-3,15). Dirençli mikroorganizmalarla oluşan enfeksiyonların tedavisinde yeni antibiyotiklere ihtiyaç vardır. Tigesiklin çoğul dirençli enfeksiyonların tedavisinde alternatif bir antimikrobiyal ajandır (8-12).

İspanya'da Sorlozano ve ark. (16) yaptığı çalışmada metisilin duyarlı ve dirençli *Staphylococcus aureus* suşlarında e-test ile tigesikline direnç saptamamışlardır. Hindistan'da Tellis ve ark. (17) e-test ile metisilin dirençli stafilokok suşlarının tamamını tigesikline duyarlı bulmuşlardır. Amerika Birleşik Devletleri'nde Sader ve ark. (18) kan dolaşım sistemi enfeksiyonlarından elde edilen *Staphylococcus aureus* ve koagülaz negatif stafilokoklarda tigesiklin duyarlılığını mikrodilusyon metodu ile çalışmışlar, *Staphylococcus aureus*'ta tigesikline %99,4 oranında, kogülaz negatif stafilokoklarda ise %97,5 oranında duyarlılık saptamışlardır. Pakistan'da Kaleem ve ark. (3) MRSA suşlarını disk difüzyon metodu ile çalışmışlar ve bütün suşları tigesikline duyarlı bulmuşlardır. İran'da Khalili ve ark. (1) yaptığı çalışmada MRSA ve metisilin duyarlı *Staphylococcus aureus* (MSSA) suşları disk difüzyon ve e-test metodu ile çalışmışlar ve tigesikline direnç saptamamışlardır. Latin Amerika'da Garza-Gonzales ve Dowzicky'nin (2) yaptığı çalışmada ise 2004-2010 yılları arasında 3126 *Staphylococcus aureus* izolatı toplanmış, bunların 1467'si (%46,9) MRSA olarak saptanmıştır. MDSA ve MRSA'larda tigesiklin duyarlılığı mikrodilüsyon metoduyla çalışılmış, stafilokok suşları tigesikline %99,9 duyarlı bulunmuştur ve üç MRSA'da tigesikline direnç saptanmıştır (Honduras'da bir suş ve El Salvador'da iki suş).

Türkiye'de yapılan çalışmalarda ise, Öksüz ve Gürler (19) e-test metodu ile tigesiklin duyarlılığı çalışmış, 49 MRSA suşunda %2,59 MRKNS suşunda ise %3 oranında direnç saptamışlardır. Suşların izole edildiği hastaların tedavisinde tigesiklin kullanılmadığından, antibiyotik kullanımına bağlı olmayan bir mekanizma ile örneğin MATE atım pompası yoluyla direnç gelişmiş olabileceğini düşünmüşlerdir (19). Opuş ve ark.'nın (20) çalışmasında da MRSA suşlarında e-test metodu ile tigesiklin duyarlılığı araştırılmış ve bütün suşlar tigesikline duyarlı bulunmuştur. Köse ve ark. (21) çalışmalarında tigesiklin e-test metodu ile çalışılmış, MSSA ve MRSA suşlarının tamamı tigesikline duyarlı bulunmuştur. Zarakolu ve ark.'nın (22) çalışmasında MRSA suşlarının e-test metodu ile tigesiklin duyarlılığı araştırılmış ve bütün suşlar tigesikline duyarlı bulunmuştur. Bizim çalışmamızda da YBÜ'lerimizden izole ettiğimiz metisilin dirençli stafilokoklarda tigesikline direnç saptanmamıştır ve yurt dışı ve yurt içinde yapılan çalışmalarla uyumlu bulunmuştur.

Sonuç

Çalışmamızda, metisilin dirençli *Staphylococcus aureus* ve koagülaz negatif stafilokok suşlarında tigesikline direnç saptanmadı. Hastanemizde MRSA enfeksiyonlarının tedavisi için tigesiklin alternatif bir ilaç olabilir.

Etik

Hasta Onayı: Çalışmamız *in vitro* olup laboratuvar şartlarında gerçekleştirilmiştir. Konu ile ilgili hastaların tedavilerine müdahale edilmemiştir.

Hakem Değerlendirmesi: Editörler kurulu tarafınca değerlendirilmiştir.

Yazarlık Katkıları

Konsept: Emine Küçükateş, Nazmi Gültekin. Dizayn: Emine Küçükateş, Nazmi Gültekin. Veri Toplama veya İşleme: Emine Küçükateş. Analiz veya Yorumlama: Emine Küçükateş, Nazmi Gültekin. Literatür Arama: Emine Küçükateş, Nazmi Gültekin. Yazan: Emine Küçükateş, Nazmi Gülltekin.

Çıkar Çatışması: Yazarlar tarafından çıkar çatışması bildirilmemiştir.

Finansal Destek: Yazarlar tarafından finansal destek almadıkları bildirilmiştir.

Kaynaklar

1. Khalili H, Dashti-Khavidaki S, Khaleghi S, Maleki Z, Rasoolinejad M. Evaluation of tigecycline activity against methicillin-resistance Staphylococcus aureus isolated from biological samples. Iran J Pharm Res 2010;9:61-5.
2. Garza-Gonzales E, Dowzicky MJ. Changes in Staphylococcus aureus susceptibility across Latin America between 2004 and 2010. Braz J Infect Dis 2013;17:13-9.
3. Kaleem F, Usman J, Hassan A, Omair M, Khalid A, Uddin R. Sensitivity pattern of methicillin resistant Staphylococcus aureus isolated from patients admitted in a tertiary care hospital of Pakistan. Iran J Microbiol 2010;2:141-3.
4. Vincent JL. Nosocomial infections in adult intensive-care units. Lancet 2003;361:2068-77.
5. Warren DK, Kollef MH. Prevention of hospital infection. Microbes Infect 2005;7:268-74.
6. Vincent JL, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of infection in Intensive Care (EPIC) study. EPIC International Advisory Committee. JAMA 1995;274:639-44.
7. Cartolano GL, Cheron M, Benabid D, Leneveu M, Boisivon A; Association of Hospital Bacteriologists, Virologists and Hygiene Professionals. Methicillin-resistant Staphylococcus

aureus (MRSA) with reduced susceptibility to glycopeptides (GISA) in 63 French general hospitals. Clin Microbiol Infect 2004;10:448-51.

8. Petersen PJ, Jacobus NV, Weiss WJ, Sum PE, Testa RT. In vitro and in vivo antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivate of minocycline (GAR-936). Antimicrob Agents Chemother 1999;43:738-44.
9. Garrison MW, Neumiller JJ, Seter SM. Tigecycline: an investigational glycylcycline antimicrobial with activity against resistant gram-positive organisims. Clin Ther 2005;27:12-22.
10. Noksin GA. Tigecycline: a new glycylcycline for treatment of serious infections. Clin Infect Dis 2005;41:303-14.
11. Projan SJ. Preclinical pharmacologyof GAR-936 , a novel glycylcycline antibacterial agent. Pharmacotherapy 2000;20:219-23.
12. Zinner SH. Overwiev of antibiotic use and resistance: setting the stage for tigecycline. Clin Infect Dis 2005;41:289-92.
13. Lee SY, Kuti JL, Nicolau DP. Polymyxins: older antibiotics for a new threat. Conn Med 2006;70:25-8.
14. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing, 19 th informational supplements, 2009; M100-S19. Wayne, PA: Clinical and Laboratory Standards Institute, 2009.
15. Barsanti MC, Woeltjie KF. Infection prevention in the intensive care unit. Inf Dis Clin N Am 2009;23:703-25.
16. Sorlozano A, Gutierrez J, Salmeron A, et al. Activity of tigecycline against clinical isolates of Staphylococcus aureus and extended-spectrum β-lactamase-producing Escherichia coli in Granada, Spain. Int J Antimicrob Agents 2006;28:532-6.
17. Tellis R, Rao S, Lobo A. An in-vitro study of tigecycline susceptibility among multidrug resistant bacteria in a tertiary care hospital. IJBR 2012;3:192-5.
18. Sader HS, Jones RN, Stilwell MG, Dowzicky MJ, Fritsche TR. Tigecycline activity tested against 26,474 bloodstream infection isolates: a collection from 6 continents. Diagn Microbiol Infect Dis 2005;52:181-6.
19. Öksüz L, Gürler N. Klinik örneklerden izole edilen metisiline dirençli stafilokok suşlarının son yıllarda kullanıma giren antibiyotiklere in vitro duyarlılık sonuçları. Ankem Derg 2009;23:71-7.
20. Opuş A, Keşli R, Kurtoğlu MG, Güzelant A, Uysal EB. Metisiline dirençli stafilokok suşlarında tigesiklin etkinliğinin araştırılması. Turk Hij Den Biyol Derg 2012;69:121-6.
21. Köse S, Ece G, Türken M, Gözaydın A, Tatar B. Tepecik Eğitim ve Araştırma Hastanesi infeksiyon hastalıkları ve mikrobiyoloji laboratuarında izole edilen bakterilerin tigesiklin ve diğer antibiyotiklere duyarlılığının incelenmesi. Fırat Tıp Derg 2012;17:10-3.
22. Zarakolu P, Metan G, Altun B, Hasçelik G, Ünal S. Antimicrobial susceptibility, inducible macrolide-lincosamide-streptogramin B, and clonal diversity patterns of nosocomial methicillin-resistant Staphylococcus aureus strains isolated in Hacettepe University adult hospital. Turk J Med Sci 2009;39:783-9.

Özgün Araştırma / *Original Article*

DOI: 10.4274/haseki.3031
Med Bull Haseki 2017;55:56-60

Diyabetik Ayak Enfeksiyonlu Yirmi Yedi Olgunun Retrospektif Olarak Değerlendirilmesi

Retrospective Evaluation of Twenty Seven Patients with Diabetic Foot Infection

Sevtap Şenoğlu, Şemsi Nur Karabela, Kadriye Kart Yaşar, Bülent Durdu*, Habip Gedik, Birsen Ersöz, Vesile Şahin, Nuray Güleç

Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği, İstanbul, Türkiye
**Bezmialem Vakıf Üniversitesi Tıp Fakültesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, İstanbul, Türkiye*

Öz

Amaç: Çalışmamızda, izlediğimiz diyabetik ayak enfeksiyonlu (DAE) olgular irdelenmiştir.

Yöntemler: Haziran 2013-Ocak 2014 tarihleri arasında kliniğimizde takip edilen 27 DAE'li olgu; demografik özellikleri, klinik ve laboratuvar bulguları açısından retrospektif olarak değerlendirildi. Hastaların ayak lezyonları, Wagner sınıflamasına göre sınıflandırıldı.

Bulgular: Hastaların 12'si kadın, 15'i erkek ve yaş ortalaması 59 idi. Hastaların %89'unda eritrosit sedimentasyon hızı (ESR), %78'inde C-reaktif protein (CRP) ve sadece %22'sinde beyaz kan hücre yüksekliği saptandı. Hastaların %78'i evre 2 ve daha düşük evreliydi. Derin doku kültürü yapılabilen 18 olgudan beşinde (%28) metisiline dirençli *Staphylococcus aureus, Enterobacter cloacae* ve *Enterococcus spp*. üredi.

Sonuç: DAE'li olguların klinik, nörolojik, vasküler durum ve ülser derinliğini dikkate alarak yapılan ve yol gösterici olan sınıflandırmalarla; uygun tanı ve tedavileri planlanabilir. Bu olguların takibinde ESR ve CRP testleri, osteomiyelit gibi ampütasyonu kolaylaştıran komplikasyonların tanı ve tedavisinde oldukça faydalıdır. Tedavi, üçüncü basamak sağlık kuruluşlarında multidisipliner bir yaklaşımla yapılmalıdır.

Anahtar Sözcükler: Diyabetik ayak enfeksiyonu, Wagner sınıflaması, diabetes mellitus

Abstract

Aim: This study analyzed diabetic foot infections (DFI) in patients who were followed up in our clinic.

Methods: We retrospectively evaluated demographic characteristics and clinical and laboratory findings in 27 patients (12 female, 15 male) with DFI who were followed up in our clinic between June 2013 and January 2014. The foot ulcerations in the patients were classified according to Wagner's classification.

Results: The mean age of the patients was 59 years. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and white blood cell levels were found to be high in 89%, 78% and only 22% of patients, respectively. 78% of patients had grade 2 and lower grade ulcerations. Growth of methicillin-resistant *Staphylococcus aureus, Enterobacter cloacae* and *Enterococcus spp*. was encountered in five (28%) of 18 patients in whom deep tissue culture test could be performed.

Conclusion: Appropriate diagnosis and treatment planning can be achieved by guiding classifications performed by regarding clinical, neurological and vascular conditions as well as ulcer depth. In follow-up of cases, ESR and CRP tests are very useful in diagnosis and treatment of the complications such as osteomyelitis, which may lead to amputation. Treatment should be conducted with a multidisciplinary approach in tertiary healthcare facilities.

Keywords: Diabetic foot infection, Wagner's classification, diabetes mellitus

Giriş

Diyabetin en sık komplikasyonlarından biri olan diyabetik ayak enfeksiyonu (DAE) tüm dünyada olduğu gibi ülkemizde de hastaneye yatışların ve diyabetik olgulardaki non-travmatik ayak ampütasyonlarının önemli bir sebebidir (1-3). DAE; immün sistem bozukluğunun bulunduğu kişide dış travma, biyomekanik streste artış, periferik nöropati ve damar hastalığına sekonder iskemi

Yazışma Adresi/Address for Correspondence: Sevtap Şenoğlu
Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği, İstanbul, Türkiye E-posta: drsevtap@yahoo.com
Geliş Tarihi/Received: 21 Ocak 2016 **Kabul Tarihi/Accepted:** 19 Nisan 2016

Bu çalışma 3. Ulusal Diyabetik Ayak İnfeksiyonları Sempozyumu'nda, 8-10 Mayıs 2014 tarihleri arasında sunulmuştur, İstanbul, Türkiye

zeminine enfeksiyonun eklenmesiyle ortaya çıkar (4). Glisemik kontrolün sağlanamadığı olgularda, hemoglobin A1c seviyesindeki yüksekliğin de diyabetik ülser gelişimi ve yara iyileşmesindeki gecikmeyle olan yakın ilişkisi de bilinmektedir (5). Tedavisi multidisipliner olup, enfeksiyon hastalıkları, cerrahi, vasküler cerrahi, ortopedi gibi pek çok kliniğin multidisipliner yaklaşımını gerektirir (6).

DAE'de genellikle uzun süreyle, geniş spektrumlu antibiyotikler kullanılmaktadır. Antibiyotik tedavisi yanında cerrahi debridman, yara bakımı ve hiperbarik oksijen (HBO) tedavisi gibi, maliyeti yüksek, yönetimi zor ve tedavi şansı düşük yardımcı tedavi yöntemleri de denenmektedir (4,6-8). Bu tedavilerle hastane maliyetleri artmakta, yatak işgal süresi uzamakta ve bu konuda deneyimli personel ihtiyacı da ayrı bir problem olarak karşımıza çıkmaktadır. DAE'lerin; iş gücü kaybına, sakatlıklara ve hastayı umutsuzluğa sürükleyen psikososyal travmalara da yol açabilmesi, buzdağının görünmeyen kısmıdır (9). Önceki yıllarda anaerob bakteriler ve Gram pozitif koklarla DAE sıklığı daha yaygın iken, artık pek çok ilaca dirençli Gram negatif bakterilerle oluşan enfeksiyonlar klinisyeni zorlamakta, etkin bir şekilde tedavi edilemeyen DAE'ler sonrası ayak ampütasyonu riski artmaktadır (2,10,11).

Bu çalışmada, Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği'nde izlenen DAE'li olgular irdelenmiştir.

Yöntemler

Haziran 2013-Ocak 2014 tarihleri arasında kliniğimizde takip edilen 27 DAE'li olgu; demografik özellikleri, klinik ve laboratuvar bulguları açısından retrospektif olarak değerlendirildi. Hastaların ayak lezyonları, Wagner sınıflamasına göre sınıflandırıldı (Tablo 1) (12,13).

Kültür örneği sadece derin doku kültürü ve apse kültürü şeklinde alındı. Sürüntü kültürleri çalışma kapsamında değerlendirilmedi. Kültür alındığı sırada hastaların çoğu, ampirik olarak reçete edilmiş oral antibiyotik tedavisi almaktaydı (kinolon ve betalaktamaz inhibitörlü aminopenisilin grubu). Alınan derin doku ve apse kültürleri, tiyoglikolat buyyon, koyun kanlı ve eozin metilen mavisi agara ekilerek 35°C'de 24-48 saat inkübe edildi.

Tablo 1. Meggit-Wagner sınıflaması
Evre tanımı
0: Sağlam deri, pre-ülseratif lezyon
1: Lokalize yüzeyel ülser
2a: Derin ülser
2b-2a +: enfeksiyon/selülit
3a: Derin apse ± selülit
3b: Osteomiyelit ± selülit
4: Parmaklar veya ayak ucunda kangren
5: Tüm ayakta kangren

Üreyen bakterilerin koloni morfolojisi ve üreme özellikleri incelenerek Gram boyama yapıldı. Bakteri identifikasyonu ve antimikrobiyal duyarlılığı otomatize Becton-Dickinson Phoenix 100 (Becton-Dickinson, Maryland, USA) cihazı ile yapıldı.

Bulgular

Hastaların 12'si kadın, 15'i erkek ve yaş ortalaması 59 idi. Hastalara ait özellikler Tablo 2'de özetlenmiştir.

Diyabet tanısının konmasından bu yana geçen süre ortalama 19,5 yıl olup dördü hariç hastaların %85'i insülin kullanmaktaydı. Wagner sınıflamasına göre değerlendirildiğinde, hastaların %78'i evre 2 ve düşük evreliydi (Resim 1, 2, 3).

Hastaların %89'unda eritrosit sedimentasyon hızı (ESR), %78'inde C-reaktif protein (CRP) ve sadece %22'sinde beyaz kan hücresi yüksekliği saptandı. Derin doku ve apse kültürü yapılabilen 18 olgudan beşinde (%28) metisiline dirençli *Staphylococcus aureus, Enterobacter cloacae* ve *Enterococcus spp*. üredi. Olguların tedavisi (glisemik kontrol, parenteral antibiyotik, cerrahi debridman, apse boşaltılması, HBO tedavisi vb.) yapılarak poliklinik takibine alındı.

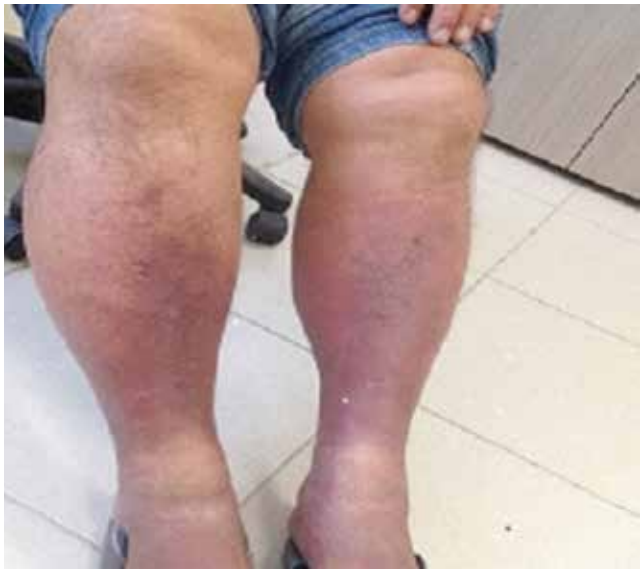
Tartışma

DAE, yüksek mortalite ve morbidite nedeniyle önemli olup her dört diyabetikten birinin sağlık kuruluşlarına

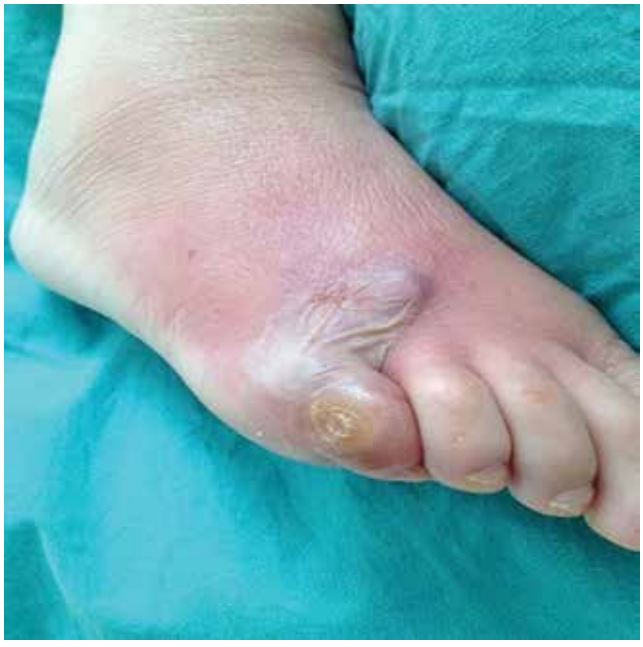
Tablo 2. Olguların klinik ve laboratuvar özellikleri			
	Kadın (n=12)	**Erkek (n=15)**	**Toplam (n=27)**
Yaş ortalaması (Yıl)	62,3	56,4	59
Diyabetin süresi (yıl)	22,9	16,7	19,5
İnsülin kullanımı (n)	11/12	12/15	23/27
HbA1c düzeyi ortalaması	8,3	7,9	8,1
Wagner evre 1 (n)	6	5	11
Wagner evre 2 (n)	4	6	10
Wagner evre 3 (n)	1	4	5
Wagner evre 4 (n)	1	-	1
WBC ortalaması (mm^3)	8,6	8,546	8,57
CRP ortalaması (mg/dL)	9,5	7,4	8,4
ESR ortalaması (mm/sa)	59,6	48,3	53,3
Kültür yapılabilen olgu (n)	6	12	18
Kültürde üremesi olan olgu (n)	2	3	5
DAE süresi ortalaması (ay)	2,5	5,1	3,9
Önceki ampütasyon varlığı (n)	1	2	3
Selülit varlığı (n)	8	6	14
Osteomiyelit varlığı (n)	2	2	4

HbA1c: Hemoglobin A1c, DAE: Diyabetik ayak enfeksiyonu, ESR: Eritrosit sedimentasyon hızı, WBC: Beyaz kan hücresi, CRP: C-reaktif protein

başvuru sebebi olması yanında, uzun ve sık hastane yatışlarına da yol açmaktadır. Diyabetik olgularda ayak ülserlerinin yıllık insidansı %1-4; prevalansı ise %5-10 civarındadır (14). DAE insidansının yaş ilerledikçe arttığı bilinmektedir (15). Çalışmamızdaki olguların da yaş ortalaması 59 idi. DAE ve bu olgulardaki ampütasyon sıklığının, erkek olgularda daha sık görüldüğü gösterilmiştir (15-18). Gerçekten de gerek olgularımızdaki erkek oranı (%56), gerekse erkek olgulardaki eski ampütasyon öyküsü ve ileri evre olma özelliği kadın olgularımıza göre daha yüksek bulunmuştur.



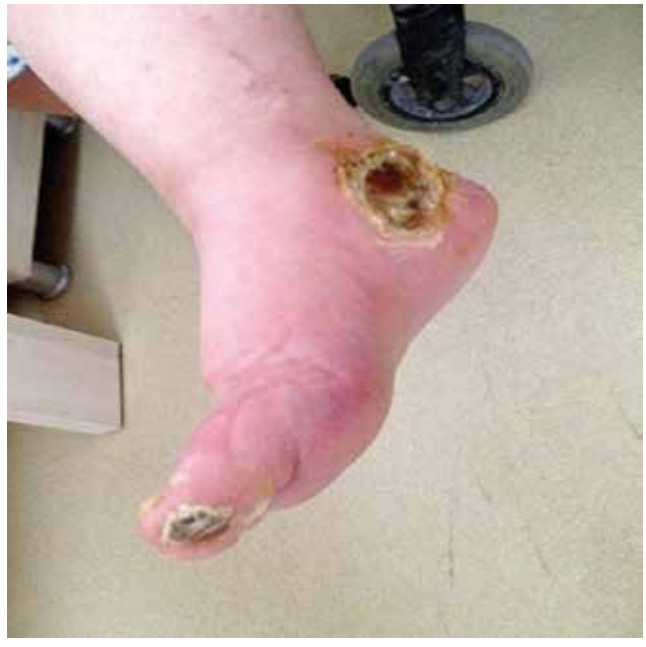
Resim 1. Selülit tanılı Wagner evre 1 olgu



Resim 2. Ayakta lezyonu bulunan Wagner evre 2 olgu

DAE ile diyabetli olarak geçirilen süre ve diyabetin tipi arasında bilinen bir ilişki söz konusudur (15,19). Olgularımız arasında, diyabet tanısının konmasından bu yana geçen süre ortalama 19,5 yıl olup dördü hariç hastaların %85'i insülin kullanan tip 2 diyabetli hastalardı. Ayrıca üç olguda eski ampütasyon ile dört olgumuzdaki ciddi osteomiyelit varlığı, diyabetin süresiyle ciddi DAE gelişimi arasındaki ilişkiyi doğrulamaktadır.

Diyabetik hastalar, gerek diyabetin enfeksiyonlara yatkınlık oluşturması gerekse mikroanjiyopati ve nöropati nedeniyle sık hastaneye yatan ve cerrahi işlem uygulanan, geniş spektrumlu ve uzun süreyle antibiyotik kullanan hastalardır. Diyabetik ayak bölgesindeki dolaşım bozuklukları, antibiyotiklerin doku penetrasyonunu azalttığı gibi doku iyileşmesini de geciktirerek enfeksiyonun ciddiyetine katkıda bulunur. Diyabetiklerdeki aterosklerotik tıkayıcı lezyonlar, diyabetik olmayanlarla benzerdir, sadece insidans ve gelişme hızı diyabetiklerde anlamlı olarak daha fazladır (8). İyi kanlanan doku ülser gelişimine dirençli olduğu gibi, iyi kanlanan dokuda ülser gelişse de iyi ve etkin tedaviyle komplikasyonsuz iyileşme mümkündür. DAE'li olgularda ayak bileği ve parmak arter basınç muayenesi, Doppler incelemeleri ve anjiyografi teknikleri, ayak dolaşımının değerlendirilmesinde olmazsa olmazdır. Doppler incelemede trifazik dalgalanmanın kaybolması, monofazik patern varlığı, vasküler rekonstrüksiyon gerektiğininin göstergesidir (8). DAE'li olgulardaki patolojiden önemli oranda bu olgulardaki nöropati de sorumlu olup olguların çoğunda mevcuttur (15). DAE'li olguların klinik, nörolojik, vasküler durum ve ülser derinliğini dikkate alarak yapılan sınıflandırmalar, gerek tanı gerek tedavide yol göstericidir.



Resim 3. Derin topuk yarası olan Wagner evre 3 olgu

Çalışmamızda da bugüne kadar kullanılan sınıflandırmalar içinde yaygın, standart, pratik ve kullanışlı olduğu bilinen Meggit-Wagner sınıflaması kullanılmıştır (12,13,20,21). Bu sınıflamaya göre yarayı ve ayağın durumunu tanımlayan beş evre olup evre 0'da ayakkabının basınç etkisi, evre 1'de yüzeyel, evre 2'de derin açık ülser mevcuttur. Evre 3, derin ülsere enfeksiyonun eklendiği durum olup antibiyotik tedavisi yanında cerrahi derbritman, lokal tedaviler uygulanmalıdır. Evre 4'te enfeksiyona kangren bulguları eşlik eder. HBO tedavisi, diğer tedavilere eklenebilir. Evre 5, yaygın ülser ve kangrenin olduğu evre olup ampütasyon riski yüksektir (21). Çalışmamızdaki olguların çoğu evre 1 ve 2 olan olgulardı. Enfeksiyon hastalıkları ve klinik mikrobiyoloji kliniği, hastanemizde DAE'li olguların gerek ayaktan gerekse yatırılarak takip ve tedavi edildiği bir klinik olduğundan; cildiye, ortopedi, kalp damar cerrahisi ve plastik cerrahi kliniklerinin de desteğiyle erken dönemdeki DAE'li olgular sıklıkla kliniğimizde izlenmektedir. Evre 3 ve daha ileri olguların cerrahi işlem sonrası uzun dönem takipleri de kliniğimizde yapılmaktadır.

Özellikle geriatrik hasta popülasyonun önemli bir sağlık problemi olan DAE'lerin tanı ve tedavi takibinde ESR ve CRP testleri vazgeçilmez testlerdir. Çalışmamızdaki olguların %89'unda ESR, %78'inde CRP ve sadece %22'sinde beyaz kan hücresi yüksekliği saptandı. Lökositoz olmamasına rağmen özellikle ESR takibinin osteomiyelit varlığı ve şüphesinde önemli bir indikatör olması yanında, ≥70 mm/saat olduğunda ampütasyon için önemli bir prediktör olduğu da gösterilmiştir (18). Çalışmamızda derin doku ve apse kültürü yapılabilen 18 olgudan beşinde metisiline dirençli *Staphylococcus aureus, Enterobacter cloacae* ve *Enterococcus spp*. üretilmiştir (%28). Olguların çoğu, kültür alındığı sırada ampirik olarak başlanmış olan oral kinolon, ampisilin-sulbaktam veya amoksisilin-klavulunat gibi antibiyotikleri kullanmaktaydı. Kültür pozitiflik oranımızın düşüklüğü bu durumla ilgili olabilir. Ülkemizde yapılan çalışmalarda derin doku kültürlerinden en çok izole edilen patojenler Pseudomonas, E.coli olmuş ve bu Gram negatif basillerin gerek prognoz gerek ampütasyon için belirleyici olduğu gösterilmiştir. Aynı çalışmalarda en sık izole edilen gram pozitif patojenler ise, çalışmamızda da izole ettiğimiz metisilin dirençli Staphylococcus aureus ve enterokoklar olmuştur (18,22,23).

Sonuç

DAE'li olguların klinik, nörolojik, vasküler durum ve ülser derinliğini dikkate alarak yapılan ve yol gösterici olan sınıflandırmalarla; uygun tanı ve tedavileri planlanabilir. Bu olguların takibinde ESR ve CRP testleri, osteomiyelit gibi ampütasyonu kolaylaştıran komplikasyonların tanı ve tedavisinde oldukça faydalıdır. Erken evrede sıklıkla aile hekimlerince ampirik olarak tedavi edilen; uzun yıllardır diyabeti olan ve ayak bakımının yapılmadığı, glisemik kontrolün olmadığı yaşlı olgularda yönetimi oldukça güç olan DAE tedavisi; enfeksiyon hastalıkları, ortopedi, plastik cerrahi ve kalp-damar cerrahisi gibi kliniklerin bulunduğu, üçüncü basamak sağlık kuruluşlarında multidisipliner bir yaklaşımla yapılmalıdır. Aksi halde tanı ve tedavideki gecikme, hayatı tehdit eden komplikasyonlara yol açabilir.

Etik

Hakem Değerlendirmesi: Editörler kurulu dışındaki kişiler tarafınca değerlendirilmiştir.

Yazarlık Katkıları

Cerrahi ve Medikal Uygulama: Sevtap Gürsoy, Kadriye Kart Yaşar. Konsept: Sevtap Gürsoy, Şemsi Nur Karabela. Dizayn: Sevtap Gürsoy, Kadriye Kart Yaşar, Şemsi Nur Karabela. Veri Toplama ve İşleme: Sevtap Gürsoy, Habip Gedik, Bülent Durdu, Vesile Şahin, Birsen Ersöz. Analiz ve Yorumlama: Sevtap Gürsoy, Kadriye Kart Yaşar, Şemsi Nur Karabela, Nuray Güleç. Literatür Arama: Sevtap Gürsoy, Kadriye Kart Yaşar, Şemsi Nur Karabela. Yazan: Sevtap Gürsoy.

Çıkar Çatışması: Yazarlar bu makale ile ilgili herhangi bir çıkar çatışması bildirmemiştir.

Finansal Destek: Çalışmamız için hiçbir kurum ya da kişiden finansal destek alınmamıştır.

Kaynaklar

1. Gariani K, Uckay I, Lipsky BA. Managing diabetic foot infections: a review of new guidelines. Acta Chir Belg 2014;114:7-16.
2. Hatipoglu M, Mutluoglu M, Uzun G, Karabacak E, Turhan V, Lipsky BA. The microbiologic profile of diabetic foot infections in Turkey: a 20-year systematic review: diabetic foot infections in Turkey. Eur J Clin Microbiol Infect Dis 2014;33:871-8.
3. do Amaral Junior AH, do Amaral LA, Bastos MG, do Nascimento LC, Alves MJ, de Andrade MA. Prevention of lower-limb lesions and reduction of morbidity in diabetic patients. Rev Bras Ortop 2014;49:482-7.
4. Hobizal KB, Wukich DK. Diabetic foot infections: current concept review. Diabet Foot Ankle 2012:3.
5. Akçay S, Satoğlu İS, Kurtulmuş A, Harman E, Erpala F. HbA1c'nin diyabetik ayak ülseri iyileşmesindeki prognostik önemi. Fırat Tıp Dergisi 2013;18:48-50.
6. Uçkay I, Aragon-Sanchez J, Lew D, Lipsky BA. Diabetic foot infections: what have we learned in the last 30 years? Int J Infect Dis 2015;40:81-91.
7. Markakis K, Bowling FL, Boulton AJ. The diabetic foot in 2015: an overview. Diabetes Metab Res Rev 2016;31(Suppl 1)169-78.
8. Demir Y, Demir S, Gökçe Ç. Diabetik ayak: Fizyopatolojisi, tanısı ve rekonstrüksiyon öncesi tedavisinde güncel yaklaşımlar. Kocatepe Tıp Dergisi 2004;5:1-12.
9. Brem H, Sheehan P, Rosenberg HJ, Schneider JS, Boulton AJ. Evidence-based protocol for diabetic foot ulcers. Plast Reconstr Surg 2006;117(7 Suppl):193-209.

10. Arıkan Y, Kuzgun Ü, Sever C, Armağan R. Diyabetik ayak yarası olan hastalara multidisipliner yaklaşımda ortopedinin yeri. Şişli Etfal Hastanesi Tıp Bülteni 2010;44:106-12.
11. Muhammad-Lutfi AR, Zaraihah MR, Anuar-Ramdhan IM. Knowledge and practice of diabetic foot care in an in-patient setting at a tertiary medical center. Malays Orthop J 2014;8:22-6.
12. Meggit B. Surgical management of the diabetic foot. Br J Hosp Med 1976;16:227-332.
13. Wagner FW Jr. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle 1981;2:64-122.
14. Moulik P, Mtonga R, Gill GV. Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. Diabetes Care 2003;26:491-4.
15. Özkan Y, Çolak R, Demirdağ K, Yıldırım MA, Özalp G, Koca SS. Diyabetik ayak sendromlu 142 olgunun retrospektif değerlendirilmesi. Turkiye Klinikleri J Endocrin 2004;2:191-5.
16. Hekimsoy Z, Tarhan O, Çömlekçi A, et al. Diabetic Extremity Infections. Turk J Endocrinol Metab 1998;1:25-30.
17. Armstrong DG, Lavery LA, van Houtum WH, Harkless LB. The impact of gender on amputation. J Foot Ankle Surg 1997;36:66-9.
18. Saltoglu N, Yemisen M, Ergonul O, et al. Predictors for limb loss among patient with diabetic foot infections: an observational retrospective multicentric study in Turkey. Clin Microbiol Infect 2015;21:659-64.
19. Joseph WS. Treatment of lower extremity infections in diabetics. Drugs 1991;42:984-96.
20. Parisi MC, Zantut-Wittmannn DE, Pavin EJ, Machado H, Nery M, Jeffcoate WJ. Comparison of three systems of classification in predicting the outcome of diabetic foot ulcers in a Brazilian population. Eur J Endocrinol 2008;159:417-22.
21. Aktürk M, Demirci H, Karakoç A, et al. Wagner sınıflamasına göre evre 3 ve 4 olan diabetik ayak olgularında alt ekstremite amputasyon sıklığı. GMJ 2006;17:49-52.
22. Bozkurt F, Tekin R, Çelen MK, Ayaz C. Diyabetik ayak enfeksiyonlarında tedavi yaklaşımı. Konuralp Tıp Dergisi 2012;4:15-9.
23. Turhan V, Mutluoglu M, Acar A, et al. Increasing incidence of Gram-negative organisms in bacterial agents isolated from diabetic foot ulcers. J Infect Dev Ctries 2013;7:707-12.

Case Report / *Olgu Sunumu*

DOI: 10.4274/haseki.3073
Med Bull Haseki 2017;55:61-3

An Unusual Case of Cushing's Syndrome: Coexistence of Functional Pituitary and Adrenal Adenoma

Nadir Bir Cushing Sendromu Olgusu: Fonksiyonel Hipofiz ve Adrenal Adenom Birlikteliği

Muzaffer İlhan, Özcan Karaman*, İrem Yasin Çetin**, Nur Büyükpınarbaşılı***, Jamshid Hamdard**, Ertuğrul Taşan*

Ümraniye Training and Research Hospital, Clinic of Endocrinology and Metabolism Diseases, İstanbul, Turkey

**Bezmialem Vakıf University Faculty of Medicine, Department of Endocrinology and Metabolism Diseases, İstanbul, Turkey*

***Bezmialem Vakıf University Faculty of Medicine, Department of Internal Diseases, İstanbul, Turkey*

****Bezmialem Vakıf University Faculty of Medicine, Department of Pathology, İstanbul, Turkey*

Abstract

A case of adrenocorticotropic hormone (ACTH)-independent Cushing's syndrome, which develops in the course of ACTH-dependent Cushing's disease, is presented in this report. A 47-year-old woman with a past history of surgery and gamma knife radiosurgery because of Cushing's disease was admitted to the endocrinology clinic with weight gain and unregulated blood glucose levels. Hypercortisolemia was still persisting and diagnostic work-up indicated ACTH-independent Cushing's syndrome. Along with the rare possibility of this coexistence, longstanding ACTH hypersecretion can play a role in functional transition of adrenal adenomas. Further studies are needed to clarify the underlying mechanisms.

Keywords: Cushing's syndrome, Cushing's disease, adrenal adenoma

Öz

Bu olgu sunumunda aynı hastada adrenokortikotropik hormon (ACTH) bağımlı Cushing hastalığı seyrinde gelişen ACTH bağımsız Cushing sendromu sunulacaktır. Cushing hastalığı sebebiyle cerrahi ve gamma knife uygulanmış olan 47 yaşındaki hasta endokrinoloji kliniğine kilo alma ve regüle olmayan kan şekeri sebebiyle başvurmuştur. Yapılan tetkikler hiperkortizolemisinin bulunduğunu ve hiperkortizoleminin ACTH bağımsız hale geldiğini göstermiştir. Bu ko-insidansın çok nadir bir olasılık olmasıyla beraber, uzun dönem ACTH hipersekresyonu daha önceden fonksiyonel olmayan adrenal adenomun fonksiyonel hale gelmesinde rol oynamış olabilir. Bu konuda altta yatan mekanizmaların aydınlatılması için ileri araştırmalara ihtiyaç bulunmaktadır.

Anahtar Sözcükler: Cushing sendromu, Cushing hastalığı, adrenal adenom

Introduction

Cushing's syndrome (CS) is a disorder that results from pathological exposure to excess glucocorticoids (1). Endogenous CS is a rare entity with an incidence of 2-4 cases per million per year (2,3). Approximately 80-85% of cases result from adrenocorticotropic hormone (ACTH)-dependent causes and an accurate endocrine evaluation is mandatory in every steps of CS diagnosis (4,5). In this report, we present a case of ACTH-independent CS developing in the course of ACTH-dependent Cushing's disease (CD).

Case

A 47-year-old woman was admitted to the endocrinology outpatient clinic with weight gain, fatigue and unregulated blood glucose levels. She had a 13-year history of type 2 diabetes mellitus, which was uncontrolled despite basal-bolus insulin treatment [hemoglobin A1c (HbA1c): 9%]. She was examined for CS four years ago. Her basal serum

Address for Correspondence/Yazışma Adresi: Muzaffer İlhan
Ümraniye Training and Research Hospital, Clinic of Endocrinology and Metabolism Diseases, İstanbul, Turkey
E-mail: muzoilhan@yahoo.com

Received/Geliş Tarihi: 21 January 2016 **Accepted/Kabul Tarihi:** 23 March 2016

This study was presented as a poster on 21-25 May 2014 in the Congress of Endocrine and Metabolism Diseases of Turkey.

cortisol and ACTH levels were 10.74 ug/dL (6.7-22.6) and 65.3 pg/mL (7.2-63.3 pg/mL), respectively. The serum cortisol level after 1 mg dexamethasone suppression test was 6.57 ug/dL and it was 5.15 ug/dL after 8-mg dexamethasone suppression test. Pituitary magnetic resonance imaging (MRI) showed a 5x5 mm adenoma on the right hemisphere of the hypophysis and her abdominal MRI showed an adrenal adenoma measuring 1 cm in diameter on the left side. Bilateral inferior petrosal sinus sampling (BIPSS) was performed for differential diagnosis. Right inferior petrosal sinus basal central/peripheral ratio was 12:1 and corticotrophin-releasing hormone (CRH)-stimulated ratio was 8:1, which were compatible with CD (Table). The pituitary adenoma was removed with transnasal transsphenoidal surgery. Pathology of the mass was compatible with adenohypophysis tissue showing diffuse fibrosis and positivity with prolactin, growth hormone, follicle-stimulating hormone, thyroid stimulating hormone and ACTH. However, it was consistent neither with microadenoma nor with hyperplasia.

Three months after the operation, her serum cortisol level after 1-mg dexamethasone suppression test was 7.5 ug/dL. Basal serum cortisol level was 12.3 ug/dL and after 8-mg dexamethasone, it was 7.7 ug/dL. BIPSS was repeated to confirm the diagnosis of CD and on the right inferior petrosal sinus, basal central/peripheral ratio was <2:1, but CRH-stimulated ratio was 17:1. BIPSS results showed that right lateralized CD was persisting (Table). Pituitary MRI showed no adenoma and gamma knife radiosurgery was performed.

In the third year of gamma knife radiosurgery, the patient was admitted to our outpatient clinic with weight gain and unregulated blood glucose levels (HbA1c: 11%). 1 mg and 2 mg dexamethasone suppression tests revealed no suppression and hypercortisolemia were persisting, but ACTH level was suppressed (4.29 pg/mL) for the first time since she was diagnosed with CD. 8 mg-dexamethasone suppression test showed also no suppression. Abdominal MRI showed 24x18x22 mm adenoma on the left adrenal gland and there was no hyperplasia on both adrenal glands (Figure 1). The patient was diagnosed with adrenal CS and left adrenalectomy was performed. Histological investigation revealed an adrenal adenoma without any hyperplasia or atrophy in the surrounding cortex (Figure 2, Figure 3). One month after adrenalectomy, her serum cortisol level was suppressed with 1 mg dexamethasone (0.55 ug/dL) and the patient was considered cured. After three months, she had a 10 kg weight loss; her HbA1c level decreased from 11% to 9% and, her cortisol level was suppressed with 1-mg dexamethasone (0.73 ug/dL).

Table. Bilateral inferior petrosal sinus sampling results

	ACTH (pg/mL)			
	Before pituitary surgery		Before gamma knife	
	Before CRH	After CRH	Before CRH	After CRH
Right petrosal sinus	1250	1250	49	1250
Left petrosal sinus	87	16	52	98
Peripheral	109	152	52	103

ACTH: Adrenocorticotropic hormone, CRH: Corticotropin releasing hormone

Discussion

We presented an unusual Cushing case that pituitary and adrenal CS were coexisting in the same patient. The combined findings of the right- sided pituitary lesion on MRI and demonstration of the central source of ACTH secretion by BIPSS were considered to be sufficient evidence for CD and she was treated with pituitary surgery. After surgery, because of persisting hypercortisolemia and BIPSS results indicating pituitary source, gamma knife radiosurgery was performed. Three years after gamma knife radiosurgery, hypercortisolemia was still persisting and differential

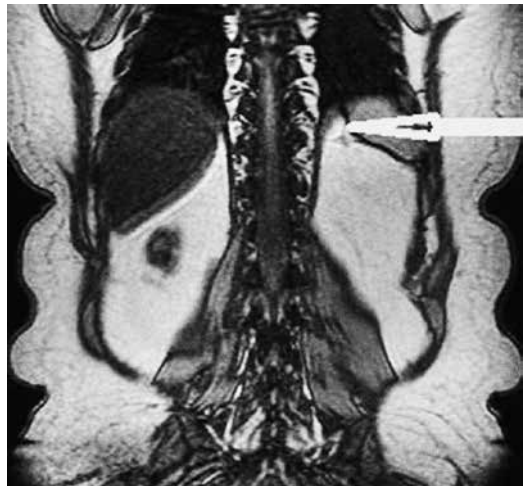


Figure 1. 24*18*22 mm large adrenal adenoma (left side)

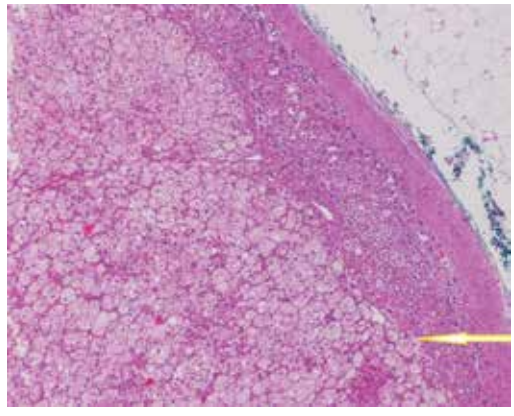


Figure 2. Adrenal adenoma (left side) and residual adrenal tissue (right side)

diagnoses were persistent CD, macronodular adrenal hyperplasia and adrenal adenoma. Diagnostic work up with suppressed ACTH levels indicated that the left adrenal adenoma became functional. The observed response to 1 mg dexamethasone suppression test after left adrenalectomy also pointed towards unilateral adrenal autonomous hypersecretion of cortisol.

Despite bilateral adrenocortical hyperplasia in CD is a well-defined entity and can be found in 70-80% of patients with CD, autonomic transformation of adrenal glands due to longstanding ACTH hypersecretion is still a matter of debate (6,7). Although coincidence of non-functioning tumors in adrenal or pituitary is a common finding in diagnostic steps of CS, coexistence of both functional pituitary and adrenal lesions in same patient has been reported in only a few cases. Timmers et al. (6) reported a case of CD which reoccurred after ten months of transsphenoidal surgery because of autonomous cortisol secretion of adrenal macronodule. In that case, coexistent macro and microhyperplasia in the resected adrenal gland suggested that macronodular hyperplasia could be the later stage of micronodular hyperplasia and indicated the possible transition of pituitary-dependent to adrenal-dependent CS. Hermus et al. (7) reported that removal of ACTH stain-positive pituitary adenoma and subsequent resection of the left adrenal gland with 3.5 cm adrenal nodule which was surrounded by an atrophic cortex did not cure hypercortisolism in a patient with CS. Contralateral adrenalectomy which histologically showed micronodular hyperplasia suggested that ACTH-dependent CS might lead to adrenal-dependent CS. In our case, when the shift of ACTH dependency to ACTH independency of recurrent hypercortisolism was detected at the third year of gamma knife surgery, abdomen MRI showed left adrenal adenoma without any hyperplasia. Histological investigation revealed an adrenal adenoma without any hyperplasia or atrophy in the surrounding cortex which was distinct from other two cases. To our knowledge, this is the first case of coexistence of functional pituitary and adrenal adenoma.

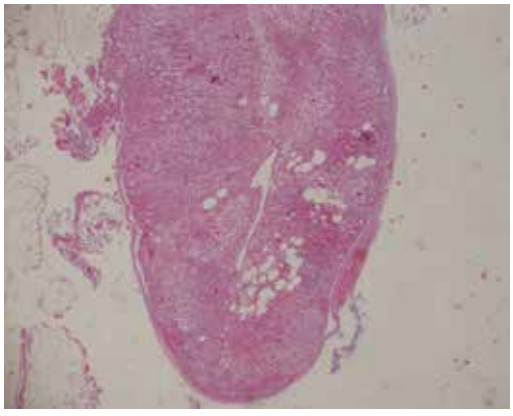


Figure 3. Normal adrenal tissue without hyperplasia or atrophy

In conclusion, along with the rare possibility of this coexistence, evolving of nonfunctional adrenal adenoma to cortisol hypersecreting adenoma in the course of CD suggests that longstanding ACTH hypersecretion can play a role in functional transition of adrenal adenomas, although underlying mechanisms are still not clarified. An accurate endocrine evaluation is always mandatory and CS should be considered carefully in follow-up, as well as every steps of diagnosis, to provide successful and appreciate management.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Özcan Karaman, Muzaffer İlhan. Concept: Muzaffer İlhan, Ertuğrul Taşan, Nur Büyükpınarbaşılı. Design: Muzaffer İlhan, Ertuğrul Taşan. Analysis or Interpretation: İrem Yasin Çetin, Jamshid Hamdard, Nur Büyükpınarbaşılı. Literature Search: İrem Yasin Çetin, Jamshid Hamdard. Writing: Muzaffer İlhan, İrem Yasin Çetin.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Sharma ST, Nieman LK. Cushing's syndrome: all variants, detection, and treatment. Endocrinol Metab Clinics North Am 2011;40:379-91.
2. Etxabe J, Vazquez JA. Morbidity and mortality in Cushing's disease: an epidemiological approach. Clin Endocrinol (oxf) 1994;40:479-84.
3. Lahera Vargas M, da Costa CV. [Prevalence, etiology and clinical findings of Cushing's syndrome]. Endocrinol Nutr 2009;56:32-9.
4. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. Endocr Rev 1998;19:647-72.
5. Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. Lancet 2006;367:1605-17.
6. Timmers HJ, van Ginneken EM, Wesseling P, Sweep CG, Hermus AR. A patient with recurrent hypercortisolism after removal of an ACTH-secreting pituitary adenoma due to an adrenal macronodule. J Endocrinol Invest 2006;29:934-9.
7. Hermus AR, Pieters GF, Smals AG, et al. Transition from pituitary-dependent to adrenal-dependent Cushing's syndrome. N Engl J Med 1988;318:966-70.

Case Report / *Olgu Sunumu*

DOI: 10.4274/haseki.3198
Med Bull Haseki 2017;55:64-6

A Rare Case of Zosteriform Cutaneous Metastasis from Breast Cancer

Meme Kanserli Bir Olguda Zosteriform Deri Metastazı

Filiz Topaloğlu Demir, Kenyul Salaeva, İlknur Kıvanç Altunay, Özben Yalçın*

Şişli Training and Research Hospital, Clinic of Dermatology, İstanbul, Turkey
**Şişli Training and Research Hospital, Clinic of Pathology, İstanbul, Turkey*

Abstract

Breast cancer is the most common cancer among women and the second leading cause of cancer deaths, after lung cancer. Cutaneous breast cancer metastases often develop as direct involvement and local spread and often manifest as solid painless nodules in the anterior chest wall. Internal malignant skin metastases rarely present like soft nodules, telangiectasia-like lesions, neoplastic alopecia, erysipeloides carcinoma, erythema annulare-like, herpetiformis or zosteriform, target-like, pyodermic and morphea-like lesions. In this article, we present a 49-year-old female patient describing a sensation of burning pain with erythematous papules and plaques in a zosteriform distribution. The diagnosis of zosteriform cutaneous metastases from a breast cancer was made. Majority of these cases may be misdiagnosed as herpes zoster infection and can be treated with antiviral drugs. Therefore, cutaneous metastases should be kept in mind in the differential diagnosis of lesions in zosteriform distribution.

Keywords: Cutaneous metastasis, zosteriform cutaneous metastasis, breast cancer

Öz

Meme kanseri kadınlar arasında en sık görülen kanserdir ve akciğer kanserinden sonra, kansere bağlı ölümlerin en sık sebebidir. Meme kanserinin deri metastazı genellikle direkt invazyon ve lokal yayılma şeklinde gelişir ve sıklıkla göğüs ön duvarında solid ve ağrısız nodüller şeklinde ortaya çıkar. İnternal malignitelerin deri metastazları nadiren yumuşak nodüller, telenjiektazi benzeri lezyonlar, neoplastik alopesi, karsinoma erizipeloides, eritema anüler benzeri, herpetiform veya zosteriform, target benzeri, piyodermatik ve morfea benzeri lezyonlar ile prezente olabilmektedir. Bu makalede zosteriform dizilimli, deriden kabarık, eritematöz papül ve plaklarla polikliniğimize başvuran, lezyonlarında yanma tarifleyen, bilateral mastektomi, kemoterapi ve radyoterapi öyküsü olan 49 yaşında bir kadın hasta, deri metastazların nadir görülen zosteriform dağılımına dikkat çekmek ve herpes zoster enfeksiyonlarının ayırıcı tanısında deri metastazlarını hatırlatmak amacıyla sunulmaktadır.

Anahtar Sözcükler: Deri metastazı, zosteriform deri metastazı, meme kanseri

Introduction

Cutaneous metastases from internal malignancies are rather rare, seen in only 0.7-10% of cases (1,2). Breast cancer is the most common cancer in women and causes metastasis to the skin at the highest rate (1). Cutaneous metastases in breast cancer are mostly observed as rapidly developing, scattered, firm, painless, atypical papules and nodules located in the anterior thoracic wall, whereas zosteriform type cutaneous metastases are rarely encountered (1,3-5). Herein, we present a 49-year-old female patient with a history of bilateral mastectomy, chemotherapy and radiotherapy who was referred to our outpatient clinic with burning, erythematous-raised papules and plaques in zosteriform distribution. Our aim was to draw attention to the fact that zosteriform distribution is rarely observed in cutaneous metastases and to remind that there are many diseases that can present with zosteriform distribution.

Case

A 49-year-old female patient was referred to our outpatient clinic due to burning rash and eruptions at the edge of the right mastectomy area spreading around that started 20 days ago. The patient was previously evaluated as herpes zoster and received systemic antiviral treatment, however, the lesions had not regressed. Her

Address for Correspondence/Yazışma Adresi: Filiz Topaloğlu Demir
Şişli Training and Research Hospital, Clinic of Dermatology, İstanbul, Turkey
E-mail: filizsvet@hotmail.com
Received/Geliş Tarihi: 20 March 2016 **Accepted/Kabul Tarihi:** 20 April 2016

medical history revealed, that the patient had been diagnosed with multifocal invasive ductal carcinoma in March 2013 based on the tests conducted due to a palpable mass at the upper outer quadrant of the right breast. At that time, only partial mastectomy and right axillary dissection had been performed. The patient had been given adjuvant chemotherapy and radiotherapy postoperatively. In the follow-up of the patient, nodular lesions and *lymphadenopathy* in the left axillary region of the right breast compatible with cutaneous metastasis had been detected in November 2014. Therefore, Taxol and platinum Gemzar treatment had been started. In the follow-ups, no regression had been observed in the lesions and therefore the patient underwent bilateral mastectomy and left lymph node dissection four months ago. In the family history, it was noted that the patient's older sister also had breast cancer. In the systemic examination of the patient, who was still receiving chemotherapy, no pathology was observed. Dermatologic examination showed that there were erythematous papules and plaques in the outer side of the right mastectomy area extending to the lateral region of the trunk and the lower parts of the posterior region of the trunk with zosteriform distribution, occasionally showing pseudovesicular appearance and fading with pressure. Laboratory tests were normal. In the histopathologic examination of the incisional biopsy from the lesion, there were large, atypical, pleomorphic, hyperchromatic cells in the dermis with vesicular nuclei and distinct nucleolus observed in lymphovascular structures and occasionally forming ductal structures and solid groups. Based on these clinical and histopathologic findings, the patient was diagnosed with zosteriform-type cutaneous metastasis of breast cancer and was referred to the oncology clinic (Figure 1, 2).

Discussion

Breast cancer in women metastasizes to the skin frequently and cutaneous metastasis is observed in 23.9% of patients (1,6). Although it it (cutaneous metastasis) is generally detected in patients diagnosed with breast cancer, it can be also observed as the primary finding of the malignity (6). It is most frequently observed in the anterior thoracic wall as scattered, rapidly growing, erythematous, skin-colored, firm, painless, and atypical papulonodular lesions (7). It rarely presents as erysipeloid, telangiectasia, generalized erythematous patches, neoplastic alopecia, erythema annulare centrifugum, and zosteriform distribution (1,8). Mordenti et al. (9) evaluated 164 breast cancer patients with cutaneous metastasis having an average age of 67 years. In this study, 131 patients were detected with papular and/or nodular lesions, 19 with telangiectasia carcinoma, five with erysipeloid carcinoma, five with carcinoma en cuirasse, three with neoplastic alopecia, and only one with zosteriform pattern cutaneous metastasis. They reported that the lesions were localized at the anterior thoracic wall in 75 patients. Spontaneous pain was observed in many patients with zosteriform cutaneous metastases just like in our case and most of the cases were given antiviral treatment (2,10).

Skin cancers such as malignant melanoma and squamous cell carcinoma and ovarian and lung

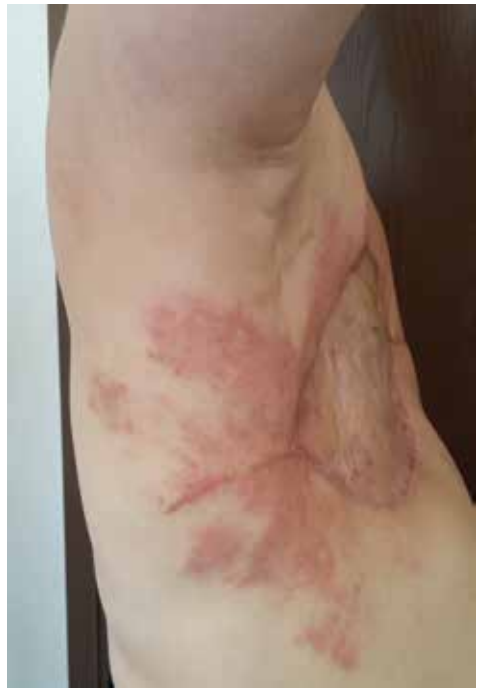


Figure 1. Erythematous papules and plaques as a zosteriform cutaneous metastasis from a breast cancer

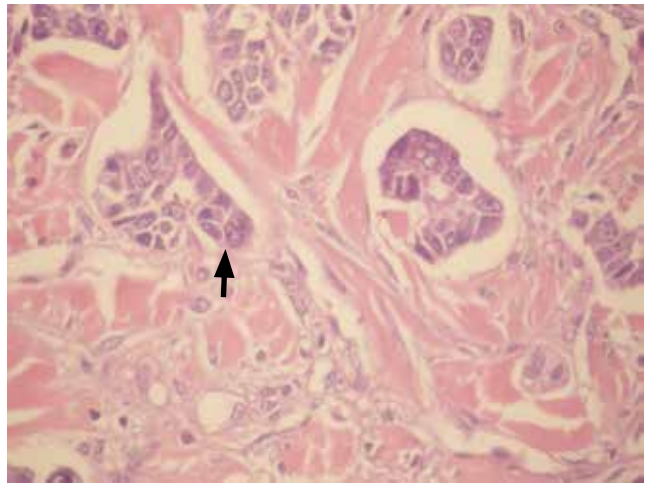


Figure 2. Large, atypical, pleomorphic, hyperchromatic cells in the dermis with vesicular nucleus and distinct nucleolus, observed in lymphovascular structures and occasionally forming ductal structures and solid groups (hematoxylin and eosin X40)

carcinoma may also represent with zosteriform cutaneous metastases (11). The zosteriform distribution pattern may be observed in many dermatoses other than herpes zoster infection such as morphea, lichen, pityriasis rubra pilaris, spiradenoma, lentiginous nevus, papillary mucinous, and drug reactions.

There are many theories about the occurrence of zosteriform cutaneous metastasis which include occurrence due to koebnerization at the region which previously had herpes zoster infection, perineural spread, lymphatic spread, spread in dorsal root ganglion veins through fenestral route, or coincidentally during surgery (2,10,12).

Although the prognosis of cutaneous metastasis depends on the type and the character of the primary tumor as well as the response to treatment, it is generally considered severe as it accompanies advance stage tumors (13). In breast cancer, cutaneous metastasis is usually evaluated as a severe prognostic factor in which life expectancy is several months, only few patients surviving for years (7,14).

In conclusion, the zosteriform distribution pattern may be observed in many diseases, including herpes zoster infection, particularly. Among these diseases, cutaneous metastasis is very important as it may be the first symptom of cancer or recurrence thereof. In patients who do not show regression with antiviral treatments and demonstrate atypical morphological and distribution characteristics, cutaneous metastasis should be considered in differential diagnosis and biopsy must be performed.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Filiz Topaloğlu Demir. Concept: Filiz Topaloğlu Demir. Design: Filiz Topaloğlu Demir. Data Collection or Processing: Kenyul Salaeva, Filiz Topaloğlu Demir, Özben Yalçın. Analysis or Interpretation: Filiz Topaloğlu Demir, İlknur Kıvanç Altunay. Literature Search: Kenyul Salaeva, Filiz Topaloğlu Demir. Writing: Filiz Topaloğlu Demir, Kenyul Salaeva.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. J Am Acad Dermatol 1993;29:228-36.
2. LeSueur BW, Abraham RJ, DiCaudo DJ, O'Connor WJ. Zosteriform skin metastases. Int J Dermatol 2004;43:126-8.
3. Schwartz RA. Cutaneous metastatic disease. J Am Acad Dermatol 1995;33:161-82.
4. Kikuchi Y, Matsuyama A, Nomura K. Zosteriform metastatic skin cancer: report of three cases and review of the literature. Dermatology 2001;202: 336-8.
5. Santos-Juanes J, López-Escobar M, Villanueva Palicio N, et al. Zosteriform cutaneous metastasis from a breast carcinoma. Med Cutan Iber Lat Am 2007;35:89-93.
6. De Giorgi V, Grazzini M, Alfaioli B, et al. Cutaneous manifestations of breast carcinoma. Dermatol Ther 2010;23:581-9.
7. Zindanci İ, Can B, Zemheri E, Kavala M. Two Cases of Breast Cancer Presented with Skin Metastasis as First Signs. Turkderm 2006;40:31-3.
8. Bassioukas K, Nakuci M, Dimou S, Kanellopoulou M, Alexis I. Zosteriform cutaneous metastases from breast adenocarcinoma. J Eur Acad Dermatol Venereol 2005;19:593-6.
9. Mordenti C, Peris K, Fargnoli C, Cerroni L, Chimenti S. Cutaneous metastatic breast carcinoma: a study of 164 patients. Acta DermatovenAPA 2000;9:4.
10. Williams LR, Levine LJ, Kauh YC. Cutaneous malignancies mimicking herpes zoster. Int J Dermatol 1991;30:432-4.
11. Rao R, Balachandran C, Rao L. Zosteriform cutaneous metastases: a case report and brief review of literature. İndian J Dermatol Venereol Leprol 2010;76:447.
12. Atış G, Tükenmez Demirci G, Atunay Kıvanç İ, Sakız D. The clinical characteristics and the frequency of metastatic cutaneous tumors among primary skin tumors. Türkderm 2013;47:166-9.
13. Schwartz RA. Histopathologic aspects of cutaneous metastatic disease. J Am Acad Dermatol 1995;33:649-57.
14. Schoenlaub P, Sarraux A, Grosshans E, Heid E, Cribier B. Survival after cutaneous metastasis: a study of 200 cases. Ann Dermatol Venéreol 2001;128:1310-5.

Case Report / *Olgu Sunumu*

DOI: 10.4274/haseki.3237
Med Bull Haseki 2017;55:67-9

Permanent Junctional Reciprocating Tachycardia-induced Dilated Cardiomyopathy: A Case Report

Permanent Resiprokan Kavşak Taşikardisine Bağlı Dilate Kardiyomiyopati: Bir Olgu Sunumu

Fatih Battal, Şule Yıldırım, Hakan Aylanç, Fatih Köksal Binnetoğlu, Nazan Kaymaz, Celal Akdeniz*

Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Pediatrics, Çanakkale, Turkey
**İstanbul Medipol University Faculty of Medicine, Department of Pediatrics, İstanbul, Turkey*

Abstract

We present a four-year-old girl who was admitted to our hospital with the complaints of dyspnea, tachypnea, cough, excess sweating and fatigue. Electrocardiogram (ECG) in the tachycardic girl showed inverted P waves in leads 2, 3 and aVF along with a P-R interval of 0.16 sec and an R-P interval of 0.28 sec. Transthoracic echocardiography revealed an enlarged and spherical left ventricle with diminished systolic functions. Holter ECG confirmed long R-P tachycardia with a rate of 140-160 beats/minute. She was diagnosed as having permanent junctional reciprocating tachycardia-induced dilated cardiomyopathy and successfully treated with catheter ablation and flecainide.

Keywords: Electrocardiography, child, catheter ablation

Öz

Bu olgu sunumunda hastanemize dispne, takipne, öksürük, aşırı terleme ve yorgunluk yakınması ile başvuran dört yaşında kız olgu sunduk. Taşikardik olan hastanın elektrokardiyografisinde (EKG) V2, V3 ve aVF derivasyonlarında ters P dalgaları ile birlikte 0,16 sn P-R aralığı ve 0,28 sn R-P aralığı mevcuttu. Transtorasik ekokardiyografide sistolik fonksiyonları azalmış, geniş ve sferik sol ventrikül saptandı. Holter EKG'de kalp hızı 140-160/dk olan uzun R-P intervalli taşikardi konfirme edildi. Hastaya permanent resiprokan kavşak taşikardisine bağlı dilate kardiyomiyopati tanısı kondu ve hasta kateter ablasyonu ve flekainamid tedavisi ile başarılı bir şekilde tedavi edildi.

Anahtar Sözcükler: Elektrokardiyografi, çocuk, kateter ablasyonu

Introduction

Permanent junctional reciprocating tachycardia (PJRT) is a rare form of orthodromic atrioventicular (AV) re-entry tachycardia with antegrade conduction through the AV node and retrograde conduction through a concealed accessory pathway which has very slow retrograde conduction. It is characterized by deeply inverted P waves in lead 2, 3, aVF and left precordial leads (1). It may be diagnosed incidentally, but mostly presents with dilated cardiomyopathy resulting from incessant tachycardia at a rate ranging from 120 to 250 beats/minute. PJRT is usually refractory to medical treatment, thus, early recognition and treatment with non-pharmacological methods, such as surgery or catheter ablation of the disease is essential (2). Herein, we present a four-year-old girl with PJRT-related dilated cardiomyopathy who was successfully treated with catheter ablation and flecainide.

Case

A 4-year-old girl was admitted to our hospital with the complaints of dyspnea, tachypnea, cough, excess sweating, and fatigue. She had been evaluated at another hospital where the chest X-ray revealed cardiomegaly. On admission to our hospital, physical examination revealed normal blood pressure (100/60 mmHg), tachycardia (180 beats/minute), tachypnea (50 breaths/minute), crackles at the basal areas of the lungs, hepatomegaly and a mild 1-2/6 systolic murmur. The electrocardiogram (ECG) showed inverted P waves in leads 2, 3 and aVF along with a P-R interval of 0.16 sec and an R-P interval of 0.28 sec (Figure 1). Transthoracic echocardiography revealed

Address for Correspondence/Yazışma Adresi: Şule Yıldırım
Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Pediatrics, Çanakkale, Turkey
Phone: +90 505 828 07 07 E-mail: sule.yildirim@comu.edu.tr
Received/Geliş Tarihi: 14 April 2016 **Accepted/Kabul Tarihi:** 06 June 2016

The Turkish abstract was presented as a poster in "14th National Congress of Pediatric Cardiology and Cardiac Surgery" at 15-18 April 2015 in Denizli, Turkey.

an enlarged and spherical left ventricle with diminished systolic functions (ejection fraction: 27%, fractioned shortening: 13%) (Figures 2A and 2B). Biochemical and hematological parameters were within the normal limits. Viral markers were negative. Laboratory tests for inborn errors of metabolism were all negative. Cardiac magnetic resonance imaging was performed to detect possible myocarditis and it was normal. Digoxin, angiotensin-converting enzyme inhibitor and furosemide were started. Holter ECG confirmed long R-P tachycardia with a rate of 140-160 beats/minute. We used amiodarone and propafenone to achieve the sinus rhythm but we failed. Finally, the patient underwent radiofrequency ablation. The accessory pathway was interrupted successfully. No complication developed during the procedure. After two weeks of the procedure, Holter ECG was again positive for PJRT with a rate of 150 beats/minute. Before the second attempt for ablation, oral flecainide was started. After one week of flecainide, the ECG showed a sinus rhythm with a rate of 90-100 beats/minute and Holter was also normal. Additionally, one month after the flecainide treatment, transthoracic echocardiology demonstrated progressive improvement of the ventricular functions (ejection fraction was 57% and fractional shortening was 29%).

Discussion

Tachycardia-induced dilated cardiomyopathy is a relatively rare but treatable type of cardiomyopathy. There are various tachyarrhythmias associated with tachycardia-induced cardiomyopathy, such as atrial fibrillation, atrial flutter, ectopic atrial tachycardia, incessant atrioventricular reciprocating tachycardia/PJRT, and ventricular tachycardia (3). Restoring the sinus rhythm or to slow the ventricular rate may result in an improvement in left ventricular functions.

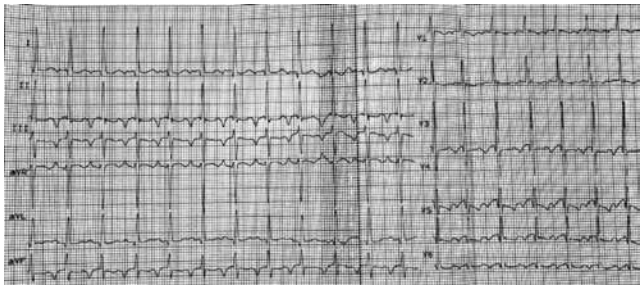


Figure 1. The electrocardiogram of the patient

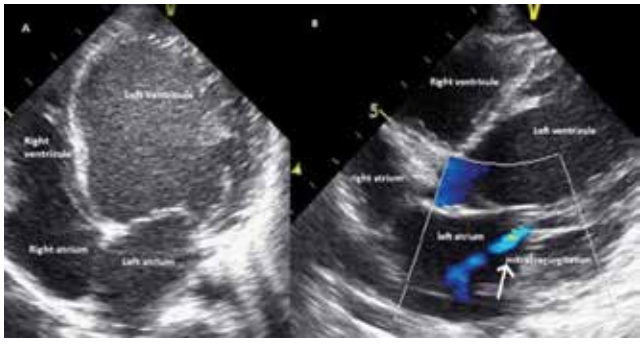


Figure 2. A and B; transthoracic echocardiography images of the patient

Although the animal models have showed that rapid pacing produces marked depression of left ventricular ejection fraction, depressed cardiac output and increased systemic vascular resistance, the exact mechanism of tachycardia-induced cardiomyopathy is unclear (4). Depletion of myocardial energy stores and myocardial ischemia, abnormal calcium handling and beta adrenergic responsiveness and increased oxidative stress, and injury are the most studied mechanisms (5-8).

The manifestations of PJRT usually occur in childhood and may not be recognized until adult ages. The most important complication of PJRT is the development of tachycardia-induced cardiomyopathy (9). During PJRT-induced tachycardia the cardiac stimuli conduct antegrade through the AV node and return retrograde through a slowly conducting accessory pathway that is usually located near the ostium of the coronary sinus. It is characterized by deeply inverted P waves in lead 2, 3 and aVF. Our patient had the clinical signs and symptoms of congestive heart failure due to tachycardia-induced cardiomyopathy with specific ECG characteristics.

PJRT is usually resistant to medical treatment. Most of the patients with PJRT undergo various antiarrhythmic regimens to prevent tachycardia-induced cardiomyopathy. Most of the patients finally require catheter ablation procedures. Although there is a disagreement regarding the most useful therapeutic regimen, most of the studies support catheter ablation (9). Because the heart rate of infants and children with PJRT decreases with age, some reports suggest to postpone catheter ablation i older ages and to try medical regimes before ablation (10). Due to the resistance to medical regimen, we preferred ablation in our patient but after unsuccessful ablation, sinus rhythm was achieved with flecainide.

In conclusion, children with dilated cardiomyopathy should undergo a comprehensive evaluation of tachyarrhythmia such as PJRT. Medical regimens should be tried before ablation in small children and infants. If PJRT is considered refractory to medical regimens in the presence of ventricular dysfunction, catheter ablation should be preferred. Recognition and appropriate treatment of PJRT is important to prevent or reduce the complications such as tachycardia-induced cardiomyopathy.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Fatih Battal, Şule Yıldırım, Hakan Aylanç, Fatih Köksal Binnetoğlu, Nazan Kaymaz, Celal Akdeniz. Design: Fatih Battal, Şule Yıldırım, Hakan Aylanç, Fatih Köksal Binnetoğlu, Nazan Kaymaz, Celal Akdeniz. Data Collection or Processing: Fatih Battal, Şule Yıldırım, Hakan Aylanç, Fatih Köksal Binnetoğlu, Nazan Kaymaz, Celal Akdeniz. Analysis or Interpretation: Fatih Battal, Şule Yıldırım, Hakan Aylanç, Fatih Köksal Binnetoğlu, Nazan Kaymaz, Celal Akdeniz. Literature Search: Fatih Battal, Şule Yıldırım, Hakan Aylanç, Fatih Köksal Binnetoğlu, Nazan Kaymaz, Celal Akdeniz. Writing: Fatih Battal, Şule Yıldırım, Hakan Aylanç, Fatih Köksal Binnetoğlu, Nazan Kaymaz, Celal Akdeniz.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Aguinaga L, Primo J, Anguera I, et al. Long-term follow-up in patients with the permanent form of junctional reciprocating tachycardia treated with radiofrequency ablation. Pacing Clin Electrophysiol 1998;21:2073-8.
2. Cruz FE, Cheriex EC, Smeets JL, et al. Reversibility of tachycardia-induced cardiomyopathy after cure of incessant supraventricular tachycardia. J Am Coll Cardiol 1990;16:739-44.
3. Baman TS, Lange DC, Ilg KJ, et al. Relationship between burden of premature ventricular complexes and left ventricular function. Heart Rhythm 2010;7:865-9.
4. Spinale FG, Tomita M, Zellner JL, Cook JC, Crawford FA, Zile MR, et al. Collagen remodeling and changes in LV function during development and recovery from supraventricular tachycardia. Am J Physiol 1991;261:308-18.
5. Spinale FG, Clayton C, Tanaka R, et al. Myocardial Na+,K(+)-ATPase in tachycardia induced cardiomyopathy. J Mol Cell Cardiol 1992;24:277-94.
6. Perreault CL, Shannon RP, Komamura K, Vatner SF, Morgan JP, et al. Abnormalities in intracellular calcium regulation and contractile function in myocardium from dogs with pacing-induced heart failure. J Clin Invest 1992;89:932-8.
7. Marzo KP, Frey MJ, Wilson JR, et al. Beta-adrenergic receptor-G protein-adenylate cyclase complex in experimental canine congestive heart failure produced by rapid ventricular pacing. Circ Res 1991;69:1546-56.
8. Mihm MJ, Yu F, Carnes CA, et al. Impaired myofibrillar energetics and oxidative injury during human atrial fibrillation. Circulation 2001;104:174-80.
9. Kang KT, Potts JE, Radbill AE, et al. Permanent junctional reciprocating tachycardia in children: a multicenter experience. Heart Rhythm 2014;11:1426-32.
10. Semizel E, Ayabakan C, Ceviz N, Celiker A. Permanent form of junctional reciprocating tachycardia and tachycardia-induced cardiomyopathy treated by catheter ablation: a case report. Turk J Pediatr 2003;45:338-41.

Case Report / *Olgu Sunumu*

DOI: 10.4274/haseki.3321
Med Bull Haseki 2017;55:70-3

Percutaneous Removal of a Broken and Embolized Transvenous Chemotherapy Port Catheter in the Left Pulmonary Artery by Using a Snare-loop Catheter

Kırılmış Transvenöz Kemoterapi Portunun Sol Pulmoner Arterden Snare Katater Kullanılarak Perkütan Olarak Çıkarılması

Muhsin Kalyoncuoğlu, Semi Öztürk, Gündüz Durmuş, Mustafa Sarı, Mehmet Mustafa Can

Haseki Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey

Abstract

Totally subcutaneous intravascular portacath provide safe and reliable vascular access and is widely utilized for venous access for long-term parenteral administration of medications. Catheter fracture and/or embolization of the catheter fragment in to the heart and or pulmonary artery is a rare and potentially serious complication. When it occurs, a prompt surgical or percutaneous extraction of the embolized foreign body is necessary. We present an asymptomatic case of metastatic colon adenocarcinoma in a patient who had fragmentation of catheter from the connection of the port and migration to left pulmonary arteries. We successfully removed the 10-cm long and 6-Fr diameter fractured catheter segment from the left pulmonary artery via the right femoral vein using a snare catheter with triple loop without complication. Post-procedure course was uneventful and the nature of the vascular access made early ambulation possible. Compared to surgery, percutaneous approach is a less invasive, safe, reliable and effective technique. Therefore, we suggest that percutaneous transcatheter technique for retrieval of embolized or broken catheter fragments should be considered as the first-choice treatment.

Keywords: Endovascular, portcath, left pulmonary artery, snare catheter

Öz

Total subkutan intravasküler portacath, uzun süreli parenteral ilaç uygulaması için yaygın olarak kullanılan güvenli venöz giriş yoludur. Port kateterinin kırılması ve/veya kateter parçasının kalp boşluklarına ve/veya pulmoner sisteme embolizasyonu nadir fakat potansiyel olarak ciddi bir komplikasyondur. Böyle bir durumla karşılaşılması durumunda, embolize yabancı cismin bir an önce cerrahi ya da perkütan çıkarılması gerekir. Biz bu yazıda, metastatik adenokarsinom nedeniyle subkutan venöz port yoluyla ilaç kullanan, ilaç uygulanımı sırasında portun bağlantı noktasından koparak, kırılmış ve sol pulmoner artere embolize olmuş olan yaklaşık 10 cm uzunluğunda ve 6 Fr çapında katater parçasının sağ femoral ven yoluyla 3 looplu mikro snare katater kullanılarak perkütan yolla çıkarıldığı bir olguyu sunmaktayız. İşlem sonrası dönemde herhangi bir komplikasyon olmadı ve hasta erken dönemde mobilize edildi. Cerrahi ile karşılaştırıldığında perkütan yol ile kırılmış ve/veya kalp boşluklarına ve/veya pulmoner sisteme embolize olmuş katater parçalarının perkütan yolla çıkarılmasının daha az invaziv, güvenli ve etkili tedavi seçeneği olduğunu düşünmekteyiz.

Anahtar Sözcükler: Endovasküler, portcath, sol pulmoner arter, snare katater

Introduction

Totally subcutaneous intravascular portacath provides safe and reliable vascular access and is widely utilized for venous access for long-term parenteral administration of medications, such as chemotherapy, in patients with malignancy (1-4). Catheter fracture and or embolization of the catheter fragment in to the heart and or pulmonary artery is a rare and potentially serious complication. When it occurs, prompt extraction of the embolized foreign body is necessary (1,3,5,6). While surgery was

Address for Correspondence/Yazışma Adresi: Muhsin Kalyoncuoğlu
Haseki Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
Phone: +90 533 714 45 47 E-mail: mkalyoncuoglu80@gmail.com
Received/Geliş Tarihi: 10 June 2016 **Accepted/Kabul Tarihi:** 10 July 2016

performed in the past, currently, endovascular retrieval of embolized catheter fragment is mostly preferred and can be performed easily, safely, and successfully (3,7-11).

We present an asymptomatic patient who had fragmentation of catheter from the connection of the port and migration to left pulmonary arteries. Endovascular removal of the catheter fragment from the left pulmonary artery via the right femoral vein using a snare catheter with triple loop was successfully performed without any complication.

Case

A 34-year-old male with metastatic colon adenocarcinoma diagnosed in July 2015 was receiving monthly chemotherapy through a central venous port implanted into his right subclavian area about three months ago. On December 25, 2015, he experienced local pain during fluid injection in the right subclavian area and impossible fluid injection or blood aspiration via venous port. Chest X-ray revealed migration of the proximal catheter fragment into the left pulmonary artery (Figure 1). Echocardiography showed preserved left ventricular function with ejection fraction of about 55% to 60%. No regional wall motion abnormality was observed. Linear shadow in the left pulmonary artery was seen on echocardiography, representing the retained fragment. After the patient was evaluated by a cardiovascular surgeon and interventional cardiologist; an emergency percutaneous removal of the catheter was planned. Thus, he was referred to the interventional cardiology clinic for minimally-invasive percutaneous removal. Therefore, the patient was admitted to our hospital for retrieval of the embolized catheter fragment on the same day. On admission, his vital signs were stable. On the physical examination, there were subcutaneous swelling and erythema in the right subclavian area, and the other physical examination findings were within the normal limits. The patient and his family were informed in detail about the possible consequences of the presence of a foreign material in the left pulmonary artery. After informed consent was obtained, the patient was taken to the cardiac catheterization laboratory. The procedure was performed under local anesthesia and fluoroscopic guidance. A 6-Fr pigtail catheter was advanced to the left pulmonary artery through the right femoral vein using an 8-Fr sheath. Then, the pigtail catheter was exchanged with an 8-Fr guiding catheter. Approximately 10-cm long and 6-Fr diameter fractured catheter segment that was lodged in the left pulmonary artery was successfully grasped by using a 25 mm snare with triple loops (ev3™Amplatz Goose Neck snare Kit, A111044) and pulled into the right femoral vein along with the sheath and was externalized (Figure 2, 3). We administered intravenous unfractionated heparin at a dose of 70 U/kg (up to a maximum 5000 U) during the procedure. After the activated partial thromboplastin time was maintained at <50 seconds, we

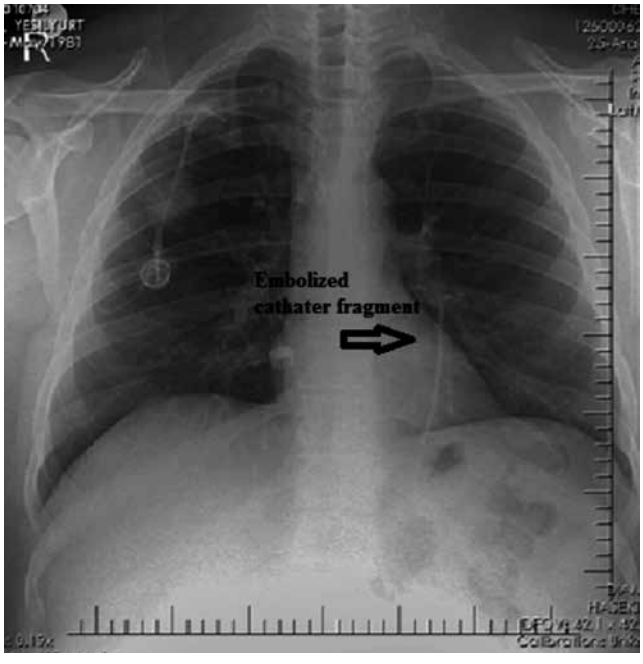


Figure 1. Chest radiograph of a 34 years old man shows cardiac migration of the fragment of a fractured portacath

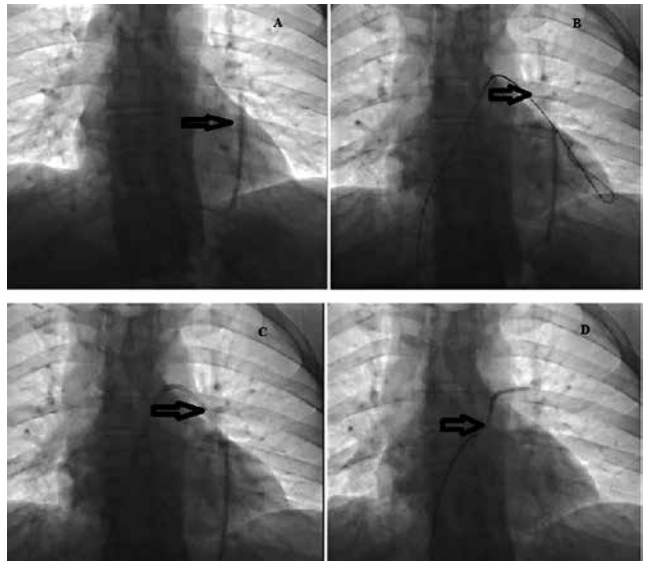


Figure 2. The embolized cathater fragment was seen into the left pulmonary artery (A). The guidewire advanced the left pulmonary arter via 6F pigtail catheter (B). After that, the pigtail catheter was exchanged with 8-Fr guiding catheter (C). Thereafter its distal free end was captured by a snare in SVC and removed successfully. The approximately 10-cm long and 6-Fr diameter fractured catheter segment was successfully grasped by using a 25 mm snare with triple loops (D)

removed the femoral vein sheath and hemostasis was achieved through manual pressure. Post-procedure course was uneventful and the nature of vascular access made early ambulation possible.

Discussion

A broken and migrated peripherally inserted central venous port in the right subclavian vein was successfully retrieved using a snare with triple loops.

Port-a-Cath is a totally implantable venous access device in which a conventional central venous catheter is attached to a subcutaneous injection port usually on the chest wall. It has been reported that application of port catheters is safe. Complications after catheter insertion include embolization, infection, venous thrombosis, occlusion of the catheters, venous perforation, atrial perforation, arrhythmias, flebitis, leakage, dislodgement, subintimal entrapment, and fracture and/or migration of the catheters (11-15). Port-a-Catheter fracture with or without embolization is a serious and rare complication in adult patients. The estimated incidence is between 0.2% and 1.1% of all insertions, and the reported mortality rate is approximately 60% (1,5,11,16,17). The present case suffered embolization of a broken catheter material into the left pulmonary artery. The intravascular fragment lodges more distally within the pulmonary artery especially in the left pulmonary artery with the risk of causing a pulmonary infarction whereas mostly becomes lodged within the right heart (1). Although the exact mechanism of portacath fracture is unknown, the impingement of the port catheter between the first rib and the clavicle by surrounding musculoskeletal system was thought by many authors as a possible cause, known as "pinch off syndrome" or thoracic inlet syndrome. (1,16-20). It was also supposed that factors such as venous flow, negative inspiratory pressure in the thoracic cavity, changes in thoracic pressure with coughing and vomiting, vigorous movement of the upper arms, neck flexion, were thought to lead to migration of fractured material (21,22). In this case, we could not speculate on the cause of migration in our patient.

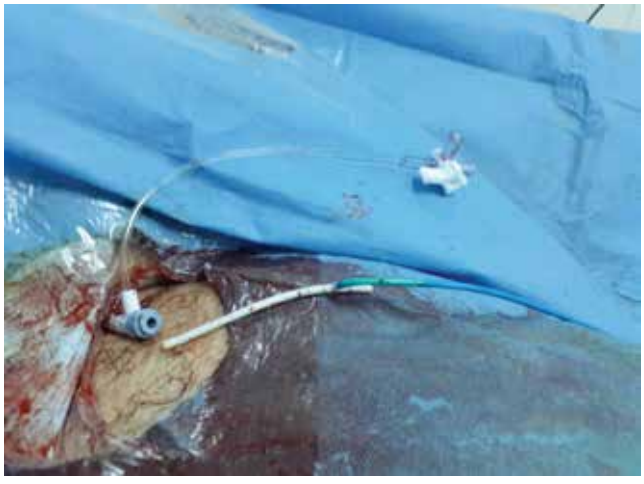


Figure 3. Fractured catheter segment removed by using snare with triple loops

The patient in our case report complained of local pain, subcutaneous swelling and erythema in the right subclavian area. Most of the patients with the fractured catheter embolization remain asymptomatic. Besides that, they may complain of palpitation, cough, dyspnea, thoracic pain, or local swelling and erythema due to serious complications such as infection, pulmonary embolism, arrhythmia, cardiac perforation, ventricular tachydysrhythmia, cardiac arrest, and endocarditis. The first sign of catheter embolization mostly is catheter malfunction precluding fluid injection or blood aspiration and or local pain and subcutaneous swelling at the injection site as seen in our case (2,16,18,22). Therefore, prompt removal of the catheter fragments should be done.

While surgery was the only choice in the treatment of broken and migrated catheters in the past, currently, percutaneous transcatheter retrieval of the portacath fractured fragment by interventional endovascular techniques is the most common technique and successfully performed with much lower morbidity and mortality rates when compared with surgery in adult patients even in neonates (1,5,6,14,23-25). The reported success rates of percutaneous retrieval of fractured fragment in the literature are between 71% and 100% (5,17,25).

Although, there are several available tools for retrieving intravascular foreign bodies from the vascular system, such as endovascular forceps, pigtail catheter, ablation catheter and retrieval baskets, snare-loop catheter is the most commonly used devise for intravascular catheter fragment retrieval (1,5,6,23). Additionally, the most often preferred access route is the right common femoral vein due to advantages such as convenience in handling material, access to main sites of venous foreign body migration, the possibility of using larger-calibre sheaths, easier puncture procedure, and safety of effective compression after the end of the procedure (17).

In our case, the fragment was successfully removed from the left pulmonary artery using snare with triple loops via the right femoral vein by endovascular technique under local anesthesia.

Catheter fraction and migration into the left pulmonary artery is a rare and potentially severe life-threatening complication with high mortality rate. Therefore, retrieval of embolized fractured catheter material should be considered. Since percutaneous transcatheter retrieval

using loop-snare is a less invasive, safe, reliable and effective technique, which avoids open surgery and surgery-related complications, we suggest that percutaneous transcatheter technique for retrieval of embolized or broken catheter fragments should be considered as the first-choice treatment.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Mehmet Mustafa Can, Muhsin Kalyoncuoğlu. Concept: Semi Öztürk. Design: Muhsin Kalyoncuoğlu, Gündüz Durmuş. Data Collection or Processing: Gündüz Durmuş. Analysis or Interpretation: Mehmet Mustafa Can, Mustafa Sarı. Literature Search: Semi Öztürk. Writing: Muhsin Kalyoncuoğlu.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Bouzelmat H, Kheyi J, Raissuni Z, Chaib A, Moustaghfir A. Percutaneous Extraction of a Catheter Fragment of Totally Implantable Venous Device Migrating into the Left Pulmonary Artery. J Clin Exp Cardiolog 2014;5:324.
2. Wassef A. WA, Kass M, Parmar G, Ravandi A. An unusual cause of ventricular tachycardia: Port-A-Cath fracture and embolization into the pulmonary artery. Heart Int 2014;9:30-2.
3. Teragawa H, Sueda T, Fujii Y, et al. Endovascular technique using a snare and suture for retrieving a migrated peripherally inserted central catheter in the left pulmonary artery. World J Cardiol 2013;5:369-72.
4. Ananthakrishnan G, McDonald R, Moss J, Kasthuri R. Central venous access port devices-a pictorial review of common complications from the interventional radiology perspective. J Vasc Access 2012;13:9-15.
5. Şenocak F, Örün UA, Ceylan Ö, Doğan V, Keskin M, Karademir S. Percutaneous Transvenous Removal of an Entire Detached Port Catheter by Using a Snare-Loop Catheter in a 13-Month-Old Child. J Turgut Ozal Med Cent 2011;18:263-5.
6. Ghaderian M, Sabri MR, Ahmadi AR. Percutaneous retrieval of an intracardiac central venous port fragment using snare with triple loops. J Res Med Sci 2015;20:97-9.
7. Motta Leal Filho JM, Carnevale FC, Nasser F, et al. Endovascular techniques and procedures, methods for removal of intravascular foreign bodies. Rev Bras Cir Cardiovasc 2010;25:202-8.
8. Kawata M, Ozawa K, Matsuura T, et al. Percutaneous interventional techniques to remove embolized silicone port catheters from heart and great vessels. Cardiovasc Interv Ther 2012;27:196-200.
9. Liem TK, Yanit KE, Moseley SE, et al. Peripherally inserted central catheter usage patterns and associated symptomatic upper extremity venous thrombosis. J Vasc Surg 2012;55:761-7.
10. Teragawa H, Sueda T, Fujii Y, et al. Endovascular technique using a snare and suture for retrieving a migrated peripherally inserted central catheter in the left pulmonary artery. World J Cardiol 2013;5:369-72.
11. Choksy P, Zaidi SS, Kapoor D. Removal of intracardiac fractured port-A catheter utilizing an existing forearm peripheral intravenous access site in the cath lab. J Invasive Cardiol 2014;26:75-6.
12. Amerasekera SS, Jones CM, Patel R, Cleasby MJ. Imaging of the complications of peripherally inserted central venous catheters. Clin Radiol 2009;64:832-40.
13. Kock HJ, Pietsch M, Krause U, Wilke H, Eigler FW. Implantable vascular access systems: Experience in 1500 patients with totally implanted central venous port systems. World J Surg 1998;22:12-6.
14. Cakır F, Geze S, Ozturk MH, Dınc H. Percutaneous endovascular removal of intracardiac migrated port: A catheter in a child with acute lymphoblastic leukemia. Braz J Anesthesiol 2014;64:275-7.
15. Polderman KH, Girbes AJ. Central venous catheter use. Part 1: mechanical complications. Intensive Care Med 2002;28:1-17.
16. Samad AMA, Ibrahim YA. Complications of Port A Cath implantation: A single institution experience. The Egyptian Journal of Radiology and Nuclear Medicine 2015;46:907-11.
17. de Castro Bienerti IR, Chiozzi RLLAF, Mota Carlos EC, Braga JS, Bombanato R, Kajita LJ. Percutaneous Removal of Intravascular Catheter Fragment-an Adaptation of the Toolbox. Rev Bras Cardiol Invasiva 2013;21:291-4.
18. Çilingiroğlu M, Akkuş NI. Embolization of a PORT-A-CATH device in the main pulmonary artery and its percutaneous extraction in a patient with pinch-off syndrome. Türk Kardiyol Dern Ars 2012;40:162-4.
19. Cil BE, Canyiğit M, Peynircioğlu B, et al. Subcutaneous venous port implantation in adult patients: a single center experience. Diagn Interv Radiol 2006;12:93-8.
20. Cho JB, Sung IY, Baek JM, Lee JH, Lee DS. Pinch-off syndrome. J Korean Surg Soc 2013;85:139-44.
21. Dagdelen S, Yuce M, Caglar N. Percutaneous removal of two intracardiac and pulmonary truncal catheter fragment by using a snare-loop catheter. Int J Cardiol 2007;116:413-5.
22. Doley RP, Brar P, Chaudhary S, Bedi R, Swami AC, Wig JD. Port catheter fracture and migration in Internal Jugular Vein. Am J Case Rep 2012;13:14-6.
23. Önal B, Coşkun B, Karabulut R, Ilgıt ET, Türkyilmaz Z, Sönmez K. Interventional radiological retrieval of embolized vascular access device fragments. Diag Interv Radiol 2012;18:87-91.
24. Motta Leal Filho JM, Carnevale FC, Nasser F, et al. Endovascular techniques and procedures, methods for removal of intravascular foreign bodies. Rev Bras Cir Cardiovasc 2010;25:202-8.
25. Santos MA, Silva AG, Pivatelli FC, Godoy MF. Retirada de corpo estranho na artéria pulmonar de neonato por técnica intravascular. Rev Bras Cardiol Invas 2008;16:362-4.

Olgu Sunumu / *Case Report*

DOI: 10.4274/haseki.3011
Med Bull Haseki 2017;55:74-7

Down Sendromlu Bir Yenidoğanda Konjenital Şilotoraks

Congenital Chylothorax in a Newborn with Down Syndrome

Nazan Neslihan Doğan, Dilek Dilli, Nurdan Fettah Dinlen, Derya Erdoğan*, Ece Koyuncu, Ayşegül Zenciroğlu, Ayşe Karaman*, Nurullah Okumuş

Dr. Sami Ulus Kadın Doğum Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi, Yenidoğan Kliniği, Ankara, Türkiye
**Dr. Sami Ulus Kadın Doğum Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi, Çocuk Cerrahisi Kliniği, Ankara, Türkiye*

Öz

Yenidoğan döneminde saptanan plevral efüzyonun en sık nedeni etiyolojisi bilinmeyen (idiyopatik) konjenital şilotoraksdır. Konjenital şilotoraks nadiren kromozomal anomalilerle (Down, Turner ve Noonan sendromları) birlikte olabilir. Tanı plevral efüzyonun torasentez veya toraks tüpü ile boşaltılarak analiz edilmesiyle konulur. Yenidoğan döneminde şilotoraks tedavisinde konservatif yaklaşımlar ve cerrahi yöntemler kullanılmaktadır. Günümüzde konservatif yaklaşımlara yanıt vermeyen olgularda, oktreotid tedavisi ile başarılı sonuçlar alındığı bildirilmektedir. Bu yazıda toraks tüpü ile drenaja ek olarak medikal tedaviye (total parenteral nütrisyon ve orta zincirli yağ asiti içeren formül mama) yanıt alınamayan ve oktreotid ile tedavi edilen Down sendromlu bir konjenital şilotoraks olgusu sunulmuştur.

Anahtar Sözcükler: Yenidoğan, konjenital şilotoraks, Down sendromu, oktreotid

Abstract

In the neonatal period, the most common cause of pleural effusion is idiopathic congenital chylothorax. Congenital chylothorax is rarely associated with chromosomal abnormalities, such as Down, Turner and Noonan syndromes. The diagnosis can be made after analysis of the pleural fluid drained by thoracentesis or chest tube placement. During the neonatal period, chylothorax treatment is composed of conservative and surgical therapies. Nowadays, for cases among which conservative therapies fail, treatment with octreotide has been reported to be beneficial with promising results. In this report, a case of congenital chylothorax, in a newborn with Down syndrome, treated by octreotide after failure of chest tube drainage and medical treatment (total parenteral nutrition and medium chain fatty acid formula) is presented.

Keywords: Newborn, congenital chylothorax, Down syndrome, octreotide

Giriş

Şilotoraks plevral boşlukta lenfatik sıvının birikmesi olarak tanımlanır. Görülme sıklığı 1/10,000- 15,000 olup erkeklerde iki kat fazladır (1). Doğumsal veya edinsel olarak görülebilen şilotoraks tek veya her iki akciğeri birden etkileyebilir. Konjenital şilotoraks, hidrops fetalisin bir komponenti olarak ortaya çıkabileceği gibi trizomi 21, monozomi X, Noonan sendromu gibi çeşitli kromozomal bozukluklar, doğumsal pulmoner lenfanjiektazi ve yaygın lenfanjiomatozis gibi lenfatik sistem anomalileri, H tipi trakeo-özofageal fistül varlığında da gelişebilir. Ancak altta yatan patoloji çoğunlukla tespit edilemez ve idiyopatik konjenital şilotoraks olarak tanımlanır. Mortalite oranı altta yatan nedene bağlı olarak değişir (2,3). Edinsel şilotoraks, yenidoğanlarda genellikle kardiyak (konjenital kalp hastalıkları) veya torasik cerrahi (konjenital diyafragma hernisi) sonrasında, duktus torasikus zedelenmesine sekonder olarak gelişir (3). Şilotoraksta sıklıkla konservatif tedavi yeterlidir, nadiren cerrahi girişim gerekebilir (4). Günümüzde konservatif yaklaşımlarla sonuç alınamayan olgularda, oktreotid tedavisi ile başarılı sonuçlar alındığı bildirilmektedir (2).

Bu yazıda toraks tüpü ile drenaja ek olarak medikal tedaviye (total parenteral nütrisyon ve orta zincirli yağ asiti içeren formül mama) yanıt alınamayan ve oktreotid ile tedavi edilen Down sendromlu bir konjenital şilotoraks olgusu sunuldu.

Olgu

Antenatal izleminde fetal minimal plevral efüzyon saptanan 28 yaşındaki gebenin, 37. gebelik haftasında,

Yazışma Adresi/Address for Correspondence: Nazan Neslihan Doğan
Dr. Sami Ulus Kadın Doğum Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi, Yenidoğan Kliniği, Ankara, Türkiye E-posta: drnazan396@gmail.com
Geliş Tarihi/Received: 22 Aralık 2015 **Kabul Tarihi/Accepted:** 28 Mart 2016

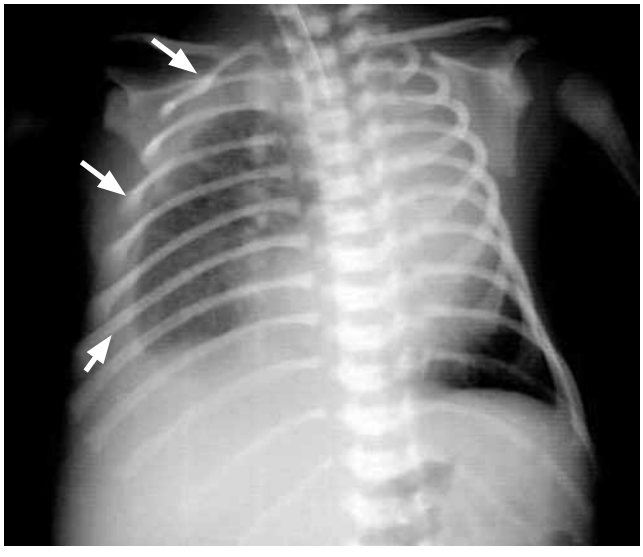
G2 P2 Y2 olarak, 2890 g ağırlığında C/S ile doğan erkek bebeği, postnatal ilk saatlerde solunum sıkıntısı gelişmesi nedeniyle yenidoğan yoğun bakım ünitesine yatırıldı. Nazal devamlı end-ekspiratuvar pozitif basınçlı ventilasyon (CPAP) uygulandı. Akciğer grafisinde bilateral havalanma azlığı dışında patoloji yoktu. Göbek ven kateterizasyonu yapılarak uygun sıvı yönetimi ve ampirik antibiyotik tedavisi başlandı. Hasta hemodinamik olarak stabilize edildikten sonra anne sütü ile minimal enteral beslenme başlatıldı.

Fizik muayenede, hafif hipotonisite, mongoloid yüz görünümü ve her iki elde simian çizgisi dikkati çekti. Transfontanel ve abdominal ultrasonografisi (USG) normaldi, ekokardiyografide patolojik bulgu yoktu. Fenotipik özellikleri Down sendromu ile uyumlu olan hastanın kromozom analizi Trizomi 21 (47, XY, +21) olarak raporlandı.

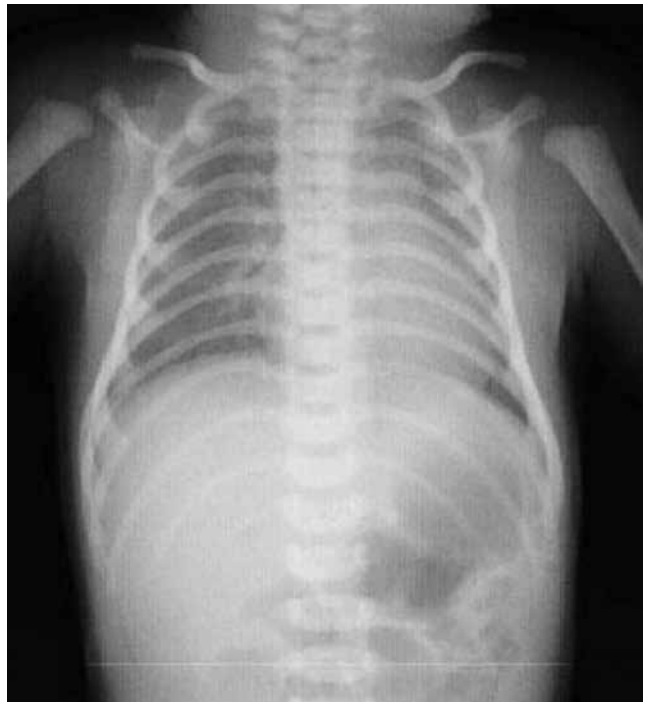
İzlemde, postnatal ikinci günde hastanın solunum sıkıntısının artması üzerine çekilen akciğer grafisinde sağ akciğerde plevral efüzyon görüldü (Resim 1). Arteriyel kan gazı incelemesinde de karbondioksit (CO_2) retansiyonu saptanması nedeniyle hasta entübe edilerek mekanik ventilatörde izleme alındı. Toraks USG ile sağ akciğer alt lobda 50 mm derinliğinde plevral efüzyon olduğu doğrulandı. Toraks tüpü takılan hastadan alınan plevral sıvının berrak-sarı renkte olduğu görüldü. Sıvının laboratuvar analizinde; beyaz küre 5200/mm^3, lenfosit hakimiyeti (%85), trigliserid 310 mg/dL, laktat dehidrogenaz (LDH) 314 U/L ve protein 0,8 g/dL idi. Bu bulgularla şilotoraks düşünüldü. Enteral beslenme kesilerek total parenteral beslenme (TPN) başlandı. Hastada klinik iyileşmenin yanı sıra kontrol akciğer grafilerinde efüzyonun gerilediği görüldü ve postnatal 10. günde toraks tüpü çıkarıldı. Arteryel kan gazı sonuçlarına göre ventilatör parametreleri azaltıldı ve hasta tekrar nazal CPAP'ye alındı. Anne sütü ile beslenmeye başlandı. Ancak beslenme intoleransı gelişmesi üzerine enteral beslenmeye ara verildi.

Postnatal 14. günde, hastanın solunum sıkıntısı arttı ve kan gazında CO_2 retansiyonu gelişti. Akciğer grafisinde atelektazi ve sağda belirgin efüzyon görülmesi nedeniyle ikinci kez toraks tüpü takıldı. Plevral sıvının şilöz görünümde olduğu dikkati çekti. İncelemede; beyaz küre 6800/mm^3, lenfosit hakimiyeti (%91), trigliserid 476 mg/dL, LDH 215 U/L ve protein 0,9 g/dL tespit edildi. Plevral sıvı kültürlerinde üreme olmadı. TPN ile beslenmeye devam edildi. Toraks tüpünden gelen sıvı miktarları hesaplanarak taze donmuş plazma replasmanı ile volüm ve pıhtılaşma faktörleri kaybı önlendi. Serum elektrolit ve albümin düzeyleri uygun şekilde monitorize edildi. Serum immünglobulin düzeyleri yaşa göre normal sınırlarda seyretti.

Bu tedavilere rağmen plevral efüzyonu giderek artan ve mekanik ventilatörden ayrılamayan hastaya oktreotid (1 mcg/kg/saat) infüzyonu başlandı. Efüzyonun gerilememesi üzerine oktreotid dozu bir hafta içinde kademeli olarak 7 mcg/kg/saat'e kadar artırıldı. Oktreotid ilişkili yan etki gözlenmedi. Postnatal 25. günde klinik ve radyolojik iyileşme gözlenen hastaya orta zincirli yağ asiti içeren formül mama [%50 orta zincirli trigliseridler (MCT), Pepti Junior®] ile enteral beslenme başlatıldı ve miktarı kademeli olarak artırıldı. İzlemde, plevral boşlukta sıvı birikiminin tekrarlamaması üzerine oktreotid infüzyonu kademeli olarak azaltılarak tedavinin 14. gününde kesildi (Resim 2). Postnatal 30. günde toraks tüpü çıkarılan hasta ekstübe



Resim 1. Akciğer grafisinde sağda plevral efüzyon görülmektedir



Resim 2. Hastanın tedavi sonrası akciğer grafisi

edildi, kısa süreli serbest oksijen desteğinin ardından oda havasında izlenmeye başlandı. Hasta postnatal 49. günden sonra tam enteral beslenmeyi tolere etmeye başladı.

Anne sütü ile beslenme öncelikle düşük miktarda başlatıldı. Günler içerisinde anne sütü giderek artırılırken MCT mama miktarı azaltıldı. Postnatal 54. gününde tam enteral anne sütü ile beslenen hasta önerilerle taburcu edildi.

Tartışma

Şilotoraksta, duktus torasikustaki tıkanıklık veya hasara bağlı olarak şilöz mayi sızar ve plevral boşlukta toplanır. Konjenital şilotoraksın anatomik nedenleri arasında pulmoner lenfanjiektazi, ekstralobüler pulmoner sekestrasyon, konjenital fistül ve duktus torasikus atrezisi sayılabilir. Diğer nedenler konjenital guatr, akciğer tümörleri ve intrauterin enfeksiyonlardır (2). İlaveten, konjenital kalp hastalıkları, diyafragmatik herni, polidaktili ile de beraberlik tanımlanmıştır (5). Anormal lenfatik drenajla seyreden anöploidi sendromlarında şilotoraks görülebilir. Konjenital şilotoraks ve Down sendromu beraberliği ilk defa Yoss ve Lipsitz (6) tarafından tanımlanmıştır. Beraberinde lenfatik anomali olan Turner ve Noonan sendromunda da plevral efüzyon görülebilir. Trizomi 22 ile de plevral efüzyon beraberliği gösterilmiştir (7). Hastamız da Down sendromlu olup şilöz karakterde konjenital plevral efüzyon saptanmıştı.

Literatürdeki olgularda genellikle preterm eylem ve polihidramniyoz nedeni ile yapılan USG değerlendirmede veya rutin obstetrik USG sırasında fetal plevral efüzyon saptanmıştır. Olgumuzda antenatal izlemde minimal plevral efüzyon rapor edilmişti; ancak postnatal ilk saatlerde çekilen akciğer grafisinde efüzyon saptanmadı. İlerleyen saatlerde enteral beslenmenin başlatılmasının ardından sıvı birikiminin arttığı ve solunum sıkıntısına neden olduğu düşünüldü.

Yenidoğanlar, efüzyonun yaygınlığına bağlı olarak asemptomatik kalabileceği gibi doğum sonrası ilk saatlerde mekanik ventilasyon desteği gerektirecek kadar ağır respiratuvar distres geliştirebilir. Solunum sıkıntısı olan yenidoğanda plevral efüzyon tanısı radyolojik olarak hasta başında uygulanabilen tetkiklerle (direkt akciğer grafisi ve toraks USG) erken dönemde konulabilir. Hastamızda da solunum sıkıntısı artması nedeniyle çekilen akciğer grafisi ve toraks USG'de plevral efüzyon saptandı.

Şilotoraks tanısında plevral sıvı analizi yararlıdır. Şilöz sıvı süt görünümündedir. Ancak enteral beslenme miktarı fazla değilse süt görünümü olmayabilir. Bu durumda plevral sıvı örneği berrak-açık sarı renktedir. Trigliserid düzeyi >1,1 mmol/L (110 mg/dL), hücre sayısı ≥1000/mm^3 olup en az %80'i lenfosit olmalıdır (8). Olgumuzun plevral sıvı incelemesi şilotoraksla uyumluydu. Sıvı rengi başlangıçta açık-sarı olmasına rağmen anne sütü ile beslenme sonrası şilöz karaktere dönüştü.

Konjenital şilotorakslı yenidoğanların yönetiminde en etkin tedavinin ne olduğu tartışmalıdır. Postnatal dönemde solunum sıkıntısı giderek artan bir bebekte akciğer grafisinde plevral sıvı saptanmışsa, sıvı iğne ile aspire edilmeli, gerekirse mekanik ventilasyon desteği sağlanmalıdır. Solunum sıkıntısı giderek artıyor ve görüntülemede plevral efüzyon persiste ediyorsa toraks tüpü takılmalıdır (8). Şilöz efüzyonlar, anlamlı miktarlarda sıvı-elektrolit kaybına ilaveten, içerdiği yüksek protein nedeniyle de albümin, pıhtılaşma faktörleri ve immünglobulin kaybına yol açabilir (9). Toraks tüpü yoluyla uzamış drenajlar bu durumu kolaylaştırır. Bu nedenle, serum elektrolit, protein ve immünglobulin düzeyleri yakından izlenmeli, gerektiğinde albümin ve taze donmuş plazma verilmelidir. Enteral beslenme MCT'den zengin mama ile yapılmalıdır. Enteral beslenme tolere edilemiyorsa bir süre ara verilerek TPN'ye geçilmelidir. Bu tedavilere rağmen plevral efüzyon tekrarlıyor veya sebat ediyorsa bir somatostatin analoğu olan "oktreotid" başlanması düşünülmelidir.

Somatostatin ilk kez 2001 yılında, bir yenidoğan şilotoraks olgusunda, oktreotid ise 2003'te konjenital diyafragma herni ameliyatına sekonder gelişen şilotoraksta kullanılmıştır (10,11). Oktreotidin splanknik kan akımını azaltarak, lenfatik sıvı oluşumunu azaltıcı etkisi olduğu kabul edilmektedir. Yenidoğanlarda oktreotid kullanımı ile ilgili veri kısıtlıdır (12,13). Her olgu kendi içinde değerlendirilerek tedavi gerekliliğine karar verilmelidir. Ancak öncesinde aile medikal tedavinin potansiyel yarar ve zararları hakkında bilgilendirilmelidir. Oktreotid, birçok sistem üzerine etkili olmakla birlikte gastrointestinal sistemde serotonin, gastrin, vazoaktif intestinal peptid, sekretin, safra ve pankreatik polipeptidlerin üretimini azaltır. Oktreotid tedavisi subkütan veya intravenöz yolla uygulanabilir. Oktreotid kullanımına bağlı istenmeyen etkiler olarak; aritmi, enjeksiyon yerinde lokalize reaksiyonlar, bulantı, kusma, diyare, konstipasyon, karaciğer fonksiyon testlerinde geçici bozulma, geçici hipotiroidi, nekrotizan enterokolit görülebilir. Preterm bebeklerde oktreotide bağlı hipoksemi, pulmoner hipertansiyon ve retinopati gelişebileceği bildirilmiştir. İnsülin salınımını etkilediğinden kan glukoz düzeyleri monitörize edilmelidir. Yenidoğanlarda 1 mcg/kg/saat dozunda sürekli infüzyonla tedaviye başlanarak hasta yanıtına göre 10 mcg/kg/saat'e kadar artırılabilir. Konservatif yaklaşım ve medikal tedaviye yanıt vermeyen olgularda, mekanik plöredezis, plöro-peritoneal şant ve duktus torasikus ligasyonu gibi cerrahi tedavi seçenekleri düşünülebilir (1,2,8,14,15). Olgumuzda, toraks tüpü ile drenaja ek olarak medikal tedaviye yanıt alınamaması üzerine aile onamı da alınarak, oktreotid tedavisine başlandı. Tedaviye yanıtın ardından infüzyon

dozu kademeli olarak azaltılarak oktreotid tedavisi 14 günde kesildi.

Sonuç olarak, Down sendromlu olgularda konjenital şilotoraks gelişebileceği akılda tutulmalıdır. Konservatif tedaviye yanıtsız konjenital şilotoraks olgularında oktreotid kullanılması düşünülmelidir.

Etik

Hakem Değerlendirmesi: Editörler kurulu ve Editörler kurulu dışındaki kişilerce değerlendirilmiştir.

Yazarlık Katkıları

Cerrahi ve Medikal Uygulama: Nazan Neslihan Doğan, Dilek Dilli. Konsept: Nazan Neslihan Doğan, Dilek Dilli. Dizayn: Nazan Neslihan Doğan, Dilek Dilli. Veri Toplama veya İşleme: Nazan Neslihan Doğan. Analiz veya Yorumlama: Nurdan Fettah Dinlen, Derya Erdoğan, Ece Koyuncu, Ayşegül Zencirlioğlu, Nurullah Okumuş. Nazan Neslihan Doğan, Dilek Dilli. Literatür Arama: Nazan Neslihan Doğan. Yazan: Nazan Neslihan Doğan.

Çıkar Çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemiştir.

Finansal Destek: Çalışmamız için hiçbir kurum ya da kişiden finansal destek alınmamıştır.

Kaynaklar

1. Tutor JD. Chylothorax in infants and children. Pediatrics 2014;133:722-33.
2. Das A, Shah PS. Octreotide for the treatment of chylothorax in neonates. Cochrane Database Syst Rev 2010:CD006388.
3. Paramés F, Freitas I, Fragata J, Trigo C, Pinto MF. Octreotide-additional conservative therapy for postoperative chylothorax in congenital heart disease. Rev Port Cardiol 2009;28:799-807.
4. Bulbul A, Okan F, Nuhoglu A. Idiopathic congenital chylothorax presented with severe hydrops and treated with octreotide in term newborn. J Matern Fetal Neonatal Med 2009;22:1197-200.
5. Hagay Z, Reece A, Roberts A, Hobbins JC. Isolated fetal pleural effusion: a prenatal management dilemma. Obstet Gynecol 1993;81:147-52.
6. Yoss BS, Lipsitz PJ. Chylothorax in two mongoloid infants. Clin Genet 1977;12:357-60.
7. Sepulveda W, Be C, Schnapp C, Roy M, Wimalasundera R. Second-trimester sonographic findings in trisomy 22: report of 3 cases and review of the literature. J Ultrasound Med 2003;22:1271-5.
8. Soto-Martinez M, Massie J. Chylothorax: Diagnosis and management in children. Paediatr Respir Rev 2009;10:199-207.
9. Kovacikova L, Lakomy M, Skrak P, Cingelova D. Immunologic status in pediatric cardiosurgical patients with chylothorax. Bratisl Lek Listy 2007;108:3-6.
10. Goyal A, Smith NP, Jesudason EC, Kerr S, Losty PD. Octreotide for treatment of chylothorax after repair of congenital diahragmatic hernia. J Pediatr Surg 2003;38:19-20.
11. Uettiker V, Hug MI, Burger R, Baenziger O. Somatostatin: a new therapeutic option for the treatment of chylothorax. Intensive Care Med 2001;27:1083-6.
12. Kalomenidis I. Octreotide and chylothorax. Curr Opin Pulm Med 2006;12:264-7.
13. Lam JC, Aters S, Tobias JD. Initial experience with octreotide in the pediatric population. Am J Ther 2001;8:409-15.
14. Zanin A, Padalino MA, Cerutti A, et al. Surgical ligation of cisterna chyli: An alternative treatment for chronic chylothorax in children. Ann Thorac Surg 2010;90:1732-4.
15. Shah D, Sinn JK. Octreotide as therapeutic option for congenital idiopathic chylothorax: a case series. Acta Paediatr 2012;101:151-5.

Olgu Sunumu / *Case Report*

DOI: 10.4274/haseki.3095
Med Bull Haseki 2017;55:78-81

Deride Nodüler Lezyonlarla Seyreden Krukenberg Tümörü: Olgu Sunumu

A Case Report: Krukenberg Tumour with Nodular Skin Lesions

Özden Demir, Selcan Cesur, Zeynep Karaali

Haseki Eğitim ve Araştırma Hastanesi, İç Hastalıkları Kliniği, İstanbul, Türkiye

Öz

Krukenberg tümörü overin metastatik tümörüdür. Primer malignite odağı en sık mide olmakla beraber meme, safra kesesi, kolon ve pankreas kanseri de overe metastaz yapabilmektedir. Malignite odağı bilinmeyen hastalarda over metastazlarını primer over kitlelerinden ayırt edebilmek her zaman mümkün olmamaktadır. Yazımızda deride yaygın nodüler lezyonlar, gezici artrit bulgularıyla başvuran ve hızlı ilerleyen kliniği olan, ileri tetkikler sonucu Krukenberg tümörü tanısı konulan bir hastamız sunulmuş ve Krukenberg tümörü gözden geçirilmiştir.

Anahtar Sözcükler: Krukenberg tümörü, mide kanseri, deride nodüler lezyon, artrit

Abstract

The Krukenberg tumor is a rare variety of metastatic cancer to the ovary. The stomach is the most common site for the primary tumor, followed by the breast, gall bladder, colon and pancreas. It is not always possible to distinguish ovarian metastasis from primary ovarian masses in patients in whom the malignancy center is unidentified. This case report firstly aims to present a patient who presented with common nodular skin lesions, migrating arthritis and severe clinical characteristics, and diagnosed with Krukenberg tumor with further examinations.

Keywords: Krukenberg tumour, gastric carcinoma, nodular lesions on the skin, arthritis

Giriş

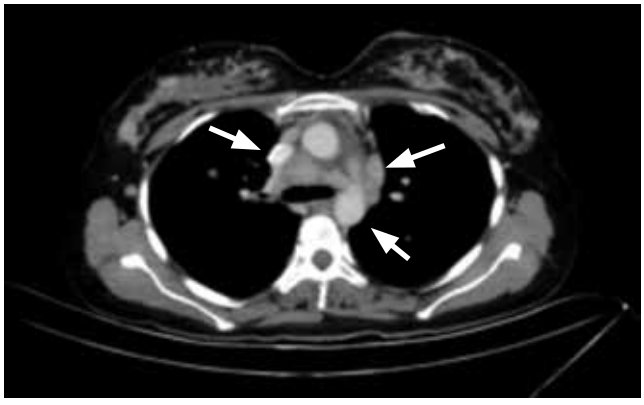
Krukenberg tümörü gastrik tümörlerin overlere metastazıdır ve tüm over kanserlerinin %1-2'sini oluşturur (1). Morfolojik olarak primer over tümörlerini ve Krukenberg tümörleri ayırt etmek zordur (2). Krukenberg tümörleri olgularının en sık primer kaynağı midedir (%70). Bunu kolon, apendiks ve meme izler. Nadir olarak da safra kesesi ve safra yolları, pankreas, ince barsak, ampulla vateri, mesane, serviks de bildirilen diğer primer karsinomlardır. Krukenberg tümörü her yaşta görülmekle birlikte, en sık görülgüğü yaş ortalaması 45'tir (3). Tüm metastatik over tümörleri Krukenberg tümörü olarak değerlendirilemez. Genellikle primer mide tanısı konulduktan yaklaşık altı ay ve daha kısa süre zarfında overlere de metastaz olduğu görülür Ancak olguların çoğunda primer tümör odağı çok küçüktür ve gözden kaçabilir (3). Krukenberg tümörü diyebilmek için histopatolojik incelemede stromal invazyon varlığı, stromal sarkomatoid proliferasyon ve müsin üreten neoplazik taşlı yüzük formunda hücreler görülmelidir (4). Taşlı yüzük hücreli adenokarsinomlar diğer histolojik tipteki adenokarsinomlara göre overlere metastaz yapmaya daha meyillidir (3). Mide ile over arasındaki yayılım tam net açıklığa kavuşmuş olmasa da günümüzde retrograd lenfatik yayılım olduğu kuvvetle düşünülmektedir. Krukenberg tümörlerinde periton yayılımı sıklıkla yoktur. Bu tümörlerde over yüzeyinde tomurcuklanma, implantasyon, infiltrasyon olmaması periton yayılımının olmadığını ve lenfatik yayılımın esas olduğunu desteklemektedir (3).

Olgu

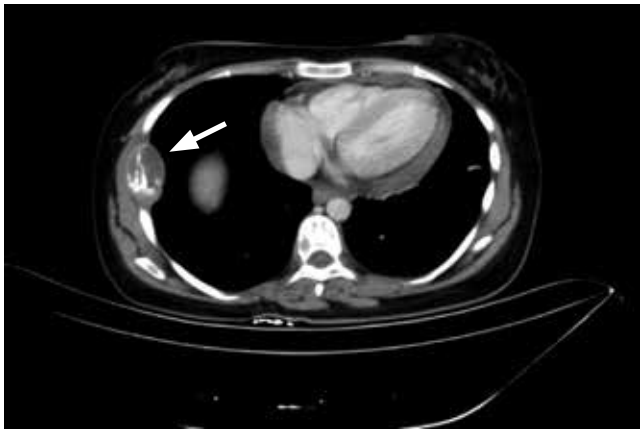
Yirmi dört yaşında kadın hasta son iki aydır diz ekleminde başlayan ardından sırtta ve el bileğinde gezici tarzda devam eden, ağrılar ve bunlara eşlik eden saçlı deride, göğüste, sırtta nodüler lezyonlar, nefes darlığı, halsizlik nedeniyle dış merkez fizik tedavi ve rehabilitasyon, romatoloji ve dermatoloji bölümlerine başvurmuş, semptomatik tedavi verilmiş. Şikayetleri gerilemeyen ve daha da artan hasta ileri tetkik amacıyla dahiliye servisimize yatırıldı. Fizik muayenede genel durum iyi-orta, inspeksiyonda saçlı

Yazışma Adresi/Address for Correspondence: Özden Demir
Haseki Eğitim ve Araştırma Hastanesi, İç Hastalıkları Kliniği, İstanbul, Türkiye
Tel.: +90 545 436 99 59 E-posta: guvenozden_4545@hotmail.com
Geliş Tarihi/Received: 27 Ocak 2016 **Kabul Tarihi/Accepted:** 13 Nisan 2016

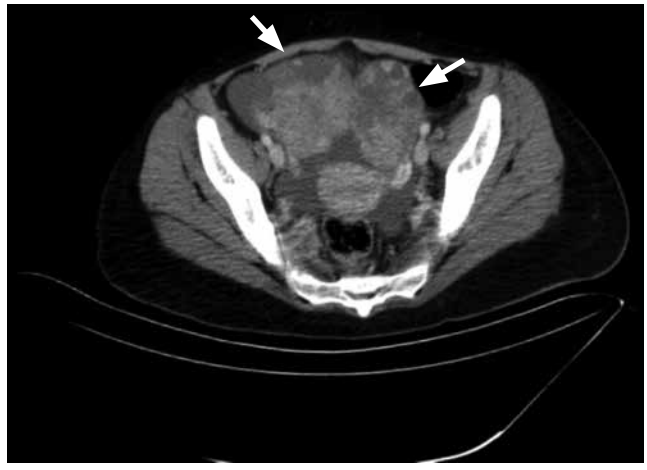
deride, göğüs ön yüzünde, sağ omuzda, sırtta yaygın 0,5-1 cm çaplı nodüler lezyonlar mevcuttu. Sistem muayeneleri doğaldı. Laboratuvarda özellikli olarak lökosit: 10,94; eritrosit: 3,48; hemoglobin: 9,2 g/dL; hematokrit: %28,8; alkalen fosfataz: 233 U/L (N: 30-120); laktat dehidrogenez: 477 U/L (N: <247); c-reaktif protein: 37 mg/L; sedimantasyon: 22 mm/saat; CA-125: 83,9 U/mL; CA19-9: 1926 U/mL; d-dimer: 34800 µg fibrinojen eşdeğer birimi saptandı. Akciğer grafisinde bilateral hiler dolgunluk, sağda şüpheli kitle görüntüsü dikkati çekmekteydi. Hastanın gezici artriti, deride nodüler döküntüleri olması ve akciğer grafisinde bilateral hiler dolgunluk saptanması nedeniyle ön planda Sarkoidoz - Loefgren sendromu düşünüldü. Ancak akciğer grafisinde sağda şüpheli kitle görünümü ve laboratuvar testlerinde, tümör belirteçlerinde yükseklik saptanması nedeniyle kontrastlı batın ve toraks tomografi çekildi. Tomografilerinde; perikardial efüzyon (en kalın yeri 8 mm) bilateral hiler prevasküler aortikopulmoner pretrakeal alanda çok sayıda lenfadenopati (Şekil 1), sağ akciğer apekste 9 mm'lik bir adet nodül, torakal vertebralarda yaygın litik lezyonlar, 6. kot lateral kısımda kemikte destrüksiyon ve eşlik eden 45x27 mm'lik yumuşak doku kitlesi (metastaz?) (Şekil 2) karaciğer hilusunda, çölyak trunkus çevresinde, paraaortik, alanda çok sayıda lenfadenopati (lenfoma?) batında asit, sağ overde 72x61 sol overde 69x51 mm'lik, kistik alanlar içeren kitleler (Şekil 3), kemik yapıda yaygın litik lezyonlar saptandı. Tomografi bulguları ile hasta kadın hastalıkları ve doğum ile genel cerrahi branşlarına konsülte edildi. Kadın hastalıkları ve doğum kliniği batında Douglas'ta yaygın sıvı nedeniyle overlerin net değerlendirilemediğini ve laparoskopik olarak batından kitle eksizyonunun zor olacağı düşünülerek ileri tetkik için pozitron emisyon tomografisi önerdi. Bu süre zarfında göğüs ön yüzündeki nodülden punch biyopsi yapılarak patolojiye gönderildi. Klinik bulgular (nodüler lezyonlar, artrit, bilateral hiler dolgunluk, ateş) başlangıçta sarkoidoz düşündürse de tomografi bizi bu tanıdan uzaklaştırıp yaygın lenfadenopatiler ve overlerdeki kitle nedeniyle lenfoma ve bilateral over kanseri ön tanılarını aklımıza getirdi. Bu süre zarfında genel durumu stabil olan hasta araya giren bayram tatilinde izinli olarak evine gönderildi. Bayram tatili dönüşü hastanın kliniği bozulmuş ve laboratuvar değerleri büyük ölçüde değişmiş olarak izlendi. Hastada derin anemi, artmış bilirubin, laktat dehidrogenaz, alkalen fosfataz, azalmış haptoglobin ve trombosit saptandı. Hemoglobin ve trombosit düşüklüğü "Maligniteye sekonder trombotik trombositopenik purpura olabilir mi?" sorusunu akla getirdi. Hematolojiye danışıldı ancak bu tanıdan uzaklaşıldı. Pozitron emisyon tomografi sonucu batın ve toraks tomografiyi destekleyip plevral ve perikardiyal sıvının artmış olduğunu, yaygın lenfadenopatileri ve kemikteki destrüktif değişiklikleri gösterdi. Perikardiyal sıvıda masif artış sonucu hasta kardiyak tamponada girdi. Koroner yoğun bakıma alınarak 1000 cc perikardiyosentez yapıldı. Perikardiyal mayiden sitolojik örnek gönderildi. Takiplerde perikardiyal ve plevral sıvı artışları oldu, solunum sıkıntısı artınca pleuroken takıldı. Üç kez perikardiyosentez yapılınca kalp damar cerrahi,



Şekil 1. Bilateral hiler prevasküler aortikopulmoner pretrakeal alanda çok sayıda lenfadenopati



Şekil 2. Altıncı kot lateral kısımda kemikte destrüksiyon ve yumuşak doku kitlesi



Şekil 3. Bilgisayarlı tomografide belirgin bilateral over kitleleri

kardiyoloji ve göğüs cerrahisi ile görüşülüp perikardiyal pencere açıldı. Hastanın punch biyopsi raporu karsinomla uyumlu geldi, kemik iliği biyopsisi planlandı ancak geç sonuç çıkacağı ve hastanın kliniği hızlı progresyon gösterdiği için vazgeçildi. Sağ omuz üzerindeki bir nodülden eksizyonel biyopsi yapılarak patolojiye gönderildi. Perikardiyal sıvıdan gönderilen patoloji örneğinde taşlı yüzük hücreli karsinom sonucu geldi. Hastaya gastrointestinal sistem malignitesi açısından endoskopi planlandı. Ancak özofagus Z çizgisi hizasında darlık (muhtemelen dıştan lenfadenopati basısı) nedeniyle mideye girilemedi. Hastanın takiplerde hemoglobin düşüklüğü devam etti, ara ara eritrosit süspansiyonu transfüze edildi. Eksizyonel biyopsi sonucu da perikardiyal mayi sitolojisini destekleyerek taşlı yüzük hücre diferansiasyonu gösteren az diferansiye karsinom ile uyumlu geldi. Patoloji görüşü de alınarak hastanın primeri mide kabul edildi. Yaygın metastatik kitleleri olan hasta onkoloji ve genel cerrahi ile görüşülerek inoperabl kabul edildi, Krukenberg tümörü tanısıyla kemoterapi başlandı. Takiplerde perikardiyal, plevral efüzyon ve batında asit sıvısı artmaya devam etti. Boşaltıcı parasentez sırasında hipotansif şoka giren hastada kardiyak arrest gelişti. Kardiyopulmoner resüstasyon yapılan, entübe edilen hasta yoğun bakımda takibe devam edildi. Burada ekstübe edilen hastanın takiplerde tekrar genel durumu bozuldu, asistoli gelişti ve yatışının 70. gününde eksitus kabul edildi.

Tartışma

Krukenberg tümörünün histolojik görünümü orijinal olarak 1896 yılında Krukenberg tarafından tanımlanmıştır. Schlagunhaufer ise 1902 yılında Krukenberg tümörünün metastatik olduğunu ve gastrointestinal sistem tümörlerinin sıklıkla primer kaynaklı olduğunu göstermiştir (5). Metastazın en sık retrograd lenfatik yayılım yolu ile meydana geldiği tespit edilmiştir (6). Peritoneal ve vasküler yayılım ise mide kanserinin over metastazının daha nadir şekilleridir (6,7). Asit Krukenberg tümörüne eşlik eden bulgulardan biridir. Asit genellikle malign hücreler içerir (3). Krukenberg tümörü pek çok farklı semptomlarla ortaya çıkabilir. Literatüre baktığımızda; Horimatsu ve ark.'nın (8) sunduğu olguda 50 yaşında bir aydır başlayan karında şişkinlik ve nefes darlığı ile başvuran hastanın yapılan endoskopik incelemesiyle hastaya gastrik kanser tanısı konulmuş, tomografisinde olgumuzda olduğu gibi bilateral overlerde kitle, yaygın plevral efüzyon ve asit tespit edilmiştir. Ancak bizim olgumuzdan farklı olarak sıvıların sitolojik incelemesinde malign hücreye rastlanmamış, bilateral ooferektomi sonrası plevral efüzyon ve asitin gerilediği izlenmiş ve gastrik kansere bağlı Psödo Meigs sendromu olarak değerlendirilmiştir. Khan ve ark.'nın (9) sunduğu olguda ise 26 yaşında dizüri, pelvik ağrı ve menometroraji ile başvuran hastanın yapılan endometriyal biyopsisinde sarkom saptanarak cerrahi uygulanmıştır. Cerrahiyi takiben bir hafta sonra hasta hematemez ile başvurmuş yapılan gastroskopisinde gastrik adenokarsinom tespit edilmiştir. Doku örnekleri ile hasta Krukenberg kabul edilmiştir. Sahin ve ark.'nın (10) sunduğu olguda hiçbir gastrik yakınması olmayan amenore şikayeti ile tetkik edilen hastada Krukenberg tümörü saptanmıştır. Das ve ark.'nın (11) sunduğu olguda da sağ alt kadran ağrısı ile başvuran hastada teşhis konulmuştur. Literatürde olgumuzda olduğu gibi deri döküntüleri, gezici artrit ile başvuran olguya rastlamadık. Olgumuzda hastamız genç yaşta olup hastaneye başvurmasını gerektirecek bir mide şikayetine sahip değildi. Hastaneye başvurma nedeni nefes darlığı, deride döküntüler ve gezici artrit idi. Ön tanı olarak Sarkoidoz-Löfgren sendromu düşünülmekle birlikte laboratuvar, radyoloji ve hızla bozulan kliniği ile bu tanıdan uzaklaşılıp lenfoma, over tümörü tanıları düşünüldü. Seyri sırasında gelişen perikardiyal mayi sitolojisi taşlı yüzük hücreli karsinom ile uyumlu geldi. Yine nodülden yapılan eksizyonel biyopsi sonucu da bu tanıyı destekledi. Yapılan tetkikleri ile primeri mide Krukenberg tümörü teşhisi konuldu.

Krukenberg tümöründe cerrahi, uygun hastalar için metastaz yokluğunda ana tedavidir. Ancak mide kanserinin lokal ve uzak nüksü dikkate alınarak, kemoterapi ve radyasyon tedavisi de cerrahi tedaviye eklenebilir (12). Sadece metastatik over kitlesi olduğunda, metastazektomi yaşam süresini uzatabilir. Bizim hastamızda yaygın metastazlar olduğu için cerrahi uygulanamadı. Kemoterapi tedavisi uygulandı, yatışı sırasında yaygın perikardiyal, plevral efüzyon ve asit gelişti. Hastamızın yatışının 70. gününde solunum sıkıntısı gelişerek yoğun bakıma alındı ve entübe edildi, ancak hasta ex oldu.

Sonuç olarak overlerde bilateral, düzgün kenarlı kitleler saptanması durumunda, tanı anında hastada herhangi bir primer odak bulunmasa dahi Krukenberg tümörü akılda bulundurulmalıdır.

Etik

Hakem Değerlendirmesi: Editörler kurulu tarafınca değerlendirilmiştir.

Yazarlık Katkıları

Cerrahi ve Medikal Uygulama: Özden Demir, Selcan Cesur, Zeynep Karaali. Konsept: Özden Demir, Zeynep Karaali. Dizayn: Özden Demir, Zeynep Karaali. Veri Toplama veya İşleme: Özden Demir, Zeynep Karaali. Analiz veya Yorumlama: Özden Demir, Zeynep Karaali. Literatür Arama: Özden Demir. Yazan: Özden Demir.

Çıkar Çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemiştir.

Finansal Destek: Çalışmamız için hiçbir kurum ya da kişiden finansal destek alınmamıştır.

Kaynaklar

1. Yoldemir T. Bilateral ovarian Krukenberg tümör at mid-gestation. Marmara Medical Journal2014;27:207-9.
2. Özmen Z, Aktaş F, Aslan K ve ark. Bilateral over kitlesi: Primer over tümörü? Krukenberg tümörü? J Contemp Med2015;5:47.
3. Al-Agha O, Nicastri A. An in-depth look at Krukenberg tumor. Arch Pathol Lab Med 2006;130:1725-30.
4. Turan T, Bozok S, Köse MF. Primer odağı ekstragenital organlar olan metastatik over tümörleri. Türk Jinekolojik Onkoloji Dergisi 2006;9:55-61.
5. Gülhan Y, Yener O, İpekçi F, Vural E. Mide Kanserine Bağlı Krukenberg Tümörü. Göztepe Tıp Dergisi 2002;17:235-6.
6. Kakushima N, Kamoshida T, Hirai S, et al. Early gastric cancer with Krukenberg tumor and review of cases of intramucosal gastric cancers with Krukenberg tumor. J Gastroenterol 2003;38:1176-80.
7. Kim NK, Kim HK, Park BJ, et al. Risk factors for ovarian metastases following curative resection of gastric adenocarcinoma. Cancer 1999;85:1490-9.
8. Horimatsu T, Miyamoto S, Mashimo Y, et al. Pseudo-Meigs' syndrome caused by a Krukenberg tumour of gastric cancer. Intern Med2015;54:2595-7.
9. Khan M, Bhatti RP, Mukherjee S, et al. A 26-year-old female with metastatic primary gastrointestinal malignancy presenting as menorrhagia. J Gastrointest Oncol 2015;6:21-5.
10. Sahin S, Karatas F, Hacioglu B, ve ark. Krukenberg tumor presenting with amenorrhea as the sole initial symptom: Case report and review of the literature. J Cancer Res Ther 2015;11:1024.
11. Das S, Sahu D, Wani M, Reddy PK. A curious discourse of Krukenberg tumor: a case report. J Gastrointest Oncol2014;5:117-20.
12. Quiros RM, Desai DC. Multidisciplinary approach for the treatment of gastric cancer. Minerva Gastroenterol Dietol 2011;57:53-68.

Olgu Sunumu / *Case Report*

DOI: 10.4274/haseki.3224
Med Bull Haseki 2017;55:82-4

Nadir Bir Olgu: Touraine Solente Gole Sendromu

A Rare Case: Touraine Solente Gole Syndrome

Kamil Şahin, Nurcan Keskin Osmanoğlu, Hümeyra Öztürk Emre*, Tarkan Kalkan**, Murat Elevli

Haseki Eğitim ve Araştırma Hastanesi, Çocuk Hastalıkları Kliniği, İstanbul, Türkiye

**Haseki Eğitim ve Araştırma Hastanesi, Tıbbi Biyokimya Laboratuvarı, İstanbul, Türkiye*

***Haseki Eğitim ve Araştırma Hastanesi, Tıbbi Genetik, İstanbul, Türkiye*

Öz

Touraine Solente Gole sendromu, pakidermoperiostozisin otosomal resesif geçen bir formudur. Karakteristik üçlemesi el ve ayak parmaklarında genişleme, deride kalınlaşma, el-ayaklarda terleme ve ağrıdır. Biz, bu tanıyı almış dokuz yaşındaki bir hastayı, çok nadir görülmesi nedeni ile, konuya dikkat çekmek amacı ile sunuyoruz.

Dokuz yaşındaki kız hasta, polikliniğe el ve ayaklarda terleme ve kalınlaşma şikayeti ile başvurdu. Birinci derece akraba evliliği olan ailenin dördüncü çocuğu olup, 26 yaşındaki ablada da benzer bulgular var idi. Fizik muayenede el parmaklarında çomaklaşma olup, el parmakları kalın ve terli idi. Hastanın tetkiklerinde özellik yoktu. El grafisinde epifiz ve metafizlerde kalınlaşma ve periostal kemik oluşumu vardı. Pakidermaperiostozis, genellikle çocuklukta başlar ve 20 yaşına kadar ilerleyip sonra sabit bir hal alır. Otozomal dominant formları da vardır. Bebeklik döneminde fontanellerin geç kapanması ve patent duktus arteriosus, hastalığın bir bulgusu olarak görülebilir.

15-hidroksi prostoglandin dehidrogenaz genindeki (4q33-q34) delesyon ve mutasyonlar da, bu fenotipi vermektedir. Kızlarda daha sık görülen bu sendrom genellikle romatizmal hastalıkları taklit eder. Kemik ağrılarında ibuprofen tedavisi kullanılabilir. Alternatif tedavi kolşisindir.

Küçük yaşta başlayıp devam eden el ayak terlemelerine elde çomak parmak eşlik ediyor ise pakidermaperiostozis akla gelmelidir.

Anahtar Sözcükler: Pakidermaperiostozis, Touraine Solente Gole sendromu, el terlemesi

Abstract

Touraine-Solente-Gole syndrome, also known as pachydermoperiostosis, is transmitted as an autosomal recessive trait. It is characterized by enlargement of fingers and toes, pachyderma, excessive sweating, and pain. In this paper, we present a 9-year-old patient to attract attention to this rare disease. A 9-year-old female patient was brought to our outpatient clinics with sweating and enlargement of hands and feet. She was the fourth child born to consanguineous parents. Her 26-year-old elder sister also had the same symptoms. Her physical examination revealed clubbing of the hands, and thick and sweating fingers. Her test results were unremarkable. Hand x-ray revealed epiphyseal, and metaphyseal thickening of the hands, and periostal hyperosteosis. Pachydermoperiostosis usually begins in childhood, progresses till 20 years of age, then, ceases. Delayed closure of fontanelles, and patent ductus arteriosus may be symptoms of the disease.

Patients with deletions and mutations in HPGD (15-hydroxy prostaglandin dehydrogenase) gene (4q33-q34) demonstrate this phenotype. This syndrome is more frequent in females, and mimics rheumatic diseases. Ibuprofen therapy may be used for bone pain. Colchicine is the alternative treatment. In cases of excessive hand and feet sweating associated with clubbed fingers pachydermoperiostosis should be brought to mind.

Keywords: Pachydermoperiostosis, Touraine Solente Gole syndrome, sweating of hands

Giriş

Pakidermaperiostozis (PDP) nadir görülen genetik bir hastalıktır. Karakteristik üçlemesi el ve ayak parmaklarında genişleme (çomak parmak), deride kalınlaşma, el-ayakta terleme ve subperiostal yeni kemik oluşumu nedeni ile zamanla ortaya çıkan ağrıdır. Hastalarda çoklu eklem iltihabı, deride uzunlamasına deri çizgi oluşumları, deride yağlanma ve aşırı terleme görülebilir. Aşırı terleme tüm vücutta olmakla birlikte, el ve ayaklarda daha yoğun görülür. Hastalığın klinik olarak üç farklı formu tanımlanmıştır (1-3).

1. Tam formu; deri kalınlaşması ve periostitin birlikte olduğu form yaklaşık %40 olguda.

Yazışma Adresi/Address for Correspondence: Kamil Şahin
Haseki Eğitim ve Araştırma Hastanesi, Çocuk Hastalıkları Kliniği, İstanbul, Türkiye
Tel.: +90 532 405 97 06 E-posta: drkamil_sahin@hotmail.com

Geliş Tarihi/Received: 12 Nisan 2016 **Kabul Tarihi/Accepted:** 08 Haziran 2016

Bu çalışma 24-26 Mart 2016 tarihlerinde İstanbul 4. Çocuk Dostları Kongresi'nde, poster olarak sunulmuştur.

2. Tam olmayan formu; kemik anomalileri varken, deri kalınlaşmasının olmadığı form yaklaşık %58 olguda.

3. Frusta form; deri kalınlaşmasının çok belirgin olduğu, kemik bulguların çok hafif görüldüğü form %2 olguda.

Touraine Solente Gole sendromu bu hastalığın otosomal resesif geçen ve en sık görülen tam olmayan formudur.

PDP'nin prevalansı bilinmemektedir. Ancak dişi fenotipte erkek fenotipe oranla yedi kat sık görülmektedir. Erkek fenotipte ise klinik bulgular daha belirgin olmaktadır (4). Biz, el ve ayakta terleme şikayeti ile kliniğimize başvurup, bu tanıyı almış dokuz yaşındaki bir kız hastayı, çok nadir görülmesi nedeni ile, konuya dikkat çekmek amacı ile sunuyoruz.

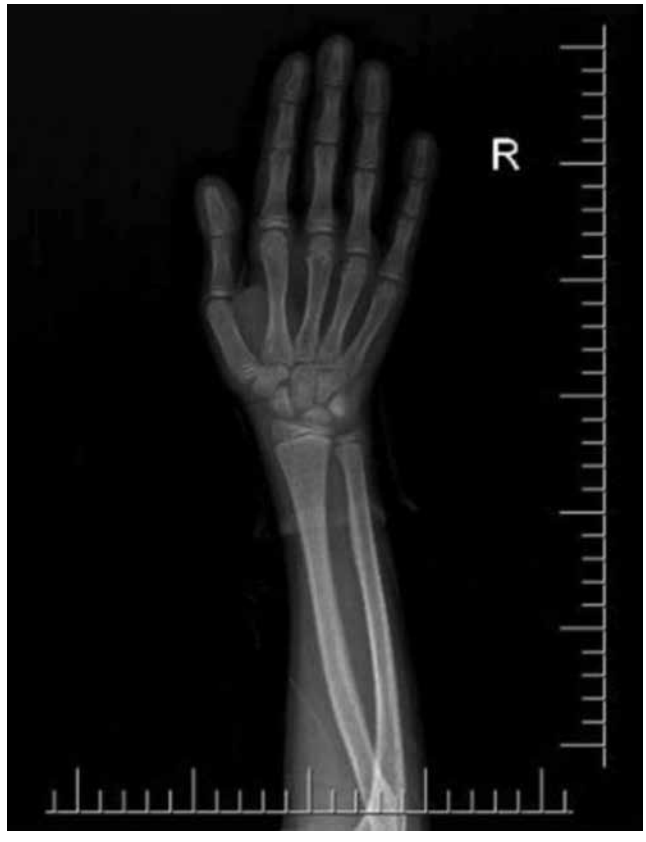
Olgu

Dokuz yaşındaki kız hasta, Haseki Eğitim ve Araştırma Hastanesi Çocuk Polikliniği'ne el ve ayaklarda terleme ve kalınlaşma şikayeti ile başvurdu. Birinci derece akraba evliliği olan ailenin dördüncü çocuğu olup, 26 yaşındaki ablada da benzer bulgular vardı. Özgeçmişinde; sık gribal enfeksiyon geçirme hikayesi alındı. Aile, bir yaşında iken çocuğun ellerinde, çomaklaşma fark ettiklerini ifade etti. Fizik muayenede el parmaklarında çomaklaşma vardı. El parmakları kalın ve terli idi. Sarı saçlı açık tenli ve boynunda 2 cm çapında sütlü kahve rengi lekesi vardı. Diğer sistem muayeneleri normal bulundu. Kalpte üfürüm duyulmadı. Hastanın hemogram ve biyokimya tetkiklerinde özellik yoktu. Beyin tomografisi ve karın ultrasonografisi normal bulundu. El grafisinde epifiz ve metafizlerde kalınlaşma ve periostal yeni kemik oluşumu vardı (Şekil 1).

Tartışma

PDP genellikle çocukluk ve ergenlik döneminde başlayıp, yaklaşık 5-20 yıl arası ilerleyici bir seyir gösterdikten sonra sabit bir hal almaktadır. Bebeklik döneminde fontanellerin geç kapanması ve patent duktus arteriozus (PDA) görülmesi hastalığın bir bulgusu olabilir. Hastalarda deri kalınlaşması, çomak parmak gelişimi, deride yağlanma ve ödem ve aşırı terleme vardır. Daha sonra eklem efüzyonu, artrit, periostal kemikleşme bulguları belirgenleşmeye başlar. Hastalarda şiddetli kanburluk, eklem kısıtlılığı ve nörolojik bulgular gelişebilmektedir. Doğumsal kalp hastalığı, özellikle PDA sık görülmektedir (1-3).

Hastanın fenotipik özellikleri ve ön planda kemik tutulumu olduğu için tam olmayan Primer Hipertrofik Osteoartropati Otozomal Resesif 1(PHOAR1) veya diğer ismi ile Touraine Solente Gole sendromu olabileceğini düşündük. PHOAR1 sendromu ilk defa 1868 yılında Friedrich tarafından tanımlanmıştır (5). 15-hidroksi prostaglandin dehidrogenaz (15-HPGD) geni (4q33-q34) delesyon ve mutasyonlarında bu fenotipi vermektedir. 15-PGDH enzimi prostoglandin yıkımının temel enzimidir. Homozigot mutasyon olan hastalarda prostoglandin E2 yükselir ve idrarda atılımı tespit edilebilir. Bu gen üzerindeki farklı mutasyonlar da fenotipteki farklılıklara neden olmaktadır. Bu gen mutasyonlarında uzun boy (Marfan sendromuna benzer), kaba yüz yapısı, yüzde belirgin kıvrımlar, deride kalınlaşma, göz kapağında pitoz, huni şeklinde göğüs, uzun klavikulalar, ince kalvayum, fontanellerde geç kapanma, wormian kemiği, uzun kemiklerde periostal kemik oluşumu, diafiz ve metafizlerde genişleme, diz ekleminde efüzyon, geniş el yapısı ve el ve ayak parmaklarında çomak parmak bulgusu, aşırı terleme, palmoplantar hiperkeratoz, egzama ve tırnakların kaplumbağa sırtı şeklini alması gibi bulgular daha belirgindir (2). Ayrıca; primer hipertrofik osteoartropati otozomal resesif 2 fenotipine neden olan SLCO2A1 gen mutasyonları bulunmaktadır. Bu gen mutasyonu ile ortaya çıkan fenotipte ise yüz derisinde ilerleyici kalınlaşma, periost iltihabı, artralji, dizlerde şişlik, diz ekleminde periost kemikleşmesi, pateller skleroz, distal femur sklerozu, metekarp ve falanks normal tubulasyon kaybı, çomak parmak, hipertrofik osteoartropati daha belirgin olarak kendini gösterir (6). Otosomal resesif kalıtılan PDP'nin taşıyıcı kişilerinde, hafif fenotipik özellikler görülebilmektedir. Hasta kliniği açısından taşıyıcıların belirlenmesi ve hastalarda görülen klinik bulguların etiyolojisinin açıklanması da önemlidir.



Şekil 1. Epifiz ve metafizlerde kalınlaşma ve periostal hiperostozis

Ayrıca; primer hipertrofik osteoartropati otozomal dominant, fenotipine neden olan gen henüz belirlenmemiş olmakla birlikte otozomal dominant geçiş göstermesi ile diğer iki gen mutasyonlarından ayrılmaktadır. Aralıklarla gelen pitoz, parmaklarda çomaklaşma, osteoartropati, kaba deri, derin girintili deri, seboreik hiperplazi, aşırı terleme temel bulgular olarak gözlenmektedir (4).

Romatizmal belirtiler için nonsteroid antienflamatuvar ilaçlar öncelikli kullanılmalıdır. Steroidler dirençli olgularda kullanılabilmektedir. Ayrıca bazı hastalarda kolşisinin etkili olabileceği unutulmamalıdır. Dermatolojik semptomların klinik iyileşmesi retinoidler ile sağlanabilmektedir. Çomak parmak cerrahi olarak düzeltilebilir (7).

Hastamızın ablasında özellikle eklem şikayetleri bulunmakta olup, hastaya 26 yaşa kadar tanı konamamıştır. Yine ailede romatizmal şikayetlerin sık görüldüğü öğrenilmiştir. Kadınlarda erkeklere oranla yedi kat sık rastlanmasına rağmen erkeklerde belirtilerin daha belirgin olması taşıyıcı erkekleri eklem ve deri sorunları açısından değerlendirmek gerektiğini düşündürmektedir.

Küçük yaşta başlayıp devam eden el ve ayak terlemelerine, çomak parmak eşlik ediyor ise, PDP akla gelmelidir.

Etik

Hakem Değerlendirmesi: Editörler kurulu tarafınca değerlendirilmiştir.

Yazarlık Katkıları

Cerrahi ve Medikal Uygulama: Nurcan Keskin Osmanoğlu, Tarkan Kalkan. Konsept: Kamil Şahin. Dizayn: Tarkan Kalkan, Hümeyra Öztürk Emre. Veri Toplama ve İşleme: Nurcan Keskin Osmanoğlu, Tarkan Kalkan. Analiz ve Yorumlama: Tarkan Kalkan, Murat Elevli. Literatür Arama: Kamil Şahin, Tarkan Kalkan. Yazan: Kamil Şahin, Murat Elevli.

Kaynaklar

1. Rastogi R, Suma GN, Prakash R, Rastogi UC, Bhargava S, Rastogi V. Pachydermoperiostosis or primary hypertrophic osteoarthropathy: A rare clinicoradiologic case. Indian J Radiol Imaging 2009;19:123-6.
2. Uppal S, Diggle CP, Carr IM, et al. Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. Nat Genet 2008;40:789-93.
3. Touraine A, Solente G, Gole L. Un syndrome osteodermopathique: la pachydermie plicaturee avec pachyperiostose des extremites. Presse Med 1935;43:1820-4.
4. Sahasrabhojaney VS, Hinge AV, Ghodeswar SS, et al. Touraine-Solente-Gole' syndrome. J Indian Acad Community Med 2005;6:152-4.
5. Iftikhar A, Hamid MH, Rathore AW et al. Touraine-Solente-Gole syndrome in two siblings. Physicians Surg Pak 2014;24(Suppl 3):247-9.
6. Zhang Z, Xia W, He J, et al. Exome sequencing identifies SLCO2A1 mutations as a cause of primary hypertrophic osteoarthropathy. Am J Hum Genet 2012;90:125-32.
7. Auger M, Stavrianeas N. Pachydermoperiostosis. Orphanet Encylcopedia. Available from:http://www.orpha.net [cited in 2004].